

WEBVTT

NOTE duration:"05:02:29.3130000"

NOTE language:en-us

NOTE Confidence: 0.903091728687286

00:00:00.000 --> 00:00:03.580 I think I'll actually get going with.

NOTE Confidence: 0.903091728687286

00:00:03.580 --> 00:00:05.948 I think I'm all set right?

NOTE Confidence: 0.903091728687286

00:00:05.948 --> 00:00:09.240 So why don't we just keep it this way?

NOTE Confidence: 0.903091728687286

00:00:09.240 --> 00:00:12.008 Not upset the Apple cart and then we'll

NOTE Confidence: 0.903091728687286

00:00:12.008 --> 00:00:14.943 go with that and I just wanted to

NOTE Confidence: 0.903091728687286

00:00:14.943 --> 00:00:16.837 welcome the already 161 participants

NOTE Confidence: 0.903091728687286

00:00:16.837 --> 00:00:19.837 that we have and I think it's really

NOTE Confidence: 0.903091728687286

00:00:19.837 --> 00:00:22.050 a reflection of what an outstanding

NOTE Confidence: 0.903091728687286

00:00:22.050 --> 00:00:24.608 schedule that we have planned for today.

NOTE Confidence: 0.903091728687286

00:00:24.608 --> 00:00:26.072 I'm really, really excited

NOTE Confidence: 0.903091728687286

00:00:26.072 --> 00:00:27.538 on Marcus Bosenberg, um,

NOTE Confidence: 0.903091728687286

00:00:27.538 --> 00:00:29.368 the interim director for the

NOTE Confidence: 0.903091728687286

00:00:29.370 --> 00:00:30.837 El Center for immunooncology.

NOTE Confidence: 0.903091728687286

00:00:30.837 --> 00:00:33.773 This is a center that is based on.

NOTE Confidence: 0.903091728687286
00:00:33.780 --> 00:00:34.950 Collaborative interaction between
NOTE Confidence: 0.903091728687286
00:00:34.950 --> 00:00:36.510 the Yale Cancer Center,
NOTE Confidence: 0.903091728687286
00:00:36.510 --> 00:00:38.838 led by Charlie Fuchs and the
NOTE Confidence: 0.903091728687286
00:00:38.838 --> 00:00:39.594 Immunobiology Department,
NOTE Confidence: 0.903091728687286
00:00:39.594 --> 00:00:42.723 led by David shots as well as other
NOTE Confidence: 0.903091728687286
00:00:42.723 --> 00:00:44.700 aspects of at Yale University
NOTE Confidence: 0.903091728687286
00:00:44.700 --> 00:00:46.650 and we're trying to coordinate
NOTE Confidence: 0.903091728687286
00:00:46.650 --> 00:00:49.380 an enhanced the work and I'm now
NOTE Confidence: 0.903091728687286
00:00:49.380 --> 00:00:52.110 on Koleji at Yale and you know,
NOTE Confidence: 0.903091728687286
00:00:52.110 --> 00:00:55.212 it's I guess one Boone of not being
NOTE Confidence: 0.903091728687286
00:00:55.212 --> 00:00:58.188 able to travel is that it's hard to
NOTE Confidence: 0.903091728687286
00:00:58.188 --> 00:01:00.689 imagine getting a slate of external
NOTE Confidence: 0.903091728687286
00:01:00.690 --> 00:01:03.480 speakers like this if everyone has to
NOTE Confidence: 0.903091728687286
00:01:03.480 --> 00:01:06.540 be moving around and traveling all the time,
NOTE Confidence: 0.903091728687286
00:01:06.540 --> 00:01:06.935 so.
NOTE Confidence: 0.903091728687286

00:01:06.935 --> 00:01:09.598 Will really enjoy the day I think for
NOTE Confidence: 0.903091728687286

00:01:09.598 --> 00:01:12.057 the trainees at Yale and the faculty,
NOTE Confidence: 0.903091728687286

00:01:12.060 --> 00:01:14.426 this is going to be really exciting.
NOTE Confidence: 0.903091728687286

00:01:14.426 --> 00:01:16.452 A couple of things in terms
NOTE Confidence: 0.903091728687286

00:01:16.452 --> 00:01:17.466 of procedural things.
NOTE Confidence: 0.903091728687286

00:01:17.470 --> 00:01:20.166 I think all of you have the agenda.
NOTE Confidence: 0.903091728687286

00:01:20.170 --> 00:01:22.954 That will be a couple of breaks throughout
NOTE Confidence: 0.903091728687286

00:01:22.954 --> 00:01:25.238 and a half an hour lunch session.
NOTE Confidence: 0.903091728687286

00:01:25.240 --> 00:01:26.260 We may need
NOTE Confidence: 0.837537169456482

00:01:26.260 --> 00:01:27.268 to adjust times
NOTE Confidence: 0.837537169456482

00:01:27.270 --> 00:01:29.636 a little bit. We hope that the
NOTE Confidence: 0.837537169456482

00:01:29.640 --> 00:01:31.656 speakers can roughly stay on time
NOTE Confidence: 0.837537169456482

00:01:31.660 --> 00:01:34.370 for a total of 1/2 an hour per
NOTE Confidence: 0.837537169456482

00:01:34.370 --> 00:01:36.058 slot, which will include some
NOTE Confidence: 0.837537169456482

00:01:36.060 --> 00:01:37.080 questions. Panelists including
NOTE Confidence: 0.837537169456482

00:01:37.080 --> 00:01:38.780 speakers can actually ask questions.

NOTE Confidence: 0.837537169456482
00:01:38.780 --> 00:01:40.880 For those of you as attendees,
NOTE Confidence: 0.837537169456482
00:01:40.880 --> 00:01:42.455 there's a chat function that
NOTE Confidence: 0.837537169456482
00:01:42.455 --> 00:01:44.730 you should use to ask questions,
NOTE Confidence: 0.837537169456482
00:01:44.730 --> 00:01:46.480 and the moderate yrs will
NOTE Confidence: 0.837537169456482
00:01:46.480 --> 00:01:48.230 help monitor that Anne will
NOTE Confidence: 0.863619446754456
00:01:48.230 --> 00:01:49.630 guide the question period.
NOTE Confidence: 0.87241667509079
00:01:50.290 --> 00:01:52.126 And so I think, you know,
NOTE Confidence: 0.87241667509079
00:01:52.130 --> 00:01:53.660 we're probably going to need
NOTE Confidence: 0.87241667509079
00:01:53.660 --> 00:01:55.795 all the time we can get today.
NOTE Confidence: 0.87241667509079
00:01:55.795 --> 00:01:57.625 So with all this exciting science,
NOTE Confidence: 0.87241667509079
00:01:57.630 --> 00:01:59.746 I want to thank all those speakers
NOTE Confidence: 0.87241667509079
00:01:59.746 --> 00:02:01.211 really very, very much for
NOTE Confidence: 0.87241667509079
00:02:01.211 --> 00:02:02.839 participating in this upfront 'cause.
NOTE Confidence: 0.87241667509079
00:02:02.840 --> 00:02:05.284 I'm sure some people will have to go
NOTE Confidence: 0.87241667509079
00:02:05.284 --> 00:02:07.730 in and out during the day and stuff,
NOTE Confidence: 0.87241667509079

00:02:07.730 --> 00:02:09.260 but you know, up front,
NOTE Confidence: 0.87241667509079

00:02:09.260 --> 00:02:11.098 at least for our first session,
NOTE Confidence: 0.87241667509079

00:02:11.100 --> 00:02:12.630 for those who are here.
NOTE Confidence: 0.87241667509079

00:02:12.630 --> 00:02:13.546 Thanks so much.
NOTE Confidence: 0.87241667509079

00:02:13.546 --> 00:02:15.685 And I'd like to introduce Jeff Ishizuka
NOTE Confidence: 0.87241667509079

00:02:15.685 --> 00:02:17.522 who is an assistant professor at
NOTE Confidence: 0.87241667509079

00:02:17.522 --> 00:02:19.050 Yale University and medical oncology,
NOTE Confidence: 0.87241667509079

00:02:19.050 --> 00:02:20.298 who has a background.
NOTE Confidence: 0.87241667509079

00:02:20.300 --> 00:02:21.720 In immunology as well,
NOTE Confidence: 0.87241667509079

00:02:21.720 --> 00:02:23.850 and we're very excited to have
NOTE Confidence: 0.87241667509079

00:02:23.918 --> 00:02:25.660 him as a faculty member here.
NOTE Confidence: 0.87241667509079

00:02:25.660 --> 00:02:27.670 Also, as a colleague of some
NOTE Confidence: 0.87241667509079

00:02:27.670 --> 00:02:29.679 of the folks who were speaking,
NOTE Confidence: 0.87241667509079

00:02:29.680 --> 00:02:30.352 I think,
NOTE Confidence: 0.87241667509079

00:02:30.352 --> 00:02:32.698 and even this first session and Jeff,
NOTE Confidence: 0.87241667509079

00:02:32.698 --> 00:02:33.700 please proceed with

NOTE Confidence: 0.825356423854828
00:02:33.700 --> 00:02:34.708 the first session.
NOTE Confidence: 0.815905332565308
00:02:35.490 --> 00:02:36.710 Great, just echo at
NOTE Confidence: 0.815905332565308
00:02:36.710 --> 00:02:37.628 Marcus said it's
NOTE Confidence: 0.815905332565308
00:02:37.630 --> 00:02:39.772 it's fantastic lineup today and it's an
NOTE Confidence: 0.815905332565308
00:02:39.772 --> 00:02:41.916 honor and pleasure to moderate the session.
NOTE Confidence: 0.815905332565308
00:02:41.916 --> 00:02:44.058 I'm really excited to be here and
NOTE Confidence: 0.815905332565308
00:02:44.060 --> 00:02:45.586 to introduce our fantastic speakers.
NOTE Confidence: 0.815905332565308
00:02:45.586 --> 00:02:47.116 Our first speaker is doctor
NOTE Confidence: 0.815905332565308
00:02:47.116 --> 00:02:48.950 rafi Ahmed Rafi along with some
NOTE Confidence: 0.815905332565308
00:02:48.950 --> 00:02:49.868 of our other
NOTE Confidence: 0.815905332565308
00:02:49.870 --> 00:02:51.098 speakers today is responsible
NOTE Confidence: 0.815905332565308
00:02:51.100 --> 00:02:53.235 for laying a great deal of the
NOTE Confidence: 0.815905332565308
00:02:53.240 --> 00:02:55.685 groundwork for there to be a Center for,
NOTE Confidence: 0.815905332565308
00:02:55.685 --> 00:02:57.828 you know, oncologix, Here or anywhere else.
NOTE Confidence: 0.858892500400543
00:02:58.370 --> 00:02:59.288 His investigations into
NOTE Confidence: 0.858892500400543

00:02:59.290 --> 00:03:00.208 T cell differentiation
NOTE Confidence: 0.858892500400543

00:03:00.210 --> 00:03:01.438 and function have guided
NOTE Confidence: 0.858892500400543

00:03:01.440 --> 00:03:03.282 the way to our current understandings
NOTE Confidence: 0.858892500400543

00:03:03.282 --> 00:03:06.376 of T cell memory and T cell exhaustion.
NOTE Confidence: 0.858892500400543

00:03:06.380 --> 00:03:08.018 In his foundational work in acute
NOTE Confidence: 0.858892500400543

00:03:08.018 --> 00:03:09.656 and chronic else, MV have been
NOTE Confidence: 0.858892500400543

00:03:09.656 --> 00:03:11.570 essential in defining the role of PD.
NOTE Confidence: 0.858892500400543

00:03:11.570 --> 00:03:13.208 One in limiting T cell function.
NOTE Confidence: 0.821625769138336

00:03:13.960 --> 00:03:15.040 Raffi is the
NOTE Confidence: 0.821625769138336

00:03:15.040 --> 00:03:16.120 Charles Howard Candler
NOTE Confidence: 0.821625769138336

00:03:16.120 --> 00:03:17.200 Professor of Microbiology
NOTE Confidence: 0.821625769138336

00:03:17.200 --> 00:03:18.280 and immunology at
NOTE Confidence: 0.821625769138336

00:03:18.280 --> 00:03:19.360 Emory University and
NOTE Confidence: 0.821625769138336

00:03:19.360 --> 00:03:21.880 director of the Emory Vaccine Center. The
NOTE Confidence: 0.821625769138336

00:03:21.880 --> 00:03:22.960 title of his
NOTE Confidence: 0.821625769138336

00:03:22.960 --> 00:03:24.040 talk today is

NOTE Confidence: 0.821625769138336

00:03:24.040 --> 00:03:25.840 T cell lifestyle and chronic

NOTE Confidence: 0.821625769138336

00:03:25.840 --> 00:03:27.280 viral infection and cancer.

NOTE Confidence: 0.821625769138336

00:03:27.280 --> 00:03:29.080 Be shows after the infection

NOTE Confidence: 0.821625769138336

00:03:29.080 --> 00:03:30.880 is cleared and in striking

NOTE Confidence: 0.821625769138336

00:03:30.880 --> 00:03:32.680 contrast of the virus persist,

NOTE Confidence: 0.821625769138336

00:03:32.680 --> 00:03:34.120 specially at very high

NOTE Confidence: 0.821625769138336

00:03:34.120 --> 00:03:36.640 levels. But you get T cell dysfunction.

NOTE Confidence: 0.828418910503387

00:03:37.370 --> 00:03:38.420 The conceptual breakthrough

NOTE Confidence: 0.828418910503387

00:03:38.420 --> 00:03:40.502 in understanding T cell dysfunction that

NOTE Confidence: 0.828418910503387

00:03:40.502 --> 00:03:43.320 came from the studies of Valenzia. So I'm

NOTE Confidence: 0.828418910503387

00:03:43.320 --> 00:03:44.720 excited to introduce our

NOTE Confidence: 0.828418910503387

00:03:44.720 --> 00:03:46.120 last speaker of the

NOTE Confidence: 0.828418910503387

00:03:46.120 --> 00:03:47.870 session. Doctor Amanda Lund. Amanda

NOTE Confidence: 0.828418910503387

00:03:47.870 --> 00:03:49.270 has made Seminole contributions

NOTE Confidence: 0.828418910503387

00:03:49.270 --> 00:03:51.370 to our understanding of the regulation

NOTE Confidence: 0.828418910503387

00:03:51.370 --> 00:03:53.120 of immune function by lymphatic
NOTE Confidence: 0.828418910503387

00:03:53.120 --> 00:03:54.170 vessels and organs
NOTE Confidence: 0.828418910503387

00:03:54.170 --> 00:03:56.970 and of their role in shaping the anti
NOTE Confidence: 0.822038605809212

00:03:56.970 --> 00:03:59.190 tumor immune response. Her
NOTE Confidence: 0.802897691726685

00:03:59.190 --> 00:04:00.168 elegant work has
NOTE Confidence: 0.802897691726685

00:04:00.170 --> 00:04:01.148 spanned from fundamental
NOTE Confidence: 0.802897691726685

00:04:01.150 --> 00:04:02.454 immunological discovery to the
NOTE Confidence: 0.802897691726685

00:04:02.454 --> 00:04:04.096 development of quantitative and bio
NOTE Confidence: 0.802897691726685

00:04:04.096 --> 00:04:05.727 engineering tools and human translation.
NOTE Confidence: 0.802897691726685

00:04:05.727 --> 00:04:07.688 Amanda is associate professor in the
NOTE Confidence: 0.802897691726685

00:04:07.690 --> 00:04:08.998 Ronald Oper Element Department
NOTE Confidence: 0.802897691726685

00:04:09.000 --> 00:04:09.978 of dermatology in
NOTE Confidence: 0.802897691726685

00:04:09.980 --> 00:04:12.269 the Department of pathology at the end,
NOTE Confidence: 0.802897691726685

00:04:12.270 --> 00:04:13.578 why you, Grossman, School
NOTE Confidence: 0.802897691726685

00:04:13.580 --> 00:04:14.558 of Medicine. The
NOTE Confidence: 0.802897691726685

00:04:14.560 --> 00:04:16.190 title over talked today is

NOTE Confidence: 0.802897691726685
00:04:16.190 --> 00:04:17.498 lymphatic vessels, immune surveillance
NOTE Confidence: 0.802897691726685
00:04:17.500 --> 00:04:19.130 and immune escape in Melanoma.
NOTE Confidence: 0.889913499355316
00:04:20.780 --> 00:04:22.220 Thank you very much.
NOTE Confidence: 0.889913499355316
00:04:22.220 --> 00:04:24.380 It's really a pleasure and an
NOTE Confidence: 0.889913499355316
00:04:24.456 --> 00:04:26.822 honor to be here today and able
NOTE Confidence: 0.889913499355316
00:04:26.822 --> 00:04:28.779 to present some of our work.
NOTE Confidence: 0.889913499355316
00:04:28.780 --> 00:04:30.868 So I think the organizers very
NOTE Confidence: 0.889913499355316
00:04:30.868 --> 00:04:32.316 much for this opportunity.
NOTE Confidence: 0.889913499355316
00:04:32.316 --> 00:04:34.710 Like really everyone else here today,
NOTE Confidence: 0.889913499355316
00:04:34.710 --> 00:04:37.188 my lab is interested in understanding how
NOTE Confidence: 0.889913499355316
00:04:37.188 --> 00:04:39.677 we can generate and mobilize effective
NOTE Confidence: 0.889913499355316
00:04:39.677 --> 00:04:42.407 immune responses that enable tumor control,
NOTE Confidence: 0.889913499355316
00:04:42.410 --> 00:04:44.835 and there's really three main ways
NOTE Confidence: 0.889913499355316
00:04:44.835 --> 00:04:47.265 that we think about doing that,
NOTE Confidence: 0.889913499355316
00:04:47.270 --> 00:04:48.239 and that is.
NOTE Confidence: 0.889913499355316

00:04:48.239 --> 00:04:50.500 First we need to activate the Antigen
NOTE Confidence: 0.889913499355316

00:04:50.566 --> 00:04:53.006 specific sort of adaptive immune
NOTE Confidence: 0.889913499355316

00:04:53.006 --> 00:04:54.958 responses during tumor development.
NOTE Confidence: 0.889913499355316

00:04:54.960 --> 00:04:57.070 Second, we mobilize that effector
NOTE Confidence: 0.889913499355316

00:04:57.070 --> 00:04:59.636 immunity into the tumor micro environment
NOTE Confidence: 0.889913499355316

00:04:59.636 --> 00:05:02.676 where it can engage its target and 3rd.
NOTE Confidence: 0.889913499355316

00:05:02.680 --> 00:05:04.996 We are designing strategies to combat
NOTE Confidence: 0.889913499355316

00:05:04.996 --> 00:05:06.981 the multiple mechanisms of immune
NOTE Confidence: 0.889913499355316

00:05:06.981 --> 00:05:09.261 suppression that we know are present
NOTE Confidence: 0.889913499355316

00:05:09.261 --> 00:05:11.171 within these tumors and suppress
NOTE Confidence: 0.889913499355316

00:05:11.171 --> 00:05:13.301 the ability of the effector immune
NOTE Confidence: 0.889913499355316

00:05:13.301 --> 00:05:15.340 response to mediate tumor killing.
NOTE Confidence: 0.889913499355316

00:05:15.340 --> 00:05:17.100 And it's been clear,
NOTE Confidence: 0.889913499355316

00:05:17.100 --> 00:05:17.820 of course,
NOTE Confidence: 0.889913499355316

00:05:17.820 --> 00:05:19.980 through the seminal work of the
NOTE Confidence: 0.889913499355316

00:05:19.980 --> 00:05:21.960 presenters before me and many others

NOTE Confidence: 0.889913499355316
00:05:21.960 --> 00:05:23.760 that we can target tumor immune
NOTE Confidence: 0.889913499355316
00:05:23.820 --> 00:05:25.770 surveillance in tumor immune responses
NOTE Confidence: 0.889913499355316
00:05:25.770 --> 00:05:28.074 at each of these different points.
NOTE Confidence: 0.889913499355316
00:05:28.074 --> 00:05:29.844 But it's clear that they
NOTE Confidence: 0.889913499355316
00:05:29.844 --> 00:05:31.260 are the challenges remain,
NOTE Confidence: 0.889913499355316
00:05:31.260 --> 00:05:33.040 and there remains subsets of
NOTE Confidence: 0.889913499355316
00:05:33.040 --> 00:05:35.245 patients and types of tumors where
NOTE Confidence: 0.889913499355316
00:05:35.245 --> 00:05:37.779 we have not been able to mobilize
NOTE Confidence: 0.889913499355316
00:05:37.779 --> 00:05:38.995 really significant responses
NOTE Confidence: 0.889913499355316
00:05:38.995 --> 00:05:41.125 and tumor control and patience.
NOTE Confidence: 0.889913499355316
00:05:41.130 --> 00:05:43.930 And one thing that I think we should
NOTE Confidence: 0.889913499355316
00:05:43.930 --> 00:05:46.433 remember is that there's an
NOTE Confidence: 0.889913499355316
00:05:46.433 --> 00:05:48.588 Amazon anatomic framework over which
NOTE Confidence: 0.889913499355316
00:05:48.588 --> 00:05:51.077 we mobilize these effector responses
NOTE Confidence: 0.889913499355316
00:05:51.077 --> 00:05:54.053 that is critical for allowing both
NOTE Confidence: 0.889913499355316

00:05:54.060 --> 00:05:56.232 the initial sensing of a primary
NOTE Confidence: 0.889913499355316

00:05:56.232 --> 00:05:58.725 tumor as well as the infiltration
NOTE Confidence: 0.889913499355316

00:05:58.725 --> 00:06:01.130 and retention of that affect
NOTE Confidence: 0.889913499355316

00:06:01.130 --> 00:06:03.539 immunity within the tumor space.
NOTE Confidence: 0.889913499355316

00:06:03.540 --> 00:06:05.695 And while we appreciate that
NOTE Confidence: 0.889913499355316

00:06:05.695 --> 00:06:07.850 this framework is certainly in,
NOTE Confidence: 0.889913499355316

00:06:07.850 --> 00:06:10.040 in some ways designed to
NOTE Confidence: 0.889913499355316

00:06:10.040 --> 00:06:11.354 facilitate immune surveillance.
NOTE Confidence: 0.889913499355316

00:06:11.360 --> 00:06:13.928 In the setting of cancer where we get
NOTE Confidence: 0.889913499355316

00:06:13.928 --> 00:06:16.272 Ramada Ling and dysfunction within
NOTE Confidence: 0.889913499355316

00:06:16.272 --> 00:06:17.904 various different onomatopoeic
NOTE Confidence: 0.889913499355316

00:06:17.904 --> 00:06:20.080 structures within the entire
NOTE Confidence: 0.889913499355316

00:06:20.152 --> 00:06:22.120 body of the animal or patient,
NOTE Confidence: 0.889913499355316

00:06:22.120 --> 00:06:24.600 that these changes may present
NOTE Confidence: 0.889913499355316

00:06:24.600 --> 00:06:27.080 additional barriers to the ability
NOTE Confidence: 0.889913499355316

00:06:27.160 --> 00:06:29.883 of the effective T cell or more

NOTE Confidence: 0.889913499355316
00:06:29.883 --> 00:06:32.199 responses to really do their jobs.
NOTE Confidence: 0.889913499355316
00:06:32.200 --> 00:06:34.636 And when my lab has been interested
NOTE Confidence: 0.889913499355316
00:06:34.636 --> 00:06:37.192 now and for quite some time
NOTE Confidence: 0.889913499355316
00:06:37.192 --> 00:06:39.100 as the lymphatic vasculature,
NOTE Confidence: 0.889913499355316
00:06:39.100 --> 00:06:42.348 this is a part of our vascular system,
NOTE Confidence: 0.889913499355316
00:06:42.350 --> 00:06:43.866 which mediates the unidirectional
NOTE Confidence: 0.889913499355316
00:06:43.866 --> 00:06:46.140 transport of fluid and cells and
NOTE Confidence: 0.889913499355316
00:06:46.206 --> 00:06:47.930 lipids from peripheral tissues
NOTE Confidence: 0.889913499355316
00:06:47.930 --> 00:06:49.654 to secondary lymphoid organs.
NOTE Confidence: 0.889913499355316
00:06:49.660 --> 00:06:52.090 Where adaptive immune responses are initiated.
NOTE Confidence: 0.889913499355316
00:06:52.090 --> 00:06:54.442 We know that this is the necessary
NOTE Confidence: 0.889913499355316
00:06:54.442 --> 00:06:56.734 in requisite route for the movement
NOTE Confidence: 0.889913499355316
00:06:56.734 --> 00:06:58.764 of Antigen loaded antigen presenting
NOTE Confidence: 0.889913499355316
00:06:58.764 --> 00:07:01.028 cells that leave peripheral tissues
NOTE Confidence: 0.889913499355316
00:07:01.028 --> 00:07:03.343 migrate towards draining lymph nodes
NOTE Confidence: 0.889913499355316

00:07:03.343 --> 00:07:06.196 and thereby activate robust antitumor.
NOTE Confidence: 0.889913499355316

00:07:06.196 --> 00:07:07.480 Immune responses.
NOTE Confidence: 0.889913499355316

00:07:07.480 --> 00:07:09.704 And work that I'm not going to be
NOTE Confidence: 0.889913499355316

00:07:09.704 --> 00:07:12.708 able to show you today from my lab is
NOTE Confidence: 0.889913499355316

00:07:12.708 --> 00:07:14.684 really learning that the lymphatic
NOTE Confidence: 0.889913499355316

00:07:14.684 --> 00:07:16.889 vasculature can tune its transport
NOTE Confidence: 0.889913499355316

00:07:16.889 --> 00:07:19.588 function both at the level of the
NOTE Confidence: 0.889913499355316

00:07:19.588 --> 00:07:22.160 lymphatic capillary and from work by others.
NOTE Confidence: 0.889913499355316

00:07:22.160 --> 00:07:24.498 Also at the level of the collecting
NOTE Confidence: 0.889913499355316

00:07:24.498 --> 00:07:27.005 lymphatic to in some way change the
NOTE Confidence: 0.889913499355316

00:07:27.005 --> 00:07:28.805 quantitative amount and the type
NOTE Confidence: 0.889913499355316

00:07:28.805 --> 00:07:31.429 of information that is able to be
NOTE Confidence: 0.889913499355316

00:07:31.429 --> 00:07:33.602 delivered to the Sentinel Lymph node.
NOTE Confidence: 0.889913499355316

00:07:33.602 --> 00:07:35.357 So in this way really,
NOTE Confidence: 0.889913499355316

00:07:35.360 --> 00:07:36.380 I think we played,
NOTE Confidence: 0.889913499355316

00:07:36.380 --> 00:07:37.910 we think of at least the

NOTE Confidence: 0.85740339756012
00:07:37.973 --> 00:07:39.493 lymphatic vasculature is a
NOTE Confidence: 0.85740339756012
00:07:39.493 --> 00:07:41.393 really critical arm of the
NOTE Confidence: 0.85740339756012
00:07:41.393 --> 00:07:43.199 peripheral tissue immune response.
NOTE Confidence: 0.85740339756012
00:07:43.200 --> 00:07:45.780 That of course we are very
NOTE Confidence: 0.85740339756012
00:07:45.780 --> 00:07:48.220 interested in continuing to explore.
NOTE Confidence: 0.85740339756012
00:07:48.220 --> 00:07:50.570 In the context of cancer, however,
NOTE Confidence: 0.85740339756012
00:07:50.570 --> 00:07:52.150 lymphatic vasculature has been
NOTE Confidence: 0.85740339756012
00:07:52.150 --> 00:07:53.730 largely appreciated for its
NOTE Confidence: 0.85740339756012
00:07:53.785 --> 00:07:55.257 role in regional metastasis.
NOTE Confidence: 0.85740339756012
00:07:55.260 --> 00:07:57.600 We know that, particularly in Melanoma,
NOTE Confidence: 0.85740339756012
00:07:57.600 --> 00:07:59.555 the presence of tumor cells
NOTE Confidence: 0.85740339756012
00:07:59.555 --> 00:08:01.510 in the Sentinel Lymph node,
NOTE Confidence: 0.85740339756012
00:08:01.510 --> 00:08:03.880 which is the lymph node directly
NOTE Confidence: 0.85740339756012
00:08:03.880 --> 00:08:06.209 draining from the primary tumor bed,
NOTE Confidence: 0.85740339756012
00:08:06.210 --> 00:08:08.550 is A is a negative prognostic.
NOTE Confidence: 0.85740339756012

00:08:08.550 --> 00:08:12.753 This is true also in other types of tumors.

NOTE Confidence: 0.85740339756012

00:08:12.760 --> 00:08:15.182 We know that we can find these

NOTE Confidence: 0.85740339756012

00:08:15.182 --> 00:08:16.974 lymphatic vessels which were shown

NOTE Confidence: 0.85740339756012

00:08:16.974 --> 00:08:19.368 here in Green both within and around,

NOTE Confidence: 0.85740339756012

00:08:19.370 --> 00:08:20.381 developing tumor beds,

NOTE Confidence: 0.85740339756012

00:08:20.381 --> 00:08:22.403 and that the increased density of

NOTE Confidence: 0.85740339756012

00:08:22.403 --> 00:08:23.898 these lymphatic vessels increases

NOTE Confidence: 0.85740339756012

00:08:23.898 --> 00:08:26.088 with stage and is associated with

NOTE Confidence: 0.85740339756012

00:08:26.088 --> 00:08:27.777 lived in a metastasis, impatience.

NOTE Confidence: 0.85740339756012

00:08:27.777 --> 00:08:28.571 And importantly,

NOTE Confidence: 0.85740339756012

00:08:28.571 --> 00:08:31.350 we know that either in humans where

NOTE Confidence: 0.85740339756012

00:08:31.419 --> 00:08:33.279 we see overexpression of edge FC

NOTE Confidence: 0.85740339756012

00:08:33.279 --> 00:08:35.558 by tumor cells or by myeloid cells

NOTE Confidence: 0.85740339756012

00:08:35.558 --> 00:08:37.819 infiltrating the tumor bed or in my

NOTE Confidence: 0.85740339756012

00:08:37.820 --> 00:08:39.625 swear we engineer the overexpression

NOTE Confidence: 0.85740339756012

00:08:39.625 --> 00:08:42.338 of edge of see that this is both,

NOTE Confidence: 0.85740339756012
00:08:42.340 --> 00:08:43.980 this is associated with.
NOTE Confidence: 0.85740339756012
00:08:43.980 --> 00:08:45.210 Increased metastatic potential
NOTE Confidence: 0.85740339756012
00:08:45.210 --> 00:08:47.461 to the regional lymph node bed
NOTE Confidence: 0.85740339756012
00:08:47.461 --> 00:08:48.745 of those primary tumors.
NOTE Confidence: 0.85740339756012
00:08:48.750 --> 00:08:51.525 But when I started my post doc
NOTE Confidence: 0.85740339756012
00:08:51.525 --> 00:08:53.510 now sometime ago with melody
NOTE Confidence: 0.85740339756012
00:08:53.595 --> 00:08:55.899 sorts at the PFL in Lausanne,
NOTE Confidence: 0.85740339756012
00:08:55.900 --> 00:08:58.276 we were really interested in challenging.
NOTE Confidence: 0.85740339756012
00:08:58.280 --> 00:09:00.639 This is so the complete story and
NOTE Confidence: 0.85740339756012
00:09:00.639 --> 00:09:02.930 asking instead how the biology of
NOTE Confidence: 0.85740339756012
00:09:02.930 --> 00:09:04.940 lymphatic transport and the Sentinel
NOTE Confidence: 0.85740339756012
00:09:04.940 --> 00:09:07.865 Lymph node really impacts tumor immunity
NOTE Confidence: 0.85740339756012
00:09:07.865 --> 00:09:10.425 and thereby influences tumor progression.
NOTE Confidence: 0.85740339756012
00:09:10.430 --> 00:09:12.915 And we've learned a lot since then,
NOTE Confidence: 0.85740339756012
00:09:12.920 --> 00:09:14.915 and I think it's pretty clear that
NOTE Confidence: 0.85740339756012

00:09:14.915 --> 00:09:17.853 even in the context of tumors at these
NOTE Confidence: 0.85740339756012

00:09:17.853 --> 00:09:19.868 lymphatic vasculature plays are really
NOTE Confidence: 0.85740339756012

00:09:19.937 --> 00:09:21.767 critical role in determining the
NOTE Confidence: 0.85740339756012

00:09:21.767 --> 00:09:23.955 extent to which the immune responses,
NOTE Confidence: 0.85740339756012

00:09:23.955 --> 00:09:26.085 both activated against the developing tumor.
NOTE Confidence: 0.85740339756012

00:09:26.090 --> 00:09:29.296 But also how these responses are maintained.
NOTE Confidence: 0.85740339756012

00:09:29.300 --> 00:09:31.820 Are we first showed up back in really
NOTE Confidence: 0.85740339756012

00:09:31.820 --> 00:09:34.289 in 2012 that the overexpression of
NOTE Confidence: 0.85740339756012

00:09:34.289 --> 00:09:36.935 edge FC by tumor experimental tumors
NOTE Confidence: 0.85740339756012

00:09:37.013 --> 00:09:39.288 not only increases the metastatic
NOTE Confidence: 0.85740339756012

00:09:39.288 --> 00:09:41.563 potential for these tumor cells
NOTE Confidence: 0.85740339756012

00:09:41.570 --> 00:09:44.018 to migrate towards a limp mode,
NOTE Confidence: 0.85740339756012

00:09:44.020 --> 00:09:46.120 but also generated a much more
NOTE Confidence: 0.85740339756012

00:09:46.120 --> 00:09:47.170 inflamed tumor microenvironment
NOTE Confidence: 0.85740339756012

00:09:47.170 --> 00:09:49.036 that subsequently activated multiple
NOTE Confidence: 0.85740339756012

00:09:49.036 --> 00:09:50.980 mechanisms of immune suppression,

NOTE Confidence: 0.85740339756012
00:09:50.980 --> 00:09:53.465 both within the primary tumor bed as
NOTE Confidence: 0.85740339756012
00:09:53.465 --> 00:09:57.108 well as in the Sentinel draining lymph node?
NOTE Confidence: 0.85740339756012
00:09:57.110 --> 00:09:59.606 And this work really sort of.
NOTE Confidence: 0.85740339756012
00:09:59.610 --> 00:10:01.695 Established the paradigm by which
NOTE Confidence: 0.85740339756012
00:10:01.695 --> 00:10:04.271 we could think about perhaps the
NOTE Confidence: 0.85740339756012
00:10:04.271 --> 00:10:06.346 idea that olymp angiogenic tumor,
NOTE Confidence: 0.85740339756012
00:10:06.350 --> 00:10:08.450 one that is really engaged,
NOTE Confidence: 0.85740339756012
00:10:08.450 --> 00:10:10.555 the tumor associated news about
NOTE Confidence: 0.85740339756012
00:10:10.555 --> 00:10:11.397 across culture,
NOTE Confidence: 0.85740339756012
00:10:11.400 --> 00:10:13.920 might be more responsive to immunotherapy.
NOTE Confidence: 0.85740339756012
00:10:13.920 --> 00:10:15.655 And that hypothesis was tested
NOTE Confidence: 0.85740339756012
00:10:15.655 --> 00:10:17.878 by melodies group where we showed
NOTE Confidence: 0.85740339756012
00:10:17.878 --> 00:10:20.008 in Melanoma that over legacy
NOTE Confidence: 0.85740339756012
00:10:20.008 --> 00:10:21.712 overexpressing tumors are actually
NOTE Confidence: 0.85740339756012
00:10:21.777 --> 00:10:24.029 potently responsive to immunotherapy,
NOTE Confidence: 0.85740339756012

00:10:24.030 --> 00:10:26.050 including immune checkpoint blockade.

NOTE Confidence: 0.85740339756012

00:10:26.050 --> 00:10:29.080 And this was really beautifully shown

NOTE Confidence: 0.85740339756012

00:10:29.157 --> 00:10:31.717 also more recently by a group at Yale.

NOTE Confidence: 0.85740339756012

00:10:31.720 --> 00:10:34.135 He was lucky group who showed in

NOTE Confidence: 0.85740339756012

00:10:34.135 --> 00:10:36.104 glioblastoma that the induction of

NOTE Confidence: 0.85740339756012

00:10:36.104 --> 00:10:38.274 a lymph angiogenic response within

NOTE Confidence: 0.85740339756012

00:10:38.274 --> 00:10:40.779 what's more normally thought of as

NOTE Confidence: 0.85740339756012

00:10:40.779 --> 00:10:42.664 an immune compromised or privilege

NOTE Confidence: 0.85740339756012

00:10:42.664 --> 00:10:44.590 site could really drive potent

NOTE Confidence: 0.85740339756012

00:10:44.590 --> 00:10:46.930 immune responses and response to me.

NOTE Confidence: 0.85740339756012

00:10:46.930 --> 00:10:48.190 A checkpoint blockade.

NOTE Confidence: 0.85740339756012

00:10:48.190 --> 00:10:50.710 And so this altogether has really

NOTE Confidence: 0.85740339756012

00:10:50.710 --> 00:10:53.030 suggested the potential for using

NOTE Confidence: 0.85740339756012

00:10:53.030 --> 00:10:54.862 the lymphatic vasculature in

NOTE Confidence: 0.85740339756012

00:10:54.862 --> 00:10:55.778 lymphatic transport

NOTE Confidence: 0.840481125882694

00:10:55.847 --> 00:10:57.947 as a new target for immunotherapy

NOTE Confidence: 0.840481125882694
00:10:57.947 --> 00:10:59.841 to improve immune surveillance and
NOTE Confidence: 0.840481125882694
00:10:59.841 --> 00:11:01.832 really turned on they response
NOTE Confidence: 0.840481125882694
00:11:01.832 --> 00:11:03.424 against the developing tumor.
NOTE Confidence: 0.840481125882694
00:11:03.430 --> 00:11:05.430 But since starting my lab,
NOTE Confidence: 0.840481125882694
00:11:05.430 --> 00:11:07.775 we were really interested in exploring
NOTE Confidence: 0.840481125882694
00:11:07.775 --> 00:11:10.220 some additional parts of lymphatic biology,
NOTE Confidence: 0.840481125882694
00:11:10.220 --> 00:11:12.768 and that was really how to lymphatic
NOTE Confidence: 0.840481125882694
00:11:12.768 --> 00:11:15.245 vessels in the context of a
NOTE Confidence: 0.840481125882694
00:11:15.245 --> 00:11:16.997 tumor that's already inflamed.
NOTE Confidence: 0.840481125882694
00:11:17.000 --> 00:11:19.400 How do they interact with that
NOTE Confidence: 0.840481125882694
00:11:19.400 --> 00:11:20.600 inflamed tumor biology?
NOTE Confidence: 0.840481125882694
00:11:20.600 --> 00:11:23.106 And might they continue to regulate the
NOTE Confidence: 0.840481125882694
00:11:23.106 --> 00:11:25.254 effector phase of the immune response
NOTE Confidence: 0.840481125882694
00:11:25.254 --> 00:11:26.684 within that tumor microenvironment?
NOTE Confidence: 0.840481125882694
00:11:26.684 --> 00:11:30.160 An in work that I'm not going to be able
NOTE Confidence: 0.840481125882694

00:11:30.160 --> 00:11:33.487 to show you today for the sake of time,
NOTE Confidence: 0.840481125882694

00:11:33.490 --> 00:11:35.275 we've now learned that after
NOTE Confidence: 0.840481125882694

00:11:35.275 --> 00:11:36.346 mobilization of Antigen,
NOTE Confidence: 0.840481125882694

00:11:36.350 --> 00:11:38.135 specific immune responses and recruitment
NOTE Confidence: 0.840481125882694

00:11:38.135 --> 00:11:39.563 into tumor micro environments,
NOTE Confidence: 0.840481125882694

00:11:39.570 --> 00:11:41.570 that we in fact see that a subset
NOTE Confidence: 0.840481125882694

00:11:41.570 --> 00:11:43.387 of these antigen specific T
NOTE Confidence: 0.840481125882694

00:11:43.387 --> 00:11:45.472 cells actually leave those tumors
NOTE Confidence: 0.840481125882694

00:11:45.472 --> 00:11:47.090 through lymphatic vasculature,
NOTE Confidence: 0.840481125882694

00:11:47.090 --> 00:11:49.238 that their exit is regulated by
NOTE Confidence: 0.840481125882694

00:11:49.238 --> 00:11:51.050 lymphatic vessel, derived Chemo Kines.
NOTE Confidence: 0.840481125882694

00:11:51.050 --> 00:11:53.640 And and that these exiting T cells
NOTE Confidence: 0.840481125882694

00:11:53.640 --> 00:11:56.018 are actually quite functional and in
NOTE Confidence: 0.840481125882694

00:11:56.018 --> 00:11:58.406 so doing their exit actually limits
NOTE Confidence: 0.840481125882694

00:11:58.406 --> 00:12:01.307 the ability for these tumors to be
NOTE Confidence: 0.840481125882694

00:12:01.307 --> 00:12:04.023 controlled and for response to immunotherapy.

NOTE Confidence: 0.840481125882694
00:12:04.023 --> 00:12:07.726 What I want to talk to you about
NOTE Confidence: 0.840481125882694
00:12:07.726 --> 00:12:10.048 today was sort of our first insight
NOTE Confidence: 0.840481125882694
00:12:10.048 --> 00:12:11.820 into how the lymphatic vasculature
NOTE Confidence: 0.840481125882694
00:12:11.820 --> 00:12:14.280 might be contributing to the efficacy
NOTE Confidence: 0.840481125882694
00:12:14.280 --> 00:12:16.886 of tumor control within the tumor
NOTE Confidence: 0.840481125882694
00:12:16.886 --> 00:12:17.756 micro environment,
NOTE Confidence: 0.840481125882694
00:12:17.760 --> 00:12:20.567 and that work was the work of
NOTE Confidence: 0.840481125882694
00:12:20.567 --> 00:12:22.778 a graduate student in the lab,
NOTE Confidence: 0.840481125882694
00:12:22.780 --> 00:12:23.484 Ryan Lane,
NOTE Confidence: 0.840481125882694
00:12:23.484 --> 00:12:25.244 where we learned that lymphatic
NOTE Confidence: 0.840481125882694
00:12:25.244 --> 00:12:27.123 vessels are exquisitely sensitive to
NOTE Confidence: 0.840481125882694
00:12:27.123 --> 00:12:28.659 cytotoxic community that accumulates
NOTE Confidence: 0.840481125882694
00:12:28.659 --> 00:12:30.890 within the tumor micro environment.
NOTE Confidence: 0.840481125882694
00:12:30.890 --> 00:12:33.326 They adapt to that side of toxicity
NOTE Confidence: 0.840481125882694
00:12:33.326 --> 00:12:34.895 by expressing multiple different
NOTE Confidence: 0.840481125882694

00:12:34.895 --> 00:12:36.686 factors including PD, L1,
NOTE Confidence: 0.840481125882694

00:12:36.686 --> 00:12:38.666 which will talk more about.
NOTE Confidence: 0.840481125882694

00:12:38.670 --> 00:12:41.394 And by decoupling the ability of
NOTE Confidence: 0.840481125882694

00:12:41.394 --> 00:12:42.756 the lymphatic vessels,
NOTE Confidence: 0.840481125882694

00:12:42.760 --> 00:12:44.293 descent cytotoxic community,
NOTE Confidence: 0.840481125882694

00:12:44.293 --> 00:12:46.337 we could actually significantly
NOTE Confidence: 0.840481125882694

00:12:46.337 --> 00:12:48.420 improve antitumor immune control.
NOTE Confidence: 0.840481125882694

00:12:48.420 --> 00:12:50.717 And so all this together has
NOTE Confidence: 0.840481125882694

00:12:50.717 --> 00:12:51.431 really suggested,
NOTE Confidence: 0.840481125882694

00:12:51.431 --> 00:12:53.573 along with work from many other
NOTE Confidence: 0.840481125882694

00:12:53.573 --> 00:12:55.789 labs at the lymphatic vasculature,
NOTE Confidence: 0.840481125882694

00:12:55.790 --> 00:12:58.058 in addition to playing an important
NOTE Confidence: 0.840481125882694

00:12:58.058 --> 00:13:00.026 role in immune surveillance and
NOTE Confidence: 0.840481125882694

00:13:00.026 --> 00:13:01.610 immune and tumor recognition,
NOTE Confidence: 0.840481125882694

00:13:01.610 --> 00:13:03.595 can critically also regulate the
NOTE Confidence: 0.840481125882694

00:13:03.595 --> 00:13:05.580 ongoing immune responses in the

NOTE Confidence: 0.840481125882694

00:13:05.651 --> 00:13:07.239 tumor microenvironment and maybe

NOTE Confidence: 0.840481125882694

00:13:07.239 --> 00:13:10.139 plays an important role in sort of

NOTE Confidence: 0.840481125882694

00:13:10.139 --> 00:13:11.927 immune escape burning resolution.

NOTE Confidence: 0.840481125882694

00:13:11.930 --> 00:13:14.323 I think one of the experiments that

NOTE Confidence: 0.840481125882694

00:13:14.323 --> 00:13:16.078 really for me best illustrates

NOTE Confidence: 0.840481125882694

00:13:16.078 --> 00:13:17.640 this point is shown here.

NOTE Confidence: 0.840481125882694

00:13:17.640 --> 00:13:19.985 So what we did is we have.

NOTE Confidence: 0.840481125882694

00:13:19.990 --> 00:13:22.440 We took mice that lack dermal lymphatic

NOTE Confidence: 0.840481125882694

00:13:22.440 --> 00:13:24.807 vessels in the skin which you can

NOTE Confidence: 0.840481125882694

00:13:24.807 --> 00:13:27.718 see here in green compared to wild type mice.

NOTE Confidence: 0.840481125882694

00:13:27.720 --> 00:13:29.520 We immunize both of these mice

NOTE Confidence: 0.840481125882694

00:13:29.520 --> 00:13:31.915 with LC MB Armstrong to setup a

NOTE Confidence: 0.840481125882694

00:13:31.915 --> 00:13:33.427 potent protective immune response,

NOTE Confidence: 0.840481125882694

00:13:33.430 --> 00:13:35.943 and then we came in and challenge

NOTE Confidence: 0.840481125882694

00:13:35.943 --> 00:13:37.845 these animals with vaccinia virus

NOTE Confidence: 0.840481125882694

00:13:37.845 --> 00:13:40.477 expressing an LC MB antigen GP 33.

NOTE Confidence: 0.840481125882694

00:13:40.480 --> 00:13:43.120 And what you can see is that in

NOTE Confidence: 0.840481125882694

00:13:43.120 --> 00:13:44.510 wild type animals,

NOTE Confidence: 0.840481125882694

00:13:44.510 --> 00:13:46.114 upon this secondary challenge,

NOTE Confidence: 0.840481125882694

00:13:46.114 --> 00:13:48.119 you get an initial inflammatory

NOTE Confidence: 0.840481125882694

00:13:48.119 --> 00:13:49.259 response in the skin,

NOTE Confidence: 0.840481125882694

00:13:49.260 --> 00:13:51.941 which is shown here by ear swelling

NOTE Confidence: 0.840481125882694

00:13:51.941 --> 00:13:54.329 that resolves fairly quickly overtime.

NOTE Confidence: 0.840481125882694

00:13:54.330 --> 00:13:57.170 But we do this in my side completely

NOTE Confidence: 0.840481125882694

00:13:57.170 --> 00:13:58.650 lack lymphatic transport,

NOTE Confidence: 0.840481125882694

00:13:58.650 --> 00:14:00.610 despite seeing no difference in

NOTE Confidence: 0.840481125882694

00:14:00.610 --> 00:14:01.394 viral control.

NOTE Confidence: 0.840481125882694

00:14:01.400 --> 00:14:03.370 In this particular experimental setting,

NOTE Confidence: 0.840481125882694

00:14:03.370 --> 00:14:05.743 what we see is a progressive and

NOTE Confidence: 0.840481125882694

00:14:05.743 --> 00:14:07.576 dramatic and long lived pathology

NOTE Confidence: 0.840481125882694

00:14:07.576 --> 00:14:09.814 within this year tissue and you

NOTE Confidence: 0.840481125882694
00:14:09.814 --> 00:14:10.560 can see
NOTE Confidence: 0.828280866146088
00:14:10.629 --> 00:14:12.797 that even better histologically,
NOTE Confidence: 0.828280866146088
00:14:12.800 --> 00:14:15.544 where we get epidermal hyper proliferation,
NOTE Confidence: 0.828280866146088
00:14:15.550 --> 00:14:17.867 we see an expansion of the dermis
NOTE Confidence: 0.828280866146088
00:14:17.867 --> 00:14:19.420 and a dramatic accumulation
NOTE Confidence: 0.828280866146088
00:14:19.420 --> 00:14:21.835 of CD 45 positive leucocytes.
NOTE Confidence: 0.828280866146088
00:14:21.840 --> 00:14:24.535 Even at this time point well past
NOTE Confidence: 0.828280866146088
00:14:24.535 --> 00:14:26.998 when the wild type mice have.
NOTE Confidence: 0.828280866146088
00:14:27.000 --> 00:14:29.040 Resolved, and so this really tells
NOTE Confidence: 0.828280866146088
00:14:29.040 --> 00:14:32.112 us that in the absence of an exit
NOTE Confidence: 0.828280866146088
00:14:32.112 --> 00:14:34.157 route in this lymphatic transport,
NOTE Confidence: 0.828280866146088
00:14:34.160 --> 00:14:36.554 that that tissues have an impaired
NOTE Confidence: 0.828280866146088
00:14:36.554 --> 00:14:39.100 ability to return to homeostasis.
NOTE Confidence: 0.828280866146088
00:14:39.100 --> 00:14:41.554 Well, we also know from work
NOTE Confidence: 0.828280866146088
00:14:41.554 --> 00:14:44.534 from back I'm going hard as well
NOTE Confidence: 0.828280866146088

00:14:44.534 --> 00:14:47.036 as our group melody and others.
NOTE Confidence: 0.828280866146088

00:14:47.040 --> 00:14:49.130 Is that the lymphatic individual
NOTE Confidence: 0.828280866146088

00:14:49.130 --> 00:14:51.220 cell present within the unique
NOTE Confidence: 0.828280866146088

00:14:51.286 --> 00:14:53.792 structure of the lymph node has some
NOTE Confidence: 0.828280866146088

00:14:53.792 --> 00:14:55.864 really unique and interesting and
NOTE Confidence: 0.828280866146088

00:14:55.864 --> 00:14:57.720 immunological properties that allow
NOTE Confidence: 0.828280866146088

00:14:57.720 --> 00:15:00.430 it to scavenge and present anagen
NOTE Confidence: 0.828280866146088

00:15:00.430 --> 00:15:02.980 that allow these cells to interact
NOTE Confidence: 0.828280866146088

00:15:02.980 --> 00:15:05.849 with both CD8 and CD4T cells through.
NOTE Confidence: 0.828280866146088

00:15:05.850 --> 00:15:08.358 Most notably the inhibitory molecule PD,
NOTE Confidence: 0.828280866146088

00:15:08.360 --> 00:15:10.480 L1 to drive dysfunctional CD8T
NOTE Confidence: 0.828280866146088

00:15:10.480 --> 00:15:12.200 cell activation. And or deletion.
NOTE Confidence: 0.828280866146088

00:15:12.200 --> 00:15:13.940 And so this is really exciting,
NOTE Confidence: 0.828280866146088

00:15:13.940 --> 00:15:15.100 interesting paradigm where at
NOTE Confidence: 0.828280866146088

00:15:15.100 --> 00:15:16.260 least these endothelial cells,
NOTE Confidence: 0.828280866146088

00:15:16.260 --> 00:15:18.955 and at least in the lymph node.

NOTE Confidence: 0.828280866146088

00:15:18.960 --> 00:15:20.845 Played a really interesting and

NOTE Confidence: 0.828280866146088

00:15:20.845 --> 00:15:22.353 unappreciated role in maintaining

NOTE Confidence: 0.828280866146088

00:15:22.353 --> 00:15:23.280 peripheral tolerance,

NOTE Confidence: 0.828280866146088

00:15:23.280 --> 00:15:25.250 at least at steady state.

NOTE Confidence: 0.828280866146088

00:15:25.250 --> 00:15:27.994 And so when Ryan joined the lab,

NOTE Confidence: 0.828280866146088

00:15:28.000 --> 00:15:30.744 we were really interested in two questions.

NOTE Confidence: 0.828280866146088

00:15:30.750 --> 00:15:32.615 One is are these immunological

NOTE Confidence: 0.828280866146088

00:15:32.615 --> 00:15:34.480 properties really unique to the

NOTE Confidence: 0.828280866146088

00:15:34.545 --> 00:15:36.177 lymphatic endothelia cell found

NOTE Confidence: 0.828280866146088

00:15:36.177 --> 00:15:38.217 within the lymph node itself?

NOTE Confidence: 0.828280866146088

00:15:38.220 --> 00:15:40.602 Or might they be activated in

NOTE Confidence: 0.828280866146088

00:15:40.602 --> 00:15:42.764 the context of challenge and

NOTE Confidence: 0.828280866146088

00:15:42.764 --> 00:15:45.219 peripheral tissues and organ tumors?

NOTE Confidence: 0.828280866146088

00:15:45.220 --> 00:15:46.165 And if so,

NOTE Confidence: 0.828280866146088

00:15:46.165 --> 00:15:48.370 is there really any reason to believe

NOTE Confidence: 0.828280866146088

00:15:48.437 --> 00:15:50.667 that the lymphatic vasculature out
NOTE Confidence: 0.828280866146088

00:15:50.667 --> 00:15:52.897 in these peripheral tissues might
NOTE Confidence: 0.828280866146088

00:15:52.966 --> 00:15:54.870 be interacting with affecter,
NOTE Confidence: 0.828280866146088

00:15:54.870 --> 00:15:56.594 CDA positive T cells?
NOTE Confidence: 0.828280866146088

00:15:56.594 --> 00:15:59.520 So what Ryan first started to do?
NOTE Confidence: 0.828280866146088

00:15:59.520 --> 00:16:00.510 Is he he?
NOTE Confidence: 0.828280866146088

00:16:00.510 --> 00:16:01.830 He said, OK, well,
NOTE Confidence: 0.828280866146088

00:16:01.830 --> 00:16:04.470 let's look in the in our implantable tumors.
NOTE Confidence: 0.828280866146088

00:16:04.470 --> 00:16:06.794 And let's ask whether or not competitive
NOTE Confidence: 0.828280866146088

00:16:06.794 --> 00:16:08.902 deals with in this contest expressed
NOTE Confidence: 0.828280866146088

00:16:08.902 --> 00:16:11.352 PD L1 so big Englehart had already
NOTE Confidence: 0.828280866146088

00:16:11.418 --> 00:16:13.483 shown and we had seen ourselves that
NOTE Confidence: 0.828280866146088

00:16:13.483 --> 00:16:15.477 if you look at cutaneous lymphatic
NOTE Confidence: 0.828280866146088

00:16:15.477 --> 00:16:17.691 vasculature in the absence of any
NOTE Confidence: 0.828280866146088

00:16:17.691 --> 00:16:19.760 kind of challenge there fairly PD
NOTE Confidence: 0.828280866146088

00:16:19.760 --> 00:16:22.007 L one negative and that's what you

NOTE Confidence: 0.828280866146088

00:16:22.007 --> 00:16:23.932 can see here in this black line.

NOTE Confidence: 0.828280866146088

00:16:23.940 --> 00:16:25.716 But what was really exciting to

NOTE Confidence: 0.828280866146088

00:16:25.716 --> 00:16:28.335 see was that if we look at the

NOTE Confidence: 0.828280866146088

00:16:28.335 --> 00:16:29.699 lymphatic endothelia cells here

NOTE Confidence: 0.828280866146088

00:16:29.699 --> 00:16:32.012 in Read that have been extracted

NOTE Confidence: 0.828280866146088

00:16:32.012 --> 00:16:33.972 from a tumor micro environment.

NOTE Confidence: 0.828280866146088

00:16:33.980 --> 00:16:37.445 They expressed elevated levels of PD L1.

NOTE Confidence: 0.828280866146088

00:16:37.450 --> 00:16:39.178 And this was distinct from the

NOTE Confidence: 0.828280866146088

00:16:39.178 --> 00:16:40.330 blood vasculature which actually

NOTE Confidence: 0.828280866146088

00:16:40.380 --> 00:16:41.568 expresses consecutive PDL.

NOTE Confidence: 0.828280866146088

00:16:41.570 --> 00:16:43.817 One and remains more or less unchanged

NOTE Confidence: 0.828280866146088

00:16:43.817 --> 00:16:45.499 by the tumor micro environment

NOTE Confidence: 0.828280866146088

00:16:45.499 --> 00:16:47.788 and what was really clear to us

NOTE Confidence: 0.828280866146088

00:16:47.788 --> 00:16:49.917 as we looked at them botic in

NOTE Confidence: 0.828280866146088

00:16:49.917 --> 00:16:52.348 ethereal cell PDL 1 / a range of

NOTE Confidence: 0.828280866146088

00:16:52.348 --> 00:16:53.616 different tumor micro environments.
NOTE Confidence: 0.828280866146088

00:16:53.620 --> 00:16:56.028 We saw the the level of expression and
NOTE Confidence: 0.828280866146088

00:16:56.028 --> 00:16:58.328 the number of cells that were expressing
NOTE Confidence: 0.828280866146088

00:16:58.328 --> 00:17:01.120 it appeared to be tuned by context.
NOTE Confidence: 0.828280866146088

00:17:01.120 --> 00:17:03.740 And if you actually look across these
NOTE Confidence: 0.828280866146088

00:17:03.740 --> 00:17:05.757 models and you correlate the level
NOTE Confidence: 0.828280866146088

00:17:05.757 --> 00:17:07.850 of expression of PDL one with the
NOTE Confidence: 0.828280866146088

00:17:07.850 --> 00:17:09.787 numbers of infiltrating CD8T cells,
NOTE Confidence: 0.828280866146088

00:17:09.790 --> 00:17:11.776 you can see a nice correlation
NOTE Confidence: 0.828280866146088

00:17:11.776 --> 00:17:13.461 across these models which really
NOTE Confidence: 0.828280866146088

00:17:13.461 --> 00:17:15.869 suggested to us sort of in a sensing
NOTE Confidence: 0.828280866146088

00:17:15.869 --> 00:17:17.698 ability of the lymphatic endothelium
NOTE Confidence: 0.828280866146088

00:17:17.698 --> 00:17:19.894 to respond to the accumulation of
NOTE Confidence: 0.834909379482269

00:17:19.900 --> 00:17:21.388 Antigen, specific immune
NOTE Confidence: 0.834909379482269

00:17:21.388 --> 00:17:23.868 response and activate PDL 1.
NOTE Confidence: 0.834909379482269

00:17:23.870 --> 00:17:26.495 But the really important first question was,

NOTE Confidence: 0.834909379482269

00:17:26.500 --> 00:17:29.524 is there any reason to think that an

NOTE Confidence: 0.834909379482269

00:17:29.524 --> 00:17:31.571 onomatopoeitic non tumor source of

NOTE Confidence: 0.834909379482269

00:17:31.571 --> 00:17:34.007 PDL one is relevant for antitumor

NOTE Confidence: 0.834909379482269

00:17:34.007 --> 00:17:36.461 immunity and so we decided to take

NOTE Confidence: 0.834909379482269

00:17:36.461 --> 00:17:38.532 a bone marrow chimera approach to.

NOTE Confidence: 0.834909379482269

00:17:38.532 --> 00:17:40.036 To answer that question,

NOTE Confidence: 0.834909379482269

00:17:40.040 --> 00:17:41.540 Ryan generated bone marrow

NOTE Confidence: 0.834909379482269

00:17:41.540 --> 00:17:42.665 chimeras using PDL.

NOTE Confidence: 0.834909379482269

00:17:42.670 --> 00:17:44.608 One knockout mice such that in

NOTE Confidence: 0.834909379482269

00:17:44.608 --> 00:17:47.319 red here PDL one was lost on non

NOTE Confidence: 0.834909379482269

00:17:47.319 --> 00:17:49.341 hematopoietic cells or in blue PDL

NOTE Confidence: 0.834909379482269

00:17:49.410 --> 00:17:52.134 one was lost in the hematopoietic

NOTE Confidence: 0.834909379482269

00:17:52.134 --> 00:17:53.950 compartment we implanted B16F-10

NOTE Confidence: 0.834909379482269

00:17:53.950 --> 00:17:56.392 urine melanomas which are PDL one

NOTE Confidence: 0.834909379482269

00:17:56.392 --> 00:17:58.880 expressing but known to be poor RE.

NOTE Confidence: 0.834909379482269

00:17:58.880 --> 00:18:01.028 Ponders to single agent I mean
NOTE Confidence: 0.834909379482269

00:18:01.028 --> 00:18:03.180 checkpoint blockade and we got equal
NOTE Confidence: 0.834909379482269

00:18:03.180 --> 00:18:05.154 tumor growth in all our cameras.
NOTE Confidence: 0.834909379482269

00:18:05.160 --> 00:18:07.696 But if we actually looked at the T
NOTE Confidence: 0.834909379482269

00:18:07.696 --> 00:18:09.699 cell compartment within these animals,
NOTE Confidence: 0.834909379482269

00:18:09.700 --> 00:18:11.302 we were really intrigued to see
NOTE Confidence: 0.834909379482269

00:18:11.302 --> 00:18:13.029 that within the tumor infiltrating
NOTE Confidence: 0.834909379482269

00:18:13.029 --> 00:18:14.239 lymphocyte compartment,
NOTE Confidence: 0.834909379482269

00:18:14.240 --> 00:18:16.292 whether we lost PDL one onomatopoetic
NOTE Confidence: 0.834909379482269

00:18:16.292 --> 00:18:18.080 or amount of poetic cells.
NOTE Confidence: 0.834909379482269

00:18:18.080 --> 00:18:20.404 We saw this boost in overall proportion
NOTE Confidence: 0.834909379482269

00:18:20.404 --> 00:18:23.311 of CD T cells present and that of
NOTE Confidence: 0.834909379482269

00:18:23.311 --> 00:18:25.889 those PDT cell presence we saw this
NOTE Confidence: 0.834909379482269

00:18:25.889 --> 00:18:28.213 elevation of PD one as we would
NOTE Confidence: 0.834909379482269

00:18:28.213 --> 00:18:31.958 expect to see in the full knockout.
NOTE Confidence: 0.834909379482269

00:18:31.960 --> 00:18:32.656 Interesting Lee,

NOTE Confidence: 0.834909379482269
00:18:32.656 --> 00:18:34.396 this seemed to be segregated
NOTE Confidence: 0.834909379482269
00:18:34.396 --> 00:18:35.440 by anatomic location,
NOTE Confidence: 0.834909379482269
00:18:35.440 --> 00:18:37.505 so if you actually looks in circulating
NOTE Confidence: 0.834909379482269
00:18:37.505 --> 00:18:39.620 populations in the hematopoietic knockout,
NOTE Confidence: 0.834909379482269
00:18:39.620 --> 00:18:41.355 this elevation and number was
NOTE Confidence: 0.834909379482269
00:18:41.355 --> 00:18:42.049 already present.
NOTE Confidence: 0.834909379482269
00:18:42.050 --> 00:18:44.437 We look in the spleen or the
NOTE Confidence: 0.834909379482269
00:18:44.437 --> 00:18:45.880 tumor draining lymph node,
NOTE Confidence: 0.834909379482269
00:18:45.880 --> 00:18:47.968 but not in an Onomatopoetic Control,
NOTE Confidence: 0.834909379482269
00:18:47.970 --> 00:18:49.740 which really suggested that the
NOTE Confidence: 0.834909379482269
00:18:49.740 --> 00:18:51.800 effect of non amounted poetic PDL.
NOTE Confidence: 0.834909379482269
00:18:51.800 --> 00:18:54.232 One seems to be limited to the
NOTE Confidence: 0.834909379482269
00:18:54.232 --> 00:18:55.744 tumor micro environment itself.
NOTE Confidence: 0.834909379482269
00:18:55.744 --> 00:18:58.975 I'm in order to sort of resolve more
NOTE Confidence: 0.834909379482269
00:18:58.975 --> 00:19:01.657 functional effect on the immune response.
NOTE Confidence: 0.834909379482269

00:19:01.660 --> 00:19:04.126 We performed adoptive T cell transfer
NOTE Confidence: 0.834909379482269

00:19:04.126 --> 00:19:05.770 experiments where we activated
NOTE Confidence: 0.834909379482269

00:19:05.834 --> 00:19:07.766 antigen specific OT one T cells,
NOTE Confidence: 0.834909379482269

00:19:07.770 --> 00:19:09.680 transfer those into B16F-10 ova,
NOTE Confidence: 0.834909379482269

00:19:09.680 --> 00:19:11.208 expressing tumor bearing mice,
NOTE Confidence: 0.834909379482269

00:19:11.208 --> 00:19:13.118 and then asked whether or
NOTE Confidence: 0.834909379482269

00:19:13.118 --> 00:19:15.029 not these effector T cells,
NOTE Confidence: 0.834909379482269

00:19:15.030 --> 00:19:16.940 which would directly home to
NOTE Confidence: 0.834909379482269

00:19:16.940 --> 00:19:18.468 the tumor micro environment.
NOTE Confidence: 0.834909379482269

00:19:18.470 --> 00:19:20.445 We're capable of enhanced tumor
NOTE Confidence: 0.834909379482269

00:19:20.445 --> 00:19:23.049 control in the absence of PDL one,
NOTE Confidence: 0.834909379482269

00:19:23.050 --> 00:19:25.922 and what we saw in fact was that
NOTE Confidence: 0.834909379482269

00:19:25.922 --> 00:19:28.777 of course had aquatic loss of PDL.
NOTE Confidence: 0.834909379482269

00:19:28.780 --> 00:19:30.760 One had a significant effect.
NOTE Confidence: 0.834909379482269

00:19:30.760 --> 00:19:33.042 On the ability of these T cells
NOTE Confidence: 0.834909379482269

00:19:33.042 --> 00:19:34.640 to mediate tumor control,

NOTE Confidence: 0.834909379482269
00:19:34.640 --> 00:19:36.410 but really interesting, of course,
NOTE Confidence: 0.834909379482269
00:19:36.410 --> 00:19:38.350 is not what aquatic compartment
NOTE Confidence: 0.834909379482269
00:19:38.350 --> 00:19:40.722 also seemed to be playing some
NOTE Confidence: 0.834909379482269
00:19:40.722 --> 00:19:42.527 role in limiting the effector
NOTE Confidence: 0.834909379482269
00:19:42.527 --> 00:19:44.380 T cell response in Vivo.
NOTE Confidence: 0.834909379482269
00:19:44.380 --> 00:19:45.684 And perhaps most strikingly,
NOTE Confidence: 0.834909379482269
00:19:45.684 --> 00:19:47.640 we then decided to take an
NOTE Confidence: 0.834909379482269
00:19:47.700 --> 00:19:49.420 immuno genic murine Melanoma.
NOTE Confidence: 0.834909379482269
00:19:49.420 --> 00:19:50.485 The younger 1.7,
NOTE Confidence: 0.834909379482269
00:19:50.485 --> 00:19:52.970 which we know is exquisitely sensitive to
NOTE Confidence: 0.834909379482269
00:19:53.031 --> 00:19:55.537 to checkpoint blockade as a single agent,
NOTE Confidence: 0.834909379482269
00:19:55.540 --> 00:19:57.736 and we're able to see now
NOTE Confidence: 0.834909379482269
00:19:57.736 --> 00:19:59.859 that in the absence of PDL,
NOTE Confidence: 0.834909379482269
00:19:59.860 --> 00:20:02.515 one on non amount of poetic cells that we
NOTE Confidence: 0.834909379482269
00:20:02.515 --> 00:20:05.256 were putting tumors essentially in stasis,
NOTE Confidence: 0.834909379482269

00:20:05.260 --> 00:20:07.675 leading to really significant changes
NOTE Confidence: 0.834909379482269

00:20:07.675 --> 00:20:10.560 in tumor control in these mice.
NOTE Confidence: 0.834909379482269

00:20:10.560 --> 00:20:12.588 And so this suggested that yes,
NOTE Confidence: 0.834909379482269

00:20:12.590 --> 00:20:13.140 they not.
NOTE Confidence: 0.834909379482269

00:20:13.140 --> 00:20:14.515 Amount of product compartment may
NOTE Confidence: 0.834909379482269

00:20:14.515 --> 00:20:16.650 contribute to T cell dysfunction within
NOTE Confidence: 0.834909379482269

00:20:16.650 --> 00:20:18.330 the tumor microenvironment environment,
NOTE Confidence: 0.834909379482269

00:20:18.330 --> 00:20:21.034 and I'll remind you that from our analysis,
NOTE Confidence: 0.834909379482269

00:20:21.040 --> 00:20:22.388 the main expressing cells
NOTE Confidence: 0.834909379482269

00:20:22.388 --> 00:20:23.736 were really the endothelium.
NOTE Confidence: 0.834909379482269

00:20:23.740 --> 00:20:25.532 Both blood and lymphatic.
NOTE Confidence: 0.834909379482269

00:20:25.532 --> 00:20:26.876 So we were
NOTE Confidence: 0.880864977836609

00:20:26.880 --> 00:20:28.854 curious as to whether or not
NOTE Confidence: 0.880864977836609

00:20:28.854 --> 00:20:30.816 this was specific to the tumor.
NOTE Confidence: 0.880864977836609

00:20:30.820 --> 00:20:32.460 We presumed it was not,
NOTE Confidence: 0.880864977836609

00:20:32.460 --> 00:20:34.100 and we went through an,

NOTE Confidence: 0.880864977836609

00:20:34.100 --> 00:20:35.755 looked at a variety of

NOTE Confidence: 0.880864977836609

00:20:35.755 --> 00:20:36.417 different inflammatory.

NOTE Confidence: 0.880864977836609

00:20:36.420 --> 00:20:39.248 Responses in specifically in skin in mice,

NOTE Confidence: 0.880864977836609

00:20:39.250 --> 00:20:41.344 we infected mice with vaccinia virus

NOTE Confidence: 0.880864977836609

00:20:41.344 --> 00:20:43.712 in the skin initiated delayed type

NOTE Confidence: 0.880864977836609

00:20:43.712 --> 00:20:45.520 hypersensitivity responses or induced

NOTE Confidence: 0.880864977836609

00:20:45.520 --> 00:20:48.136 in imiquimod based model of psoriasis

NOTE Confidence: 0.880864977836609

00:20:48.136 --> 00:20:50.664 and what you can appreciate is that

NOTE Confidence: 0.880864977836609

00:20:50.664 --> 00:20:53.515 in all three cases we see this really

NOTE Confidence: 0.880864977836609

00:20:53.515 --> 00:20:56.131 dramatic increase in PD L1 on the

NOTE Confidence: 0.880864977836609

00:20:56.131 --> 00:20:58.143 lymphatic endothelium within the

NOTE Confidence: 0.880864977836609

00:20:58.143 --> 00:21:01.064 inflamed skin and specifically not in

NOTE Confidence: 0.880864977836609

00:21:01.064 --> 00:21:02.680 Contra lateral distal compartments.

NOTE Confidence: 0.880864977836609

00:21:02.680 --> 00:21:04.966 Really suggesting that this was a

NOTE Confidence: 0.880864977836609

00:21:04.966 --> 00:21:07.170 lymphatic and a filial response.

NOTE Confidence: 0.880864977836609

00:21:07.170 --> 00:21:10.710 To the accumulation of potent inflammation

NOTE Confidence: 0.880864977836609

00:21:10.710 --> 00:21:14.600 within that within that cutaneous space.

NOTE Confidence: 0.880864977836609

00:21:14.600 --> 00:21:16.255 These models also provided the

NOTE Confidence: 0.880864977836609

00:21:16.255 --> 00:21:17.910 opportunity to actually look at

NOTE Confidence: 0.880864977836609

00:21:17.967 --> 00:21:19.567 the kinetics of this response,

NOTE Confidence: 0.880864977836609

00:21:19.570 --> 00:21:21.550 which I think is really valuable.

NOTE Confidence: 0.880864977836609

00:21:21.550 --> 00:21:23.608 So we took the vaccinia virus model

NOTE Confidence: 0.880864977836609

00:21:23.608 --> 00:21:25.735 and we looked at the expression of

NOTE Confidence: 0.880864977836609

00:21:25.735 --> 00:21:27.959 PDL one overtime on both the blood

NOTE Confidence: 0.880864977836609

00:21:27.959 --> 00:21:30.305 endothelial cells as well as the

NOTE Confidence: 0.880864977836609

00:21:30.305 --> 00:21:32.473 lymphatic endothelia cells and you can

NOTE Confidence: 0.880864977836609

00:21:32.473 --> 00:21:34.790 see that again as I mentioned before,

NOTE Confidence: 0.880864977836609

00:21:34.790 --> 00:21:36.435 blended filial cells have some

NOTE Confidence: 0.880864977836609

00:21:36.435 --> 00:21:38.080 constituent of expression which is

NOTE Confidence: 0.880864977836609

00:21:38.137 --> 00:21:39.757 enhanced overtime in this model,

NOTE Confidence: 0.880864977836609

00:21:39.760 --> 00:21:41.280 but with the lymphatic endothelia

NOTE Confidence: 0.880864977836609

00:21:41.280 --> 00:21:43.227 mu really see a cell population

NOTE Confidence: 0.880864977836609

00:21:43.227 --> 00:21:45.057 that goes from absolutely 0.

NOTE Confidence: 0.880864977836609

00:21:45.060 --> 00:21:47.447 It's almost 100% expressing PD L1 over

NOTE Confidence: 0.880864977836609

00:21:47.447 --> 00:21:49.670 the time course of this infection.

NOTE Confidence: 0.880864977836609

00:21:49.670 --> 00:21:51.728 And what we now, of course,

NOTE Confidence: 0.880864977836609

00:21:51.730 --> 00:21:53.510 is that this transition recruiting

NOTE Confidence: 0.880864977836609

00:21:53.510 --> 00:21:55.941 day three and a seven is exactly

NOTE Confidence: 0.880864977836609

00:21:55.941 --> 00:21:57.985 the time point at which we would

NOTE Confidence: 0.880864977836609

00:21:57.985 --> 00:22:00.072 be expecting the accumulation of

NOTE Confidence: 0.880864977836609

00:22:00.072 --> 00:22:02.227 a cytotoxic CD8T cell response.

NOTE Confidence: 0.880864977836609

00:22:02.230 --> 00:22:04.239 And so this suggested to us that

NOTE Confidence: 0.880864977836609

00:22:04.239 --> 00:22:06.127 perhaps the CD8T cell and its

NOTE Confidence: 0.880864977836609

00:22:06.127 --> 00:22:07.737 effector molecules where the QQ

NOTE Confidence: 0.880864977836609

00:22:07.737 --> 00:22:09.227 leading to increased expression

NOTE Confidence: 0.880864977836609

00:22:09.227 --> 00:22:11.971 as one might expect based on our

NOTE Confidence: 0.880864977836609

00:22:11.971 --> 00:22:14.758 understanding of PDL one biology.
NOTE Confidence: 0.880864977836609

00:22:14.760 --> 00:22:18.200 But we tested this specifically in two ways.
NOTE Confidence: 0.880864977836609

00:22:18.200 --> 00:22:18.599 First,
NOTE Confidence: 0.880864977836609

00:22:18.599 --> 00:22:20.993 we vaccinated are tumor bearing mice
NOTE Confidence: 0.880864977836609

00:22:20.993 --> 00:22:23.359 with an attenuated listeria vaccine,
NOTE Confidence: 0.880864977836609

00:22:23.360 --> 00:22:25.940 either expressing a matched tumor antigen,
NOTE Confidence: 0.880864977836609

00:22:25.940 --> 00:22:28.412 ovalbumin or not to generate non
NOTE Confidence: 0.880864977836609

00:22:28.412 --> 00:22:30.060 specific inflammation and boost
NOTE Confidence: 0.880864977836609

00:22:30.132 --> 00:22:32.387 CD8T cell infiltration into tumors.
NOTE Confidence: 0.880864977836609

00:22:32.390 --> 00:22:35.498 In the absence of antigen recognition.
NOTE Confidence: 0.880864977836609

00:22:35.500 --> 00:22:38.492 And you can see were successful in their
NOTE Confidence: 0.880864977836609

00:22:38.492 --> 00:22:40.721 vaccines strategy and when we look at
NOTE Confidence: 0.880864977836609

00:22:40.721 --> 00:22:42.569 PDL one in the lymphatic endothelia
NOTE Confidence: 0.880864977836609

00:22:42.569 --> 00:22:45.096 you can see that it's really only
NOTE Confidence: 0.880864977836609

00:22:45.096 --> 00:22:48.105 elevated in the context of potent and
NOTE Confidence: 0.880864977836609

00:22:48.105 --> 00:22:50.390 boosted antigen specific immune responses.

NOTE Confidence: 0.880864977836609
00:22:50.390 --> 00:22:53.070 We can do that using our adoptive T
NOTE Confidence: 0.880864977836609
00:22:53.070 --> 00:22:54.829 cell transfer therapy experimental
NOTE Confidence: 0.880864977836609
00:22:54.829 --> 00:22:56.350 therapy as well,
NOTE Confidence: 0.880864977836609
00:22:56.350 --> 00:22:59.115 where we activate OT one T cells,
NOTE Confidence: 0.880864977836609
00:22:59.120 --> 00:23:01.110 we transfer those into established.
NOTE Confidence: 0.880864977836609
00:23:01.110 --> 00:23:02.301 In this case,
NOTE Confidence: 0.880864977836609
00:23:02.301 --> 00:23:03.889 B16F-10 ova during melanomas,
NOTE Confidence: 0.880864977836609
00:23:03.890 --> 00:23:05.870 and then take those animals
NOTE Confidence: 0.880864977836609
00:23:05.870 --> 00:23:07.454 down seven days later,
NOTE Confidence: 0.880864977836609
00:23:07.460 --> 00:23:10.444 and what you see is that the lymphatic
NOTE Confidence: 0.880864977836609
00:23:10.444 --> 00:23:12.182 endothelia has really responded
NOTE Confidence: 0.880864977836609
00:23:12.182 --> 00:23:14.930 potentially to the infiltration of these
NOTE Confidence: 0.880864977836609
00:23:14.930 --> 00:23:17.297 effector T cells and upregulated PD
NOTE Confidence: 0.880864977836609
00:23:17.297 --> 00:23:21.030 L1 as compared to two no transfer.
NOTE Confidence: 0.880864977836609
00:23:21.030 --> 00:23:23.228 And so I think you know the
NOTE Confidence: 0.880864977836609

00:23:23.228 --> 00:23:24.701 obvious molecule here mediating
NOTE Confidence: 0.880864977836609

00:23:24.701 --> 00:23:26.549 this was interferon gamma,
NOTE Confidence: 0.880864977836609

00:23:26.550 --> 00:23:28.578 and indeed that is the case
NOTE Confidence: 0.880864977836609

00:23:28.578 --> 00:23:30.970 whether we look in our vaccinia,
NOTE Confidence: 0.880864977836609

00:23:30.970 --> 00:23:32.805 viral infected skin or in
NOTE Confidence: 0.880864977836609

00:23:32.805 --> 00:23:34.273 our tumor bearing animals,
NOTE Confidence: 0.880864977836609

00:23:34.280 --> 00:23:36.849 we see a dramatic reduction in PDL,
NOTE Confidence: 0.880864977836609

00:23:36.850 --> 00:23:38.480 one on lymphatic endothelia cells
NOTE Confidence: 0.880864977836609

00:23:38.480 --> 00:23:40.110 when the animals are treated
NOTE Confidence: 0.812137484550476

00:23:40.164 --> 00:23:41.760 with Interferon Gamma neutralizing
NOTE Confidence: 0.812137484550476

00:23:41.760 --> 00:23:43.755 antibodies and of course interferon
NOTE Confidence: 0.812137484550476

00:23:43.755 --> 00:23:45.319 gamma itself is sufficient.
NOTE Confidence: 0.812137484550476

00:23:45.320 --> 00:23:47.834 Let cultures in vitro to induce
NOTE Confidence: 0.812137484550476

00:23:47.834 --> 00:23:50.708 expression of PD L1 and it does
NOTE Confidence: 0.812137484550476

00:23:50.708 --> 00:23:53.298 so in a stat one mediated manner.
NOTE Confidence: 0.812137484550476

00:23:53.300 --> 00:23:55.540 And so, in the absence of having

NOTE Confidence: 0.812137484550476
00:23:55.540 --> 00:23:58.087 the PDL one flox mouse is really
NOTE Confidence: 0.812137484550476
00:23:58.087 --> 00:24:00.355 gave us the opportunity to say,
NOTE Confidence: 0.812137484550476
00:24:00.360 --> 00:24:02.705 well we can now D couple lymphatic
NOTE Confidence: 0.812137484550476
00:24:02.705 --> 00:24:04.572 endothelia cell biology from cytotoxic
NOTE Confidence: 0.812137484550476
00:24:04.572 --> 00:24:06.567 community by removing the Interferon
NOTE Confidence: 0.812137484550476
00:24:06.567 --> 00:24:08.761 Gamma Receptor on epithelial cells to
NOTE Confidence: 0.812137484550476
00:24:08.761 --> 00:24:11.395 ask whether or not this allows for more
NOTE Confidence: 0.812137484550476
00:24:11.395 --> 00:24:13.620 persistent effective T cell immunity.
NOTE Confidence: 0.812137484550476
00:24:13.620 --> 00:24:16.260 And so we did that we generated lymphatic
NOTE Confidence: 0.812137484550476
00:24:16.260 --> 00:24:17.656 specific interferon gamma receptor
NOTE Confidence: 0.812137484550476
00:24:17.656 --> 00:24:19.684 knockouts first using the live one.
NOTE Confidence: 0.812137484550476
00:24:19.690 --> 00:24:21.993 Cree, we could show that lymphatic in
NOTE Confidence: 0.812137484550476
00:24:21.993 --> 00:24:24.005 Attilio cells extracted from those animals
NOTE Confidence: 0.812137484550476
00:24:24.005 --> 00:24:25.943 no longer could phosphorylate stat one
NOTE Confidence: 0.812137484550476
00:24:25.943 --> 00:24:28.109 in the presence of Interferon Gamma,
NOTE Confidence: 0.812137484550476

00:24:28.110 --> 00:24:30.126 which is what you see here.
NOTE Confidence: 0.812137484550476

00:24:30.130 --> 00:24:32.188 While we maintain that responsiveness and
NOTE Confidence: 0.812137484550476

00:24:32.188 --> 00:24:34.508 all other cell types that we checked,
NOTE Confidence: 0.812137484550476

00:24:34.510 --> 00:24:36.638 we could show further that when we
NOTE Confidence: 0.812137484550476

00:24:36.638 --> 00:24:38.899 treat these cells with Interferon Gamma,
NOTE Confidence: 0.812137484550476

00:24:38.900 --> 00:24:40.922 where we normally see this nice
NOTE Confidence: 0.812137484550476

00:24:40.922 --> 00:24:42.270 expression of PDL one,
NOTE Confidence: 0.812137484550476

00:24:42.270 --> 00:24:44.346 that that's really completely lost in.
NOTE Confidence: 0.812137484550476

00:24:44.350 --> 00:24:47.158 In vitro and so we now have a really
NOTE Confidence: 0.812137484550476

00:24:47.158 --> 00:24:48.731 interesting tool to understand
NOTE Confidence: 0.812137484550476

00:24:48.731 --> 00:24:50.716 the interplay between cytotoxic T
NOTE Confidence: 0.812137484550476

00:24:50.716 --> 00:24:53.269 cells in lymphatic vessels in Bebo.
NOTE Confidence: 0.812137484550476

00:24:53.270 --> 00:24:54.640 And so we did that.
NOTE Confidence: 0.812137484550476

00:24:54.640 --> 00:24:56.320 I'm going to show you some work
NOTE Confidence: 0.812137484550476

00:24:56.320 --> 00:24:57.930 with the viral infection first,
NOTE Confidence: 0.812137484550476

00:24:57.930 --> 00:24:59.902 'cause I think it's a really nice.

NOTE Confidence: 0.812137484550476

00:24:59.902 --> 00:25:02.200 A way to think about this model,

NOTE Confidence: 0.812137484550476

00:25:02.200 --> 00:25:05.053 and So what we did is we first looked

NOTE Confidence: 0.812137484550476

00:25:05.053 --> 00:25:07.909 at PDL one in vivo at these seven,

NOTE Confidence: 0.812137484550476

00:25:07.910 --> 00:25:09.898 which was our peak level of expression

NOTE Confidence: 0.812137484550476

00:25:09.898 --> 00:25:12.409 and you can see that in the absence

NOTE Confidence: 0.812137484550476

00:25:12.409 --> 00:25:14.004 of the Interferon gamma receptor

NOTE Confidence: 0.812137484550476

00:25:14.061 --> 00:25:16.021 that we dramatically reduce the

NOTE Confidence: 0.812137484550476

00:25:16.021 --> 00:25:17.981 ability of these lymphatic individual

NOTE Confidence: 0.812137484550476

00:25:17.990 --> 00:25:20.405 cells to produce PDL one during the

NOTE Confidence: 0.812137484550476

00:25:20.405 --> 00:25:22.210 course of this infection.

NOTE Confidence: 0.812137484550476

00:25:22.210 --> 00:25:24.842 It was really interesting is that this was

NOTE Confidence: 0.812137484550476

00:25:24.842 --> 00:25:26.809 associated with an enhanced pathology,

NOTE Confidence: 0.812137484550476

00:25:26.810 --> 00:25:29.288 so this is 10 days post infection.

NOTE Confidence: 0.812137484550476

00:25:29.290 --> 00:25:31.495 You can see that we have some

NOTE Confidence: 0.812137484550476

00:25:31.495 --> 00:25:33.180 thickening of the epidermis.

NOTE Confidence: 0.812137484550476

00:25:33.180 --> 00:25:34.600 We have keratinocyte necrosis,
NOTE Confidence: 0.812137484550476

00:25:34.600 --> 00:25:36.020 enhanced accumulation of leukocytes,
NOTE Confidence: 0.812137484550476

00:25:36.020 --> 00:25:37.133 and dermal thickening,
NOTE Confidence: 0.812137484550476

00:25:37.133 --> 00:25:39.359 and really in what was a
NOTE Confidence: 0.812137484550476

00:25:39.359 --> 00:25:41.327 lot of work done by Ryan.
NOTE Confidence: 0.812137484550476

00:25:41.330 --> 00:25:43.460 He eventually really narrowed it down
NOTE Confidence: 0.812137484550476

00:25:43.460 --> 00:25:46.600 to an elevation in the number of T cells
NOTE Confidence: 0.812137484550476

00:25:46.600 --> 00:25:48.760 that were present within these tissue.
NOTE Confidence: 0.812137484550476

00:25:48.760 --> 00:25:50.530 Really over most other cell
NOTE Confidence: 0.812137484550476

00:25:50.530 --> 00:25:52.300 types that we looked at.
NOTE Confidence: 0.812137484550476

00:25:52.300 --> 00:25:54.065 We saw accumulation of both
NOTE Confidence: 0.812137484550476

00:25:54.065 --> 00:25:56.220 the force and CD 8 San.
NOTE Confidence: 0.812137484550476

00:25:56.220 --> 00:25:58.628 If we looked at a vaccinia specific
NOTE Confidence: 0.812137484550476

00:25:58.628 --> 00:26:00.850 response to be using Betar tetramer
NOTE Confidence: 0.812137484550476

00:26:00.850 --> 00:26:03.861 we saw almost a two fold increase in
NOTE Confidence: 0.812137484550476

00:26:03.861 --> 00:26:06.220 CD 8 positive beat our specific T

NOTE Confidence: 0.812137484550476

00:26:06.220 --> 00:26:08.252 cells within these tissues and I'll

NOTE Confidence: 0.812137484550476

00:26:08.252 --> 00:26:10.280 remind you that these tissues are

NOTE Confidence: 0.812137484550476

00:26:10.349 --> 00:26:12.946 already incredibly inflamed to CDA T cells,

NOTE Confidence: 0.812137484550476

00:26:12.950 --> 00:26:15.798 and so this is really striking to me.

NOTE Confidence: 0.812137484550476

00:26:15.800 --> 00:26:18.299 What was perhaps more striking is that

NOTE Confidence: 0.812137484550476

00:26:18.299 --> 00:26:21.846 it did not help in any way to improve tumor.

NOTE Confidence: 0.812137484550476

00:26:21.850 --> 00:26:22.248 Sorry,

NOTE Confidence: 0.812137484550476

00:26:22.248 --> 00:26:23.044 antiviral control.

NOTE Confidence: 0.812137484550476

00:26:23.044 --> 00:26:25.830 And So what this really suggested to

NOTE Confidence: 0.812137484550476

00:26:25.899 --> 00:26:28.315 us is this idea that of course many

NOTE Confidence: 0.812137484550476

00:26:28.315 --> 00:26:30.588 others have think about all the time,

NOTE Confidence: 0.812137484550476

00:26:30.590 --> 00:26:32.402 which is that we must always

NOTE Confidence: 0.812137484550476

00:26:32.402 --> 00:26:34.038 maintain the production and rapid

NOTE Confidence: 0.812137484550476

00:26:34.038 --> 00:26:35.506 mobilization of protective immunity

NOTE Confidence: 0.812137484550476

00:26:35.506 --> 00:26:37.341 with our ability to return

NOTE Confidence: 0.86006110906601

00:26:37.401 --> 00:26:38.589 to tissue homeostasis.
NOTE Confidence: 0.86006110906601

00:26:38.590 --> 00:26:40.974 And perhaps what we're seeing in this data
NOTE Confidence: 0.86006110906601

00:26:40.974 --> 00:26:43.810 is an inability to maintain that balance,
NOTE Confidence: 0.86006110906601

00:26:43.810 --> 00:26:45.898 and that by enhancing protective immunity,
NOTE Confidence: 0.86006110906601

00:26:45.900 --> 00:26:48.372 it's really at a cost of
NOTE Confidence: 0.86006110906601

00:26:48.372 --> 00:26:50.020 tissue structure and function.
NOTE Confidence: 0.86006110906601

00:26:50.020 --> 00:26:52.526 But what this data would also suggest
NOTE Confidence: 0.86006110906601

00:26:52.526 --> 00:26:55.208 is that there's now an opportunity to
NOTE Confidence: 0.86006110906601

00:26:55.208 --> 00:26:57.518 think about tipping this balance in
NOTE Confidence: 0.86006110906601

00:26:57.586 --> 00:26:59.946 the context of tumor immunotherapy.
NOTE Confidence: 0.86006110906601

00:26:59.950 --> 00:27:02.332 And might these animals now see
NOTE Confidence: 0.86006110906601

00:27:02.332 --> 00:27:03.920 improved antitumor immune control?
NOTE Confidence: 0.86006110906601

00:27:03.920 --> 00:27:06.536 And so we turned back to the Yammer
NOTE Confidence: 0.86006110906601

00:27:06.536 --> 00:27:08.073 1.7 immunogenic mirroring Melanoma
NOTE Confidence: 0.86006110906601

00:27:08.073 --> 00:27:10.503 line that again is very responsive
NOTE Confidence: 0.86006110906601

00:27:10.503 --> 00:27:13.049 to single agent checkpoint blockade.

NOTE Confidence: 0.86006110906601
00:27:13.050 --> 00:27:15.466 We could see in these tumors now that
NOTE Confidence: 0.86006110906601
00:27:15.466 --> 00:27:18.069 in the absence of lymphatic interferon
NOTE Confidence: 0.86006110906601
00:27:18.069 --> 00:27:21.440 gamma receptor that these added filial cells.
NOTE Confidence: 0.86006110906601
00:27:21.440 --> 00:27:25.128 In the tumor failed to upregulate PDL 1.
NOTE Confidence: 0.86006110906601
00:27:25.130 --> 00:27:27.482 And what was really exciting to see
NOTE Confidence: 0.86006110906601
00:27:27.482 --> 00:27:29.960 was that this was functionally very
NOTE Confidence: 0.86006110906601
00:27:29.960 --> 00:27:32.290 relevant that tumors implanted into
NOTE Confidence: 0.86006110906601
00:27:32.290 --> 00:27:34.738 these mice exhibited more tumor,
NOTE Confidence: 0.86006110906601
00:27:34.740 --> 00:27:37.122 more immune control then those implanted
NOTE Confidence: 0.86006110906601
00:27:37.122 --> 00:27:39.340 into the Cree negative controls,
NOTE Confidence: 0.86006110906601
00:27:39.340 --> 00:27:42.280 and then that sort of stabilization of
NOTE Confidence: 0.86006110906601
00:27:42.280 --> 00:27:45.607 tumor growth was dependent upon CD T cells,
NOTE Confidence: 0.86006110906601
00:27:45.610 --> 00:27:48.118 because when we depleted these cells,
NOTE Confidence: 0.86006110906601
00:27:48.120 --> 00:27:50.628 which is shown here in green,
NOTE Confidence: 0.86006110906601
00:27:50.630 --> 00:27:53.870 we completely rescued tumor growth kinetics.
NOTE Confidence: 0.86006110906601

00:27:53.870 --> 00:27:56.824 Ryan confirmed this in a second pre.
NOTE Confidence: 0.86006110906601

00:27:56.830 --> 00:27:59.511 This is now an inducible Creed driven
NOTE Confidence: 0.86006110906601

00:27:59.511 --> 00:28:02.862 by prox one where we see really very
NOTE Confidence: 0.86006110906601

00:28:02.862 --> 00:28:05.501 very similar results which is this
NOTE Confidence: 0.86006110906601

00:28:05.501 --> 00:28:08.623 delayed tumor growth and sort of stasis
NOTE Confidence: 0.86006110906601

00:28:08.623 --> 00:28:11.004 in aggregate that leads to improved
NOTE Confidence: 0.86006110906601

00:28:11.004 --> 00:28:13.686 control and so this is really the
NOTE Confidence: 0.86006110906601

00:28:13.686 --> 00:28:16.710 first data to my knowledge that in vivo
NOTE Confidence: 0.86006110906601

00:28:16.710 --> 00:28:19.668 disrupted lymphatic vessel intrinsic biology,
NOTE Confidence: 0.86006110906601

00:28:19.670 --> 00:28:21.815 independent of its proliferative growth
NOTE Confidence: 0.86006110906601

00:28:21.815 --> 00:28:23.960 and demonstrated Anna direct effect.
NOTE Confidence: 0.86006110906601

00:28:23.960 --> 00:28:27.965 On the accumulation and functionality
NOTE Confidence: 0.86006110906601

00:28:27.965 --> 00:28:31.970 of a factor immune responses.
NOTE Confidence: 0.86006110906601

00:28:31.970 --> 00:28:35.138 I just want to make this one last point,
NOTE Confidence: 0.86006110906601

00:28:35.140 --> 00:28:37.471 which is that we do not know if in
NOTE Confidence: 0.86006110906601

00:28:37.471 --> 00:28:40.456 fact PD L1 on the endothelium might be

NOTE Confidence: 0.86006110906601
00:28:40.456 --> 00:28:42.530 working through antigen presentation,
NOTE Confidence: 0.86006110906601
00:28:42.530 --> 00:28:44.792 but we do know that lymphatic
NOTE Confidence: 0.86006110906601
00:28:44.792 --> 00:28:46.666 endothelia cells can present Antigen
NOTE Confidence: 0.86006110906601
00:28:46.666 --> 00:28:49.357 and this is work that we did back with
NOTE Confidence: 0.86006110906601
00:28:49.424 --> 00:28:51.698 Melody Swartz where we showed that.
NOTE Confidence: 0.86006110906601
00:28:51.700 --> 00:28:52.064 Uh,
NOTE Confidence: 0.86006110906601
00:28:52.064 --> 00:28:54.612 not a bit too am chimeras where
NOTE Confidence: 0.86006110906601
00:28:54.612 --> 00:28:57.474 we've lost all him out of poetic
NOTE Confidence: 0.86006110906601
00:28:57.474 --> 00:28:59.529 presentation that we still see
NOTE Confidence: 0.86006110906601
00:28:59.614 --> 00:29:02.698 presentation and activation of T cells,
NOTE Confidence: 0.86006110906601
00:29:02.700 --> 00:29:04.388 particularly when we overexpress
NOTE Confidence: 0.86006110906601
00:29:04.388 --> 00:29:06.076 edge of see OneDrive,
NOTE Confidence: 0.86006110906601
00:29:06.080 --> 00:29:07.772 Lymphangiogenesis and that lymphatic
NOTE Confidence: 0.86006110906601
00:29:07.772 --> 00:29:09.464 endothelia cells in vitro,
NOTE Confidence: 0.86006110906601
00:29:09.470 --> 00:29:10.613 or really good,
NOTE Confidence: 0.86006110906601

00:29:10.613 --> 00:29:12.899 better than other sort of control

NOTE Confidence: 0.86006110906601

00:29:12.899 --> 00:29:16.095 lines at taking up an antigen that

NOTE Confidence: 0.86006110906601

00:29:16.095 --> 00:29:17.923 requires processing for presentation.

NOTE Confidence: 0.86006110906601

00:29:17.930 --> 00:29:20.174 And so there certainly is this

NOTE Confidence: 0.86006110906601

00:29:20.174 --> 00:29:22.729 idea out there that these cells

NOTE Confidence: 0.86006110906601

00:29:22.729 --> 00:29:25.184 could be cross presenting antigen.

NOTE Confidence: 0.86006110906601

00:29:25.190 --> 00:29:27.558 How all that works in the context of

NOTE Confidence: 0.86006110906601

00:29:27.558 --> 00:29:29.378 the Imperial system still remains

NOTE Confidence: 0.86006110906601

00:29:29.378 --> 00:29:31.308 to be really carefully tested,

NOTE Confidence: 0.86006110906601

00:29:31.310 --> 00:29:32.430 and so with that,

NOTE Confidence: 0.86006110906601

00:29:32.430 --> 00:29:34.921 I think what I've shown you today is

NOTE Confidence: 0.86006110906601

00:29:34.921 --> 00:29:37.532 all very consistent with the idea that

NOTE Confidence: 0.86006110906601

00:29:37.532 --> 00:29:39.467 inflammation itself is self limiting.

NOTE Confidence: 0.86006110906601

00:29:39.470 --> 00:29:41.510 What I think our work demonstrates,

NOTE Confidence: 0.86006110906601

00:29:41.510 --> 00:29:43.550 in addition to lots of other

NOTE Confidence: 0.86006110906601

00:29:43.550 --> 00:29:44.910 work by other people,

NOTE Confidence: 0.86006110906601

00:29:44.910 --> 00:29:46.740 is that interferon gamma helps the

NOTE Confidence: 0.86006110906601

00:29:46.740 --> 00:29:48.392 threshold a response by activating

NOTE Confidence: 0.86006110906601

00:29:48.392 --> 00:29:50.262 can pensa Tori immune resolution

NOTE Confidence: 0.86006110906601

00:29:50.262 --> 00:29:52.389 mechanisms in multiple both cell types,

NOTE Confidence: 0.86006110906601

00:29:52.390 --> 00:29:53.630 both local and systemic,

NOTE Confidence: 0.86006110906601

00:29:53.630 --> 00:29:55.928 and this altogether is in crucial for

NOTE Confidence: 0.86006110906601

00:29:55.928 --> 00:29:58.178 maintaining the Fidelity of immune responses.

NOTE Confidence: 0.79868620634079

00:29:58.180 --> 00:30:01.148 We should I showed you today that non

NOTE Confidence: 0.79868620634079

00:30:01.148 --> 00:30:03.708 about aquatic PDL one limits effector

NOTE Confidence: 0.79868620634079

00:30:03.708 --> 00:30:06.324 T cell function into specifically in

NOTE Confidence: 0.79868620634079

00:30:06.403 --> 00:30:09.128 tumor micro environments that dermal

NOTE Confidence: 0.79868620634079

00:30:09.128 --> 00:30:11.853 lymphatic vessels and tumor associated

NOTE Confidence: 0.79868620634079

00:30:11.860 --> 00:30:14.140 lymphatic vessels are really exquisite

NOTE Confidence: 0.79868620634079

00:30:14.140 --> 00:30:16.422 sensors of local interferon gamma

NOTE Confidence: 0.79868620634079

00:30:16.422 --> 00:30:18.532 production and that by interrupting

NOTE Confidence: 0.79868620634079

00:30:18.532 --> 00:30:21.010 the ability of the lymphatic desens
NOTE Confidence: 0.79868620634079

00:30:21.086 --> 00:30:23.426 accumulation of the cytotoxic immune
NOTE Confidence: 0.79868620634079

00:30:23.426 --> 00:30:26.326 responses we can actually drive more
NOTE Confidence: 0.79868620634079

00:30:26.326 --> 00:30:28.736 durable and persistent tumor control.
NOTE Confidence: 0.79868620634079

00:30:28.740 --> 00:30:32.763 In Marion Melanoma And with that I will stop.
NOTE Confidence: 0.79868620634079

00:30:32.770 --> 00:30:35.713 I want to thank you all very much for
NOTE Confidence: 0.79868620634079

00:30:35.713 --> 00:30:38.204 listening as I sort of resent this work.
NOTE Confidence: 0.79868620634079

00:30:38.210 --> 00:30:40.205 All this work was done at Oregon
NOTE Confidence: 0.79868620634079

00:30:40.205 --> 00:30:41.730 Health and Science University.
NOTE Confidence: 0.79868620634079

00:30:41.730 --> 00:30:43.330 We've since moved to NYU,
NOTE Confidence: 0.79868620634079

00:30:43.330 --> 00:30:45.810 but I'm grateful very much to all my
NOTE Confidence: 0.79868620634079

00:30:45.810 --> 00:30:48.176 colleagues at OHSU for all their support.
NOTE Confidence: 0.79868620634079

00:30:48.180 --> 00:30:48.688 Of course,
NOTE Confidence: 0.79868620634079

00:30:48.688 --> 00:30:51.103 Ryan Lane did all the work that I showed
NOTE Confidence: 0.79868620634079

00:30:51.103 --> 00:30:53.647 you today and that is project is being
NOTE Confidence: 0.79868620634079

00:30:53.647 --> 00:30:55.686 continued by Teddy Moody on to who is

NOTE Confidence: 0.79868620634079

00:30:55.686 --> 00:30:57.834 a new student in the lab and I'd be

NOTE Confidence: 0.79868620634079

00:30:57.834 --> 00:30:59.959 happy to take all of your questions.

NOTE Confidence: 0.79868620634079

00:30:59.960 --> 00:31:00.510 Thank you.

NOTE Confidence: 0.813724398612976

00:31:01.640 --> 00:31:02.678 Thank you so

NOTE Confidence: 0.813724398612976

00:31:02.680 --> 00:31:04.400 much, Amanda. That was wonderful.

NOTE Confidence: 0.813724398612976

00:31:04.400 --> 00:31:05.438 Maybe I can

NOTE Confidence: 0.813724398612976

00:31:05.440 --> 00:31:06.469 start off actually,

NOTE Confidence: 0.813724398612976

00:31:06.470 --> 00:31:07.508 so I'm really

NOTE Confidence: 0.813724398612976

00:31:07.510 --> 00:31:08.539 interested in this.

NOTE Confidence: 0.813724398612976

00:31:08.540 --> 00:31:09.578 Finding that interferon

NOTE Confidence: 0.813724398612976

00:31:09.580 --> 00:31:11.300 gamma can actually limit anti

NOTE Confidence: 0.813724398612976

00:31:11.300 --> 00:31:13.372 tumor immunity. And of course a

NOTE Confidence: 0.813724398612976

00:31:13.372 --> 00:31:15.100 couple other groups have suggested

NOTE Confidence: 0.813724398612976

00:31:15.100 --> 00:31:17.170 similar things, although not with this

NOTE Confidence: 0.813724398612976

00:31:17.170 --> 00:31:18.895 mechanism. To my knowledge, Danny

NOTE Confidence: 0.813724398612976

00:31:18.895 --> 00:31:20.959 Mens group or new medicines group.
NOTE Confidence: 0.841000914573669

00:31:22.020 --> 00:31:22.950 We also know
NOTE Confidence: 0.841000914573669

00:31:22.950 --> 00:31:24.190 that Interferon Gamma is
NOTE Confidence: 0.841000914573669

00:31:24.190 --> 00:31:25.120 required for some
NOTE Confidence: 0.841000914573669

00:31:25.120 --> 00:31:27.600 of the key functions and anti tumor immunity.
NOTE Confidence: 0.841000914573669

00:31:27.600 --> 00:31:29.690 How do you think about targeting interferon
NOTE Confidence: 0.841000914573669

00:31:29.690 --> 00:31:31.630 gamma to improve anti tumor immunity?
NOTE Confidence: 0.844914615154266

00:31:32.280 --> 00:31:34.284 Yeah, I mean I think it's
NOTE Confidence: 0.844914615154266

00:31:34.284 --> 00:31:35.286 an important question.
NOTE Confidence: 0.844914615154266

00:31:35.290 --> 00:31:37.972 I think what our work and as well as
NOTE Confidence: 0.844914615154266

00:31:37.972 --> 00:31:40.960 all of the other work that's been done,
NOTE Confidence: 0.844914615154266

00:31:40.960 --> 00:31:43.064 really points to is that this all of
NOTE Confidence: 0.844914615154266

00:31:43.064 --> 00:31:45.315 the cells in the tumor microenvironment
NOTE Confidence: 0.844914615154266

00:31:45.315 --> 00:31:46.975 are integrating this signal,
NOTE Confidence: 0.844914615154266

00:31:46.980 --> 00:31:48.650 potentially in different ways, right?
NOTE Confidence: 0.844914615154266

00:31:48.650 --> 00:31:50.320 And so as an aggregate,

NOTE Confidence: 0.844914615154266

00:31:50.320 --> 00:31:51.990 just neutralization of the cytokine,

NOTE Confidence: 0.844914615154266

00:31:51.990 --> 00:31:54.542 you know clearly may not have the kind

NOTE Confidence: 0.844914615154266

00:31:54.542 --> 00:31:56.657 of intended results that you want,

NOTE Confidence: 0.844914615154266

00:31:56.660 --> 00:31:59.236 so I think it is really challenging

NOTE Confidence: 0.844914615154266

00:31:59.236 --> 00:32:01.667 to think about how we use it for

NOTE Confidence: 0.844914615154266

00:32:01.670 --> 00:32:02.974 therapeutic purposes, but it.

NOTE Confidence: 0.844914615154266

00:32:02.974 --> 00:32:05.406 I think very clear from all this work

NOTE Confidence: 0.844914615154266

00:32:05.406 --> 00:32:08.276 that if you can start to tease out

NOTE Confidence: 0.844914615154266

00:32:08.276 --> 00:32:10.107 the different mechanisms that are

NOTE Confidence: 0.844914615154266

00:32:10.107 --> 00:32:12.189 activated in a cell specific way,

NOTE Confidence: 0.844914615154266

00:32:12.190 --> 00:32:14.194 we really understand all of these

NOTE Confidence: 0.844914615154266

00:32:14.194 --> 00:32:15.890 nuances and perhaps that will

NOTE Confidence: 0.844914615154266

00:32:15.890 --> 00:32:17.086 lead us eventually to

NOTE Confidence: 0.789005398750305

00:32:17.090 --> 00:32:19.058 a better understanding for how we

NOTE Confidence: 0.789005398750305

00:32:19.060 --> 00:32:21.668 use it. Thank you. We have one for

NOTE Confidence: 0.789005398750305

00:32:21.670 --> 00:32:22.978 Nick Joe Sheehan which
NOTE Confidence: 0.789005398750305

00:32:22.980 --> 00:32:24.288 is on cross presentation
NOTE Confidence: 0.789005398750305

00:32:24.290 --> 00:32:25.268 of antigens by
NOTE Confidence: 0.789005398750305

00:32:25.270 --> 00:32:26.578 Ellie Elks. Is it
NOTE Confidence: 0.789005398750305

00:32:26.580 --> 00:32:27.558 possible that this
NOTE Confidence: 0.789005398750305

00:32:27.560 --> 00:32:29.516 serves as a sensing mechanism for
NOTE Confidence: 0.789005398750305

00:32:29.520 --> 00:32:31.486 the presence of Antigen and tissues?
NOTE Confidence: 0.789005398750305

00:32:31.486 --> 00:32:33.524 Are ATRM cells located near the?
NOTE Confidence: 0.789005398750305

00:32:33.524 --> 00:32:34.920 Else sees, yeah, that's
NOTE Confidence: 0.759889423847198

00:32:34.920 --> 00:32:35.979 great, but I
NOTE Confidence: 0.759889423847198

00:32:35.980 --> 00:32:38.098 think that's exactly how we initially
NOTE Confidence: 0.759889423847198

00:32:38.098 --> 00:32:39.952 thought about this, so it's clear.
NOTE Confidence: 0.759889423847198

00:32:39.952 --> 00:32:41.536 Sort of two things that lymph
NOTE Confidence: 0.759889423847198

00:32:41.536 --> 00:32:43.099 node lymphatic endothelia cells
NOTE Confidence: 0.759889423847198

00:32:43.099 --> 00:32:44.759 actually promiscuously express a
NOTE Confidence: 0.759889423847198

00:32:44.759 --> 00:32:46.920 lot of peripheral tissue antigens,

NOTE Confidence: 0.759889423847198
00:32:46.920 --> 00:32:48.320 so it's steady state.
NOTE Confidence: 0.759889423847198
00:32:48.320 --> 00:32:49.720 They are presenting things
NOTE Confidence: 0.759889423847198
00:32:49.720 --> 00:32:50.810 like tyrosinase which,
NOTE Confidence: 0.759889423847198
00:32:50.810 --> 00:32:53.127 when we think and again these are
NOTE Confidence: 0.759889423847198
00:32:53.127 --> 00:32:55.667 all limited by the lack of really
NOTE Confidence: 0.759889423847198
00:32:55.667 --> 00:32:57.507 sell specific in vivo models.
NOTE Confidence: 0.759889423847198
00:32:57.510 --> 00:32:59.822 But we think that that expression of PD
NOTE Confidence: 0.759889423847198
00:32:59.822 --> 00:33:02.459 L1 on the lymphatic individual cells,
NOTE Confidence: 0.759889423847198
00:33:02.460 --> 00:33:03.900 an expression of something
NOTE Confidence: 0.759889423847198
00:33:03.900 --> 00:33:05.700 might draw says actually limits.
NOTE Confidence: 0.759889423847198
00:33:05.700 --> 00:33:07.819 The generation and an mobilization
NOTE Confidence: 0.759889423847198
00:33:07.820 --> 00:33:09.083 of Malana site.
NOTE Confidence: 0.759889423847198
00:33:09.083 --> 00:33:10.346 Specific T cells.
NOTE Confidence: 0.759889423847198
00:33:10.350 --> 00:33:11.244 For example,
NOTE Confidence: 0.759889423847198
00:33:11.244 --> 00:33:13.926 we have evidence that they are
NOTE Confidence: 0.759889423847198

00:33:13.926 --> 00:33:15.853 also presenting in that issue,
NOTE Confidence: 0.759889423847198

00:33:15.853 --> 00:33:18.690 and we know limp itself is full
NOTE Confidence: 0.759889423847198

00:33:18.690 --> 00:33:20.680 of processed antigens and that
NOTE Confidence: 0.759889423847198

00:33:20.761 --> 00:33:23.587 there's reason to believe that the
NOTE Confidence: 0.759889423847198

00:33:23.587 --> 00:33:25.931 lymphatic endothelia cells are in
NOTE Confidence: 0.759889423847198

00:33:25.931 --> 00:33:28.619 some ways bathed in sort of tissue
NOTE Confidence: 0.759889423847198

00:33:28.619 --> 00:33:30.158 derived factors and antigens.
NOTE Confidence: 0.759889423847198

00:33:30.158 --> 00:33:33.230 So you know how they might interact with
NOTE Confidence: 0.759889423847198

00:33:33.309 --> 00:33:36.159 local more quiescent T cell populations.
NOTE Confidence: 0.759889423847198

00:33:36.160 --> 00:33:37.122 It's really.
NOTE Confidence: 0.759889423847198

00:33:37.122 --> 00:33:40.030 A current area of study that
NOTE Confidence: 0.759889423847198

00:33:40.030 --> 00:33:42.530 we know not enough about.
NOTE Confidence: 0.842281997203827

00:33:43.940 --> 00:33:45.832 Great, another question from the from
NOTE Confidence: 0.842281997203827

00:33:45.832 --> 00:33:48.352 the chat is how important is this pathway
NOTE Confidence: 0.842281997203827

00:33:48.352 --> 00:33:49.906 for non antigen specific immunity?
NOTE Confidence: 0.842281997203827

00:33:49.906 --> 00:33:52.696 We saw the T cell immunity but you see

NOTE Confidence: 0.842281997203827

00:33:52.696 --> 00:33:54.817 other anti tumor immune cells kind of

NOTE Confidence: 0.842281997203827

00:33:54.817 --> 00:33:56.860 changing or biology here. Yeah that's

NOTE Confidence: 0.842281997203827

00:33:56.860 --> 00:33:57.793 a great question.

NOTE Confidence: 0.842281997203827

00:33:57.793 --> 00:33:59.970 We you know we haven't looked as

NOTE Confidence: 0.842281997203827

00:34:00.038 --> 00:34:02.526 carefully at that as we should still do.

NOTE Confidence: 0.842281997203827

00:34:02.530 --> 00:34:04.210 Really understand what else is changing

NOTE Confidence: 0.842281997203827

00:34:04.210 --> 00:34:05.990 in these tumor micro environments.

NOTE Confidence: 0.842281997203827

00:34:05.990 --> 00:34:07.688 That is either sort of dependent

NOTE Confidence: 0.842281997203827

00:34:07.688 --> 00:34:09.574 upon the changes in affect or

NOTE Confidence: 0.842281997203827

00:34:09.574 --> 00:34:10.962 immunity or completely independent

NOTE Confidence: 0.842281997203827

00:34:10.962 --> 00:34:13.216 and so that still remains an open

NOTE Confidence: 0.842281997203827

00:34:13.216 --> 00:34:15.034 question and something we need to

NOTE Confidence: 0.842281997203827

00:34:15.034 --> 00:34:17.017 look more carefully at for sure.

NOTE Confidence: 0.799646079540253

00:34:18.300 --> 00:34:19.810 But thank you so much.

NOTE Confidence: 0.799646079540253

00:34:19.810 --> 00:34:21.318 I think, no, Marcus, I'll

NOTE Confidence: 0.799646079540253

00:34:21.320 --> 00:34:22.830 just ask one quick question.
NOTE Confidence: 0.799646079540253

00:34:22.830 --> 00:34:24.937 It will break very soon after that.
NOTE Confidence: 0.799646079540253

00:34:24.940 --> 00:34:27.030 So Amanda, I think it's striking with
NOTE Confidence: 0.799646079540253

00:34:27.030 --> 00:34:28.650 the gamma induced changes that you're
NOTE Confidence: 0.799646079540253

00:34:28.650 --> 00:34:30.379 seeing in the endothelial cells.
NOTE Confidence: 0.799646079540253

00:34:30.380 --> 00:34:32.354 Do you think there are endothelial
NOTE Confidence: 0.799646079540253

00:34:32.354 --> 00:34:33.670 specific suppressive mechanisms that
NOTE Confidence: 0.799646079540253

00:34:33.716 --> 00:34:35.492 might be targetable 'cause we talked
NOTE Confidence: 0.799646079540253

00:34:35.492 --> 00:34:37.328 about gamma being difficult to work with?
NOTE Confidence: 0.799646079540253

00:34:37.330 --> 00:34:37.930 Bizarre things?
NOTE Confidence: 0.799646079540253

00:34:37.930 --> 00:34:40.350 Are there changes by single cell RNA seq,
NOTE Confidence: 0.799646079540253

00:34:40.350 --> 00:34:42.156 or other approaches that you think
NOTE Confidence: 0.799646079540253

00:34:42.156 --> 00:34:43.624 there's new suppressive pathways
NOTE Confidence: 0.799646079540253

00:34:43.624 --> 00:34:45.176 that are endothelial specific?
NOTE Confidence: 0.799646079540253

00:34:45.180 --> 00:34:45.490 That's
NOTE Confidence: 0.858711659908295

00:34:45.490 --> 00:34:46.112 really interesting.

NOTE Confidence: 0.858711659908295

00:34:46.112 --> 00:34:48.920 So yeah, so we have been thinking about that,

NOTE Confidence: 0.858711659908295

00:34:48.920 --> 00:34:50.168 but haven't really gotten.

NOTE Confidence: 0.858711659908295

00:34:50.168 --> 00:34:52.040 We don't answer for you, right?

NOTE Confidence: 0.858711659908295

00:34:52.040 --> 00:34:53.984 So what is really happening downstream

NOTE Confidence: 0.858711659908295

00:34:53.984 --> 00:34:55.480 in the lymphatic endothelia am?

NOTE Confidence: 0.858711659908295

00:34:55.480 --> 00:34:57.038 That might be more specific.

NOTE Confidence: 0.858711659908295

00:34:57.040 --> 00:34:59.217 It was just exactly what you're getting.

NOTE Confidence: 0.858711659908295

00:34:59.220 --> 00:35:00.924 I think I think that's something

NOTE Confidence: 0.858711659908295

00:35:00.924 --> 00:35:03.276 that you know we certainly should do.

NOTE Confidence: 0.858711659908295

00:35:03.276 --> 00:35:04.834 And we've been thinking about,

NOTE Confidence: 0.858711659908295

00:35:04.834 --> 00:35:07.334 I think the other way to think about

NOTE Confidence: 0.858711659908295

00:35:07.334 --> 00:35:09.518 your question from the perspective of the

NOTE Confidence: 0.858711659908295

00:35:09.520 --> 00:35:11.080 endothelium is engineering strategies to

NOTE Confidence: 0.858711659908295

00:35:11.080 --> 00:35:13.257 actually target in a more specific way.

NOTE Confidence: 0.858711659908295

00:35:13.260 --> 00:35:14.855 And there's certainly people have

NOTE Confidence: 0.858711659908295

00:35:14.855 --> 00:35:16.131 been thinking about vascular
NOTE Confidence: 0.858711659908295

00:35:16.131 --> 00:35:17.070 targeting therapies or.
NOTE Confidence: 0.858711659908295

00:35:17.070 --> 00:35:19.050 Or are ways in which to
NOTE Confidence: 0.858711659908295

00:35:19.050 --> 00:35:20.040 administer checkpoint on.
NOTE Confidence: 0.858711659908295

00:35:20.040 --> 00:35:21.930 There was some nice study by
NOTE Confidence: 0.858711659908295

00:35:21.930 --> 00:35:23.603 Susan Thomas recently where you
NOTE Confidence: 0.858711659908295

00:35:23.603 --> 00:35:24.990 could actually target lymphatic
NOTE Confidence: 0.858711659908295

00:35:24.990 --> 00:35:26.580 transport in the lymph node.
NOTE Confidence: 0.858711659908295

00:35:26.580 --> 00:35:28.750 And so I think it's probably going
NOTE Confidence: 0.858711659908295

00:35:28.818 --> 00:35:30.930 to be combination of these things.
NOTE Confidence: 0.858711659908295

00:35:30.930 --> 00:35:32.375 It's a better understanding of
NOTE Confidence: 0.858711659908295

00:35:32.375 --> 00:35:34.532 the biology as well as maybe some
NOTE Confidence: 0.858711659908295

00:35:34.532 --> 00:35:36.167 delivery strategies that will help
NOTE Confidence: 0.858711659908295

00:35:36.167 --> 00:35:38.189 us target this more specifically.
NOTE Confidence: 0.849495649337769

00:35:40.020 --> 00:35:40.929 Well, great, thanks.
NOTE Confidence: 0.849495649337769

00:35:40.929 --> 00:35:42.747 I think I'll take over Jeff

NOTE Confidence: 0.849495649337769
00:35:42.747 --> 00:35:44.658 Real quickly and will take care.
NOTE Confidence: 0.849495649337769
00:35:44.660 --> 00:35:46.508 Thanks so much, Jeff for moderating.
NOTE Confidence: 0.849495649337769
00:35:46.510 --> 00:35:48.364 But really thanks so much to
NOTE Confidence: 0.849495649337769
00:35:48.364 --> 00:35:49.909 the speakers to Raffi, Arlene,
NOTE Confidence: 0.849495649337769
00:35:49.909 --> 00:35:51.454 Ann, Amanda for really great
NOTE Confidence: 0.849495649337769
00:35:51.454 --> 00:35:53.310 talks with a lot of interest.
NOTE Confidence: 0.849495649337769
00:35:53.310 --> 00:35:54.546 A lot of stimulation,
NOTE Confidence: 0.849495649337769
00:35:54.546 --> 00:35:56.394 so we'll have a brief break.
NOTE Confidence: 0.849495649337769
00:35:56.400 --> 00:35:57.020 It's 1135
NOTE Confidence: 0.849495649337769
00:35:57.020 --> 00:35:58.560 now will be starting back
NOTE Confidence: 0.849495649337769
00:35:58.560 --> 00:35:59.490 up promptly at
NOTE Confidence: 0.849495649337769
00:35:59.490 --> 00:36:01.030 11:45 in about 10 minutes,
NOTE Confidence: 0.849495649337769
00:36:01.030 --> 00:36:03.506 so will be signed back on, you know,
NOTE Confidence: 0.849495649337769
00:36:03.506 --> 00:36:05.046 a couple minutes before that,
NOTE Confidence: 0.849495649337769
00:36:05.050 --> 00:36:07.210 and make sure that doctor Rosenberg stock
NOTE Confidence: 0.849495649337769

00:36:07.210 --> 00:36:10.012 is all good to go for the next session.
NOTE Confidence: 0.849495649337769

00:36:10.012 --> 00:36:11.660 But thanks again and we'll
NOTE Confidence: 0.849495649337769

00:36:11.660 --> 00:36:13.284 see you guys very shortly.
NOTE Confidence: 0.849495649337769

00:36:13.284 --> 00:36:14.910 Alright. See in a few.
NOTE Confidence: 0.700629591941834

00:36:28.360 --> 00:36:29.140 Alyssa.
NOTE Confidence: 0.845088541507721

00:36:31.250 --> 00:36:33.410 Yes Hello, it's Tristan Park.
NOTE Confidence: 0.845088541507721

00:36:33.410 --> 00:36:36.863 Am I supposed to log onto a separate
NOTE Confidence: 0.845088541507721

00:36:36.863 --> 00:36:39.890 link or just stay on this note
NOTE Confidence: 0.845088541507721

00:36:39.890 --> 00:36:42.476 Erie rate in advance cell Therapeutics
NOTE Confidence: 0.845088541507721

00:36:42.476 --> 00:36:45.070 Laboratory that's run by Diane Kraus
NOTE Confidence: 0.845088541507721

00:36:45.070 --> 00:36:47.663 with assistance from a variety of
NOTE Confidence: 0.845088541507721

00:36:47.663 --> 00:36:50.290 other individuals at yell that is
NOTE Confidence: 0.845088541507721

00:36:50.290 --> 00:36:52.490 doing till harvest and expansion
NOTE Confidence: 0.845088541507721

00:36:52.490 --> 00:36:55.496 in a GNP compatible way that is
NOTE Confidence: 0.845088541507721

00:36:55.496 --> 00:36:57.600 also now being really confused
NOTE Confidence: 0.845088541507721

00:36:57.600 --> 00:36:59.764 in patients were obviously very

NOTE Confidence: 0.845088541507721

00:36:59.764 --> 00:37:01.941 interested in developing these areas.

NOTE Confidence: 0.845088541507721

00:37:01.941 --> 00:37:04.115 Further and so you know,

NOTE Confidence: 0.845088541507721

00:37:04.115 --> 00:37:06.244 I think not just us,

NOTE Confidence: 0.845088541507721

00:37:06.244 --> 00:37:10.065 but a lot of the world owes a debt

NOTE Confidence: 0.845088541507721

00:37:10.065 --> 00:37:12.189 of gratitude to doctor Rosenberg

NOTE Confidence: 0.845088541507721

00:37:12.190 --> 00:37:13.890 and the longstanding approaches

NOTE Confidence: 0.846253275871277

00:37:13.890 --> 00:37:15.590 that he's developed in

NOTE Confidence: 0.846253275871277

00:37:15.590 --> 00:37:17.290 cellular therapy overtime. And

NOTE Confidence: 0.846253275871277

00:37:17.290 --> 00:37:19.416 I think it's really exciting

NOTE Confidence: 0.846253275871277

00:37:19.416 --> 00:37:21.545 and low mutation burden tumors.

NOTE Confidence: 0.846253275871277

00:37:21.545 --> 00:37:24.520 How these approaches still really are as

NOTE Confidence: 0.846253275871277

00:37:24.520 --> 00:37:27.066 promising as anything that's out there.

NOTE Confidence: 0.846253275871277

00:37:27.066 --> 00:37:29.615 And I'd also like to introduce

NOTE Confidence: 0.846253275871277

00:37:29.615 --> 00:37:30.890 doctor Kristen Park,

NOTE Confidence: 0.846253275871277

00:37:30.890 --> 00:37:33.880 who is an assistant professor of surgery.

NOTE Confidence: 0.846253275871277

00:37:33.880 --> 00:37:36.750 At Yale, Ann had I think previously
NOTE Confidence: 0.846253275871277

00:37:36.750 --> 00:37:39.733 at least cross paths with doctor
NOTE Confidence: 0.846253275871277

00:37:39.733 --> 00:37:43.040 Rosenberg at some point in her training,
NOTE Confidence: 0.846253275871277

00:37:43.040 --> 00:37:45.785 and she is both a practicing
NOTE Confidence: 0.846253275871277

00:37:45.785 --> 00:37:46.699 surgical oncologist,
NOTE Confidence: 0.846253275871277

00:37:46.700 --> 00:37:50.046 but also has interests in a variety
NOTE Confidence: 0.846253275871277

00:37:50.046 --> 00:37:52.660 of different aspects of anti cancer.
NOTE Confidence: 0.846253275871277

00:37:52.660 --> 00:37:54.950 Immune responses including cell therapies.
NOTE Confidence: 0.846253275871277

00:37:54.950 --> 00:37:56.644 Kristen, if you wanted to introduce doctor
NOTE Confidence: 0.846253275871277

00:37:56.644 --> 00:37:58.139 Rosenberg and get the session going,
NOTE Confidence: 0.846253275871277

00:37:58.140 --> 00:37:58.380 that
NOTE Confidence: 0.790907874703407

00:37:58.380 --> 00:38:00.108 would be great. Hello
NOTE Confidence: 0.83035284280777

00:38:00.110 --> 00:38:02.329 everyone, it is my great pleasure to
NOTE Confidence: 0.83035284280777

00:38:02.329 --> 00:38:04.106 moderate the session and introduce
NOTE Confidence: 0.83035284280777

00:38:04.106 --> 00:38:06.316 doctor Steven Rosenberg MD, pH, MD,
NOTE Confidence: 0.83035284280777

00:38:06.316 --> 00:38:08.732 PhD is currently the chief of surgery

NOTE Confidence: 0.83035284280777

00:38:08.732 --> 00:38:10.800 for the National Cancer Institute and

NOTE Confidence: 0.83035284280777

00:38:10.800 --> 00:38:12.525 the National Institutes of Health.

NOTE Confidence: 0.83035284280777

00:38:12.525 --> 00:38:14.598 Doctor Rosenberg is considered one of

NOTE Confidence: 0.83035284280777

00:38:14.598 --> 00:38:17.013 the Founding Fathers of the field of

NOTE Confidence: 0.83035284280777

00:38:17.013 --> 00:38:18.735 amino therapy and his groundbreaking

NOTE Confidence: 0.83035284280777

00:38:18.735 --> 00:38:21.155 work enabled the use of high dose

NOTE Confidence: 0.83035284280777

00:38:21.155 --> 00:38:23.222 interleukin two as one of the

NOTE Confidence: 0.83035284280777

00:38:23.222 --> 00:38:24.945 first immuno therapies for solid

NOTE Confidence: 0.83035284280777

00:38:24.945 --> 00:38:27.018 organ cancers and his studies on

NOTE Confidence: 0.83035284280777

00:38:27.020 --> 00:38:28.755 the cell. Transfer of immunotherapy

NOTE Confidence: 0.83035284280777

00:38:28.755 --> 00:38:30.143 using bulk Tills Mutation.

NOTE Confidence: 0.83035284280777

00:38:30.150 --> 00:38:32.542 Reactive tools party at TC are

NOTE Confidence: 0.83035284280777

00:38:32.542 --> 00:38:33.740 transduced. Lymphocytes have

NOTE Confidence: 0.83035284280777

00:38:33.740 --> 00:38:35.340 resulted in complete, durable

NOTE Confidence: 0.806664049625397

00:38:35.340 --> 00:38:36.528 remissions in patients

NOTE Confidence: 0.806664049625397

00:38:36.530 --> 00:38:37.781 with metastatic Melanoma,
NOTE Confidence: 0.806664049625397

00:38:37.781 --> 00:38:39.866 other organ tumors and lymphomas
NOTE Confidence: 0.806664049625397

00:38:39.866 --> 00:38:42.201 which I was able to personally
NOTE Confidence: 0.806664049625397

00:38:42.201 --> 00:38:44.120 witness and participate in as
NOTE Confidence: 0.806664049625397

00:38:44.120 --> 00:38:45.708 a immunotherapy and surgical
NOTE Confidence: 0.806664049625397

00:38:45.710 --> 00:38:46.910 oncology fellow back
NOTE Confidence: 0.806664049625397

00:38:46.910 --> 00:38:49.700 in the day, doctor Rosenberg has received
NOTE Confidence: 0.806664049625397

00:38:49.700 --> 00:38:52.100 many numerous prizes, including the 2013
NOTE Confidence: 0.806664049625397

00:38:52.100 --> 00:38:53.692 Keio Medical Science Prize,
NOTE Confidence: 0.806664049625397

00:38:53.692 --> 00:38:55.284 the Albany Medical Center,
NOTE Confidence: 0.806664049625397

00:38:55.290 --> 00:38:58.080 Price in 2018, and the and the
NOTE Confidence: 0.806664049625397

00:38:58.080 --> 00:39:00.552 2015 Medal of Honor of the.
NOTE Confidence: 0.806664049625397

00:39:00.552 --> 00:39:01.966 American Cancer Society.
NOTE Confidence: 0.806664049625397

00:39:01.966 --> 00:39:04.900 We're extremely excited to hear about
NOTE Confidence: 0.791703999042511

00:39:04.900 --> 00:39:07.350 your latest work and your
NOTE Confidence: 0.791703999042511

00:39:07.350 --> 00:39:09.788 thoughts. The title of this

NOTE Confidence: 0.791703999042511
00:39:09.790 --> 00:39:12.230 talk is self transfer immunotherapy
NOTE Confidence: 0.791703999042511
00:39:12.230 --> 00:39:14.182 for patients with metastatic,
NOTE Confidence: 0.791703999042511
00:39:14.190 --> 00:39:15.660 metastatic solid cancer.
NOTE Confidence: 0.840103685855865
00:39:26.750 --> 00:39:30.770 good to good to see you again.
NOTE Confidence: 0.840103685855865
00:39:30.770 --> 00:39:33.070 Going to be talking
NOTE Confidence: 0.840103685855865
00:39:33.070 --> 00:39:36.409 next 25 minutes or so on the
NOTE Confidence: 0.840103685855865
00:39:36.409 --> 00:39:38.688 development of cellular immunotherapy's
NOTE Confidence: 0.840103685855865
00:39:38.688 --> 00:39:41.696 for patients with cancer.
NOTE Confidence: 0.898131310939789
00:39:44.100 --> 00:39:46.000 I work for the US government,
NOTE Confidence: 0.898131310939789
00:39:46.000 --> 00:39:49.409 so sadly I have no personal disclosures.
NOTE Confidence: 0.898131310939789
00:39:49.410 --> 00:39:51.867 The goal of the efforts that I'll
NOTE Confidence: 0.898131310939789
00:39:51.867 --> 00:39:54.113 be describing of the development
NOTE Confidence: 0.898131310939789
00:39:54.113 --> 00:39:56.357 of effective immunotherapy's for
NOTE Confidence: 0.898131310939789
00:39:56.357 --> 00:39:59.071 patients with metastatic cancer based
NOTE Confidence: 0.898131310939789
00:39:59.071 --> 00:40:01.429 on the adoptive transfer of immune
NOTE Confidence: 0.898131310939789

00:40:01.429 --> 00:40:03.462 cells with anti cancer activity
NOTE Confidence: 0.898131310939789

00:40:03.462 --> 00:40:06.018 were using lymphocytes as a living
NOTE Confidence: 0.898131310939789

00:40:06.018 --> 00:40:10.760 drug for the treatment of patients.
NOTE Confidence: 0.898131310939789

00:40:10.760 --> 00:40:13.752 There are two critical issues in the
NOTE Confidence: 0.898131310939789

00:40:13.752 --> 00:40:15.480 development of cancer immunotherapy's
NOTE Confidence: 0.898131310939789

00:40:15.545 --> 00:40:17.960 that I'd like to discuss this morning.
NOTE Confidence: 0.898131310939789

00:40:17.960 --> 00:40:19.672 First, the identification of
NOTE Confidence: 0.898131310939789

00:40:19.672 --> 00:40:22.240 antigenic targets on the cancer cell.
NOTE Confidence: 0.898131310939789

00:40:22.240 --> 00:40:24.075 Can potentially lead to the
NOTE Confidence: 0.898131310939789

00:40:24.075 --> 00:40:25.543 development of new treatments.
NOTE Confidence: 0.898131310939789

00:40:25.550 --> 00:40:26.669 And of course,
NOTE Confidence: 0.898131310939789

00:40:26.669 --> 00:40:28.161 the identification of the
NOTE Confidence: 0.898131310939789

00:40:28.161 --> 00:40:30.054 characteristics of the immune cells
NOTE Confidence: 0.898131310939789

00:40:30.054 --> 00:40:32.184 that can recognize and destroy cancer
NOTE Confidence: 0.898131310939789

00:40:32.184 --> 00:40:34.408 cells and will touch briefly on
NOTE Confidence: 0.898131310939789

00:40:34.408 --> 00:40:36.218 those efforts in this discussion.

NOTE Confidence: 0.911773920059204

00:40:38.260 --> 00:40:41.372 Or attempt to answer some of those questions

NOTE Confidence: 0.911773920059204

00:40:41.372 --> 00:40:43.860 using cell transfer immunotherapy.

NOTE Confidence: 0.911773920059204

00:40:43.860 --> 00:40:46.204 That has multiple advantages

NOTE Confidence: 0.911773920059204

00:40:46.204 --> 00:40:48.548 as an immunotherapy approach.

NOTE Confidence: 0.911773920059204

00:40:48.550 --> 00:40:50.950 For one, we can administer large

NOTE Confidence: 0.911773920059204

00:40:50.950 --> 00:40:53.454 numbers of highly selected cells with

NOTE Confidence: 0.911773920059204

00:40:53.454 --> 00:40:55.534 high avidity for tumor antigens.

NOTE Confidence: 0.911773920059204

00:40:55.540 --> 00:40:58.324 We can potentially identify the exact

NOTE Confidence: 0.911773920059204

00:40:58.324 --> 00:41:00.180 cell subpopulations and effector

NOTE Confidence: 0.911773920059204

00:41:00.247 --> 00:41:02.367 functions required for cancer regression

NOTE Confidence: 0.911773920059204

00:41:02.367 --> 00:41:05.548 in vivo because we have the cells that

NOTE Confidence: 0.911773920059204

00:41:05.548 --> 00:41:07.865 are being administered as a drug in

NOTE Confidence: 0.911773920059204

00:41:07.870 --> 00:41:10.593 a test tube and can therefore study

NOTE Confidence: 0.911773920059204

00:41:10.593 --> 00:41:12.771 them of provides advantages compared

NOTE Confidence: 0.911773920059204

00:41:12.771 --> 00:41:16.019 to other approaches like the use of

NOTE Confidence: 0.911773920059204

00:41:16.019 --> 00:41:18.738 cancer vaccines or immunomodulators.
NOTE Confidence: 0.911773920059204

00:41:18.740 --> 00:41:20.172 And perhaps most importantly,
NOTE Confidence: 0.911773920059204

00:41:20.172 --> 00:41:22.840 we can manipulate the host prior to sell,
NOTE Confidence: 0.911773920059204

00:41:22.840 --> 00:41:24.550 transfer to provide an altered
NOTE Confidence: 0.911773920059204

00:41:24.550 --> 00:41:25.918 environment for the transfer.
NOTE Confidence: 0.911773920059204

00:41:25.920 --> 00:41:29.448 It sells because the drug we're going to
NOTE Confidence: 0.911773920059204

00:41:29.448 --> 00:41:33.714 use is no longer no longer in the patient.
NOTE Confidence: 0.911773920059204

00:41:33.720 --> 00:41:35.628 And so as we begin this,
NOTE Confidence: 0.911773920059204

00:41:35.630 --> 00:41:37.694 it's important to understand and I
NOTE Confidence: 0.911773920059204

00:41:37.694 --> 00:41:40.270 want to emphasize this to the non
NOTE Confidence: 0.911773920059204

00:41:40.270 --> 00:41:41.786 immunologists that are listening.
NOTE Confidence: 0.911773920059204

00:41:41.790 --> 00:41:44.450 The conventional T cell receptor
NOTE Confidence: 0.911773920059204

00:41:44.450 --> 00:41:46.578 recognizes its target because
NOTE Confidence: 0.911773920059204

00:41:46.578 --> 00:41:49.317 it has Alpha and beta chains,
NOTE Confidence: 0.911773920059204

00:41:49.320 --> 00:41:52.902 where on the left that recognize
NOTE Confidence: 0.911773920059204

00:41:52.902 --> 00:41:54.693 a processed peptide.

NOTE Confidence: 0.911773920059204
00:41:54.700 --> 00:41:56.830 That's presented on the surface
NOTE Confidence: 0.911773920059204
00:41:56.830 --> 00:41:58.960 of that particular patients M.
NOTE Confidence: 0.911773920059204
00:41:58.960 --> 00:42:02.368 HC molecule, either class one or Class 2.
NOTE Confidence: 0.911773920059204
00:42:02.370 --> 00:42:05.004 That's very different from a chimeric
NOTE Confidence: 0.911773920059204
00:42:05.004 --> 00:42:07.760 antigen receptor Here on the right.
NOTE Confidence: 0.911773920059204
00:42:07.760 --> 00:42:11.466 In which we take a take an antibody
NOTE Confidence: 0.911773920059204
00:42:11.466 --> 00:42:13.870 and isolate the variable region
NOTE Confidence: 0.911773920059204
00:42:13.870 --> 00:42:16.948 of the heavy and light chains.
NOTE Confidence: 0.839311301708221
00:42:19.530 --> 00:42:21.930 Combine them into a single chain
NOTE Confidence: 0.839311301708221
00:42:21.930 --> 00:42:24.114 antibody and attach that single
NOTE Confidence: 0.839311301708221
00:42:24.114 --> 00:42:26.138 chain antibody to intracellular
NOTE Confidence: 0.839311301708221
00:42:26.138 --> 00:42:28.668 signaling chains in a lymphocyte.
NOTE Confidence: 0.839311301708221
00:42:28.670 --> 00:42:31.658 So when this chimeric antigen receptor
NOTE Confidence: 0.839311301708221
00:42:31.658 --> 00:42:34.156 is inserted into lymphocytes and
NOTE Confidence: 0.839311301708221
00:42:34.156 --> 00:42:36.700 now converts a lymphocyte from its
NOTE Confidence: 0.839311301708221

00:42:36.700 --> 00:42:38.909 recognition from a conventional T
NOTE Confidence: 0.839311301708221

00:42:38.909 --> 00:42:41.919 cell receptor to that of an antibody,
NOTE Confidence: 0.839311301708221

00:42:41.920 --> 00:42:44.832 and the recent success of the use
NOTE Confidence: 0.839311301708221

00:42:44.832 --> 00:42:46.950 of chimeric antigen receptors,
NOTE Confidence: 0.839311301708221

00:42:46.950 --> 00:42:49.740 in fact, the first FDA approved.
NOTE Confidence: 0.839311301708221

00:42:49.740 --> 00:42:52.316 Cell and gene therapy has come from its
NOTE Confidence: 0.839311301708221

00:42:52.316 --> 00:42:54.858 success in the treatment of patients
NOTE Confidence: 0.839311301708221

00:42:54.858 --> 00:42:57.148 with advanced lymphomas and leukemias,
NOTE Confidence: 0.839311301708221

00:42:57.150 --> 00:42:59.990 we learned a great deal from even the
NOTE Confidence: 0.839311301708221

00:42:59.990 --> 00:43:02.998 very first patient that was ever treated.
NOTE Confidence: 0.839311301708221

00:43:03.000 --> 00:43:05.429 A patient here in the surgery branch
NOTE Confidence: 0.839311301708221

00:43:05.429 --> 00:43:07.840 who had an advanced lymphoma who
NOTE Confidence: 0.839311301708221

00:43:07.840 --> 00:43:10.843 taught us about some of the problems
NOTE Confidence: 0.839311301708221

00:43:10.920 --> 00:43:13.140 involved in using car T cells.
NOTE Confidence: 0.839311301708221

00:43:13.140 --> 00:43:15.480 This was a patient who had
NOTE Confidence: 0.839311301708221

00:43:15.480 --> 00:43:16.650 multiple prior treatments.

NOTE Confidence: 0.839311301708221
00:43:16.650 --> 00:43:18.214 As you can see,
NOTE Confidence: 0.839311301708221
00:43:18.214 --> 00:43:20.560 starting with a an aggressive combination.
NOTE Confidence: 0.839311301708221
00:43:20.560 --> 00:43:22.216 Chemotherapy than a vaccine
NOTE Confidence: 0.839311301708221
00:43:22.216 --> 00:43:23.458 that checkpoint modulator.
NOTE Confidence: 0.839311301708221
00:43:23.460 --> 00:43:23.874 Then,
NOTE Confidence: 0.839311301708221
00:43:23.874 --> 00:43:25.530 in another aggressive chemotherapy,
NOTE Confidence: 0.839311301708221
00:43:25.530 --> 00:43:27.555 progress through all of these
NOTE Confidence: 0.839311301708221
00:43:27.555 --> 00:43:30.503 until he came to the surgery branch
NOTE Confidence: 0.839311301708221
00:43:30.503 --> 00:43:33.450 NCI in May of 2009 for treatment
NOTE Confidence: 0.839311301708221
00:43:33.450 --> 00:43:35.979 with his own autologous cells.
NOTE Confidence: 0.839311301708221
00:43:35.980 --> 00:43:38.675 Into which an anti CD 19 Chimeric
NOTE Confidence: 0.839311301708221
00:43:38.675 --> 00:43:40.875 Antigen Receptor was transduced and
NOTE Confidence: 0.839311301708221
00:43:40.875 --> 00:43:43.767 despite all of these prior recurrences,
NOTE Confidence: 0.839311301708221
00:43:43.770 --> 00:43:46.062 he underwent a complete regression and
NOTE Confidence: 0.839311301708221
00:43:46.062 --> 00:43:48.644 is an on going complete progression
NOTE Confidence: 0.839311301708221

00:43:48.644 --> 00:43:52.003 free survival over 10 years later and
NOTE Confidence: 0.839311301708221

00:43:52.003 --> 00:43:54.870 this showed in fact that very large
NOTE Confidence: 0.839311301708221

00:43:54.870 --> 00:43:58.498 amounts of tumor can be can be progressed.
NOTE Confidence: 0.839311301708221

00:43:58.500 --> 00:44:02.046 You see here in these slides on the left
NOTE Confidence: 0.839311301708221

00:44:02.046 --> 00:44:05.857 the media steinem had a large tumor mass,
NOTE Confidence: 0.839311301708221

00:44:05.860 --> 00:44:06.308 the.
NOTE Confidence: 0.839311301708221

00:44:06.308 --> 00:44:08.548 Second down on the right,
NOTE Confidence: 0.839311301708221

00:44:08.550 --> 00:44:11.175 another large mediastinal mass you
NOTE Confidence: 0.839311301708221

00:44:11.175 --> 00:44:14.910 see in the third slide down large.
NOTE Confidence: 0.839311301708221

00:44:14.910 --> 00:44:15.353 Again,
NOTE Confidence: 0.839311301708221

00:44:15.353 --> 00:44:17.568 shown by these yellow arrows,
NOTE Confidence: 0.839311301708221

00:44:17.570 --> 00:44:20.228 large lymph lymph nodes that are
NOTE Confidence: 0.839311301708221

00:44:20.228 --> 00:44:21.557 surrounding the aorta,
NOTE Confidence: 0.839311301708221

00:44:21.560 --> 00:44:24.486 vena cava and finally a very large
NOTE Confidence: 0.839311301708221

00:44:24.486 --> 00:44:27.310 spleen and large iliac lymph nodes,
NOTE Confidence: 0.839311301708221

00:44:27.310 --> 00:44:30.500 all of which regressed completely.

NOTE Confidence: 0.839311301708221
00:44:30.500 --> 00:44:32.656 Bone marrow is full of tumor cells
NOTE Confidence: 0.839311301708221
00:44:32.656 --> 00:44:35.544 that you see on the left and they
NOTE Confidence: 0.839311301708221
00:44:35.544 --> 00:44:37.060 disappeared completely as well.
NOTE Confidence: 0.839311301708221
00:44:37.060 --> 00:44:39.823 But there was a price to pay for this
NOTE Confidence: 0.839311301708221
00:44:39.823 --> 00:44:42.419 because these car T cells recognized CD
NOTE Confidence: 0.839311301708221
00:44:42.419 --> 00:44:44.988 19 that's present than normal B cells,
NOTE Confidence: 0.839311301708221
00:44:44.990 --> 00:44:47.328 and it's just as easy to eliminate
NOTE Confidence: 0.839311301708221
00:44:47.328 --> 00:44:49.801 a normal cell as a tumor cell
NOTE Confidence: 0.839311301708221
00:44:49.801 --> 00:44:51.193 when cells are reacting,
NOTE Confidence: 0.839311301708221
00:44:51.200 --> 00:44:52.930 and as you can see,
NOTE Confidence: 0.839311301708221
00:44:52.930 --> 00:44:54.805 these B cells disappeared completely
NOTE Confidence: 0.839311301708221
00:44:54.805 --> 00:44:57.357 at a time when the normal T
NOTE Confidence: 0.839311301708221
00:44:57.357 --> 00:44:59.478 cells as you see in the bottom,
NOTE Confidence: 0.839311301708221
00:44:59.480 --> 00:45:01.610 recovered completely after about 8 days.
NOTE Confidence: 0.839311301708221
00:45:01.610 --> 00:45:04.270 And the natural killer cells were covered.
NOTE Confidence: 0.839311301708221

00:45:04.270 --> 00:45:07.710 It took about 7 or 8 months for
NOTE Confidence: 0.839311301708221

00:45:07.710 --> 00:45:11.596 the B cells to recover as well.
NOTE Confidence: 0.839311301708221

00:45:11.600 --> 00:45:14.740 We went on to treat a large number
NOTE Confidence: 0.839311301708221

00:45:14.740 --> 00:45:17.619 of patients in the surgery branch.
NOTE Confidence: 0.839311301708221

00:45:17.620 --> 00:45:21.466 You see a about a 50% complete response rate.
NOTE Confidence: 0.839311301708221

00:45:21.466 --> 00:45:23.998 Kite Pharma then performed a multi
NOTE Confidence: 0.839311301708221

00:45:23.998 --> 00:45:25.360 institutional study received.
NOTE Confidence: 0.839311301708221

00:45:25.360 --> 00:45:27.240 Gotta almost identical results.
NOTE Confidence: 0.839311301708221

00:45:27.240 --> 00:45:29.590 We then transferred our technology
NOTE Confidence: 0.839311301708221

00:45:29.590 --> 00:45:31.741 in a cooperative research agreement
NOTE Confidence: 0.839311301708221

00:45:31.741 --> 00:45:35.022 to Kite Pharma in 2012 and 2017 they
NOTE Confidence: 0.839311301708221

00:45:35.022 --> 00:45:37.017 received FDA approval for this,
NOTE Confidence: 0.839311301708221

00:45:37.020 --> 00:45:39.498 and this then received a fair
NOTE Confidence: 0.839311301708221

00:45:39.498 --> 00:45:41.583 amount of publicity because in
NOTE Confidence: 0.839311301708221

00:45:41.583 --> 00:45:44.068 2017 kite was sold to ghillic add
NOTE Confidence: 0.839311301708221

00:45:44.068 --> 00:45:46.380 Sciences for 11.9 million dollars,

NOTE Confidence: 0.839311301708221

00:45:46.380 --> 00:45:49.085 just five years after this

NOTE Confidence: 0.839311301708221

00:45:49.085 --> 00:45:51.790 technology was transferred to do

NOTE Confidence: 0.874750733375549

00:45:51.891 --> 00:45:53.490 that. So this treatment,

NOTE Confidence: 0.874750733375549

00:45:53.490 --> 00:45:55.760 which can reduce the number of

NOTE Confidence: 0.874750733375549

00:45:55.760 --> 00:45:57.660 normal cells expressing CD 19,

NOTE Confidence: 0.874750733375549

00:45:57.660 --> 00:45:59.615 is now available for treatment

NOTE Confidence: 0.874750733375549

00:45:59.615 --> 00:46:01.570 around the United States face

NOTE Confidence: 0.874750733375549

00:46:01.635 --> 00:46:03.717 and beginning in Europe as well.

NOTE Confidence: 0.874750733375549

00:46:03.720 --> 00:46:06.212 But here we see the cancer deaths

NOTE Confidence: 0.874750733375549

00:46:06.212 --> 00:46:08.648 in the United States last year.

NOTE Confidence: 0.874750733375549

00:46:08.650 --> 00:46:12.314 As you can see, 600,000 deaths in total.

NOTE Confidence: 0.874750733375549

00:46:12.320 --> 00:46:14.620 About 10% or 58 thousand

NOTE Confidence: 0.874750733375549

00:46:14.620 --> 00:46:16.920 were of the humid logic.

NOTE Confidence: 0.874750733375549

00:46:16.920 --> 00:46:18.348 The blood cancers,

NOTE Confidence: 0.874750733375549

00:46:18.348 --> 00:46:21.204 but the solid epithelial cancers accounted

NOTE Confidence: 0.874750733375549

00:46:21.204 --> 00:46:26.318 for 90% of all of all cancer deaths.
NOTE Confidence: 0.874750733375549

00:46:26.320 --> 00:46:28.546 And so the major challenge that's
NOTE Confidence: 0.874750733375549

00:46:28.546 --> 00:46:30.470 confronting oncologix as a whole.
NOTE Confidence: 0.874750733375549

00:46:30.470 --> 00:46:32.090 But certainly cancer immunotherapy,
NOTE Confidence: 0.874750733375549

00:46:32.090 --> 00:46:34.520 is the development of effective immune
NOTE Confidence: 0.874750733375549

00:46:34.576 --> 00:46:36.904 or therapies for patients with metastatic
NOTE Confidence: 0.874750733375549

00:46:36.904 --> 00:46:38.810 epithelial solid cancers that cannot
NOTE Confidence: 0.874750733375549

00:46:38.810 --> 00:46:40.646 be cured by any available treatment
NOTE Confidence: 0.874750733375549

00:46:40.646 --> 00:46:43.290 and result in 90% of cancer deaths.
NOTE Confidence: 0.874750733375549

00:46:43.290 --> 00:46:43.666 Again,
NOTE Confidence: 0.874750733375549

00:46:43.666 --> 00:46:45.546 these epithelial cancers have ducts.
NOTE Confidence: 0.874750733375549

00:46:45.550 --> 00:46:47.872 The lining of the Ducks are
NOTE Confidence: 0.874750733375549

00:46:47.872 --> 00:46:50.070 constantly turning over as they do.
NOTE Confidence: 0.874750733375549

00:46:50.070 --> 00:46:52.401 Mistakes are made in the DNA called
NOTE Confidence: 0.874750733375549

00:46:52.401 --> 00:46:54.333 mutations and its accumulation of
NOTE Confidence: 0.874750733375549

00:46:54.333 --> 00:46:56.925 mutations that actually results in the.

NOTE Confidence: 0.874750733375549
00:46:56.930 --> 00:46:57.719 And the cancer.
NOTE Confidence: 0.853808879852295
00:47:00.240 --> 00:47:02.985 So will car T cells be useful for the
NOTE Confidence: 0.853808879852295
00:47:02.985 --> 00:47:05.180 treatment of solid epithelial cancers?
NOTE Confidence: 0.853808879852295
00:47:05.180 --> 00:47:08.004 Certainly not based on what we know now.
NOTE Confidence: 0.853808879852295
00:47:08.010 --> 00:47:10.537 Car T cells require the use of
NOTE Confidence: 0.853808879852295
00:47:10.537 --> 00:47:12.114 monoclonal antibodies that recognize
NOTE Confidence: 0.853808879852295
00:47:12.114 --> 00:47:14.229 molecules on the cell surface.
NOTE Confidence: 0.853808879852295
00:47:14.230 --> 00:47:15.994 These monoclonal antibodies were
NOTE Confidence: 0.853808879852295
00:47:15.994 --> 00:47:18.640 first described by Kohler and Milstein
NOTE Confidence: 0.853808879852295
00:47:18.706 --> 00:47:20.818 45 years ago in a paper in nature.
NOTE Confidence: 0.853808879852295
00:47:20.820 --> 00:47:23.548 But there are two major problems as we
NOTE Confidence: 0.853808879852295
00:47:23.548 --> 00:47:26.307 look to apply this to solid tumors.
NOTE Confidence: 0.853808879852295
00:47:26.310 --> 00:47:28.290 There's been no monoclonal antibody
NOTE Confidence: 0.853808879852295
00:47:28.290 --> 00:47:29.874 ever identified that recognizes
NOTE Confidence: 0.853808879852295
00:47:29.874 --> 00:47:31.873 cell surface molecules that are
NOTE Confidence: 0.853808879852295

00:47:31.873 --> 00:47:33.413 unique to epithelial cancers.
NOTE Confidence: 0.853808879852295

00:47:33.420 --> 00:47:34.728 And as I mentioned,
NOTE Confidence: 0.853808879852295

00:47:34.728 --> 00:47:37.568 it's just as easy to kill these normal
NOTE Confidence: 0.853808879852295

00:47:37.568 --> 00:47:39.968 cells as there are tumor cells,
NOTE Confidence: 0.853808879852295

00:47:39.970 --> 00:47:42.184 and so the destruction of essential
NOTE Confidence: 0.853808879852295

00:47:42.184 --> 00:47:44.775 organs when using our T cells as
NOTE Confidence: 0.853808879852295

00:47:44.775 --> 00:47:46.515 a major major potential problem.
NOTE Confidence: 0.900330066680908

00:47:49.120 --> 00:47:51.850 And so it's mainly the use of
NOTE Confidence: 0.900330066680908

00:47:51.850 --> 00:47:54.330 conventional T cells with T cell
NOTE Confidence: 0.900330066680908

00:47:54.330 --> 00:47:57.494 receptors that I think have the highest
NOTE Confidence: 0.900330066680908

00:47:57.494 --> 00:47:59.908 likelihood of being effective in
NOTE Confidence: 0.900330066680908

00:47:59.908 --> 00:48:02.764 the treatment of these solid tumors.
NOTE Confidence: 0.900330066680908

00:48:02.770 --> 00:48:04.612 I'm going to concentrate remarks on
NOTE Confidence: 0.900330066680908

00:48:04.612 --> 00:48:07.030 the on the solid epithelial cancers,
NOTE Confidence: 0.900330066680908

00:48:07.030 --> 00:48:09.452 but we've learned so much from the
NOTE Confidence: 0.900330066680908

00:48:09.452 --> 00:48:11.486 treatment of Melanoma that we're now

NOTE Confidence: 0.900330066680908
00:48:11.486 --> 00:48:13.649 applying that I'd like to just very
NOTE Confidence: 0.900330066680908
00:48:13.717 --> 00:48:16.489 briefly review our results of 190 four
NOTE Confidence: 0.900330066680908
00:48:16.489 --> 00:48:18.390 consecutive patients that were treated
NOTE Confidence: 0.900330066680908
00:48:18.390 --> 00:48:20.520 with the patients own autologous tumor,
NOTE Confidence: 0.900330066680908
00:48:20.520 --> 00:48:21.230 infiltrating lymphocytes,
NOTE Confidence: 0.900330066680908
00:48:21.230 --> 00:48:23.966 and you can see a 55% recist objective
NOTE Confidence: 0.900330066680908
00:48:23.966 --> 00:48:26.390 response rate with about 1/4 of the patients
NOTE Confidence: 0.900330066680908
00:48:26.441 --> 00:48:28.329 undergoing complete durable responses,
NOTE Confidence: 0.900330066680908
00:48:28.330 --> 00:48:30.370 and this provided a valuable resource
NOTE Confidence: 0.900330066680908
00:48:30.370 --> 00:48:33.244 because we had about half of patients that
NOTE Confidence: 0.900330066680908
00:48:33.244 --> 00:48:35.422 were responding and half not responding,
NOTE Confidence: 0.900330066680908
00:48:35.430 --> 00:48:36.630 that enabled us.
NOTE Confidence: 0.900330066680908
00:48:36.630 --> 00:48:39.948 To do experiments to try to identify the
NOTE Confidence: 0.900330066680908
00:48:39.948 --> 00:48:42.600 reasons for response or non response,
NOTE Confidence: 0.900330066680908
00:48:42.600 --> 00:48:45.198 I should mention that of these
NOTE Confidence: 0.900330066680908

00:48:45.198 --> 00:48:46.497 46 complete responders,
NOTE Confidence: 0.900330066680908
00:48:46.500 --> 00:48:49.964 44 of them received just a single treatment.
NOTE Confidence: 0.900330066680908
00:48:49.970 --> 00:48:50.435 Again,
NOTE Confidence: 0.900330066680908
00:48:50.435 --> 00:48:53.225 it's a living treatment of cells
NOTE Confidence: 0.900330066680908
00:48:53.225 --> 00:48:55.853 can expand 10,000 fold over the
NOTE Confidence: 0.900330066680908
00:48:55.853 --> 00:48:58.534 first 2 weeks and patrol the body
NOTE Confidence: 0.900330066680908
00:48:58.622 --> 00:49:02.480 looking for their target antigens.
NOTE Confidence: 0.900330066680908
00:49:02.480 --> 00:49:05.168 But without the cell therapy with
NOTE Confidence: 0.900330066680908
00:49:05.168 --> 00:49:07.456 till therefore appears able to
NOTE Confidence: 0.900330066680908
00:49:07.456 --> 00:49:09.536 eliminate the last Melanoma so.
NOTE Confidence: 0.900330066680908
00:49:09.540 --> 00:49:11.972 And that then leads to the question of
NOTE Confidence: 0.900330066680908
00:49:11.972 --> 00:49:14.521 what till recognize that enables the in
NOTE Confidence: 0.900330066680908
00:49:14.521 --> 00:49:17.349 vivo destruction of this last Melanoma cell.
NOTE Confidence: 0.900330066680908
00:49:17.350 --> 00:49:19.718 And it was the clue that I mentioned
NOTE Confidence: 0.900330066680908
00:49:19.718 --> 00:49:22.058 here on the bottom of this slide,
NOTE Confidence: 0.900330066680908
00:49:22.060 --> 00:49:23.260 that specific cancer regression,

NOTE Confidence: 0.900330066680908

00:49:23.260 --> 00:49:25.446 in the absence of off tumor on

NOTE Confidence: 0.900330066680908

00:49:25.446 --> 00:49:26.766 target toxicities in patients.

NOTE Confidence: 0.900330066680908

00:49:26.770 --> 00:49:29.794 Let us to explore the role of specific

NOTE Confidence: 0.900330066680908

00:49:29.794 --> 00:49:32.206 cancer mutations as the targets of till.

NOTE Confidence: 0.900330066680908

00:49:32.210 --> 00:49:34.886 Because it's these mutations that actually

NOTE Confidence: 0.900330066680908

00:49:34.886 --> 00:49:37.829 causes the cancer and of course will

NOTE Confidence: 0.900330066680908

00:49:37.829 --> 00:49:40.363 not be expressed will be president or

NOTE Confidence: 0.900330066680908

00:49:40.440 --> 00:49:43.020 expressed in normal and normal cells.

NOTE Confidence: 0.900330066680908

00:49:43.020 --> 00:49:45.075 Adjust a point very important to

NOTE Confidence: 0.900330066680908

00:49:45.075 --> 00:49:47.246 understand as we mine the cancer

NOTE Confidence: 0.900330066680908

00:49:47.246 --> 00:49:49.808 exomes that is all expressed cells

NOTE Confidence: 0.900330066680908

00:49:49.808 --> 00:49:51.514 to identify immunogenic cancer

NOTE Confidence: 0.900330066680908

00:49:51.514 --> 00:49:53.999 mutations and that is for a mutation

NOTE Confidence: 0.900330066680908

00:49:53.999 --> 00:49:56.610 product to be a cancer antigen.

NOTE Confidence: 0.900330066680908

00:49:56.610 --> 00:49:59.460 It has to be processed intracellularly

NOTE Confidence: 0.900330066680908

00:49:59.548 --> 00:50:02.284 into a 9 or 11 amino acid peptide.
NOTE Confidence: 0.900330066680908

00:50:02.290 --> 00:50:06.130 And that pep side ask to fit and be presented
NOTE Confidence: 0.900330066680908

00:50:06.219 --> 00:50:09.379 in the groove of one of the patients.
NOTE Confidence: 0.900330066680908

00:50:09.380 --> 00:50:11.918 Surface MFC molecules and therefore only
NOTE Confidence: 0.900330066680908

00:50:11.918 --> 00:50:14.752 rare mutations are going to be antigenic
NOTE Confidence: 0.900330066680908

00:50:14.752 --> 00:50:17.258 because they have to fulfill these two.
NOTE Confidence: 0.900330066680908

00:50:17.260 --> 00:50:18.346 These two properties.
NOTE Confidence: 0.900330066680908

00:50:18.346 --> 00:50:20.880 And so we developed an assay to
NOTE Confidence: 0.900330066680908

00:50:20.949 --> 00:50:23.409 identify mutation reactive cells in
NOTE Confidence: 0.900330066680908

00:50:23.409 --> 00:50:25.869 common epithelial cancers that would
NOTE Confidence: 0.900330066680908

00:50:25.937 --> 00:50:28.135 enable us to identify not only to
NOTE Confidence: 0.900330066680908

00:50:28.135 --> 00:50:30.688 sell but the antigen being recognized.
NOTE Confidence: 0.900330066680908

00:50:30.688 --> 00:50:33.904 And if you follow this cartoon
NOTE Confidence: 0.900330066680908

00:50:33.904 --> 00:50:36.284 gastrointestinal tumor deposit or an
NOTE Confidence: 0.900330066680908

00:50:36.284 --> 00:50:38.930 epithelial cancer deposit is for sected,
NOTE Confidence: 0.900330066680908

00:50:38.930 --> 00:50:41.720 we isolate genomic DNA and RNA.

NOTE Confidence: 0.900330066680908

00:50:41.720 --> 00:50:44.858 We identify the whole exome and

NOTE Confidence: 0.900330066680908

00:50:44.858 --> 00:50:46.950 transcriptome sequencing to identify

NOTE Confidence: 0.900330066680908

00:50:47.027 --> 00:50:49.283 every mutation in the cell by

NOTE Confidence: 0.900330066680908

00:50:49.283 --> 00:50:51.949 comparing it to the normal genome.

NOTE Confidence: 0.900330066680908

00:50:51.950 --> 00:50:54.968 That can be accomplished in a

NOTE Confidence: 0.900330066680908

00:50:54.968 --> 00:50:57.680 laboratory in about 2 weeks.

NOTE Confidence: 0.900330066680908

00:50:57.680 --> 00:51:01.586 We then Spencer synthesize all of the

NOTE Confidence: 0.900330066680908

00:51:01.586 --> 00:51:05.799 mini genes that encode these mutations.

NOTE Confidence: 0.900330066680908

00:51:05.800 --> 00:51:09.646 Or identify peptides that encode the

NOTE Confidence: 0.900330066680908

00:51:09.646 --> 00:51:13.619 mutations that represent 25 Mer peptides.

NOTE Confidence: 0.900330066680908

00:51:13.620 --> 00:51:14.973 With the mutated.

NOTE Confidence: 0.900330066680908

00:51:14.973 --> 00:51:18.130 Amino acid in the middle of that,

NOTE Confidence: 0.825791776180268

00:51:18.130 --> 00:51:21.525 25 more. We then express those tandem.

NOTE Confidence: 0.825791776180268

00:51:21.530 --> 00:51:23.385 Any jeans or peptides representing

NOTE Confidence: 0.825791776180268

00:51:23.385 --> 00:51:25.742 every mutation in the patient's own

NOTE Confidence: 0.825791776180268

00:51:25.742 --> 00:51:27.498 autologous antigen presenting cell,
NOTE Confidence: 0.825791776180268

00:51:27.500 --> 00:51:30.604 and so any mutations that can be presented
NOTE Confidence: 0.825791776180268

00:51:30.604 --> 00:51:33.291 will be presented on the surface
NOTE Confidence: 0.825791776180268

00:51:33.291 --> 00:51:36.039 of that patients on MFC molecules.
NOTE Confidence: 0.825791776180268

00:51:36.040 --> 00:51:38.120 We then expand till and
NOTE Confidence: 0.825791776180268

00:51:38.120 --> 00:51:39.784 used in these melanin.
NOTE Confidence: 0.825791776180268

00:51:39.790 --> 00:51:42.075 These experiments till that mediated
NOTE Confidence: 0.825791776180268

00:51:42.075 --> 00:51:44.360 complete durable regressions as I've
NOTE Confidence: 0.825791776180268

00:51:44.428 --> 00:51:46.794 shown before and when they are code
NOTE Confidence: 0.825791776180268

00:51:46.794 --> 00:51:49.379 incubated with the antigen presenting cell.
NOTE Confidence: 0.825791776180268

00:51:49.380 --> 00:51:51.672 If any antigens are recognized we
NOTE Confidence: 0.825791776180268

00:51:51.672 --> 00:51:54.342 can detect them by using interferon
NOTE Confidence: 0.825791776180268

00:51:54.342 --> 00:51:56.992 gamma elispot assays or upregulation
NOTE Confidence: 0.825791776180268

00:51:56.992 --> 00:51:59.687 of Owenby Bierocks 40 activation
NOTE Confidence: 0.825791776180268

00:51:59.687 --> 00:52:01.747 molecules by flow cytometry.
NOTE Confidence: 0.825791776180268

00:52:01.750 --> 00:52:03.530 Again, it's the 25 more.

NOTE Confidence: 0.825791776180268
00:52:03.530 --> 00:52:05.310 That's the key to this.
NOTE Confidence: 0.825791776180268
00:52:05.310 --> 00:52:07.375 With the mutation in the middle because
NOTE Confidence: 0.825791776180268
00:52:07.375 --> 00:52:09.557 it has to encompass every peptide
NOTE Confidence: 0.825791776180268
00:52:09.557 --> 00:52:12.427 possibly presented by that by that mutation.
NOTE Confidence: 0.825791776180268
00:52:12.430 --> 00:52:14.728 This mutated amino acid can be
NOTE Confidence: 0.825791776180268
00:52:14.728 --> 00:52:17.409 the first of the 9 or 10 more.
NOTE Confidence: 0.825791776180268
00:52:17.410 --> 00:52:21.330 It can be the last of the 9 or 10 more,
NOTE Confidence: 0.825791776180268
00:52:21.330 --> 00:52:23.466 but there's no need to predict
NOTE Confidence: 0.825791776180268
00:52:23.466 --> 00:52:24.178 peptide binding.
NOTE Confidence: 0.825791776180268
00:52:24.180 --> 00:52:26.651 Every candidate peptide and all them HC
NOTE Confidence: 0.825791776180268
00:52:26.651 --> 00:52:29.518 of the patients are included in the screen,
NOTE Confidence: 0.825791776180268
00:52:29.520 --> 00:52:31.968 and there's no tumor cell line
NOTE Confidence: 0.825791776180268
00:52:31.968 --> 00:52:34.230 necessary to do these assays.
NOTE Confidence: 0.825791776180268
00:52:34.230 --> 00:52:34.566 Well,
NOTE Confidence: 0.825791776180268
00:52:34.566 --> 00:52:36.918 we perform this in 20 two consecutive
NOTE Confidence: 0.825791776180268

00:52:36.918 --> 00:52:38.829 patients with metastatic Melanoma.
NOTE Confidence: 0.825791776180268

00:52:38.830 --> 00:52:41.217 They had a total of those patients
NOTE Confidence: 0.825791776180268

00:52:41.217 --> 00:52:43.808 had a total of 13,000 mutations,
NOTE Confidence: 0.825791776180268

00:52:43.810 --> 00:52:47.062 but we screened about 4000 that
NOTE Confidence: 0.825791776180268

00:52:47.062 --> 00:52:48.146 were expressed.
NOTE Confidence: 0.825791776180268

00:52:48.150 --> 00:52:49.254 In the cell,
NOTE Confidence: 0.825791776180268

00:52:49.254 --> 00:52:52.937 based on the RNA seq data that led to
NOTE Confidence: 0.825791776180268

00:52:52.937 --> 00:52:55.467 the identification of 54 immunogenic
NOTE Confidence: 0.825791776180268

00:52:55.467 --> 00:52:58.316 neo epitopes at 82% of Melanoma,
NOTE Confidence: 0.825791776180268

00:52:58.316 --> 00:53:00.781 pets of patients have these
NOTE Confidence: 0.825791776180268

00:53:00.781 --> 00:53:03.150 mute these antigenic mutations.
NOTE Confidence: 0.825791776180268

00:53:03.150 --> 00:53:05.915 About 1.4% of all of the mutations
NOTE Confidence: 0.825791776180268

00:53:05.915 --> 00:53:08.186 were recognized and almost exclusively
NOTE Confidence: 0.825791776180268

00:53:08.186 --> 00:53:11.204 by CD8 cells and quite surprisingly,
NOTE Confidence: 0.825791776180268

00:53:11.210 --> 00:53:14.346 all of these 54 neoantigens were unique.
NOTE Confidence: 0.825791776180268

00:53:14.350 --> 00:53:18.438 None were shared among any Melanoma patient.

NOTE Confidence: 0.825791776180268
00:53:18.440 --> 00:53:21.688 Among any Melanoma patients.
NOTE Confidence: 0.825791776180268
00:53:21.690 --> 00:53:24.672 We then extended this 230 patients
NOTE Confidence: 0.825791776180268
00:53:24.672 --> 00:53:26.163 consecutive patients with
NOTE Confidence: 0.825791776180268
00:53:26.163 --> 00:53:27.250 gastrointestinal cancers.
NOTE Confidence: 0.825791776180268
00:53:27.250 --> 00:53:30.274 About 80% of these patients had
NOTE Confidence: 0.825791776180268
00:53:30.274 --> 00:53:32.290 immunogenic mutations that were
NOTE Confidence: 0.825791776180268
00:53:32.370 --> 00:53:35.328 recognized by the patients own cells.
NOTE Confidence: 0.825791776180268
00:53:35.330 --> 00:53:37.535 We screamed about 15,000 of
NOTE Confidence: 0.825791776180268
00:53:37.535 --> 00:53:39.740 these mutations to identify 210
NOTE Confidence: 0.825791776180268
00:53:39.819 --> 00:53:41.389 immunogenic epitopes.
NOTE Confidence: 0.825791776180268
00:53:41.390 --> 00:53:41.894 Again,
NOTE Confidence: 0.825791776180268
00:53:41.894 --> 00:53:46.250 only one point 3% of all of the
NOTE Confidence: 0.825791776180268
00:53:46.250 --> 00:53:48.590 mutations were actually immunogenic.
NOTE Confidence: 0.825791776180268
00:53:48.590 --> 00:53:50.778 And interesting Lee in
NOTE Confidence: 0.825791776180268
00:53:50.778 --> 00:53:52.419 the epithelial cancers?
NOTE Confidence: 0.825791776180268

00:53:52.420 --> 00:53:55.605 Almost half of these antigens are recognized

NOTE Confidence: 0.825791776180268

00:53:55.605 --> 00:53:58.808 by CD4 cells and half by CDA cells.

NOTE Confidence: 0.825791776180268

00:53:58.810 --> 00:54:01.596 In contrast to the CD 8 recognition

NOTE Confidence: 0.825791776180268

00:54:01.596 --> 00:54:03.789 in melanomas and once again

NOTE Confidence: 0.825791776180268

00:54:03.789 --> 00:54:05.625 of these 210 Neoantigens,

NOTE Confidence: 0.825791776180268

00:54:05.630 --> 00:54:09.277 all were completely unique to that patient.

NOTE Confidence: 0.825791776180268

00:54:09.280 --> 00:54:11.849 Except for two patients who shared the

NOTE Confidence: 0.825791776180268

00:54:11.849 --> 00:54:14.294 same cave rats immuno genic mutation

NOTE Confidence: 0.825791776180268

00:54:14.294 --> 00:54:16.832 that was restricted by the class.

NOTE Confidence: 0.825791776180268

00:54:16.840 --> 00:54:19.728 One antigen CW 0802.

NOTE Confidence: 0.825791776180268

00:54:19.730 --> 00:54:20.580 Back then,

NOTE Confidence: 0.825791776180268

00:54:20.580 --> 00:54:24.840 Let us do not only look at the GI cancers,

NOTE Confidence: 0.825791776180268

00:54:24.840 --> 00:54:29.100 but is UK and see in the left breast cancers,

NOTE Confidence: 0.825791776180268

00:54:29.100 --> 00:54:31.172 colon cancers, ovarian cancers,

NOTE Confidence: 0.825791776180268

00:54:31.172 --> 00:54:32.208 prostate cancer.

NOTE Confidence: 0.825791776180268

00:54:32.210 --> 00:54:36.347 In 195 consecutive patients that we studied.

NOTE Confidence: 0.825791776180268
00:54:36.350 --> 00:54:36.875 77%,
NOTE Confidence: 0.825791776180268
00:54:36.875 --> 00:54:38.975 regardless of the Histology
NOTE Confidence: 0.825791776180268
00:54:38.975 --> 00:54:42.256 appeared to contain T cells that
NOTE Confidence: 0.825791776180268
00:54:42.256 --> 00:54:45.096 recognize antigens on that cancer,
NOTE Confidence: 0.825791776180268
00:54:45.100 --> 00:54:48.376 that was a total of 360.
NOTE Confidence: 0.825791776180268
00:54:48.380 --> 00:54:52.316 Three immunogenic neoantigens and once again.
NOTE Confidence: 0.825791776180268
00:54:52.320 --> 00:54:53.014 Repeated story,
NOTE Confidence: 0.825791776180268
00:54:53.014 --> 00:54:55.096 all of these were unique except
NOTE Confidence: 0.825791776180268
00:54:55.096 --> 00:54:57.826 for 2K grass antigens expressed on
NOTE Confidence: 0.825791776180268
00:54:57.826 --> 00:54:59.790 a particular restriction element.
NOTE Confidence: 0.825791776180268
00:54:59.790 --> 00:55:02.628 We're the only ones shared except
NOTE Confidence: 0.825791776180268
00:55:02.628 --> 00:55:04.047 for those two.
NOTE Confidence: 0.851911008358002
00:55:04.050 --> 00:55:06.390 All of the remaining neoantigens were
NOTE Confidence: 0.851911008358002
00:55:06.390 --> 00:55:09.210 completely unique to the individual patient.
NOTE Confidence: 0.879645943641663
00:55:11.490 --> 00:55:13.740 Now, an advantage of targeting
NOTE Confidence: 0.879645943641663

00:55:13.740 --> 00:55:15.540 mutations is its applicability
NOTE Confidence: 0.879645943641663

00:55:15.540 --> 00:55:18.108 to target multiple cancer types.
NOTE Confidence: 0.879645943641663

00:55:18.110 --> 00:55:20.222 Now, most patients that were attempting
NOTE Confidence: 0.879645943641663

00:55:20.222 --> 00:55:22.564 to treat with these selected cells
NOTE Confidence: 0.879645943641663

00:55:22.564 --> 00:55:24.739 that recognize the mutated antigens.
NOTE Confidence: 0.879645943641663

00:55:24.740 --> 00:55:26.690 Most patients do not respond,
NOTE Confidence: 0.879645943641663

00:55:26.690 --> 00:55:30.200 then I'll go to the numbers in a minute,
NOTE Confidence: 0.879645943641663

00:55:30.200 --> 00:55:33.120 but I want to emphasize the advantage of
NOTE Confidence: 0.879645943641663

00:55:33.120 --> 00:55:35.646 this approach because it's not specific
NOTE Confidence: 0.879645943641663

00:55:35.646 --> 00:55:37.806 to any individual cancer diagnosis
NOTE Confidence: 0.879645943641663

00:55:37.806 --> 00:55:40.340 and let me show you some examples.
NOTE Confidence: 0.879645943641663

00:55:40.340 --> 00:55:43.007 The first patient that ever responded to
NOTE Confidence: 0.879645943641663

00:55:43.007 --> 00:55:46.478 the use of cells selected for reactivity.
NOTE Confidence: 0.879645943641663

00:55:46.480 --> 00:55:48.335 To these immunogenic mutations and
NOTE Confidence: 0.879645943641663

00:55:48.335 --> 00:55:50.824 we're still learning on how to best
NOTE Confidence: 0.879645943641663

00:55:50.824 --> 00:55:52.546 select those cells with a patient

NOTE Confidence: 0.879645943641663
00:55:52.546 --> 00:55:54.454 with a metastatic cholangio carcinoma
NOTE Confidence: 0.879645943641663
00:55:54.454 --> 00:55:56.998 should have detected me Jed resection
NOTE Confidence: 0.879645943641663
00:55:56.998 --> 00:55:58.890 of lung and liver metastases.
NOTE Confidence: 0.879645943641663
00:55:58.890 --> 00:56:00.350 She had received multiple
NOTE Confidence: 0.879645943641663
00:56:00.350 --> 00:56:01.080 chemotherapy regiments.
NOTE Confidence: 0.879645943641663
00:56:01.080 --> 00:56:03.690 We treated our first with unselected
NOTE Confidence: 0.879645943641663
00:56:03.690 --> 00:56:06.429 till from a resected lung lesion.
NOTE Confidence: 0.879645943641663
00:56:06.430 --> 00:56:08.050 She did not respond.
NOTE Confidence: 0.879645943641663
00:56:08.050 --> 00:56:10.480 We then used our tandem minigene
NOTE Confidence: 0.879645943641663
00:56:10.557 --> 00:56:12.657 and peptide approach to select
NOTE Confidence: 0.879645943641663
00:56:12.657 --> 00:56:14.757 cells to treat her with.
NOTE Confidence: 0.879645943641663
00:56:14.760 --> 00:56:17.800 She had a unique population of cells at
NOTE Confidence: 0.879645943641663
00:56:17.800 --> 00:56:20.758 targeted the nerby two IP cancer mutation,
NOTE Confidence: 0.879645943641663
00:56:20.760 --> 00:56:23.301 one of 26 mutations that we screen
NOTE Confidence: 0.879645943641663
00:56:23.301 --> 00:56:25.958 and this patient underwent a complete,
NOTE Confidence: 0.879645943641663

00:56:25.960 --> 00:56:26.800 durable regression.
NOTE Confidence: 0.879645943641663

00:56:26.800 --> 00:56:30.160 Now I'm going over seven years later you
NOTE Confidence: 0.879645943641663

00:56:30.236 --> 00:56:32.756 see the lung metastases on the left,
NOTE Confidence: 0.879645943641663

00:56:32.760 --> 00:56:33.924 which disappeared completely.
NOTE Confidence: 0.879645943641663

00:56:33.924 --> 00:56:36.640 She also had three liver metastases at
NOTE Confidence: 0.879645943641663

00:56:36.703 --> 00:56:38.758 disappeared completely on the right.
NOTE Confidence: 0.879645943641663

00:56:38.760 --> 00:56:41.329 That's just a whole left in the
NOTE Confidence: 0.879645943641663

00:56:41.329 --> 00:56:43.433 liver following the elimination of
NOTE Confidence: 0.879645943641663

00:56:43.433 --> 00:56:44.816 that meta static.
NOTE Confidence: 0.879645943641663

00:56:44.820 --> 00:56:45.420 Composite.
NOTE Confidence: 0.86041384935379

00:56:48.800 --> 00:56:51.176 This is a patient with a breast
NOTE Confidence: 0.86041384935379

00:56:51.176 --> 00:56:53.870 cancer who showed a dramatic response.
NOTE Confidence: 0.86041384935379

00:56:53.870 --> 00:56:56.854 She had a as an estrogen and progesterone
NOTE Confidence: 0.86041384935379

00:56:56.854 --> 00:56:58.549 positive invasive breast cancer.
NOTE Confidence: 0.86041384935379

00:56:58.550 --> 00:57:01.630 As you can see, received seven different
NOTE Confidence: 0.86041384935379

00:57:01.630 --> 00:57:04.007 treatment regiments before she came to us.

NOTE Confidence: 0.86041384935379
00:57:04.010 --> 00:57:05.180 Chemotherapy hormonal treatments,
NOTE Confidence: 0.86041384935379
00:57:05.180 --> 00:57:05.960 targeted therapies,
NOTE Confidence: 0.86041384935379
00:57:05.960 --> 00:57:09.080 until she came to the NCI in 2015,
NOTE Confidence: 0.86041384935379
00:57:09.080 --> 00:57:10.420 she had 62 mutations.
NOTE Confidence: 0.86041384935379
00:57:10.420 --> 00:57:12.971 We targeted four of them and she
NOTE Confidence: 0.86041384935379
00:57:12.971 --> 00:57:15.316 underwent a complete tumor regression.
NOTE Confidence: 0.86041384935379
00:57:15.320 --> 00:57:17.630 You can see on the left that
NOTE Confidence: 0.86041384935379
00:57:17.630 --> 00:57:20.085 large mass that was beginning to
NOTE Confidence: 0.86041384935379
00:57:20.085 --> 00:57:22.385 protrude through the chest wall.
NOTE Confidence: 0.86041384935379
00:57:22.390 --> 00:57:23.794 You can that disappeared.
NOTE Confidence: 0.86041384935379
00:57:23.794 --> 00:57:26.384 You can see in the lower portion
NOTE Confidence: 0.86041384935379
00:57:26.384 --> 00:57:28.826 on the right with the yellow
NOTE Confidence: 0.86041384935379
00:57:28.826 --> 00:57:30.900 arrows multiple liver metastases.
NOTE Confidence: 0.86041384935379
00:57:30.900 --> 00:57:32.920 It disappeared completely as well,
NOTE Confidence: 0.86041384935379
00:57:32.920 --> 00:57:35.480 and she remains disease free
NOTE Confidence: 0.86041384935379

00:57:35.480 --> 00:57:38.040 almost almost five years later.
NOTE Confidence: 0.86041384935379

00:57:38.040 --> 00:57:40.945 We target in that patient for different
NOTE Confidence: 0.86041384935379

00:57:40.945 --> 00:57:43.774 what appeared to be random somatic
NOTE Confidence: 0.86041384935379

00:57:43.774 --> 00:57:46.279 mutations of no particular interest,
NOTE Confidence: 0.86041384935379

00:57:46.280 --> 00:57:48.860 as oncogenic mutations that
NOTE Confidence: 0.86041384935379

00:57:48.860 --> 00:57:52.085 lead to her tumor regression.
NOTE Confidence: 0.86041384935379

00:57:52.090 --> 00:57:55.289 Another patient, now in the cervical cancer,
NOTE Confidence: 0.86041384935379

00:57:55.290 --> 00:57:57.570 was treated with this approach.
NOTE Confidence: 0.86041384935379

00:57:57.570 --> 00:58:00.210 She presented with the fan gating
NOTE Confidence: 0.86041384935379

00:58:00.210 --> 00:58:03.044 cervical mass into the vagina, lung,
NOTE Confidence: 0.86041384935379

00:58:03.044 --> 00:58:04.376 and intraperitoneal metastases.
NOTE Confidence: 0.86041384935379

00:58:04.376 --> 00:58:06.152 Received radiation therapy and
NOTE Confidence: 0.86041384935379

00:58:06.152 --> 00:58:07.630 cisplatin chemotherapy progressed,
NOTE Confidence: 0.86041384935379

00:58:07.630 --> 00:58:09.682 underwent hysterectomy and excision
NOTE Confidence: 0.86041384935379

00:58:09.682 --> 00:58:12.760 of ovaries but develop multiple liver
NOTE Confidence: 0.86041384935379

00:58:12.831 --> 00:58:14.459 lymph node intrabdominal metastases

NOTE Confidence: 0.86041384935379

00:58:14.459 --> 00:58:17.679 came to the NCI in May excuse me.

NOTE Confidence: 0.86041384935379

00:58:17.680 --> 00:58:20.880 In March of 2013 with three to 1775

NOTE Confidence: 0.86041384935379

00:58:20.880 --> 00:58:24.129 billion of our own tumor infiltrating.

NOTE Confidence: 0.86041384935379

00:58:24.130 --> 00:58:25.914 Lymphocytes selected for antitumor

NOTE Confidence: 0.86041384935379

00:58:25.914 --> 00:58:27.698 reactivity and experienced a

NOTE Confidence: 0.86041384935379

00:58:27.698 --> 00:58:29.448 complete regression of all disease,

NOTE Confidence: 0.86041384935379

00:58:29.450 --> 00:58:32.000 including a relief of our urinary

NOTE Confidence: 0.86041384935379

00:58:32.000 --> 00:58:33.700 obstruction and remains disease

NOTE Confidence: 0.86041384935379

00:58:33.766 --> 00:58:35.986 free over seven years later again,

NOTE Confidence: 0.86041384935379

00:58:35.990 --> 00:58:39.142 you see on the left yellow arrows pointing

NOTE Confidence: 0.86041384935379

00:58:39.142 --> 00:58:42.937 to each of these cancers deposits on the top,

NOTE Confidence: 0.86041384935379

00:58:42.940 --> 00:58:44.170 the lymph node,

NOTE Confidence: 0.86041384935379

00:58:44.170 --> 00:58:46.220 the next abdominal wall mass,

NOTE Confidence: 0.86041384935379

00:58:46.220 --> 00:58:47.444 another intraperitoneal lymph

NOTE Confidence: 0.86041384935379

00:58:47.444 --> 00:58:49.892 node and on the lower left,

NOTE Confidence: 0.86041384935379

00:58:49.900 --> 00:58:52.492 the lymph node that was obstructing
NOTE Confidence: 0.86041384935379

00:58:52.492 --> 00:58:55.660 arview order that the white area is the.
NOTE Confidence: 0.86041384935379

00:58:55.660 --> 00:58:58.153 Stand in her urine are you can see on
NOTE Confidence: 0.86041384935379

00:58:58.153 --> 00:59:00.810 the right all of these it disappeared.
NOTE Confidence: 0.86041384935379

00:59:00.810 --> 00:59:02.742 We remove the sense that she
NOTE Confidence: 0.86041384935379

00:59:02.742 --> 00:59:04.030 remains completely disease free.
NOTE Confidence: 0.86041384935379

00:59:04.030 --> 00:59:05.318 Now seven years later.
NOTE Confidence: 0.812483668327332

00:59:07.370 --> 00:59:09.575 And finally, a patient with colon
NOTE Confidence: 0.812483668327332

00:59:09.575 --> 00:59:12.392 cancer who had a meta static and
NOTE Confidence: 0.812483668327332

00:59:12.392 --> 00:59:14.300 aggressive metastatic colon cancer
NOTE Confidence: 0.812483668327332

00:59:14.300 --> 00:59:17.120 that was invading into her bladder.
NOTE Confidence: 0.812483668327332

00:59:17.120 --> 00:59:19.010 She had a partial cystectomy
NOTE Confidence: 0.812483668327332

00:59:19.010 --> 00:59:20.900 along with their sigmoid colectomy
NOTE Confidence: 0.812483668327332

00:59:20.960 --> 00:59:23.060 developed multiple lung metastases,
NOTE Confidence: 0.812483668327332

00:59:23.060 --> 00:59:25.180 radiation therapy to the bladder,
NOTE Confidence: 0.812483668327332

00:59:25.180 --> 00:59:26.800 suture wall combination chemotherapy.

NOTE Confidence: 0.812483668327332

00:59:26.800 --> 00:59:29.741 We respected too long metastases for to

NOTE Confidence: 0.812483668327332

00:59:29.741 --> 00:59:31.537 obtain tumor infiltrating lymphocytes.

NOTE Confidence: 0.812483668327332

00:59:31.540 --> 00:59:34.557 We selected the populations that could target

NOTE Confidence: 0.812483668327332

00:59:34.557 --> 00:59:37.500 her unique cancer mutations based on our.

NOTE Confidence: 0.812483668327332

00:59:37.500 --> 00:59:42.096 RSA, she had 61 somatic mutations.

NOTE Confidence: 0.812483668327332

00:59:42.100 --> 00:59:44.200 She had seven lung metastases,

NOTE Confidence: 0.812483668327332

00:59:44.200 --> 00:59:46.300 six of them disappeared completely,

NOTE Confidence: 0.812483668327332

00:59:46.300 --> 00:59:48.598 but one the 3rd row down

NOTE Confidence: 0.812483668327332

00:59:48.598 --> 00:59:51.339 on the on the right grew.

NOTE Confidence: 0.812483668327332

00:59:51.340 --> 00:59:53.440 We then respected that lesion,

NOTE Confidence: 0.812483668327332

00:59:53.440 --> 00:59:56.240 leaving her disease free and in the

NOTE Confidence: 0.812483668327332

00:59:56.240 --> 00:59:59.089 analysis of that respected lesion we found

NOTE Confidence: 0.812483668327332

00:59:59.089 --> 01:00:02.679 that she had lost part of chromosome six,

NOTE Confidence: 0.812483668327332

01:00:02.680 --> 01:00:04.780 which encodes her major history

NOTE Confidence: 0.812483668327332

01:00:04.780 --> 01:00:06.460 of Pat ability antigens.

NOTE Confidence: 0.812483668327332

01:00:06.460 --> 01:00:06.880 Therefore,
NOTE Confidence: 0.812483668327332

01:00:06.880 --> 01:00:08.980 no mutation could be presented,
NOTE Confidence: 0.812483668327332

01:00:08.980 --> 01:00:11.105 and that probably explains why
NOTE Confidence: 0.812483668327332

01:00:11.105 --> 01:00:12.380 that lesion progressed.
NOTE Confidence: 0.812483668327332

01:00:12.380 --> 01:00:15.866 But with respecting that she has remained
NOTE Confidence: 0.812483668327332

01:00:15.866 --> 01:00:19.167 now disease free over far five years,
NOTE Confidence: 0.812483668327332

01:00:19.170 --> 01:00:21.990 five years later.
NOTE Confidence: 0.812483668327332

01:00:21.990 --> 01:00:24.524 And so our results are summarized here.
NOTE Confidence: 0.812483668327332

01:00:24.530 --> 01:00:27.434 This is very much a work in progress.
NOTE Confidence: 0.812483668327332

01:00:27.440 --> 01:00:29.911 If you give unselected till in these
NOTE Confidence: 0.812483668327332

01:00:29.911 --> 01:00:31.430 chemorefractory metastatic solid cancers.
NOTE Confidence: 0.812483668327332

01:00:31.430 --> 01:00:34.697 What works in Melanoma does not work in them.
NOTE Confidence: 0.812483668327332

01:00:34.700 --> 01:00:36.788 We had no responses when we
NOTE Confidence: 0.812483668327332

01:00:36.788 --> 01:00:38.690 selected the till we began.
NOTE Confidence: 0.812483668327332

01:00:38.690 --> 01:00:41.621 We're beginning to see responses of 12% rate.
NOTE Confidence: 0.812483668327332

01:00:41.621 --> 01:00:44.358 We studied the shells and showed that

NOTE Confidence: 0.812483668327332

01:00:44.358 --> 01:00:47.249 they would express PD one after they

NOTE Confidence: 0.812483668327332

01:00:47.249 --> 01:00:49.860 were administered at very high levels.

NOTE Confidence: 0.812483668327332

01:00:49.860 --> 01:00:51.700 When we edit checkpoint modulators,

NOTE Confidence: 0.812483668327332

01:00:51.700 --> 01:00:53.160 our response rate in

NOTE Confidence: 0.812483668327332

01:00:53.160 --> 01:00:54.255 these epithelial cancers,

NOTE Confidence: 0.812483668327332

01:00:54.260 --> 01:00:56.900 it's now 23% and we're continuing

NOTE Confidence: 0.812483668327332

01:00:56.900 --> 01:00:59.970 to work on improving this treatment.

NOTE Confidence: 0.812483668327332

01:00:59.970 --> 01:01:02.805 So I would raise then two hypothesis,

NOTE Confidence: 0.812483668327332

01:01:02.810 --> 01:01:04.830 one that it's the recognition

NOTE Confidence: 0.812483668327332

01:01:04.830 --> 01:01:06.446 of random somatic mutations.

NOTE Confidence: 0.812483668327332

01:01:06.450 --> 01:01:09.192 That is the final common pathway

NOTE Confidence: 0.812483668327332

01:01:09.192 --> 01:01:11.523 explaining cancer regression for most

NOTE Confidence: 0.812483668327332

01:01:11.523 --> 01:01:14.533 immuno therapies for solid cancers and it's.

NOTE Confidence: 0.812483668327332

01:01:14.540 --> 01:01:16.622 Evidenced in part by the studies

NOTE Confidence: 0.812483668327332

01:01:16.622 --> 01:01:18.010 I've just shown you,

NOTE Confidence: 0.812483668327332

01:01:18.010 --> 01:01:20.404 but also by showing that by data
NOTE Confidence: 0.812483668327332

01:01:20.404 --> 01:01:21.843 showing that checkpoint modulators
NOTE Confidence: 0.812483668327332

01:01:21.843 --> 01:01:23.901 tend to be more effective when
NOTE Confidence: 0.812483668327332

01:01:23.901 --> 01:01:26.017 there are more mutations and you've
NOTE Confidence: 0.812483668327332

01:01:26.017 --> 01:01:28.411 seen the data with respect to tumor
NOTE Confidence: 0.812483668327332

01:01:28.420 --> 01:01:31.018 infiltrating lymphocyte therapy.
NOTE Confidence: 0.812483668327332

01:01:31.018 --> 01:01:32.750 Second hypothesis.
NOTE Confidence: 0.812483668327332

01:01:32.750 --> 01:01:34.474 Revolves around the identification
NOTE Confidence: 0.812483668327332

01:01:34.474 --> 01:01:35.767 of cancer antigens.
NOTE Confidence: 0.812483668327332

01:01:35.770 --> 01:01:36.448 We finally,
NOTE Confidence: 0.812483668327332

01:01:36.448 --> 01:01:37.126 I believe,
NOTE Confidence: 0.812483668327332

01:01:37.126 --> 01:01:39.684 no at a cancer antigen is any
NOTE Confidence: 0.812483668327332

01:01:39.684 --> 01:01:41.492 intracellular protein can potentially
NOTE Confidence: 0.812483668327332

01:01:41.492 --> 01:01:44.799 be a cancer antigen if it's mutated
NOTE Confidence: 0.812483668327332

01:01:44.799 --> 01:01:46.260 and processed intracellularly
NOTE Confidence: 0.812483668327332

01:01:46.260 --> 01:01:49.418 to a peptide that combined to

NOTE Confidence: 0.812483668327332
01:01:49.418 --> 01:01:53.008 the autologous M HC mols.
NOTE Confidence: 0.812483668327332
01:01:53.010 --> 01:01:54.889 Good news and bad news.
NOTE Confidence: 0.812483668327332
01:01:54.889 --> 01:01:57.487 The good news is that since
NOTE Confidence: 0.812483668327332
01:01:57.487 --> 01:02:00.228 all cancers have mutations,
NOTE Confidence: 0.812483668327332
01:02:00.230 --> 01:02:02.242 virtually all cancer histologies
NOTE Confidence: 0.812483668327332
01:02:02.242 --> 01:02:04.254 are potentially eligible for
NOTE Confidence: 0.812483668327332
01:02:04.254 --> 01:02:06.189 this kind of approach.
NOTE Confidence: 0.812483668327332
01:02:06.190 --> 01:02:08.178 The bad news, however,
NOTE Confidence: 0.812483668327332
01:02:08.178 --> 01:02:11.160 is that the treatment will be.
NOTE Confidence: 0.812483668327332
01:02:11.160 --> 01:02:14.485 It will have to be highly individualized
NOTE Confidence: 0.812483668327332
01:02:14.485 --> 01:02:17.173 for patients because each express
NOTE Confidence: 0.812483668327332
01:02:17.173 --> 01:02:19.541 different immunogenic mutations and
NOTE Confidence: 0.812483668327332
01:02:19.541 --> 01:02:22.337 therefore this treatment is going
NOTE Confidence: 0.812483668327332
01:02:22.337 --> 01:02:24.580 to be very complex to administer.
NOTE Confidence: 0.893496096134186
01:02:27.470 --> 01:02:29.696 Well, we're looking at a whole variety
NOTE Confidence: 0.893496096134186

01:02:29.696 --> 01:02:31.490 of improvements to simplify this.
NOTE Confidence: 0.893496096134186

01:02:31.490 --> 01:02:33.786 To make it more effective with the idea
NOTE Confidence: 0.893496096134186

01:02:33.786 --> 01:02:36.335 that if we can develop highly effective
NOTE Confidence: 0.893496096134186

01:02:36.335 --> 01:02:38.562 treatments for these 90% of patients,
NOTE Confidence: 0.893496096134186

01:02:38.562 --> 01:02:40.317 the genius of American industry
NOTE Confidence: 0.893496096134186

01:02:40.317 --> 01:02:42.548 will figure out ways to deliver it,
NOTE Confidence: 0.893496096134186

01:02:42.550 --> 01:02:45.966 as was the case for car T cells.
NOTE Confidence: 0.893496096134186

01:02:45.970 --> 01:02:47.820 There are a variety of
NOTE Confidence: 0.893496096134186

01:02:47.820 --> 01:02:49.670 areas that we're looking at.
NOTE Confidence: 0.893496096134186

01:02:49.670 --> 01:02:51.812 Each one could be the subject
NOTE Confidence: 0.893496096134186

01:02:51.812 --> 01:02:53.740 of a one hour talk,
NOTE Confidence: 0.893496096134186

01:02:53.740 --> 01:02:56.085 but I just like today to discuss
NOTE Confidence: 0.893496096134186

01:02:56.085 --> 01:02:58.266 the one that I've listed here
NOTE Confidence: 0.893496096134186

01:02:58.266 --> 01:03:00.821 in red and that is to transduced
NOTE Confidence: 0.893496096134186

01:03:00.900 --> 01:03:03.660 mutation reactive TCT cell receptors.
NOTE Confidence: 0.893496096134186

01:03:03.660 --> 01:03:05.288 That recognizes immunogenicity stations

NOTE Confidence: 0.893496096134186
01:03:05.288 --> 01:03:07.730 into naive or central memory cells.
NOTE Confidence: 0.893496096134186
01:03:07.730 --> 01:03:10.285 So we now have FDA approval to
NOTE Confidence: 0.893496096134186
01:03:10.285 --> 01:03:12.406 use transient vectors with minimal
NOTE Confidence: 0.893496096134186
01:03:12.406 --> 01:03:13.837 with minimal testing.
NOTE Confidence: 0.893496096134186
01:03:13.840 --> 01:03:15.268 That makes this practical.
NOTE Confidence: 0.893496096134186
01:03:15.268 --> 01:03:17.410 The idea behind this is that
NOTE Confidence: 0.893496096134186
01:03:17.477 --> 01:03:19.522 conventional tool sales have under
NOTE Confidence: 0.893496096134186
01:03:19.522 --> 01:03:22.075 God Replication for years in the
NOTE Confidence: 0.893496096134186
01:03:22.075 --> 01:03:24.280 patient in vivo and therefore
NOTE Confidence: 0.893496096134186
01:03:24.280 --> 01:03:26.044 developed an exhaustive phenotype.
NOTE Confidence: 0.893496096134186
01:03:26.050 --> 01:03:28.080 PD one expression lag 310.
NOTE Confidence: 0.893496096134186
01:03:28.080 --> 01:03:31.072 Three if we can take these T cell
NOTE Confidence: 0.893496096134186
01:03:31.072 --> 01:03:33.656 receptors and put them into naive
NOTE Confidence: 0.893496096134186
01:03:33.656 --> 01:03:35.408 or central memory cells,
NOTE Confidence: 0.893496096134186
01:03:35.410 --> 01:03:39.074 we might have a cell with an explosive.
NOTE Confidence: 0.893496096134186

01:03:39.080 --> 01:03:40.748 Proliferative potential to
NOTE Confidence: 0.893496096134186

01:03:40.748 --> 01:03:44.084 administer to the to the patient.
NOTE Confidence: 0.893496096134186

01:03:44.090 --> 01:03:46.076 In the first patient,
NOTE Confidence: 0.893496096134186

01:03:46.076 --> 01:03:50.060 we actually have done that with factors only.
NOTE Confidence: 0.893496096134186

01:03:50.060 --> 01:03:51.090 Uh huh.
NOTE Confidence: 0.893496096134186

01:03:51.090 --> 01:03:54.695 Been done with one in one patient
NOTE Confidence: 0.893496096134186

01:03:54.695 --> 01:03:57.340 receiving these P53 mutations.
NOTE Confidence: 0.893496096134186

01:03:57.340 --> 01:04:01.336 We've identified a whole series of.
NOTE Confidence: 0.893496096134186

01:04:01.340 --> 01:04:02.423 T cell receptors.
NOTE Confidence: 0.893496096134186

01:04:02.423 --> 01:04:05.949 As you can see here in this second and
NOTE Confidence: 0.893496096134186

01:04:05.949 --> 01:04:09.148 this from a variety of patients that
NOTE Confidence: 0.893496096134186

01:04:09.148 --> 01:04:11.619 recognize a variety of P53 mutations
NOTE Confidence: 0.893496096134186

01:04:11.619 --> 01:04:15.038 on a variety of class one and Class
NOTE Confidence: 0.893496096134186

01:04:15.038 --> 01:04:18.510 2 immuno genic class 2M HC molecules.
NOTE Confidence: 0.893496096134186

01:04:18.510 --> 01:04:21.968 We saw a patient that had a
NOTE Confidence: 0.893496096134186

01:04:21.968 --> 01:04:24.310 meta static breast cancer.

NOTE Confidence: 0.893496096134186
01:04:24.310 --> 01:04:28.290 That had a P53 mutation.
NOTE Confidence: 0.893496096134186
01:04:28.290 --> 01:04:30.838 That was in fact.
NOTE Confidence: 0.893496096134186
01:04:30.840 --> 01:04:33.820 R175 H 175th amino acid.
NOTE Confidence: 0.893496096134186
01:04:33.820 --> 01:04:37.390 A mutation that's present in about
NOTE Confidence: 0.893496096134186
01:04:37.390 --> 01:04:41.566 2% of all patients with with cancer.
NOTE Confidence: 0.893496096134186
01:04:41.570 --> 01:04:46.370 She was oh 201 as well.
NOTE Confidence: 0.893496096134186
01:04:46.370 --> 01:04:49.202 She was a patient who had a metastatic
NOTE Confidence: 0.893496096134186
01:04:49.202 --> 01:04:51.861 breast cancer again on who had
NOTE Confidence: 0.893496096134186
01:04:51.861 --> 01:04:53.271 undergone multiple treatments
NOTE Confidence: 0.893496096134186
01:04:53.271 --> 01:04:55.090 and progressed through them.
NOTE Confidence: 0.893496096134186
01:04:55.090 --> 01:04:57.160 Came to us quite ill.
NOTE Confidence: 0.893496096134186
01:04:57.160 --> 01:05:00.046 September of 2019 she had tumor
NOTE Confidence: 0.893496096134186
01:05:00.046 --> 01:05:01.489 surrounding her heart.
NOTE Confidence: 0.893496096134186
01:05:01.490 --> 01:05:04.675 We had to perform a pericardial window
NOTE Confidence: 0.893496096134186
01:05:04.675 --> 01:05:07.260 three days before her treatment,
NOTE Confidence: 0.893496096134186

01:05:07.260 --> 01:05:10.501 with 550 billion of our own cells
NOTE Confidence: 0.893496096134186

01:05:10.501 --> 01:05:12.907 that were reactive against P53
NOTE Confidence: 0.893496096134186

01:05:12.907 --> 01:05:15.685 that would taken from this Library
NOTE Confidence: 0.893496096134186

01:05:15.685 --> 01:05:19.192 of of T cell receptors that the
NOTE Confidence: 0.893496096134186

01:05:19.192 --> 01:05:22.341 doctor Peter Kim had developed along
NOTE Confidence: 0.893496096134186

01:05:22.341 --> 01:05:26.247 with others in the surgery branch.
NOTE Confidence: 0.893496096134186

01:05:26.250 --> 01:05:28.070 You underwent a 90% response,
NOTE Confidence: 0.893496096134186

01:05:28.070 --> 01:05:30.618 but then recovered it about six months.
NOTE Confidence: 0.893496096134186

01:05:30.620 --> 01:05:33.524 You can see on our X Ray here.
NOTE Confidence: 0.893496096134186

01:05:33.530 --> 01:05:36.434 She had on the left surrounding our heart,
NOTE Confidence: 0.893496096134186

01:05:36.440 --> 01:05:38.260 extensive disease in the pericardium.
NOTE Confidence: 0.893496096134186

01:05:38.260 --> 01:05:40.808 It was biopsy proven to be tumor
NOTE Confidence: 0.893496096134186

01:05:40.808 --> 01:05:41.900 that disappeared completely.
NOTE Confidence: 0.893496096134186

01:05:41.900 --> 01:05:45.890 As you can see on the right.
NOTE Confidence: 0.893496096134186

01:05:45.890 --> 01:05:47.602 She also had a.
NOTE Confidence: 0.893496096134186

01:05:47.602 --> 01:05:49.742 Extensive disease in her breast

NOTE Confidence: 0.893496096134186

01:05:49.742 --> 01:05:51.783 extending super subcutaneously and

NOTE Confidence: 0.893496096134186

01:05:51.783 --> 01:05:53.827 intracutaneous that was extending

NOTE Confidence: 0.893496096134186

01:05:53.827 --> 01:05:56.340 on to the left breast,

NOTE Confidence: 0.893496096134186

01:05:56.340 --> 01:05:58.740 all of which disappeared completely,

NOTE Confidence: 0.893496096134186

01:05:58.740 --> 01:06:02.580 but again about six months later she did.

NOTE Confidence: 0.893496096134186

01:06:02.580 --> 01:06:03.855 She did recur.

NOTE Confidence: 0.893496096134186

01:06:03.855 --> 01:06:06.405 And so we're continuing to pursue

NOTE Confidence: 0.893496096134186

01:06:06.405 --> 01:06:07.640 that approach,

NOTE Confidence: 0.893496096134186

01:06:07.640 --> 01:06:09.915 but as well are asking the second

NOTE Confidence: 0.893496096134186

01:06:09.915 --> 01:06:12.750 question that I mentioned at the beginning,

NOTE Confidence: 0.835798263549805

01:06:12.750 --> 01:06:15.670 and that is what is what are the

NOTE Confidence: 0.835798263549805

01:06:15.670 --> 01:06:17.542 phenotypic characteristics of the cells

NOTE Confidence: 0.835798263549805

01:06:17.542 --> 01:06:19.690 that mediate cancer regression in vivo?

NOTE Confidence: 0.835798263549805

01:06:19.690 --> 01:06:22.966 Because we have the cells in a test tube,

NOTE Confidence: 0.835798263549805

01:06:22.970 --> 01:06:25.364 we can apply a new approach of

NOTE Confidence: 0.835798263549805

01:06:25.364 --> 01:06:26.866 high dimensional singles del
NOTE Confidence: 0.835798263549805

01:06:26.866 --> 01:06:28.506 transcriptome analysis that analyzes
NOTE Confidence: 0.835798263549805

01:06:28.506 --> 01:06:30.999 the transcript tone of up to it.
NOTE Confidence: 0.835798263549805

01:06:31.000 --> 01:06:32.332 10,000 cells all-in-one assay
NOTE Confidence: 0.835798263549805

01:06:32.332 --> 01:06:35.030 and we use a T Sne analysis.
NOTE Confidence: 0.835798263549805

01:06:35.030 --> 01:06:38.498 A way to reduce the multiple
NOTE Confidence: 0.835798263549805

01:06:38.498 --> 01:06:42.089 dimensions of this of this data.
NOTE Confidence: 0.835798263549805

01:06:42.090 --> 01:06:42.862 Into clusters.
NOTE Confidence: 0.835798263549805

01:06:42.862 --> 01:06:44.792 After all, we're dealing with
NOTE Confidence: 0.835798263549805

01:06:44.792 --> 01:06:46.819 a high number of patients.
NOTE Confidence: 0.835798263549805

01:06:46.820 --> 01:06:49.184 Each one of Mitch maybe expressing
NOTE Confidence: 0.835798263549805

01:06:49.184 --> 01:06:50.760 up to 20,000 antigens.
NOTE Confidence: 0.835798263549805

01:06:50.760 --> 01:06:53.118 It's an immense amount of data,
NOTE Confidence: 0.835798263549805

01:06:53.120 --> 01:06:56.319 but by doing a stochastic near neighbor
NOTE Confidence: 0.835798263549805

01:06:56.319 --> 01:06:58.762 embedding analysis we can divide all
NOTE Confidence: 0.835798263549805

01:06:58.762 --> 01:07:01.899 of that data and reduce it to a 2

NOTE Confidence: 0.835798263549805
01:07:01.899 --> 01:07:04.149 dimensional plot called AT sne plot.
NOTE Confidence: 0.835798263549805
01:07:04.150 --> 01:07:07.310 And here is one of our first experiments.
NOTE Confidence: 0.835798263549805
01:07:07.310 --> 01:07:08.062 Doing that,
NOTE Confidence: 0.835798263549805
01:07:08.062 --> 01:07:10.318 we could take Melanoma samples that
NOTE Confidence: 0.835798263549805
01:07:10.318 --> 01:07:12.428 were analyzed by mass spectrometry,
NOTE Confidence: 0.835798263549805
01:07:12.430 --> 01:07:14.420 but you can of course.
NOTE Confidence: 0.835798263549805
01:07:14.420 --> 01:07:17.408 Do the entire transcriptome
NOTE Confidence: 0.835798263549805
01:07:17.408 --> 01:07:19.649 utilizing other techniques.
NOTE Confidence: 0.835798263549805
01:07:19.650 --> 01:07:23.650 It divided those cells
NOTE Confidence: 0.835798263549805
01:07:23.650 --> 01:07:26.650 into multiple clusters.
NOTE Confidence: 0.835798263549805
01:07:26.650 --> 01:07:29.093 And you can see here up to
NOTE Confidence: 0.835798263549805
01:07:29.093 --> 01:07:30.960 20 two different clusters,
NOTE Confidence: 0.835798263549805
01:07:30.960 --> 01:07:33.522 but 'cause we knew the exact
NOTE Confidence: 0.835798263549805
01:07:33.522 --> 01:07:35.646 transcriptomes the exact antigens that
NOTE Confidence: 0.835798263549805
01:07:35.646 --> 01:07:38.012 were being expressed by every cell and
NOTE Confidence: 0.835798263549805

01:07:38.012 --> 01:07:40.759 the T cell receptor in those cells.
NOTE Confidence: 0.835798263549805

01:07:40.760 --> 01:07:43.898 From this analysis we then examined.
NOTE Confidence: 0.835798263549805

01:07:43.900 --> 01:07:47.266 Each one of these 22 clusters.
NOTE Confidence: 0.835798263549805

01:07:47.270 --> 01:07:49.100 Looking at the transcriptomes to see
NOTE Confidence: 0.835798263549805

01:07:49.100 --> 01:07:51.869 if any group of these clusters would
NOTE Confidence: 0.835798263549805

01:07:51.869 --> 01:07:53.849 separate responders and Nonresponders.
NOTE Confidence: 0.835798263549805

01:07:53.850 --> 01:07:56.253 And as you can see here in this first
NOTE Confidence: 0.835798263549805

01:07:56.253 --> 01:07:58.119 and in this analysis of cluster
NOTE Confidence: 0.835798263549805

01:07:58.119 --> 01:08:00.868 one it was the only cluster that
NOTE Confidence: 0.835798263549805

01:08:00.868 --> 01:08:02.590 statistically significantly separated
NOTE Confidence: 0.835798263549805

01:08:02.590 --> 01:08:04.886 responders from Nonresponders and
NOTE Confidence: 0.835798263549805

01:08:04.886 --> 01:08:10.148 you can see that on the on the left.
NOTE Confidence: 0.835798263549805

01:08:10.150 --> 01:08:12.390 Cluster one, it turns out,
NOTE Confidence: 0.835798263549805

01:08:12.390 --> 01:08:15.066 was highly enriched for CD39 CD,
NOTE Confidence: 0.835798263549805

01:08:15.070 --> 01:08:17.105 69 stemlike lymphocytes that appeared
NOTE Confidence: 0.835798263549805

01:08:17.105 --> 01:08:19.720 to be the effector cells responsible

NOTE Confidence: 0.835798263549805

01:08:19.720 --> 01:08:21.768 for her Melanoma treatment.

NOTE Confidence: 0.835798263549805

01:08:21.770 --> 01:08:25.550 And as you can see here in the middle,

NOTE Confidence: 0.835798263549805

01:08:25.550 --> 01:08:29.004 if you look at the total number of

NOTE Confidence: 0.835798263549805

01:08:29.004 --> 01:08:32.154 cells that were administered that did

NOTE Confidence: 0.835798263549805

01:08:32.154 --> 01:08:35.929 not separate responders from Nonresponders.

NOTE Confidence: 0.835798263549805

01:08:35.930 --> 01:08:38.440 Respond as being in red.

NOTE Confidence: 0.835798263549805

01:08:38.440 --> 01:08:41.590 But when we took those same populations

NOTE Confidence: 0.835798263549805

01:08:41.590 --> 01:08:44.339 and analyze the double negative.

NOTE Confidence: 0.835798263549805

01:08:44.340 --> 01:08:46.540 Cells that administration of high

NOTE Confidence: 0.835798263549805

01:08:46.540 --> 01:08:48.740 an low numbers highly statistically

NOTE Confidence: 0.835798263549805

01:08:48.808 --> 01:08:50.340 significantly separated.

NOTE Confidence: 0.835798263549805

01:08:50.340 --> 01:08:52.840 The responder's for the high

NOTE Confidence: 0.835798263549805

01:08:52.840 --> 01:08:54.840 survival from the nonresponders,

NOTE Confidence: 0.835798263549805

01:08:54.840 --> 01:08:57.068 with a low survival,

NOTE Confidence: 0.835798263549805

01:08:57.068 --> 01:08:59.853 and so we're vigorously approaching

NOTE Confidence: 0.835798263549805

01:08:59.853 --> 01:09:02.746 approaching now the use of these
NOTE Confidence: 0.835798263549805

01:09:02.746 --> 01:09:04.996 high dimensional techniques to try
NOTE Confidence: 0.835798263549805

01:09:05.086 --> 01:09:07.461 to identify the transcriptomes of
NOTE Confidence: 0.835798263549805

01:09:07.461 --> 01:09:10.610 the exact cells that are responsible
NOTE Confidence: 0.835798263549805

01:09:10.610 --> 01:09:13.690 for a tumor regression.
NOTE Confidence: 0.835798263549805

01:09:13.690 --> 01:09:14.038 Well,
NOTE Confidence: 0.835798263549805

01:09:14.038 --> 01:09:15.778 I've attempted to describe our
NOTE Confidence: 0.835798263549805

01:09:15.778 --> 01:09:18.109 efforts to develop a blueprint for
NOTE Confidence: 0.835798263549805

01:09:18.109 --> 01:09:20.304 cancer immunotherapy that we can
NOTE Confidence: 0.835798263549805

01:09:20.304 --> 01:09:22.109 direct against epithelial cancers
NOTE Confidence: 0.835798263549805

01:09:22.109 --> 01:09:24.214 by targeting the immunogenic somatic
NOTE Confidence: 0.835798263549805

01:09:24.214 --> 01:09:26.287 mutations unique to that patients
NOTE Confidence: 0.835798263549805

01:09:26.287 --> 01:09:28.609 cancer and by raising libraries of
NOTE Confidence: 0.835798263549805

01:09:28.609 --> 01:09:30.737 T cell receptors against shared
NOTE Confidence: 0.835798263549805

01:09:30.737 --> 01:09:31.596 cancer antigens,
NOTE Confidence: 0.835798263549805

01:09:31.596 --> 01:09:33.925 each with a different restriction

NOTE Confidence: 0.835798263549805
01:09:33.925 --> 01:09:37.460 element for K brass and P53 mutations.
NOTE Confidence: 0.835798263549805
01:09:37.460 --> 01:09:39.890 I might conclude.
NOTE Confidence: 0.835798263549805
01:09:39.890 --> 01:09:42.004 With the with the following and
NOTE Confidence: 0.835798263549805
01:09:42.004 --> 01:09:43.990 that is at cell transfer therapy
NOTE Confidence: 0.835798263549805
01:09:44.057 --> 01:09:46.377 can mediate durable regressions in
NOTE Confidence: 0.835798263549805
01:09:46.377 --> 01:09:48.233 patients with metastatic cancer
NOTE Confidence: 0.835798263549805
01:09:48.233 --> 01:09:49.880 refractory to other treatments
NOTE Confidence: 0.835798263549805
01:09:49.880 --> 01:09:52.118 that T cells that recognize unique
NOTE Confidence: 0.835798263549805
01:09:52.118 --> 01:09:53.748 somatic mutations can be found
NOTE Confidence: 0.835798263549805
01:09:53.748 --> 01:09:55.620 until and also in PBL in
NOTE Confidence: 0.840443670749664
01:09:55.687 --> 01:09:57.571 patients with common epithelial
NOTE Confidence: 0.840443670749664
01:09:57.571 --> 01:09:59.926 cancers and that the identification
NOTE Confidence: 0.840443670749664
01:09:59.926 --> 01:10:02.394 and targeting of the mutations unique
NOTE Confidence: 0.840443670749664
01:10:02.394 --> 01:10:04.695 to each cancer or shared mutations
NOTE Confidence: 0.840443670749664
01:10:04.695 --> 01:10:07.695 such as KRS or P53 has the potential
NOTE Confidence: 0.840443670749664

01:10:07.695 --> 01:10:10.443 to extend cell therapy to patients.
NOTE Confidence: 0.840443670749664

01:10:10.443 --> 01:10:12.780 With Comrent Epithelial cancers?
NOTE Confidence: 0.840443670749664

01:10:12.780 --> 01:10:15.000 Thank you for your
NOTE Confidence: 0.926428496837616

01:10:15.000 --> 01:10:15.780 very kind attention.
NOTE Confidence: 0.829641342163086

01:10:17.970 --> 01:10:20.495 Thank you so much doctor Rosenberg
NOTE Confidence: 0.829641342163086

01:10:20.495 --> 01:10:22.179 for that marvelous talk.
NOTE Confidence: 0.829641342163086

01:10:22.180 --> 01:10:25.550 It was wonderful to hear all of these.
NOTE Confidence: 0.829641342163086

01:10:25.550 --> 01:10:28.914 All of this data, so I'm going to
NOTE Confidence: 0.829641342163086

01:10:28.914 --> 01:10:31.440 start reading the questions from the
NOTE Confidence: 0.829641342163086

01:10:31.440 --> 01:10:34.560 Q&A so this is from each young Kim
NOTE Confidence: 0.829641342163086

01:10:34.560 --> 01:10:36.635 success of tumor mutation reactive
NOTE Confidence: 0.829641342163086

01:10:36.635 --> 01:10:39.035 lymphocytes over bulk till suggest
NOTE Confidence: 0.829641342163086

01:10:39.035 --> 01:10:41.809 number of cells infused matters as
NOTE Confidence: 0.829641342163086

01:10:41.809 --> 01:10:44.131 both till probably has the specific
NOTE Confidence: 0.829641342163086

01:10:44.131 --> 01:10:46.185 T cells recognizing the antigens.
NOTE Confidence: 0.829641342163086

01:10:46.185 --> 01:10:48.735 What are the T cell numbers?

NOTE Confidence: 0.829641342163086

01:10:48.740 --> 01:10:52.200 That are needed to give the effect in bulk

NOTE Confidence: 0.829641342163086

01:10:52.200 --> 01:10:54.499 till versus tumor mutation reactive tools.

NOTE Confidence: 0.870073676109314

01:10:55.580 --> 01:10:58.877 So we give all the till that

NOTE Confidence: 0.870073676109314

01:10:58.877 --> 01:11:01.950 we can grow an virtually.

NOTE Confidence: 0.870073676109314

01:11:01.950 --> 01:11:04.682 All patients have received

NOTE Confidence: 0.870073676109314

01:11:04.682 --> 01:11:08.097 somewhere between 2:00 and 10:00.

NOTE Confidence: 0.870073676109314

01:11:08.100 --> 01:11:11.262 Times 10 of the 10 cells

NOTE Confidence: 0.870073676109314

01:11:11.262 --> 01:11:14.560 up to about 100 billion.

NOTE Confidence: 0.870073676109314

01:11:14.560 --> 01:11:16.426 Sells well 10 billion cells but

NOTE Confidence: 0.870073676109314

01:11:16.426 --> 01:11:18.859 we don't know the number that are

NOTE Confidence: 0.870073676109314

01:11:18.859 --> 01:11:20.724 actually required when it used.

NOTE Confidence: 0.870073676109314

01:11:20.730 --> 01:11:22.788 When one uses car T cells.

NOTE Confidence: 0.870073676109314

01:11:22.790 --> 01:11:25.877 Carl June has shown that even a single clone,

NOTE Confidence: 0.870073676109314

01:11:25.880 --> 01:11:27.016 a Type 1 cell,

NOTE Confidence: 0.870073676109314

01:11:27.016 --> 01:11:28.720 can expand to large numbers and

NOTE Confidence: 0.870073676109314

01:11:28.791 --> 01:11:31.016 mediate the regression of lymphomas.
NOTE Confidence: 0.870073676109314

01:11:31.020 --> 01:11:32.987 So if you have the right cell
NOTE Confidence: 0.870073676109314

01:11:32.987 --> 01:11:35.201 that can grow and have a
NOTE Confidence: 0.870073676109314

01:11:35.201 --> 01:11:36.506 high proliferative potential,
NOTE Confidence: 0.870073676109314

01:11:36.510 --> 01:11:39.300 you may not need many cells.
NOTE Confidence: 0.870073676109314

01:11:39.300 --> 01:11:40.210 OK, the
NOTE Confidence: 0.831646740436554

01:11:40.210 --> 01:11:43.826 next question is, are the CD 39 CD,
NOTE Confidence: 0.831646740436554

01:11:43.830 --> 01:11:46.994 69 negative resource like stem memory cells.
NOTE Confidence: 0.831646740436554

01:11:47.000 --> 01:11:49.640 Doctor Raffi discussed and if so,
NOTE Confidence: 0.831646740436554

01:11:49.640 --> 01:11:52.545 would T cells drip from draining lymph
NOTE Confidence: 0.831646740436554

01:11:52.545 --> 01:11:55.159 nodes or metastatic lymph nodes?
NOTE Confidence: 0.831646740436554

01:11:55.160 --> 01:11:59.426 Be more effective as a till source then.
NOTE Confidence: 0.831646740436554

01:11:59.430 --> 01:12:00.452 Tumor infiltrating lymphocytes
NOTE Confidence: 0.831646740436554

01:12:00.452 --> 01:12:03.630 from the primary tumor. So
NOTE Confidence: 0.841076493263245

01:12:03.630 --> 01:12:06.168 mouse studies have identified the phenotype
NOTE Confidence: 0.841076493263245

01:12:06.168 --> 01:12:09.179 of cells that can that are involved.

NOTE Confidence: 0.841076493263245

01:12:09.180 --> 01:12:12.818 CD 39 has been one. I don't think C.

NOTE Confidence: 0.841076493263245

01:12:12.818 --> 01:12:16.105 69 in combination with it has been recognized

NOTE Confidence: 0.841076493263245

01:12:16.105 --> 01:12:19.849 'cause there are very few of those cells.

NOTE Confidence: 0.841076493263245

01:12:19.850 --> 01:12:22.030 CD 103 is been identified.

NOTE Confidence: 0.841076493263245

01:12:22.030 --> 01:12:24.260 So there's some similarity with

NOTE Confidence: 0.841076493263245

01:12:24.260 --> 01:12:27.120 what's been seen in other models,

NOTE Confidence: 0.841076493263245

01:12:27.120 --> 01:12:30.354 but it is very unique and rare.

NOTE Confidence: 0.841076493263245

01:12:30.360 --> 01:12:33.601 CD39 CD, 69 cell that appears to

NOTE Confidence: 0.841076493263245

01:12:33.601 --> 01:12:35.453 mediate the regression. Again,

NOTE Confidence: 0.841076493263245

01:12:35.453 --> 01:12:38.694 most effector cells are CD 39 positive.

NOTE Confidence: 0.841076493263245

01:12:38.700 --> 01:12:41.731 It's only the stem like cell that

NOTE Confidence: 0.841076493263245

01:12:41.731 --> 01:12:45.433 gives rise to CD 39 positive cells that

NOTE Confidence: 0.841076493263245

01:12:45.433 --> 01:12:48.939 appears to be appears to be critical.

NOTE Confidence: 0.841076493263245

01:12:48.940 --> 01:12:50.540 Strictly a tumor infiltrating lymphocytes,

NOTE Confidence: 0.841076493263245

01:12:50.540 --> 01:12:52.130 but haven't looked at draining

NOTE Confidence: 0.841076493263245

01:12:52.130 --> 01:12:53.084 lymph node cells.
NOTE Confidence: 0.841076493263245

01:12:53.090 --> 01:12:55.316 They may well be a better source,
NOTE Confidence: 0.841076493263245

01:12:55.320 --> 01:12:56.736 but are, of course,
NOTE Confidence: 0.841076493263245

01:12:56.736 --> 01:12:58.506 a little more difficult to
NOTE Confidence: 0.841076493263245

01:12:58.506 --> 01:13:00.130 obtain from all patients.
NOTE Confidence: 0.841076493263245

01:13:00.130 --> 01:13:00.810 OK, and
NOTE Confidence: 0.768946826457977

01:13:00.810 --> 01:13:02.862 a question from one of our
NOTE Confidence: 0.768946826457977

01:13:02.862 --> 01:13:03.873 surgical Oncologist. Spectrally,
NOTE Confidence: 0.768946826457977

01:13:03.873 --> 01:13:06.134 no have you used a bit genetic
NOTE Confidence: 0.768946826457977

01:13:06.134 --> 01:13:08.613 drugs to attempt to increase M HC
NOTE Confidence: 0.768946826457977

01:13:08.613 --> 01:13:10.383 expression on tumor cells prior
NOTE Confidence: 0.768946826457977

01:13:10.390 --> 01:13:11.758 to utilizing till treatments?
NOTE Confidence: 0.897592306137085

01:13:11.820 --> 01:13:15.312 About 10 years ago we did a study giving.
NOTE Confidence: 0.897592306137085

01:13:15.320 --> 01:13:17.650 Escalating doses of Interferon Gamma,
NOTE Confidence: 0.897592306137085

01:13:17.650 --> 01:13:20.434 which is a very potent molecule
NOTE Confidence: 0.897592306137085

01:13:20.434 --> 01:13:23.751 that can up regulate class one and

NOTE Confidence: 0.897592306137085
01:13:23.751 --> 01:13:26.487 Class 2 antigens on tumor cells.
NOTE Confidence: 0.897592306137085
01:13:26.490 --> 01:13:29.706 But we reached very toxic levels
NOTE Confidence: 0.897592306137085
01:13:29.706 --> 01:13:31.850 of Interferon Gamma administration
NOTE Confidence: 0.897592306137085
01:13:31.930 --> 01:13:34.234 and did not see any significant
NOTE Confidence: 0.897592306137085
01:13:34.234 --> 01:13:36.650 increase in MA C molecules.
NOTE Confidence: 0.897592306137085
01:13:36.650 --> 01:13:39.554 If there are ways to up
NOTE Confidence: 0.897592306137085
01:13:39.554 --> 01:13:41.490 regulate them in Vivo,
NOTE Confidence: 0.897592306137085
01:13:41.490 --> 01:13:44.878 I think one could improve the effectiveness
NOTE Confidence: 0.854975409805775
01:13:44.880 --> 01:13:46.074 of these treatments.
NOTE Confidence: 0.854975409805775
01:13:46.074 --> 01:13:48.064 Can I ask a question?
NOTE Confidence: 0.854975409805775
01:13:48.070 --> 01:13:50.116 Sure, there are a couple of.
NOTE Confidence: 0.854975409805775
01:13:50.120 --> 01:13:52.178 Maybe it's a really great talk.
NOTE Confidence: 0.854975409805775
01:13:52.180 --> 01:13:53.548 Really, really enjoyed that.
NOTE Confidence: 0.854975409805775
01:13:53.548 --> 01:13:55.560 Also, I think I want to.
NOTE Confidence: 0.854975409805775
01:13:55.560 --> 01:13:57.432 I'm sure everyone or many people
NOTE Confidence: 0.854975409805775

01:13:57.432 --> 01:13:59.752 realize how much of a Tour de
NOTE Confidence: 0.854975409805775

01:13:59.752 --> 01:14:01.432 force identifying all those antigen
NOTE Confidence: 0.854975409805775

01:14:01.432 --> 01:14:03.548 specific T cells and epitopes are,
NOTE Confidence: 0.854975409805775

01:14:03.550 --> 01:14:06.206 but it's not trivial answer reason why not.
NOTE Confidence: 0.854975409805775

01:14:06.210 --> 01:14:07.880 Many people have done that,
NOTE Confidence: 0.854975409805775

01:14:07.880 --> 01:14:09.212 but identifying tumor reactive
NOTE Confidence: 0.854975409805775

01:14:09.212 --> 01:14:11.562 T cells up front in a high
NOTE Confidence: 0.854975409805775

01:14:11.562 --> 01:14:13.590 throughput way I'm sure is something
NOTE Confidence: 0.854975409805775

01:14:13.655 --> 01:14:15.539 that you thought a lot about.
NOTE Confidence: 0.854975409805775

01:14:15.540 --> 01:14:17.200 You mentioned for one BB.
NOTE Confidence: 0.854975409805775

01:14:17.200 --> 01:14:19.864 Now the CD 39 C 69 double negatives.
NOTE Confidence: 0.854975409805775

01:14:19.870 --> 01:14:21.868 What are your thoughts moving forward
NOTE Confidence: 0.854975409805775

01:14:21.870 --> 01:14:23.684 about identifying tumor reactive till?
NOTE Confidence: 0.854975409805775

01:14:23.684 --> 01:14:26.104 Prior to expansion and focusing
NOTE Confidence: 0.854975409805775

01:14:26.104 --> 01:14:27.556 on that subset.
NOTE Confidence: 0.854975409805775

01:14:27.560 --> 01:14:27.990 So

NOTE Confidence: 0.860600233078003
01:14:27.990 --> 01:14:30.570 I haven't talked about that much,
NOTE Confidence: 0.860600233078003
01:14:30.570 --> 01:14:33.930 but one of We are pursuing these high
NOTE Confidence: 0.860600233078003
01:14:33.930 --> 01:14:36.445 dimensional analysis approach is to try
NOTE Confidence: 0.860600233078003
01:14:36.445 --> 01:14:38.689 to answer that question starting with
NOTE Confidence: 0.860600233078003
01:14:38.689 --> 01:14:41.342 cells that are isolated from individual
NOTE Confidence: 0.860600233078003
01:14:41.342 --> 01:14:44.264 single cell suspensions from a respective
NOTE Confidence: 0.860600233078003
01:14:44.264 --> 01:14:47.082 lesion and he studies being done by
NOTE Confidence: 0.860600233078003
01:14:47.082 --> 01:14:49.919 Frank Lowery in the surgery branch,
NOTE Confidence: 0.860600233078003
01:14:49.920 --> 01:14:52.980 and in fact we can in fact do this
NOTE Confidence: 0.860600233078003
01:14:52.980 --> 01:14:55.460 analysis on these individual and
NOTE Confidence: 0.860600233078003
01:14:55.460 --> 01:14:58.544 individual cells and attempt to identify.
NOTE Confidence: 0.860600233078003
01:14:58.550 --> 01:15:01.595 Markers that might be significant and there
NOTE Confidence: 0.860600233078003
01:15:01.595 --> 01:15:05.229 are about 19 markers that he's identified.
NOTE Confidence: 0.860600233078003
01:15:05.230 --> 01:15:09.514 Perhaps the most prominent one is CX CL 13.
NOTE Confidence: 0.860600233078003
01:15:09.520 --> 01:15:11.910 As a as a marker,
NOTE Confidence: 0.860600233078003

01:15:11.910 --> 01:15:15.249 but there are gene signatures that can.
NOTE Confidence: 0.860600233078003

01:15:15.250 --> 01:15:17.630 We believe very early work.
NOTE Confidence: 0.860600233078003

01:15:17.630 --> 01:15:20.492 Identify the cells from the original
NOTE Confidence: 0.860600233078003

01:15:20.492 --> 01:15:22.400 tumor before their cultured.
NOTE Confidence: 0.860600233078003

01:15:22.400 --> 01:15:25.935 That might be a means of identifying
NOTE Confidence: 0.860600233078003

01:15:25.935 --> 01:15:29.319 those those cells and expanding them.
NOTE Confidence: 0.860600233078003

01:15:29.320 --> 01:15:30.530 So that's that's a challenge,
NOTE Confidence: 0.860600233078003

01:15:30.530 --> 01:15:32.726 but I think one that is.
NOTE Confidence: 0.860600233078003

01:15:32.730 --> 01:15:36.440 That will likely be possible to accomplish.
NOTE Confidence: 0.827853083610535

01:15:38.500 --> 01:15:43.546 Right Crystal maybe will. Thanks so much.
NOTE Confidence: 0.827853083610535

01:15:43.550 --> 01:15:46.710 Doctor Rosenberg. Yeah. It's
NOTE Confidence: 0.85187703371048

01:15:46.710 --> 01:15:48.894 my great the my great pleasure and
NOTE Confidence: 0.85187703371048

01:15:48.894 --> 01:15:51.439 it was a great pleasure to have
NOTE Confidence: 0.85187703371048

01:15:51.439 --> 01:15:53.743 Tristan be one of our fellows.
NOTE Confidence: 0.85187703371048

01:15:53.750 --> 01:15:55.784 I should mention that virtually all
NOTE Confidence: 0.85187703371048

01:15:55.784 --> 01:15:58.281 the work that I've presented over has

NOTE Confidence: 0.85187703371048
01:15:58.281 --> 01:16:00.429 accumulated over the last 20 years
NOTE Confidence: 0.85187703371048
01:16:00.429 --> 01:16:02.923 was done by Clinical Fellows who come
NOTE Confidence: 0.85187703371048
01:16:02.923 --> 01:16:05.366 to the surgery branch to do research.
NOTE Confidence: 0.85187703371048
01:16:05.366 --> 01:16:06.780 So Tristan, thank you
NOTE Confidence: 0.85187703371048
01:16:06.780 --> 01:16:08.540 for your contributions. Thank you
NOTE Confidence: 0.85187703371048
01:16:08.540 --> 01:16:10.300 so much. There's a picture
NOTE Confidence: 0.85187703371048
01:16:10.300 --> 01:16:12.406 of me with with the other
NOTE Confidence: 0.85187703371048
01:16:12.406 --> 01:16:13.460 fellows behind their
NOTE Confidence: 0.85187703371048
01:16:13.460 --> 01:16:14.519 strategically placed it
NOTE Confidence: 0.85187703371048
01:16:14.519 --> 01:16:17.030 over there for. They are
NOTE Confidence: 0.833613932132721
01:16:17.030 --> 01:16:19.780 good zoom work OK,
NOTE Confidence: 0.833613932132721
01:16:19.780 --> 01:16:26.620 so I guess I will introduce the next speaker.
NOTE Confidence: 0.833613932132721
01:16:26.620 --> 01:16:33.050 How do I do this? Alesso do we? So if
NOTE Confidence: 0.723658978939056
01:16:33.050 --> 01:16:34.490 crystal just goes ahead
NOTE Confidence: 0.723658978939056
01:16:34.490 --> 01:16:37.280 and shares her screen.
NOTE Confidence: 0.834475576877594

01:16:37.280 --> 01:16:38.868 Myself Crystal yeah yeah,
NOTE Confidence: 0.834475576877594

01:16:38.870 --> 01:16:41.660 so can you go to the two?
NOTE Confidence: 0.834475576877594

01:16:41.660 --> 01:16:44.708 Can you go to the green share screen
NOTE Confidence: 0.834475576877594

01:16:44.708 --> 01:16:47.627 button at the bottom of the window?
NOTE Confidence: 0.834475576877594

01:16:47.630 --> 01:16:49.254 You're my screen. Yep,
NOTE Confidence: 0.834475576877594

01:16:49.254 --> 01:16:52.098 great, I assume OK, it is my
NOTE Confidence: 0.820855259895325

01:16:52.100 --> 01:16:54.125 great pleasure also to introduce
NOTE Confidence: 0.820855259895325

01:16:54.125 --> 01:16:55.340 Doctor Crystal Mackall.
NOTE Confidence: 0.820855259895325

01:16:55.340 --> 01:16:57.750 She's currently the earnest and Amelia
NOTE Confidence: 0.820855259895325

01:16:57.750 --> 01:17:00.030 Gallo family professor of Medicine and
NOTE Confidence: 0.820855259895325

01:17:00.030 --> 01:17:01.840 Pediatrics at Stanford University.
NOTE Confidence: 0.820855259895325

01:17:01.840 --> 01:17:04.272 She's also the founding director of
NOTE Confidence: 0.820855259895325

01:17:04.272 --> 01:17:06.712 the Stanford Center for cell therapy.
NOTE Confidence: 0.820855259895325

01:17:06.712 --> 01:17:09.556 Prior to this, she was at the
NOTE Confidence: 0.820855259895325

01:17:09.556 --> 01:17:11.180 National Cancer Cancer Institute,
NOTE Confidence: 0.820855259895325

01:17:11.180 --> 01:17:13.628 initially as a fellow in pediatric

NOTE Confidence: 0.820855259895325

01:17:13.628 --> 01:17:16.050 oncology and remained there until 2016,

NOTE Confidence: 0.820855259895325

01:17:16.050 --> 01:17:17.682 serving as the chief.

NOTE Confidence: 0.820855259895325

01:17:17.682 --> 01:17:19.314 Of Pediatric Oncology Branch.

NOTE Confidence: 0.820855259895325

01:17:19.320 --> 01:17:21.721 Doctor Michael is a leading pioneer in

NOTE Confidence: 0.820855259895325

01:17:21.721 --> 01:17:23.833 the development of cancer immunotherapy's

NOTE Confidence: 0.820855259895325

01:17:23.833 --> 01:17:25.877 in the pediatric population.

NOTE Confidence: 0.820855259895325

01:17:25.880 --> 01:17:28.701 Her group was among the first to

NOTE Confidence: 0.820855259895325

01:17:28.701 --> 01:17:30.812 impressive the impressive activity of

NOTE Confidence: 0.820855259895325

01:17:30.812 --> 01:17:33.308 the CD 19 Chimeric Antigen Receptor

NOTE Confidence: 0.820855259895325

01:17:33.308 --> 01:17:35.407 in childhood leukemia and also

NOTE Confidence: 0.820855259895325

01:17:35.407 --> 01:17:37.387 developed a car product targeting

NOTE Confidence: 0.820855259895325

01:17:37.387 --> 01:17:41.426 CD 22 and is active in this disease.

NOTE Confidence: 0.820855259895325

01:17:41.430 --> 01:17:44.238 The title of her talk is next generation

NOTE Confidence: 0.820855259895325

01:17:44.238 --> 01:17:47.239 car T cells to overcome resistance.

NOTE Confidence: 0.820855259895325

01:17:47.240 --> 01:17:47.710 Well

NOTE Confidence: 0.857698261737823

01:17:47.710 --> 01:17:49.980 thank you Tristan and it's
NOTE Confidence: 0.857698261737823

01:17:49.980 --> 01:17:52.820 a real pleasure to be here.
NOTE Confidence: 0.857698261737823

01:17:52.820 --> 01:17:55.430 Many valued friends and colleagues at
NOTE Confidence: 0.857698261737823

01:17:55.430 --> 01:17:58.873 at Yale and clearly a center that is
NOTE Confidence: 0.857698261737823

01:17:58.873 --> 01:18:01.303 contributed greatly in always to our
NOTE Confidence: 0.857698261737823

01:18:01.381 --> 01:18:03.977 understanding of human immunology.
NOTE Confidence: 0.857698261737823

01:18:03.980 --> 01:18:08.165 So it's great to speak with you all today,
NOTE Confidence: 0.857698261737823

01:18:08.170 --> 01:18:11.563 and even even better than I have the honor
NOTE Confidence: 0.857698261737823

01:18:11.563 --> 01:18:15.139 and pleasure or following Steve Rosenberg,
NOTE Confidence: 0.857698261737823

01:18:15.140 --> 01:18:19.343 who is clearly a giant in this field and.
NOTE Confidence: 0.857698261737823

01:18:19.350 --> 01:18:20.854 You know, in fact,
NOTE Confidence: 0.857698261737823

01:18:20.854 --> 01:18:23.670 the reason I got involved in cancer
NOTE Confidence: 0.857698261737823

01:18:23.670 --> 01:18:26.974 immunotherapy back in the 80s was due
NOTE Confidence: 0.857698261737823

01:18:26.974 --> 01:18:29.450 to inspiration from Steve's work.
NOTE Confidence: 0.857698261737823

01:18:29.450 --> 01:18:33.050 So it's always great to hear his updates.
NOTE Confidence: 0.857698261737823

01:18:33.050 --> 01:18:36.340 So here are some of my disclosures

NOTE Confidence: 0.857698261737823
01:18:36.340 --> 01:18:39.669 and I guess I'm going to focus
NOTE Confidence: 0.857698261737823
01:18:39.669 --> 01:18:41.939 on car T cells today,
NOTE Confidence: 0.857698261737823
01:18:41.940 --> 01:18:44.808 but hopefully can provide some stories
NOTE Confidence: 0.857698261737823
01:18:44.808 --> 01:18:47.716 that will give value to understanding
NOTE Confidence: 0.857698261737823
01:18:47.716 --> 01:18:50.894 of General T cell Biology that might
NOTE Confidence: 0.857698261737823
01:18:50.894 --> 01:18:54.109 be relevant even beyond car T cells.
NOTE Confidence: 0.857698261737823
01:18:54.110 --> 01:18:57.617 And, as Steve alluded to following the
NOTE Confidence: 0.857698261737823
01:18:57.617 --> 01:18:59.998 first demonstration of the effectiveness
NOTE Confidence: 0.857698261737823
01:18:59.998 --> 01:19:03.980 of the CD 19 car in large cell lymphoma.
NOTE Confidence: 0.857698261737823
01:19:03.980 --> 01:19:06.548 At the surgery branch.
NOTE Confidence: 0.857698261737823
01:19:06.548 --> 01:19:09.758 The decade of remarkable progress.
NOTE Confidence: 0.857698261737823
01:19:09.760 --> 01:19:10.534 A Kurd,
NOTE Confidence: 0.857698261737823
01:19:10.534 --> 01:19:12.856 culminating in FDA approval of the
NOTE Confidence: 0.857698261737823
01:19:12.856 --> 01:19:15.941 first cell therapies and the first gene
NOTE Confidence: 0.857698261737823
01:19:15.941 --> 01:19:18.760 therapies approved in the United States.
NOTE Confidence: 0.857698261737823

01:19:18.760 --> 01:19:21.112 Kymriah forbis OLL and yes Carta
NOTE Confidence: 0.857698261737823

01:19:21.112 --> 01:19:23.480 for large B cell lymphoma.
NOTE Confidence: 0.857698261737823

01:19:23.480 --> 01:19:26.112 These were the first out of the
NOTE Confidence: 0.857698261737823

01:19:26.112 --> 01:19:28.998 gate and and you know this is
NOTE Confidence: 0.857698261737823

01:19:28.998 --> 01:19:31.506 an immense success story that is
NOTE Confidence: 0.857698261737823

01:19:31.600 --> 01:19:34.250 just catalyzed the whole field.
NOTE Confidence: 0.857698261737823

01:19:34.250 --> 01:19:36.818 As an academic in the space,
NOTE Confidence: 0.857698261737823

01:19:36.820 --> 01:19:39.548 what what we see as our job at
NOTE Confidence: 0.857698261737823

01:19:39.548 --> 01:19:42.262 Stanford is to understand the failures
NOTE Confidence: 0.857698261737823

01:19:42.262 --> 01:19:45.184 that remain in this space because
NOTE Confidence: 0.857698261737823

01:19:45.272 --> 01:19:47.900 despite all of the progress for
NOTE Confidence: 0.857698261737823

01:19:47.900 --> 01:19:50.494 both the children with beef lol.
NOTE Confidence: 0.857698261737823

01:19:50.494 --> 01:19:53.413 Elan or adult patients who get treated
NOTE Confidence: 0.857698261737823

01:19:53.413 --> 01:19:56.077 with these agents were still under
NOTE Confidence: 0.857698261737823

01:19:56.077 --> 01:19:58.330 50% for long-term Disease Control.
NOTE Confidence: 0.857698261737823

01:19:58.330 --> 01:20:02.317 And it is our belief that we can use

NOTE Confidence: 0.857698261737823

01:20:02.317 --> 01:20:05.540 this model system to really dive deep into.

NOTE Confidence: 0.857698261737823

01:20:05.540 --> 01:20:08.669 The factors that are required for the

NOTE Confidence: 0.857698261737823

01:20:08.669 --> 01:20:11.360 success, particularly in car T cells,

NOTE Confidence: 0.857698261737823

01:20:11.360 --> 01:20:13.904 and that these insights will fuel

NOTE Confidence: 0.857698261737823

01:20:13.904 --> 01:20:17.188 our work in going toward solid tumors.

NOTE Confidence: 0.857698261737823

01:20:17.190 --> 01:20:20.326 I do disagree with Steve that Cartis

NOTE Confidence: 0.857698261737823

01:20:20.326 --> 01:20:22.948 Osar Fatalii flawed for solid tumors,

NOTE Confidence: 0.857698261737823

01:20:22.948 --> 01:20:26.170 and I hope to prove him wrong.

NOTE Confidence: 0.857698261737823

01:20:26.170 --> 01:20:29.506 In my in the coming years.

NOTE Confidence: 0.857698261737823

01:20:29.510 --> 01:20:32.885 So as far as yescarta for B cell lymphoma,

NOTE Confidence: 0.857698261737823

01:20:32.890 --> 01:20:34.390 as I mentioned there,

NOTE Confidence: 0.857698261737823

01:20:34.390 --> 01:20:37.590 about 60% of the patients who go on to

NOTE Confidence: 0.857698261737823

01:20:37.590 --> 01:20:39.640 progress after receiving other therapy.

NOTE Confidence: 0.857698261737823

01:20:39.640 --> 01:20:41.872 And the interesting thing is that

NOTE Confidence: 0.857698261737823

01:20:41.872 --> 01:20:44.832 most of the action nearly all of the

NOTE Confidence: 0.857698261737823

01:20:44.832 --> 01:20:47.510 action happens in the first six months.
NOTE Confidence: 0.857698261737823

01:20:47.510 --> 01:20:49.760 If you are still in remission
NOTE Confidence: 0.857698261737823

01:20:49.760 --> 01:20:50.885 after six months,
NOTE Confidence: 0.857698261737823

01:20:50.890 --> 01:20:53.098 we have this really amazing long
NOTE Confidence: 0.857698261737823

01:20:53.098 --> 01:20:55.426 tail that looks to be curatives
NOTE Confidence: 0.857698261737823

01:20:55.426 --> 01:20:58.156 and so it helps in terms of
NOTE Confidence: 0.857698261737823

01:20:58.156 --> 01:20:59.920 understanding the those who are.
NOTE Confidence: 0.857698261737823

01:20:59.920 --> 01:21:00.940 Successes versus failures.
NOTE Confidence: 0.857698261737823

01:21:00.940 --> 01:21:03.720 By focusing on that six month time point,
NOTE Confidence: 0.857698261737823

01:21:03.720 --> 01:21:06.480 Anne and there are clearly a lot of
NOTE Confidence: 0.857698261737823

01:21:06.480 --> 01:21:09.239 ways that car T cells can fail here.
NOTE Confidence: 0.857698261737823

01:21:09.240 --> 01:21:11.376 From a recent review were sort
NOTE Confidence: 0.857698261737823

01:21:11.376 --> 01:21:13.258 of highlighting those that we
NOTE Confidence: 0.857698261737823

01:21:13.258 --> 01:21:15.616 think are the most important tumor
NOTE Confidence: 0.857698261737823

01:21:15.616 --> 01:21:17.128 heterogeneity and antigen loss
NOTE Confidence: 0.857698261737823

01:21:17.128 --> 01:21:19.232 is an area of great focus for us.

NOTE Confidence: 0.857698261737823
01:21:19.240 --> 01:21:22.000 I'm not going to talk about it today,
NOTE Confidence: 0.847586452960968
01:21:22.000 --> 01:21:23.897 but Suffice it to say that clearly
NOTE Confidence: 0.847586452960968
01:21:23.897 --> 01:21:25.847 1/3 of the yescarta failures or
NOTE Confidence: 0.847586452960968
01:21:25.847 --> 01:21:27.983 associated with complete loss of CD
NOTE Confidence: 0.847586452960968
01:21:27.983 --> 01:21:30.618 19 and another third are associated
NOTE Confidence: 0.847586452960968
01:21:30.618 --> 01:21:32.390 with significant down regulation.
NOTE Confidence: 0.847586452960968
01:21:32.390 --> 01:21:35.382 But the other piece of this is really
NOTE Confidence: 0.847586452960968
01:21:35.382 --> 01:21:37.220 the functionality of the T cells,
NOTE Confidence: 0.847586452960968
01:21:37.220 --> 01:21:40.670 and we've spent a lot of time in that area,
NOTE Confidence: 0.847586452960968
01:21:40.670 --> 01:21:42.400 so I want to start.
NOTE Confidence: 0.847586452960968
01:21:42.400 --> 01:21:44.157 The first story is to talk about
NOTE Confidence: 0.847586452960968
01:21:44.157 --> 01:21:46.164 a cohort of patients treated with
NOTE Confidence: 0.847586452960968
01:21:46.164 --> 01:21:48.558 yescarta at Stanford on the commercial
NOTE Confidence: 0.847586452960968
01:21:48.558 --> 01:21:50.329 receiving the commercial product,
NOTE Confidence: 0.847586452960968
01:21:50.330 --> 01:21:52.745 and you know, the sad truth is,
NOTE Confidence: 0.847586452960968

01:21:52.750 --> 01:21:54.622 you can't get your hands on
NOTE Confidence: 0.847586452960968

01:21:54.622 --> 01:21:56.317 the product for those patients
NOTE Confidence: 0.847586452960968

01:21:56.317 --> 01:21:58.609 because of the contract you sign.
NOTE Confidence: 0.847586452960968

01:21:58.610 --> 01:22:00.680 You really aren't permitted to go
NOTE Confidence: 0.847586452960968

01:22:00.680 --> 01:22:03.540 into the bag, but what we can do?
NOTE Confidence: 0.847586452960968

01:22:03.540 --> 01:22:05.364 As we can study these patients
NOTE Confidence: 0.847586452960968

01:22:05.364 --> 01:22:07.049 after they receive their commercial
NOTE Confidence: 0.847586452960968

01:22:07.049 --> 01:22:09.119 product and try to understand
NOTE Confidence: 0.847586452960968

01:22:09.119 --> 01:22:10.775 what distinguishes those patients,
NOTE Confidence: 0.847586452960968

01:22:10.780 --> 01:22:11.782 who, for whom.
NOTE Confidence: 0.847586452960968

01:22:11.782 --> 01:22:14.120 The treatment is a success versus for
NOTE Confidence: 0.847586452960968

01:22:14.190 --> 01:22:16.566 those whom they treatment fails them.
NOTE Confidence: 0.847586452960968

01:22:16.570 --> 01:22:18.742 And this is our outcomes for
NOTE Confidence: 0.847586452960968

01:22:18.742 --> 01:22:19.828 the Yescarta Cohort.
NOTE Confidence: 0.847586452960968

01:22:19.830 --> 01:22:21.640 This is 32 patients that
NOTE Confidence: 0.847586452960968

01:22:21.640 --> 01:22:23.450 we are working with here,

NOTE Confidence: 0.847586452960968
01:22:23.450 --> 01:22:25.640 and the purpose of this story
NOTE Confidence: 0.847586452960968
01:22:25.640 --> 01:22:27.430 and you can see it.
NOTE Confidence: 0.847586452960968
01:22:27.430 --> 01:22:29.775 It exactly mirrors the Zuma one data
NOTE Confidence: 0.847586452960968
01:22:29.775 --> 01:22:32.498 and if you ask the question first,
NOTE Confidence: 0.847586452960968
01:22:32.500 --> 01:22:34.612 well maybe it just relates to
NOTE Confidence: 0.847586452960968
01:22:34.612 --> 01:22:37.250 how well the car T cells expand.
NOTE Confidence: 0.847586452960968
01:22:37.250 --> 01:22:40.445 In our hands we do not see a correlation
NOTE Confidence: 0.847586452960968
01:22:40.445 --> 01:22:42.729 between the area under the curve.
NOTE Confidence: 0.847586452960968
01:22:42.730 --> 01:22:43.681 In other words,
NOTE Confidence: 0.847586452960968
01:22:43.681 --> 01:22:45.583 the height and the duration of
NOTE Confidence: 0.847586452960968
01:22:45.583 --> 01:22:47.626 expansion and overall outcome that
NOTE Confidence: 0.847586452960968
01:22:47.626 --> 01:22:49.294 does correlate with neurotoxicity,
NOTE Confidence: 0.847586452960968
01:22:49.300 --> 01:22:52.276 but we do not see it correlating with
NOTE Confidence: 0.847586452960968
01:22:52.276 --> 01:22:55.140 overall outcome and so we asked the question,
NOTE Confidence: 0.847586452960968
01:22:55.140 --> 01:22:57.772 might we be able to dive deeper
NOTE Confidence: 0.847586452960968

01:22:57.772 --> 01:22:59.714 into these populations that expand
NOTE Confidence: 0.847586452960968

01:22:59.714 --> 01:23:02.297 after infusion and at an early time
NOTE Confidence: 0.847586452960968

01:23:02.297 --> 01:23:04.412 point be able to predict what's
NOTE Confidence: 0.847586452960968

01:23:04.412 --> 01:23:06.458 going to happen at six months,
NOTE Confidence: 0.847586452960968

01:23:06.458 --> 01:23:08.298 and so to do this.
NOTE Confidence: 0.847586452960968

01:23:08.300 --> 01:23:11.114 We've leveraged the power of mass cytometry,
NOTE Confidence: 0.847586452960968

01:23:11.120 --> 01:23:13.538 a technique that has been developed
NOTE Confidence: 0.847586452960968

01:23:13.538 --> 01:23:15.150 at Stanford and optimized,
NOTE Confidence: 0.847586452960968

01:23:15.150 --> 01:23:17.165 and there's lots of expertise
NOTE Confidence: 0.847586452960968

01:23:17.165 --> 01:23:18.777 in our community here,
NOTE Confidence: 0.847586452960968

01:23:18.780 --> 01:23:21.125 and I have the pleasure on working
NOTE Confidence: 0.847586452960968

01:23:21.125 --> 01:23:23.716 on this project with a very
NOTE Confidence: 0.847586452960968

01:23:23.716 --> 01:23:25.225 talented computational urologist,
NOTE Confidence: 0.847586452960968

01:23:25.230 --> 01:23:28.044 azina good and So what Xena asked,
NOTE Confidence: 0.847586452960968

01:23:28.050 --> 01:23:30.140 was whether she could identify
NOTE Confidence: 0.847586452960968

01:23:30.140 --> 01:23:32.230 early after infusion and now

NOTE Confidence: 0.847586452960968
01:23:32.303 --> 01:23:34.499 she is talking about day seven.
NOTE Confidence: 0.847586452960968
01:23:34.500 --> 01:23:36.864 So seven days after infusion she
NOTE Confidence: 0.847586452960968
01:23:36.864 --> 01:23:38.872 wants to understand whether there
NOTE Confidence: 0.847586452960968
01:23:38.872 --> 01:23:40.707 might be an early predictive
NOTE Confidence: 0.847586452960968
01:23:40.707 --> 01:23:42.970 biomarker that can be identified.
NOTE Confidence: 0.847586452960968
01:23:42.970 --> 01:23:44.925 That might predict what happens
NOTE Confidence: 0.847586452960968
01:23:44.925 --> 01:23:47.316 to these patients six months down
NOTE Confidence: 0.847586452960968
01:23:47.316 --> 01:23:49.494 the line and using flow cytometry.
NOTE Confidence: 0.847586452960968
01:23:49.500 --> 01:23:50.622 With these targets,
NOTE Confidence: 0.847586452960968
01:23:50.622 --> 01:23:52.866 she identified a total of 10
NOTE Confidence: 0.847586452960968
01:23:52.866 --> 01:23:54.868 meta clusters on day seven,
NOTE Confidence: 0.847586452960968
01:23:54.870 --> 01:23:57.478 and each of these meta clusters can be
NOTE Confidence: 0.847586452960968
01:23:57.478 --> 01:23:59.868 shown here visually as encompassing.
NOTE Confidence: 0.847586452960968
01:23:59.870 --> 01:24:01.790 You know there are subsets
NOTE Confidence: 0.847586452960968
01:24:01.790 --> 01:24:03.710 of meta clusters as well.
NOTE Confidence: 0.847586452960968

01:24:03.710 --> 01:24:06.398 You can see meta cluster 3 here

NOTE Confidence: 0.847586452960968

01:24:06.398 --> 01:24:08.252 has two subsets, for instance,

NOTE Confidence: 0.847586452960968

01:24:08.252 --> 01:24:10.709 and each of these subsets is defined

NOTE Confidence: 0.847586452960968

01:24:10.709 --> 01:24:12.978 by its own special combination.

NOTE Confidence: 0.847586452960968

01:24:12.980 --> 01:24:15.055 Of the cell surface and

NOTE Confidence: 0.847586452960968

01:24:15.055 --> 01:24:15.885 intracellular markers.

NOTE Confidence: 0.847586452960968

01:24:15.890 --> 01:24:17.140 Now of course,

NOTE Confidence: 0.847586452960968

01:24:17.140 --> 01:24:19.630 you can't do this with the

NOTE Confidence: 0.847586452960968

01:24:19.630 --> 01:24:20.875 without some computation,

NOTE Confidence: 0.847586452960968

01:24:20.880 --> 01:24:21.736 computational assistance,

NOTE Confidence: 0.847586452960968

01:24:21.736 --> 01:24:23.876 and so there are variety

NOTE Confidence: 0.847586452960968

01:24:23.876 --> 01:24:25.879 of these models out there.

NOTE Confidence: 0.847586452960968

01:24:25.880 --> 01:24:27.304 The lasso analysis was

NOTE Confidence: 0.847586452960968

01:24:27.304 --> 01:24:29.440 developed at Stanford to try to

NOTE Confidence: 0.836430728435516

01:24:29.512 --> 01:24:31.852 identify those clusters which are

NOTE Confidence: 0.836430728435516

01:24:31.852 --> 01:24:34.192 associated with a particular outcome,

NOTE Confidence: 0.836430728435516

01:24:34.200 --> 01:24:36.414 and again, here were asking whether

NOTE Confidence: 0.836430728435516

01:24:36.414 --> 01:24:38.876 we can identify an early biomarker

NOTE Confidence: 0.836430728435516

01:24:38.876 --> 01:24:40.708 associated with complete response

NOTE Confidence: 0.836430728435516

01:24:40.708 --> 01:24:43.839 at six months and the Lasso decided

NOTE Confidence: 0.836430728435516

01:24:43.839 --> 01:24:45.889 that three meta clusters were.

NOTE Confidence: 0.836430728435516

01:24:45.890 --> 01:24:48.396 The sweet spot at which you could

NOTE Confidence: 0.836430728435516

01:24:48.396 --> 01:24:50.839 get your highest level of accuracy,

NOTE Confidence: 0.836430728435516

01:24:50.840 --> 01:24:52.856 and so indeed what we've identified

NOTE Confidence: 0.836430728435516

01:24:52.856 --> 01:24:55.139 is there are three meta clusters

NOTE Confidence: 0.836430728435516

01:24:55.139 --> 01:24:57.319 associated with a positive outcome.

NOTE Confidence: 0.836430728435516

01:24:57.320 --> 01:25:00.056 The 1st two are Co expression of the

NOTE Confidence: 0.836430728435516

01:25:00.056 --> 01:25:02.463 marker CD57A marker that has been

NOTE Confidence: 0.836430728435516

01:25:02.463 --> 01:25:04.935 associated with senescence in T cells,

NOTE Confidence: 0.836430728435516

01:25:04.940 --> 01:25:07.214 and this is true whether it

NOTE Confidence: 0.836430728435516

01:25:07.214 --> 01:25:09.510 is a neither car T cells.

NOTE Confidence: 0.836430728435516

01:25:09.510 --> 01:25:12.939 Now we're not talking about non car T cells,
NOTE Confidence: 0.836430728435516

01:25:12.940 --> 01:25:16.770 these are only the car T cells on Day 7.
NOTE Confidence: 0.836430728435516

01:25:16.770 --> 01:25:19.605 And if you have more CD4 or CD8 cells
NOTE Confidence: 0.836430728435516

01:25:19.605 --> 01:25:22.029 that express CD 57 on day seven,
NOTE Confidence: 0.836430728435516

01:25:22.030 --> 01:25:23.760 you're much more likely with
NOTE Confidence: 0.836430728435516

01:25:23.760 --> 01:25:26.146 these very strong P values to be
NOTE Confidence: 0.836430728435516

01:25:26.146 --> 01:25:27.626 in remission at six months.
NOTE Confidence: 0.836430728435516

01:25:27.630 --> 01:25:29.340 There was a third meta cluster
NOTE Confidence: 0.836430728435516

01:25:29.340 --> 01:25:31.250 which had the inverse relationship,
NOTE Confidence: 0.836430728435516

01:25:31.250 --> 01:25:33.850 wherein if you had expansion of these cells
NOTE Confidence: 0.836430728435516

01:25:33.850 --> 01:25:36.507 you were less likely to be in remission,
NOTE Confidence: 0.836430728435516

01:25:36.510 --> 01:25:38.274 and that is a meta cluster that
NOTE Confidence: 0.836430728435516

01:25:38.274 --> 01:25:40.790 is CD 4 positive pelayos positive.
NOTE Confidence: 0.836430728435516

01:25:40.790 --> 01:25:42.782 So now the power of the
NOTE Confidence: 0.836430728435516

01:25:42.782 --> 01:25:44.410 of the mass cytometry is.
NOTE Confidence: 0.836430728435516

01:25:44.410 --> 01:25:46.390 You can learn a lot about

NOTE Confidence: 0.836430728435516
01:25:46.390 --> 01:25:47.380 these meta clusters.
NOTE Confidence: 0.836430728435516
01:25:47.380 --> 01:25:49.750 By looking at whatever your favorite
NOTE Confidence: 0.836430728435516
01:25:49.750 --> 01:25:52.160 antigen of interest is and Steve
NOTE Confidence: 0.836430728435516
01:25:52.160 --> 01:25:54.446 mentioned CD39A marker of T cell
NOTE Confidence: 0.836430728435516
01:25:54.446 --> 01:25:56.420 exhaustion and not surprisingly,
NOTE Confidence: 0.836430728435516
01:25:56.420 --> 01:25:58.886 these cells are CD 39 negative,
NOTE Confidence: 0.836430728435516
01:25:58.890 --> 01:26:01.350 but surprisingly they are 57 positive,
NOTE Confidence: 0.836430728435516
01:26:01.350 --> 01:26:03.415 which is typically been associated
NOTE Confidence: 0.836430728435516
01:26:03.415 --> 01:26:05.880 with senescence in the spent cell.
NOTE Confidence: 0.836430728435516
01:26:05.880 --> 01:26:08.778 And so I think this was really
NOTE Confidence: 0.836430728435516
01:26:08.778 --> 01:26:10.400 a surprise to us.
NOTE Confidence: 0.836430728435516
01:26:10.400 --> 01:26:12.990 They tend to express some PD one
NOTE Confidence: 0.836430728435516
01:26:12.990 --> 01:26:15.972 you can see here the Meta cluster
NOTE Confidence: 0.836430728435516
01:26:15.972 --> 01:26:18.648 that is the Helios positive is.
NOTE Confidence: 0.836430728435516
01:26:18.650 --> 01:26:21.990 The one that is likely to be a T Reg.
NOTE Confidence: 0.836430728435516

01:26:21.990 --> 01:26:24.302 So now you know it's nice if you
NOTE Confidence: 0.836430728435516

01:26:24.302 --> 01:26:26.669 can do this by mass cytometry,
NOTE Confidence: 0.836430728435516

01:26:26.670 --> 01:26:28.870 but the truth is mass cytometry is not
NOTE Confidence: 0.836430728435516

01:26:28.870 --> 01:26:30.669 a particularly iaccessible technology,
NOTE Confidence: 0.836430728435516

01:26:30.670 --> 01:26:32.990 and So what Xena wanted to do is
NOTE Confidence: 0.836430728435516

01:26:32.990 --> 01:26:35.019 now armed with these insights.
NOTE Confidence: 0.836430728435516

01:26:35.020 --> 01:26:37.309 Should could she go back to simple
NOTE Confidence: 0.836430728435516

01:26:37.309 --> 01:26:39.380 flow cytometry and create a simple
NOTE Confidence: 0.836430728435516

01:26:39.380 --> 01:26:41.420 flow cytometry assay that might be
NOTE Confidence: 0.836430728435516

01:26:41.420 --> 01:26:43.750 able to be used widely to identify
NOTE Confidence: 0.836430728435516

01:26:43.750 --> 01:26:45.704 those patients who are likely to
NOTE Confidence: 0.836430728435516

01:26:45.704 --> 01:26:47.364 have good versus negative outcomes,
NOTE Confidence: 0.836430728435516

01:26:47.370 --> 01:26:49.090 and indeed a relatively simple
NOTE Confidence: 0.836430728435516

01:26:49.090 --> 01:26:50.466 flow cytometry panel was.
NOTE Confidence: 0.836430728435516

01:26:50.470 --> 01:26:52.325 Able to identify these patients
NOTE Confidence: 0.836430728435516

01:26:52.325 --> 01:26:53.438 as shown here.

NOTE Confidence: 0.836430728435516

01:26:53.440 --> 01:26:55.978 Here's an example patient with a

NOTE Confidence: 0.836430728435516

01:26:55.978 --> 01:26:58.361 complete response and you can see

NOTE Confidence: 0.836430728435516

01:26:58.361 --> 01:27:00.809 how how many car T cells all these

NOTE Confidence: 0.836430728435516

01:27:00.889 --> 01:27:03.079 are car T cells now expressed.

NOTE Confidence: 0.836430728435516

01:27:03.080 --> 01:27:03.860 CD 57.

NOTE Confidence: 0.836430728435516

01:27:03.860 --> 01:27:05.810 They're also Tibet positive and

NOTE Confidence: 0.836430728435516

01:27:05.810 --> 01:27:08.280 the same for the CD 8 subset.

NOTE Confidence: 0.836430728435516

01:27:08.280 --> 01:27:10.758 Here's an example of a patient

NOTE Confidence: 0.836430728435516

01:27:10.758 --> 01:27:12.822 with progressive disease at six

NOTE Confidence: 0.836430728435516

01:27:12.822 --> 01:27:15.209 months and you can see this patient

NOTE Confidence: 0.836430728435516

01:27:15.209 --> 01:27:17.178 had very little of the CD.

NOTE Confidence: 0.836430728435516

01:27:17.180 --> 01:27:18.317 57 positive cells,

NOTE Confidence: 0.836430728435516

01:27:18.317 --> 01:27:20.970 but in contrast had a high number.

NOTE Confidence: 0.836430728435516

01:27:20.970 --> 01:27:23.490 Of cells that Express Helios and these were

NOTE Confidence: 0.836430728435516

01:27:23.490 --> 01:27:25.670 all clearly statistically significant.

NOTE Confidence: 0.836430728435516

01:27:25.670 --> 01:27:26.062 Now,
NOTE Confidence: 0.836430728435516

01:27:26.062 --> 01:27:28.806 what are the functionality of these cells?
NOTE Confidence: 0.836430728435516

01:27:28.810 --> 01:27:31.418 So now we go back and we start
NOTE Confidence: 0.836430728435516

01:27:31.418 --> 01:27:33.545 to stimulate the specific cells
NOTE Confidence: 0.836430728435516

01:27:33.545 --> 01:27:35.870 with either PMA and ionomycin,
NOTE Confidence: 0.835059285163879

01:27:35.870 --> 01:27:37.830 or through the car itself,
NOTE Confidence: 0.835059285163879

01:27:37.830 --> 01:27:39.486 and perhaps not surprisingly,
NOTE Confidence: 0.835059285163879

01:27:39.486 --> 01:27:43.524 given what we know about CD 57 we see that
NOTE Confidence: 0.835059285163879

01:27:43.524 --> 01:27:46.193 these cells express very high levels of
NOTE Confidence: 0.835059285163879

01:27:46.193 --> 01:27:48.797 grandson be they don't make very much.
NOTE Confidence: 0.835059285163879

01:27:48.800 --> 01:27:51.600 I'll two and it's true whether you.
NOTE Confidence: 0.835059285163879

01:27:51.600 --> 01:27:52.791 Simulate with PMA,
NOTE Confidence: 0.835059285163879

01:27:52.791 --> 01:27:54.776 ionophore or through the car.
NOTE Confidence: 0.835059285163879

01:27:54.780 --> 01:27:56.364 The Helios positive cells,
NOTE Confidence: 0.835059285163879

01:27:56.364 --> 01:27:57.574 not surprisingly, however,
NOTE Confidence: 0.835059285163879

01:27:57.574 --> 01:28:00.058 are not granzyme B positive and

NOTE Confidence: 0.835059285163879
01:28:00.058 --> 01:28:03.108 look for all the world like T regs.
NOTE Confidence: 0.835059285163879
01:28:03.110 --> 01:28:05.700 Now we can use an even deeper
NOTE Confidence: 0.835059285163879
01:28:05.700 --> 01:28:07.879 dive using that NX platform.
NOTE Confidence: 0.835059285163879
01:28:07.880 --> 01:28:10.184 Now we're doing single cell RNA
NOTE Confidence: 0.835059285163879
01:28:10.184 --> 01:28:12.972 seq with site seek to really try
NOTE Confidence: 0.835059285163879
01:28:12.972 --> 01:28:15.318 to confirm more about these cells
NOTE Confidence: 0.835059285163879
01:28:15.318 --> 01:28:18.188 and it really all panned out the
NOTE Confidence: 0.835059285163879
01:28:18.188 --> 01:28:20.594 way we expected because here now
NOTE Confidence: 0.835059285163879
01:28:20.594 --> 01:28:23.006 using site seek you can define.
NOTE Confidence: 0.835059285163879
01:28:23.010 --> 01:28:25.880 The cells that are CD 57 positive
NOTE Confidence: 0.835059285163879
01:28:25.880 --> 01:28:28.897 CD 4 positive and now you can look
NOTE Confidence: 0.835059285163879
01:28:28.897 --> 01:28:32.073 at the RNA seq for each of these
NOTE Confidence: 0.835059285163879
01:28:32.073 --> 01:28:35.307 populations shown here on you map plot.
NOTE Confidence: 0.835059285163879
01:28:35.310 --> 01:28:39.000 So here are the T Reg sitting up here.
NOTE Confidence: 0.835059285163879
01:28:39.000 --> 01:28:42.402 Here are the CD 4 positive in the blue
NOTE Confidence: 0.835059285163879

01:28:42.402 --> 01:28:46.378 57 positive in the CD 857 shown in Green.

NOTE Confidence: 0.835059285163879

01:28:46.380 --> 01:28:49.236 You can see that the whereas the T

NOTE Confidence: 0.835059285163879

01:28:49.236 --> 01:28:52.120 regs are a very narrow population.

NOTE Confidence: 0.835059285163879

01:28:52.120 --> 01:28:54.598 The 57 is really distributed throughout.

NOTE Confidence: 0.835059285163879

01:28:54.600 --> 01:28:56.750 A more broad based population,

NOTE Confidence: 0.835059285163879

01:28:56.750 --> 01:28:59.746 so here are your CD four cells.

NOTE Confidence: 0.835059285163879

01:28:59.750 --> 01:29:02.582 You've got the T regs here that are

NOTE Confidence: 0.835059285163879

01:29:02.582 --> 01:29:05.984 Fox P3 positive helio cells are not

NOTE Confidence: 0.835059285163879

01:29:05.984 --> 01:29:09.190 expressing TCF one nor expressing CD 39,

NOTE Confidence: 0.835059285163879

01:29:09.190 --> 01:29:11.872 so this is exactly what you

NOTE Confidence: 0.835059285163879

01:29:11.872 --> 01:29:14.329 would expect from a T Reg.

NOTE Confidence: 0.835059285163879

01:29:14.330 --> 01:29:17.418 Here are your CD 8 cells that are

NOTE Confidence: 0.835059285163879

01:29:17.418 --> 01:29:20.338 expressing CD 57 also expressing Tibet,

NOTE Confidence: 0.835059285163879

01:29:20.340 --> 01:29:22.926 the enzyme that gives rise to

NOTE Confidence: 0.835059285163879

01:29:22.926 --> 01:29:24.650 the CD 57 epitope.

NOTE Confidence: 0.835059285163879

01:29:24.650 --> 01:29:26.530 Granzyme B and also talks,

NOTE Confidence: 0.835059285163879
01:29:26.530 --> 01:29:28.405 although talks really was not
NOTE Confidence: 0.835059285163879
01:29:28.405 --> 01:29:29.905 a good discriminator here,
NOTE Confidence: 0.835059285163879
01:29:29.910 --> 01:29:32.087 and so these cells do not appear
NOTE Confidence: 0.835059285163879
01:29:32.087 --> 01:29:34.800 to show a features of exhaustion.
NOTE Confidence: 0.835059285163879
01:29:34.800 --> 01:29:37.608 And then if you dive even deeper into
NOTE Confidence: 0.835059285163879
01:29:37.608 --> 01:29:39.931 these cell populations now we can
NOTE Confidence: 0.835059285163879
01:29:39.931 --> 01:29:42.706 start looking at the degree to which
NOTE Confidence: 0.835059285163879
01:29:42.706 --> 01:29:45.324 these cells are cycling and the CD.
NOTE Confidence: 0.835059285163879
01:29:45.330 --> 01:29:47.577 57 positive cells is shown here on
NOTE Confidence: 0.835059285163879
01:29:47.577 --> 01:29:50.345 a new map showing the cell cycling
NOTE Confidence: 0.835059285163879
01:29:50.345 --> 01:29:52.500 are really showing lower levels
NOTE Confidence: 0.835059285163879
01:29:52.500 --> 01:29:55.127 of cell cycling than than on 57.
NOTE Confidence: 0.835059285163879
01:29:55.130 --> 01:29:57.811 Positive self so they really are showing
NOTE Confidence: 0.835059285163879
01:29:57.811 --> 01:29:59.757 features that would be associated
NOTE Confidence: 0.835059285163879
01:29:59.757 --> 01:30:01.941 with senescence already at day seven
NOTE Confidence: 0.835059285163879

01:30:01.941 --> 01:30:04.268 in the blood of these patients.
NOTE Confidence: 0.835059285163879

01:30:04.270 --> 01:30:05.044 Not surprisingly,
NOTE Confidence: 0.835059285163879

01:30:05.044 --> 01:30:06.979 there are clonally expanded as
NOTE Confidence: 0.835059285163879

01:30:06.979 --> 01:30:09.230 shown in the orange and blue,
NOTE Confidence: 0.835059285163879

01:30:09.230 --> 01:30:11.576 looking at clones that are expanded
NOTE Confidence: 0.835059285163879

01:30:11.576 --> 01:30:14.707 greater or less than 10% compared to the
NOTE Confidence: 0.835059285163879

01:30:14.707 --> 01:30:18.250 non expanded in the grey and the blue.
NOTE Confidence: 0.835059285163879

01:30:18.250 --> 01:30:20.896 So this is been a surprise.
NOTE Confidence: 0.835059285163879

01:30:20.900 --> 01:30:23.110 It's not what we expected,
NOTE Confidence: 0.835059285163879

01:30:23.110 --> 01:30:25.973 but when you take these high dimensional
NOTE Confidence: 0.835059285163879

01:30:25.973 --> 01:30:27.970 single cell immune profiling,
NOTE Confidence: 0.835059285163879

01:30:27.970 --> 01:30:30.460 sometimes I think this is the
NOTE Confidence: 0.835059285163879

01:30:30.460 --> 01:30:33.300 power of it that without the.
NOTE Confidence: 0.835059285163879

01:30:33.300 --> 01:30:34.736 Burden of a hypothesis.
NOTE Confidence: 0.835059285163879

01:30:34.736 --> 01:30:37.380 Sometimes you find things you don't expect,
NOTE Confidence: 0.835059285163879

01:30:37.380 --> 01:30:40.308 and in fact what we found was that

NOTE Confidence: 0.835059285163879

01:30:40.308 --> 01:30:42.427 higher numbers of CD 57 positive

NOTE Confidence: 0.835059285163879

01:30:42.427 --> 01:30:44.879 car T cells that look like they

NOTE Confidence: 0.835059285163879

01:30:44.879 --> 01:30:47.297 have a senescent phenotype on day

NOTE Confidence: 0.835059285163879

01:30:47.297 --> 01:30:49.252 seven predict a favorable outcome.

NOTE Confidence: 0.835059285163879

01:30:49.252 --> 01:30:52.220 Now what do we think is happening here?

NOTE Confidence: 0.835059285163879

01:30:52.220 --> 01:30:55.188 We think that when you have these cells,

NOTE Confidence: 0.835059285163879

01:30:55.190 --> 01:30:57.566 what this is telling you is

NOTE Confidence: 0.835059285163879

01:30:57.566 --> 01:30:59.150 that the product that

NOTE Confidence: 0.868375658988953

01:30:59.238 --> 01:31:01.834 was infused. Contained potent T cells

NOTE Confidence: 0.868375658988953

01:31:01.834 --> 01:31:04.270 that were able to become activated

NOTE Confidence: 0.868375658988953

01:31:04.343 --> 01:31:06.508 that the tumor expressed adequate

NOTE Confidence: 0.868375658988953

01:31:06.508 --> 01:31:09.369 antigen expression to be able to drive

NOTE Confidence: 0.868375658988953

01:31:09.369 --> 01:31:11.841 expansion of your car T and that the

NOTE Confidence: 0.868375658988953

01:31:11.850 --> 01:31:14.135 micro environment of the lymphoma

NOTE Confidence: 0.868375658988953

01:31:14.135 --> 01:31:17.234 was also receptive and so in some

NOTE Confidence: 0.868375658988953

01:31:17.234 --> 01:31:19.782 ways this is a biomarker we believe
NOTE Confidence: 0.868375658988953

01:31:19.782 --> 01:31:22.181 for all of the factors that line
NOTE Confidence: 0.868375658988953

01:31:22.181 --> 01:31:24.378 up to allow a productive response.
NOTE Confidence: 0.868375658988953

01:31:24.378 --> 01:31:27.486 The car T regs are another interesting
NOTE Confidence: 0.868375658988953

01:31:27.486 --> 01:31:30.470 twist we had not seen any evidence of car.
NOTE Confidence: 0.868375658988953

01:31:30.470 --> 01:31:31.484 T regs this.
NOTE Confidence: 0.868375658988953

01:31:31.484 --> 01:31:33.512 Bite lots of looking for them
NOTE Confidence: 0.868375658988953

01:31:33.512 --> 01:31:35.889 in our manufactured products,
NOTE Confidence: 0.868375658988953

01:31:35.890 --> 01:31:38.946 and so it suggests to us that maybe
NOTE Confidence: 0.868375658988953

01:31:38.946 --> 01:31:42.047 these are being induced in vivo and I
NOTE Confidence: 0.868375658988953

01:31:42.047 --> 01:31:45.966 think this is an area where we need to
NOTE Confidence: 0.868375658988953

01:31:45.966 --> 01:31:48.748 understand more why some patients do
NOTE Confidence: 0.868375658988953

01:31:48.748 --> 01:31:50.938 have this predisposition to generating
NOTE Confidence: 0.868375658988953

01:31:50.938 --> 01:31:54.108 T regs from their CD 19 car product.
NOTE Confidence: 0.868375658988953

01:31:54.110 --> 01:31:56.486 It's possible that with this in
NOTE Confidence: 0.868375658988953

01:31:56.486 --> 01:31:59.018 hand we can intervene earlier for

NOTE Confidence: 0.868375658988953
01:31:59.018 --> 01:32:01.600 these patients to improve outcomes.
NOTE Confidence: 0.868375658988953
01:32:01.600 --> 01:32:02.240 Alright,
NOTE Confidence: 0.868375658988953
01:32:02.240 --> 01:32:04.538 so now let's move onto another
NOTE Confidence: 0.868375658988953
01:32:04.538 --> 01:32:07.330 story and this is really trying to
NOTE Confidence: 0.868375658988953
01:32:07.330 --> 01:32:10.067 get to this issue that Steve was
NOTE Confidence: 0.868375658988953
01:32:10.153 --> 01:32:12.610 alluding to that you know car T
NOTE Confidence: 0.868375658988953
01:32:12.610 --> 01:32:15.422 cells so far in solid tumors have
NOTE Confidence: 0.868375658988953
01:32:15.422 --> 01:32:17.174 not demonstrated reliable activity
NOTE Confidence: 0.868375658988953
01:32:17.174 --> 01:32:20.148 and there are a lot of reasons for that.
NOTE Confidence: 0.868375658988953
01:32:20.150 --> 01:32:21.674 As I've alluded to,
NOTE Confidence: 0.868375658988953
01:32:21.674 --> 01:32:23.198 the tumor heterogeneity problem,
NOTE Confidence: 0.868375658988953
01:32:23.200 --> 01:32:24.277 difficulties with trafficking
NOTE Confidence: 0.868375658988953
01:32:24.277 --> 01:32:26.790 and also the fact that the solid
NOTE Confidence: 0.868375658988953
01:32:26.849 --> 01:32:28.445 tumors really induce substantial
NOTE Confidence: 0.868375658988953
01:32:28.445 --> 01:32:30.440 amount of T cell dysfunction,
NOTE Confidence: 0.868375658988953

01:32:30.440 --> 01:32:32.550 much of which is characterized
NOTE Confidence: 0.868375658988953

01:32:32.550 --> 01:32:34.238 by T cell exhaustion.
NOTE Confidence: 0.868375658988953

01:32:34.240 --> 01:32:34.546 Now,
NOTE Confidence: 0.868375658988953

01:32:34.546 --> 01:32:36.688 we also believe that this is compounded
NOTE Confidence: 0.868375658988953

01:32:36.688 --> 01:32:39.340 with car T cells because car T cells
NOTE Confidence: 0.868375658988953

01:32:39.340 --> 01:32:41.360 themselves are predisposed to exhaustion.
NOTE Confidence: 0.868375658988953

01:32:41.360 --> 01:32:43.388 And why do we believe that?
NOTE Confidence: 0.868375658988953

01:32:43.390 --> 01:32:43.674 Well,
NOTE Confidence: 0.868375658988953

01:32:43.674 --> 01:32:46.230 this is work that we did while I was
NOTE Confidence: 0.868375658988953

01:32:46.305 --> 01:32:48.793 still at the MCI when we were trying
NOTE Confidence: 0.868375658988953

01:32:48.793 --> 01:32:51.522 to induce car T cells that could
NOTE Confidence: 0.868375658988953

01:32:51.522 --> 01:32:53.552 induce regression of an osteosarcoma,
NOTE Confidence: 0.868375658988953

01:32:53.560 --> 01:32:54.952 and we wanted to,
NOTE Confidence: 0.868375658988953

01:32:54.952 --> 01:32:55.648 you know.
NOTE Confidence: 0.868375658988953

01:32:55.650 --> 01:32:57.837 Only look to see if we had a car
NOTE Confidence: 0.868375658988953

01:32:57.837 --> 01:32:59.899 that we knew was highly efficacious

NOTE Confidence: 0.868375658988953

01:32:59.899 --> 01:33:01.910 and that really is the CD.

NOTE Confidence: 0.868375658988953

01:33:01.910 --> 01:33:03.998 19 car up to now it remains kind of

NOTE Confidence: 0.868375658988953

01:33:03.998 --> 01:33:06.220 the gold standard in the field and

NOTE Confidence: 0.868375658988953

01:33:06.220 --> 01:33:08.226 we wanted to understand whether you

NOTE Confidence: 0.868375658988953

01:33:08.226 --> 01:33:10.515 could regress a solid tumor with the

NOTE Confidence: 0.868375658988953

01:33:10.515 --> 01:33:12.340 hostel micro environment with the car.

NOTE Confidence: 0.868375658988953

01:33:12.340 --> 01:33:14.725 If you had a good target and so we

NOTE Confidence: 0.868375658988953

01:33:14.725 --> 01:33:16.509 express CD 19 and Osteosarcoma,

NOTE Confidence: 0.868375658988953

01:33:16.510 --> 01:33:18.298 and indeed we saw a regression.

NOTE Confidence: 0.868375658988953

01:33:18.300 --> 01:33:20.540 But when we tried to target a second

NOTE Confidence: 0.868375658988953

01:33:20.540 --> 01:33:22.652 antigen GD 2 which is also expressed

NOTE Confidence: 0.868375658988953

01:33:22.652 --> 01:33:24.560 on osteosarcoma or car T cells,

NOTE Confidence: 0.868375658988953

01:33:24.560 --> 01:33:25.547 had no effect,

NOTE Confidence: 0.868375658988953

01:33:25.547 --> 01:33:25.876 and.

NOTE Confidence: 0.868375658988953

01:33:25.876 --> 01:33:28.811 And what we ended up learning was that the

NOTE Confidence: 0.868375658988953

01:33:28.811 --> 01:33:31.690 problem was not at the level of the inogen,
NOTE Confidence: 0.868375658988953

01:33:31.690 --> 01:33:34.298 but rather at the level of the car,
NOTE Confidence: 0.868375658988953

01:33:34.300 --> 01:33:36.575 and in this case the GD2 car,
NOTE Confidence: 0.868375658988953

01:33:36.580 --> 01:33:37.534 like many cars,
NOTE Confidence: 0.868375658988953

01:33:37.534 --> 01:33:39.442 tended to aggregate on the surface
NOTE Confidence: 0.868375658988953

01:33:39.442 --> 01:33:41.500 of the cells due to hydrophobic
NOTE Confidence: 0.868375658988953

01:33:41.500 --> 01:33:43.420 regions in the single chain FV,
NOTE Confidence: 0.868375658988953

01:33:43.420 --> 01:33:45.466 which led to signaling even in
NOTE Confidence: 0.868375658988953

01:33:45.466 --> 01:33:47.524 the absence of Antigen and when
NOTE Confidence: 0.868375658988953

01:33:47.524 --> 01:33:49.414 T cells received too much signal
NOTE Confidence: 0.868375658988953

01:33:49.414 --> 01:33:51.960 for too long of a time they become
NOTE Confidence: 0.868375658988953

01:33:51.960 --> 01:33:53.816 exhausted and So what we learned
NOTE Confidence: 0.868375658988953

01:33:53.816 --> 01:33:56.280 from this work was it this is an
NOTE Confidence: 0.868375658988953

01:33:56.353 --> 01:33:58.789 Achilles heel of car T cells that.
NOTE Confidence: 0.855923235416412

01:33:58.790 --> 01:34:00.620 Unlike the CD 19 car,
NOTE Confidence: 0.855923235416412

01:34:00.620 --> 01:34:02.816 which really does not show a

NOTE Confidence: 0.855923235416412
01:34:02.816 --> 01:34:04.280 propensity for tonic signaling,
NOTE Confidence: 0.855923235416412
01:34:04.280 --> 01:34:07.104 the vast majority of other car T cells
NOTE Confidence: 0.855923235416412
01:34:07.104 --> 01:34:10.135 do this to some extent, and the GD
NOTE Confidence: 0.855923235416412
01:34:10.135 --> 01:34:12.325 two was a particularly egregious example,
NOTE Confidence: 0.855923235416412
01:34:12.330 --> 01:34:15.258 and so we we tried to fix it.
NOTE Confidence: 0.855923235416412
01:34:15.260 --> 01:34:18.131 We've had trouble doing it to be honest and
NOTE Confidence: 0.855923235416412
01:34:18.131 --> 01:34:20.377 retaining the antigen binding properties,
NOTE Confidence: 0.855923235416412
01:34:20.380 --> 01:34:22.660 but but we thought we might be able
NOTE Confidence: 0.855923235416412
01:34:22.660 --> 01:34:25.593 to turn lemons into lemonade by simply
NOTE Confidence: 0.855923235416412
01:34:25.593 --> 01:34:27.883 using these highly tonically signaling
NOTE Confidence: 0.855923235416412
01:34:27.954 --> 01:34:30.278 cars to begin to study the biology.
NOTE Confidence: 0.855923235416412
01:34:30.280 --> 01:34:32.220 Of human T cell exhaustion.
NOTE Confidence: 0.855923235416412
01:34:32.220 --> 01:34:35.156 Because the truth is we didn't have a
NOTE Confidence: 0.855923235416412
01:34:35.156 --> 01:34:38.037 good model of human T cell exhaustion.
NOTE Confidence: 0.855923235416412
01:34:38.040 --> 01:34:39.945 We were really relying mostly
NOTE Confidence: 0.855923235416412

01:34:39.945 --> 01:34:42.310 on LC MGMV models in mice,
NOTE Confidence: 0.855923235416412

01:34:42.310 --> 01:34:44.806 which are of course very valuable
NOTE Confidence: 0.855923235416412

01:34:44.806 --> 01:34:47.359 but may not reflect what happens
NOTE Confidence: 0.855923235416412

01:34:47.359 --> 01:34:50.166 in human cells and and using a
NOTE Confidence: 0.855923235416412

01:34:50.166 --> 01:34:52.627 mutated version of the GD2 car we
NOTE Confidence: 0.855923235416412

01:34:52.627 --> 01:34:55.111 were able to see that within 12
NOTE Confidence: 0.855923235416412

01:34:55.111 --> 01:34:57.433 days we could take perfectly normal,
NOTE Confidence: 0.855923235416412

01:34:57.440 --> 01:35:00.584 naive healthy human T cells and convert them.
NOTE Confidence: 0.855923235416412

01:35:00.590 --> 01:35:02.305 Two full blown exhausted cells
NOTE Confidence: 0.855923235416412

01:35:02.305 --> 01:35:03.677 and using the CD.
NOTE Confidence: 0.855923235416412

01:35:03.680 --> 01:35:05.390 19 cars are controlled group.
NOTE Confidence: 0.855923235416412

01:35:05.390 --> 01:35:07.840 We had really good controls and so
NOTE Confidence: 0.855923235416412

01:35:07.840 --> 01:35:10.496 this was work led by Rachel Lynn in
NOTE Confidence: 0.855923235416412

01:35:10.496 --> 01:35:13.532 the lab and it shows you some of the
NOTE Confidence: 0.855923235416412

01:35:13.532 --> 01:35:16.366 evidence for this exhaustion in a dish model.
NOTE Confidence: 0.855923235416412

01:35:16.366 --> 01:35:18.767 The exhausting cells don't grow as well.

NOTE Confidence: 0.855923235416412
01:35:18.770 --> 01:35:20.597 They don't make much in the way
NOTE Confidence: 0.855923235416412
01:35:20.597 --> 01:35:23.246 of I'll two and they also have
NOTE Confidence: 0.855923235416412
01:35:23.246 --> 01:35:24.599 diminished interferon production.
NOTE Confidence: 0.855923235416412
01:35:24.600 --> 01:35:25.964 They terminally differentiate and
NOTE Confidence: 0.855923235416412
01:35:25.964 --> 01:35:28.406 they express all of the hallmark cell
NOTE Confidence: 0.855923235416412
01:35:28.406 --> 01:35:30.086 surface markers you would express.
NOTE Confidence: 0.855923235416412
01:35:30.090 --> 01:35:32.470 Expect of an exhausted cells.
NOTE Confidence: 0.855923235416412
01:35:32.470 --> 01:35:35.508 If you look at the transcriptome they
NOTE Confidence: 0.855923235416412
01:35:35.508 --> 01:35:37.743 really nearer the transcriptome of
NOTE Confidence: 0.855923235416412
01:35:37.743 --> 01:35:41.151 the T cells that are exhausted in the
NOTE Confidence: 0.855923235416412
01:35:41.232 --> 01:35:44.320 LC MV model or in let's say humans
NOTE Confidence: 0.855923235416412
01:35:44.320 --> 01:35:46.844 with hepatitis or other chronic viral
NOTE Confidence: 0.855923235416412
01:35:46.844 --> 01:35:49.460 infections and so now after validating
NOTE Confidence: 0.855923235416412
01:35:49.539 --> 01:35:52.255 that this is a valid exhaustion model,
NOTE Confidence: 0.855923235416412
01:35:52.260 --> 01:35:54.864 we set out to understand the biology
NOTE Confidence: 0.855923235416412

01:35:54.864 --> 01:35:58.027 a bit better and using a taxi quicker
NOTE Confidence: 0.855923235416412

01:35:58.027 --> 01:36:00.651 the genome wide approach to look
NOTE Confidence: 0.855923235416412

01:36:00.651 --> 01:36:02.358 at enhancer availability,
NOTE Confidence: 0.855923235416412

01:36:02.360 --> 01:36:05.146 we were able to identify that the
NOTE Confidence: 0.855923235416412

01:36:05.146 --> 01:36:07.060 greatest difference between exhausted.
NOTE Confidence: 0.855923235416412

01:36:07.060 --> 01:36:09.460 And non exhausted T cells.
NOTE Confidence: 0.855923235416412

01:36:09.460 --> 01:36:11.730 In terms of the epigenome,
NOTE Confidence: 0.855923235416412

01:36:11.730 --> 01:36:13.860 was the increased availability of
NOTE Confidence: 0.855923235416412

01:36:13.860 --> 01:36:17.047 enhancers that turn on the AP one
NOTE Confidence: 0.855923235416412

01:36:17.047 --> 01:36:19.497 transcription factor family and we
NOTE Confidence: 0.855923235416412

01:36:19.497 --> 01:36:21.877 saw dramatic overexpression of the
NOTE Confidence: 0.855923235416412

01:36:21.877 --> 01:36:23.957 AP one transcription factors here,
NOTE Confidence: 0.855923235416412

01:36:23.960 --> 01:36:26.492 and this was the puzzling result
NOTE Confidence: 0.855923235416412

01:36:26.492 --> 01:36:29.295 because of course we all think of
NOTE Confidence: 0.855923235416412

01:36:29.295 --> 01:36:32.383 AP one at least faucet in June as
NOTE Confidence: 0.855923235416412

01:36:32.383 --> 01:36:34.207 Canonical transcription factors

NOTE Confidence: 0.855923235416412
01:36:34.207 --> 01:36:36.639 that drive tso activation.
NOTE Confidence: 0.855923235416412
01:36:36.640 --> 01:36:39.352 So why would this be implicated
NOTE Confidence: 0.855923235416412
01:36:39.352 --> 01:36:40.602 in exhaustion? Well?
NOTE Confidence: 0.855923235416412
01:36:40.602 --> 01:36:43.338 It turns out there are a lot of
NOTE Confidence: 0.855923235416412
01:36:43.338 --> 01:36:45.588 other members of this family,
NOTE Confidence: 0.855923235416412
01:36:45.590 --> 01:36:48.236 and many of them actually induces
NOTE Confidence: 0.855923235416412
01:36:48.236 --> 01:36:49.559 suppressive transcriptional program
NOTE Confidence: 0.855923235416412
01:36:49.559 --> 01:36:52.290 and so we it LED us to the hypothesis
NOTE Confidence: 0.855923235416412
01:36:52.290 --> 01:36:54.433 that perhaps there was an overexpression
NOTE Confidence: 0.855923235416412
01:36:54.433 --> 01:36:56.719 of the exhausting or suppressive AP
NOTE Confidence: 0.855923235416412
01:36:56.720 --> 01:36:59.012 one family members in a relative
NOTE Confidence: 0.855923235416412
01:36:59.012 --> 01:37:00.800 deficiency of the activating AP,
NOTE Confidence: 0.855923235416412
01:37:00.800 --> 01:37:03.026 one of Foss in June and,
NOTE Confidence: 0.855923235416412
01:37:03.030 --> 01:37:05.627 and so we tested this by overexpressing
NOTE Confidence: 0.855923235416412
01:37:05.627 --> 01:37:06.740 Foss in June.
NOTE Confidence: 0.855923235416412

01:37:06.740 --> 01:37:08.140 Foss had no effect,
NOTE Confidence: 0.855923235416412

01:37:08.140 --> 01:37:10.240 but overexpression of Thi June in
NOTE Confidence: 0.855923235416412

01:37:10.308 --> 01:37:11.960 these exhausting T cells.
NOTE Confidence: 0.855923235416412

01:37:11.960 --> 01:37:14.036 Had a significant impact on the
NOTE Confidence: 0.855923235416412

01:37:14.036 --> 01:37:15.420 ability of these cells
NOTE Confidence: 0.859505534172058

01:37:15.489 --> 01:37:18.113 to perform most notably here with I'll 2.
NOTE Confidence: 0.859505534172058

01:37:18.120 --> 01:37:20.388 Now we also did the opposite experiment
NOTE Confidence: 0.859505534172058

01:37:20.388 --> 01:37:22.897 because if it was really an imbalance.
NOTE Confidence: 0.859505534172058

01:37:22.900 --> 01:37:25.161 Then, perhaps we could also restore the
NOTE Confidence: 0.859505534172058

01:37:25.161 --> 01:37:27.349 balance by using crisper to knockout.
NOTE Confidence: 0.859505534172058

01:37:27.350 --> 01:37:28.834 These inhibitory transcription factors
NOTE Confidence: 0.859505534172058

01:37:28.834 --> 01:37:31.799 and we found indeed that to be the case,
NOTE Confidence: 0.859505534172058

01:37:31.800 --> 01:37:33.456 especially June be bad.
NOTE Confidence: 0.859505534172058

01:37:33.456 --> 01:37:35.526 If 3 and IRF 4.
NOTE Confidence: 0.859505534172058

01:37:35.530 --> 01:37:37.876 And so now what we showed,
NOTE Confidence: 0.859505534172058

01:37:37.880 --> 01:37:41.005 and this is detailed in this nature paper.

NOTE Confidence: 0.859505534172058
01:37:41.005 --> 01:37:43.740 I know lots of data in there
NOTE Confidence: 0.859505534172058
01:37:43.740 --> 01:37:44.910 if you're interested.
NOTE Confidence: 0.859505534172058
01:37:44.910 --> 01:37:47.088 But basically in many models where
NOTE Confidence: 0.859505534172058
01:37:47.088 --> 01:37:49.451 we look if we simply overexpress
NOTE Confidence: 0.859505534172058
01:37:49.451 --> 01:37:51.947 see June and car T cells,
NOTE Confidence: 0.859505534172058
01:37:51.950 --> 01:37:53.850 we're able to dramatically change
NOTE Confidence: 0.859505534172058
01:37:53.850 --> 01:37:56.250 the potency of car T cells,
NOTE Confidence: 0.859505534172058
01:37:56.250 --> 01:37:57.814 especially against solid tumors.
NOTE Confidence: 0.859505534172058
01:37:57.814 --> 01:37:59.771 Here's an example using, uh,
NOTE Confidence: 0.859505534172058
01:37:59.771 --> 01:38:02.117 her two car against in Osteosarcoma,
NOTE Confidence: 0.859505534172058
01:38:02.120 --> 01:38:05.248 and you can see the dramatic regression when,
NOTE Confidence: 0.859505534172058
01:38:05.250 --> 01:38:06.814 see June is incorporated
NOTE Confidence: 0.859505534172058
01:38:06.814 --> 01:38:08.378 into the car construct.
NOTE Confidence: 0.859505534172058
01:38:08.380 --> 01:38:10.685 We see increased numbers of
NOTE Confidence: 0.859505534172058
01:38:10.685 --> 01:38:12.068 tumor infiltrating cells.
NOTE Confidence: 0.859505534172058

01:38:12.070 --> 01:38:14.370 We see decreased exhaustion expression.
NOTE Confidence: 0.859505534172058

01:38:14.370 --> 01:38:16.475 We see decreased terminal differentiation
NOTE Confidence: 0.859505534172058

01:38:16.475 --> 01:38:20.081 an we see that the say cells retain
NOTE Confidence: 0.859505534172058

01:38:20.081 --> 01:38:21.989 Poly functionality here increased
NOTE Confidence: 0.859505534172058

01:38:21.989 --> 01:38:24.910 out to production and also increased
NOTE Confidence: 0.859505534172058

01:38:24.910 --> 01:38:27.275 TF and Interferon gamma production.
NOTE Confidence: 0.859505534172058

01:38:27.280 --> 01:38:30.507 So what is the C Jun doing?
NOTE Confidence: 0.859505534172058

01:38:30.510 --> 01:38:30.971 Well,
NOTE Confidence: 0.859505534172058

01:38:30.971 --> 01:38:32.815 it's inducing really widespread
NOTE Confidence: 0.859505534172058

01:38:32.815 --> 01:38:35.120 transcriptional reprogramming in these cells.
NOTE Confidence: 0.859505534172058

01:38:35.120 --> 01:38:38.776 You can see that here are the June
NOTE Confidence: 0.859505534172058

01:38:38.776 --> 01:38:40.240 overexpressing cells compared
NOTE Confidence: 0.859505534172058

01:38:40.240 --> 01:38:42.530 to the HA control cells.
NOTE Confidence: 0.859505534172058

01:38:42.530 --> 01:38:45.533 You can see all of these cells
NOTE Confidence: 0.859505534172058

01:38:45.533 --> 01:38:46.820 associated with Stemness.
NOTE Confidence: 0.859505534172058

01:38:46.820 --> 01:38:49.388 All of these genes associated stemness,

NOTE Confidence: 0.859505534172058

01:38:49.390 --> 01:38:50.254 are overexpressed,

NOTE Confidence: 0.859505534172058

01:38:50.254 --> 01:38:52.846 and all of these genes associated

NOTE Confidence: 0.859505534172058

01:38:52.846 --> 01:38:55.018 with exhaustion or under expressed

NOTE Confidence: 0.859505534172058

01:38:55.018 --> 01:38:56.257 but interesting Lee.

NOTE Confidence: 0.859505534172058

01:38:56.260 --> 01:38:57.544 The exhaustion associated

NOTE Confidence: 0.859505534172058

01:38:57.544 --> 01:38:59.256 footprint did not change.

NOTE Confidence: 0.859505534172058

01:38:59.260 --> 01:39:01.828 We saw no difference in the

NOTE Confidence: 0.859505534172058

01:39:01.828 --> 01:39:03.112 exhaustion associated footprint,

NOTE Confidence: 0.859505534172058

01:39:03.120 --> 01:39:05.562 and so it was interesting because

NOTE Confidence: 0.859505534172058

01:39:05.562 --> 01:39:07.190 this demonstrated you could

NOTE Confidence: 0.859505534172058

01:39:07.262 --> 01:39:09.042 divorce the transcriptome from

NOTE Confidence: 0.859505534172058

01:39:09.042 --> 01:39:11.267 the epigenome of these cells,

NOTE Confidence: 0.859505534172058

01:39:11.270 --> 01:39:12.479 but it also.

NOTE Confidence: 0.859505534172058

01:39:12.479 --> 01:39:13.688 Raised the question,

NOTE Confidence: 0.859505534172058

01:39:13.690 --> 01:39:16.749 can you reverse the the epigenetic footprint?

NOTE Confidence: 0.859505534172058

01:39:16.750 --> 01:39:18.622 And so we've been working on
NOTE Confidence: 0.859505534172058

01:39:18.622 --> 01:39:20.405 another approach and this has been
NOTE Confidence: 0.859505534172058

01:39:20.405 --> 01:39:22.301 led by Evan Weber in the lab who
NOTE Confidence: 0.859505534172058

01:39:22.361 --> 01:39:24.299 has been looking to regulate car
NOTE Confidence: 0.859505534172058

01:39:24.299 --> 01:39:26.650 expression and chords a lot of folks
NOTE Confidence: 0.859505534172058

01:39:26.650 --> 01:39:28.400 want to regulate car expression
NOTE Confidence: 0.859505534172058

01:39:28.400 --> 01:39:30.037 mostly because they are thinking
NOTE Confidence: 0.859505534172058

01:39:30.037 --> 01:39:32.074 that this will help car T cells
NOTE Confidence: 0.859505534172058

01:39:32.134 --> 01:39:33.982 be more safe that we can tune the
NOTE Confidence: 0.859505534172058

01:39:33.982 --> 01:39:35.694 car T cell response and diminish
NOTE Confidence: 0.859505534172058

01:39:35.694 --> 01:39:36.938 the cytokine release syndrome
NOTE Confidence: 0.859505534172058

01:39:36.938 --> 01:39:38.708 and some of the other toxicities
NOTE Confidence: 0.859505534172058

01:39:38.708 --> 01:39:40.346 that have been observed in there,
NOTE Confidence: 0.859505534172058

01:39:40.350 --> 01:39:40.894 of course,
NOTE Confidence: 0.859505534172058

01:39:40.894 --> 01:39:43.070 numerous ways to do this one that we
NOTE Confidence: 0.859505534172058

01:39:43.136 --> 01:39:45.201 developed in our lab with Evan is

NOTE Confidence: 0.859505534172058
01:39:45.201 --> 01:39:47.140 this degra based system where you.
NOTE Confidence: 0.859505534172058
01:39:47.140 --> 01:39:49.768 Attach a peptide that tags the car
NOTE Confidence: 0.859505534172058
01:39:49.768 --> 01:39:51.648 for degradation in the proteasome,
NOTE Confidence: 0.859505534172058
01:39:51.650 --> 01:39:54.233 but the peptide is also druggable and
NOTE Confidence: 0.859505534172058
01:39:54.233 --> 01:39:56.914 can be inhibited with a small molecule
NOTE Confidence: 0.859505534172058
01:39:56.914 --> 01:39:59.170 and this works really quite well.
NOTE Confidence: 0.859505534172058
01:39:59.170 --> 01:40:02.554 You can see that with this drug on system.
NOTE Confidence: 0.859505534172058
01:40:02.560 --> 01:40:04.440 If you give the drug,
NOTE Confidence: 0.859505534172058
01:40:04.440 --> 01:40:05.804 and in this case,
NOTE Confidence: 0.859505534172058
01:40:05.804 --> 01:40:07.850 some of these are very antibiotics
NOTE Confidence: 0.859505534172058
01:40:07.925 --> 01:40:09.697 that are readily available.
NOTE Confidence: 0.859505534172058
01:40:09.700 --> 01:40:12.748 You can see a high levels of surface
NOTE Confidence: 0.859505534172058
01:40:12.748 --> 01:40:15.086 car expression versus when you take
NOTE Confidence: 0.859505534172058
01:40:15.086 --> 01:40:17.630 the drug away it degrades and it.
NOTE Confidence: 0.859505534172058
01:40:17.630 --> 01:40:19.982 And it works through the biologically
NOTE Confidence: 0.859505534172058

01:40:19.982 --> 01:40:21.550 relevant level of expression.
NOTE Confidence: 0.859505534172058

01:40:21.550 --> 01:40:23.118 You can see here.
NOTE Confidence: 0.859505534172058

01:40:23.118 --> 01:40:25.078 The difference in aisle 2.
NOTE Confidence: 0.859505534172058

01:40:25.080 --> 01:40:27.040 Another way to do this.
NOTE Confidence: 0.836485862731934

01:40:27.040 --> 01:40:29.070 However, rather than just engineering
NOTE Confidence: 0.836485862731934

01:40:29.070 --> 01:40:31.931 a specific decron to simply to use
NOTE Confidence: 0.836485862731934

01:40:31.931 --> 01:40:33.836 small molecules that inhibit cortisol
NOTE Confidence: 0.836485862731934

01:40:33.836 --> 01:40:36.172 signaling and we discovered that dissent
NOTE Confidence: 0.836485862731934

01:40:36.172 --> 01:40:38.797 nib is one of these small molecules,
NOTE Confidence: 0.836485862731934

01:40:38.800 --> 01:40:41.117 which can really quite potently as you
NOTE Confidence: 0.836485862731934

01:40:41.117 --> 01:40:43.993 can see here at modest concentrations can
NOTE Confidence: 0.836485862731934

01:40:43.993 --> 01:40:46.263 quite potently inhibit car activation
NOTE Confidence: 0.836485862731934

01:40:46.263 --> 01:40:49.055 and we think that this happens through.
NOTE Confidence: 0.836485862731934

01:40:49.060 --> 01:40:51.724 Inhibition of LCK now the beauty
NOTE Confidence: 0.836485862731934

01:40:51.724 --> 01:40:53.500 of this at neighbors.
NOTE Confidence: 0.836485862731934

01:40:53.500 --> 01:40:54.856 It's very reversible.

NOTE Confidence: 0.836485862731934
01:40:54.856 --> 01:40:59.290 So here you can have this at nib you know.
NOTE Confidence: 0.836485862731934
01:40:59.290 --> 01:41:00.690 In in you know,
NOTE Confidence: 0.836485862731934
01:41:00.690 --> 01:41:02.440 inhibiting you're killing but then,
NOTE Confidence: 0.836485862731934
01:41:02.440 --> 01:41:04.190 when you wash it out.
NOTE Confidence: 0.836485862731934
01:41:04.190 --> 01:41:05.940 You get the reverse so
NOTE Confidence: 0.836485862731934
01:41:05.940 --> 01:41:07.340 the disat nib inhibits,
NOTE Confidence: 0.836485862731934
01:41:07.340 --> 01:41:09.790 killing but when you wash it out.
NOTE Confidence: 0.836485862731934
01:41:09.790 --> 01:41:12.058 You can get the reverse so it's
NOTE Confidence: 0.836485862731934
01:41:12.058 --> 01:41:14.179 really quite a nimble system so
NOTE Confidence: 0.836485862731934
01:41:14.179 --> 01:41:16.692 whatever has been trying to do now
NOTE Confidence: 0.836485862731934
01:41:16.767 --> 01:41:19.231 is to look in the exhausting model
NOTE Confidence: 0.836485862731934
01:41:19.231 --> 01:41:21.690 and ask whether you could take a
NOTE Confidence: 0.836485862731934
01:41:21.690 --> 01:41:23.790 cell that is now already exhausted.
NOTE Confidence: 0.836485862731934
01:41:23.790 --> 01:41:25.650 It's already gone down the path
NOTE Confidence: 0.836485862731934
01:41:25.650 --> 01:41:27.668 remember what June was doing it
NOTE Confidence: 0.836485862731934

01:41:27.668 --> 01:41:29.448 with preventing exhaustion were now
NOTE Confidence: 0.836485862731934

01:41:29.448 --> 01:41:31.560 allowing cells to become exhausted.
NOTE Confidence: 0.836485862731934

01:41:31.560 --> 01:41:33.989 And then we're giving them a period
NOTE Confidence: 0.836485862731934

01:41:33.989 --> 01:41:36.955 of rest and we want to know can
NOTE Confidence: 0.836485862731934

01:41:36.955 --> 01:41:38.800 you reverse the exhaustion and
NOTE Confidence: 0.836485862731934

01:41:38.882 --> 01:41:41.538 the data with this at nib and with
NOTE Confidence: 0.836485862731934

01:41:41.538 --> 01:41:43.630 the degron model is really very
NOTE Confidence: 0.836485862731934

01:41:43.630 --> 01:41:45.760 impressive here you can see sales,
NOTE Confidence: 0.836485862731934

01:41:45.760 --> 01:41:48.343 now in a day 25 assay where you have
NOTE Confidence: 0.836485862731934

01:41:48.343 --> 01:41:50.728 high levels of exhaustion markers,
NOTE Confidence: 0.836485862731934

01:41:50.730 --> 01:41:53.845 but when you incorporate the fat nearby
NOTE Confidence: 0.836485862731934

01:41:53.845 --> 01:41:56.943 there from Day 4 or you can see from
NOTE Confidence: 0.836485862731934

01:41:56.943 --> 01:41:59.959 Day 7 Day 11 Day 14 or even Day 18.
NOTE Confidence: 0.836485862731934

01:41:59.960 --> 01:42:01.356 You start to see.
NOTE Confidence: 0.836485862731934

01:42:01.356 --> 01:42:03.101 Now reversal of these checkpoint
NOTE Confidence: 0.836485862731934

01:42:03.101 --> 01:42:04.620 molecules an acquisition now.

NOTE Confidence: 0.836485862731934

01:42:04.620 --> 01:42:06.216 Of your stem like molecules and

NOTE Confidence: 0.836485862731934

01:42:06.216 --> 01:42:08.143 even a change in the transcriptome

NOTE Confidence: 0.836485862731934

01:42:08.143 --> 01:42:10.543 and this is associated now with

NOTE Confidence: 0.836485862731934

01:42:10.543 --> 01:42:11.999 improved functionality and are

NOTE Confidence: 0.836485862731934

01:42:11.999 --> 01:42:13.799 feeling from these data were that

NOTE Confidence: 0.836485862731934

01:42:13.799 --> 01:42:16.030 there wasn't a point of no return.

NOTE Confidence: 0.836485862731934

01:42:16.030 --> 01:42:18.614 We simply got a more potent effect if

NOTE Confidence: 0.836485862731934

01:42:18.614 --> 01:42:21.576 the rest was allowed to go on for a

NOTE Confidence: 0.836485862731934

01:42:21.576 --> 01:42:23.850 longer period, but but we didn't know.

NOTE Confidence: 0.836485862731934

01:42:23.850 --> 01:42:26.458 Maybe there was a point of no return.

NOTE Confidence: 0.836485862731934

01:42:26.460 --> 01:42:28.416 So now, what Evan is done.

NOTE Confidence: 0.836485862731934

01:42:28.420 --> 01:42:30.695 His take this all the way out.

NOTE Confidence: 0.836485862731934

01:42:30.700 --> 01:42:31.068 Today,

NOTE Confidence: 0.836485862731934

01:42:31.068 --> 01:42:33.644 53 and you can see that applying

NOTE Confidence: 0.836485862731934

01:42:33.644 --> 01:42:36.009 the Saturn IB as late as Day 46.

NOTE Confidence: 0.836485862731934

01:42:36.010 --> 01:42:38.338 Is still enough to retrieve the
NOTE Confidence: 0.836485862731934

01:42:38.338 --> 01:42:40.374 cytolytic capacity of these cells
NOTE Confidence: 0.836485862731934

01:42:40.374 --> 01:42:42.444 and to greatly improve their
NOTE Confidence: 0.836485862731934

01:42:42.444 --> 01:42:44.370 ability to produce cytokinin OK,
NOTE Confidence: 0.836485862731934

01:42:44.370 --> 01:42:47.556 so now let's go back to the transcriptome.
NOTE Confidence: 0.836485862731934

01:42:47.556 --> 01:42:48.750 What's happening here?
NOTE Confidence: 0.836485862731934

01:42:48.750 --> 01:42:50.740 It's quite similar to what
NOTE Confidence: 0.836485862731934

01:42:50.740 --> 01:42:52.730 I showed you with June.
NOTE Confidence: 0.836485862731934

01:42:52.730 --> 01:42:54.720 You get massive transcriptional rewiring.
NOTE Confidence: 0.836485862731934

01:42:54.720 --> 01:42:55.216 Now.
NOTE Confidence: 0.836485862731934

01:42:55.216 --> 01:42:57.696 Another interesting piece of these
NOTE Confidence: 0.836485862731934

01:42:57.696 --> 01:43:00.456 experiments is Evan also used to
NOTE Confidence: 0.836485862731934

01:43:00.456 --> 01:43:02.892 control where he used anti PD one
NOTE Confidence: 0.836485862731934

01:43:02.892 --> 01:43:05.657 and just to make it clear anti PD
NOTE Confidence: 0.836485862731934

01:43:05.657 --> 01:43:07.851 one didn't do anything in terms
NOTE Confidence: 0.836485862731934

01:43:07.851 --> 01:43:09.439 of functional re invigoration,

NOTE Confidence: 0.836485862731934
01:43:09.440 --> 01:43:10.256 immodest invigoration.
NOTE Confidence: 0.836485862731934
01:43:10.256 --> 01:43:11.480 Of cytolytic capacity,
NOTE Confidence: 0.836485862731934
01:43:11.480 --> 01:43:13.500 but no ability to improve
NOTE Confidence: 0.836485862731934
01:43:13.500 --> 01:43:15.116 proliferation or or cytokine,
NOTE Confidence: 0.836485862731934
01:43:15.120 --> 01:43:16.185 and not surprisingly,
NOTE Confidence: 0.836485862731934
01:43:16.185 --> 01:43:16.540 therefore,
NOTE Confidence: 0.836485862731934
01:43:16.540 --> 01:43:19.580 PD one did not reverse the transcriptome,
NOTE Confidence: 0.836485862731934
01:43:19.580 --> 01:43:22.280 but the the rested period did
NOTE Confidence: 0.836485862731934
01:43:22.280 --> 01:43:24.493 reverse the transcriptome and we
NOTE Confidence: 0.836485862731934
01:43:24.493 --> 01:43:26.461 saw an owl acquisition of left
NOTE Confidence: 0.836485862731934
01:43:26.461 --> 01:43:29.627 one TCF 7 and diminished I RF 4
NOTE Confidence: 0.836485862731934
01:43:29.627 --> 01:43:31.727 so that's perhaps not surprising,
NOTE Confidence: 0.836485862731934
01:43:31.730 --> 01:43:33.730 but what was really notable
NOTE Confidence: 0.836485862731934
01:43:33.730 --> 01:43:35.730 in surprising was the degree
NOTE Confidence: 0.815743684768677
01:43:35.804 --> 01:43:39.020 to which rest is now reversing the epigenome.
NOTE Confidence: 0.815743684768677

01:43:39.020 --> 01:43:42.316 So here now is the A Taxi Cavan.
NOTE Confidence: 0.815743684768677

01:43:42.320 --> 01:43:44.777 Always off car you can see very
NOTE Confidence: 0.815743684768677

01:43:44.777 --> 01:43:46.983 different from the always signaling car
NOTE Confidence: 0.815743684768677

01:43:46.983 --> 01:43:49.920 and again PD 1 does not change this.
NOTE Confidence: 0.815743684768677

01:43:49.920 --> 01:43:52.224 But when you give these cells periods of
NOTE Confidence: 0.815743684768677

01:43:52.224 --> 01:43:54.004 rest you see epigenetic reprogramming
NOTE Confidence: 0.815743684768677

01:43:54.004 --> 01:43:56.678 and this isn't simply selection of a
NOTE Confidence: 0.815743684768677

01:43:56.737 --> 01:43:58.967 rare population that wasn't exhausted.
NOTE Confidence: 0.815743684768677

01:43:58.970 --> 01:44:00.979 We can show that by looking at
NOTE Confidence: 0.815743684768677

01:44:00.979 --> 01:44:03.663 the TC are receptors and it shows
NOTE Confidence: 0.815743684768677

01:44:03.663 --> 01:44:05.843 no evidence for clonal expansion.
NOTE Confidence: 0.815743684768677

01:44:05.850 --> 01:44:08.685 But we also see this by using test meta
NOTE Confidence: 0.815743684768677

01:44:08.685 --> 01:44:11.740 stat because what we see now is that
NOTE Confidence: 0.815743684768677

01:44:11.740 --> 01:44:13.889 this reprogramming is dependent on.
NOTE Confidence: 0.815743684768677

01:44:13.890 --> 01:44:16.265 EV H2 Mediated Trimethylation because
NOTE Confidence: 0.815743684768677

01:44:16.265 --> 01:44:19.759 it can be inhibited by an inhibitor.

NOTE Confidence: 0.815743684768677
01:44:19.760 --> 01:44:21.710 OK, so if you've been following
NOTE Confidence: 0.815743684768677
01:44:21.710 --> 01:44:22.685 the car field,
NOTE Confidence: 0.815743684768677
01:44:22.690 --> 01:44:24.951 you've seen that there are a lot
NOTE Confidence: 0.815743684768677
01:44:24.951 --> 01:44:26.610 of regulatable cars out there,
NOTE Confidence: 0.815743684768677
01:44:26.610 --> 01:44:29.210 and there are many ways to do this,
NOTE Confidence: 0.815743684768677
01:44:29.210 --> 01:44:31.482 and I think you know a lead candidate
NOTE Confidence: 0.815743684768677
01:44:31.482 --> 01:44:33.224 in terms of optimal platform
NOTE Confidence: 0.815743684768677
01:44:33.224 --> 01:44:35.074 has not yet been identified.
NOTE Confidence: 0.815743684768677
01:44:35.080 --> 01:44:37.579 Louis lemania is a very talented bio
NOTE Confidence: 0.815743684768677
01:44:37.579 --> 01:44:39.320 engineering graduate student in the lab,
NOTE Confidence: 0.815743684768677
01:44:39.320 --> 01:44:41.742 and he's been working on a regulatable
NOTE Confidence: 0.815743684768677
01:44:41.742 --> 01:44:44.476 system and he wants to use an FDA
NOTE Confidence: 0.815743684768677
01:44:44.476 --> 01:44:46.106 approved small molecule to be
NOTE Confidence: 0.815743684768677
01:44:46.173 --> 01:44:48.217 able to regulate these car T cells
NOTE Confidence: 0.815743684768677
01:44:48.217 --> 01:44:51.110 and so at Looe is done is use a.
NOTE Confidence: 0.815743684768677

01:44:51.110 --> 01:44:53.721 Protease that is derived from hepatitis
NOTE Confidence: 0.815743684768677

01:44:53.721 --> 01:44:56.339 C that at baseline essentially cleaves
NOTE Confidence: 0.815743684768677

01:44:56.339 --> 01:44:59.664 the signaling domain off of the car.
NOTE Confidence: 0.815743684768677

01:44:59.670 --> 01:45:03.086 But when you apply now the small molecule,
NOTE Confidence: 0.815743684768677

01:45:03.090 --> 01:45:05.230 you prevent cleavage and this
NOTE Confidence: 0.815743684768677

01:45:05.230 --> 01:45:07.370 is shown on a western.
NOTE Confidence: 0.815743684768677

01:45:07.370 --> 01:45:10.385 You can see the full length car with the
NOTE Confidence: 0.815743684768677

01:45:10.385 --> 01:45:13.789 drug present because the proteases inhibited,
NOTE Confidence: 0.815743684768677

01:45:13.790 --> 01:45:16.695 but the absence of the full length
NOTE Confidence: 0.815743684768677

01:45:16.695 --> 01:45:19.360 car when the drug is absent,
NOTE Confidence: 0.815743684768677

01:45:19.360 --> 01:45:22.377 and we know that in this car.
NOTE Confidence: 0.815743684768677

01:45:22.380 --> 01:45:23.736 There is tonic signaling,
NOTE Confidence: 0.815743684768677

01:45:23.736 --> 01:45:26.144 and so it tends to express leg
NOTE Confidence: 0.815743684768677

01:45:26.144 --> 01:45:27.986 three and again with drug on.
NOTE Confidence: 0.815743684768677

01:45:27.990 --> 01:45:30.630 We get the lag three expression with drug
NOTE Confidence: 0.815743684768677

01:45:30.630 --> 01:45:33.600 off, we don't, so it's a drug on system.

NOTE Confidence: 0.815743684768677
01:45:33.600 --> 01:45:35.910 You're using a hepatitis C based antiviral,
NOTE Confidence: 0.815743684768677
01:45:35.910 --> 01:45:38.220 and when the antiviral drug falls below,
NOTE Confidence: 0.815743684768677
01:45:38.220 --> 01:45:39.870 then the car is degraded.
NOTE Confidence: 0.815743684768677
01:45:39.870 --> 01:45:40.174 Anne,
NOTE Confidence: 0.815743684768677
01:45:40.174 --> 01:45:42.302 I'm not going to show you today
NOTE Confidence: 0.815743684768677
01:45:42.302 --> 01:45:44.160 in the interest of time,
NOTE Confidence: 0.815743684768677
01:45:44.160 --> 01:45:46.358 but this model does show Efficacy in
NOTE Confidence: 0.815743684768677
01:45:46.358 --> 01:45:48.119 reversing toxicity in animal models,
NOTE Confidence: 0.815743684768677
01:45:48.120 --> 01:45:49.440 but perhaps more interesting,
NOTE Confidence: 0.815743684768677
01:45:49.440 --> 01:45:51.090 Lee is the question is,
NOTE Confidence: 0.815743684768677
01:45:51.090 --> 01:45:52.740 does this enhance efficacy and
NOTE Confidence: 0.815743684768677
01:45:52.740 --> 01:45:54.060 what Luis is found?
NOTE Confidence: 0.815743684768677
01:45:54.060 --> 01:45:55.760 Is that in multiple systems?
NOTE Confidence: 0.815743684768677
01:45:55.760 --> 01:45:58.462 That compared to a constitutive on
NOTE Confidence: 0.815743684768677
01:45:58.462 --> 01:46:01.630 car which we just show here in black,
NOTE Confidence: 0.815743684768677

01:46:01.630 --> 01:46:04.360 the on off system using the antiviral,
NOTE Confidence: 0.815743684768677

01:46:04.360 --> 01:46:07.879 and he gives the antiviral daily to the mice.
NOTE Confidence: 0.815743684768677

01:46:07.880 --> 01:46:09.840 He gets better antitumor effect.
NOTE Confidence: 0.815743684768677

01:46:09.840 --> 01:46:12.432 We see this with a GD2 car with a
NOTE Confidence: 0.815743684768677

01:46:12.432 --> 01:46:14.895 B7H3 car against modulo blastoma with
NOTE Confidence: 0.815743684768677

01:46:14.895 --> 01:46:18.050 uh her two car against Osteosarcoma.
NOTE Confidence: 0.815743684768677

01:46:18.050 --> 01:46:20.626 The only exception is the CD 19 car
NOTE Confidence: 0.815743684768677

01:46:20.626 --> 01:46:24.366 and we believe that this is a car that
NOTE Confidence: 0.815743684768677

01:46:24.366 --> 01:46:26.659 doesn't tonically signal and doesn't.
NOTE Confidence: 0.815743684768677

01:46:26.660 --> 01:46:28.312 Rapidly acquire hallmark features
NOTE Confidence: 0.815743684768677

01:46:28.312 --> 01:46:29.138 of exhaustion,
NOTE Confidence: 0.815743684768677

01:46:29.140 --> 01:46:32.164 and so when you look at the fells in
NOTE Confidence: 0.815743684768677

01:46:32.164 --> 01:46:34.704 these animals that are receiving the
NOTE Confidence: 0.815743684768677

01:46:34.704 --> 01:46:38.669 Snip Trans car and the hepatitis C antiviral.
NOTE Confidence: 0.815743684768677

01:46:38.670 --> 01:46:41.148 Compared to the constitu tive again,
NOTE Confidence: 0.815743684768677

01:46:41.150 --> 01:46:44.570 what you see is a retention of more of a

NOTE Confidence: 0.816061317920685

01:46:44.663 --> 01:46:47.206 stemness profile, whereas the

NOTE Confidence: 0.816061317920685

01:46:47.206 --> 01:46:49.921 constitutive cells rapidly terminally

NOTE Confidence: 0.816061317920685

01:46:49.921 --> 01:46:52.281 differentiate and again you can

NOTE Confidence: 0.816061317920685

01:46:52.281 --> 01:46:54.570 use this single cell RNA seq data

NOTE Confidence: 0.816061317920685

01:46:54.570 --> 01:46:56.907 to show a more in depth view.

NOTE Confidence: 0.816061317920685

01:46:56.910 --> 01:46:59.616 But there are no surprises here.

NOTE Confidence: 0.816061317920685

01:46:59.620 --> 01:47:01.870 Again, the Constitutive cells

NOTE Confidence: 0.816061317920685

01:47:01.870 --> 01:47:05.029 are in pink and they are here,

NOTE Confidence: 0.816061317920685

01:47:05.030 --> 01:47:07.280 they lack I'll 7 receptor.

NOTE Confidence: 0.816061317920685

01:47:07.280 --> 01:47:10.360 They lacked 7 but the Snip based cell

NOTE Confidence: 0.816061317920685

01:47:10.360 --> 01:47:13.154 retains a population that is stemlike

NOTE Confidence: 0.816061317920685

01:47:13.154 --> 01:47:16.064 but also is able to transition

NOTE Confidence: 0.816061317920685

01:47:16.153 --> 01:47:18.578 to the Granzyme B expressing.

NOTE Confidence: 0.816061317920685

01:47:18.580 --> 01:47:21.135 Factor which is so critical because stem.

NOTE Confidence: 0.816061317920685

01:47:21.140 --> 01:47:22.037 This is important,

NOTE Confidence: 0.816061317920685

01:47:22.037 --> 01:47:24.595 but the cells also need to be able
NOTE Confidence: 0.816061317920685

01:47:24.595 --> 01:47:26.590 to traffic through the process
NOTE Confidence: 0.816061317920685

01:47:26.590 --> 01:47:28.186 of differentiation to become
NOTE Confidence: 0.816061317920685

01:47:28.250 --> 01:47:29.558 full blown effectors.
NOTE Confidence: 0.816061317920685

01:47:29.560 --> 01:47:32.297 So conclusion from this T cell exhaustion
NOTE Confidence: 0.816061317920685

01:47:32.297 --> 01:47:34.318 occurs commonly in car T cells,
NOTE Confidence: 0.816061317920685

01:47:34.320 --> 01:47:36.516 and we believe it's a major
NOTE Confidence: 0.816061317920685

01:47:36.516 --> 01:47:37.980 factor limiting excess success,
NOTE Confidence: 0.816061317920685

01:47:37.980 --> 01:47:39.444 especially in solid tumors.
NOTE Confidence: 0.816061317920685

01:47:39.444 --> 01:47:40.542 See June overexpression
NOTE Confidence: 0.816061317920685

01:47:40.542 --> 01:47:41.640 endows exhaustion resistance,
NOTE Confidence: 0.816061317920685

01:47:41.640 --> 01:47:43.340 both in tonically signaling card
NOTE Confidence: 0.816061317920685

01:47:43.340 --> 01:47:46.029 details and also a non tonically ones.
NOTE Confidence: 0.816061317920685

01:47:46.030 --> 01:47:48.226 I didn't show you that today,
NOTE Confidence: 0.816061317920685

01:47:48.230 --> 01:47:50.350 but it's in the manuscript.
NOTE Confidence: 0.816061317920685

01:47:50.350 --> 01:47:53.266 And this occurs by potent transcriptional

NOTE Confidence: 0.816061317920685
01:47:53.266 --> 01:47:55.210 reprogramming that does prevent
NOTE Confidence: 0.816061317920685
01:47:55.281 --> 01:47:57.276 many of the hallmark features,
NOTE Confidence: 0.816061317920685
01:47:57.280 --> 01:47:59.590 but it doesn't alter the
NOTE Confidence: 0.816061317920685
01:47:59.590 --> 01:48:00.614 epigenetic footprint.
NOTE Confidence: 0.816061317920685
01:48:00.614 --> 01:48:01.638 In contrast,
NOTE Confidence: 0.816061317920685
01:48:01.638 --> 01:48:03.174 transient rest induces
NOTE Confidence: 0.816061317920685
01:48:03.174 --> 01:48:05.175 transcriptional reprogram but also
NOTE Confidence: 0.816061317920685
01:48:05.175 --> 01:48:06.799 the epigenetic reprogramming through
NOTE Confidence: 0.816061317920685
01:48:06.799 --> 01:48:09.290 a process that requires the Z,
NOTE Confidence: 0.816061317920685
01:48:09.290 --> 01:48:11.394 H2 and we find therefore,
NOTE Confidence: 0.816061317920685
01:48:11.394 --> 01:48:13.860 that regulated car T cells which
NOTE Confidence: 0.816061317920685
01:48:13.936 --> 01:48:16.056 were initially developed to
NOTE Confidence: 0.816061317920685
01:48:16.056 --> 01:48:18.706 prevent toxicity also show enhanced
NOTE Confidence: 0.816061317920685
01:48:18.706 --> 01:48:20.438 potency and we believe.
NOTE Confidence: 0.816061317920685
01:48:20.440 --> 01:48:23.807 That this result from the transient Reston
NOTE Confidence: 0.816061317920685

01:48:23.807 --> 01:48:26.129 tuning that's occurring due to the.
NOTE Confidence: 0.816061317920685

01:48:26.130 --> 01:48:27.093 The various system,
NOTE Confidence: 0.816061317920685

01:48:27.093 --> 01:48:28.377 so I want to.
NOTE Confidence: 0.816061317920685

01:48:28.380 --> 01:48:30.613 I think I've given credit to the
NOTE Confidence: 0.816061317920685

01:48:30.613 --> 01:48:33.210 people who did the work along the way.
NOTE Confidence: 0.816061317920685

01:48:33.210 --> 01:48:35.464 We've got a fantastic team at Stanford,
NOTE Confidence: 0.816061317920685

01:48:35.470 --> 01:48:37.432 a great clinical team that is
NOTE Confidence: 0.816061317920685

01:48:37.432 --> 01:48:38.740 conducting clinical trials alongside
NOTE Confidence: 0.816061317920685

01:48:38.797 --> 01:48:40.946 this fundamental work and also want to
NOTE Confidence: 0.816061317920685

01:48:40.946 --> 01:48:42.244 highlight the important collaboration
NOTE Confidence: 0.816061317920685

01:48:42.244 --> 01:48:44.158 with Howard Chang on this work.
NOTE Confidence: 0.816061317920685

01:48:44.160 --> 01:48:45.770 And these are our funders,
NOTE Confidence: 0.816061317920685

01:48:45.770 --> 01:48:48.990 and many of the folks so I can stop there.
NOTE Confidence: 0.816061317920685

01:48:48.990 --> 01:48:49.640 Thank you.
NOTE Confidence: 0.787633776664734

01:48:52.770 --> 01:48:54.150 Great, thank you so
NOTE Confidence: 0.787633776664734

01:48:54.150 --> 01:48:55.179 much doctor Mackle

NOTE Confidence: 0.787633776664734

01:48:55.180 --> 01:48:56.436 for that marvelous talk,

NOTE Confidence: 0.787633776664734

01:48:56.436 --> 01:48:58.960 I'm going to start asking the questions.

NOTE Confidence: 0.787633776664734

01:48:58.960 --> 01:49:00.192 That's all the Q&A.

NOTE Confidence: 0.787633776664734

01:49:00.192 --> 01:49:02.933 This is by Adam Rubin is the phenotypic

NOTE Confidence: 0.787633776664734

01:49:02.933 --> 01:49:05.782 diversity of Carti at day seven of

NOTE Confidence: 0.787633776664734

01:49:05.782 --> 01:49:08.067 function of the cells taken from the

NOTE Confidence: 0.787633776664734

01:49:08.067 --> 01:49:10.776 patient as as I can you predict the

NOTE Confidence: 0.787633776664734

01:49:10.776 --> 01:49:12.272 effectiveness of the transfusion

NOTE Confidence: 0.787633776664734

01:49:12.272 --> 01:49:14.099 product early on in the process.

NOTE Confidence: 0.847963750362396

01:49:14.870 --> 01:49:18.227 Yeah, I think as I as I alluded to,

NOTE Confidence: 0.847963750362396

01:49:18.230 --> 01:49:21.578 we would love to be able to go back

NOTE Confidence: 0.847963750362396

01:49:21.580 --> 01:49:24.044 to the product and the A Pheresis and

NOTE Confidence: 0.847963750362396

01:49:24.044 --> 01:49:27.314 we have work ongoing to do that with

NOTE Confidence: 0.847963750362396

01:49:27.314 --> 01:49:29.038 our investigator initiated trials.

NOTE Confidence: 0.847963750362396

01:49:29.040 --> 01:49:31.278 This is one of the problems

NOTE Confidence: 0.847963750362396

01:49:31.278 --> 01:49:32.770 with the commercial product.
NOTE Confidence: 0.847963750362396

01:49:32.770 --> 01:49:35.178 We are not permitted to analyze the
NOTE Confidence: 0.847963750362396

01:49:35.178 --> 01:49:37.619 A Pheresis or the product itself.
NOTE Confidence: 0.847963750362396

01:49:37.620 --> 01:49:39.490 It really negates our contract.
NOTE Confidence: 0.847963750362396

01:49:39.490 --> 01:49:41.350 So much for science there,
NOTE Confidence: 0.847963750362396

01:49:41.350 --> 01:49:43.588 so I can't answer the question.
NOTE Confidence: 0.814919054508209

01:49:44.560 --> 01:49:47.528 OK, this next question is from doctor Nick
NOTE Confidence: 0.814919054508209

01:49:47.528 --> 01:49:50.740 Josie is also one of our speakers later on,
NOTE Confidence: 0.814919054508209

01:49:50.740 --> 01:49:52.900 and faculty member here at Yale
NOTE Confidence: 0.814919054508209

01:49:52.900 --> 01:49:55.491 High Crystal CD 57 in CMD is
NOTE Confidence: 0.814919054508209

01:49:55.491 --> 01:49:56.568 associated with senescence,
NOTE Confidence: 0.814919054508209

01:49:56.570 --> 01:49:59.461 but is also representative of a functional
NOTE Confidence: 0.814919054508209

01:49:59.461 --> 01:50:01.298 effector response mediated by CD 50.
NOTE Confidence: 0.814919054508209

01:50:01.300 --> 01:50:03.120 Seven negative T cells because
NOTE Confidence: 0.814919054508209

01:50:03.120 --> 01:50:04.940 the immune system control CMP,
NOTE Confidence: 0.814919054508209

01:50:04.940 --> 01:50:06.760 do you think the presidents,

NOTE Confidence: 0.814919054508209

01:50:06.760 --> 01:50:09.408 the presence of CD 57 positive car T

NOTE Confidence: 0.814919054508209

01:50:09.408 --> 01:50:12.089 cells is telling us more that you're

NOTE Confidence: 0.814919054508209

01:50:12.089 --> 01:50:14.760 getting a good effector T cell pool?

NOTE Confidence: 0.814919054508209

01:50:14.760 --> 01:50:16.692 Which is the precursor cell for

NOTE Confidence: 0.814919054508209

01:50:16.692 --> 01:50:18.550 the city of positive self. This

NOTE Confidence: 0.863209903240204

01:50:18.550 --> 01:50:20.706 is exactly what I think is happening.

NOTE Confidence: 0.863209903240204

01:50:20.710 --> 01:50:21.942 I'm surprised it's already

NOTE Confidence: 0.863209903240204

01:50:21.942 --> 01:50:23.798 there at day seven, day seven.

NOTE Confidence: 0.863209903240204

01:50:23.798 --> 01:50:26.270 You've already taken a cell all away too.

NOTE Confidence: 0.863209903240204

01:50:26.270 --> 01:50:27.820 That's in essence, into me.

NOTE Confidence: 0.863209903240204

01:50:27.820 --> 01:50:29.976 It means they've gotten to the tumor.

NOTE Confidence: 0.863209903240204

01:50:29.980 --> 01:50:31.292 They found an antigen,

NOTE Confidence: 0.863209903240204

01:50:31.292 --> 01:50:33.689 and they've done what they need to do.

NOTE Confidence: 0.863209903240204

01:50:33.690 --> 01:50:35.846 And now they're back in the blood.

NOTE Confidence: 0.863209903240204

01:50:35.850 --> 01:50:37.716 I mean, this is the only

NOTE Confidence: 0.863209903240204

01:50:37.716 --> 01:50:39.250 way we can explain it.
NOTE Confidence: 0.863209903240204

01:50:39.250 --> 01:50:41.110 It is not what we expected.
NOTE Confidence: 0.863209903240204

01:50:41.110 --> 01:50:43.574 We expected to find a stem like phenotype.
NOTE Confidence: 0.863209903240204

01:50:43.580 --> 01:50:45.506 You know, all of these beautiful.
NOTE Confidence: 0.863209903240204

01:50:45.510 --> 01:50:47.808 You know, stem cell memory markers,
NOTE Confidence: 0.863209903240204

01:50:47.810 --> 01:50:50.120 and it's not what we found.
NOTE Confidence: 0.797098457813263

01:50:50.960 --> 01:50:54.186 OK, this next question is by Sue Keck.
NOTE Confidence: 0.797098457813263

01:50:54.186 --> 01:50:57.006 the CD 57 CD, 8 positive T
NOTE Confidence: 0.797098457813263

01:50:57.006 --> 01:50:59.418 cells also express CX3 CR 1.
NOTE Confidence: 0.797098457813263

01:50:59.420 --> 01:51:01.838 Ann are mostly found in blood.
NOTE Confidence: 0.797098457813263

01:51:01.840 --> 01:51:03.892 Do you think this migration pattern
NOTE Confidence: 0.797098457813263

01:51:03.892 --> 01:51:06.772 is one of the reasons why this
NOTE Confidence: 0.797098457813263

01:51:06.772 --> 01:51:08.688 populations associated with CR?
NOTE Confidence: 0.723242104053497

01:51:09.380 --> 01:51:11.528 Sue, I don't know. I I.
NOTE Confidence: 0.723242104053497

01:51:11.530 --> 01:51:14.218 My guess is you have a better
NOTE Confidence: 0.723242104053497

01:51:14.218 --> 01:51:16.200 understanding of that than I do.

NOTE Confidence: 0.723242104053497
01:51:16.200 --> 01:51:18.000 Maybe I will look into
NOTE Confidence: 0.808350026607513
01:51:18.000 --> 01:51:19.938 it. OK, and
NOTE Confidence: 0.850903987884521
01:51:19.940 --> 01:51:22.668 I think this will be our last question.
NOTE Confidence: 0.850903987884521
01:51:22.670 --> 01:51:25.057 Have you thought of a role for
NOTE Confidence: 0.850903987884521
01:51:25.060 --> 01:51:26.410 surface receptor signaling expense?
NOTE Confidence: 0.850903987884521
01:51:26.410 --> 01:51:28.720 Specifically CD 28 that may be further
NOTE Confidence: 0.850903987884521
01:51:28.720 --> 01:51:30.849 enhancing the tonics signaling driven by
NOTE Confidence: 0.850903987884521
01:51:30.850 --> 01:51:33.242 the car. Yeah, oh boy, so we,
NOTE Confidence: 0.850903987884521
01:51:33.242 --> 01:51:35.629 you know I'm not sharing that today,
NOTE Confidence: 0.850903987884521
01:51:35.630 --> 01:51:38.143 but we've spent so much time thinking
NOTE Confidence: 0.850903987884521
01:51:38.143 --> 01:51:39.932 about these proximal signaling features
NOTE Confidence: 0.850903987884521
01:51:39.932 --> 01:51:42.902 because one of the I mean in this gets
NOTE Confidence: 0.850903987884521
01:51:42.902 --> 01:51:45.198 to Steve's point that his concern that
NOTE Confidence: 0.850903987884521
01:51:45.198 --> 01:51:47.585 you won't ever find a truly tumor
NOTE Confidence: 0.850903987884521
01:51:47.585 --> 01:51:49.310 specific service cell surface molecule.
NOTE Confidence: 0.850903987884521

01:51:49.310 --> 01:51:50.850 I don't think you will,
NOTE Confidence: 0.850903987884521

01:51:50.850 --> 01:51:53.514 but I think what we have our therapeutic
NOTE Confidence: 0.850903987884521

01:51:53.514 --> 01:51:55.689 windows with car T cells and our
NOTE Confidence: 0.850903987884521

01:51:55.689 --> 01:51:57.777 work is shown very clearly that you
NOTE Confidence: 0.850903987884521

01:51:57.777 --> 01:51:59.800 need high levels of Antigen for car
NOTE Confidence: 0.850903987884521

01:51:59.800 --> 01:52:01.660 T cell to become fully activated.
NOTE Confidence: 0.850903987884521

01:52:01.660 --> 01:52:03.004 There are numerous examples.
NOTE Confidence: 0.850903987884521

01:52:03.004 --> 01:52:05.685 The GD two is a perfect one where
NOTE Confidence: 0.850903987884521

01:52:05.685 --> 01:52:06.576 we have that.
NOTE Confidence: 0.850903987884521

01:52:06.580 --> 01:52:08.820 In the clinic we get good expansion
NOTE Confidence: 0.850903987884521

01:52:08.820 --> 01:52:11.216 and we don't see any toxicity even
NOTE Confidence: 0.850903987884521

01:52:11.216 --> 01:52:13.800 though there is low levels on the on.
NOTE Confidence: 0.850903987884521

01:52:13.800 --> 01:52:15.108 The neural tissues peripherally
NOTE Confidence: 0.850903987884521

01:52:15.108 --> 01:52:16.089 and Centrally so,
NOTE Confidence: 0.850903987884521

01:52:16.090 --> 01:52:17.162 so why is that?
NOTE Confidence: 0.850903987884521

01:52:17.162 --> 01:52:19.175 And one of the things we've learned

NOTE Confidence: 0.850903987884521
01:52:19.175 --> 01:52:21.197 is that the transmembrane domain of
NOTE Confidence: 0.850903987884521
01:52:21.197 --> 01:52:23.958 the car is a really important feature.
NOTE Confidence: 0.850903987884521
01:52:23.960 --> 01:52:25.535 Determining the degree to which
NOTE Confidence: 0.850903987884521
01:52:25.535 --> 01:52:27.110 the proximal signaling that the
NOTE Confidence: 0.850903987884521
01:52:27.163 --> 01:52:29.263 strength of signal needed to activate
NOTE Confidence: 0.850903987884521
01:52:29.263 --> 01:52:30.663 the proximal signaling apparatus
NOTE Confidence: 0.850903987884521
01:52:30.717 --> 01:52:32.607 and a CD 28 transmembrane domain
NOTE Confidence: 0.850903987884521
01:52:32.607 --> 01:52:33.867 lowers your antigen threshold.
NOTE Confidence: 0.850903987884521
01:52:33.870 --> 01:52:36.262 And it appears that this may be related
NOTE Confidence: 0.850903987884521
01:52:36.262 --> 01:52:38.116 to interactions with the native CD 28.
NOTE Confidence: 0.850903987884521
01:52:38.120 --> 01:52:38.610 So yes,
NOTE Confidence: 0.850903987884521
01:52:38.610 --> 01:52:41.230 I think all of this could be very important.
NOTE Confidence: 0.850903987884521
01:52:41.230 --> 01:52:43.777 And then when you add tonic signaling to it,
NOTE Confidence: 0.850903987884521
01:52:43.780 --> 01:52:45.688 clearly the 28 transmembrane cards are
NOTE Confidence: 0.850903987884521
01:52:45.688 --> 01:52:47.731 more likely to Tonic Tonic Lee signal
NOTE Confidence: 0.850903987884521

01:52:47.731 --> 01:52:49.720 and this may all be part of that,
NOTE Confidence: 0.850903987884521

01:52:49.720 --> 01:52:51.418 and whether that's a good thing
NOTE Confidence: 0.850903987884521

01:52:51.418 --> 01:52:52.550 or a bad thing,
NOTE Confidence: 0.850903987884521

01:52:52.550 --> 01:52:53.965 you know it's just now
NOTE Confidence: 0.850903987884521

01:52:53.965 --> 01:52:55.097 that you understand it.
NOTE Confidence: 0.850903987884521

01:52:55.100 --> 01:52:57.638 You can use it as part of your engineering.
NOTE Confidence: 0.851938962936401

01:52:58.740 --> 01:53:01.184 Thank you so much, doctor, Michael.
NOTE Confidence: 0.851938962936401

01:53:01.184 --> 01:53:04.152 I think you've gotta break for our
NOTE Confidence: 0.851938962936401

01:53:04.152 --> 01:53:06.564 lunch period now and then will
NOTE Confidence: 0.851938962936401

01:53:06.564 --> 01:53:08.790 see you will see everyone again
NOTE Confidence: 0.851938962936401

01:53:08.869 --> 01:53:11.266 and for the afternoon session we
NOTE Confidence: 0.851938962936401

01:53:11.266 --> 01:53:13.278 look forward to seeing everybody.
NOTE Confidence: 0.851938962936401

01:53:13.280 --> 01:53:16.520 Thanks so much trust and also for moderating.
NOTE Confidence: 0.851938962936401

01:53:16.520 --> 01:53:18.938 I think there's a great session.
NOTE Confidence: 0.851938962936401

01:53:18.940 --> 01:53:20.371 Thanks doctor Rosenberg
NOTE Confidence: 0.851938962936401

01:53:20.371 --> 01:53:22.756 Crystal as well doctor McCall.

NOTE Confidence: 0.851938962936401
01:53:22.760 --> 01:53:25.460 11 oh 1:15 so just 15 minutes eat quickly.
NOTE Confidence: 0.851938962936401
01:53:25.460 --> 01:53:27.964 I know you just have to go to
NOTE Confidence: 0.851938962936401
01:53:27.964 --> 01:53:29.360 your refrigerator for at home,
NOTE Confidence: 0.851938962936401
01:53:29.360 --> 01:53:30.830 so we'll see you back.
NOTE Confidence: 0.851938962936401
01:53:30.830 --> 01:53:32.540 And we have a great session
NOTE Confidence: 0.851938962936401
01:53:32.540 --> 01:53:34.138 where halfway through Pam Sharma
NOTE Confidence: 0.851938962936401
01:53:34.138 --> 01:53:35.944 will lead us off at 1:15.
NOTE Confidence: 0.851938962936401
01:53:35.944 --> 01:53:38.660 So please check back in then thanks so much.
NOTE Confidence: 0.841944456100464
01:53:38.660 --> 01:53:39.560 See you soon.
NOTE Confidence: 0.833135783672333
01:58:12.370 --> 01:58:14.416 Good markets how are you Jim
NOTE Confidence: 0.833135783672333
01:58:14.416 --> 01:58:16.801 says hello as well thanks a bunch
NOTE Confidence: 0.833135783672333
01:58:16.801 --> 01:58:18.847 often in his office over there.
NOTE Confidence: 0.833135783672333
01:58:18.850 --> 01:58:19.870 I'm sure things
NOTE Confidence: 0.833135783672333
01:58:19.870 --> 01:58:22.600 were crazy down in Houston as well, you
NOTE Confidence: 0.833135783672333
01:58:22.600 --> 01:58:24.805 know, so you know it gets crazier
NOTE Confidence: 0.833135783672333

01:58:24.805 --> 01:58:26.952 by the minute just because it's
NOTE Confidence: 0.833135783672333

01:58:26.952 --> 01:58:29.208 Texas and it's it's just not
NOTE Confidence: 0.833135783672333

01:58:29.208 --> 01:58:31.557 complying with the way we think, but.
NOTE Confidence: 0.833135783672333

01:58:31.557 --> 01:58:33.236 Hopefully we're trying to
NOTE Confidence: 0.833135783672333

01:58:33.236 --> 01:58:35.209 survive as we all are,
NOTE Confidence: 0.836756229400635

01:58:35.210 --> 01:58:37.982 I think, yeah, so I think we'll
NOTE Confidence: 0.836756229400635

01:58:37.982 --> 01:58:40.360 try to get ourselves going here.
NOTE Confidence: 0.836756229400635

01:58:40.360 --> 01:58:43.924 So so for all of you who are back,
NOTE Confidence: 0.836756229400635

01:58:43.930 --> 01:58:45.910 which is actually the majority,
NOTE Confidence: 0.836756229400635

01:58:45.910 --> 01:58:47.890 you can always check attendance
NOTE Confidence: 0.836756229400635

01:58:47.890 --> 01:58:49.442 pretty quickly and zoom.
NOTE Confidence: 0.836756229400635

01:58:49.442 --> 01:58:50.930 At least by computer,
NOTE Confidence: 0.836756229400635

01:58:50.930 --> 01:58:53.071 but the next section would be
NOTE Confidence: 0.836756229400635

01:58:53.071 --> 01:58:55.570 session 3 and we have three speakers,
NOTE Confidence: 0.836756229400635

01:58:55.570 --> 01:58:58.069 a couple from Yale an we have
NOTE Confidence: 0.836756229400635

01:58:58.070 --> 01:58:59.852 Pam Sharma who our moderate

NOTE Confidence: 0.836756229400635

01:58:59.852 --> 01:59:01.276 are Cellino will introduce.

NOTE Confidence: 0.836756229400635

01:59:01.280 --> 01:59:03.778 Kelly is an assistant professor in surgery

NOTE Confidence: 0.808875441551209

01:59:03.780 --> 01:59:04.848 who I worked

NOTE Confidence: 0.808875441551209

01:59:04.850 --> 01:59:06.278 with very closely on

NOTE Confidence: 0.808875441551209

01:59:06.280 --> 01:59:08.420 the Melanoma unit has been a

NOTE Confidence: 0.808875441551209

01:59:08.420 --> 01:59:12.348 great addition to Yale a couple

NOTE Confidence: 0.808875441551209

01:59:10.560 --> 01:59:12.350 years back. Has experience in

NOTE Confidence: 0.808875441551209

01:59:12.350 --> 01:59:14.135 designing and evaluating immune therapies

NOTE Confidence: 0.808875441551209

01:59:14.135 --> 01:59:16.628 and it's very actively involved in both

NOTE Confidence: 0.808875441551209

01:59:16.630 --> 01:59:19.128 our clinical Melanoma unit as well as

NOTE Confidence: 0.808875441551209

01:59:19.130 --> 01:59:20.940 trying to advance anti cancer

NOTE Confidence: 0.808875441551209

01:59:20.940 --> 01:59:22.570 immune therapies. At Yale,

NOTE Confidence: 0.670442223548889

01:59:22.570 --> 01:59:25.270 so Kelly feel free to start.

NOTE Confidence: 0.779358685016632

01:59:25.930 --> 01:59:28.340 At its my absolute pleasure to

NOTE Confidence: 0.779358685016632

01:59:28.340 --> 01:59:29.950 introduce doctor Pam Sharma,

NOTE Confidence: 0.779358685016632

01:59:29.950 --> 01:59:33.163 who is a model for what all physician
NOTE Confidence: 0.779358685016632

01:59:33.163 --> 01:59:35.176 scientists really aspire to be.
NOTE Confidence: 0.779358685016632

01:59:35.176 --> 01:59:36.380 She's been highlighting
NOTE Confidence: 0.779358685016632

01:59:36.380 --> 01:59:37.590 major discoveries beginning
NOTE Confidence: 0.779358685016632

01:59:37.590 --> 01:59:40.000 in 2003 while she was still
NOTE Confidence: 0.779358685016632

01:59:40.000 --> 01:59:41.209 a fellow with
NOTE Confidence: 0.779358685016632

01:59:41.210 --> 01:59:44.418 looking at the New York new NYSE one.
NOTE Confidence: 0.779358685016632

01:59:44.420 --> 01:59:47.634 T cell epitope while she was still a
NOTE Confidence: 0.779358685016632

01:59:47.634 --> 01:59:49.649 fellow excellent Kettering and then
NOTE Confidence: 0.779358685016632

01:59:49.650 --> 01:59:51.660 some of her seminal work,
NOTE Confidence: 0.779358685016632

01:59:51.660 --> 01:59:53.262 and identifying Icos is
NOTE Confidence: 0.779358685016632

01:59:53.262 --> 01:59:55.674 expressing T cells as being part
NOTE Confidence: 0.798663690686226

01:59:55.680 --> 01:59:57.260 of the mechanism. Actions
NOTE Confidence: 0.856578707695007

01:59:57.260 --> 01:59:58.289 he till 8
NOTE Confidence: 0.856578707695007

01:59:58.290 --> 02:00:00.348 four. As you can see here,
NOTE Confidence: 0.856578707695007

02:00:00.350 --> 02:00:01.718 she's a scientific director

NOTE Confidence: 0.856578707695007
02:00:01.718 --> 02:00:03.086 of the immunotherapy platform
NOTE Confidence: 0.856578707695007
02:00:03.090 --> 02:00:04.119 at MD Anderson.
NOTE Confidence: 0.856578707695007
02:00:04.120 --> 02:00:06.524 She's a professor of Gu medical oncology
NOTE Confidence: 0.856578707695007
02:00:06.524 --> 02:00:08.579 there, and also the Co director
NOTE Confidence: 0.856578707695007
02:00:08.580 --> 02:00:10.639 of the Parker Institute and the
NOTE Confidence: 0.856578707695007
02:00:10.640 --> 02:00:12.360 Pi of many, many trials.
NOTE Confidence: 0.856578707695007
02:00:12.360 --> 02:00:14.409 And you know, really was a
NOTE Confidence: 0.856578707695007
02:00:14.410 --> 02:00:16.468 visionary in doing what we now
NOTE Confidence: 0.856578707695007
02:00:16.470 --> 02:00:18.528 call window of opportunity trials and
NOTE Confidence: 0.856578707695007
02:00:18.528 --> 02:00:20.928 trying to study while people are on
NOTE Confidence: 0.856578707695007
02:00:20.930 --> 02:00:23.326 therapy to figure out why things work,
NOTE Confidence: 0.856578707695007
02:00:23.326 --> 02:00:25.392 why they don't work. So again,
NOTE Confidence: 0.856578707695007
02:00:25.392 --> 02:00:27.870 we're all delighted to have you here.
NOTE Confidence: 0.856578707695007
02:00:27.870 --> 02:00:29.421 And welcome from another Queens
NOTE Confidence: 0.856578707695007
02:00:29.421 --> 02:00:31.598 girl who was in Texas and then
NOTE Confidence: 0.885932564735413

02:00:31.600 --> 02:00:33.780 came back home to the East Coast.
NOTE Confidence: 0.885932564735413

02:00:33.780 --> 02:00:36.237 So you're speaking about but what my
NOTE Confidence: 0.885932564735413

02:00:36.237 --> 02:00:38.759 whole family wants me to do is come back,
NOTE Confidence: 0.885932564735413

02:00:38.760 --> 02:00:41.010 but I'm having a lot of fun in Texas
NOTE Confidence: 0.885932564735413

02:00:41.010 --> 02:00:43.587 too and I'm really grateful for this
NOTE Confidence: 0.885932564735413

02:00:43.587 --> 02:00:45.910 opportunity to present some of our work.
NOTE Confidence: 0.885932564735413

02:00:45.910 --> 02:00:47.961 Thank you so much for that kind
NOTE Confidence: 0.885932564735413

02:00:47.961 --> 02:00:50.024 introduction an I am going to be
NOTE Confidence: 0.885932564735413

02:00:50.024 --> 02:00:51.710 talking a lot about the clinical
NOTE Confidence: 0.885932564735413

02:00:51.771 --> 02:00:53.847 trials today and how we interrogate
NOTE Confidence: 0.885932564735413

02:00:53.847 --> 02:00:55.930 the clinical trials in the laboratory.
NOTE Confidence: 0.885932564735413

02:00:55.930 --> 02:00:58.345 Let me see advancing here we go.
NOTE Confidence: 0.885932564735413

02:00:58.350 --> 02:01:00.548 So as many of you are aware,
NOTE Confidence: 0.885932564735413

02:01:00.550 --> 02:01:02.734 anti see teleport clearly open an entire
NOTE Confidence: 0.885932564735413

02:01:02.734 --> 02:01:04.471 new field called immune checkpoint
NOTE Confidence: 0.885932564735413

02:01:04.471 --> 02:01:06.703 therapy that goes without saying that

NOTE Confidence: 0.885932564735413

02:01:06.703 --> 02:01:08.981 the paradigm shifted as a curd in the

NOTE Confidence: 0.885932564735413

02:01:08.981 --> 02:01:10.650 last decade has been monumental in

NOTE Confidence: 0.885932564735413

02:01:10.650 --> 02:01:13.030 terms of the advances that we've seen

NOTE Confidence: 0.885932564735413

02:01:13.030 --> 02:01:15.296 not only for anti see till 8 four,

NOTE Confidence: 0.885932564735413

02:01:15.300 --> 02:01:16.664 but other immunotherapy agents.

NOTE Confidence: 0.885932564735413

02:01:16.664 --> 02:01:18.710 And of course the clinical benefit

NOTE Confidence: 0.885932564735413

02:01:18.768 --> 02:01:20.008 for all of our patients.

NOTE Confidence: 0.885932564735413

02:01:20.010 --> 02:01:22.208 So this cartoon is a bit outdated,

NOTE Confidence: 0.885932564735413

02:01:22.210 --> 02:01:24.106 but I will highlight sitali for

NOTE Confidence: 0.885932564735413

02:01:24.106 --> 02:01:26.658 here and PD one and PDL one which.

NOTE Confidence: 0.885932564735413

02:01:26.660 --> 02:01:28.514 Is the other agent actually anti

NOTE Confidence: 0.885932564735413

02:01:28.514 --> 02:01:30.918 PD one and anti PD L1 antibodies?

NOTE Confidence: 0.885932564735413

02:01:30.920 --> 02:01:33.125 Both agents that are now in an

NOTE Confidence: 0.885932564735413

02:01:33.125 --> 02:01:34.810 FDA approval Arsenal for patients

NOTE Confidence: 0.885932564735413

02:01:34.810 --> 02:01:36.166 with cancer as well.

NOTE Confidence: 0.885932564735413

02:01:36.170 --> 02:01:38.368 Obviously there are a lot of other
NOTE Confidence: 0.885932564735413

02:01:38.368 --> 02:01:40.048 targets that are being explored
NOTE Confidence: 0.885932564735413

02:01:40.048 --> 02:01:42.393 and we'll talk about some of them,
NOTE Confidence: 0.885932564735413

02:01:42.400 --> 02:01:44.368 but it's impossible to talk about
NOTE Confidence: 0.885932564735413

02:01:44.368 --> 02:01:45.680 all of them clearly,
NOTE Confidence: 0.885932564735413

02:01:45.680 --> 02:01:47.312 but these are other targets now
NOTE Confidence: 0.885932564735413

02:01:47.312 --> 02:01:49.133 that have come to the forefront
NOTE Confidence: 0.885932564735413

02:01:49.133 --> 02:01:50.823 of regulating T cell responses
NOTE Confidence: 0.885932564735413

02:01:50.823 --> 02:01:52.900 within the tumor micro environment.
NOTE Confidence: 0.885932564735413

02:01:52.900 --> 02:01:53.818 As I mentioned,
NOTE Confidence: 0.885932564735413

02:01:53.818 --> 02:01:55.654 the last decade has seen many
NOTE Confidence: 0.885932564735413

02:01:55.654 --> 02:01:56.889 many FDA approvals.
NOTE Confidence: 0.885932564735413

02:01:56.890 --> 02:01:58.730 Obviously a pillow Melbourne Sisi
NOTE Confidence: 0.885932564735413

02:01:58.730 --> 02:02:01.248 telephone was in 2011 and was the
NOTE Confidence: 0.885932564735413

02:02:01.248 --> 02:02:03.390 first but I just wanted to give
NOTE Confidence: 0.885932564735413

02:02:03.390 --> 02:02:05.318 everybody a broad overview of all

NOTE Confidence: 0.885932564735413
02:02:05.318 --> 02:02:07.544 of the approvals that have been in
NOTE Confidence: 0.885932564735413
02:02:07.544 --> 02:02:09.204 Kering across multiple tumor types,
NOTE Confidence: 0.885932564735413
02:02:09.210 --> 02:02:10.965 because really these agents are
NOTE Confidence: 0.885932564735413
02:02:10.965 --> 02:02:12.720 targeting the immune response and
NOTE Confidence: 0.885932564735413
02:02:12.774 --> 02:02:14.394 they don't really target anything
NOTE Confidence: 0.885932564735413
02:02:14.394 --> 02:02:16.694 related to the cancer cell itself and
NOTE Confidence: 0.885932564735413
02:02:16.694 --> 02:02:18.885 that makes it applicable then to many
NOTE Confidence: 0.885932564735413
02:02:18.885 --> 02:02:20.532 different tumor types and possibly
NOTE Confidence: 0.885932564735413
02:02:20.532 --> 02:02:21.864 for many different combinations.
NOTE Confidence: 0.885932564735413
02:02:21.870 --> 02:02:24.600 Strategies as well talk about.
NOTE Confidence: 0.885932564735413
02:02:24.600 --> 02:02:26.110 So the research questions though,
NOTE Confidence: 0.885932564735413
02:02:26.110 --> 02:02:27.958 that come to mind as we take
NOTE Confidence: 0.885932564735413
02:02:27.958 --> 02:02:30.019 care of these patients in clinic,
NOTE Confidence: 0.885932564735413
02:02:30.020 --> 02:02:31.850 is that clearly some patients are
NOTE Confidence: 0.885932564735413
02:02:31.850 --> 02:02:33.330 responding and others are not.
NOTE Confidence: 0.885932564735413

02:02:33.330 --> 02:02:34.830 So why is this happening?
NOTE Confidence: 0.885932564735413

02:02:34.830 --> 02:02:36.455 Are there biomarkers to predict
NOTE Confidence: 0.885932564735413

02:02:36.455 --> 02:02:38.080 a response and immune related
NOTE Confidence: 0.885932564735413

02:02:38.143 --> 02:02:39.798 toxicities that are associated with
NOTE Confidence: 0.885932564735413

02:02:39.798 --> 02:02:41.979 these agents and I'm sorry I won't
NOTE Confidence: 0.885932564735413

02:02:41.979 --> 02:02:43.624 be able to talk about the artwork
NOTE Confidence: 0.885932564735413

02:02:43.624 --> 02:02:45.076 on immune related toxicities today,
NOTE Confidence: 0.885932564735413

02:02:45.076 --> 02:02:46.900 but happy to take questions if
NOTE Confidence: 0.885932564735413

02:02:46.957 --> 02:02:47.779 someone has them.
NOTE Confidence: 0.885932564735413

02:02:47.780 --> 02:02:49.100 Are there biomarkers to enable
NOTE Confidence: 0.885932564735413

02:02:49.100 --> 02:02:50.420 patient selection for treatment with
NOTE Confidence: 0.885932564735413

02:02:50.466 --> 02:02:51.690 monotherapy versus combination?
NOTE Confidence: 0.885932564735413

02:02:51.690 --> 02:02:53.346 Can we increase the number of
NOTE Confidence: 0.885932564735413

02:02:53.346 --> 02:02:55.080 patients who respond and are there
NOTE Confidence: 0.885932564735413

02:02:55.080 --> 02:02:56.796 other pathways that can be targeted
NOTE Confidence: 0.885932564735413

02:02:56.796 --> 02:02:58.350 to improve clinical outcomes?

NOTE Confidence: 0.885932564735413
02:02:58.350 --> 02:03:00.456 So in order for us to try and answer
NOTE Confidence: 0.885932564735413
02:03:00.456 --> 02:03:02.490 some of these questions really we
NOTE Confidence: 0.885932564735413
02:03:02.490 --> 02:03:04.230 have to integrate the laboratory
NOTE Confidence: 0.885932564735413
02:03:04.294 --> 02:03:06.450 in the clinical research in a very
NOTE Confidence: 0.885932564735413
02:03:06.450 --> 02:03:07.681 efficient and rapid manner.
NOTE Confidence: 0.885932564735413
02:03:07.681 --> 02:03:10.089 At this point we have about actually 3000,
NOTE Confidence: 0.885932564735413
02:03:10.090 --> 02:03:12.799 so this slide is also a little bit outdated.
NOTE Confidence: 0.852807343006134
02:03:12.800 --> 02:03:14.004 About 3000 clinical trials,
NOTE Confidence: 0.852807343006134
02:03:14.004 --> 02:03:15.509 ongoing with either anti sitella.
NOTE Confidence: 0.852807343006134
02:03:15.510 --> 02:03:17.418 For anti PD one or anti PD L1 and
NOTE Confidence: 0.852807343006134
02:03:17.418 --> 02:03:19.609 so so clearly the clinical aspect
NOTE Confidence: 0.852807343006134
02:03:19.609 --> 02:03:21.524 has outstripped the basic science.
NOTE Confidence: 0.852807343006134
02:03:21.530 --> 02:03:23.810 I mean we know that the basic signs
NOTE Confidence: 0.852807343006134
02:03:23.810 --> 02:03:26.109 led to the development of this field
NOTE Confidence: 0.852807343006134
02:03:26.109 --> 02:03:28.928 as many of you know that the mice in
NOTE Confidence: 0.852807343006134

02:03:28.928 --> 02:03:31.493 the lab or in bread and the disease is
NOTE Confidence: 0.852807343006134

02:03:31.493 --> 02:03:33.359 homogeneous and that leads to great.
NOTE Confidence: 0.852807343006134

02:03:33.360 --> 02:03:35.544 Hypothesis testing that we can then take
NOTE Confidence: 0.852807343006134

02:03:35.544 --> 02:03:38.217 the data from the laboratory to the clinic.
NOTE Confidence: 0.852807343006134

02:03:38.220 --> 02:03:39.268 But as I mentioned,
NOTE Confidence: 0.852807343006134

02:03:39.268 --> 02:03:40.578 the clinic is now outstripping
NOTE Confidence: 0.852807343006134

02:03:40.578 --> 02:03:42.110 our scientific understanding,
NOTE Confidence: 0.852807343006134

02:03:42.110 --> 02:03:44.054 so we're really dealing with a
NOTE Confidence: 0.852807343006134

02:03:44.054 --> 02:03:45.350 lot of clinical data.
NOTE Confidence: 0.852807343006134

02:03:45.350 --> 02:03:48.590 And how do we get that back to the lab?
NOTE Confidence: 0.852807343006134

02:03:48.590 --> 02:03:50.205 So really, we're dealing with
NOTE Confidence: 0.852807343006134

02:03:50.205 --> 02:03:51.497 patients who are polymorphic.
NOTE Confidence: 0.852807343006134

02:03:51.500 --> 02:03:52.876 The disease is heterogeneous
NOTE Confidence: 0.852807343006134

02:03:52.876 --> 02:03:54.596 and this is called hypothesis
NOTE Confidence: 0.852807343006134

02:03:54.596 --> 02:03:56.040 generating data from the clinic,
NOTE Confidence: 0.852807343006134

02:03:56.040 --> 02:03:58.308 so we have to take this hypothesis,

NOTE Confidence: 0.852807343006134
02:03:58.310 --> 02:03:59.985 generating data back to the
NOTE Confidence: 0.852807343006134
02:03:59.985 --> 02:04:01.325 laboratory design the appropriate
NOTE Confidence: 0.852807343006134
02:04:01.325 --> 02:04:03.276 models in the laboratory to then
NOTE Confidence: 0.852807343006134
02:04:03.276 --> 02:04:04.524 test the hypothesis rigorously.
NOTE Confidence: 0.852807343006134
02:04:04.530 --> 02:04:07.293 So how do we do that in the clinic?
NOTE Confidence: 0.852807343006134
02:04:07.300 --> 02:04:07.589 Well,
NOTE Confidence: 0.852807343006134
02:04:07.589 --> 02:04:09.612 we have to rethink clinical trial design
NOTE Confidence: 0.852807343006134
02:04:09.612 --> 02:04:12.205 for one and many of you are aware that
NOTE Confidence: 0.852807343006134
02:04:12.205 --> 02:04:13.817 clinical trial design release phase
NOTE Confidence: 0.852807343006134
02:04:13.817 --> 02:04:15.617 one safety dose escalation phase,
NOTE Confidence: 0.852807343006134
02:04:15.620 --> 02:04:17.160 two efficacy in phase three
NOTE Confidence: 0.852807343006134
02:04:17.160 --> 02:04:18.700 comparison to standard of care.
NOTE Confidence: 0.852807343006134
02:04:18.700 --> 02:04:20.330 What we proposed was conducting
NOTE Confidence: 0.852807343006134
02:04:20.330 --> 02:04:22.316 these pre surgical or tissue based
NOTE Confidence: 0.852807343006134
02:04:22.316 --> 02:04:23.786 clinical trials which we call
NOTE Confidence: 0.852807343006134

02:04:23.786 --> 02:04:25.780 phase one or phase two a studies.
NOTE Confidence: 0.852807343006134

02:04:25.780 --> 02:04:27.025 And really these trials will
NOTE Confidence: 0.852807343006134

02:04:27.025 --> 02:04:28.949 allow us to not only have clinical
NOTE Confidence: 0.852807343006134

02:04:28.949 --> 02:04:30.809 signals but also to have biomarker
NOTE Confidence: 0.852807343006134

02:04:30.809 --> 02:04:32.559 analysis and mechanistic insights.
NOTE Confidence: 0.852807343006134

02:04:32.560 --> 02:04:34.709 And we started these studies in 2004
NOTE Confidence: 0.852807343006134

02:04:34.709 --> 02:04:36.622 and reported on our first trial.
NOTE Confidence: 0.852807343006134

02:04:36.622 --> 02:04:38.638 I'm around 2006 and the paper
NOTE Confidence: 0.852807343006134

02:04:38.638 --> 02:04:39.859 was published in 2008,
NOTE Confidence: 0.852807343006134

02:04:39.860 --> 02:04:41.558 but since then it's really taken
NOTE Confidence: 0.852807343006134

02:04:41.558 --> 02:04:44.235 off as a way for us to interrogate
NOTE Confidence: 0.852807343006134

02:04:44.235 --> 02:04:46.085 the immune responses in humans.
NOTE Confidence: 0.852807343006134

02:04:46.090 --> 02:04:47.402 Because these responses are
NOTE Confidence: 0.852807343006134

02:04:47.402 --> 02:04:48.058 slightly different.
NOTE Confidence: 0.852807343006134

02:04:48.060 --> 02:04:49.164 As you can imagine,
NOTE Confidence: 0.852807343006134

02:04:49.164 --> 02:04:51.536 then mice and also gives us a chance

NOTE Confidence: 0.852807343006134

02:04:51.536 --> 02:04:53.804 to study the lanja tude inal responses

NOTE Confidence: 0.852807343006134

02:04:53.804 --> 02:04:56.414 because in humans this is a dynamic

NOTE Confidence: 0.852807343006134

02:04:56.414 --> 02:04:57.898 process occurring multiple multiple

NOTE Confidence: 0.852807343006134

02:04:57.900 --> 02:05:00.574 stages of the disease as well as

NOTE Confidence: 0.852807343006134

02:05:00.574 --> 02:05:02.194 after multiple different treatment

NOTE Confidence: 0.852807343006134

02:05:02.194 --> 02:05:04.606 regimen that a patient can have.

NOTE Confidence: 0.852807343006134

02:05:04.610 --> 02:05:06.266 So the first trial we conducted

NOTE Confidence: 0.852807343006134

02:05:06.266 --> 02:05:08.100 in this way is shown here,

NOTE Confidence: 0.852807343006134

02:05:08.100 --> 02:05:08.973 and this again,

NOTE Confidence: 0.852807343006134

02:05:08.973 --> 02:05:10.719 this protocol is written in 2006,

NOTE Confidence: 0.852807343006134

02:05:10.720 --> 02:05:12.180 and as you can see,

NOTE Confidence: 0.852807343006134

02:05:12.180 --> 02:05:13.630 it's a small clinical trial.

NOTE Confidence: 0.852807343006134

02:05:13.630 --> 02:05:15.359 These do not need to be large

NOTE Confidence: 0.852807343006134

02:05:15.359 --> 02:05:17.176 trials as we think about phase

NOTE Confidence: 0.852807343006134

02:05:17.176 --> 02:05:18.866 two and Phase Three Studies.

NOTE Confidence: 0.852807343006134

02:05:18.870 --> 02:05:19.850 These are small trials.
NOTE Confidence: 0.852807343006134

02:05:19.850 --> 02:05:22.026 This was a 12 patient trial in patients
NOTE Confidence: 0.852807343006134

02:05:22.026 --> 02:05:23.661 with localized bladder cancer who
NOTE Confidence: 0.852807343006134

02:05:23.661 --> 02:05:25.269 were already scheduled for surgery,
NOTE Confidence: 0.852807343006134

02:05:25.270 --> 02:05:27.566 and we administered two doses of anti
NOTE Confidence: 0.852807343006134

02:05:27.566 --> 02:05:29.395 sitella for antibody prior to surgery
NOTE Confidence: 0.852807343006134

02:05:29.395 --> 02:05:31.823 so that we can have access to all of
NOTE Confidence: 0.852807343006134

02:05:31.823 --> 02:05:33.727 the tumor material at the time of
NOTE Confidence: 0.852807343006134

02:05:33.727 --> 02:05:35.204 surgery for the laboratory studies.
NOTE Confidence: 0.852807343006134

02:05:35.204 --> 02:05:38.188 But the trial gave us a lot of information.
NOTE Confidence: 0.852807343006134

02:05:38.190 --> 02:05:38.842 For one,
NOTE Confidence: 0.852807343006134

02:05:38.842 --> 02:05:41.450 it gave us a clinical signal for safety.
NOTE Confidence: 0.852807343006134

02:05:41.450 --> 02:05:43.406 So if you think about it,
NOTE Confidence: 0.852807343006134

02:05:43.410 --> 02:05:45.040 this was the first neoadjuvant
NOTE Confidence: 0.852807343006134

02:05:45.040 --> 02:05:46.344 clinical trial with immune
NOTE Confidence: 0.852807343006134

02:05:46.344 --> 02:05:47.970 checkpoint therapy conducted in 2006.

NOTE Confidence: 0.852807343006134

02:05:47.970 --> 02:05:49.600 Prior to any FDA approvals.

NOTE Confidence: 0.852807343006134

02:05:49.600 --> 02:05:51.455 And so it told us that we

NOTE Confidence: 0.852807343006134

02:05:51.455 --> 02:05:52.250 can actually give

NOTE Confidence: 0.852524995803833

02:05:52.319 --> 02:05:53.498 immune checkpoint therapy

NOTE Confidence: 0.852524995803833

02:05:53.498 --> 02:05:55.463 prior to surgery and now,

NOTE Confidence: 0.852524995803833

02:05:55.470 --> 02:05:57.010 of course there are multiple

NOTE Confidence: 0.852524995803833

02:05:57.010 --> 02:05:58.242 neoadjuvant clinical trials ongoing

NOTE Confidence: 0.852524995803833

02:05:58.242 --> 02:05:59.710 with immune checkpoint agents.

NOTE Confidence: 0.852524995803833

02:05:59.710 --> 02:06:01.660 It also gave us a clinical

NOTE Confidence: 0.852524995803833

02:06:01.660 --> 02:06:02.635 signal for efficacy,

NOTE Confidence: 0.852524995803833

02:06:02.640 --> 02:06:04.488 because this was the first clinical

NOTE Confidence: 0.852524995803833

02:06:04.488 --> 02:06:06.569 trial in patients with bladder cancer.

NOTE Confidence: 0.852524995803833

02:06:06.570 --> 02:06:08.593 And so clinical trials were on going

NOTE Confidence: 0.852524995803833

02:06:08.593 --> 02:06:10.737 in Melanoma but not in bladder cancer.

NOTE Confidence: 0.852524995803833

02:06:10.740 --> 02:06:12.721 And so three patients in this bladder

NOTE Confidence: 0.852524995803833

02:06:12.721 --> 02:06:14.224 cancer study actually had pathologic
NOTE Confidence: 0.852524995803833

02:06:14.224 --> 02:06:15.734 complete response is where all
NOTE Confidence: 0.852524995803833

02:06:15.734 --> 02:06:17.586 disease went away and the pathologist
NOTE Confidence: 0.852524995803833

02:06:17.586 --> 02:06:19.374 could not find any remaining tumors.
NOTE Confidence: 0.852524995803833

02:06:19.380 --> 02:06:21.291 So this was an indication that bladder
NOTE Confidence: 0.852524995803833

02:06:21.291 --> 02:06:23.142 cancer was going to be responsive
NOTE Confidence: 0.852524995803833

02:06:23.142 --> 02:06:24.446 to immune checkpoint therapy.
NOTE Confidence: 0.852524995803833

02:06:24.450 --> 02:06:26.235 And of course we design those studies
NOTE Confidence: 0.852524995803833

02:06:26.235 --> 02:06:27.928 later in the meta static setting
NOTE Confidence: 0.852524995803833

02:06:27.928 --> 02:06:29.674 for FDA approval in bladder cancer
NOTE Confidence: 0.852524995803833

02:06:29.674 --> 02:06:31.597 or from the laboratory standpoint,
NOTE Confidence: 0.852524995803833

02:06:31.600 --> 02:06:33.686 we really had a lot of access.
NOTE Confidence: 0.852524995803833

02:06:33.690 --> 02:06:35.699 Now to these large tumor samples that
NOTE Confidence: 0.852524995803833

02:06:35.699 --> 02:06:37.919 were taken in large amounts of cells.
NOTE Confidence: 0.852524995803833

02:06:37.920 --> 02:06:40.674 For all of the assays that we were proposing,
NOTE Confidence: 0.852524995803833

02:06:40.680 --> 02:06:42.558 so without looked at the pre

NOTE Confidence: 0.852524995803833

02:06:42.558 --> 02:06:44.473 treatment and I should point out

NOTE Confidence: 0.852524995803833

02:06:44.473 --> 02:06:46.573 here that we had some pre treatment

NOTE Confidence: 0.852524995803833

02:06:46.573 --> 02:06:49.001 but for those of you who take care

NOTE Confidence: 0.852524995803833

02:06:49.001 --> 02:06:50.811 of bladder cancer patients you know

NOTE Confidence: 0.852524995803833

02:06:50.811 --> 02:06:52.346 the pretreatment is very small.

NOTE Confidence: 0.852524995803833

02:06:52.350 --> 02:06:52.666 Biopsies,

NOTE Confidence: 0.852524995803833

02:06:52.666 --> 02:06:54.246 sewer pretreatment cohort actually was

NOTE Confidence: 0.852524995803833

02:06:54.246 --> 02:06:56.030 an untreated cohort that was staged,

NOTE Confidence: 0.852524995803833

02:06:56.030 --> 02:06:57.565 matched and went directly to

NOTE Confidence: 0.852524995803833

02:06:57.565 --> 02:06:58.179 radical cystectomy.

NOTE Confidence: 0.852524995803833

02:06:58.180 --> 02:07:00.329 So they did not receive the anti.

NOTE Confidence: 0.852524995803833

02:07:00.330 --> 02:07:02.074 See Tilly for drug and we were able

NOTE Confidence: 0.852524995803833

02:07:02.074 --> 02:07:03.932 to use that released comparison for

NOTE Confidence: 0.852524995803833

02:07:03.932 --> 02:07:05.642 posttreatment samples and you can

NOTE Confidence: 0.852524995803833

02:07:05.642 --> 02:07:07.835 see in the posttreatment samples we

NOTE Confidence: 0.852524995803833

02:07:07.835 --> 02:07:09.625 had lots of infiltrating lymphocytes.
NOTE Confidence: 0.852524995803833

02:07:09.630 --> 02:07:11.808 And these staying with CD3CD4 CD
NOTE Confidence: 0.852524995803833

02:07:11.808 --> 02:07:14.089 8 Granzyme indicating T cells on
NOTE Confidence: 0.852524995803833

02:07:14.089 --> 02:07:15.989 activated T cells with Granzyme,
NOTE Confidence: 0.852524995803833

02:07:15.990 --> 02:07:18.643 and we also found B cells which
NOTE Confidence: 0.852524995803833

02:07:18.643 --> 02:07:22.008 are CD 20 positive is shown here.
NOTE Confidence: 0.852524995803833

02:07:22.010 --> 02:07:24.190 And when we compare the pre an
NOTE Confidence: 0.852524995803833

02:07:24.190 --> 02:07:25.615 post treatment or to untreated
NOTE Confidence: 0.852524995803833

02:07:25.615 --> 02:07:26.919 and posttreatment samples for
NOTE Confidence: 0.852524995803833

02:07:26.919 --> 02:07:28.107 differentially expressed genes,
NOTE Confidence: 0.852524995803833

02:07:28.110 --> 02:07:29.715 obviously with lots of lymphocytes
NOTE Confidence: 0.852524995803833

02:07:29.715 --> 02:07:30.678 infiltrating into tumor,
NOTE Confidence: 0.852524995803833

02:07:30.680 --> 02:07:32.780 we had lots of signaling pathways that
NOTE Confidence: 0.852524995803833

02:07:32.780 --> 02:07:34.848 were related to the immune response.
NOTE Confidence: 0.852524995803833

02:07:34.850 --> 02:07:37.194 What was surprising to us was that I
NOTE Confidence: 0.852524995803833

02:07:37.194 --> 02:07:39.666 cost was the top pathway listed here.

NOTE Confidence: 0.852524995803833

02:07:39.670 --> 02:07:42.110 So I cast had not been studied in

NOTE Confidence: 0.852524995803833

02:07:42.110 --> 02:07:44.144 human immune responses before and so

NOTE Confidence: 0.852524995803833

02:07:44.144 --> 02:07:46.548 we were puzzled by this and wanted

NOTE Confidence: 0.852524995803833

02:07:46.548 --> 02:07:48.964 to look at it a little bit deeper.

NOTE Confidence: 0.852524995803833

02:07:48.970 --> 02:07:50.938 So I cross again is inducible

NOTE Confidence: 0.852524995803833

02:07:50.938 --> 02:07:52.576 costimulator it belongs to the

NOTE Confidence: 0.852524995803833

02:07:52.576 --> 02:07:54.417 CD 20 agency tally for family is

NOTE Confidence: 0.852524995803833

02:07:54.417 --> 02:07:56.358 shown in this phylogenetic tree.

NOTE Confidence: 0.852524995803833

02:07:56.360 --> 02:07:56.942 Its expression.

NOTE Confidence: 0.852524995803833

02:07:56.942 --> 02:07:58.688 It has been known to maybe

NOTE Confidence: 0.852524995803833

02:07:58.688 --> 02:08:00.300 increase on activated T cells,

NOTE Confidence: 0.852524995803833

02:08:00.300 --> 02:08:02.088 however it has a very diverse

NOTE Confidence: 0.852524995803833

02:08:02.088 --> 02:08:03.280 role that's been reported,

NOTE Confidence: 0.852524995803833

02:08:03.280 --> 02:08:05.359 including a roll on regulatory T cells.

NOTE Confidence: 0.852524995803833

02:08:05.360 --> 02:08:06.460 Follicular helper T cells,

NOTE Confidence: 0.852524995803833

02:08:06.460 --> 02:08:08.640 and no role really an antitumor responses.

NOTE Confidence: 0.852524995803833

02:08:08.640 --> 02:08:10.284 So because we had access to

NOTE Confidence: 0.852524995803833

02:08:10.284 --> 02:08:11.920 all of these tumor tissues,

NOTE Confidence: 0.852524995803833

02:08:11.920 --> 02:08:13.943 now we can ask the question about

NOTE Confidence: 0.852524995803833

02:08:13.943 --> 02:08:15.772 what was happening with this icos

NOTE Confidence: 0.852524995803833

02:08:15.772 --> 02:08:17.872 positive subset in the setting of anti.

NOTE Confidence: 0.852524995803833

02:08:17.880 --> 02:08:19.405 See telling for treatment and

NOTE Confidence: 0.852524995803833

02:08:19.405 --> 02:08:20.930 you can see in nonmalignant

NOTE Confidence: 0.852524995803833

02:08:20.989 --> 02:08:22.645 tissues which we had access to.

NOTE Confidence: 0.852524995803833

02:08:22.650 --> 02:08:25.651 There were very few or about 13% of the CD.

NOTE Confidence: 0.852524995803833

02:08:25.651 --> 02:08:27.186 Four cells expressed I costs.

NOTE Confidence: 0.852524995803833

02:08:27.190 --> 02:08:28.660 Any untreated tumor tissues were

NOTE Confidence: 0.852524995803833

02:08:28.660 --> 02:08:30.130 somewhat similar in about 16%

NOTE Confidence: 0.818335831165314

02:08:30.130 --> 02:08:32.474 of the CD. Four cells expressing high costs,

NOTE Confidence: 0.818335831165314

02:08:32.480 --> 02:08:34.391 but after treatment with anti CD like

NOTE Confidence: 0.818335831165314

02:08:34.391 --> 02:08:36.598 for all of our patients, had this

NOTE Confidence: 0.818335831165314

02:08:36.598 --> 02:08:38.656 increase in the eye cast positive CD,
NOTE Confidence: 0.818335831165314

02:08:38.660 --> 02:08:41.060 four subset and some of our patients also
NOTE Confidence: 0.818335831165314

02:08:41.060 --> 02:08:43.709 had an increase in the eye cause positive
NOTE Confidence: 0.818335831165314

02:08:43.709 --> 02:08:46.160 CDs upset that I'm not showing here.
NOTE Confidence: 0.818335831165314

02:08:46.160 --> 02:08:47.875 At the same time, Jadwal Chuck was
NOTE Confidence: 0.818335831165314

02:08:47.875 --> 02:08:49.663 conducting a phase three clinical trial
NOTE Confidence: 0.818335831165314

02:08:49.663 --> 02:08:51.338 in patients with metastatic Melanoma,
NOTE Confidence: 0.818335831165314

02:08:51.340 --> 02:08:54.220 and so we had access to some of the blood.
NOTE Confidence: 0.818335831165314

02:08:54.220 --> 02:08:55.660 Samples of Judd had collected
NOTE Confidence: 0.818335831165314

02:08:55.660 --> 02:08:56.524 from those patients,
NOTE Confidence: 0.818335831165314

02:08:56.530 --> 02:08:58.386 and we could look to see whether or
NOTE Confidence: 0.818335831165314

02:08:58.386 --> 02:09:00.558 not I cast correlated with outcome,
NOTE Confidence: 0.818335831165314

02:09:00.560 --> 02:09:02.422 and you can see here to patients
NOTE Confidence: 0.818335831165314

02:09:02.422 --> 02:09:03.900 who had increased the levels
NOTE Confidence: 0.818335831165314

02:09:03.900 --> 02:09:05.460 and sustained levels of icons.
NOTE Confidence: 0.818335831165314

02:09:05.460 --> 02:09:07.490 Positive CD 4T cells had much better
NOTE Confidence: 0.818335831165314

02:09:07.490 --> 02:09:09.487 survival compared to patients who did not,
NOTE Confidence: 0.818335831165314

02:09:09.490 --> 02:09:11.499 so we also did another clinical trial.
NOTE Confidence: 0.818335831165314

02:09:11.500 --> 02:09:13.228 I want to point out here.
NOTE Confidence: 0.818335831165314

02:09:13.230 --> 02:09:15.390 This is an anti sitali 4 plus anti PDL
NOTE Confidence: 0.818335831165314

02:09:15.390 --> 02:09:17.257 one since of course combination therapy
NOTE Confidence: 0.818335831165314

02:09:17.257 --> 02:09:19.629 has been the way to move forward.
NOTE Confidence: 0.818335831165314

02:09:19.630 --> 02:09:21.255 This paper was just published
NOTE Confidence: 0.818335831165314

02:09:21.255 --> 02:09:22.555 about a week ago,
NOTE Confidence: 0.818335831165314

02:09:22.560 --> 02:09:24.330 but this is the combination neoadjuvant
NOTE Confidence: 0.818335831165314

02:09:24.330 --> 02:09:26.586 trial now and this is the first
NOTE Confidence: 0.818335831165314

02:09:26.586 --> 02:09:27.609 combination neoadjuvant trial
NOTE Confidence: 0.818335831165314

02:09:27.609 --> 02:09:29.380 in patients with bladder cancer.
NOTE Confidence: 0.818335831165314

02:09:29.380 --> 02:09:31.412 And again we were able to show that
NOTE Confidence: 0.818335831165314

02:09:31.412 --> 02:09:33.796 the trial led to patients having these
NOTE Confidence: 0.818335831165314

02:09:33.796 --> 02:09:35.606 pathologic complete response is not

NOTE Confidence: 0.818335831165314
02:09:35.668 --> 02:09:38.160 only in all patients who completely surgery,
NOTE Confidence: 0.818335831165314
02:09:38.160 --> 02:09:39.460 which are 24 patients.
NOTE Confidence: 0.818335831165314
02:09:39.460 --> 02:09:41.921 We had a 37.5% pathologic complete response,
NOTE Confidence: 0.818335831165314
02:09:41.921 --> 02:09:44.630 but we also found that in patients
NOTE Confidence: 0.818335831165314
02:09:44.696 --> 02:09:46.776 with 3D masses or T for a disease
NOTE Confidence: 0.818335831165314
02:09:46.776 --> 02:09:48.617 were very these patients do very
NOTE Confidence: 0.818335831165314
02:09:48.617 --> 02:09:50.867 poorly and I should point out that.
NOTE Confidence: 0.818335831165314
02:09:50.867 --> 02:09:53.009 All of these patients were also
NOTE Confidence: 0.818335831165314
02:09:53.009 --> 02:09:54.562 cisplatin ineligible so they
NOTE Confidence: 0.818335831165314
02:09:54.562 --> 02:09:56.246 could not receive chemotherapy.
NOTE Confidence: 0.818335831165314
02:09:56.250 --> 02:09:58.734 We also found a pathologic complete
NOTE Confidence: 0.818335831165314
02:09:58.734 --> 02:10:00.850 response for these patients of 42%
NOTE Confidence: 0.818335831165314
02:10:00.850 --> 02:10:03.154 and what we found that correlated
NOTE Confidence: 0.818335831165314
02:10:03.154 --> 02:10:05.560 with these outcomes you can see
NOTE Confidence: 0.818335831165314
02:10:05.560 --> 02:10:07.550 here the biomarkers of response
NOTE Confidence: 0.818335831165314

02:10:07.550 --> 02:10:09.689 were really related to T&B cells,
NOTE Confidence: 0.818335831165314

02:10:09.690 --> 02:10:11.605 and this was known as
NOTE Confidence: 0.818335831165314

02:10:11.605 --> 02:10:12.754 tertiary lymphoid structures.
NOTE Confidence: 0.818335831165314

02:10:12.760 --> 02:10:13.084 Again,
NOTE Confidence: 0.818335831165314

02:10:13.084 --> 02:10:14.704 in the Association between the
NOTE Confidence: 0.818335831165314

02:10:14.704 --> 02:10:17.308 T&B cells so the patients who had
NOTE Confidence: 0.818335831165314

02:10:17.308 --> 02:10:18.964 pretreatment samples with higher
NOTE Confidence: 0.818335831165314

02:10:18.964 --> 02:10:21.084 density of tertiary lymphoid structures
NOTE Confidence: 0.818335831165314

02:10:21.084 --> 02:10:23.514 did better in terms of responders.
NOTE Confidence: 0.818335831165314

02:10:23.520 --> 02:10:25.669 And again when we compare pre and
NOTE Confidence: 0.818335831165314

02:10:25.669 --> 02:10:27.419 post treatment samples is shown here.
NOTE Confidence: 0.818335831165314

02:10:27.420 --> 02:10:29.282 Also the patients who had an increase
NOTE Confidence: 0.818335831165314

02:10:29.282 --> 02:10:31.461 in the icons positive CD 4T cells
NOTE Confidence: 0.818335831165314

02:10:31.461 --> 02:10:33.116 within the tumor micro environment.
NOTE Confidence: 0.818335831165314

02:10:33.120 --> 02:10:34.900 Those patients did better in
NOTE Confidence: 0.818335831165314

02:10:34.900 --> 02:10:36.680 terms of responses as well.

NOTE Confidence: 0.818335831165314
02:10:36.680 --> 02:10:38.773 So these clinical data of course let
NOTE Confidence: 0.818335831165314
02:10:38.773 --> 02:10:40.999 us generate the hypothesis shown here,
NOTE Confidence: 0.818335831165314
02:10:41.000 --> 02:10:43.280 one of them being that the icon cycles
NOTE Confidence: 0.818335831165314
02:10:43.280 --> 02:10:44.999 legal pathways necessary for effective
NOTE Confidence: 0.818335831165314
02:10:44.999 --> 02:10:46.824 antitumor immune responses in the
NOTE Confidence: 0.818335831165314
02:10:46.824 --> 02:10:48.959 setting of anti seating for therapy.
NOTE Confidence: 0.818335831165314
02:10:48.960 --> 02:10:51.102 And to test this hypothesis we
NOTE Confidence: 0.818335831165314
02:10:51.102 --> 02:10:53.273 actually went back to the laboratory
NOTE Confidence: 0.818335831165314
02:10:53.273 --> 02:10:55.961 and we could end look at wild type
NOTE Confidence: 0.818335831165314
02:10:56.035 --> 02:10:58.339 mice as well as I cast knockout mice
NOTE Confidence: 0.818335831165314
02:10:58.339 --> 02:11:00.805 and I costly good knockout mice and
NOTE Confidence: 0.818335831165314
02:11:00.805 --> 02:11:02.690 wildtype mice injected with Melanoma
NOTE Confidence: 0.818335831165314
02:11:02.748 --> 02:11:04.318 cells could reject these tumors
NOTE Confidence: 0.818335831165314
02:11:04.318 --> 02:11:06.224 very well with anti see telling
NOTE Confidence: 0.818335831165314
02:11:06.224 --> 02:11:08.570 for therapy with 80 to 90% of the
NOTE Confidence: 0.818335831165314

02:11:08.570 --> 02:11:10.270 mice having long term survival.
NOTE Confidence: 0.818335831165314

02:11:10.270 --> 02:11:11.402 Where is the icons,
NOTE Confidence: 0.818335831165314

02:11:11.402 --> 02:11:13.100 knockout mice and Icos ligand knockout
NOTE Confidence: 0.761455953121185

02:11:13.153 --> 02:11:14.369 mice had impaired antitumor
NOTE Confidence: 0.761455953121185

02:11:14.369 --> 02:11:16.330 responses and only about 40% of
NOTE Confidence: 0.761455953121185

02:11:16.330 --> 02:11:18.970 these mice could reject or tumors.
NOTE Confidence: 0.761455953121185

02:11:18.970 --> 02:11:20.536 The second hypothesis that we had
NOTE Confidence: 0.761455953121185

02:11:20.536 --> 02:11:22.221 was that the icon Psychostick in
NOTE Confidence: 0.761455953121185

02:11:22.221 --> 02:11:23.973 pathway can be targeted and developed
NOTE Confidence: 0.761455953121185

02:11:23.973 --> 02:11:26.100 as a combination therapy strategy.
NOTE Confidence: 0.761455953121185

02:11:26.100 --> 02:11:28.420 And again we went back to doing this
NOTE Confidence: 0.761455953121185

02:11:28.420 --> 02:11:30.783 in wild type mice where we could
NOTE Confidence: 0.761455953121185

02:11:30.783 --> 02:11:32.847 target both icos and tally for
NOTE Confidence: 0.761455953121185

02:11:32.847 --> 02:11:35.111 at the same time and in the blue
NOTE Confidence: 0.761455953121185

02:11:35.111 --> 02:11:37.045 dotted line you can see combination
NOTE Confidence: 0.761455953121185

02:11:37.045 --> 02:11:38.361 therapy had significantly improved

NOTE Confidence: 0.761455953121185
02:11:38.361 --> 02:11:40.171 the responses in this model compared
NOTE Confidence: 0.761455953121185
02:11:40.171 --> 02:11:41.954 to any of the monotherapy ardion
NOTE Confidence: 0.761455953121185
02:11:41.954 --> 02:11:43.784 treated mice and the same experiments
NOTE Confidence: 0.761455953121185
02:11:43.784 --> 02:11:45.274 conducted in icos knockout mice.
NOTE Confidence: 0.761455953121185
02:11:45.274 --> 02:11:45.848 Of course,
NOTE Confidence: 0.761455953121185
02:11:45.848 --> 02:11:48.216 we lost the ability to have this response
NOTE Confidence: 0.761455953121185
02:11:48.216 --> 02:11:50.267 and so these data were published and
NOTE Confidence: 0.761455953121185
02:11:50.267 --> 02:11:52.460 now multiple companies have anti icos.
NOTE Confidence: 0.761455953121185
02:11:52.460 --> 02:11:54.656 Antibodies that they have in clinical
NOTE Confidence: 0.761455953121185
02:11:54.656 --> 02:11:56.440 trials and GlaxoSmithKline just reported
NOTE Confidence: 0.761455953121185
02:11:56.440 --> 02:11:58.512 on their data as as more this year,
NOTE Confidence: 0.761455953121185
02:11:58.520 --> 02:11:59.480 showing clinical responses
NOTE Confidence: 0.761455953121185
02:11:59.480 --> 02:12:00.440 with their antibody.
NOTE Confidence: 0.761455953121185
02:12:00.440 --> 02:12:02.768 So now I just want to switch gears
NOTE Confidence: 0.761455953121185
02:12:02.768 --> 02:12:04.881 a little bit because all of that
NOTE Confidence: 0.761455953121185

02:12:04.881 --> 02:12:07.490 data we did a while ago and I'm
NOTE Confidence: 0.761455953121185

02:12:07.490 --> 02:12:09.285 looking forward to clinical data
NOTE Confidence: 0.761455953121185

02:12:09.285 --> 02:12:11.434 with the anti icos antibodies but
NOTE Confidence: 0.761455953121185

02:12:11.434 --> 02:12:13.900 we had other questions we wanted to
NOTE Confidence: 0.761455953121185

02:12:13.900 --> 02:12:15.996 ask as well because as you can see
NOTE Confidence: 0.761455953121185

02:12:15.996 --> 02:12:18.277 from the list that I showed with
NOTE Confidence: 0.761455953121185

02:12:18.277 --> 02:12:19.885 the FDA approvals immune checkpoint
NOTE Confidence: 0.761455953121185

02:12:19.885 --> 02:12:21.715 therapy has been approved in lung
NOTE Confidence: 0.761455953121185

02:12:21.715 --> 02:12:23.400 cancer and Melanoma bladder cancer,
NOTE Confidence: 0.761455953121185

02:12:23.400 --> 02:12:24.616 head and neck cancers.
NOTE Confidence: 0.761455953121185

02:12:24.616 --> 02:12:26.440 And from this figure that I'm
NOTE Confidence: 0.761455953121185

02:12:26.502 --> 02:12:27.790 showing on this slide,
NOTE Confidence: 0.761455953121185

02:12:27.790 --> 02:12:30.580 these tumor types are known to be hot tumors,
NOTE Confidence: 0.761455953121185

02:12:30.580 --> 02:12:32.338 meaning they have lots of mutations
NOTE Confidence: 0.761455953121185

02:12:32.338 --> 02:12:34.609 and a result of lots of mutations.
NOTE Confidence: 0.761455953121185

02:12:34.610 --> 02:12:36.105 They have neo antigens that

NOTE Confidence: 0.761455953121185
02:12:36.105 --> 02:12:38.020 can be recognized by T cells,
NOTE Confidence: 0.761455953121185
02:12:38.020 --> 02:12:39.840 and so they have lots of infiltrating
NOTE Confidence: 0.761455953121185
02:12:39.840 --> 02:12:41.623 T cells within the tumor micro
NOTE Confidence: 0.761455953121185
02:12:41.623 --> 02:12:43.198 environment and therefore can respond
NOTE Confidence: 0.761455953121185
02:12:43.198 --> 02:12:44.839 to immune checkpoint therapy,
NOTE Confidence: 0.761455953121185
02:12:44.840 --> 02:12:46.700 which is, you know, puzzling tests,
NOTE Confidence: 0.761455953121185
02:12:46.700 --> 02:12:47.320 because, again,
NOTE Confidence: 0.761455953121185
02:12:47.320 --> 02:12:48.870 all tumor should have antigens,
NOTE Confidence: 0.761455953121185
02:12:48.870 --> 02:12:50.730 because all tumors are made up
NOTE Confidence: 0.761455953121185
02:12:50.730 --> 02:12:51.660 with some mutations,
NOTE Confidence: 0.761455953121185
02:12:51.660 --> 02:12:53.056 and so prostate cancer,
NOTE Confidence: 0.761455953121185
02:12:53.056 --> 02:12:55.150 which is shown here is considered
NOTE Confidence: 0.761455953121185
02:12:55.215 --> 02:12:56.380 to be a cold tumor.
NOTE Confidence: 0.761455953121185
02:12:56.380 --> 02:12:58.276 Because it has very few mutations,
NOTE Confidence: 0.761455953121185
02:12:58.280 --> 02:12:59.996 it does not have many infiltrating
NOTE Confidence: 0.761455953121185

02:12:59.996 --> 02:13:02.495 T cells and there have been 2 failed
NOTE Confidence: 0.761455953121185

02:13:02.495 --> 02:13:04.115 phase three clinical trials with
NOTE Confidence: 0.761455953121185

02:13:04.115 --> 02:13:06.208 antisec selling for in prostate cancer.
NOTE Confidence: 0.761455953121185

02:13:06.210 --> 02:13:08.478 So as a clinician I agree that
NOTE Confidence: 0.761455953121185

02:13:08.478 --> 02:13:10.110 immune checkpoint therapy is not
NOTE Confidence: 0.761455953121185

02:13:10.110 --> 02:13:11.600 working on these cold tumors,
NOTE Confidence: 0.761455953121185

02:13:11.600 --> 02:13:12.784 but as an immunologist.
NOTE Confidence: 0.761455953121185

02:13:12.784 --> 02:13:14.919 It puzzles me because the cold tumor
NOTE Confidence: 0.761455953121185

02:13:14.919 --> 02:13:16.695 should still also have antigens and
NOTE Confidence: 0.761455953121185

02:13:16.695 --> 02:13:19.031 T cells only really need one antigen
NOTE Confidence: 0.761455953121185

02:13:19.031 --> 02:13:21.107 before they can proliferate and expand.
NOTE Confidence: 0.761455953121185

02:13:21.110 --> 02:13:22.951 So we wanted to ask the question
NOTE Confidence: 0.761455953121185

02:13:22.951 --> 02:13:24.876 whether or not prostate cancer the
NOTE Confidence: 0.761455953121185

02:13:24.876 --> 02:13:26.666 antigens on prostate cancer really
NOTE Confidence: 0.761455953121185

02:13:26.666 --> 02:13:29.034 not being recognized by the T cells.
NOTE Confidence: 0.761455953121185

02:13:29.034 --> 02:13:31.362 Is there an issue with?

NOTE Confidence: 0.761455953121185

02:13:31.362 --> 02:13:32.490 Antigen recognition

NOTE Confidence: 0.834120452404022

02:13:31.280 --> 02:13:32.490 and in order to

NOTE Confidence: 0.834120452404022

02:13:32.490 --> 02:13:34.044 do that, we conducted this small

NOTE Confidence: 0.834120452404022

02:13:34.044 --> 02:13:35.902 clinical trial in 30 patients where

NOTE Confidence: 0.834120452404022

02:13:35.902 --> 02:13:37.812 we had metastatic castration resistant

NOTE Confidence: 0.834120452404022

02:13:37.812 --> 02:13:39.529 prostate cancer patients where we

NOTE Confidence: 0.834120452404022

02:13:39.529 --> 02:13:41.083 can respect one of the metastatic

NOTE Confidence: 0.834120452404022

02:13:41.083 --> 02:13:42.702 lesions or to primary prostate tumor.

NOTE Confidence: 0.834120452404022

02:13:42.702 --> 02:13:44.691 We can perform X omen RNA sequencing

NOTE Confidence: 0.834120452404022

02:13:44.691 --> 02:13:46.485 to identify to tumor mutations and

NOTE Confidence: 0.834120452404022

02:13:46.485 --> 02:13:48.765 then in the setting of giving these

NOTE Confidence: 0.834120452404022

02:13:48.765 --> 02:13:50.425 patients anti sitali for therapy.

NOTE Confidence: 0.834120452404022

02:13:50.430 --> 02:13:52.478 We can then take T cells and ask

NOTE Confidence: 0.834120452404022

02:13:52.478 --> 02:13:54.778 whether or not these T cells are

NOTE Confidence: 0.834120452404022

02:13:54.778 --> 02:13:56.503 capable of recognizing the antigens.

NOTE Confidence: 0.834120452404022

02:13:56.510 --> 02:13:58.544 Again, this paper was just recently
NOTE Confidence: 0.834120452404022

02:13:58.544 --> 02:14:00.682 published a couple of months ago so
NOTE Confidence: 0.834120452404022

02:14:00.682 --> 02:14:02.890 I won't go into all of the details,
NOTE Confidence: 0.834120452404022

02:14:02.890 --> 02:14:05.680 but I do want to show you this one.
NOTE Confidence: 0.834120452404022

02:14:05.680 --> 02:14:07.530 Figure when patients 7 where
NOTE Confidence: 0.834120452404022

02:14:07.530 --> 02:14:09.380 this patient had two mutations,
NOTE Confidence: 0.834120452404022

02:14:09.380 --> 02:14:11.582 one in Rogue wanting nucleotide exchange
NOTE Confidence: 0.834120452404022

02:14:11.582 --> 02:14:13.908 factor 37 and one in Dihydropyrimidine
NOTE Confidence: 0.834120452404022

02:14:13.908 --> 02:14:16.659 is shown here and these were single
NOTE Confidence: 0.834120452404022

02:14:16.659 --> 02:14:18.798 amino acid changes for these mutations
NOTE Confidence: 0.834120452404022

02:14:18.798 --> 02:14:21.176 and you can see that this patient
NOTE Confidence: 0.834120452404022

02:14:21.176 --> 02:14:23.612 did not have any detectable T cell
NOTE Confidence: 0.834120452404022

02:14:23.612 --> 02:14:25.580 responses in the Elispot assay
NOTE Confidence: 0.834120452404022

02:14:25.580 --> 02:14:27.136 at the pretreatment timepoint,
NOTE Confidence: 0.834120452404022

02:14:27.140 --> 02:14:28.990 which is which is noted.
NOTE Confidence: 0.834120452404022

02:14:28.990 --> 02:14:31.590 Noted here is pre AP but after giving

NOTE Confidence: 0.834120452404022
02:14:31.590 --> 02:14:34.356 anti see teleforce at the post AP
NOTE Confidence: 0.834120452404022
02:14:34.356 --> 02:14:36.401 one posted between posted before.
NOTE Confidence: 0.834120452404022
02:14:36.410 --> 02:14:38.279 Now you can see that these T
NOTE Confidence: 0.834120452404022
02:14:38.279 --> 02:14:40.469 cells are quite clearly capable of
NOTE Confidence: 0.834120452404022
02:14:40.469 --> 02:14:42.237 recognizing the mutated antigen,
NOTE Confidence: 0.834120452404022
02:14:42.240 --> 02:14:44.298 but not the Wild Type Antigen,
NOTE Confidence: 0.834120452404022
02:14:44.300 --> 02:14:46.981 and this is shown in relationship to
NOTE Confidence: 0.834120452404022
02:14:46.981 --> 02:14:49.050 negative into positive control here.
NOTE Confidence: 0.834120452404022
02:14:49.050 --> 02:14:51.101 So clearly the T cells are capable
NOTE Confidence: 0.834120452404022
02:14:51.101 --> 02:14:52.439 of recognizing these mutations
NOTE Confidence: 0.834120452404022
02:14:52.439 --> 02:14:53.639 and prostate cancer.
NOTE Confidence: 0.834120452404022
02:14:53.640 --> 02:14:55.280 So then the question becomes,
NOTE Confidence: 0.834120452404022
02:14:55.280 --> 02:14:57.352 is it possible T cells are not
NOTE Confidence: 0.834120452404022
02:14:57.352 --> 02:14:59.220 infiltrating into the prostate tumors?
NOTE Confidence: 0.834120452404022
02:14:59.220 --> 02:15:01.292 Is that the reason that prostate cancers
NOTE Confidence: 0.834120452404022

02:15:01.292 --> 02:15:03.184 are not responding to immune checkpoint
NOTE Confidence: 0.834120452404022

02:15:03.184 --> 02:15:04.764 therapy and in another clinical
NOTE Confidence: 0.834120452404022

02:15:04.764 --> 02:15:06.758 trial that we'd previously conducted,
NOTE Confidence: 0.834120452404022

02:15:06.760 --> 02:15:08.874 we were able to look at the
NOTE Confidence: 0.834120452404022

02:15:08.874 --> 02:15:10.700 data from these 20 patients,
NOTE Confidence: 0.834120452404022

02:15:10.700 --> 02:15:12.340 who then underwent antiseptic delay
NOTE Confidence: 0.834120452404022

02:15:12.340 --> 02:15:13.980 for therapy prior to surgery,
NOTE Confidence: 0.834120452404022

02:15:13.980 --> 02:15:16.276 and we had access to all of
NOTE Confidence: 0.834120452404022

02:15:16.276 --> 02:15:17.260 the tumor tissues.
NOTE Confidence: 0.834120452404022

02:15:17.260 --> 02:15:19.628 So then look to see what was happening
NOTE Confidence: 0.834120452404022

02:15:19.628 --> 02:15:22.178 in terms of tumor infiltrating T cells.
NOTE Confidence: 0.834120452404022

02:15:22.180 --> 02:15:24.796 And you can see here in the pretreatment
NOTE Confidence: 0.834120452404022

02:15:24.796 --> 02:15:26.786 samples there are very few T cells,
NOTE Confidence: 0.834120452404022

02:15:26.790 --> 02:15:27.342 of course,
NOTE Confidence: 0.834120452404022

02:15:27.342 --> 02:15:29.274 so this is really a cold tumor
NOTE Confidence: 0.834120452404022

02:15:29.274 --> 02:15:31.600 and I don't have the slide to

NOTE Confidence: 0.834120452404022

02:15:31.600 --> 02:15:32.924 show comparison to Melanoma.

NOTE Confidence: 0.834120452404022

02:15:32.930 --> 02:15:35.378 But if you were to compare prostate Melanoma,

NOTE Confidence: 0.834120452404022

02:15:35.380 --> 02:15:37.476 you would note that this is a very

NOTE Confidence: 0.834120452404022

02:15:37.476 --> 02:15:39.458 cold tumor with very few infiltrating

NOTE Confidence: 0.834120452404022

02:15:39.458 --> 02:15:41.203 T cells prior to treatment.

NOTE Confidence: 0.834120452404022

02:15:41.210 --> 02:15:42.176 However, after treatment,

NOTE Confidence: 0.834120452404022

02:15:42.176 --> 02:15:44.900 you can see now lots of infiltrating T cells,

NOTE Confidence: 0.834120452404022

02:15:44.900 --> 02:15:47.049 as shown here by the ihcc study.

NOTE Confidence: 0.834120452404022

02:15:47.050 --> 02:15:49.199 What we should have been prepared for,

NOTE Confidence: 0.834120452404022

02:15:49.200 --> 02:15:51.264 but we were in is that the immune

NOTE Confidence: 0.834120452404022

02:15:51.264 --> 02:15:52.930 response is tightly controlled.

NOTE Confidence: 0.834120452404022

02:15:52.930 --> 02:15:55.506 So if you drive it in One Direction,

NOTE Confidence: 0.834120452404022

02:15:55.510 --> 02:15:57.490 there will be compensable Tori pathways

NOTE Confidence: 0.834120452404022

02:15:57.490 --> 02:15:59.765 that are up regulated in order to

NOTE Confidence: 0.834120452404022

02:15:59.765 --> 02:16:01.698 control the response, and so on.

NOTE Confidence: 0.834120452404022

02:16:01.698 --> 02:16:03.774 Our gene expression studies with this
NOTE Confidence: 0.834120452404022

02:16:03.774 --> 02:16:05.822 clinical trial we found that PD L1
NOTE Confidence: 0.834120452404022

02:16:05.822 --> 02:16:07.980 in Vista was highly expressed as a
NOTE Confidence: 0.834120452404022

02:16:07.980 --> 02:16:09.984 result of treatment with anti sitali
NOTE Confidence: 0.834120452404022

02:16:09.984 --> 02:16:12.182 for so not only were We driving the
NOTE Confidence: 0.834120452404022

02:16:12.182 --> 02:16:15.053 T cells in but now we were having
NOTE Confidence: 0.834120452404022

02:16:15.053 --> 02:16:17.053 compensable Tori inhibitory pathways and
NOTE Confidence: 0.838605880737305

02:16:17.120 --> 02:16:19.408 just to show that we were able to
NOTE Confidence: 0.838605880737305

02:16:19.408 --> 02:16:21.585 confirm the gene expression data by HC
NOTE Confidence: 0.838605880737305

02:16:21.585 --> 02:16:23.900 in the protein expression is shown here.
NOTE Confidence: 0.838605880737305

02:16:23.900 --> 02:16:25.604 Prior to treatment, there really is
NOTE Confidence: 0.838605880737305

02:16:25.604 --> 02:16:28.170 no PD one PD L1 or Vista Expression.
NOTE Confidence: 0.838605880737305

02:16:28.170 --> 02:16:28.980 However, after treatment,
NOTE Confidence: 0.838605880737305

02:16:28.980 --> 02:16:30.600 I see telephone now that we
NOTE Confidence: 0.838605880737305

02:16:30.600 --> 02:16:32.138 have infiltrating immune cells,
NOTE Confidence: 0.838605880737305

02:16:32.140 --> 02:16:34.114 you can see PD one is highly

NOTE Confidence: 0.838605880737305
02:16:34.114 --> 02:16:36.099 expressed on the immune cells PDL.
NOTE Confidence: 0.838605880737305
02:16:36.100 --> 02:16:37.918 One is on the immune cells
NOTE Confidence: 0.838605880737305
02:16:37.918 --> 02:16:39.760 an on tumor cells as well.
NOTE Confidence: 0.838605880737305
02:16:39.760 --> 02:16:42.016 And now Vista is also on the immune
NOTE Confidence: 0.838605880737305
02:16:42.016 --> 02:16:44.031 cells and I should point out if
NOTE Confidence: 0.838605880737305
02:16:44.031 --> 02:16:46.170 this is a novel immune checkpoint.
NOTE Confidence: 0.838605880737305
02:16:46.170 --> 02:16:48.319 There was identified by Randy Noel's group.
NOTE Confidence: 0.838605880737305
02:16:48.320 --> 02:16:50.258 I'm just showing you hear the
NOTE Confidence: 0.838605880737305
02:16:50.258 --> 02:16:52.120 pre and post treatment samples.
NOTE Confidence: 0.838605880737305
02:16:52.120 --> 02:16:54.112 Pretreatment is in the black triangle
NOTE Confidence: 0.838605880737305
02:16:54.112 --> 02:16:55.910 and post treatment interent circles.
NOTE Confidence: 0.838605880737305
02:16:55.910 --> 02:16:58.526 You can see the PDL one is highly
NOTE Confidence: 0.838605880737305
02:16:58.526 --> 02:17:01.066 expressed now after true or the anti
NOTE Confidence: 0.838605880737305
02:17:01.066 --> 02:17:03.160 setelah foreign CD8T cells on CD.
NOTE Confidence: 0.838605880737305
02:17:03.160 --> 02:17:05.442 68 myeloid cells and on tumor cells
NOTE Confidence: 0.838605880737305

02:17:05.442 --> 02:17:07.543 and similarly for Vista you can city
NOTE Confidence: 0.838605880737305

02:17:07.543 --> 02:17:10.060 to CD4 and CD8T cells do have some
NOTE Confidence: 0.838605880737305

02:17:10.060 --> 02:17:12.646 Vista expression but Vista is really
NOTE Confidence: 0.838605880737305

02:17:12.646 --> 02:17:14.392 predominantly expressed on my lawd
NOTE Confidence: 0.838605880737305

02:17:14.392 --> 02:17:16.450 cells here so we wanted to compare
NOTE Confidence: 0.838605880737305

02:17:16.520 --> 02:17:18.680 to Melanoma and prostate samples.
NOTE Confidence: 0.838605880737305

02:17:18.680 --> 02:17:20.948 Since we all know when we give
NOTE Confidence: 0.838605880737305

02:17:20.948 --> 02:17:22.570 anti see teleported Melanoma.
NOTE Confidence: 0.838605880737305

02:17:22.570 --> 02:17:24.220 These patients have nice responses.
NOTE Confidence: 0.838605880737305

02:17:24.220 --> 02:17:24.550 However,
NOTE Confidence: 0.838605880737305

02:17:24.550 --> 02:17:26.200 when we give antisecc teleporter
NOTE Confidence: 0.838605880737305

02:17:26.200 --> 02:17:26.860 prostate tumors.
NOTE Confidence: 0.838605880737305

02:17:26.860 --> 02:17:27.817 As I mentioned,
NOTE Confidence: 0.838605880737305

02:17:27.817 --> 02:17:29.412 there were two failed phase
NOTE Confidence: 0.838605880737305

02:17:29.412 --> 02:17:30.490 three clinical trials,
NOTE Confidence: 0.838605880737305

02:17:30.490 --> 02:17:31.658 so in Melanoma samples,

NOTE Confidence: 0.838605880737305
02:17:31.658 --> 02:17:33.805 what we found was we also had
NOTE Confidence: 0.838605880737305
02:17:33.805 --> 02:17:35.445 myeloid cells that were infiltrating
NOTE Confidence: 0.838605880737305
02:17:35.445 --> 02:17:37.420 as a result of treatment.
NOTE Confidence: 0.838605880737305
02:17:37.420 --> 02:17:38.890 But these myeloid cells tend
NOTE Confidence: 0.838605880737305
02:17:38.890 --> 02:17:41.050 to have an M1 Gene signature,
NOTE Confidence: 0.838605880737305
02:17:41.050 --> 02:17:42.660 meaning that they are participating
NOTE Confidence: 0.838605880737305
02:17:42.660 --> 02:17:44.270 in the antitumor response and
NOTE Confidence: 0.838605880737305
02:17:44.329 --> 02:17:45.669 leading to tumor rejection.
NOTE Confidence: 0.838605880737305
02:17:45.670 --> 02:17:45.966 However,
NOTE Confidence: 0.838605880737305
02:17:45.966 --> 02:17:48.038 in prostate tumors we found an M2
NOTE Confidence: 0.838605880737305
02:17:48.038 --> 02:17:49.771 gene signature meaning these myeloid
NOTE Confidence: 0.838605880737305
02:17:49.771 --> 02:17:51.586 cells are more immunosuppressive and
NOTE Confidence: 0.838605880737305
02:17:51.586 --> 02:17:54.004 we're still trying to figure out the
NOTE Confidence: 0.838605880737305
02:17:54.004 --> 02:17:55.639 signaling mechanisms that would allow.
NOTE Confidence: 0.838605880737305
02:17:55.640 --> 02:17:57.476 In one tumor micro environment from
NOTE Confidence: 0.838605880737305

02:17:57.476 --> 02:18:00.598 my lawd cells to be M1 and it had a
NOTE Confidence: 0.838605880737305

02:18:00.598 --> 02:18:02.170 different tumor micro environment for
NOTE Confidence: 0.838605880737305

02:18:02.170 --> 02:18:04.179 Milo excels to BM2 service and PDL.
NOTE Confidence: 0.838605880737305

02:18:04.180 --> 02:18:05.705 One are definitely potent inhibitors
NOTE Confidence: 0.838605880737305

02:18:05.705 --> 02:18:07.230 of human T cell responses.
NOTE Confidence: 0.838605880737305

02:18:07.230 --> 02:18:09.246 We took the T cells from these
NOTE Confidence: 0.838605880737305

02:18:09.246 --> 02:18:10.983 patients and we placed them in
NOTE Confidence: 0.838605880737305

02:18:10.983 --> 02:18:13.277 vitro with anti CD 3 and you can
NOTE Confidence: 0.838605880737305

02:18:13.277 --> 02:18:15.341 see that they can produce interferon
NOTE Confidence: 0.838605880737305

02:18:15.341 --> 02:18:17.313 gamma and Tina Fafa very well.
NOTE Confidence: 0.838605880737305

02:18:17.313 --> 02:18:19.740 However if the plate is coated with PD,
NOTE Confidence: 0.838605880737305

02:18:19.740 --> 02:18:21.490 L1 IG or Vista idea two together
NOTE Confidence: 0.838605880737305

02:18:21.490 --> 02:18:23.798 the T cells are no longer capable
NOTE Confidence: 0.838605880737305

02:18:23.798 --> 02:18:24.920 of producing interferon,
NOTE Confidence: 0.838605880737305

02:18:24.920 --> 02:18:26.846 gamma and TNF Alpha as well.
NOTE Confidence: 0.838605880737305

02:18:26.850 --> 02:18:27.638 So really,

NOTE Confidence: 0.838605880737305
02:18:27.638 --> 02:18:29.214 they're being suppressed by
NOTE Confidence: 0.838605880737305
02:18:29.214 --> 02:18:31.506 the Vista in the PDL 1.
NOTE Confidence: 0.838605880737305
02:18:31.506 --> 02:18:33.136 With that data in mind,
NOTE Confidence: 0.838605880737305
02:18:33.140 --> 02:18:34.895 we convinced Bristol Myers script
NOTE Confidence: 0.838605880737305
02:18:34.895 --> 02:18:36.650 conduct a clinical trial with
NOTE Confidence: 0.838605880737305
02:18:36.711 --> 02:18:38.440 anti see Taylor for an anti PD.
NOTE Confidence: 0.838605880737305
02:18:38.440 --> 02:18:40.942 One is combination therapy in patients
NOTE Confidence: 0.838605880737305
02:18:40.942 --> 02:18:42.610 with metastatic castration resistant
NOTE Confidence: 0.838605880737305
02:18:42.674 --> 02:18:44.312 prostate cancer and for the first
NOTE Confidence: 0.838605880737305
02:18:44.312 --> 02:18:46.864 time now we can see as you can see in
NOTE Confidence: 0.838605880737305
02:18:46.864 --> 02:18:48.416 this PSA graph below that patients
NOTE Confidence: 0.838605880737305
02:18:48.416 --> 02:18:50.264 who had high PSA in metastatic
NOTE Confidence: 0.838605880737305
02:18:50.264 --> 02:18:52.169 disease as a result of treatment.
NOTE Confidence: 0.838605880737305
02:18:52.170 --> 02:18:53.525 Now the PSA became undetectable
NOTE Confidence: 0.838605880737305
02:18:53.525 --> 02:18:54.880 and CT scans then showed
NOTE Confidence: 0.838605880737305

02:18:54.938 --> 02:18:56.538 resolution of metastatic disease.
NOTE Confidence: 0.838605880737305

02:18:56.540 --> 02:18:58.240 Again this paper was just
NOTE Confidence: 0.838605880737305

02:18:58.240 --> 02:18:59.940 published about a week ago
NOTE Confidence: 0.812676012516022

02:19:00.011 --> 02:19:01.908 and so the data is all there.
NOTE Confidence: 0.812676012516022

02:19:01.910 --> 02:19:04.129 I will point out that the combination
NOTE Confidence: 0.812676012516022

02:19:04.129 --> 02:19:06.225 therapy did lead to higher toxicities
NOTE Confidence: 0.812676012516022

02:19:06.225 --> 02:19:08.379 as a result of combination treatment
NOTE Confidence: 0.812676012516022

02:19:08.379 --> 02:19:10.796 and so to study was recently expanded.
NOTE Confidence: 0.812676012516022

02:19:10.800 --> 02:19:12.726 Now with four different treatment arms
NOTE Confidence: 0.812676012516022

02:19:12.726 --> 02:19:15.408 so that we can look at different doses
NOTE Confidence: 0.812676012516022

02:19:15.408 --> 02:19:17.942 and schedules of the therapy to hopefully
NOTE Confidence: 0.812676012516022

02:19:17.942 --> 02:19:20.750 minimize the toxicity but maintain efficacy.
NOTE Confidence: 0.812676012516022

02:19:20.750 --> 02:19:22.966 One of the things that we noted in
NOTE Confidence: 0.812676012516022

02:19:22.966 --> 02:19:24.824 this clinical trial that we were
NOTE Confidence: 0.812676012516022

02:19:24.824 --> 02:19:26.690 conducting is that the patients who
NOTE Confidence: 0.812676012516022

02:19:26.757 --> 02:19:28.777 were responding to treatment with

NOTE Confidence: 0.812676012516022
02:19:28.777 --> 02:19:30.393 combination therapy for patients
NOTE Confidence: 0.812676012516022
02:19:30.393 --> 02:19:32.128 who had soft tissue metastases,
NOTE Confidence: 0.812676012516022
02:19:32.128 --> 02:19:34.490 whereas as many of you may know,
NOTE Confidence: 0.812676012516022
02:19:34.490 --> 02:19:35.750 prostate cancer predominantly goes
NOTE Confidence: 0.812676012516022
02:19:35.750 --> 02:19:37.640 to the bones and patients with
NOTE Confidence: 0.812676012516022
02:19:37.694 --> 02:19:39.444 bone metastases were having less
NOTE Confidence: 0.812676012516022
02:19:39.444 --> 02:19:40.844 responses from our observations.
NOTE Confidence: 0.812676012516022
02:19:40.850 --> 02:19:43.181 So we looked at the soft tissue
NOTE Confidence: 0.812676012516022
02:19:43.181 --> 02:19:45.221 metastases from patients and the bone
NOTE Confidence: 0.812676012516022
02:19:45.221 --> 02:19:47.183 metastases from patients and what we
NOTE Confidence: 0.812676012516022
02:19:47.183 --> 02:19:49.235 found is that after treatment with
NOTE Confidence: 0.812676012516022
02:19:49.235 --> 02:19:51.243 anti sitali for soft tissue metastases
NOTE Confidence: 0.812676012516022
02:19:51.243 --> 02:19:53.987 were found to have a TH one signature.
NOTE Confidence: 0.812676012516022
02:19:53.990 --> 02:19:56.030 Meaning lots of Affecter T cells
NOTE Confidence: 0.812676012516022
02:19:56.030 --> 02:19:57.771 and interferon gamma production was
NOTE Confidence: 0.812676012516022

02:19:57.771 --> 02:19:59.406 occurring within the soft tissue.
NOTE Confidence: 0.812676012516022

02:19:59.410 --> 02:19:59.747 However,
NOTE Confidence: 0.812676012516022

02:19:59.747 --> 02:20:02.106 in bone metastases we found that there
NOTE Confidence: 0.812676012516022

02:20:02.106 --> 02:20:04.835 was no increase in the TH one response.
NOTE Confidence: 0.812676012516022

02:20:04.840 --> 02:20:05.178 Instead,
NOTE Confidence: 0.812676012516022

02:20:05.178 --> 02:20:07.882 there was an increase in TH 17 cells,
NOTE Confidence: 0.812676012516022

02:20:07.890 --> 02:20:10.256 and so that was puzzling to us.
NOTE Confidence: 0.812676012516022

02:20:10.260 --> 02:20:12.330 Why the bone metastases had an
NOTE Confidence: 0.812676012516022

02:20:12.330 --> 02:20:15.007 increase in TH 17 but not each one.
NOTE Confidence: 0.812676012516022

02:20:15.010 --> 02:20:17.258 So we took the clinical data and we
NOTE Confidence: 0.812676012516022

02:20:17.258 --> 02:20:19.349 went back to the laboratory and we
NOTE Confidence: 0.812676012516022

02:20:19.349 --> 02:20:22.263 model this in my swear we could inject
NOTE Confidence: 0.812676012516022

02:20:22.263 --> 02:20:24.563 castration resistant prostate cancer cells.
NOTE Confidence: 0.812676012516022

02:20:24.570 --> 02:20:26.270 Into the subcutaneous lesions of
NOTE Confidence: 0.812676012516022

02:20:26.270 --> 02:20:28.352 enter the subcutaneous space of mice
NOTE Confidence: 0.812676012516022

02:20:28.352 --> 02:20:30.266 to represent the soft tissue lesions.

NOTE Confidence: 0.812676012516022
02:20:30.270 --> 02:20:32.638 Or we can inject the cells into bones
NOTE Confidence: 0.812676012516022
02:20:32.638 --> 02:20:34.958 to represent the bone metastatic lesions,
NOTE Confidence: 0.812676012516022
02:20:34.960 --> 02:20:37.305 and then we treated the mice would
NOTE Confidence: 0.812676012516022
02:20:37.305 --> 02:20:38.310 anti C telephone,
NOTE Confidence: 0.812676012516022
02:20:38.310 --> 02:20:40.947 anti PD one is shown here in the red
NOTE Confidence: 0.812676012516022
02:20:40.947 --> 02:20:43.726 and you can see that again when the
NOTE Confidence: 0.812676012516022
02:20:43.726 --> 02:20:45.895 bone lesions TH one responses did
NOTE Confidence: 0.812676012516022
02:20:45.895 --> 02:20:48.745 not increase but the TH 17 did as
NOTE Confidence: 0.812676012516022
02:20:48.745 --> 02:20:50.670 compared to subcutaneous lesions where
NOTE Confidence: 0.812676012516022
02:20:50.670 --> 02:20:52.858 you had significant increase in that
NOTE Confidence: 0.812676012516022
02:20:52.858 --> 02:20:54.902 each one response and no increase in
NOTE Confidence: 0.812676012516022
02:20:54.902 --> 02:20:56.736 actually decrease in TH 17 response.
NOTE Confidence: 0.812676012516022
02:20:56.740 --> 02:20:57.344 So again,
NOTE Confidence: 0.812676012516022
02:20:57.344 --> 02:20:59.156 this was mimicking what we were
NOTE Confidence: 0.812676012516022
02:20:59.156 --> 02:21:00.469 seeing in the humans,
NOTE Confidence: 0.812676012516022

02:21:00.470 --> 02:21:02.030 and for many of you,
NOTE Confidence: 0.812676012516022

02:21:02.030 --> 02:21:04.514 you may be aware to TH 17 cells really
NOTE Confidence: 0.812676012516022

02:21:04.514 --> 02:21:06.387 their skewed into development as a
NOTE Confidence: 0.812676012516022

02:21:06.387 --> 02:21:09.179 result of Isle 6 and TGF beta signaling.
NOTE Confidence: 0.812676012516022

02:21:09.180 --> 02:21:11.367 So in this model we were able to look
NOTE Confidence: 0.812676012516022

02:21:11.367 --> 02:21:13.540 at all of the different cytokines
NOTE Confidence: 0.812676012516022

02:21:13.540 --> 02:21:15.400 in the bone micro environment,
NOTE Confidence: 0.812676012516022

02:21:15.400 --> 02:21:17.888 and again this paper was published last year,
NOTE Confidence: 0.812676012516022

02:21:17.890 --> 02:21:19.440 so the details are there.
NOTE Confidence: 0.812676012516022

02:21:19.440 --> 02:21:21.753 But focusing in on the Isle 6 and TGF
NOTE Confidence: 0.812676012516022

02:21:21.753 --> 02:21:24.131 beta pathways we can see that I'll six
NOTE Confidence: 0.812676012516022

02:21:24.131 --> 02:21:26.566 is very highly increased in the bone
NOTE Confidence: 0.812676012516022

02:21:26.566 --> 02:21:28.804 micro environment as compared to Serum.
NOTE Confidence: 0.812676012516022

02:21:28.810 --> 02:21:30.712 And it's in the bones regardless
NOTE Confidence: 0.812676012516022

02:21:30.712 --> 02:21:32.870 with if there's a tumor or not.
NOTE Confidence: 0.812676012516022

02:21:32.870 --> 02:21:35.005 So BMT is with a tumor and

NOTE Confidence: 0.812676012516022

02:21:35.005 --> 02:21:36.609 BM is without a tumor.

NOTE Confidence: 0.812676012516022

02:21:36.610 --> 02:21:36.873 However,

NOTE Confidence: 0.812676012516022

02:21:36.873 --> 02:21:38.714 TGF Beta is only high as a

NOTE Confidence: 0.812676012516022

02:21:38.714 --> 02:21:40.763 result of the tumor being within

NOTE Confidence: 0.812676012516022

02:21:40.763 --> 02:21:42.223 the bone micro environment,

NOTE Confidence: 0.812676012516022

02:21:42.230 --> 02:21:43.808 and we found the TGF beta

NOTE Confidence: 0.812676012516022

02:21:43.808 --> 02:21:44.860 was really being made

NOTE Confidence: 0.807139337062836

02:21:44.917 --> 02:21:46.795 as a result of osteoclast activity

NOTE Confidence: 0.807139337062836

02:21:46.795 --> 02:21:48.780 within the bone micro environment,

NOTE Confidence: 0.807139337062836

02:21:48.780 --> 02:21:50.636 and so with I'll 6 and TGF beta

NOTE Confidence: 0.807139337062836

02:21:50.636 --> 02:21:52.778 is a two cytokines that are

NOTE Confidence: 0.807139337062836

02:21:52.778 --> 02:21:54.390 highly elevated in bowling.

NOTE Confidence: 0.807139337062836

02:21:54.390 --> 02:21:56.392 You can imagine now that this would

NOTE Confidence: 0.807139337062836

02:21:56.392 --> 02:21:58.661 skew the T cells towards a teach

NOTE Confidence: 0.807139337062836

02:21:58.661 --> 02:22:00.677 17 phenotype rather than TH one.

NOTE Confidence: 0.807139337062836

02:22:00.680 --> 02:22:03.080 And so we propose blocking the TGF beta
NOTE Confidence: 0.807139337062836

02:22:03.080 --> 02:22:05.553 with an antibody is shown here in the
NOTE Confidence: 0.807139337062836

02:22:05.553 --> 02:22:08.170 green and when we blocked the TGF beta.
NOTE Confidence: 0.807139337062836

02:22:08.170 --> 02:22:10.060 Now for the first time we had
NOTE Confidence: 0.807139337062836

02:22:10.060 --> 02:22:11.659 decrease in tumor volume and
NOTE Confidence: 0.807139337062836

02:22:11.659 --> 02:22:13.469 increased survival of these vice.
NOTE Confidence: 0.807139337062836

02:22:13.470 --> 02:22:15.318 More importantly we were able to
NOTE Confidence: 0.807139337062836

02:22:15.318 --> 02:22:17.668 show that by blocking TGF beta in
NOTE Confidence: 0.807139337062836

02:22:17.668 --> 02:22:19.080 combination with immune checkpoint
NOTE Confidence: 0.807139337062836

02:22:19.080 --> 02:22:21.253 therapy for the first time that we
NOTE Confidence: 0.807139337062836

02:22:21.253 --> 02:22:23.159 had expansion of the TH one CD4T
NOTE Confidence: 0.807139337062836

02:22:23.159 --> 02:22:25.462 cells within the bones as well as
NOTE Confidence: 0.807139337062836

02:22:25.462 --> 02:22:27.347 expansion of CD8T cell clones within
NOTE Confidence: 0.807139337062836

02:22:27.347 --> 02:22:30.065 the bones and so as a result of this
NOTE Confidence: 0.807139337062836

02:22:30.065 --> 02:22:32.186 now we have a new clinical trial
NOTE Confidence: 0.807139337062836

02:22:32.190 --> 02:22:33.785 is currently undergoing review to

NOTE Confidence: 0.807139337062836
02:22:33.785 --> 02:22:35.690 block TGF beta in combination with.
NOTE Confidence: 0.807139337062836
02:22:35.690 --> 02:22:37.515 With immune checkpoint therapy for
NOTE Confidence: 0.807139337062836
02:22:37.515 --> 02:22:38.975 patients with bone metastases.
NOTE Confidence: 0.807139337062836
02:22:38.980 --> 02:22:41.152 But the studies with bone metastases
NOTE Confidence: 0.807139337062836
02:22:41.152 --> 02:22:43.410 actually had us thinking that there
NOTE Confidence: 0.807139337062836
02:22:43.410 --> 02:22:44.906 were unique subsets developing
NOTE Confidence: 0.807139337062836
02:22:44.906 --> 02:22:46.640 in different niche is so,
NOTE Confidence: 0.807139337062836
02:22:46.640 --> 02:22:48.896 although we may think of patients
NOTE Confidence: 0.807139337062836
02:22:48.896 --> 02:22:50.660 with metastatic disease is oh,
NOTE Confidence: 0.807139337062836
02:22:50.660 --> 02:22:52.480 they all have metastatic disease.
NOTE Confidence: 0.807139337062836
02:22:52.480 --> 02:22:54.150 The site of metastasis becomes
NOTE Confidence: 0.807139337062836
02:22:54.150 --> 02:22:56.312 very important for how the immune
NOTE Confidence: 0.807139337062836
02:22:56.312 --> 02:22:57.587 response will develop,
NOTE Confidence: 0.807139337062836
02:22:57.590 --> 02:22:59.540 and so this was also something
NOTE Confidence: 0.807139337062836
02:22:59.540 --> 02:23:01.909 we wanted to look at for other
NOTE Confidence: 0.807139337062836

02:23:01.909 --> 02:23:03.901 unique niches such as the brain
NOTE Confidence: 0.807139337062836

02:23:03.901 --> 02:23:05.999 were glioblastoma can develop.
NOTE Confidence: 0.807139337062836

02:23:06.000 --> 02:23:07.196 And as you know,
NOTE Confidence: 0.807139337062836

02:23:07.196 --> 02:23:08.392 immune checkpoint therapy does
NOTE Confidence: 0.807139337062836

02:23:08.392 --> 02:23:09.960 not work for glioblastoma,
NOTE Confidence: 0.807139337062836

02:23:09.960 --> 02:23:12.340 so we wanted to understand if there
NOTE Confidence: 0.807139337062836

02:23:12.340 --> 02:23:14.377 was also another unique immune cell
NOTE Confidence: 0.807139337062836

02:23:14.377 --> 02:23:16.968 subset that that is a part of the
NOTE Confidence: 0.807139337062836

02:23:16.968 --> 02:23:19.215 GB M micro environment and here we
NOTE Confidence: 0.807139337062836

02:23:19.215 --> 02:23:22.170 compare GB M to non small cell lung cancer,
NOTE Confidence: 0.807139337062836

02:23:22.170 --> 02:23:23.160 renal cell carcinoma,
NOTE Confidence: 0.807139337062836

02:23:23.160 --> 02:23:24.480 colorectal cancer and prostate
NOTE Confidence: 0.807139337062836

02:23:24.480 --> 02:23:25.470 cancer from patients.
NOTE Confidence: 0.807139337062836

02:23:25.470 --> 02:23:27.240 And we also compared untreated
NOTE Confidence: 0.807139337062836

02:23:27.240 --> 02:23:29.429 glioblastoma samples to anti PD one
NOTE Confidence: 0.807139337062836

02:23:29.429 --> 02:23:30.845 treated glioblastoma samples from

NOTE Confidence: 0.807139337062836

02:23:30.845 --> 02:23:33.218 our patients and what we were able

NOTE Confidence: 0.807139337062836

02:23:33.218 --> 02:23:35.101 to identify was a unique subset of

NOTE Confidence: 0.807139337062836

02:23:35.101 --> 02:23:37.095 CD 73 positive myeloid cells as

NOTE Confidence: 0.807139337062836

02:23:37.095 --> 02:23:39.557 shown here which is the L8 subset

NOTE Confidence: 0.807139337062836

02:23:39.557 --> 02:23:41.217 in our site off analysis.

NOTE Confidence: 0.807139337062836

02:23:41.220 --> 02:23:42.162 And then again,

NOTE Confidence: 0.807139337062836

02:23:42.162 --> 02:23:43.732 this paper was published recently

NOTE Confidence: 0.807139337062836

02:23:43.732 --> 02:23:45.392 in this year, so this L.

NOTE Confidence: 0.807139337062836

02:23:45.392 --> 02:23:47.439 8 so upset with the CD 73 myeloid

NOTE Confidence: 0.807139337062836

02:23:47.439 --> 02:23:49.805 cells were able to conduct a single

NOTE Confidence: 0.807139337062836

02:23:49.805 --> 02:23:51.988 cell RNA sequencing from the patient

NOTE Confidence: 0.807139337062836

02:23:51.988 --> 02:23:54.706 samples and we were able to show that

NOTE Confidence: 0.807139337062836

02:23:54.706 --> 02:23:56.404 this is a macrophage signature that

NOTE Confidence: 0.807139337062836

02:23:56.404 --> 02:23:58.035 is very immunosuppressive in terms

NOTE Confidence: 0.807139337062836

02:23:58.035 --> 02:24:00.387 of the genes being expressed as well

NOTE Confidence: 0.807139337062836

02:24:00.448 --> 02:24:02.639 as hypoxia associated based on that data.
NOTE Confidence: 0.807139337062836

02:24:02.640 --> 02:24:04.016 We then conducted trial,
NOTE Confidence: 0.807139337062836

02:24:04.016 --> 02:24:06.080 then conducted studies in a model
NOTE Confidence: 0.807139337062836

02:24:06.147 --> 02:24:07.893 of CD 73 knockout mice compared
NOTE Confidence: 0.807139337062836

02:24:07.893 --> 02:24:10.009 to wild type mice and in this
NOTE Confidence: 0.807139337062836

02:24:10.009 --> 02:24:11.494 glioblastoma model you can see
NOTE Confidence: 0.807139337062836

02:24:11.494 --> 02:24:13.670 that in the city 73 knockout mice.
NOTE Confidence: 0.807139337062836

02:24:13.670 --> 02:24:16.230 Now when we give anti PD one and.
NOTE Confidence: 0.807139337062836

02:24:16.230 --> 02:24:19.065 Stacy telling for we can have improved
NOTE Confidence: 0.807139337062836

02:24:19.065 --> 02:24:21.860 survival as compared to the wild type mice,
NOTE Confidence: 0.807139337062836

02:24:21.860 --> 02:24:24.387 and this led to discussions now with
NOTE Confidence: 0.807139337062836

02:24:24.387 --> 02:24:26.232 other companies were developing a
NOTE Confidence: 0.807139337062836

02:24:26.232 --> 02:24:27.972 clinical trial based on targeting
NOTE Confidence: 0.807139337062836

02:24:27.972 --> 02:24:30.720 CD 73 in combination with immune
NOTE Confidence: 0.807139337062836

02:24:30.720 --> 02:24:31.810 checkpoint therapy.
NOTE Confidence: 0.850646674633026

02:24:31.810 --> 02:24:33.898 So I just want to finish up on other

NOTE Confidence: 0.850646674633026

02:24:33.898 --> 02:24:35.995 targets that we're thinking about that may

NOTE Confidence: 0.850646674633026

02:24:35.995 --> 02:24:38.100 have importance in the immune response,

NOTE Confidence: 0.850646674633026

02:24:38.100 --> 02:24:39.356 such as epigenetic pathways.

NOTE Confidence: 0.850646674633026

02:24:39.356 --> 02:24:41.803 Many of you are aware that as we

NOTE Confidence: 0.850646674633026

02:24:41.803 --> 02:24:43.539 target CD 28 and T cell receptor,

NOTE Confidence: 0.850646674633026

02:24:43.540 --> 02:24:45.820 that's the way to turn on T cells.

NOTE Confidence: 0.850646674633026

02:24:45.820 --> 02:24:47.200 You need both those signals

NOTE Confidence: 0.850646674633026

02:24:47.200 --> 02:24:49.260 for T cells to be turned on.

NOTE Confidence: 0.850646674633026

02:24:49.260 --> 02:24:50.690 However, as I mentioned before,

NOTE Confidence: 0.850646674633026

02:24:50.690 --> 02:24:52.400 when you turn on T cells,

NOTE Confidence: 0.850646674633026

02:24:52.400 --> 02:24:54.122 they are tightly regulated and then

NOTE Confidence: 0.850646674633026

02:24:54.122 --> 02:24:55.595 they find different pathways in

NOTE Confidence: 0.850646674633026

02:24:55.595 --> 02:24:56.975 which to regulate their responses.

NOTE Confidence: 0.850646674633026

02:24:56.980 --> 02:24:58.982 And in this setting easy H2 is

NOTE Confidence: 0.850646674633026

02:24:58.982 --> 02:25:01.092 increased as well so that easy H

NOTE Confidence: 0.850646674633026

02:25:01.092 --> 02:25:02.880 Tuukanen stabilize the Fox P3 Gene.
NOTE Confidence: 0.850646674633026

02:25:02.880 --> 02:25:05.064 Stabilization of the Fox P3 Gene then
NOTE Confidence: 0.850646674633026

02:25:05.064 --> 02:25:06.972 allows for regulatory T cell function
NOTE Confidence: 0.850646674633026

02:25:06.972 --> 02:25:08.802 instead of effector T cell function,
NOTE Confidence: 0.850646674633026

02:25:08.810 --> 02:25:10.858 and so in our patients we saw that
NOTE Confidence: 0.850646674633026

02:25:10.858 --> 02:25:13.049 when we gave Anti Sitella for therapy
NOTE Confidence: 0.850646674633026

02:25:13.049 --> 02:25:15.085 in patients who are not responding
NOTE Confidence: 0.850646674633026

02:25:15.085 --> 02:25:17.227 as well dance I see telephone.
NOTE Confidence: 0.850646674633026

02:25:17.230 --> 02:25:18.855 We found that these patients
NOTE Confidence: 0.850646674633026

02:25:18.855 --> 02:25:20.827 had increased levels of easy H2
NOTE Confidence: 0.850646674633026

02:25:20.827 --> 02:25:22.537 expression in their CD 4T cells.
NOTE Confidence: 0.850646674633026

02:25:22.540 --> 02:25:23.965 So to understand whether or
NOTE Confidence: 0.850646674633026

02:25:23.965 --> 02:25:25.797 not targeting easy H2 would be
NOTE Confidence: 0.850646674633026

02:25:25.797 --> 02:25:27.527 worthwhile as a combination strategy,
NOTE Confidence: 0.850646674633026

02:25:27.530 --> 02:25:29.959 we went back to the laboratory and
NOTE Confidence: 0.850646674633026

02:25:29.959 --> 02:25:32.941 looked at the Fox P 3G FP Mice an in

NOTE Confidence: 0.850646674633026

02:25:32.941 --> 02:25:35.410 these mice you can insert the Fox P3.

NOTE Confidence: 0.850646674633026

02:25:35.410 --> 02:25:37.126 Sales based on GF P expression

NOTE Confidence: 0.850646674633026

02:25:37.126 --> 02:25:39.685 and now we can ask whether or not

NOTE Confidence: 0.850646674633026

02:25:39.685 --> 02:25:41.707 easy H2 inhibition in this setting

NOTE Confidence: 0.850646674633026

02:25:41.773 --> 02:25:43.583 would then change the phenotype

NOTE Confidence: 0.850646674633026

02:25:43.583 --> 02:25:45.664 and the function of these cells.

NOTE Confidence: 0.850646674633026

02:25:45.664 --> 02:25:48.040 And So what we found with easy age 2

NOTE Confidence: 0.850646674633026

02:25:48.107 --> 02:25:50.207 inhibition was that we decreased Fox

NOTE Confidence: 0.850646674633026

02:25:50.207 --> 02:25:52.428 P3 expression and we increase other

NOTE Confidence: 0.850646674633026

02:25:52.428 --> 02:25:55.060 genes such as SL10 and Interferon gamma.

NOTE Confidence: 0.850646674633026

02:25:55.060 --> 02:25:55.780 Shown here.

NOTE Confidence: 0.850646674633026

02:25:55.780 --> 02:25:57.580 Importantly, not not only to

NOTE Confidence: 0.850646674633026

02:25:57.580 --> 02:25:59.390 phenotype change without the easy H2,

NOTE Confidence: 0.850646674633026

02:25:59.390 --> 02:26:01.334 the function of these cells were

NOTE Confidence: 0.850646674633026

02:26:01.334 --> 02:26:03.050 really is regulatory T cells,

NOTE Confidence: 0.850646674633026

02:26:03.050 --> 02:26:04.970 so they could suppress effector T
NOTE Confidence: 0.850646674633026

02:26:04.970 --> 02:26:07.419 cells are shown in this CFC delusion.
NOTE Confidence: 0.850646674633026

02:26:07.420 --> 02:26:08.509 However, after easy,
NOTE Confidence: 0.850646674633026

02:26:08.509 --> 02:26:09.598 it's two inhibition.
NOTE Confidence: 0.850646674633026

02:26:09.600 --> 02:26:12.274 These T cells were no longer capable
NOTE Confidence: 0.850646674633026

02:26:12.274 --> 02:26:14.104 of suppressing effector T cells
NOTE Confidence: 0.850646674633026

02:26:14.104 --> 02:26:16.246 because they now had more of an
NOTE Confidence: 0.850646674633026

02:26:16.246 --> 02:26:18.338 effector T cell function themselves,
NOTE Confidence: 0.850646674633026

02:26:18.340 --> 02:26:20.160 and so based on that,
NOTE Confidence: 0.850646674633026

02:26:20.160 --> 02:26:21.640 in a preclinical model,
NOTE Confidence: 0.850646674633026

02:26:21.640 --> 02:26:24.287 we could show that with combining easy
NOTE Confidence: 0.850646674633026

02:26:24.287 --> 02:26:26.786 H2 inhibition with Anti Sitali for we
NOTE Confidence: 0.850646674633026

02:26:26.786 --> 02:26:29.325 now improved survival of the mice as
NOTE Confidence: 0.850646674633026

02:26:29.325 --> 02:26:31.387 shown here and decreased tumor volume.
NOTE Confidence: 0.850646674633026

02:26:31.387 --> 02:26:33.536 And this let us then to negotiate
NOTE Confidence: 0.850646674633026

02:26:33.536 --> 02:26:35.449 with two different companies.

NOTE Confidence: 0.850646674633026

02:26:35.450 --> 02:26:38.040 Daichi, sancho, for the easy H12 inhibitor.

NOTE Confidence: 0.850646674633026

02:26:38.040 --> 02:26:39.470 And Bristol Myers Squibb for

NOTE Confidence: 0.850646674633026

02:26:39.470 --> 02:26:40.900 their anti sitali for antibody.

NOTE Confidence: 0.850646674633026

02:26:40.900 --> 02:26:42.895 And we designed a new clinical trial.

NOTE Confidence: 0.850646674633026

02:26:42.900 --> 02:26:44.797 So this clinical trial is now enrolling

NOTE Confidence: 0.850646674633026

02:26:44.797 --> 02:26:46.330 patients with metastatic prostate cancer,

NOTE Confidence: 0.850646674633026

02:26:46.330 --> 02:26:46.902 bladder cancer,

NOTE Confidence: 0.850646674633026

02:26:46.902 --> 02:26:47.760 renal cell cancer.

NOTE Confidence: 0.850646674633026

02:26:47.760 --> 02:26:49.314 We've treated treated three patients to

NOTE Confidence: 0.850646674633026

02:26:49.314 --> 02:26:51.770 date and so far the therapies well tolerated.

NOTE Confidence: 0.850646674633026

02:26:51.770 --> 02:26:53.604 I hope to have more data in

NOTE Confidence: 0.850646674633026

02:26:53.604 --> 02:26:55.073 terms of Biomarkers and Efficacy

NOTE Confidence: 0.850646674633026

02:26:55.073 --> 02:26:56.628 as we continue this study,

NOTE Confidence: 0.850646674633026

02:26:56.630 --> 02:26:58.750 but I think this is a good way

NOTE Confidence: 0.850646674633026

02:26:58.750 --> 02:27:00.820 to show that we not only go

NOTE Confidence: 0.850646674633026

02:27:00.820 --> 02:27:02.640 from the clinic to the lab,
NOTE Confidence: 0.850646674633026

02:27:02.640 --> 02:27:04.872 but we also go back to the clinic
NOTE Confidence: 0.850646674633026

02:27:04.872 --> 02:27:07.227 as we use that data to design
NOTE Confidence: 0.850646674633026

02:27:07.227 --> 02:27:09.520 and next set of clinical trials.
NOTE Confidence: 0.850646674633026

02:27:09.520 --> 02:27:11.170 So just to finish up,
NOTE Confidence: 0.870876312255859

02:27:11.170 --> 02:27:12.820 that obviously there are many,
NOTE Confidence: 0.870876312255859

02:27:12.820 --> 02:27:15.130 many targets that need to be considered.
NOTE Confidence: 0.870876312255859

02:27:15.130 --> 02:27:17.110 A lot of these are in
NOTE Confidence: 0.870876312255859

02:27:17.110 --> 02:27:18.430 preclinical or clinical studies.
NOTE Confidence: 0.870876312255859

02:27:18.430 --> 02:27:20.166 I think Anti Sitali for an anti
NOTE Confidence: 0.870876312255859

02:27:20.166 --> 02:27:22.578 PD one or PDL one or definitely
NOTE Confidence: 0.870876312255859

02:27:22.578 --> 02:27:24.578 the backbone for immune checkpoint
NOTE Confidence: 0.870876312255859

02:27:24.578 --> 02:27:26.677 therapies that are ongoing right now.
NOTE Confidence: 0.870876312255859

02:27:26.680 --> 02:27:28.856 But we do have to really move quickly
NOTE Confidence: 0.870876312255859

02:27:28.856 --> 02:27:30.526 between the clinical trials and
NOTE Confidence: 0.870876312255859

02:27:30.526 --> 02:27:32.301 laboratory interrogation so that we

NOTE Confidence: 0.870876312255859

02:27:32.301 --> 02:27:34.476 can have data to generate rational

NOTE Confidence: 0.870876312255859

02:27:34.476 --> 02:27:36.226 combination strategy so that the

NOTE Confidence: 0.870876312255859

02:27:36.226 --> 02:27:37.916 3000 ongoing clinical trials are

NOTE Confidence: 0.870876312255859

02:27:37.916 --> 02:27:39.586 not just being thrown together.

NOTE Confidence: 0.870876312255859

02:27:39.590 --> 02:27:41.190 Without any thought behind him

NOTE Confidence: 0.870876312255859

02:27:41.190 --> 02:27:42.470 from a scientific perspective,

NOTE Confidence: 0.870876312255859

02:27:42.470 --> 02:27:44.390 so we set up the immunotherapy

NOTE Confidence: 0.870876312255859

02:27:44.390 --> 02:27:45.670 platform at MD Anderson.

NOTE Confidence: 0.870876312255859

02:27:45.670 --> 02:27:47.524 It's guided by an umbrella protocol

NOTE Confidence: 0.870876312255859

02:27:47.524 --> 02:27:49.769 that I wrote that allows us to

NOTE Confidence: 0.870876312255859

02:27:49.769 --> 02:27:51.344 collect samples from any and

NOTE Confidence: 0.870876312255859

02:27:51.344 --> 02:27:53.030 all patients at MD Anderson's,

NOTE Confidence: 0.870876312255859

02:27:53.030 --> 02:27:54.934 regardless of whether they are on a

NOTE Confidence: 0.870876312255859

02:27:54.934 --> 02:27:57.644 BMX trial or a regenerx on trial or

NOTE Confidence: 0.870876312255859

02:27:57.644 --> 02:27:59.108 GlaxoSmithKline trial or Genentech.

NOTE Confidence: 0.870876312255859

02:27:59.110 --> 02:28:00.064 Trial doesn't matter.
NOTE Confidence: 0.870876312255859

02:28:00.064 --> 02:28:01.972 The patient samples can be collected
NOTE Confidence: 0.870876312255859

02:28:01.972 --> 02:28:04.389 on this lab protocol and we have about
NOTE Confidence: 0.870876312255859

02:28:04.389 --> 02:28:05.997 100 ongoing clinical trials across
NOTE Confidence: 0.870876312255859

02:28:05.997 --> 02:28:07.692 18 Department where we're collecting
NOTE Confidence: 0.870876312255859

02:28:07.692 --> 02:28:09.370 the samples in these patients,
NOTE Confidence: 0.870876312255859

02:28:09.370 --> 02:28:10.690 samples can be interrogated.
NOTE Confidence: 0.870876312255859

02:28:10.690 --> 02:28:12.448 So that we can learn something
NOTE Confidence: 0.870876312255859

02:28:12.448 --> 02:28:14.659 from the patients in order to then
NOTE Confidence: 0.870876312255859

02:28:14.659 --> 02:28:16.279 design the next rational study.
NOTE Confidence: 0.870876312255859

02:28:16.280 --> 02:28:18.569 So I just want to conclude with
NOTE Confidence: 0.870876312255859

02:28:18.569 --> 02:28:20.256 immune checkpoint therapy is clearly
NOTE Confidence: 0.870876312255859

02:28:20.256 --> 02:28:21.856 joined the ranks of surgery,
NOTE Confidence: 0.870876312255859

02:28:21.860 --> 02:28:23.798 radiation and chemotherapy is a pillar
NOTE Confidence: 0.870876312255859

02:28:23.798 --> 02:28:25.475 of cancer treatment and combination
NOTE Confidence: 0.870876312255859

02:28:25.475 --> 02:28:27.757 strategies are going to be the future,

NOTE Confidence: 0.870876312255859
02:28:27.760 --> 02:28:28.416 including combination
NOTE Confidence: 0.870876312255859
02:28:28.416 --> 02:28:29.400 strategies with surgery,
NOTE Confidence: 0.870876312255859
02:28:29.400 --> 02:28:30.633 radiation and chemotherapy.
NOTE Confidence: 0.870876312255859
02:28:30.633 --> 02:28:31.044 Also,
NOTE Confidence: 0.870876312255859
02:28:31.044 --> 02:28:32.688 multiple immune checkpoints exists
NOTE Confidence: 0.870876312255859
02:28:32.688 --> 02:28:34.963 and these are very dynamic in their
NOTE Confidence: 0.870876312255859
02:28:34.963 --> 02:28:36.687 expression and they have to be
NOTE Confidence: 0.870876312255859
02:28:36.687 --> 02:28:38.577 evaluate in both pre and on treatment.
NOTE Confidence: 0.870876312255859
02:28:38.580 --> 02:28:40.570 Human tumor samples in order
NOTE Confidence: 0.870876312255859
02:28:40.570 --> 02:28:42.162 to guide therapeutic decisions.
NOTE Confidence: 0.870876312255859
02:28:42.170 --> 02:28:43.940 The organ specific micro environment
NOTE Confidence: 0.870876312255859
02:28:43.940 --> 02:28:46.060 will need to be considered in
NOTE Confidence: 0.870876312255859
02:28:46.060 --> 02:28:47.228 order to understand me.
NOTE Confidence: 0.870876312255859
02:28:47.230 --> 02:28:47.582 Logic,
NOTE Confidence: 0.870876312255859
02:28:47.582 --> 02:28:48.990 subsets and subsequent immune
NOTE Confidence: 0.870876312255859

02:28:48.990 --> 02:28:50.398 responses against cancer cells
NOTE Confidence: 0.870876312255859

02:28:50.398 --> 02:28:52.381 in these organs and pre surgical
NOTE Confidence: 0.870876312255859

02:28:52.381 --> 02:28:53.961 and tissue based clinical trials,
NOTE Confidence: 0.870876312255859

02:28:53.970 --> 02:28:56.046 really do provide a feasible platform
NOTE Confidence: 0.870876312255859

02:28:56.046 --> 02:28:57.833 to study biological effects in
NOTE Confidence: 0.870876312255859

02:28:57.833 --> 02:28:59.538 patients which then provide insights
NOTE Confidence: 0.870876312255859

02:28:59.538 --> 02:29:01.798 into mechanisms that can be targeted
NOTE Confidence: 0.870876312255859

02:29:01.798 --> 02:29:03.470 for rational combination therapies.
NOTE Confidence: 0.870876312255859

02:29:03.470 --> 02:29:04.442 So I have many,
NOTE Confidence: 0.870876312255859

02:29:04.442 --> 02:29:05.900 many people to thank and my
NOTE Confidence: 0.870876312255859

02:29:05.965 --> 02:29:07.780 funding sources are listed here.
NOTE Confidence: 0.870876312255859

02:29:07.780 --> 02:29:09.496 I definitely do want to thank
NOTE Confidence: 0.870876312255859

02:29:09.496 --> 02:29:10.354 the patients though,
NOTE Confidence: 0.870876312255859

02:29:10.360 --> 02:29:11.790 because as you can imagine,
NOTE Confidence: 0.870876312255859

02:29:11.790 --> 02:29:13.404 patients with localized disease do not
NOTE Confidence: 0.870876312255859

02:29:13.404 --> 02:29:15.240 need to participate in clinical trials.

NOTE Confidence: 0.870876312255859
02:29:15.240 --> 02:29:16.752 They can go just directly to
NOTE Confidence: 0.870876312255859
02:29:16.752 --> 02:29:18.416 surgery and we've had lots of
NOTE Confidence: 0.870876312255859
02:29:18.416 --> 02:29:19.906 success in having these patients
NOTE Confidence: 0.870876312255859
02:29:19.906 --> 02:29:21.260 participate in our studies.
NOTE Confidence: 0.870876312255859
02:29:21.260 --> 02:29:22.564 And we're very grateful.
NOTE Confidence: 0.870876312255859
02:29:22.564 --> 02:29:25.740 So thank you and I'm happy to take questions.
NOTE Confidence: 0.870876312255859
02:29:25.740 --> 02:29:26.090 So
NOTE Confidence: 0.865806341171265
02:29:26.090 --> 02:29:28.554 I'll start you off with the first
NOTE Confidence: 0.865806341171265
02:29:28.560 --> 02:29:30.320 question you based upon the
NOTE Confidence: 0.865806341171265
02:29:30.320 --> 02:29:32.429 work and that you very elegantly
NOTE Confidence: 0.865806341171265
02:29:32.430 --> 02:29:34.536 described from the 2019 cell paper
NOTE Confidence: 0.865806341171265
02:29:34.540 --> 02:29:37.360 and that you saw in humans. But when
NOTE Confidence: 0.865806341171265
02:29:37.360 --> 02:29:38.410 you're doing these
NOTE Confidence: 0.865806341171265
02:29:38.410 --> 02:29:39.469 window of opportunity
NOTE Confidence: 0.865806341171265
02:29:39.470 --> 02:29:41.230 trials, and if it does
NOTE Confidence: 0.865806341171265

02:29:41.230 --> 02:29:43.339 turn out that all of these
NOTE Confidence: 0.865806341171265

02:29:43.340 --> 02:29:44.748 different meta static niches
NOTE Confidence: 0.865806341171265

02:29:44.750 --> 02:29:45.800 which are actually
NOTE Confidence: 0.865806341171265

02:29:45.800 --> 02:29:47.560 in locations that are actually
NOTE Confidence: 0.865806341171265

02:29:47.560 --> 02:29:49.674 very difficult to get access to
NOTE Confidence: 0.865806341171265

02:29:49.674 --> 02:29:52.142 while people are on therapy at all,
NOTE Confidence: 0.865806341171265

02:29:52.142 --> 02:29:54.600 how do you? How do you think
NOTE Confidence: 0.865806341171265

02:29:54.600 --> 02:29:56.360 that you can circumvent that?
NOTE Confidence: 0.865806341171265

02:29:56.360 --> 02:29:57.768 Or what strategies do
NOTE Confidence: 0.865806341171265

02:29:57.770 --> 02:29:59.890 you think that you'll apply to?
NOTE Confidence: 0.865806341171265

02:29:59.890 --> 02:30:01.832 Towards that end. Yeah, so this.
NOTE Confidence: 0.865806341171265

02:30:01.832 --> 02:30:03.680 You know it takes a great
NOTE Confidence: 0.865806341171265

02:30:03.750 --> 02:30:05.118 deal of investments.
NOTE Confidence: 0.865806341171265

02:30:05.120 --> 02:30:06.770 I want to give our institution
NOTE Confidence: 0.865806341171265

02:30:06.770 --> 02:30:08.250 credit for putting millions and
NOTE Confidence: 0.865806341171265

02:30:08.250 --> 02:30:09.885 millions and millions of dollars

NOTE Confidence: 0.865806341171265
02:30:09.885 --> 02:30:11.193 into the immunotherapy platform.
NOTE Confidence: 0.865806341171265
02:30:11.200 --> 02:30:13.066 And all of the associated networks
NOTE Confidence: 0.865806341171265
02:30:13.066 --> 02:30:14.843 that need to support it, right?
NOTE Confidence: 0.865806341171265
02:30:14.843 --> 02:30:16.358 Because then we have dedicated
NOTE Confidence: 0.865806341171265
02:30:16.358 --> 02:30:16.964 interventional radiologists,
NOTE Confidence: 0.865806341171265
02:30:16.970 --> 02:30:18.560 dedicated surgeons and dedicated pathologists
NOTE Confidence: 0.865806341171265
02:30:18.560 --> 02:30:20.929 that work with us to try and Design.
NOTE Confidence: 0.865806341171265
02:30:20.930 --> 02:30:22.748 The best way to do this.
NOTE Confidence: 0.865806341171265
02:30:22.750 --> 02:30:24.436 So we do have access to
NOTE Confidence: 0.865806341171265
02:30:24.436 --> 02:30:26.090 them getting a soft tissue.
NOTE Confidence: 0.865806341171265
02:30:26.090 --> 02:30:27.650 Anna bone metastatic lesion from
NOTE Confidence: 0.865806341171265
02:30:27.650 --> 02:30:29.852 the same patient at the same time
NOTE Confidence: 0.865806341171265
02:30:29.852 --> 02:30:31.604 of the biopsy and those samples.
NOTE Confidence: 0.865806341171265
02:30:31.610 --> 02:30:33.731 To come directly to the laboratory in
NOTE Confidence: 0.865806341171265
02:30:33.731 --> 02:30:36.419 the you know the way we designed a tubes
NOTE Confidence: 0.865806341171265

02:30:36.419 --> 02:30:38.718 to be sent directly to the laboratory.
NOTE Confidence: 0.865806341171265

02:30:38.720 --> 02:30:40.260 For those kinds of analysis.
NOTE Confidence: 0.865806341171265

02:30:40.260 --> 02:30:42.108 So it does really take this team
NOTE Confidence: 0.865806341171265

02:30:42.108 --> 02:30:43.806 effort with a lots of support
NOTE Confidence: 0.865806341171265

02:30:43.806 --> 02:30:45.773 behind it so that the studies are
NOTE Confidence: 0.865806341171265

02:30:45.839 --> 02:30:47.679 being prioritized and scheduled.
NOTE Confidence: 0.865806341171265

02:30:47.680 --> 02:30:49.336 You know we have schedulers to
NOTE Confidence: 0.865806341171265

02:30:49.336 --> 02:30:51.080 our dedicated for the scheduling.
NOTE Confidence: 0.865806341171265

02:30:51.080 --> 02:30:51.388 These.
NOTE Confidence: 0.865806341171265

02:30:51.388 --> 02:30:53.852 We have coordinators who take care of these.
NOTE Confidence: 0.865806341171265

02:30:53.860 --> 02:30:55.012 We have, you know,
NOTE Confidence: 0.865806341171265

02:30:55.012 --> 02:30:56.740 lots of people who spend time
NOTE Confidence: 0.865806341171265

02:30:56.800 --> 02:30:57.880 with the patients.
NOTE Confidence: 0.865806341171265

02:30:57.880 --> 02:30:59.212 Getting the informed consents.
NOTE Confidence: 0.865806341171265

02:30:59.212 --> 02:31:01.620 Imagine instead of spending an hour to see.
NOTE Confidence: 0.865806341171265

02:31:01.620 --> 02:31:02.600 For patients in clinic,

NOTE Confidence: 0.865806341171265
02:31:02.600 --> 02:31:04.651 I get to spend an hour with one
NOTE Confidence: 0.865806341171265
02:31:04.651 --> 02:31:06.217 patient to explain all of these
NOTE Confidence: 0.865806341171265
02:31:06.217 --> 02:31:08.205 steps so you know the institution
NOTE Confidence: 0.865806341171265
02:31:08.205 --> 02:31:09.613 is losing clinical billing
NOTE Confidence: 0.865806341171265
02:31:09.613 --> 02:31:11.480 dollars 'cause they don't get to
NOTE Confidence: 0.865806341171265
02:31:11.480 --> 02:31:12.930 bill all my clinical time,
NOTE Confidence: 0.865806341171265
02:31:12.930 --> 02:31:14.544 but they're gaining on the research
NOTE Confidence: 0.865806341171265
02:31:14.544 --> 02:31:16.309 side and not really takes foresight
NOTE Confidence: 0.865806341171265
02:31:16.309 --> 02:31:18.217 and insight and leadership for the
NOTE Confidence: 0.865806341171265
02:31:18.217 --> 02:31:20.176 institution to have made that a priority.
NOTE Confidence: 0.865806341171265
02:31:20.180 --> 02:31:22.007 So I really think that's what makes
NOTE Confidence: 0.865806341171265
02:31:22.007 --> 02:31:23.660 it work from our standpoint.
NOTE Confidence: 0.828651905059814
02:31:25.260 --> 02:31:27.993 I have a question Kelly if that's OK.
NOTE Confidence: 0.828651905059814
02:31:27.993 --> 02:31:29.613 So yeah, so you know.
NOTE Confidence: 0.828651905059814
02:31:29.613 --> 02:31:31.790 I actually also have to applaud your
NOTE Confidence: 0.828651905059814

02:31:31.859 --> 02:31:33.699 institution for the support they've
NOTE Confidence: 0.828651905059814

02:31:33.699 --> 02:31:35.943 given for a window out because
NOTE Confidence: 0.828651905059814

02:31:35.943 --> 02:31:37.935 it's pretty unusual as you know
NOTE Confidence: 0.828651905059814

02:31:37.935 --> 02:31:40.311 to have that level of support an.
NOTE Confidence: 0.828651905059814

02:31:40.311 --> 02:31:43.039 I think this also Harkins back to the
NOTE Confidence: 0.828651905059814

02:31:43.040 --> 02:31:44.408 kinetic nature of response
NOTE Confidence: 0.828651905059814

02:31:44.410 --> 02:31:45.439 of hot versus
NOTE Confidence: 0.828651905059814

02:31:45.440 --> 02:31:47.827 cold where this not as pathologist do.
NOTE Confidence: 0.828651905059814

02:31:47.830 --> 02:31:50.632 I look at plenty of these responses.
NOTE Confidence: 0.828651905059814

02:31:50.632 --> 02:31:51.790 It's not you.
NOTE Confidence: 0.828651905059814

02:31:51.790 --> 02:31:53.010 It's not uniform overtime,
NOTE Confidence: 0.828651905059814

02:31:53.010 --> 02:31:54.833 so when you look is important
NOTE Confidence: 0.828651905059814

02:31:54.833 --> 02:31:56.348 and with that in mind,
NOTE Confidence: 0.828651905059814

02:31:56.350 --> 02:31:57.865 with these window opportunity trials
NOTE Confidence: 0.828651905059814

02:31:57.865 --> 02:32:00.300 you had like week seven after two cycles,
NOTE Confidence: 0.828651905059814

02:32:00.300 --> 02:32:02.352 an initial trials with you have paths

NOTE Confidence: 0.828651905059814

02:32:02.352 --> 02:32:04.863 ers which are useful in a certain sense.

NOTE Confidence: 0.828651905059814

02:32:04.863 --> 02:32:07.295 But if you want to actually check out

NOTE Confidence: 0.828651905059814

02:32:07.295 --> 02:32:09.122 the immune response in earlier time,

NOTE Confidence: 0.828651905059814

02:32:09.122 --> 02:32:10.642 point probably would be nice

NOTE Confidence: 0.828651905059814

02:32:10.642 --> 02:32:12.458 where you actually see some tumor

NOTE Confidence: 0.856637358665466

02:32:12.460 --> 02:32:13.680 cells left that are

NOTE Confidence: 0.856637358665466

02:32:13.680 --> 02:32:14.589 being killed. So

NOTE Confidence: 0.856637358665466

02:32:14.590 --> 02:32:17.633 do you have some insight as to what you like

NOTE Confidence: 0.856637358665466

02:32:17.633 --> 02:32:20.058 right now in terms of optimal time points?

NOTE Confidence: 0.856637358665466

02:32:20.060 --> 02:32:21.892 'cause it's variable? I get that.

NOTE Confidence: 0.856637358665466

02:32:21.892 --> 02:32:24.619 But what sort of the window arranged for you

NOTE Confidence: 0.844183536512511

02:32:24.620 --> 02:32:26.867 now? You asked the question that our

NOTE Confidence: 0.844183536512511

02:32:26.867 --> 02:32:28.791 students always ask if we're looking

NOTE Confidence: 0.844183536512511

02:32:28.791 --> 02:32:30.877 at the tumors just when we actually

NOTE Confidence: 0.844183536512511

02:32:30.943 --> 02:32:33.063 have tumors or we don't have to more,

NOTE Confidence: 0.844183536512511

02:32:33.070 --> 02:32:34.756 then we're really defining just a
NOTE Confidence: 0.844183536512511

02:32:34.756 --> 02:32:36.640 response that leads to tumor growing.
NOTE Confidence: 0.844183536512511

02:32:36.640 --> 02:32:38.427 Or Jim are going away, right?
NOTE Confidence: 0.844183536512511

02:32:38.427 --> 02:32:40.803 You're not getting that real lanja tude inal.
NOTE Confidence: 0.844183536512511

02:32:40.810 --> 02:32:42.245 So we have been designing
NOTE Confidence: 0.844183536512511

02:32:42.245 --> 02:32:43.680 experiments where we're getting now
NOTE Confidence: 0.844183536512511

02:32:43.727 --> 02:32:45.277 weekly samples from our patients.
NOTE Confidence: 0.844183536512511

02:32:45.280 --> 02:32:46.770 Of course, that got interrupted
NOTE Confidence: 0.844183536512511

02:32:46.770 --> 02:32:49.110 a bit by Kovid, and so you know,
NOTE Confidence: 0.844183536512511

02:32:49.110 --> 02:32:50.535 we're trying to get everything
NOTE Confidence: 0.844183536512511

02:32:50.535 --> 02:32:52.138 back online for having more,
NOTE Confidence: 0.844183536512511

02:32:52.140 --> 02:32:53.940 but we do have small numbers
NOTE Confidence: 0.844183536512511

02:32:53.940 --> 02:32:55.140 now in our cohorts.
NOTE Confidence: 0.844183536512511

02:32:55.140 --> 02:32:56.682 Where we have weekly samples and
NOTE Confidence: 0.844183536512511

02:32:56.682 --> 02:32:58.839 we are able to see that the other
NOTE Confidence: 0.844183536512511

02:32:58.839 --> 02:33:00.823 thing is because we're able to now

NOTE Confidence: 0.844183536512511
02:33:00.823 --> 02:33:02.418 prioritize single cell RNA seq.
NOTE Confidence: 0.844183536512511
02:33:02.420 --> 02:33:04.394 Because the assays have gotten so much
NOTE Confidence: 0.844183536512511
02:33:04.394 --> 02:33:06.305 better at doing that on the smaller
NOTE Confidence: 0.844183536512511
02:33:06.305 --> 02:33:08.460 sample size so that we don't have to
NOTE Confidence: 0.844183536512511
02:33:08.460 --> 02:33:10.532 ask our pathologists to give us everything.
NOTE Confidence: 0.844183536512511
02:33:10.540 --> 02:33:11.970 'cause That's also becoming an
NOTE Confidence: 0.844183536512511
02:33:11.970 --> 02:33:14.009 issue because we have to leave some
NOTE Confidence: 0.844183536512511
02:33:14.009 --> 02:33:15.389 for diagnostic path and figure
NOTE Confidence: 0.844183536512511
02:33:15.389 --> 02:33:17.258 out when we can get the sample.
NOTE Confidence: 0.844183536512511
02:33:17.260 --> 02:33:19.348 So I think single cell RNA seq is
NOTE Confidence: 0.844183536512511
02:33:19.348 --> 02:33:21.179 also enabling us to do those analysis
NOTE Confidence: 0.844183536512511
02:33:21.179 --> 02:33:23.139 with an assay that we can follow
NOTE Confidence: 0.844183536512511
02:33:23.139 --> 02:33:25.095 overtime on smaller amount of cells.
NOTE Confidence: 0.844183536512511
02:33:25.100 --> 02:33:27.137 So that's. Hopefully data I can show.
NOTE Confidence: 0.844183536512511
02:33:27.140 --> 02:33:28.964 I want to say the other thing I
NOTE Confidence: 0.844183536512511

02:33:28.964 --> 02:33:30.617 didn't show here is that we've
NOTE Confidence: 0.844183536512511

02:33:30.617 --> 02:33:32.333 also been using bone marrow samples
NOTE Confidence: 0.844183536512511

02:33:32.390 --> 02:33:34.140 to represent the immune response.
NOTE Confidence: 0.844183536512511

02:33:34.140 --> 02:33:36.124 Instead of trying to do a tumor biopsy
NOTE Confidence: 0.844183536512511

02:33:36.124 --> 02:33:38.205 trying to get it from the bone marrow
NOTE Confidence: 0.844183536512511

02:33:38.205 --> 02:33:39.925 because we think that obviously the
NOTE Confidence: 0.844183536512511

02:33:39.925 --> 02:33:41.555 immune response evolving and also
NOTE Confidence: 0.844183536512511

02:33:41.555 --> 02:33:42.820 the bone marrow microenvironment
NOTE Confidence: 0.844183536512511

02:33:42.820 --> 02:33:44.220 that some cells also infiltrate,
NOTE Confidence: 0.844183536512511

02:33:44.220 --> 02:33:46.110 not just bone metastases but just normal
NOTE Confidence: 0.844183536512511

02:33:46.110 --> 02:33:47.858 patients taking a bone marrow sample.
NOTE Confidence: 0.844183536512511

02:33:47.860 --> 02:33:50.148 So we've been trying to do that also
NOTE Confidence: 0.844183536512511

02:33:50.148 --> 02:33:52.132 in looking at that by sight off to
NOTE Confidence: 0.844183536512511

02:33:52.132 --> 02:33:54.359 see if we can then see those lanja
NOTE Confidence: 0.844183536512511

02:33:54.359 --> 02:33:56.255 tude onal because that does not
NOTE Confidence: 0.844183536512511

02:33:56.260 --> 02:33:57.725 require a scheduling an appointment

NOTE Confidence: 0.844183536512511
02:33:57.725 --> 02:33:58.604 with Interventional radiology.
NOTE Confidence: 0.844183536512511
02:33:58.610 --> 02:34:00.874 Bone marrow can be done directly in clinic.
NOTE Confidence: 0.844183536512511
02:34:00.880 --> 02:34:02.300 When we see the patient.
NOTE Confidence: 0.844183536512511
02:34:02.300 --> 02:34:03.968 So those are things that we're
NOTE Confidence: 0.844183536512511
02:34:03.968 --> 02:34:05.430 trying to come up with.
NOTE Confidence: 0.844183536512511
02:34:05.430 --> 02:34:06.880 Not perfect by any means.
NOTE Confidence: 0.844183536512511
02:34:06.880 --> 02:34:10.240 About one more additional question
NOTE Confidence: 0.83843857049942
02:34:08.400 --> 02:34:09.318 from Sally Church.
NOTE Confidence: 0.83843857049942
02:34:09.320 --> 02:34:10.238 So easy H2
NOTE Confidence: 0.83843857049942
02:34:10.240 --> 02:34:11.464 Inhibitors as you know,
NOTE Confidence: 0.83843857049942
02:34:11.464 --> 02:34:13.605 have a lot of off target effects
NOTE Confidence: 0.83843857049942
02:34:13.605 --> 02:34:15.130 of the question really is.
NOTE Confidence: 0.83843857049942
02:34:15.130 --> 02:34:16.972 What are some of the anticipated
NOTE Confidence: 0.83843857049942
02:34:16.972 --> 02:34:18.502 toxicities that you may see
NOTE Confidence: 0.83843857049942
02:34:18.502 --> 02:34:19.420 overlapping with combinations
NOTE Confidence: 0.83843857049942

02:34:19.420 --> 02:34:21.860 and you could say epigenetics and in general

NOTE Confidence: 0.83843857049942

02:34:21.860 --> 02:34:23.390 when you combining that with

NOTE Confidence: 0.83843857049942

02:34:23.390 --> 02:34:24.308 a drug like

NOTE Confidence: 0.83843857049942

02:34:24.310 --> 02:34:25.843 Apple in math, yeah so

NOTE Confidence: 0.83843857049942

02:34:25.843 --> 02:34:27.368 we thought we were going

NOTE Confidence: 0.83843857049942

02:34:27.370 --> 02:34:29.246 to see a lot. Actually the trial

NOTE Confidence: 0.83843857049942

02:34:29.246 --> 02:34:30.809 was written with three milligrams

NOTE Confidence: 0.83843857049942

02:34:30.809 --> 02:34:32.564 per kilogram of the Apolima,

NOTE Confidence: 0.83843857049942

02:34:32.570 --> 02:34:34.586 which as you know is the dose

NOTE Confidence: 0.83843857049942

02:34:34.586 --> 02:34:36.250 that was approved in Melanoma.

NOTE Confidence: 0.83843857049942

02:34:36.250 --> 02:34:37.840 But then in renal cell.

NOTE Confidence: 0.83843857049942

02:34:37.840 --> 02:34:40.264 Sorry, that's my new puppy in renal cell.

NOTE Confidence: 0.83843857049942

02:34:40.270 --> 02:34:42.636 The dose is 1 milligram per kilogram

NOTE Confidence: 0.83843857049942

02:34:42.636 --> 02:34:44.544 because of toxicity issues and in

NOTE Confidence: 0.83843857049942

02:34:44.544 --> 02:34:46.483 bladder in lung cancer had to be

NOTE Confidence: 0.83843857049942

02:34:46.551 --> 02:34:48.532 Q Six week dosing because the Q3

NOTE Confidence: 0.83843857049942

02:34:48.532 --> 02:34:50.206 week dosing so we actually expected

NOTE Confidence: 0.83843857049942

02:34:50.206 --> 02:34:52.110 to have a lot of toxicities and

NOTE Confidence: 0.83843857049942

02:34:52.168 --> 02:34:54.107 again just running the gamut of all

NOTE Confidence: 0.83843857049942

02:34:54.107 --> 02:34:55.700 of the toxicities associated with

NOTE Confidence: 0.83843857049942

02:34:55.700 --> 02:34:57.806 immune checkpoint that we can be

NOTE Confidence: 0.83843857049942

02:34:57.806 --> 02:34:59.452 exacerbated within easy H2 Inhibitors.

NOTE Confidence: 0.83843857049942

02:34:59.452 --> 02:35:01.650 So everything from colitis all the way

NOTE Confidence: 0.83843857049942

02:35:01.705 --> 02:35:03.977 to dermatitis we were expecting all of it.

NOTE Confidence: 0.83843857049942

02:35:03.980 --> 02:35:06.392 We have to say the 1st three patients we

NOTE Confidence: 0.83843857049942

02:35:06.392 --> 02:35:08.557 treated at three milligrams per kilogram.

NOTE Confidence: 0.83843857049942

02:35:08.560 --> 02:35:10.306 And they're doing well, you know,

NOTE Confidence: 0.83843857049942

02:35:10.310 --> 02:35:11.760 crossing my fingers that continues.

NOTE Confidence: 0.83843857049942

02:35:11.760 --> 02:35:14.379 We're only giving two doses of the flu map,

NOTE Confidence: 0.83843857049942

02:35:14.380 --> 02:35:16.126 not the four doses as approved.

NOTE Confidence: 0.83843857049942

02:35:16.130 --> 02:35:17.525 So maybe that's also helpful

NOTE Confidence: 0.83843857049942

02:35:17.525 --> 02:35:19.580 because we found a two doses works
NOTE Confidence: 0.83843857049942

02:35:19.580 --> 02:35:21.070 in our pre surgical trial,
NOTE Confidence: 0.83843857049942

02:35:21.070 --> 02:35:22.816 so we're only giving two doses.
NOTE Confidence: 0.83843857049942

02:35:22.820 --> 02:35:24.788 And the other thing is the protocol is
NOTE Confidence: 0.83843857049942

02:35:24.788 --> 02:35:26.475 written to have a dose deescalation
NOTE Confidence: 0.83843857049942

02:35:26.475 --> 02:35:28.191 from 3 milligrams to 1 milligram
NOTE Confidence: 0.83843857049942

02:35:28.243 --> 02:35:29.799 per kilogram of diplomatically.
NOTE Confidence: 0.83843857049942

02:35:29.800 --> 02:35:31.546 Do run into the toxicity issue.
NOTE Confidence: 0.83843857049942

02:35:31.550 --> 02:35:32.423 Like I said,
NOTE Confidence: 0.83843857049942

02:35:32.423 --> 02:35:33.296 we haven't yet,
NOTE Confidence: 0.83843857049942

02:35:33.300 --> 02:35:35.253 and I hope we don't because the
NOTE Confidence: 0.83843857049942

02:35:35.253 --> 02:35:36.439 three milligrams per kilogram
NOTE Confidence: 0.83843857049942

02:35:36.439 --> 02:35:38.209 really does give the best response
NOTE Confidence: 0.83843857049942

02:35:38.209 --> 02:35:40.329 in terms of CD4 and CD8 responses.
NOTE Confidence: 0.83843857049942

02:35:40.330 --> 02:35:42.121 So we're hoping to be able to keep the
NOTE Confidence: 0.83843857049942

02:35:42.121 --> 02:35:43.778 three milligram per kilogram dose Ng.

NOTE Confidence: 0.83843857049942
02:35:43.780 --> 02:35:44.274 But yes,
NOTE Confidence: 0.83843857049942
02:35:44.274 --> 02:35:45.509 toxicity is something we always
NOTE Confidence: 0.83843857049942
02:35:45.509 --> 02:35:47.565 have to be careful with when we
NOTE Confidence: 0.83843857049942
02:35:47.565 --> 02:35:48.825 designed a combination studies.
NOTE Confidence: 0.83843857049942
02:35:48.830 --> 02:35:51.150 Great, thank you.
NOTE Confidence: 0.83843857049942
02:35:51.150 --> 02:35:54.640 Thank you.
NOTE Confidence: 0.83843857049942
02:35:54.640 --> 02:35:59.660 OK.
NOTE Confidence: 0.83843857049942
02:36:00.210 --> 02:36:01.380 Doctor Joshi
NOTE Confidence: 0.810628056526184
02:36:01.380 --> 02:36:04.654 you Are you ready to share?
NOTE Confidence: 0.810628056526184
02:36:04.654 --> 02:36:06.460 My screen thanks Pam.
NOTE Confidence: 0.835343420505524
02:36:07.100 --> 02:36:08.600 So I have the
NOTE Confidence: 0.835343420505524
02:36:08.600 --> 02:36:11.236 pleasure of announcing one of my colleagues,
NOTE Confidence: 0.835343420505524
02:36:11.236 --> 02:36:13.870 doctor Nick Joshi, who is an assistant
NOTE Confidence: 0.835343420505524
02:36:13.870 --> 02:36:16.128 professor of immunobiology here at Yale.
NOTE Confidence: 0.835343420505524
02:36:16.128 --> 02:36:19.132 He had initially done his PhD and they
NOTE Confidence: 0.835343420505524

02:36:19.132 --> 02:36:21.772 were smart enough to re recruit him
NOTE Confidence: 0.835343420505524

02:36:21.772 --> 02:36:24.400 back after finishing his postdoc at MIT,
NOTE Confidence: 0.835343420505524

02:36:24.400 --> 02:36:26.275 he's been honored as a
NOTE Confidence: 0.835343420505524

02:36:26.275 --> 02:36:27.775 Damon Runyon cancer fellow,
NOTE Confidence: 0.835343420505524

02:36:27.780 --> 02:36:30.410 also by the lung Cancer Research Foundation,
NOTE Confidence: 0.835343420505524

02:36:30.410 --> 02:36:33.415 earning awards as well as some of young
NOTE Confidence: 0.835343420505524

02:36:33.415 --> 02:36:35.298 investigator awards and Immuno Oncology.
NOTE Confidence: 0.835343420505524

02:36:35.300 --> 02:36:37.931 Here I will say that Nick is
NOTE Confidence: 0.835343420505524

02:36:37.931 --> 02:36:39.062 a wonderful collaborator.
NOTE Confidence: 0.835343420505524

02:36:39.062 --> 02:36:40.940 He's praised for his teaching,
NOTE Confidence: 0.835343420505524

02:36:40.940 --> 02:36:42.029 his mentor ship.
NOTE Confidence: 0.835343420505524

02:36:42.029 --> 02:36:44.456 And his inside in a sought after
NOTE Confidence: 0.835343420505524

02:36:44.456 --> 02:36:46.803 to work on a number of different
NOTE Confidence: 0.835343420505524

02:36:46.803 --> 02:36:47.805 projects throughout Yale.
NOTE Confidence: 0.835343420505524

02:36:47.805 --> 02:36:50.486 And he's also done a lot of really
NOTE Confidence: 0.835343420505524

02:36:50.486 --> 02:36:52.496 wonderful work on creating some novel

NOTE Confidence: 0.835343420505524
02:36:52.496 --> 02:36:55.180 animal models that have the best name in
NOTE Confidence: 0.873651087284088
02:36:55.180 --> 02:36:57.524 the world, ninja which he just recently
NOTE Confidence: 0.873651087284088
02:36:57.524 --> 02:36:58.862 published in nature communications.
NOTE Confidence: 0.873651087284088
02:36:58.862 --> 02:37:01.208 And today he's going to talk to
NOTE Confidence: 0.873651087284088
02:37:01.210 --> 02:37:02.880 us about investigating T cell
NOTE Confidence: 0.873651087284088
02:37:02.880 --> 02:37:05.830 responses and engineered cancer models.
NOTE Confidence: 0.873651087284088
02:37:05.830 --> 02:37:10.170 Alright, can you guys see see the screen?
NOTE Confidence: 0.873651087284088
02:37:10.170 --> 02:37:11.398 You're all set now.
NOTE Confidence: 0.873651087284088
02:37:11.398 --> 02:37:13.540 OK, thanks so thanks for the introduction.
NOTE Confidence: 0.873651087284088
02:37:13.540 --> 02:37:14.344 As you mentioned,
NOTE Confidence: 0.873651087284088
02:37:14.344 --> 02:37:16.220 I'm going to be talking about our
NOTE Confidence: 0.873651087284088
02:37:16.276 --> 02:37:18.232 results looking at T cell responses
NOTE Confidence: 0.873651087284088
02:37:18.232 --> 02:37:19.960 in these engineered cancer models,
NOTE Confidence: 0.873651087284088
02:37:19.960 --> 02:37:22.039 so there's been a lot of introduction
NOTE Confidence: 0.873651087284088
02:37:22.039 --> 02:37:24.227 in terms of how T cells function
NOTE Confidence: 0.873651087284088

02:37:24.227 --> 02:37:25.772 in the context of tumors,
NOTE Confidence: 0.873651087284088

02:37:25.780 --> 02:37:27.803 and I'm going to not go through
NOTE Confidence: 0.873651087284088

02:37:27.803 --> 02:37:29.450 that again in any detail,
NOTE Confidence: 0.873651087284088

02:37:29.450 --> 02:37:31.094 but just highlight two basic points
NOTE Confidence: 0.873651087284088

02:37:31.094 --> 02:37:33.251 that I think are really important to
NOTE Confidence: 0.873651087284088

02:37:33.251 --> 02:37:35.255 understand what we are interested in.
NOTE Confidence: 0.873651087284088

02:37:35.260 --> 02:37:37.732 The first is that I think there's been
NOTE Confidence: 0.873651087284088

02:37:37.732 --> 02:37:40.531 a lot of work by many, many groups, and.
NOTE Confidence: 0.873651087284088

02:37:40.531 --> 02:37:42.166 Including clinical work that's really
NOTE Confidence: 0.873651087284088

02:37:42.166 --> 02:37:43.461 highlighted the important role
NOTE Confidence: 0.873651087284088

02:37:43.461 --> 02:37:44.641 that immune checkpoint receptors
NOTE Confidence: 0.873651087284088

02:37:44.641 --> 02:37:46.928 play in terms of driving an
NOTE Confidence: 0.873651087284088

02:37:46.928 --> 02:37:47.988 immunosuppressive microenvironment.
NOTE Confidence: 0.873651087284088

02:37:47.990 --> 02:37:50.838 That's present tumors and this has taught us,
NOTE Confidence: 0.873651087284088

02:37:50.840 --> 02:37:52.930 the importance of these receptors
NOTE Confidence: 0.873651087284088

02:37:52.930 --> 02:37:54.602 and actually suppressing ongoing

NOTE Confidence: 0.873651087284088
02:37:54.602 --> 02:37:56.174 and actively suppressing ongoing
NOTE Confidence: 0.873651087284088
02:37:56.174 --> 02:37:58.722 T cell responses and we give him
NOTE Confidence: 0.873651087284088
02:37:58.785 --> 02:38:00.037 you know therapy now.
NOTE Confidence: 0.873651087284088
02:38:00.040 --> 02:38:02.042 Now we can drive our these responses
NOTE Confidence: 0.873651087284088
02:38:02.042 --> 02:38:04.060 back into a more optimal zone
NOTE Confidence: 0.873651087284088
02:38:04.060 --> 02:38:05.885 and get more antitumor effects.
NOTE Confidence: 0.873651087284088
02:38:05.890 --> 02:38:06.159 However,
NOTE Confidence: 0.873651087284088
02:38:06.159 --> 02:38:08.042 the there's been a real rise as
NOTE Confidence: 0.873651087284088
02:38:08.042 --> 02:38:10.025 as more patients are being treated
NOTE Confidence: 0.873651087284088
02:38:10.025 --> 02:38:12.107 with these drugs in the development
NOTE Confidence: 0.873651087284088
02:38:12.170 --> 02:38:14.020 of immune related adverse events,
NOTE Confidence: 0.873651087284088
02:38:14.020 --> 02:38:16.620 and this is being seen now very frequently,
NOTE Confidence: 0.873651087284088
02:38:16.620 --> 02:38:18.570 especially as I'll show you in.
NOTE Confidence: 0.873651087284088
02:38:18.570 --> 02:38:19.870 Same with combination therapies,
NOTE Confidence: 0.873651087284088
02:38:19.870 --> 02:38:22.468 and so this is telling us, of course,
NOTE Confidence: 0.873651087284088

02:38:22.468 --> 02:38:24.088 that this isn't all good,
NOTE Confidence: 0.873651087284088

02:38:24.090 --> 02:38:26.232 that there is a negative consequences
NOTE Confidence: 0.873651087284088

02:38:26.232 --> 02:38:27.660 blocking these checkpoint receptors
NOTE Confidence: 0.873651087284088

02:38:27.711 --> 02:38:29.201 and that these checkpoint receptors
NOTE Confidence: 0.873651087284088

02:38:29.201 --> 02:38:30.990 really play a very active role.
NOTE Confidence: 0.873651087284088

02:38:30.990 --> 02:38:32.750 In in actually maintaining tolerance
NOTE Confidence: 0.873651087284088

02:38:32.750 --> 02:38:34.158 towards self and maintaining
NOTE Confidence: 0.873651087284088

02:38:34.158 --> 02:38:35.030 peripheral tolerance.
NOTE Confidence: 0.873651087284088

02:38:35.030 --> 02:38:36.860 And as I mentioned now
NOTE Confidence: 0.873651087284088

02:38:36.860 --> 02:38:37.958 with combination therapy,
NOTE Confidence: 0.873651087284088

02:38:37.960 --> 02:38:40.186 this is really increasing the severity
NOTE Confidence: 0.873651087284088

02:38:40.186 --> 02:38:42.445 and frequency of the adverse events
NOTE Confidence: 0.873651087284088

02:38:42.445 --> 02:38:44.569 that are that are observed in.
NOTE Confidence: 0.873651087284088

02:38:44.570 --> 02:38:47.090 This tells us that these inhibitory
NOTE Confidence: 0.873651087284088

02:38:47.090 --> 02:38:48.770 receptors play non overlapping
NOTE Confidence: 0.873651087284088

02:38:48.834 --> 02:38:50.970 functions in terms of how they

NOTE Confidence: 0.873651087284088

02:38:50.970 --> 02:38:53.395 regulate the response and so in my

NOTE Confidence: 0.873651087284088

02:38:53.395 --> 02:38:55.261 lab we're really interested in trying

NOTE Confidence: 0.873651087284088

02:38:55.261 --> 02:38:57.156 to understand this balance between

NOTE Confidence: 0.873651087284088

02:38:57.156 --> 02:38:58.732 peripheral tolerance and effector

NOTE Confidence: 0.873651087284088

02:38:58.732 --> 02:39:01.107 T cell responses in the context of.

NOTE Confidence: 0.873651087284088

02:39:01.110 --> 02:39:01.487 Cancer,

NOTE Confidence: 0.873651087284088

02:39:01.487 --> 02:39:03.372 and so we've been developing

NOTE Confidence: 0.873651087284088

02:39:03.372 --> 02:39:05.519 animal models and I'll tell you.

NOTE Confidence: 0.873651087284088

02:39:05.520 --> 02:39:07.506 To try and understand this balance,

NOTE Confidence: 0.873651087284088

02:39:07.510 --> 02:39:09.820 I'm not going to talk about today.

NOTE Confidence: 0.873651087284088

02:39:09.820 --> 02:39:12.380 We have a whole program and trying to

NOTE Confidence: 0.873651087284088

02:39:12.380 --> 02:39:13.741 understand how peripheral tolerance

NOTE Confidence: 0.873651087284088

02:39:13.741 --> 02:39:16.349 is set up and how breaks down in

NOTE Confidence: 0.873651087284088

02:39:16.419 --> 02:39:18.084 the context of immunotherapy with

NOTE Confidence: 0.873651087284088

02:39:18.084 --> 02:39:20.468 this idea that if we can identify

NOTE Confidence: 0.873651087284088

02:39:20.468 --> 02:39:21.186 those mechanisms,
NOTE Confidence: 0.873651087284088

02:39:21.186 --> 02:39:23.340 maybe we can increase this window
NOTE Confidence: 0.873651087284088

02:39:23.397 --> 02:39:25.595 in which you can make an optimal
NOTE Confidence: 0.873651087284088

02:39:25.595 --> 02:39:27.210 response by suppressing the role
NOTE Confidence: 0.873651087284088

02:39:27.210 --> 02:39:29.366 of lumen system in terms of driving
NOTE Confidence: 0.873651087284088

02:39:29.366 --> 02:39:30.152 autoimmune responses.
NOTE Confidence: 0.873651087284088

02:39:30.152 --> 02:39:32.040 On the flip side,
NOTE Confidence: 0.873651087284088

02:39:32.040 --> 02:39:33.504 we're very interested in how T
NOTE Confidence: 0.873651087284088

02:39:33.504 --> 02:39:35.101 cells function in the context of
NOTE Confidence: 0.873651087284088

02:39:35.101 --> 02:39:36.531 developing tumors and how they
NOTE Confidence: 0.873651087284088

02:39:36.531 --> 02:39:38.412 really are impacted by the immuno
NOTE Confidence: 0.873651087284088

02:39:38.412 --> 02:39:39.708 suppression that's present within
NOTE Confidence: 0.873651087284088

02:39:39.708 --> 02:39:41.472 the micro environment here I think
NOTE Confidence: 0.873651087284088

02:39:41.472 --> 02:39:43.320 like a lot of groups were really
NOTE Confidence: 0.873651087284088

02:39:43.384 --> 02:39:44.969 interested in trying to identify
NOTE Confidence: 0.873651087284088

02:39:44.969 --> 02:39:47.426 means that we can use to try and

NOTE Confidence: 0.873651087284088

02:39:47.426 --> 02:39:49.316 make T cells more resistance in the

NOTE Confidence: 0.873651087284088

02:39:49.320 --> 02:39:50.572 micro environment or understand

NOTE Confidence: 0.873651087284088

02:39:50.572 --> 02:39:52.450 the process by which cells undergo

NOTE Confidence: 0.863606870174408

02:39:52.501 --> 02:39:54.265 differentiation so that we can understand

NOTE Confidence: 0.863606870174408

02:39:54.265 --> 02:39:56.229 what are the signals that are driving

NOTE Confidence: 0.863606870174408

02:39:56.229 --> 02:39:57.951 these processes and and how to best

NOTE Confidence: 0.863606870174408

02:39:57.960 --> 02:39:59.686 manipulate those signals to try and

NOTE Confidence: 0.863606870174408

02:39:59.686 --> 02:40:00.850 get better therapeutic responses.

NOTE Confidence: 0.863606870174408

02:40:00.850 --> 02:40:02.950 So of course. To understand this problem,

NOTE Confidence: 0.863606870174408

02:40:02.950 --> 02:40:04.665 we really need a good animal model

NOTE Confidence: 0.863606870174408

02:40:04.665 --> 02:40:06.701 where we can study T cell responses

NOTE Confidence: 0.863606870174408

02:40:06.701 --> 02:40:08.573 and compare them between what's going

NOTE Confidence: 0.863606870174408

02:40:08.634 --> 02:40:11.090 on an anti cancer response and maybe a

NOTE Confidence: 0.863606870174408

02:40:11.090 --> 02:40:12.586 peripheral tolerance response and trying

NOTE Confidence: 0.863606870174408

02:40:12.586 --> 02:40:14.630 to understand how that balance is achieved.

NOTE Confidence: 0.863606870174408

02:40:14.630 --> 02:40:17.051 And it turns out that some of the models

NOTE Confidence: 0.863606870174408

02:40:17.051 --> 02:40:19.437 that we use in general have a very

NOTE Confidence: 0.863606870174408

02:40:19.437 --> 02:40:21.338 difficult time with the second part,

NOTE Confidence: 0.863606870174408

02:40:21.340 --> 02:40:23.224 the peripheral image in the peripheral

NOTE Confidence: 0.863606870174408

02:40:23.224 --> 02:40:24.772 tolerance mechanisms and so to

NOTE Confidence: 0.863606870174408

02:40:24.772 --> 02:40:26.224 illustrate that I put together kind

NOTE Confidence: 0.863606870174408

02:40:26.224 --> 02:40:28.241 of this very basic slide where I'm

NOTE Confidence: 0.863606870174408

02:40:28.241 --> 02:40:29.786 going to describe the immunologist

NOTE Confidence: 0.863606870174408

02:40:29.786 --> 02:40:31.280 favorite technique of taking model

NOTE Confidence: 0.863606870174408

02:40:31.280 --> 02:40:33.050 antigens where we understand what the.

NOTE Confidence: 0.863606870174408

02:40:33.050 --> 02:40:34.126 With the T cells,

NOTE Confidence: 0.863606870174408

02:40:34.126 --> 02:40:35.740 are there recognized those antigens and

NOTE Confidence: 0.863606870174408

02:40:35.793 --> 02:40:37.676 what we've been doing for decades really

NOTE Confidence: 0.863606870174408

02:40:37.676 --> 02:40:39.399 has been putting these antigens within

NOTE Confidence: 0.863606870174408

02:40:39.399 --> 02:40:41.415 the context of viruses or cancer cells,

NOTE Confidence: 0.863606870174408

02:40:41.420 --> 02:40:43.366 or even expressing them in self tissues.

NOTE Confidence: 0.863606870174408
02:40:43.370 --> 02:40:44.770 And when we do that,
NOTE Confidence: 0.863606870174408
02:40:44.770 --> 02:40:46.738 we can now in program them into the
NOTE Confidence: 0.863606870174408
02:40:46.738 --> 02:40:49.386 mouse and we can study T cell responses
NOTE Confidence: 0.863606870174408
02:40:49.386 --> 02:40:50.786 against these different conditions
NOTE Confidence: 0.863606870174408
02:40:50.842 --> 02:40:52.674 and this tells us a lot about how
NOTE Confidence: 0.863606870174408
02:40:52.674 --> 02:40:54.530 the same T cells are influenced by
NOTE Confidence: 0.863606870174408
02:40:54.530 --> 02:40:55.364 these different microenvironments,
NOTE Confidence: 0.863606870174408
02:40:55.370 --> 02:40:57.520 which is very powerful tool.
NOTE Confidence: 0.863606870174408
02:40:57.520 --> 02:40:57.845 However,
NOTE Confidence: 0.863606870174408
02:40:57.845 --> 02:41:00.138 the caveat has been really trying to
NOTE Confidence: 0.863606870174408
02:41:00.138 --> 02:41:01.768 understand these responses against self
NOTE Confidence: 0.863606870174408
02:41:01.770 --> 02:41:03.364 self antigens and really peripheral
NOTE Confidence: 0.863606870174408
02:41:03.364 --> 02:41:05.206 self tolerance and the reason for
NOTE Confidence: 0.863606870174408
02:41:05.206 --> 02:41:07.329 this is actually a beneficial thing.
NOTE Confidence: 0.863606870174408
02:41:07.330 --> 02:41:09.584 It turns out that all the antigens
NOTE Confidence: 0.863606870174408

02:41:09.584 --> 02:41:12.067 that your body or they are encoded in
NOTE Confidence: 0.863606870174408

02:41:12.067 --> 02:41:14.650 the genome or most of those images are
NOTE Confidence: 0.863606870174408

02:41:14.650 --> 02:41:17.135 also expressed in the famous by text,
NOTE Confidence: 0.863606870174408

02:41:17.140 --> 02:41:19.108 and then they're presented by dendritic
NOTE Confidence: 0.863606870174408

02:41:19.108 --> 02:41:21.449 cells within within the Medial of the
NOTE Confidence: 0.863606870174408

02:41:21.449 --> 02:41:23.064 Thymus and autoreactive thymocytes can
NOTE Confidence: 0.863606870174408

02:41:23.064 --> 02:41:25.357 be exposed to this dendritic cell and
NOTE Confidence: 0.863606870174408

02:41:25.357 --> 02:41:26.947 then undergo a tolerance mechanism
NOTE Confidence: 0.863606870174408

02:41:26.950 --> 02:41:28.906 where they're either deleted or there
NOTE Confidence: 0.863606870174408

02:41:28.906 --> 02:41:30.580 turned into regulatory T cells.
NOTE Confidence: 0.863606870174408

02:41:30.580 --> 02:41:32.428 And so without this intolerance mechanism,
NOTE Confidence: 0.863606870174408

02:41:32.430 --> 02:41:34.080 we would have these autoreactive
NOTE Confidence: 0.863606870174408

02:41:34.080 --> 02:41:36.330 thymocytes that would be present in the
NOTE Confidence: 0.863606870174408

02:41:36.330 --> 02:41:37.968 in the peripheral T cell repertoire.
NOTE Confidence: 0.863606870174408

02:41:37.970 --> 02:41:39.867 And we would actually be able to
NOTE Confidence: 0.863606870174408

02:41:39.867 --> 02:41:41.437 study how they undergo torrents

NOTE Confidence: 0.863606870174408

02:41:41.437 --> 02:41:43.513 in the context of self tissues.

NOTE Confidence: 0.863606870174408

02:41:43.520 --> 02:41:45.356 But because of this deletion process,

NOTE Confidence: 0.863606870174408

02:41:45.360 --> 02:41:47.208 we actually don't have this peripheral

NOTE Confidence: 0.863606870174408

02:41:47.208 --> 02:41:48.132 T cell pool,

NOTE Confidence: 0.863606870174408

02:41:48.140 --> 02:41:50.596 and this is great for blocking an immunity.

NOTE Confidence: 0.863606870174408

02:41:50.600 --> 02:41:52.448 But in terms of experimental models,

NOTE Confidence: 0.863606870174408

02:41:52.450 --> 02:41:54.196 it's actually quite a difficult thing

NOTE Confidence: 0.863606870174408

02:41:54.196 --> 02:41:55.840 because the antigen expression mechanism.

NOTE Confidence: 0.863606870174408

02:41:55.840 --> 02:41:57.989 So like I say lock style locks.

NOTE Confidence: 0.863606870174408

02:41:57.990 --> 02:41:59.838 Imagine or a 10 Dusable Antigen.

NOTE Confidence: 0.863606870174408

02:41:59.840 --> 02:42:01.395 These systems really just aren't

NOTE Confidence: 0.863606870174408

02:42:01.395 --> 02:42:02.017 tight enough.

NOTE Confidence: 0.863606870174408

02:42:02.020 --> 02:42:03.875 To keep antigen off in the context

NOTE Confidence: 0.863606870174408

02:42:03.875 --> 02:42:06.261 of the Thymus and so you do undergo

NOTE Confidence: 0.863606870174408

02:42:06.261 --> 02:42:06.875 these peripheral,

NOTE Confidence: 0.863606870174408

02:42:06.880 --> 02:42:08.596 you go under those central tolerance
NOTE Confidence: 0.863606870174408

02:42:08.596 --> 02:42:10.026 and that confounds our ability
NOTE Confidence: 0.863606870174408

02:42:10.026 --> 02:42:11.166 to understand peripheral talents.
NOTE Confidence: 0.863606870174408

02:42:11.166 --> 02:42:14.030 So when I was a postdoc in Tyler Jacks lab,
NOTE Confidence: 0.863606870174408

02:42:14.030 --> 02:42:16.318 we started to try to tackle this problem,
NOTE Confidence: 0.863606870174408

02:42:16.320 --> 02:42:18.119 trying to figure out how we could
NOTE Confidence: 0.863606870174408

02:42:18.119 --> 02:42:19.790 make a neoantigen inducible model that
NOTE Confidence: 0.863606870174408

02:42:19.790 --> 02:42:21.764 is really a little bit different in
NOTE Confidence: 0.863606870174408

02:42:21.821 --> 02:42:23.663 the sense that we're not suppressing
NOTE Confidence: 0.863606870174408

02:42:23.663 --> 02:42:24.891 the neoantigen then turn
NOTE Confidence: 0.771439850330353

02:42:24.900 --> 02:42:26.886 it on. We're actually creating a
NOTE Confidence: 0.771439850330353

02:42:26.886 --> 02:42:28.500 neoantigen through the process of
NOTE Confidence: 0.771439850330353

02:42:28.500 --> 02:42:30.624 induction and the way we came up with was.
NOTE Confidence: 0.771439850330353

02:42:30.630 --> 02:42:33.080 I have referred to earlier.
NOTE Confidence: 0.771439850330353

02:42:33.080 --> 02:42:34.079 It's called ninja.
NOTE Confidence: 0.771439850330353

02:42:34.079 --> 02:42:36.410 So we took a this this constructor

NOTE Confidence: 0.771439850330353
02:42:36.476 --> 02:42:38.738 I'm going to describe the details
NOTE Confidence: 0.771439850330353
02:42:38.738 --> 02:42:40.246 here get very complicated.
NOTE Confidence: 0.771439850330353
02:42:40.250 --> 02:42:42.000 Very quick, but the key thing is
NOTE Confidence: 0.771439850330353
02:42:42.000 --> 02:42:44.201 that it has an inducible Neo Antigen
NOTE Confidence: 0.771439850330353
02:42:44.201 --> 02:42:46.283 that is created through an inversion
NOTE Confidence: 0.771439850330353
02:42:46.345 --> 02:42:48.080 mechanism and so therefore it
NOTE Confidence: 0.771439850330353
02:42:48.080 --> 02:42:50.138 doesn't physically exist in the in
NOTE Confidence: 0.771439850330353
02:42:50.138 --> 02:42:52.682 the genome until you turn it on now.
NOTE Confidence: 0.771439850330353
02:42:52.690 --> 02:42:54.544 The genetics of this are involved
NOTE Confidence: 0.771439850330353
02:42:54.544 --> 02:42:56.200 to recombinases one called Flippo,
NOTE Confidence: 0.771439850330353
02:42:56.200 --> 02:42:57.790 which turns on the Neoantigen
NOTE Confidence: 0.771439850330353
02:42:57.790 --> 02:42:59.062 through this recombination event.
NOTE Confidence: 0.771439850330353
02:42:59.070 --> 02:43:00.725 And then there's another one
NOTE Confidence: 0.771439850330353
02:43:00.725 --> 02:43:02.702 called called pre that turns on
NOTE Confidence: 0.771439850330353
02:43:02.702 --> 02:43:04.268 the ability of this other part
NOTE Confidence: 0.771439850330353

02:43:04.268 --> 02:43:06.160 we call the regulatory module.

NOTE Confidence: 0.771439850330353

02:43:06.160 --> 02:43:07.852 To make the flippo that will

NOTE Confidence: 0.771439850330353

02:43:07.852 --> 02:43:09.750 then act on the neoantigen.

NOTE Confidence: 0.771439850330353

02:43:09.750 --> 02:43:11.598 So how does this differ from

NOTE Confidence: 0.771439850330353

02:43:11.598 --> 02:43:13.330 what people have done before?

NOTE Confidence: 0.771439850330353

02:43:13.330 --> 02:43:14.714 So as I mentioned,

NOTE Confidence: 0.771439850330353

02:43:14.714 --> 02:43:16.444 we create the neoantigen in

NOTE Confidence: 0.771439850330353

02:43:16.444 --> 02:43:17.897 the way that we do,

NOTE Confidence: 0.771439850330353

02:43:17.900 --> 02:43:20.120 that is by taking an antigen

NOTE Confidence: 0.771439850330353

02:43:20.120 --> 02:43:21.600 substrate which is recognized

NOTE Confidence: 0.771439850330353

02:43:21.671 --> 02:43:23.511 by T cells is a very common set

NOTE Confidence: 0.771439850330353

02:43:23.511 --> 02:43:25.856 of T cells that we studied both

NOTE Confidence: 0.771439850330353

02:43:25.856 --> 02:43:27.676 in chronic viral infection and

NOTE Confidence: 0.771439850330353

02:43:27.680 --> 02:43:29.630 often in tumor models as well.

NOTE Confidence: 0.771439850330353

02:43:29.630 --> 02:43:31.285 These are tells cells recognizing

NOTE Confidence: 0.771439850330353

02:43:31.285 --> 02:43:33.571 the GP 33 and GP 66 episodes

NOTE Confidence: 0.771439850330353

02:43:33.571 --> 02:43:35.795 with LC MV and so we put these

NOTE Confidence: 0.771439850330353

02:43:35.869 --> 02:43:37.859 epitopes into a DNA substrate.

NOTE Confidence: 0.771439850330353

02:43:37.860 --> 02:43:39.918 And then we used to splicing sites

NOTE Confidence: 0.771439850330353

02:43:39.918 --> 02:43:41.493 to actually create a central

NOTE Confidence: 0.771439850330353

02:43:41.493 --> 02:43:43.078 Exxon within the DNA encoding.

NOTE Confidence: 0.771439850330353

02:43:43.080 --> 02:43:43.367 This,

NOTE Confidence: 0.771439850330353

02:43:43.367 --> 02:43:45.089 this this antigen and the Central

NOTE Confidence: 0.771439850330353

02:43:45.089 --> 02:43:47.349 X on this pricing event allows us

NOTE Confidence: 0.771439850330353

02:43:47.349 --> 02:43:49.353 to actually invert the in central

NOTE Confidence: 0.771439850330353

02:43:49.416 --> 02:43:51.425 Axon so that in this off state

NOTE Confidence: 0.771439850330353

02:43:51.425 --> 02:43:53.211 the sequences that make up the

NOTE Confidence: 0.771439850330353

02:43:53.211 --> 02:43:54.746 image and are not continuous,

NOTE Confidence: 0.771439850330353

02:43:54.750 --> 02:43:56.550 so therefore they are skipped and

NOTE Confidence: 0.771439850330353

02:43:56.550 --> 02:43:58.429 really can't make a full image.

NOTE Confidence: 0.771439850330353

02:43:58.430 --> 02:44:00.242 And because of this skipping process

NOTE Confidence: 0.771439850330353

02:44:00.242 --> 02:44:02.727 so we want to turn on the antigen,
NOTE Confidence: 0.771439850330353

02:44:02.730 --> 02:44:05.402 we just need to flip this exon around
NOTE Confidence: 0.771439850330353

02:44:05.402 --> 02:44:07.999 and the way we do that is we use.
NOTE Confidence: 0.771439850330353

02:44:08.000 --> 02:44:09.470 Non compatible Fritz sites which
NOTE Confidence: 0.771439850330353

02:44:09.470 --> 02:44:10.940 are responsive to that recombinase,
NOTE Confidence: 0.771439850330353

02:44:10.940 --> 02:44:12.698 called flippo that I mentioned earlier.
NOTE Confidence: 0.771439850330353

02:44:12.700 --> 02:44:13.388 Flippo Axon,
NOTE Confidence: 0.771439850330353

02:44:13.388 --> 02:44:15.108 these recombination sites and makes
NOTE Confidence: 0.771439850330353

02:44:15.108 --> 02:44:16.925 a permanent version that lines up
NOTE Confidence: 0.771439850330353

02:44:16.925 --> 02:44:18.626 these splice sites and now you get
NOTE Confidence: 0.771439850330353

02:44:18.678 --> 02:44:20.346 the production of the new engine.
NOTE Confidence: 0.771439850330353

02:44:20.350 --> 02:44:22.108 We call this the inversion induced.
NOTE Confidence: 0.771439850330353

02:44:22.110 --> 02:44:23.874 Join neoantigen or ninja and ninja
NOTE Confidence: 0.771439850330353

02:44:23.874 --> 02:44:25.659 has one other really helpful feature
NOTE Confidence: 0.771439850330353

02:44:25.659 --> 02:44:27.605 in the fact that this this module
NOTE Confidence: 0.771439850330353

02:44:27.605 --> 02:44:29.432 is actually encoded within a GF

NOTE Confidence: 0.771439850330353

02:44:29.432 --> 02:44:31.176 molecule such that when you turn

NOTE Confidence: 0.771439850330353

02:44:31.176 --> 02:44:33.144 on the Antigen now you go from a

NOTE Confidence: 0.771439850330353

02:44:33.144 --> 02:44:35.458 GF negative state to a GF positive

NOTE Confidence: 0.771439850330353

02:44:35.458 --> 02:44:37.148 state and the antigens within

NOTE Confidence: 0.771439850330353

02:44:37.148 --> 02:44:39.199 the Gino GF so we can actually.

NOTE Confidence: 0.771439850330353

02:44:39.200 --> 02:44:41.366 Read out things like image and

NOTE Confidence: 0.771439850330353

02:44:41.366 --> 02:44:43.319 silencing directly just by looking

NOTE Confidence: 0.771439850330353

02:44:43.319 --> 02:44:44.648 at GSP fluorescence.

NOTE Confidence: 0.771439850330353

02:44:44.650 --> 02:44:46.869 So just to make things a little

NOTE Confidence: 0.771439850330353

02:44:46.869 --> 02:44:47.820 bit more complicated,

NOTE Confidence: 0.771439850330353

02:44:47.820 --> 02:44:49.735 also describe how this regulatory

NOTE Confidence: 0.771439850330353

02:44:49.735 --> 02:44:52.296 module works and this is in the

NOTE Confidence: 0.771439850330353

02:44:52.296 --> 02:44:54.616 allele just on the on the three prime

NOTE Confidence: 0.771439850330353

02:44:54.688 --> 02:44:56.800 end of the oleo and what it allows

NOTE Confidence: 0.771439850330353

02:44:56.800 --> 02:44:59.142 us to do is to really spatially and

NOTE Confidence: 0.771439850330353

02:44:59.142 --> 02:45:00.350 temporally controlled the antigen
NOTE Confidence: 0.771439850330353

02:45:00.406 --> 02:45:01.750 expression very carefully within
NOTE Confidence: 0.771439850330353

02:45:01.750 --> 02:45:03.766 genetic models and also within within
NOTE Confidence: 0.801616251468658

02:45:03.818 --> 02:45:05.258 self tissues into your models.
NOTE Confidence: 0.801616251468658

02:45:05.260 --> 02:45:07.546 So the idea here is we have a flip
NOTE Confidence: 0.801616251468658

02:45:07.546 --> 02:45:10.006 oh that's actually broken in half,
NOTE Confidence: 0.801616251468658

02:45:10.010 --> 02:45:12.075 much like the neoantigen I showed you
NOTE Confidence: 0.801616251468658

02:45:12.075 --> 02:45:14.128 was where you need Creamer comma.
NOTE Confidence: 0.801616251468658

02:45:14.130 --> 02:45:15.036 Nice to actually.
NOTE Confidence: 0.801616251468658

02:45:15.036 --> 02:45:16.848 Invert that the DNA to actually
NOTE Confidence: 0.801616251468658

02:45:16.848 --> 02:45:18.720 allow you to express the Flippo and
NOTE Confidence: 0.801616251468658

02:45:18.720 --> 02:45:20.428 then you need to give doxycycline
NOTE Confidence: 0.801616251468658

02:45:20.428 --> 02:45:22.336 and tamoxifen in order to allow
NOTE Confidence: 0.801616251468658

02:45:22.336 --> 02:45:24.435 this foot boat and then act on
NOTE Confidence: 0.801616251468658

02:45:24.435 --> 02:45:25.599 the neoantigen module itself.
NOTE Confidence: 0.801616251468658

02:45:25.600 --> 02:45:27.637 And when you do that you get

NOTE Confidence: 0.801616251468658
02:45:27.637 --> 02:45:28.510 that permanent recombination.
NOTE Confidence: 0.801616251468658
02:45:28.510 --> 02:45:30.214 Now this becomes a neoantigen express
NOTE Confidence: 0.801616251468658
02:45:30.214 --> 02:45:32.289 himself and so as Kelly alluded to,
NOTE Confidence: 0.801616251468658
02:45:32.290 --> 02:45:34.432 we recently published this so I won't
NOTE Confidence: 0.801616251468658
02:45:34.432 --> 02:45:36.572 go through the details of how the
NOTE Confidence: 0.801616251468658
02:45:36.572 --> 02:45:38.631 mouse model works or the paper really
NOTE Confidence: 0.801616251468658
02:45:38.631 --> 02:45:40.751 other than to say we spent quite a
NOTE Confidence: 0.801616251468658
02:45:40.751 --> 02:45:42.707 bit of effort in that model to show
NOTE Confidence: 0.801616251468658
02:45:42.707 --> 02:45:44.880 that you could get inducible de Novo
NOTE Confidence: 0.801616251468658
02:45:44.880 --> 02:45:46.625 Neoantigen expression that paper site.
NOTE Confidence: 0.801616251468658
02:45:46.630 --> 02:45:49.171 To show that you get Dinovo in
NOTE Confidence: 0.801616251468658
02:45:49.171 --> 02:45:50.260 these neoantigen expression,
NOTE Confidence: 0.801616251468658
02:45:50.260 --> 02:45:52.080 and that because of this,
NOTE Confidence: 0.801616251468658
02:45:52.080 --> 02:45:55.710 this system is being set up the way it is,
NOTE Confidence: 0.801616251468658
02:45:55.710 --> 02:45:58.080 there's really no tolerance prior to
NOTE Confidence: 0.801616251468658

02:45:58.080 --> 02:46:00.418 induction within the peripheral T cell pool,
NOTE Confidence: 0.801616251468658

02:46:00.420 --> 02:46:02.612 and so you get naive T cells that
NOTE Confidence: 0.801616251468658

02:46:02.612 --> 02:46:04.727 can make very robust responses
NOTE Confidence: 0.801616251468658

02:46:04.727 --> 02:46:06.227 against viral infection,
NOTE Confidence: 0.801616251468658

02:46:06.230 --> 02:46:08.050 just like a normal mouse.
NOTE Confidence: 0.801616251468658

02:46:08.050 --> 02:46:10.390 You really have an intact pre
NOTE Confidence: 0.801616251468658

02:46:10.390 --> 02:46:11.560 activation immune repertoire
NOTE Confidence: 0.801616251468658

02:46:11.560 --> 02:46:13.797 that you can study how those T
NOTE Confidence: 0.801616251468658

02:46:13.797 --> 02:46:15.670 cells in undergo these processes.
NOTE Confidence: 0.801616251468658

02:46:15.670 --> 02:46:16.657 Additionally we showed.
NOTE Confidence: 0.801616251468658

02:46:16.657 --> 02:46:18.302 Just through and fishing with
NOTE Confidence: 0.801616251468658

02:46:18.302 --> 02:46:19.680 viruses and that in code.
NOTE Confidence: 0.801616251468658

02:46:19.680 --> 02:46:21.396 Comments or flippo are also turning
NOTE Confidence: 0.801616251468658

02:46:21.396 --> 02:46:23.471 on an engine using genetic means that
NOTE Confidence: 0.801616251468658

02:46:23.471 --> 02:46:25.217 you could really nicely get robust
NOTE Confidence: 0.801616251468658

02:46:25.217 --> 02:46:27.254 T cell responses when you turn on

NOTE Confidence: 0.801616251468658
02:46:27.254 --> 02:46:29.265 antigens and that the T cells would
NOTE Confidence: 0.801616251468658
02:46:29.265 --> 02:46:31.035 home to specifically the site where
NOTE Confidence: 0.801616251468658
02:46:31.035 --> 02:46:33.291 you were where you were turning on the
NOTE Confidence: 0.801616251468658
02:46:33.291 --> 02:46:35.339 antigen so you have very good again.
NOTE Confidence: 0.801616251468658
02:46:35.340 --> 02:46:37.254 The spatial temporal control over over
NOTE Confidence: 0.801616251468658
02:46:37.254 --> 02:46:39.324 antigens in this model is very is
NOTE Confidence: 0.801616251468658
02:46:39.324 --> 02:46:41.046 one of the highlights really I think
NOTE Confidence: 0.801616251468658
02:46:41.100 --> 02:46:42.876 will enable a lot of applications,
NOTE Confidence: 0.801616251468658
02:46:42.880 --> 02:46:44.746 so there's a number of different
NOTE Confidence: 0.801616251468658
02:46:44.746 --> 02:46:46.572 applications and for people who are
NOTE Confidence: 0.801616251468658
02:46:46.572 --> 02:46:48.684 interested we put this mouse in Jackson so.
NOTE Confidence: 0.801616251468658
02:46:48.690 --> 02:46:50.690 There's a lot of access that it wouldn't
NOTE Confidence: 0.801616251468658
02:46:50.690 --> 02:46:53.069 when it becomes available for distribution.
NOTE Confidence: 0.801616251468658
02:46:53.070 --> 02:46:54.322 Everybody will have an
NOTE Confidence: 0.801616251468658
02:46:54.322 --> 02:46:55.574 opportunity to use this.
NOTE Confidence: 0.801616251468658

02:46:55.580 --> 02:46:57.025 If you think it's something
NOTE Confidence: 0.801616251468658

02:46:57.025 --> 02:46:59.020 that we use for your studies,
NOTE Confidence: 0.801616251468658

02:46:59.020 --> 02:47:01.204 we are very interested in two questions.
NOTE Confidence: 0.801616251468658

02:47:01.210 --> 02:47:02.466 The immune microenvironment associated
NOTE Confidence: 0.801616251468658

02:47:02.466 --> 02:47:04.350 with tumors in healthy cells function
NOTE Confidence: 0.801616251468658

02:47:04.392 --> 02:47:05.927 within different tumor types of
NOTE Confidence: 0.801616251468658

02:47:05.927 --> 02:47:07.155 different tumor micro environments.
NOTE Confidence: 0.801616251468658

02:47:07.160 --> 02:47:09.110 And then we're also very interested
NOTE Confidence: 0.801616251468658

02:47:09.110 --> 02:47:11.273 in how this process breaks down in
NOTE Confidence: 0.801616251468658

02:47:11.273 --> 02:47:13.448 the context of peripheral tolerance.
NOTE Confidence: 0.801616251468658

02:47:13.450 --> 02:47:16.210 So for the rest of the time I'm going to,
NOTE Confidence: 0.801616251468658

02:47:16.210 --> 02:47:17.904 I'm going to focus on the story
NOTE Confidence: 0.801616251468658

02:47:17.904 --> 02:47:19.250 that we've been developing.
NOTE Confidence: 0.801616251468658

02:47:19.250 --> 02:47:20.630 It's an unpublished story that's
NOTE Confidence: 0.801616251468658

02:47:20.630 --> 02:47:22.010 been spearheaded by Kelly Connelly,
NOTE Confidence: 0.801616251468658

02:47:22.010 --> 02:47:24.210 who's a postdoc in my in my lab,

NOTE Confidence: 0.801616251468658
02:47:24.210 --> 02:47:25.860 and she's she's been working on
NOTE Confidence: 0.801616251468658
02:47:25.860 --> 02:47:27.530 this for a couple of years.
NOTE Confidence: 0.801616251468658
02:47:27.530 --> 02:47:27.782 Also,
NOTE Confidence: 0.801616251468658
02:47:27.782 --> 02:47:28.790 collaborating with two very
NOTE Confidence: 0.801616251468658
02:47:28.790 --> 02:47:29.798 talented graduate students and
NOTE Confidence: 0.801616251468658
02:47:29.798 --> 02:47:30.839 smooth Krishnaswamy's group,
NOTE Confidence: 0.801616251468658
02:47:30.840 --> 02:47:32.220 these are folks doing really
NOTE Confidence: 0.801616251468658
02:47:32.220 --> 02:47:33.048 amazing bioinformatics work,
NOTE Confidence: 0.801616251468658
02:47:33.050 --> 02:47:34.724 and they've done all the bioinformatics
NOTE Confidence: 0.801616251468658
02:47:34.724 --> 02:47:36.629 that I'm going to tell you about.
NOTE Confidence: 0.801616251468658
02:47:36.630 --> 02:47:38.045 And when the questions that
NOTE Confidence: 0.801616251468658
02:47:38.045 --> 02:47:39.460 we were really interested in
NOTE Confidence: 0.814960479736328
02:47:39.518 --> 02:47:41.050 is, there's been a real Sergeant.
NOTE Confidence: 0.814960479736328
02:47:41.050 --> 02:47:42.430 Our understanding of T cell
NOTE Confidence: 0.814960479736328
02:47:42.430 --> 02:47:43.534 differentiation processes and how.
NOTE Confidence: 0.814960479736328

02:47:43.540 --> 02:47:45.580 Chronic Inogen and signals within
NOTE Confidence: 0.814960479736328

02:47:45.580 --> 02:47:47.620 tumors drive script drives that
NOTE Confidence: 0.814960479736328

02:47:47.685 --> 02:47:49.505 process and we're really interested
NOTE Confidence: 0.814960479736328

02:47:49.505 --> 02:47:52.064 in how this might work in the
NOTE Confidence: 0.814960479736328

02:47:52.064 --> 02:47:54.086 context of developing tumors and so.
NOTE Confidence: 0.814960479736328

02:47:54.090 --> 02:47:56.778 Rocky and others have really harped on this.
NOTE Confidence: 0.814960479736328

02:47:56.780 --> 02:47:57.758 This model here,
NOTE Confidence: 0.814960479736328

02:47:57.758 --> 02:48:00.448 so I'm not going to go into any
NOTE Confidence: 0.814960479736328

02:48:00.448 --> 02:48:02.779 real detail on it outside to say
NOTE Confidence: 0.814960479736328

02:48:02.779 --> 02:48:05.190 that the real the past three or
NOTE Confidence: 0.814960479736328

02:48:05.190 --> 02:48:07.508 four years have been a flurry of
NOTE Confidence: 0.814960479736328

02:48:07.508 --> 02:48:09.128 activity just describing how this
NOTE Confidence: 0.814960479736328

02:48:09.128 --> 02:48:11.531 process that was once thought of as
NOTE Confidence: 0.814960479736328

02:48:11.531 --> 02:48:12.907 a monolithic exhaustion process.
NOTE Confidence: 0.814960479736328

02:48:12.910 --> 02:48:14.790 Now we're starting to understand
NOTE Confidence: 0.814960479736328

02:48:14.790 --> 02:48:16.670 that there are multiple subsets

NOTE Confidence: 0.814960479736328
02:48:16.736 --> 02:48:18.619 of cells within the T cell pool,
NOTE Confidence: 0.814960479736328
02:48:18.620 --> 02:48:20.844 and then each of these T cells differ
NOTE Confidence: 0.814960479736328
02:48:20.844 --> 02:48:23.279 in terms of their potential to Mount
NOTE Confidence: 0.814960479736328
02:48:23.279 --> 02:48:25.700 responses and participate in the response.
NOTE Confidence: 0.814960479736328
02:48:25.700 --> 02:48:26.675 The exhausted cell,
NOTE Confidence: 0.814960479736328
02:48:26.675 --> 02:48:28.625 which is sort of a terminally
NOTE Confidence: 0.814960479736328
02:48:28.625 --> 02:48:30.075 differentiated so really has
NOTE Confidence: 0.814960479736328
02:48:30.075 --> 02:48:31.499 restricted its functional capacity,
NOTE Confidence: 0.814960479736328
02:48:31.500 --> 02:48:33.635 and I think the other thing that
NOTE Confidence: 0.814960479736328
02:48:33.635 --> 02:48:36.189 goes along with that is a restriction
NOTE Confidence: 0.814960479736328
02:48:36.189 --> 02:48:38.159 of proliferative capacity that make
NOTE Confidence: 0.814960479736328
02:48:38.159 --> 02:48:40.483 this cell not very good at terms
NOTE Confidence: 0.814960479736328
02:48:40.483 --> 02:48:42.068 in terms of fighting, fighting,
NOTE Confidence: 0.814960479736328
02:48:42.068 --> 02:48:43.082 infections, chronic infections,
NOTE Confidence: 0.814960479736328
02:48:43.082 --> 02:48:45.480 or in terms of fighting fighting tumors.
NOTE Confidence: 0.814960479736328

02:48:45.480 --> 02:48:46.844 It's associated, of course,
NOTE Confidence: 0.814960479736328

02:48:46.844 --> 02:48:48.890 with the up regulation of these.
NOTE Confidence: 0.814960479736328

02:48:48.890 --> 02:48:50.021 These checkpoint receptors,
NOTE Confidence: 0.814960479736328

02:48:50.021 --> 02:48:51.906 and also this down regulation
NOTE Confidence: 0.814960479736328

02:48:51.906 --> 02:48:54.559 of TCF one and so there there is
NOTE Confidence: 0.814960479736328

02:48:54.559 --> 02:48:56.179 also a positive population within
NOTE Confidence: 0.814960479736328

02:48:56.179 --> 02:48:57.499 the within the tumor.
NOTE Confidence: 0.814960479736328

02:48:57.500 --> 02:48:58.828 Or within the within,
NOTE Confidence: 0.814960479736328

02:48:58.828 --> 02:49:01.218 the chronic infection that is a stem
NOTE Confidence: 0.814960479736328

02:49:01.218 --> 02:49:03.174 like population were going to let
NOTE Confidence: 0.814960479736328

02:49:03.174 --> 02:49:05.549 this this TSL sometimes in this cell
NOTE Confidence: 0.814960479736328

02:49:05.549 --> 02:49:07.902 is marked by its expression of PD.
NOTE Confidence: 0.814960479736328

02:49:07.902 --> 02:49:09.662 One expression of slanted sticks
NOTE Confidence: 0.814960479736328

02:49:09.662 --> 02:49:11.909 and also its expression of TCF and
NOTE Confidence: 0.814960479736328

02:49:11.909 --> 02:49:13.715 so one of the elements about this
NOTE Confidence: 0.814960479736328

02:49:13.780 --> 02:49:15.690 process that I found particularly

NOTE Confidence: 0.814960479736328
02:49:15.690 --> 02:49:17.600 fascinating is that the signals
NOTE Confidence: 0.814960479736328
02:49:17.600 --> 02:49:19.358 here that are potentially going to
NOTE Confidence: 0.814960479736328
02:49:19.358 --> 02:49:20.955 drive this process of exhaustion
NOTE Confidence: 0.814960479736328
02:49:20.955 --> 02:49:22.439 of terminal differentiation or
NOTE Confidence: 0.814960479736328
02:49:22.439 --> 02:49:24.294 chronic antigen and TGF beta.
NOTE Confidence: 0.814960479736328
02:49:24.300 --> 02:49:26.330 And these are signals are very highly
NOTE Confidence: 0.814960479736328
02:49:26.330 --> 02:49:28.409 expressed within the tumor microenvironment.
NOTE Confidence: 0.814960479736328
02:49:28.410 --> 02:49:32.036 And there's been work from several groups,
NOTE Confidence: 0.814960479736328
02:49:32.040 --> 02:49:34.120 including including this Snyder
NOTE Confidence: 0.814960479736328
02:49:34.120 --> 02:49:36.200 paper here and also.
NOTE Confidence: 0.814960479736328
02:49:36.200 --> 02:49:38.456 The sticky paper from from warehouse
NOTE Confidence: 0.814960479736328
02:49:38.456 --> 02:49:40.529 group that really highlighted the idea
NOTE Confidence: 0.814960479736328
02:49:40.529 --> 02:49:42.577 that T cells these stem like T cells
NOTE Confidence: 0.814960479736328
02:49:42.580 --> 02:49:44.812 really need to be inside tumors in
NOTE Confidence: 0.814960479736328
02:49:44.812 --> 02:49:46.402 order to mediate therapeutic effects,
NOTE Confidence: 0.814960479736328

02:49:46.410 --> 02:49:48.108 and this makes sense because we
NOTE Confidence: 0.814960479736328

02:49:48.108 --> 02:49:49.678 know that the micro environment
NOTE Confidence: 0.814960479736328

02:49:49.678 --> 02:49:51.190 has expression of PDL,
NOTE Confidence: 0.814960479736328

02:49:51.190 --> 02:49:52.918 one on tumor in this correlates
NOTE Confidence: 0.814960479736328

02:49:52.918 --> 02:49:54.494 with outcomes expression on immune
NOTE Confidence: 0.814960479736328

02:49:54.494 --> 02:49:55.978 cells that correlated outcomes.
NOTE Confidence: 0.814960479736328

02:49:55.980 --> 02:49:57.982 So the thought is that the the
NOTE Confidence: 0.814960479736328

02:49:57.982 --> 02:49:59.628 antitumor effect is really mediated
NOTE Confidence: 0.814960479736328

02:49:59.628 --> 02:50:01.080 from within the tumor.
NOTE Confidence: 0.814960479736328

02:50:01.080 --> 02:50:02.922 That suggests that the stem like
NOTE Confidence: 0.814960479736328

02:50:02.922 --> 02:50:04.590 cells are in the tumor.
NOTE Confidence: 0.814960479736328

02:50:04.590 --> 02:50:06.816 But again, this chronic antigen should be.
NOTE Confidence: 0.814960479736328

02:50:06.820 --> 02:50:08.104 It should be deleterious.
NOTE Confidence: 0.814960479736328

02:50:08.104 --> 02:50:09.709 Because the big question is,
NOTE Confidence: 0.814960479736328

02:50:09.710 --> 02:50:11.996 this process should be driving terminal
NOTE Confidence: 0.814960479736328

02:50:11.996 --> 02:50:14.089 exhaustion of these cells and of

NOTE Confidence: 0.814960479736328
02:50:14.089 --> 02:50:16.105 course in a short term this is fine,
NOTE Confidence: 0.814960479736328
02:50:16.110 --> 02:50:17.670 but because tumors develop over
NOTE Confidence: 0.814960479736328
02:50:17.670 --> 02:50:19.630 the course of months or years,
NOTE Confidence: 0.814960479736328
02:50:19.630 --> 02:50:22.014 the big question we had with how do
NOTE Confidence: 0.814960479736328
02:50:22.014 --> 02:50:23.923 you maintain this dim light population
NOTE Confidence: 0.814960479736328
02:50:23.923 --> 02:50:26.350 in the face of all these signals,
NOTE Confidence: 0.814960479736328
02:50:26.350 --> 02:50:27.785 that should drive its exhaustion
NOTE Confidence: 0.814960479736328
02:50:27.785 --> 02:50:29.220 and so to try and
NOTE Confidence: 0.832723557949066
02:50:29.284 --> 02:50:31.468 understand this we used another model.
NOTE Confidence: 0.832723557949066
02:50:31.470 --> 02:50:33.577 We cross our ninja mice to another
NOTE Confidence: 0.832723557949066
02:50:33.577 --> 02:50:35.927 model that we was familiar with from
NOTE Confidence: 0.832723557949066
02:50:35.927 --> 02:50:37.997 working in Tyler Jackson Lab and
NOTE Confidence: 0.832723557949066
02:50:38.065 --> 02:50:40.200 this is called the care SP3 model.
NOTE Confidence: 0.832723557949066
02:50:40.200 --> 02:50:42.790 It's a great model for studying lung
NOTE Confidence: 0.832723557949066
02:50:42.790 --> 02:50:44.671 adenocarcinoma in other tumor types
NOTE Confidence: 0.832723557949066

02:50:44.671 --> 02:50:46.795 that are driven by oncogenic kras.
NOTE Confidence: 0.832723557949066

02:50:46.800 --> 02:50:49.401 So the idea here is we give a Cree
NOTE Confidence: 0.832723557949066

02:50:49.401 --> 02:50:51.690 expressing adeno or lentivirus and this
NOTE Confidence: 0.832723557949066

02:50:51.690 --> 02:50:53.974 acts on genetic elements within lung
NOTE Confidence: 0.832723557949066

02:50:53.974 --> 02:50:56.286 cells and so we have a oncogenic form
NOTE Confidence: 0.832723557949066

02:50:56.286 --> 02:50:58.708 of care SG-12 deform but also have two
NOTE Confidence: 0.832723557949066

02:50:58.708 --> 02:51:01.138 flocks copies of the tumor suppressor P53.
NOTE Confidence: 0.832723557949066

02:51:01.140 --> 02:51:03.191 When you give Cree you activate chaos
NOTE Confidence: 0.832723557949066

02:51:03.191 --> 02:51:05.396 and droopy 53 in this single transform
NOTE Confidence: 0.832723557949066

02:51:05.396 --> 02:51:07.709 cell will now develop over the course
NOTE Confidence: 0.832723557949066

02:51:07.709 --> 02:51:10.201 of several months through a variety of
NOTE Confidence: 0.832723557949066

02:51:10.201 --> 02:51:12.100 different stages that mirror the stages
NOTE Confidence: 0.832723557949066

02:51:12.100 --> 02:51:13.870 that happen in patients who develop
NOTE Confidence: 0.832723557949066

02:51:13.925 --> 02:51:15.810 long adenocarcinoma and these stages.
NOTE Confidence: 0.832723557949066

02:51:15.810 --> 02:51:17.022 Now we can understand.
NOTE Confidence: 0.832723557949066

02:51:17.022 --> 02:51:18.840 How the immune system interacts with

NOTE Confidence: 0.832723557949066

02:51:18.894 --> 02:51:20.589 these tumors at different stages,

NOTE Confidence: 0.832723557949066

02:51:20.590 --> 02:51:23.131 and so we've we've introduced into this

NOTE Confidence: 0.832723557949066

02:51:23.131 --> 02:51:25.406 system using using the ninja leal the

NOTE Confidence: 0.832723557949066

02:51:25.406 --> 02:51:27.448 ability now to turn on you antigens

NOTE Confidence: 0.832723557949066

02:51:27.448 --> 02:51:30.031 in this tumor and the way we do that,

NOTE Confidence: 0.832723557949066

02:51:30.040 --> 02:51:30.331 again,

NOTE Confidence: 0.832723557949066

02:51:30.331 --> 02:51:32.368 is that when we give creepy poise

NOTE Confidence: 0.832723557949066

02:51:32.368 --> 02:51:34.672 this and then we treat them isa

NOTE Confidence: 0.832723557949066

02:51:34.672 --> 02:51:36.332 few weeks later with doxycycline,

NOTE Confidence: 0.832723557949066

02:51:36.340 --> 02:51:38.218 tamoxifen and this delay in treatment

NOTE Confidence: 0.832723557949066

02:51:38.218 --> 02:51:40.846 is really just do just to allow us to

NOTE Confidence: 0.832723557949066

02:51:40.846 --> 02:51:42.939 clear all these effects of the infection

NOTE Confidence: 0.832723557949066

02:51:42.939 --> 02:51:45.466 associated with turning on the tumor genes.

NOTE Confidence: 0.832723557949066

02:51:45.470 --> 02:51:47.290 And when we do this process we

NOTE Confidence: 0.832723557949066

02:51:47.290 --> 02:51:49.303 actually see a pretty big change

NOTE Confidence: 0.832723557949066

02:51:49.303 --> 02:51:50.859 within the tumors themselves.
NOTE Confidence: 0.832723557949066

02:51:50.860 --> 02:51:53.236 So this is what we call KP tumor,
NOTE Confidence: 0.832723557949066

02:51:53.240 --> 02:51:55.186 so it doesn't have neoantigens and this
NOTE Confidence: 0.832723557949066

02:51:55.186 --> 02:51:57.418 is sort of your classic cold tumor.
NOTE Confidence: 0.832723557949066

02:51:57.420 --> 02:51:59.232 There's really it's an immune desert
NOTE Confidence: 0.832723557949066

02:51:59.232 --> 02:52:01.590 in terms of T cells and B cells.
NOTE Confidence: 0.832723557949066

02:52:01.590 --> 02:52:03.669 Almost none of them in this tumor.
NOTE Confidence: 0.832723557949066

02:52:03.670 --> 02:52:03.939 In.
NOTE Confidence: 0.832723557949066

02:52:03.939 --> 02:52:04.477 In contrast,
NOTE Confidence: 0.832723557949066

02:52:04.477 --> 02:52:06.709 if you look at a KP ninja tumor
NOTE Confidence: 0.832723557949066

02:52:06.709 --> 02:52:08.401 and this is just showing you
NOTE Confidence: 0.832723557949066

02:52:08.401 --> 02:52:10.530 an 8 week keeping into tumor,
NOTE Confidence: 0.832723557949066

02:52:10.530 --> 02:52:12.742 you see that this tumor is very
NOTE Confidence: 0.832723557949066

02:52:12.742 --> 02:52:14.400 heavily infiltrated by by T cells.
NOTE Confidence: 0.832723557949066

02:52:14.400 --> 02:52:16.182 This is a very robust and
NOTE Confidence: 0.832723557949066

02:52:16.182 --> 02:52:17.073 high penetrance phenotype.

NOTE Confidence: 0.832723557949066

02:52:17.080 --> 02:52:18.475 Almost every every tumor at

NOTE Confidence: 0.832723557949066

02:52:18.475 --> 02:52:20.244 this time point is very heavily

NOTE Confidence: 0.832723557949066

02:52:20.244 --> 02:52:22.449 infiltrated by T cells in this manner.

NOTE Confidence: 0.832723557949066

02:52:22.450 --> 02:52:24.298 So just by turning on antigens

NOTE Confidence: 0.832723557949066

02:52:24.298 --> 02:52:25.222 within the tumor,

NOTE Confidence: 0.832723557949066

02:52:25.230 --> 02:52:27.282 we can actually elicit a very

NOTE Confidence: 0.832723557949066

02:52:27.282 --> 02:52:29.055 robust response that turns the

NOTE Confidence: 0.832723557949066

02:52:29.055 --> 02:52:31.095 macro environment from cold to hot.

NOTE Confidence: 0.832723557949066

02:52:31.100 --> 02:52:32.033 That's very exciting.

NOTE Confidence: 0.832723557949066

02:52:32.033 --> 02:52:33.899 'cause it allows us to study

NOTE Confidence: 0.832723557949066

02:52:33.899 --> 02:52:35.489 how this process happens.

NOTE Confidence: 0.832723557949066

02:52:35.490 --> 02:52:36.348 And of course,

NOTE Confidence: 0.832723557949066

02:52:36.348 --> 02:52:37.206 as I mentioned,

NOTE Confidence: 0.832723557949066

02:52:37.210 --> 02:52:38.640 we're putting in own neoantigen,

NOTE Confidence: 0.832723557949066

02:52:38.640 --> 02:52:40.440 since this system so that allows us to

NOTE Confidence: 0.832723557949066

02:52:40.440 --> 02:52:42.257 now look at the tetramer specific cells
NOTE Confidence: 0.832723557949066

02:52:42.257 --> 02:52:44.407 within the tumor and try and understand
NOTE Confidence: 0.832723557949066

02:52:44.407 --> 02:52:46.357 their differentiation at different stages,
NOTE Confidence: 0.832723557949066

02:52:46.360 --> 02:52:47.785 because the tumors are extremely
NOTE Confidence: 0.832723557949066

02:52:47.785 --> 02:52:48.925 small at these stages,
NOTE Confidence: 0.832723557949066

02:52:48.930 --> 02:52:50.604 we can isolate them and then
NOTE Confidence: 0.832723557949066

02:52:50.604 --> 02:52:52.359 and then purify out the cells.
NOTE Confidence: 0.832723557949066

02:52:52.360 --> 02:52:54.362 So we need a technique to identify
NOTE Confidence: 0.832723557949066

02:52:54.362 --> 02:52:56.080 which cells are in that issue,
NOTE Confidence: 0.832723557949066

02:52:56.080 --> 02:52:57.977 and so we've been using this intravascular
NOTE Confidence: 0.832723557949066

02:52:57.977 --> 02:52:59.681 technique that a number of groups
NOTE Confidence: 0.832723557949066

02:52:59.681 --> 02:53:01.361 have used where we inject labeled
NOTE Confidence: 0.832723557949066

02:53:01.361 --> 02:53:02.660 antibodies into the circulation.
NOTE Confidence: 0.832723557949066

02:53:02.660 --> 02:53:04.442 This labels the cells in the
NOTE Confidence: 0.832723557949066

02:53:04.442 --> 02:53:05.630 circulation and the cells
NOTE Confidence: 0.83006227016449

02:53:05.685 --> 02:53:07.468 that are in that issue, or protected.

NOTE Confidence: 0.83006227016449

02:53:07.468 --> 02:53:09.540 And what you can see from this graph

NOTE Confidence: 0.83006227016449

02:53:09.596 --> 02:53:11.620 here is that when we don't have tumors,

NOTE Confidence: 0.83006227016449

02:53:11.620 --> 02:53:13.132 so this is a mouse that's

NOTE Confidence: 0.83006227016449

02:53:13.132 --> 02:53:14.420 induced in the same way,

NOTE Confidence: 0.83006227016449

02:53:14.420 --> 02:53:15.436 but doesn't have crashed,

NOTE Confidence: 0.83006227016449

02:53:15.436 --> 02:53:16.960 so it can't form a tumor.

NOTE Confidence: 0.83006227016449

02:53:16.960 --> 02:53:18.478 You don't really get any sells.

NOTE Confidence: 0.83006227016449

02:53:18.480 --> 02:53:20.010 It looks like a V6 months.

NOTE Confidence: 0.83006227016449

02:53:20.010 --> 02:53:22.305 You don't really get any cells that go into

NOTE Confidence: 0.83006227016449

02:53:22.305 --> 02:53:24.573 the into the lung tissue in CDA T cells.

NOTE Confidence: 0.83006227016449

02:53:24.580 --> 02:53:26.380 In contrast, when you have a tumor now

NOTE Confidence: 0.83006227016449

02:53:26.380 --> 02:53:28.530 you see that there are a number of CD8T

NOTE Confidence: 0.83006227016449

02:53:28.530 --> 02:53:30.169 cells within the micro environment,

NOTE Confidence: 0.83006227016449

02:53:30.170 --> 02:53:32.194 so that between the two lung tumor tissue,

NOTE Confidence: 0.83006227016449

02:53:32.200 --> 02:53:34.280 which was a nice way of just confirming

NOTE Confidence: 0.83006227016449

02:53:34.280 --> 02:53:36.004 that these T cells are going to
NOTE Confidence: 0.83006227016449

02:53:36.004 --> 02:53:37.570 the long because of the Tuners.
NOTE Confidence: 0.83006227016449

02:53:37.570 --> 02:53:39.834 From these we can get on touch more
NOTE Confidence: 0.83006227016449

02:53:39.834 --> 02:53:41.433 specific cells which would be 333
NOTE Confidence: 0.83006227016449

02:53:41.433 --> 02:53:43.239 loaded and a C class one tetramers
NOTE Confidence: 0.83006227016449

02:53:43.239 --> 02:53:45.503 and we can look at the phenotypes of
NOTE Confidence: 0.83006227016449

02:53:45.503 --> 02:53:47.428 the cells that are within the tumor.
NOTE Confidence: 0.83006227016449

02:53:47.430 --> 02:53:49.187 And here we're just we're getting on
NOTE Confidence: 0.83006227016449

02:53:49.187 --> 02:53:51.275 PD one ansi and TCF one and looking
NOTE Confidence: 0.83006227016449

02:53:51.275 --> 02:53:53.219 at looking for these stem like cells
NOTE Confidence: 0.83006227016449

02:53:53.219 --> 02:53:55.037 which are marked by their dual
NOTE Confidence: 0.83006227016449

02:53:55.037 --> 02:53:56.845 expression about TCF and PD one and
NOTE Confidence: 0.83006227016449

02:53:56.845 --> 02:53:59.037 what you can see is both at early
NOTE Confidence: 0.83006227016449

02:53:59.037 --> 02:54:01.200 time points and at late time points
NOTE Confidence: 0.83006227016449

02:54:01.263 --> 02:54:03.657 there is a robust population of these.
NOTE Confidence: 0.83006227016449

02:54:03.660 --> 02:54:05.305 These TCF one PD one positive cells

NOTE Confidence: 0.83006227016449

02:54:05.305 --> 02:54:07.387 and that they are maintained even even

NOTE Confidence: 0.83006227016449

02:54:07.387 --> 02:54:09.373 several months after we've initiated tumors.

NOTE Confidence: 0.83006227016449

02:54:09.380 --> 02:54:11.006 These tumors still contain these cells

NOTE Confidence: 0.83006227016449

02:54:11.006 --> 02:54:12.731 and what we were particularly intrigued

NOTE Confidence: 0.83006227016449

02:54:12.731 --> 02:54:14.796 was by was when we started looking

NOTE Confidence: 0.83006227016449

02:54:14.796 --> 02:54:16.491 at the tumor draining lymph node.

NOTE Confidence: 0.83006227016449

02:54:16.491 --> 02:54:18.750 When we saw that there was a very large

NOTE Confidence: 0.83006227016449

02:54:18.809 --> 02:54:20.819 population of these stem like cells.

NOTE Confidence: 0.83006227016449

02:54:20.820 --> 02:54:21.392 In fact,

NOTE Confidence: 0.83006227016449

02:54:21.392 --> 02:54:23.680 almost all the cells within the lymph node,

NOTE Confidence: 0.83006227016449

02:54:23.680 --> 02:54:25.816 both at the early time point an at

NOTE Confidence: 0.83006227016449

02:54:25.816 --> 02:54:27.632 the late time point are expressing

NOTE Confidence: 0.83006227016449

02:54:27.632 --> 02:54:30.307 this TCF one and PD one and again I

NOTE Confidence: 0.83006227016449

02:54:30.307 --> 02:54:32.226 just want to remind you everything I'm

NOTE Confidence: 0.83006227016449

02:54:32.226 --> 02:54:34.274 going to show you from this point on

NOTE Confidence: 0.83006227016449

02:54:34.274 --> 02:54:36.627 is gated on Antigen specific T cells.
NOTE Confidence: 0.83006227016449

02:54:36.630 --> 02:54:38.583 So these are all specific to the
NOTE Confidence: 0.83006227016449

02:54:38.583 --> 02:54:39.420 to the tumors,
NOTE Confidence: 0.83006227016449

02:54:39.420 --> 02:54:40.980 yet they're located in the draining
NOTE Confidence: 0.83006227016449

02:54:40.980 --> 02:54:42.770 lymph nodes in terms of numerically,
NOTE Confidence: 0.83006227016449

02:54:42.770 --> 02:54:44.165 if we quantitate the number
NOTE Confidence: 0.83006227016449

02:54:44.165 --> 02:54:45.560 of cells you can see,
NOTE Confidence: 0.83006227016449

02:54:45.560 --> 02:54:47.639 there's about the same number of total
NOTE Confidence: 0.83006227016449

02:54:47.639 --> 02:54:50.015 GP 33 cells at both times in in the,
NOTE Confidence: 0.83006227016449

02:54:50.020 --> 02:54:52.522 in the lymph node in the in the tumor.
NOTE Confidence: 0.83006227016449

02:54:52.530 --> 02:54:54.216 But there's a big increase until
NOTE Confidence: 0.83006227016449

02:54:54.216 --> 02:54:56.160 in the total number of these stem,
NOTE Confidence: 0.83006227016449

02:54:56.160 --> 02:54:58.106 like cells within the draining lymph nodes,
NOTE Confidence: 0.83006227016449

02:54:58.110 --> 02:54:59.784 suggesting maybe these cells are could
NOTE Confidence: 0.83006227016449

02:54:59.784 --> 02:55:01.738 be could be important in this location.
NOTE Confidence: 0.83006227016449

02:55:01.740 --> 02:55:03.749 The other point that we noted from

NOTE Confidence: 0.83006227016449
02:55:03.749 --> 02:55:05.468 this very early analysis was that
NOTE Confidence: 0.83006227016449
02:55:05.468 --> 02:55:06.793 the T cells in the.
NOTE Confidence: 0.83006227016449
02:55:06.800 --> 02:55:08.634 The tumor really seems to be the
NOTE Confidence: 0.83006227016449
02:55:08.634 --> 02:55:10.483 only ones these TCF one low sells
NOTE Confidence: 0.83006227016449
02:55:10.483 --> 02:55:12.354 really seemed to be the only ones
NOTE Confidence: 0.83006227016449
02:55:12.354 --> 02:55:14.190 upregulating Tim 3 which is that
NOTE Confidence: 0.83006227016449
02:55:14.190 --> 02:55:15.385 marker of terminal exhaustion?
NOTE Confidence: 0.83006227016449
02:55:15.385 --> 02:55:17.310 the T cells in the lymph node
NOTE Confidence: 0.83006227016449
02:55:17.310 --> 02:55:18.170 aren't doing this.
NOTE Confidence: 0.83006227016449
02:55:18.170 --> 02:55:19.262 Many of the populations,
NOTE Confidence: 0.83006227016449
02:55:19.262 --> 02:55:21.226 and also when we look at the
NOTE Confidence: 0.83006227016449
02:55:21.226 --> 02:55:22.846 T cells within the lymph node,
NOTE Confidence: 0.83006227016449
02:55:22.850 --> 02:55:24.775 they seem to have a very robust
NOTE Confidence: 0.83006227016449
02:55:24.775 --> 02:55:25.600 stem like phenotype,
NOTE Confidence: 0.789013981819153
02:55:25.600 --> 02:55:27.518 so they're all expressing slam up six.
NOTE Confidence: 0.789013981819153

02:55:27.520 --> 02:55:29.445 Another marker of stem like T cells,
NOTE Confidence: 0.789013981819153

02:55:29.450 --> 02:55:31.645 and we look for function. We actually see.
NOTE Confidence: 0.789013981819153

02:55:31.645 --> 02:55:33.295 These cells are are very functional.
NOTE Confidence: 0.789013981819153

02:55:33.300 --> 02:55:35.739 We can. We can send them with peptide and
NOTE Confidence: 0.789013981819153

02:55:35.739 --> 02:55:38.190 see the majority of the cells that are in
NOTE Confidence: 0.789013981819153

02:55:38.190 --> 02:55:40.996 the in the in the tumor in the lymph node
NOTE Confidence: 0.789013981819153

02:55:40.996 --> 02:55:42.954 are capable of producing T Interferon,
NOTE Confidence: 0.789013981819153

02:55:42.954 --> 02:55:45.684 whereas only a fraction of the T cells
NOTE Confidence: 0.789013981819153

02:55:45.684 --> 02:55:47.644 in the tumor are capable of this.
NOTE Confidence: 0.789013981819153

02:55:47.650 --> 02:55:50.152 So try and get a better handle on
NOTE Confidence: 0.789013981819153

02:55:50.152 --> 02:55:52.030 what's going on with these populations.
NOTE Confidence: 0.789013981819153

02:55:52.030 --> 02:55:53.878 We perform single cell RNA seq
NOTE Confidence: 0.789013981819153

02:55:53.878 --> 02:55:55.790 and we also perform PCR seeks,
NOTE Confidence: 0.789013981819153

02:55:55.790 --> 02:55:57.974 so we're looking at the endogenous GP.
NOTE Confidence: 0.789013981819153

02:55:57.980 --> 02:55:59.232 33 specific styles identified
NOTE Confidence: 0.789013981819153

02:55:59.232 --> 02:56:01.110 with me to class one tetramers,

NOTE Confidence: 0.789013981819153
02:56:01.110 --> 02:56:03.870 and then we've used a technique with smooth
NOTE Confidence: 0.789013981819153
02:56:03.870 --> 02:56:06.427 at least meet his lab to try and Co.
NOTE Confidence: 0.789013981819153
02:56:06.430 --> 02:56:07.312 Embed the secret.
NOTE Confidence: 0.789013981819153
02:56:07.312 --> 02:56:09.832 Are they seek data and try and compare
NOTE Confidence: 0.789013981819153
02:56:09.832 --> 02:56:12.196 things using a technique called fate,
NOTE Confidence: 0.789013981819153
02:56:12.200 --> 02:56:14.294 but which allows us to understand
NOTE Confidence: 0.789013981819153
02:56:14.294 --> 02:56:15.690 the trajectory of differentiation
NOTE Confidence: 0.789013981819153
02:56:15.751 --> 02:56:17.366 very nicely and visualize that.
NOTE Confidence: 0.789013981819153
02:56:17.370 --> 02:56:19.062 I'm going to show you some
NOTE Confidence: 0.789013981819153
02:56:19.062 --> 02:56:20.190 some fake plots here.
NOTE Confidence: 0.789013981819153
02:56:20.190 --> 02:56:22.233 The 1st I'm going to show you is 1
NOTE Confidence: 0.789013981819153
02:56:22.233 --> 02:56:24.114 where we're comparing 17 weak lungs
NOTE Confidence: 0.789013981819153
02:56:24.114 --> 02:56:26.110 and 17 week draining lymph nodes.
NOTE Confidence: 0.789013981819153
02:56:26.110 --> 02:56:27.818 And when you put these together into
NOTE Confidence: 0.789013981819153
02:56:27.818 --> 02:56:29.892 the same plot you can actually very
NOTE Confidence: 0.789013981819153

02:56:29.892 --> 02:56:31.180 nicely detect different populations
NOTE Confidence: 0.789013981819153

02:56:31.180 --> 02:56:32.956 and I've just highlighted why we're
NOTE Confidence: 0.789013981819153

02:56:32.956 --> 02:56:34.828 going to call naive and stem like
NOTE Confidence: 0.789013981819153

02:56:34.828 --> 02:56:36.634 an exhaustion based on based on a
NOTE Confidence: 0.789013981819153

02:56:36.634 --> 02:56:38.451 handful of markers and what's really
NOTE Confidence: 0.789013981819153

02:56:38.451 --> 02:56:40.006 interesting about this is when
NOTE Confidence: 0.789013981819153

02:56:40.006 --> 02:56:41.895 we look at the lymph node cells,
NOTE Confidence: 0.789013981819153

02:56:41.900 --> 02:56:43.592 they all fall more towards this
NOTE Confidence: 0.789013981819153

02:56:43.592 --> 02:56:44.720 side of being stemlike,
NOTE Confidence: 0.789013981819153

02:56:44.720 --> 02:56:46.856 whereas the cells within the tumor fall more
NOTE Confidence: 0.789013981819153

02:56:46.856 --> 02:56:48.757 towards this exhaustion process and this.
NOTE Confidence: 0.789013981819153

02:56:48.760 --> 02:56:49.846 Eternally exhausted state,
NOTE Confidence: 0.789013981819153

02:56:49.846 --> 02:56:52.018 and this suggests that the signals
NOTE Confidence: 0.789013981819153

02:56:52.018 --> 02:56:54.510 that are the T cells are that are
NOTE Confidence: 0.789013981819153

02:56:54.510 --> 02:56:56.115 driving exhaustion really are being
NOTE Confidence: 0.789013981819153

02:56:56.115 --> 02:56:57.760 received and driving this process

NOTE Confidence: 0.789013981819153
02:56:57.760 --> 02:56:59.340 within the tumor consistent with
NOTE Confidence: 0.789013981819153
02:56:59.340 --> 02:57:01.405 what we saw with the facts analysis
NOTE Confidence: 0.789013981819153
02:57:01.405 --> 02:57:02.972 using an unbiased technique called
NOTE Confidence: 0.789013981819153
02:57:02.972 --> 02:57:04.802 pseudo time which allows us to
NOTE Confidence: 0.789013981819153
02:57:04.857 --> 02:57:06.408 draw developmental trajectory.
NOTE Confidence: 0.789013981819153
02:57:06.410 --> 02:57:08.734 You can actually see that these stem,
NOTE Confidence: 0.789013981819153
02:57:08.740 --> 02:57:11.183 like cells are the ones that are
NOTE Confidence: 0.789013981819153
02:57:11.183 --> 02:57:12.616 turning into creatively these
NOTE Confidence: 0.789013981819153
02:57:12.616 --> 02:57:14.524 exhausted cells and this is shown
NOTE Confidence: 0.789013981819153
02:57:14.524 --> 02:57:16.728 both by the plot here and then.
NOTE Confidence: 0.789013981819153
02:57:16.730 --> 02:57:19.145 Also very nicely visualized by the histogram.
NOTE Confidence: 0.789013981819153
02:57:19.150 --> 02:57:20.865 The low the long sales are are
NOTE Confidence: 0.789013981819153
02:57:20.865 --> 02:57:22.045 really much more developmentally
NOTE Confidence: 0.789013981819153
02:57:22.045 --> 02:57:23.617 differentiate more mentally advanced
NOTE Confidence: 0.789013981819153
02:57:23.617 --> 02:57:26.399 compared to the cells in the lymph node.
NOTE Confidence: 0.789013981819153

02:57:26.400 --> 02:57:28.318 And these are the same cells 'cause
NOTE Confidence: 0.789013981819153

02:57:28.318 --> 02:57:29.860 we did PCR sequencing.
NOTE Confidence: 0.789013981819153

02:57:29.860 --> 02:57:31.624 We've actually looked to show that
NOTE Confidence: 0.789013981819153

02:57:31.624 --> 02:57:33.551 the cells within the tumor within
NOTE Confidence: 0.789013981819153

02:57:33.551 --> 02:57:35.286 the lymph node are developmentally
NOTE Confidence: 0.789013981819153

02:57:35.286 --> 02:57:37.236 the precursors of the cells within
NOTE Confidence: 0.789013981819153

02:57:37.236 --> 02:57:38.364 the within the lung.
NOTE Confidence: 0.789013981819153

02:57:38.370 --> 02:57:40.568 And we know this because these are.
NOTE Confidence: 0.789013981819153

02:57:40.570 --> 02:57:42.775 They have the same Alpha beta chains,
NOTE Confidence: 0.789013981819153

02:57:42.780 --> 02:57:45.150 so we can actually track those
NOTE Confidence: 0.789013981819153

02:57:45.150 --> 02:57:46.730 cells between these locations.
NOTE Confidence: 0.789013981819153

02:57:46.730 --> 02:57:48.515 So one of the other elements that
NOTE Confidence: 0.789013981819153

02:57:48.515 --> 02:57:50.360 I'm going to show you is about
NOTE Confidence: 0.789013981819153

02:57:50.360 --> 02:57:52.211 comparing the T cells in the tumor's
NOTE Confidence: 0.789013981819153

02:57:52.211 --> 02:57:54.299 and then in the lymph nodes to show
NOTE Confidence: 0.789013981819153

02:57:54.299 --> 02:57:55.604 you how different the developmental

NOTE Confidence: 0.789013981819153

02:57:55.604 --> 02:57:56.909 trajectory of this house is.

NOTE Confidence: 0.789013981819153

02:57:56.910 --> 02:57:58.611 So if we compare T cells within

NOTE Confidence: 0.789013981819153

02:57:58.611 --> 02:57:59.340 the context of

NOTE Confidence: 0.819144248962402

02:57:59.394 --> 02:58:01.347 the of the draining within the tumor,

NOTE Confidence: 0.819144248962402

02:58:01.350 --> 02:58:03.249 what you can see is that those T cells

NOTE Confidence: 0.819144248962402

02:58:03.249 --> 02:58:05.064 that are from an early time point in

NOTE Confidence: 0.819144248962402

02:58:05.064 --> 02:58:06.460 the tumor are developmentally less

NOTE Confidence: 0.819144248962402

02:58:06.460 --> 02:58:08.155 differentiated than the ones when

NOTE Confidence: 0.819144248962402

02:58:08.155 --> 02:58:10.445 you look later and you can see this

NOTE Confidence: 0.819144248962402

02:58:10.445 --> 02:58:12.310 both in terms of where they are,

NOTE Confidence: 0.819144248962402

02:58:12.310 --> 02:58:13.876 where they are sitting in terms

NOTE Confidence: 0.819144248962402

02:58:13.876 --> 02:58:14.398 of populations.

NOTE Confidence: 0.819144248962402

02:58:14.400 --> 02:58:16.480 You can also see this by pseudo time.

NOTE Confidence: 0.819144248962402

02:58:16.480 --> 02:58:17.492 The majority of the.

NOTE Confidence: 0.819144248962402

02:58:17.492 --> 02:58:19.010 Late to ourselves or are actually

NOTE Confidence: 0.819144248962402

02:58:19.061 --> 02:58:20.441 within this within this dance
NOTE Confidence: 0.819144248962402

02:58:20.441 --> 02:58:21.821 cluster and this makes sense.
NOTE Confidence: 0.819144248962402

02:58:21.830 --> 02:58:23.437 We actually know in this model
NOTE Confidence: 0.819144248962402

02:58:23.437 --> 02:58:25.194 something from a previous version that
NOTE Confidence: 0.819144248962402

02:58:25.194 --> 02:58:27.102 we've confirmed in our model that
NOTE Confidence: 0.819144248962402

02:58:27.102 --> 02:58:28.144 essentially the micro environment
NOTE Confidence: 0.819144248962402

02:58:28.144 --> 02:58:30.263 goes from a very hot to a very cold
NOTE Confidence: 0.819144248962402

02:58:30.263 --> 02:58:32.279 environment and you can see an early tumor.
NOTE Confidence: 0.819144248962402

02:58:32.280 --> 02:58:34.200 There's a lot of these CD 3 positive
NOTE Confidence: 0.819144248962402

02:58:34.200 --> 02:58:35.760 cells within the tumor parenchyma.
NOTE Confidence: 0.819144248962402

02:58:35.760 --> 02:58:37.636 If you look at a later tumor,
NOTE Confidence: 0.819144248962402

02:58:37.640 --> 02:58:39.248 you actually don't see very many
NOTE Confidence: 0.819144248962402

02:58:39.248 --> 02:58:40.320 T cells at all,
NOTE Confidence: 0.819144248962402

02:58:40.320 --> 02:58:41.986 and so we know that there's this
NOTE Confidence: 0.819144248962402

02:58:41.986 --> 02:58:44.026 big shift in terms of the micro
NOTE Confidence: 0.819144248962402

02:58:44.026 --> 02:58:45.611 environment and this correlate's with

NOTE Confidence: 0.819144248962402
02:58:45.611 --> 02:58:47.579 the idea that the T cells in that.
NOTE Confidence: 0.819144248962402
02:58:47.580 --> 02:58:49.232 In that micro environment,
NOTE Confidence: 0.819144248962402
02:58:49.232 --> 02:58:51.297 may be undergoing this progressive
NOTE Confidence: 0.819144248962402
02:58:51.297 --> 02:58:52.230 exhaustive process.
NOTE Confidence: 0.819144248962402
02:58:52.230 --> 02:58:55.656 Or Sing to us about this.
NOTE Confidence: 0.819144248962402
02:58:55.660 --> 02:58:58.126 Was that in the context of the lymph node,
NOTE Confidence: 0.819144248962402
02:58:58.130 --> 02:59:00.076 there really isn't much of a change.
NOTE Confidence: 0.819144248962402
02:59:00.076 --> 02:59:02.284 So despite this fact that we've now gone
NOTE Confidence: 0.819144248962402
02:59:02.284 --> 02:59:04.730 from 8 weeks to 17 weeks in this business,
NOTE Confidence: 0.819144248962402
02:59:04.730 --> 02:59:06.070 really dramatic change within the
NOTE Confidence: 0.819144248962402
02:59:06.070 --> 02:59:08.019 tumor in terms of both the phenotypes
NOTE Confidence: 0.819144248962402
02:59:08.019 --> 02:59:09.958 of the cells and also their location,
NOTE Confidence: 0.819144248962402
02:59:09.960 --> 02:59:12.130 we really don't see much of a much of a
NOTE Confidence: 0.819144248962402
02:59:12.188 --> 02:59:14.360 difference in terms of the populations.
NOTE Confidence: 0.819144248962402
02:59:14.360 --> 02:59:15.730 There may be some more,
NOTE Confidence: 0.819144248962402

02:59:15.730 --> 02:59:17.380 a few more of these exhausted,
NOTE Confidence: 0.819144248962402

02:59:17.380 --> 02:59:18.205 more terminally differentiated
NOTE Confidence: 0.819144248962402

02:59:18.205 --> 02:59:19.580 cells within the lymph node.
NOTE Confidence: 0.819144248962402

02:59:19.580 --> 02:59:21.200 But the preponderance of the
NOTE Confidence: 0.819144248962402

02:59:21.200 --> 02:59:22.820 population is now still overlapping
NOTE Confidence: 0.819144248962402

02:59:22.872 --> 02:59:24.286 with what we saw at 8 weeks.
NOTE Confidence: 0.819144248962402

02:59:24.290 --> 02:59:26.378 That suggest that this is a very stable
NOTE Confidence: 0.819144248962402

02:59:26.378 --> 02:59:27.679 population within the lymph nodes.
NOTE Confidence: 0.819144248962402

02:59:27.680 --> 02:59:28.994 So we became very interested in
NOTE Confidence: 0.819144248962402

02:59:28.994 --> 02:59:30.564 trying to figure out this relationship
NOTE Confidence: 0.819144248962402

02:59:30.564 --> 02:59:31.856 between these two locations.
NOTE Confidence: 0.819144248962402

02:59:31.860 --> 02:59:33.528 You could imagine again that it's
NOTE Confidence: 0.819144248962402

02:59:33.528 --> 02:59:34.920 still possible that the cells
NOTE Confidence: 0.819144248962402

02:59:34.920 --> 02:59:36.300 that are in the lymph node,
NOTE Confidence: 0.819144248962402

02:59:36.300 --> 02:59:37.920 even though their canal clear only
NOTE Confidence: 0.819144248962402

02:59:37.920 --> 02:59:39.690 related to the ones in the tumor.

NOTE Confidence: 0.819144248962402
02:59:39.690 --> 02:59:41.136 You could imagine that the ones
NOTE Confidence: 0.819144248962402
02:59:41.136 --> 02:59:43.419 that are in the tumor or actually
NOTE Confidence: 0.819144248962402
02:59:43.419 --> 02:59:44.679 locally maintaining themselves.
NOTE Confidence: 0.819144248962402
02:59:44.680 --> 02:59:46.381 And that that somehow this is allowing
NOTE Confidence: 0.819144248962402
02:59:46.381 --> 02:59:47.979 the population of Perpich perpetuate.
NOTE Confidence: 0.819144248962402
02:59:47.980 --> 02:59:49.495 Another possibility is that there's
NOTE Confidence: 0.819144248962402
02:59:49.495 --> 02:59:51.010 a migration process where the
NOTE Confidence: 0.819144248962402
02:59:51.056 --> 02:59:52.554 where the cells in the lymph node
NOTE Confidence: 0.819144248962402
02:59:52.554 --> 02:59:54.141 or having an important role in
NOTE Confidence: 0.819144248962402
02:59:54.141 --> 02:59:55.631 actually resupplying the tumor over
NOTE Confidence: 0.819144248962402
02:59:55.631 --> 02:59:57.330 the course of two native element
NOTE Confidence: 0.819144248962402
02:59:57.330 --> 02:59:59.530 to try and get a handle on this,
NOTE Confidence: 0.819144248962402
02:59:59.530 --> 03:00:01.730 we've treated the mice with FT by 7:20.
NOTE Confidence: 0.819144248962402
03:00:01.730 --> 03:00:03.380 These are talking this nice to
NOTE Confidence: 0.819144248962402
03:00:03.380 --> 03:00:04.760 these experiments are fairly long.
NOTE Confidence: 0.819144248962402

03:00:04.760 --> 03:00:06.020 We initiate the treatment arounds
NOTE Confidence: 0.819144248962402

03:00:06.020 --> 03:00:07.780 8 about six weeks post infection.
NOTE Confidence: 0.819144248962402

03:00:07.780 --> 03:00:09.430 So these are when they have
NOTE Confidence: 0.819144248962402

03:00:09.430 --> 03:00:10.530 really really tiny tumors,
NOTE Confidence: 0.819144248962402

03:00:10.530 --> 03:00:12.455 but there still infiltrated by T cells.
NOTE Confidence: 0.819144248962402

03:00:12.460 --> 03:00:14.863 And then now we let them go for three
NOTE Confidence: 0.819144248962402

03:00:14.863 --> 03:00:17.174 weeks and try and look at what impact?
NOTE Confidence: 0.819144248962402

03:00:17.180 --> 03:00:18.848 Treatment had on the development of
NOTE Confidence: 0.844045281410217

03:00:18.850 --> 03:00:21.370 the two of the of the T cell response,
NOTE Confidence: 0.844045281410217

03:00:21.370 --> 03:00:23.566 and So what you can see is that the
NOTE Confidence: 0.844045281410217

03:00:23.566 --> 03:00:25.658 treatment with FTY 720 actually has a
NOTE Confidence: 0.844045281410217

03:00:25.658 --> 03:00:27.478 significant effect in terms of decreasing
NOTE Confidence: 0.844045281410217

03:00:27.478 --> 03:00:29.452 the number of stem like cells that
NOTE Confidence: 0.844045281410217

03:00:29.452 --> 03:00:31.130 are present within the tumor tissue.
NOTE Confidence: 0.844045281410217

03:00:31.130 --> 03:00:32.985 Just shown here, both in terms of
NOTE Confidence: 0.844045281410217

03:00:32.985 --> 03:00:34.480 their frequency and their number,

NOTE Confidence: 0.844045281410217
03:00:34.480 --> 03:00:36.106 and this effect doesn't really seem
NOTE Confidence: 0.844045281410217
03:00:36.106 --> 03:00:37.829 to occur within the lymph nodes.
NOTE Confidence: 0.844045281410217
03:00:37.830 --> 03:00:39.748 So the lymph node seems to be
NOTE Confidence: 0.844045281410217
03:00:39.748 --> 03:00:41.449 maintained over this period of time.
NOTE Confidence: 0.844045281410217
03:00:41.450 --> 03:00:42.845 Additionally, we saw it impact
NOTE Confidence: 0.844045281410217
03:00:42.845 --> 03:00:44.240 on the T cell function,
NOTE Confidence: 0.844045281410217
03:00:44.240 --> 03:00:45.986 so now what residual function was
NOTE Confidence: 0.844045281410217
03:00:45.986 --> 03:00:47.898 present within within the tumor T cells?
NOTE Confidence: 0.844045281410217
03:00:47.900 --> 03:00:50.556 It was now lossd in the context of
NOTE Confidence: 0.844045281410217
03:00:50.556 --> 03:00:52.213 treatments suggesting that this migration
NOTE Confidence: 0.844045281410217
03:00:52.213 --> 03:00:54.376 process of T cells from the lymph
NOTE Confidence: 0.844045281410217
03:00:54.438 --> 03:00:56.538 node to the tumor is very important,
NOTE Confidence: 0.844045281410217
03:00:56.540 --> 03:00:58.375 both maintaining the stem like
NOTE Confidence: 0.844045281410217
03:00:58.375 --> 03:01:00.210 population and also maintaining T
NOTE Confidence: 0.844045281410217
03:01:00.271 --> 03:01:02.046 cell function within the tumor.
NOTE Confidence: 0.844045281410217

03:01:02.050 --> 03:01:04.152 So the last point I want to make
NOTE Confidence: 0.844045281410217

03:01:04.152 --> 03:01:05.736 we we started looking into whether
NOTE Confidence: 0.844045281410217

03:01:05.736 --> 03:01:07.582 or not we could consider this may
NOTE Confidence: 0.844045281410217

03:01:07.582 --> 03:01:09.410 be a reservoir of T cells within
NOTE Confidence: 0.844045281410217

03:01:09.410 --> 03:01:11.181 the lymph node and maybe one that
NOTE Confidence: 0.844045281410217

03:01:11.190 --> 03:01:12.750 was more of a protected niche.
NOTE Confidence: 0.844045281410217

03:01:12.750 --> 03:01:14.654 And so we've tried to try to understand
NOTE Confidence: 0.844045281410217

03:01:14.654 --> 03:01:16.013 whether they are what's driving
NOTE Confidence: 0.844045281410217

03:01:16.013 --> 03:01:17.966 differentiation and whether the T cells in
NOTE Confidence: 0.844045281410217

03:01:18.015 --> 03:01:19.800 the lymph node are protected from that.
NOTE Confidence: 0.844045281410217

03:01:19.800 --> 03:01:21.550 The first thing I want to point
NOTE Confidence: 0.844045281410217

03:01:21.550 --> 03:01:23.708 out is that we look at PCR signals.
NOTE Confidence: 0.844045281410217

03:01:23.710 --> 03:01:25.566 We can see that the TR signals are
NOTE Confidence: 0.844045281410217

03:01:25.566 --> 03:01:27.368 very heavily enriched within the tumor,
NOTE Confidence: 0.844045281410217

03:01:27.370 --> 03:01:29.458 and as I mentioned, very early on TC,
NOTE Confidence: 0.844045281410217

03:01:29.460 --> 03:01:31.175 our signals are thought to be one

NOTE Confidence: 0.844045281410217
03:01:31.175 --> 03:01:32.870 of the major major drivers of.
NOTE Confidence: 0.844045281410217
03:01:32.870 --> 03:01:33.878 Of T cell exhaustion.
NOTE Confidence: 0.844045281410217
03:01:33.878 --> 03:01:36.141 And so the fact that very few of the
NOTE Confidence: 0.844045281410217
03:01:36.141 --> 03:01:38.112 cells that are in the lymph node are
NOTE Confidence: 0.844045281410217
03:01:38.112 --> 03:01:40.212 high for a number of different markers
NOTE Confidence: 0.844045281410217
03:01:40.212 --> 03:01:41.880 downstream of the CR suggests that
NOTE Confidence: 0.844045281410217
03:01:41.880 --> 03:01:43.470 those cells were not seeing nearly
NOTE Confidence: 0.844045281410217
03:01:43.518 --> 03:01:45.326 as much energy as they would if they
NOTE Confidence: 0.844045281410217
03:01:45.326 --> 03:01:47.179 are within the tumor micro environment.
NOTE Confidence: 0.844045281410217
03:01:47.180 --> 03:01:48.510 The other question the other,
NOTE Confidence: 0.844045281410217
03:01:48.510 --> 03:01:50.162 the other element that I wanted to
NOTE Confidence: 0.844045281410217
03:01:50.162 --> 03:01:52.042 highlight is this idea that the clonal
NOTE Confidence: 0.844045281410217
03:01:52.042 --> 03:01:53.166 dominance between the populations
NOTE Confidence: 0.844045281410217
03:01:53.166 --> 03:01:54.852 is very closely maintained and Rafi
NOTE Confidence: 0.844045281410217
03:01:54.852 --> 03:01:56.712 Ahmed showed a similar graph in his
NOTE Confidence: 0.844045281410217

03:01:56.712 --> 03:01:58.728 in his data about T cells with lymph
NOTE Confidence: 0.844045281410217

03:01:58.728 --> 03:01:59.639 nodes and tumors.
NOTE Confidence: 0.844045281410217

03:01:59.640 --> 03:02:01.635 So I won't belabor this point other
NOTE Confidence: 0.844045281410217

03:02:01.635 --> 03:02:03.949 than to say that this is very nice.
NOTE Confidence: 0.844045281410217

03:02:03.950 --> 03:02:05.380 They're very good correlation between
NOTE Confidence: 0.844045281410217

03:02:05.380 --> 03:02:07.213 the two locations in terms of the
NOTE Confidence: 0.844045281410217

03:02:07.213 --> 03:02:07.925 types of T cells,
NOTE Confidence: 0.844045281410217

03:02:07.930 --> 03:02:09.764 but the other thing that this is
NOTE Confidence: 0.844045281410217

03:02:09.764 --> 03:02:11.982 allowed us to do is to try and look
NOTE Confidence: 0.844045281410217

03:02:11.982 --> 03:02:12.666 at PCR motifs,
NOTE Confidence: 0.844045281410217

03:02:12.670 --> 03:02:14.662 and this is a little bit of an
NOTE Confidence: 0.844045281410217

03:02:14.662 --> 03:02:15.160 aficionados point,
NOTE Confidence: 0.844045281410217

03:02:15.160 --> 03:02:17.392 so I apologize if I lose people on this,
NOTE Confidence: 0.844045281410217

03:02:17.400 --> 03:02:19.384 but because we sack mice at 8 weeks
NOTE Confidence: 0.844045281410217

03:02:19.384 --> 03:02:20.877 and stack mice at 17 weeks,
NOTE Confidence: 0.844045281410217

03:02:20.880 --> 03:02:22.864 we can't really compare the T cells directly,

NOTE Confidence: 0.844045281410217
03:02:22.870 --> 03:02:24.697 but what we can do is we can try
NOTE Confidence: 0.844045281410217
03:02:24.697 --> 03:02:26.428 and identify motifs that are used
NOTE Confidence: 0.844045281410217
03:02:26.428 --> 03:02:27.604 by those T cells,
NOTE Confidence: 0.844045281410217
03:02:27.610 --> 03:02:29.458 T CR motifs and try and identify
NOTE Confidence: 0.844045281410217
03:02:29.458 --> 03:02:31.219 as similar motifs are used by the
NOTE Confidence: 0.844045281410217
03:02:31.219 --> 03:02:32.885 T cells in both time points and
NOTE Confidence: 0.844045281410217
03:02:32.885 --> 03:02:34.593 what you can see from this group.
NOTE Confidence: 0.806758582592011
03:02:34.600 --> 03:02:36.664 Ask is that if we compare T cells
NOTE Confidence: 0.806758582592011
03:02:36.664 --> 03:02:38.692 at early and late time points that
NOTE Confidence: 0.806758582592011
03:02:38.692 --> 03:02:41.363 there are a number of motifs that are
NOTE Confidence: 0.806758582592011
03:02:41.363 --> 03:02:43.298 actually conserved between the early
NOTE Confidence: 0.806758582592011
03:02:43.298 --> 03:02:45.660 time point in the late time point.
NOTE Confidence: 0.806758582592011
03:02:45.660 --> 03:02:47.739 This just suggests that the T cells
NOTE Confidence: 0.806758582592011
03:02:47.739 --> 03:02:50.197 that are present early are in some way
NOTE Confidence: 0.806758582592011
03:02:50.197 --> 03:02:52.107 conserved and you might imagine that
NOTE Confidence: 0.806758582592011

03:02:52.107 --> 03:02:54.123 if there was chronic antigen exposure
NOTE Confidence: 0.806758582592011

03:02:54.123 --> 03:02:56.085 and there wasn't reservoir that you
NOTE Confidence: 0.806758582592011

03:02:56.085 --> 03:02:57.975 might lose these very high affinity.
NOTE Confidence: 0.806758582592011

03:02:57.980 --> 03:02:59.280 The higher affinity clones,
NOTE Confidence: 0.806758582592011

03:02:59.280 --> 03:03:00.905 and ultimately that would cause
NOTE Confidence: 0.806758582592011

03:03:00.905 --> 03:03:01.780 clonal Kona loss.
NOTE Confidence: 0.806758582592011

03:03:01.780 --> 03:03:03.985 Here we're not seeing that we're actually,
NOTE Confidence: 0.806758582592011

03:03:03.990 --> 03:03:06.078 we think. Seeing that there maintained
NOTE Confidence: 0.806758582592011

03:03:06.078 --> 03:03:08.080 based on this motif analysis.
NOTE Confidence: 0.806758582592011

03:03:08.080 --> 03:03:09.064 So, just to summarize,
NOTE Confidence: 0.806758582592011

03:03:09.064 --> 03:03:11.319 I would have told you today we're thinking
NOTE Confidence: 0.806758582592011

03:03:11.319 --> 03:03:13.497 that that within the tumor microenvironment,
NOTE Confidence: 0.806758582592011

03:03:13.500 --> 03:03:15.000 the signals that are there,
NOTE Confidence: 0.806758582592011

03:03:15.000 --> 03:03:17.096 like a lot of groups have shown in
NOTE Confidence: 0.806758582592011

03:03:17.096 --> 03:03:19.412 like I think we're seeing in our
NOTE Confidence: 0.806758582592011

03:03:19.412 --> 03:03:21.462 data that those signals that are

NOTE Confidence: 0.806758582592011

03:03:21.462 --> 03:03:22.830 in the tumor microenvironment are

NOTE Confidence: 0.806758582592011

03:03:22.830 --> 03:03:24.333 very important for promoting this

NOTE Confidence: 0.806758582592011

03:03:24.333 --> 03:03:25.537 progressive T cell exhaustion,

NOTE Confidence: 0.806758582592011

03:03:25.540 --> 03:03:27.241 and we think absent a mechanism to

NOTE Confidence: 0.806758582592011

03:03:27.241 --> 03:03:29.488 maintain them that these T cells would

NOTE Confidence: 0.806758582592011

03:03:29.488 --> 03:03:30.956 ultimately undergo terminal differentiation,

NOTE Confidence: 0.806758582592011

03:03:30.960 --> 03:03:32.465 and you would lose the

NOTE Confidence: 0.806758582592011

03:03:32.465 --> 03:03:33.669 response against the tumor.

NOTE Confidence: 0.806758582592011

03:03:33.670 --> 03:03:35.679 So in order to maintain that response

NOTE Confidence: 0.806758582592011

03:03:35.679 --> 03:03:37.580 over the course of several months,

NOTE Confidence: 0.806758582592011

03:03:37.580 --> 03:03:39.446 we think that the immune system.

NOTE Confidence: 0.806758582592011

03:03:39.450 --> 03:03:41.400 That's up this lymph node reservoir

NOTE Confidence: 0.806758582592011

03:03:41.400 --> 03:03:43.640 which allows us allows it to protect

NOTE Confidence: 0.806758582592011

03:03:43.640 --> 03:03:45.392 antitumor T cells over long periods

NOTE Confidence: 0.806758582592011

03:03:45.392 --> 03:03:47.265 of time and really perpetuate

NOTE Confidence: 0.806758582592011

03:03:47.265 --> 03:03:49.170 the response through migration as
NOTE Confidence: 0.806758582592011

03:03:49.170 --> 03:03:50.565 opposed to setting unnecessary
NOTE Confidence: 0.806758582592011

03:03:50.565 --> 03:03:52.240 local maintenance that doesn't rule
NOTE Confidence: 0.806758582592011

03:03:52.240 --> 03:03:54.280 out the role of local maintenance.
NOTE Confidence: 0.806758582592011

03:03:54.280 --> 03:03:56.072 And it could be there are tumors
NOTE Confidence: 0.806758582592011

03:03:56.072 --> 03:03:57.819 don't have some critical elements
NOTE Confidence: 0.806758582592011

03:03:57.819 --> 03:03:59.667 like tertiary lymphoid structures.
NOTE Confidence: 0.806758582592011

03:03:59.670 --> 03:04:01.018 They definitely early time.
NOTE Confidence: 0.806758582592011

03:04:01.018 --> 03:04:02.703 Points don't have tertiary lymphoid
NOTE Confidence: 0.806758582592011

03:04:02.703 --> 03:04:03.040 structures,
NOTE Confidence: 0.806758582592011

03:04:03.040 --> 03:04:05.084 but it does suggest that that at
NOTE Confidence: 0.806758582592011

03:04:05.084 --> 03:04:07.105 least the lymph node could serve
NOTE Confidence: 0.806758582592011

03:04:07.105 --> 03:04:08.900 this role within within patients
NOTE Confidence: 0.806758582592011

03:04:08.900 --> 03:04:10.540 or within within tumors.
NOTE Confidence: 0.806758582592011

03:04:10.540 --> 03:04:12.836 I better that are present in our animal
NOTE Confidence: 0.806758582592011

03:04:12.836 --> 03:04:14.740 models and potential in patients,

NOTE Confidence: 0.806758582592011
03:04:14.740 --> 03:04:16.812 and we also think that this is
NOTE Confidence: 0.806758582592011
03:04:16.812 --> 03:04:18.114 important for potentially protecting
NOTE Confidence: 0.806758582592011
03:04:18.114 --> 03:04:20.238 those T cells from chronic antigen
NOTE Confidence: 0.806758582592011
03:04:20.238 --> 03:04:22.210 exposure and internal differentiation.
NOTE Confidence: 0.806758582592011
03:04:22.210 --> 03:04:24.352 One of the elements that I was
NOTE Confidence: 0.806758582592011
03:04:24.352 --> 03:04:26.310 particularly intrigued by was that the stem,
NOTE Confidence: 0.806758582592011
03:04:26.310 --> 03:04:28.068 like reservoir was really very similar,
NOTE Confidence: 0.806758582592011
03:04:28.070 --> 03:04:30.121 or when the tumors were hot or
NOTE Confidence: 0.806758582592011
03:04:30.121 --> 03:04:31.000 when they're cold,
NOTE Confidence: 0.806758582592011
03:04:31.000 --> 03:04:32.488 and it's possible that this is
NOTE Confidence: 0.806758582592011
03:04:32.488 --> 03:04:34.558 telling us that a cold tumor could
NOTE Confidence: 0.806758582592011
03:04:34.558 --> 03:04:36.268 really be associated with reservoir.
NOTE Confidence: 0.806758582592011
03:04:36.270 --> 03:04:37.266 That's actually functional.
NOTE Confidence: 0.806758582592011
03:04:37.266 --> 03:04:37.598 Definitely,
NOTE Confidence: 0.806758582592011
03:04:37.598 --> 03:04:39.872 it suggests that the tumor itself is
NOTE Confidence: 0.806758582592011

03:04:39.872 --> 03:04:41.264 the place at which determination of
NOTE Confidence: 0.806758582592011

03:04:41.264 --> 03:04:43.010 hot and cold is probably occurring,
NOTE Confidence: 0.806758582592011

03:04:43.010 --> 03:04:45.054 and that that if that is true,
NOTE Confidence: 0.806758582592011

03:04:45.060 --> 03:04:46.818 it could suggest that we have
NOTE Confidence: 0.806758582592011

03:04:46.818 --> 03:04:47.697 an opportunity here,
NOTE Confidence: 0.806758582592011

03:04:47.700 --> 03:04:49.458 even in patients with cold tumors
NOTE Confidence: 0.806758582592011

03:04:49.458 --> 03:04:51.218 to try and understand what's going
NOTE Confidence: 0.806758582592011

03:04:51.220 --> 03:04:53.278 on in the lymph node and then.
NOTE Confidence: 0.806758582592011

03:04:53.280 --> 03:04:55.457 Maybe to try and target Linfo these
NOTE Confidence: 0.806758582592011

03:04:55.457 --> 03:04:57.255 lymph node reservoir T cells in
NOTE Confidence: 0.806758582592011

03:04:57.255 --> 03:04:58.590 terms of therapies and there's
NOTE Confidence: 0.806758582592011

03:04:58.590 --> 03:05:00.128 been a number of papers.
NOTE Confidence: 0.806758582592011

03:05:00.130 --> 03:05:02.216 I think someone earlier referred to this.
NOTE Confidence: 0.806758582592011

03:05:02.220 --> 03:05:03.864 There's been a couple papers in
NOTE Confidence: 0.806758582592011

03:05:03.864 --> 03:05:05.664 the past couple weeks that have
NOTE Confidence: 0.806758582592011

03:05:05.664 --> 03:05:07.289 highlighted the idea that therapy.

NOTE Confidence: 0.806758582592011
03:05:07.290 --> 03:05:09.306 Maybe if you target to the lymph node
NOTE Confidence: 0.806758582592011
03:05:09.306 --> 03:05:11.160 you might get therapeutic effects.
NOTE Confidence: 0.789272844791412
03:05:11.160 --> 03:05:13.211 So with that I'd like to thank
NOTE Confidence: 0.789272844791412
03:05:13.211 --> 03:05:15.329 the people who are on this slide.
NOTE Confidence: 0.789272844791412
03:05:15.330 --> 03:05:17.118 I mentioned Kelly and smooth group.
NOTE Confidence: 0.789272844791412
03:05:17.120 --> 03:05:19.142 Wego is a collabora longtime collaborator
NOTE Confidence: 0.789272844791412
03:05:19.142 --> 03:05:21.568 who's been who helped us out with the
NOTE Confidence: 0.789272844791412
03:05:21.568 --> 03:05:23.380 motif analysis and people in his lab.
NOTE Confidence: 0.789272844791412
03:05:23.380 --> 03:05:25.550 Britt and Martina who worked on the.
NOTE Confidence: 0.789272844791412
03:05:25.550 --> 03:05:26.865 Paper that was published recently
NOTE Confidence: 0.789272844791412
03:05:26.865 --> 03:05:28.822 and then a few other people have
NOTE Confidence: 0.789272844791412
03:05:28.822 --> 03:05:30.287 assisted Kelly through the process
NOTE Confidence: 0.789272844791412
03:05:30.287 --> 03:05:32.288 and I'm happy to take any questions.
NOTE Confidence: 0.87863951921463
03:05:34.400 --> 03:05:36.040 OK, we have time. I think
NOTE Confidence: 0.87863951921463
03:05:36.040 --> 03:05:37.400 for a couple of quick
NOTE Confidence: 0.87863951921463

03:05:37.400 --> 03:05:38.770 questions. So the first one
NOTE Confidence: 0.87863951921463

03:05:38.770 --> 03:05:40.130 is based upon the data.
NOTE Confidence: 0.87863951921463

03:05:40.130 --> 03:05:42.046 I think you alluded to this a
NOTE Confidence: 0.87863951921463

03:05:42.046 --> 03:05:43.684 little bit on your last slide
NOTE Confidence: 0.87863951921463

03:05:43.684 --> 03:05:45.588 is do you think that there would
NOTE Confidence: 0.87863951921463

03:05:45.590 --> 03:05:49.410 be a role in? Promoting T cell trafficking
NOTE Confidence: 0.87863951921463

03:05:49.410 --> 03:05:52.176 to otherwise immune excluded term.
NOTE Confidence: 0.87863951921463

03:05:52.176 --> 03:05:55.130 Rise immune excluded tumors by
NOTE Confidence: 0.87863951921463

03:05:55.130 --> 03:05:56.330 targeting lymphangiogenesis.
NOTE Confidence: 0.888306319713593

03:05:56.900 --> 03:05:57.800 Yeah it's possible.
NOTE Confidence: 0.888306319713593

03:05:57.800 --> 03:05:59.294 I mean, we don't know.
NOTE Confidence: 0.888306319713593

03:05:59.294 --> 03:06:01.228 Excuse me, we don't know
NOTE Confidence: 0.888306319713593

03:06:01.228 --> 03:06:03.904 for sure what the what the.
NOTE Confidence: 0.888306319713593

03:06:03.910 --> 03:06:05.709 Whether the T cells aren't getting to
NOTE Confidence: 0.888306319713593

03:06:05.709 --> 03:06:07.880 the to the tumors through migration,
NOTE Confidence: 0.888306319713593

03:06:07.880 --> 03:06:09.370 we think they're probably getting

NOTE Confidence: 0.888306319713593

03:06:09.370 --> 03:06:10.860 there and just something about

NOTE Confidence: 0.888306319713593

03:06:10.911 --> 03:06:12.446 the micro environment is changed.

NOTE Confidence: 0.888306319713593

03:06:12.450 --> 03:06:13.060 Increasing lymphangiogenesis

NOTE Confidence: 0.888306319713593

03:06:13.060 --> 03:06:14.585 could do a few things.

NOTE Confidence: 0.888306319713593

03:06:14.590 --> 03:06:16.725 One is to increase the rate of

NOTE Confidence: 0.888306319713593

03:06:16.725 --> 03:06:18.856 flow of antigens, and there may be

NOTE Confidence: 0.888306319713593

03:06:18.856 --> 03:06:20.376 some deficiencies in that process,

NOTE Confidence: 0.888306319713593

03:06:20.380 --> 03:06:22.234 and it does suggest our data

NOTE Confidence: 0.888306319713593

03:06:22.234 --> 03:06:24.039 we think are showing US data.

NOTE Confidence: 0.888306319713593

03:06:24.040 --> 03:06:26.480 I didn't get a chance to show you.

NOTE Confidence: 0.888306319713593

03:06:26.480 --> 03:06:28.346 We think that this idea that

NOTE Confidence: 0.888306319713593

03:06:28.346 --> 03:06:30.143 maybe the antigen from the tumor

NOTE Confidence: 0.888306319713593

03:06:30.143 --> 03:06:31.822 is having an important role in

NOTE Confidence: 0.888306319713593

03:06:31.822 --> 03:06:33.430 terms of driving the migration so

NOTE Confidence: 0.888306319713593

03:06:33.488 --> 03:06:35.328 lymphangiogenesis could help in that.

NOTE Confidence: 0.888306319713593

03:06:35.330 --> 03:06:36.610 Aspect of the process,
NOTE Confidence: 0.888306319713593

03:06:36.610 --> 03:06:38.530 but those are experiments that we
NOTE Confidence: 0.888306319713593

03:06:38.593 --> 03:06:40.923 I think will need to follow up on.
NOTE Confidence: 0.888306319713593

03:06:40.923 --> 03:06:42.498 Next question is,
NOTE Confidence: 0.888306319713593

03:06:42.498 --> 03:06:44.582 do you think that this reservoir
NOTE Confidence: 0.888306319713593

03:06:44.582 --> 03:06:45.968 and humans would be
NOTE Confidence: 0.868297040462494

03:06:45.970 --> 03:06:47.370 combined to the draining
NOTE Confidence: 0.868297040462494

03:06:47.370 --> 03:06:48.758 lymph nodes? Or do
NOTE Confidence: 0.868297040462494

03:06:48.760 --> 03:06:50.148 you think that also
NOTE Confidence: 0.868297040462494

03:06:50.150 --> 03:06:51.188 the peripheral circulation
NOTE Confidence: 0.868297040462494

03:06:51.190 --> 03:06:53.710 may have a role? Yeah,
NOTE Confidence: 0.839861869812012

03:06:53.710 --> 03:06:55.838 I think it's been shown by a number
NOTE Confidence: 0.839861869812012

03:06:55.838 --> 03:06:58.063 of different groups that there are T
NOTE Confidence: 0.839861869812012

03:06:58.063 --> 03:06:59.993 cells in the peripheral circulation is
NOTE Confidence: 0.839861869812012

03:06:59.993 --> 03:07:01.897 not clear to me if those are resident
NOTE Confidence: 0.839861869812012

03:07:01.897 --> 03:07:04.324 in the circulation or if their T cells

NOTE Confidence: 0.839861869812012

03:07:04.324 --> 03:07:06.014 that are migrating from the lymph

NOTE Confidence: 0.839861869812012

03:07:06.014 --> 03:07:08.040 node to the to the to the tumor.

NOTE Confidence: 0.839861869812012

03:07:08.040 --> 03:07:10.304 In an you just capture him as a

NOTE Confidence: 0.839861869812012

03:07:10.304 --> 03:07:12.259 snapshot during when you look at them.

NOTE Confidence: 0.839861869812012

03:07:12.260 --> 03:07:14.549 But this idea of clonal replacement is

NOTE Confidence: 0.839861869812012

03:07:14.549 --> 03:07:16.540 actually much better in terms of there

NOTE Confidence: 0.839861869812012

03:07:16.540 --> 03:07:18.826 are a couple of papers on it trying to

NOTE Confidence: 0.839861869812012

03:07:18.826 --> 03:07:20.971 compare T cells from the lymph node or

NOTE Confidence: 0.839861869812012

03:07:20.971 --> 03:07:22.938 sorry from the circulation to the tumor.

NOTE Confidence: 0.839861869812012

03:07:22.940 --> 03:07:24.420 It's actually been quite hard.

NOTE Confidence: 0.839861869812012

03:07:24.420 --> 03:07:26.366 Even for us to try and identify

NOTE Confidence: 0.839861869812012

03:07:26.366 --> 03:07:28.457 ways to get to lymph node tissue

NOTE Confidence: 0.839861869812012

03:07:28.457 --> 03:07:30.700 to try and look for these cells.

NOTE Confidence: 0.839861869812012

03:07:30.700 --> 03:07:32.681 So that's just a problem that the

NOTE Confidence: 0.839861869812012

03:07:32.681 --> 03:07:34.580 field is going to have to wrestle

NOTE Confidence: 0.839861869812012

03:07:34.580 --> 03:07:36.837 with so we don't have a good sense
NOTE Confidence: 0.839861869812012

03:07:36.837 --> 03:07:38.961 for how their circulation in patients
NOTE Confidence: 0.839861869812012

03:07:38.961 --> 03:07:41.659 compared to the lymph node.
NOTE Confidence: 0.839861869812012

03:07:41.660 --> 03:07:44.630 And there's another
NOTE Confidence: 0.834302604198456

03:07:42.650 --> 03:07:43.640 question regarding tertiary
NOTE Confidence: 0.834302604198456

03:07:43.640 --> 03:07:44.630 lymphoid structures. If
NOTE Confidence: 0.834302604198456

03:07:44.630 --> 03:07:45.950 those could serve as
NOTE Confidence: 0.834302604198456

03:07:45.950 --> 03:07:47.930 a reservoir over a longer term
NOTE Confidence: 0.834302604198456

03:07:47.930 --> 03:07:49.580 compared to the draining lymph
NOTE Confidence: 0.861068864663442

03:07:49.580 --> 03:07:52.490 nodes. That's what we were thinking.
NOTE Confidence: 0.861068864663442

03:07:52.490 --> 03:07:55.122 I will say that at later time points
NOTE Confidence: 0.861068864663442

03:07:55.122 --> 03:07:57.640 that Week 20 in our models we do
NOTE Confidence: 0.861068864663442

03:07:57.640 --> 03:07:59.004 see tertiary lymphoid structures
NOTE Confidence: 0.861068864663442

03:07:59.004 --> 03:08:01.092 and it's probably it's likely that
NOTE Confidence: 0.861068864663442

03:08:01.092 --> 03:08:02.799 the majority of the stem cells
NOTE Confidence: 0.861068864663442

03:08:02.799 --> 03:08:04.882 that are present in the tumor or

NOTE Confidence: 0.861068864663442

03:08:04.882 --> 03:08:06.338 pressing within those structures.

NOTE Confidence: 0.861068864663442

03:08:06.340 --> 03:08:08.125 I think one thing that I've always

NOTE Confidence: 0.861068864663442

03:08:08.125 --> 03:08:09.790 thought that was interesting about

NOTE Confidence: 0.861068864663442

03:08:09.790 --> 03:08:11.490 the tertiary lymphoid structures,

NOTE Confidence: 0.861068864663442

03:08:11.490 --> 03:08:13.416 given its proximity to the tumor,

NOTE Confidence: 0.861068864663442

03:08:13.420 --> 03:08:15.352 it's likely a place where there's

NOTE Confidence: 0.861068864663442

03:08:15.352 --> 03:08:16.640 a lot of images,

NOTE Confidence: 0.861068864663442

03:08:16.640 --> 03:08:18.968 presentation and so it may be hard in

NOTE Confidence: 0.861068864663442

03:08:18.968 --> 03:08:21.167 some ways to maintain a population.

NOTE Confidence: 0.861068864663442

03:08:21.170 --> 03:08:23.738 In in a in a stem like State,

NOTE Confidence: 0.861068864663442

03:08:23.740 --> 03:08:25.092 because you're constantly exposing

NOTE Confidence: 0.861068864663442

03:08:25.092 --> 03:08:27.120 advantage and the distance of the

NOTE Confidence: 0.861068864663442

03:08:27.178 --> 03:08:29.201 lymph node may decrease that and they

NOTE Confidence: 0.861068864663442

03:08:29.201 --> 03:08:31.099 ultimately helped to allow a better

NOTE Confidence: 0.861068864663442

03:08:31.099 --> 03:08:32.407 maintenance of this population.

NOTE Confidence: 0.861068864663442

03:08:32.410 --> 03:08:34.204 But it's an open question still
NOTE Confidence: 0.861068864663442

03:08:34.204 --> 03:08:36.260 that will have to be addressed.
NOTE Confidence: 0.861068864663442

03:08:36.260 --> 03:08:36.900 Doctor Sharma?
NOTE Confidence: 0.83305948972702

03:08:36.900 --> 03:08:38.180 Yes, thank you. That
NOTE Confidence: 0.83305948972702

03:08:38.180 --> 03:08:39.795 was such a great presentation
NOTE Confidence: 0.83305948972702

03:08:39.795 --> 03:08:42.040 that thank you so much for that.
NOTE Confidence: 0.83305948972702

03:08:42.040 --> 03:08:44.601 Do you know in your model if your
NOTE Confidence: 0.83305948972702

03:08:44.601 --> 03:08:46.848 change now in the Neo Antigen epitope,
NOTE Confidence: 0.83305948972702

03:08:46.850 --> 03:08:48.460 you're able to have expression?
NOTE Confidence: 0.83305948972702

03:08:48.460 --> 03:08:49.740 Are you just changing
NOTE Confidence: 0.83305948972702

03:08:49.740 --> 03:08:51.987 T cell responses? Have you seen B
NOTE Confidence: 0.83305948972702

03:08:51.990 --> 03:08:53.680 cell responses change as well?
NOTE Confidence: 0.83305948972702

03:08:53.680 --> 03:08:55.297 Because, you know, we were seeing data
NOTE Confidence: 0.83305948972702

03:08:55.297 --> 03:08:57.292 now the B cell responses are also
NOTE Confidence: 0.83305948972702

03:08:57.292 --> 03:08:58.847 very important for these antigens,
NOTE Confidence: 0.83305948972702

03:08:58.850 --> 03:09:01.234 so just curious as to whether or not

NOTE Confidence: 0.83305948972702

03:09:01.234 --> 03:09:03.820 that's a model you can use there. In

NOTE Confidence: 0.790282368659973

03:09:03.820 --> 03:09:05.766 our model, the one I showed there

NOTE Confidence: 0.790282368659973

03:09:05.766 --> 03:09:07.674 not be selling engines and actually

NOTE Confidence: 0.790282368659973

03:09:07.674 --> 03:09:10.026 we've used that in another story that

NOTE Confidence: 0.790282368659973

03:09:10.093 --> 03:09:12.319 we're still working up that we've

NOTE Confidence: 0.790282368659973

03:09:12.319 --> 03:09:14.143 actually put Decelean mentions in,

NOTE Confidence: 0.790282368659973

03:09:14.143 --> 03:09:16.474 and it has a very big effect.

NOTE Confidence: 0.790282368659973

03:09:16.480 --> 03:09:19.136 Maybe next year I can talk about that,

NOTE Confidence: 0.790282368659973

03:09:19.140 --> 03:09:21.066 but it's very exciting when you

NOTE Confidence: 0.790282368659973

03:09:21.066 --> 03:09:23.139 put the cell antigens into tumors,

NOTE Confidence: 0.790282368659973

03:09:23.140 --> 03:09:24.139 it completely changes

NOTE Confidence: 0.790282368659973

03:09:24.140 --> 03:09:25.800 things. Yes, very great model.

NOTE Confidence: 0.790282368659973

03:09:25.800 --> 03:09:28.124 Thank you, will have that the last

NOTE Confidence: 0.790282368659973

03:09:28.130 --> 03:09:30.129 question from doctor keck. Linking some

NOTE Confidence: 0.790282368659973

03:09:30.130 --> 03:09:32.128 of your work with IRA Mehlman's

NOTE Confidence: 0.790282368659973

03:09:32.128 --> 03:09:34.126 work on PDL one. Expressing DCS.
NOTE Confidence: 0.790282368659973

03:09:34.126 --> 03:09:36.126 Do you see any differences in
NOTE Confidence: 0.790282368659973

03:09:36.126 --> 03:09:38.498 the expression of PDL one on D?
NOTE Confidence: 0.790282368659973

03:09:38.500 --> 03:09:40.629 Scenes between the tumor or in
NOTE Confidence: 0.829305171966553

03:09:40.630 --> 03:09:42.050 the draining lymph nodes.
NOTE Confidence: 0.829305171966553

03:09:42.050 --> 03:09:44.535 That's a great question. So thank you.
NOTE Confidence: 0.829305171966553

03:09:44.540 --> 03:09:46.520 We have not looked at something
NOTE Confidence: 0.829305171966553

03:09:46.520 --> 03:09:48.440 that we're actively now pursuing.
NOTE Confidence: 0.829305171966553

03:09:48.440 --> 03:09:51.304 We think that it's likely that that PDL
NOTE Confidence: 0.829305171966553

03:09:51.304 --> 03:09:53.885 one expressing DC's are going to be
NOTE Confidence: 0.829305171966553

03:09:53.885 --> 03:09:56.082 important in terms of interacting with
NOTE Confidence: 0.829305171966553

03:09:56.082 --> 03:09:58.738 these cells and an Irish work is cancer.
NOTE Confidence: 0.829305171966553

03:09:58.740 --> 03:10:00.762 Is nature. Cancer paper really was
NOTE Confidence: 0.829305171966553

03:10:00.762 --> 03:10:02.911 a very exciting window into those
NOTE Confidence: 0.829305171966553

03:10:02.911 --> 03:10:04.766 into those types of interactions.
NOTE Confidence: 0.829305171966553

03:10:04.770 --> 03:10:06.545 So is something that we're

NOTE Confidence: 0.829305171966553
03:10:06.545 --> 03:10:07.610 very interested in.
NOTE Confidence: 0.829305171966553
03:10:07.610 --> 03:10:09.440 I think we're probably not.
NOTE Confidence: 0.829305171966553
03:10:09.440 --> 03:10:12.356 Not the only ones who are interested in this,
NOTE Confidence: 0.829305171966553
03:10:12.360 --> 03:10:14.316 but I think as a field,
NOTE Confidence: 0.829305171966553
03:10:14.316 --> 03:10:15.981 that's something that we're going
NOTE Confidence: 0.829305171966553
03:10:15.981 --> 03:10:18.045 to find out relatively soon in
NOTE Confidence: 0.829305171966553
03:10:18.045 --> 03:10:20.376 terms of what those cells are doing
NOTE Confidence: 0.829305171966553
03:10:20.442 --> 03:10:21.754 and how they are participating
NOTE Confidence: 0.829305171966553
03:10:21.754 --> 03:10:23.373 in these types of responses.
NOTE Confidence: 0.829305171966553
03:10:23.373 --> 03:10:24.019 OK, great,
NOTE Confidence: 0.850206851959229
03:10:24.020 --> 03:10:25.964 thank you, so we're going to
NOTE Confidence: 0.850206851959229
03:10:25.964 --> 03:10:27.910 move on to the next speaker,
NOTE Confidence: 0.850206851959229
03:10:27.910 --> 03:10:29.849 so again, I have the privilege
NOTE Confidence: 0.850206851959229
03:10:29.850 --> 03:10:31.470 of getting to introduce another
NOTE Confidence: 0.850206851959229
03:10:31.470 --> 03:10:33.090 one of our colleagues here.
NOTE Confidence: 0.850206851959229

03:10:33.090 --> 03:10:34.382 Ehrenring errands and assistant
NOTE Confidence: 0.850206851959229

03:10:34.382 --> 03:10:36.006 professor of Immunobiology at Yale,
NOTE Confidence: 0.850206851959229

03:10:36.006 --> 03:10:37.629 who was recruited here after
NOTE Confidence: 0.850206851959229

03:10:37.629 --> 03:10:39.948 he got his MD PhD at Stanford.
NOTE Confidence: 0.850206851959229

03:10:39.950 --> 03:10:41.850 Aaron's been honored as a
NOTE Confidence: 0.850206851959229

03:10:41.850 --> 03:10:43.750 30 under 30 and healthcare,
NOTE Confidence: 0.850206851959229

03:10:43.750 --> 03:10:46.030 and he's also accused Stewart scholar,
NOTE Confidence: 0.850206851959229

03:10:46.030 --> 03:10:48.310 which she was word in 2018.
NOTE Confidence: 0.850206851959229

03:10:48.310 --> 03:10:50.210 Erin is a passionate scientist
NOTE Confidence: 0.850206851959229

03:10:50.210 --> 03:10:52.490 and you if anyone spent more
NOTE Confidence: 0.850206851959229

03:10:52.490 --> 03:10:54.390 than 3 minutes with Aaron,
NOTE Confidence: 0.850206851959229

03:10:54.390 --> 03:10:55.530 you cannot help
NOTE Confidence: 0.83726304769516

03:10:55.530 --> 03:10:58.570 but be excited and and have a great
NOTE Confidence: 0.83726304769516

03:10:58.570 --> 03:11:01.230 amount of enthusiasm for the work that
NOTE Confidence: 0.83726304769516

03:11:01.230 --> 03:11:03.130 he's performing in the work
NOTE Confidence: 0.83726304769516

03:11:03.130 --> 03:11:05.410 that you can perform with him.

NOTE Confidence: 0.83726304769516

03:11:05.410 --> 03:11:08.070 And Aaron is really focused on taking

NOTE Confidence: 0.83726304769516

03:11:08.070 --> 03:11:09.970 some very unique approaches towards.

NOTE Confidence: 0.83726304769516

03:11:09.970 --> 03:11:10.730 Engineered cytokines

NOTE Confidence: 0.818450272083282

03:11:10.730 --> 03:11:11.780 and also is

NOTE Confidence: 0.818450272083282

03:11:11.780 --> 03:11:12.818 doing a ton

NOTE Confidence: 0.818450272083282

03:11:12.820 --> 03:11:13.858 of other work

NOTE Confidence: 0.818450272083282

03:11:13.860 --> 03:11:14.898 and recently is

NOTE Confidence: 0.818450272083282

03:11:14.900 --> 03:11:16.982 published some of his Seminole work

NOTE Confidence: 0.818450272083282

03:11:16.982 --> 03:11:19.062 actually in nature earlier this year.

NOTE Confidence: 0.818450272083282

03:11:19.062 --> 03:11:20.798 So in the interest of

NOTE Confidence: 0.818450272083282

03:11:20.800 --> 03:11:22.876 time air and take it away.

NOTE Confidence: 0.835446059703827

03:11:24.020 --> 03:11:25.847 Yeah, thank you so much Kelly for

NOTE Confidence: 0.835446059703827

03:11:25.847 --> 03:11:27.380 that super kind introduction.

NOTE Confidence: 0.835446059703827

03:11:27.380 --> 03:11:29.660 I just want to point out to everyone

NOTE Confidence: 0.835446059703827

03:11:29.660 --> 03:11:31.977 that I'm way over 30 now and you

NOTE Confidence: 0.835446059703827

03:11:31.977 --> 03:11:33.834 know it's funny that Suquet just
NOTE Confidence: 0.835446059703827

03:11:33.834 --> 03:11:35.850 ask the question because you know
NOTE Confidence: 0.835446059703827

03:11:35.850 --> 03:11:38.192 she saw me just last year and she
NOTE Confidence: 0.835446059703827

03:11:38.192 --> 03:11:40.190 said you've been a couple years.
NOTE Confidence: 0.835446059703827

03:11:40.190 --> 03:11:42.346 Wow. You look a lot older so.
NOTE Confidence: 0.835446059703827

03:11:42.350 --> 03:11:44.350 Yes, I'm over 30 anyway,
NOTE Confidence: 0.835446059703827

03:11:44.350 --> 03:11:47.108 delighted to talk today in in this
NOTE Confidence: 0.835446059703827

03:11:47.108 --> 03:11:49.084 really exciting symposium in my
NOTE Confidence: 0.835446059703827

03:11:49.084 --> 03:11:51.250 lab we use structure based protein
NOTE Confidence: 0.835446059703827

03:11:51.250 --> 03:11:52.899 engineering to create pharmacological
NOTE Confidence: 0.835446059703827

03:11:52.899 --> 03:11:55.888 tools that we can use to probe
NOTE Confidence: 0.835446059703827

03:11:55.888 --> 03:11:57.514 complicated immuno regulatory pathways.
NOTE Confidence: 0.835446059703827

03:11:57.514 --> 03:11:59.902 And although the goal is biology,
NOTE Confidence: 0.835446059703827

03:11:59.910 --> 03:12:02.409 sometimes you know we do make things
NOTE Confidence: 0.835446059703827

03:12:02.409 --> 03:12:04.439 that have therapeutic potential happen
NOTE Confidence: 0.835446059703827

03:12:04.439 --> 03:12:06.235 involved in the commercialization

NOTE Confidence: 0.835446059703827
03:12:06.235 --> 03:12:09.079 efforts to bring those into the clinic.
NOTE Confidence: 0.835446059703827
03:12:09.080 --> 03:12:12.460 So these are my disclosures.
NOTE Confidence: 0.835446059703827
03:12:12.460 --> 03:12:14.500 So that a longstanding interest in
NOTE Confidence: 0.835446059703827
03:12:14.500 --> 03:12:16.200 developing cytokine therapies for cancer.
NOTE Confidence: 0.835446059703827
03:12:16.200 --> 03:12:18.720 Ever since I was an MD PhD student with
NOTE Confidence: 0.835446059703827
03:12:18.720 --> 03:12:21.031 Chris Garcia about 10 years ago in one
NOTE Confidence: 0.835446059703827
03:12:21.031 --> 03:12:23.769 of the major reasons beyond the fact
NOTE Confidence: 0.835446059703827
03:12:23.769 --> 03:12:26.054 that cytokines are incredibly interesting.
NOTE Confidence: 0.835446059703827
03:12:26.060 --> 03:12:28.440 If you have any interest in immunology,
NOTE Confidence: 0.835446059703827
03:12:28.440 --> 03:12:30.736 these are the central defining molecules that
NOTE Confidence: 0.835446059703827
03:12:30.736 --> 03:12:32.858 instruct all sorts of immune activities.
NOTE Confidence: 0.835446059703827
03:12:32.860 --> 03:12:35.198 Is that the cytokines were the first
NOTE Confidence: 0.835446059703827
03:12:35.198 --> 03:12:37.160 agent to unambiguously prove the paradigm
NOTE Confidence: 0.835446059703827
03:12:37.160 --> 03:12:39.260 that the immune system could be an
NOTE Confidence: 0.835446059703827
03:12:39.320 --> 03:12:41.360 effective target for cancer therapy,
NOTE Confidence: 0.835446059703827

03:12:41.360 --> 03:12:43.792 and that was most evident in the experience
NOTE Confidence: 0.835446059703827

03:12:43.792 --> 03:12:46.189 of high dose interleukin two therapy.
NOTE Confidence: 0.835446059703827

03:12:46.190 --> 03:12:48.626 In Melanoma and renal cell cancer,
NOTE Confidence: 0.835446059703827

03:12:48.630 --> 03:12:51.886 where a small fraction of patients about 16%,
NOTE Confidence: 0.835446059703827

03:12:51.890 --> 03:12:53.018 I'm responded to,
NOTE Confidence: 0.835446059703827

03:12:53.018 --> 03:12:56.370 patient responded to L2 in of those patients,
NOTE Confidence: 0.835446059703827

03:12:56.370 --> 03:12:59.205 a total of 6% had long lasting,
NOTE Confidence: 0.835446059703827

03:12:59.210 --> 03:13:00.838 durable remissions that could
NOTE Confidence: 0.835446059703827

03:13:00.838 --> 03:13:02.873 essentially be called a cure.
NOTE Confidence: 0.835446059703827

03:13:02.880 --> 03:13:03.580 I mean,
NOTE Confidence: 0.835446059703827

03:13:03.580 --> 03:13:05.680 this is really the first example
NOTE Confidence: 0.835446059703827

03:13:05.680 --> 03:13:08.767 of a survival tale on the capital
NOTE Confidence: 0.835446059703827

03:13:08.767 --> 03:13:11.067 matter survival curve that has
NOTE Confidence: 0.835446059703827

03:13:11.146 --> 03:13:13.718 made immunotherapy so compelling.
NOTE Confidence: 0.835446059703827

03:13:13.720 --> 03:13:15.736 So cytokines themselves are really
NOTE Confidence: 0.835446059703827

03:13:15.736 --> 03:13:17.348 compelling as potential agents

NOTE Confidence: 0.835446059703827
03:13:17.348 --> 03:13:18.154 for immunotherapy.
NOTE Confidence: 0.835446059703827
03:13:18.160 --> 03:13:19.620 That's like I said,
NOTE Confidence: 0.835446059703827
03:13:19.620 --> 03:13:21.810 because they do so many diverse
NOTE Confidence: 0.835446059703827
03:13:21.886 --> 03:13:23.818 activities on immune cells.
NOTE Confidence: 0.835446059703827
03:13:23.820 --> 03:13:26.016 So I'm like a checkpoint inhibitor
NOTE Confidence: 0.835446059703827
03:13:26.016 --> 03:13:28.690 that they do more than just tune
NOTE Confidence: 0.835446059703827
03:13:28.690 --> 03:13:30.590 an existing response where they
NOTE Confidence: 0.835446059703827
03:13:30.590 --> 03:13:33.110 can tap into hardwired programs.
NOTE Confidence: 0.835446059703827
03:13:33.110 --> 03:13:34.726 That instructing mean survival,
NOTE Confidence: 0.835446059703827
03:13:34.726 --> 03:13:35.130 proliferation,
NOTE Confidence: 0.835446059703827
03:13:35.130 --> 03:13:36.375 differentiation into different
NOTE Confidence: 0.835446059703827
03:13:36.375 --> 03:13:38.035 phenotypes in ultimately control
NOTE Confidence: 0.835446059703827
03:13:38.035 --> 03:13:39.979 effector function of immune cells,
NOTE Confidence: 0.835446059703827
03:13:39.980 --> 03:13:42.430 and they can do that Locali in
NOTE Confidence: 0.835446059703827
03:13:42.430 --> 03:13:44.420 an auto repair confession,
NOTE Confidence: 0.835446059703827

03:13:44.420 --> 03:13:46.470 or even have endocrine like.
NOTE Confidence: 0.835446059703827

03:13:46.470 --> 03:13:47.332 Effects systemically,
NOTE Confidence: 0.835446059703827

03:13:47.332 --> 03:13:49.918 the problem with cytokines is that
NOTE Confidence: 0.835446059703827

03:13:49.918 --> 03:13:52.378 they did not evolve to be drugs,
NOTE Confidence: 0.835446059703827

03:13:52.380 --> 03:13:54.738 but evolved to be signaling molecules.
NOTE Confidence: 0.835446059703827

03:13:54.740 --> 03:13:57.673 The immune system and so there are
NOTE Confidence: 0.835446059703827

03:13:57.673 --> 03:13:59.261 biological limitations inherent to
NOTE Confidence: 0.835446059703827

03:13:59.261 --> 03:14:01.389 how they have evolved to play a role
NOTE Confidence: 0.835446059703827

03:14:01.389 --> 03:14:03.697 in regulating immune responses that
NOTE Confidence: 0.835446059703827

03:14:03.697 --> 03:14:06.162 have curtailed their therapeutic use.
NOTE Confidence: 0.835446059703827

03:14:06.170 --> 03:14:08.928 So I'll choose a really instructive example.
NOTE Confidence: 0.835446059703827

03:14:08.930 --> 03:14:10.169 On one hand,
NOTE Confidence: 0.835446059703827

03:14:10.169 --> 03:14:12.647 it can stimulate potent antitumor immunity
NOTE Confidence: 0.835446059703827

03:14:12.647 --> 03:14:14.838 through cytotoxic T cells as well,
NOTE Confidence: 0.835446059703827

03:14:14.840 --> 03:14:16.850 stimulation of natural killer cells.
NOTE Confidence: 0.835446059703827

03:14:16.850 --> 03:14:18.880 But on the other hand,

NOTE Confidence: 0.835446059703827

03:14:18.880 --> 03:14:21.664 it also can stimulate the proliferation

NOTE Confidence: 0.835446059703827

03:14:21.664 --> 03:14:23.520 of immunosuppressive T regulatory

NOTE Confidence: 0.835446059703827

03:14:23.589 --> 03:14:25.345 cells that paradoxically inhibit

NOTE Confidence: 0.835446059703827

03:14:25.345 --> 03:14:27.979 the antitumor functions of I'll too.

NOTE Confidence: 0.835446059703827

03:14:27.980 --> 03:14:28.396 Similarly,

NOTE Confidence: 0.835446059703827

03:14:28.396 --> 03:14:30.476 because cytokines have such potent

NOTE Confidence: 0.835446059703827

03:14:30.476 --> 03:14:32.140 effects on our Physiology,

NOTE Confidence: 0.835446059703827

03:14:32.140 --> 03:14:34.378 we've of course evolved very strong

NOTE Confidence: 0.835446059703827

03:14:34.378 --> 03:14:35.870 negative feedback mechanisms to

NOTE Confidence: 0.835446059703827

03:14:35.933 --> 03:14:37.550 prevent runaway inflammation,

NOTE Confidence: 0.815105140209198

03:14:37.550 --> 03:14:40.462 and this is great to protect us

NOTE Confidence: 0.815105140209198

03:14:40.462 --> 03:14:41.710 from autoinflammatory disease.

NOTE Confidence: 0.815105140209198

03:14:41.710 --> 03:14:44.200 But in the setting of administering

NOTE Confidence: 0.815105140209198

03:14:44.200 --> 03:14:45.445 recombinant cytokine therapies,

NOTE Confidence: 0.815105140209198

03:14:45.450 --> 03:14:47.934 these same mechanisms can curtail the

NOTE Confidence: 0.815105140209198

03:14:47.934 --> 03:14:50.030 maximal efficacy of cytokine drugs.
NOTE Confidence: 0.815105140209198

03:14:50.030 --> 03:14:51.880 So really, our conviction and
NOTE Confidence: 0.815105140209198

03:14:51.880 --> 03:14:54.600 it's not just our own conviction,
NOTE Confidence: 0.815105140209198

03:14:54.600 --> 03:14:56.292 but that basically everyone
NOTE Confidence: 0.815105140209198

03:14:56.292 --> 03:14:57.984 who works with sciatica.
NOTE Confidence: 0.815105140209198

03:14:57.990 --> 03:15:00.858 Therapies is that we can't accept
NOTE Confidence: 0.815105140209198

03:15:00.858 --> 03:15:03.450 nature solution to cite a kind,
NOTE Confidence: 0.815105140209198

03:15:03.450 --> 03:15:06.614 so we need to engineer them for
NOTE Confidence: 0.815105140209198

03:15:06.614 --> 03:15:08.516 deliberate therapeutic purpose and
NOTE Confidence: 0.815105140209198

03:15:08.516 --> 03:15:10.851 tailor their activities to maximize
NOTE Confidence: 0.815105140209198

03:15:10.851 --> 03:15:13.223 their effect and desired cell
NOTE Confidence: 0.815105140209198

03:15:13.223 --> 03:15:15.803 populations and avoid those that have
NOTE Confidence: 0.815105140209198

03:15:15.803 --> 03:15:19.150 either safety or efficacy impediments.
NOTE Confidence: 0.815105140209198

03:15:19.150 --> 03:15:22.147 So when I started my lab a few years
NOTE Confidence: 0.815105140209198

03:15:22.147 --> 03:15:24.162 back and we wondered how their
NOTE Confidence: 0.815105140209198

03:15:24.162 --> 03:15:25.867 statically pathways that have been

NOTE Confidence: 0.815105140209198
03:15:25.867 --> 03:15:27.690 overlooked in tumor immunotherapy.
NOTE Confidence: 0.815105140209198
03:15:27.690 --> 03:15:28.450 In particular,
NOTE Confidence: 0.815105140209198
03:15:28.450 --> 03:15:30.730 we wondered if there were cytokines
NOTE Confidence: 0.815105140209198
03:15:30.730 --> 03:15:32.897 that had more selectivity to the
NOTE Confidence: 0.815105140209198
03:15:32.897 --> 03:15:34.907 very T cells that were doing
NOTE Confidence: 0.815105140209198
03:15:34.972 --> 03:15:36.970 the heavy lifting in the tumor.
NOTE Confidence: 0.815105140209198
03:15:36.970 --> 03:15:38.282 That is to say,
NOTE Confidence: 0.815105140209198
03:15:38.282 --> 03:15:39.594 tumor reactive antigen specific
NOTE Confidence: 0.815105140209198
03:15:39.594 --> 03:15:40.900 tumor infiltrating lymphocytes.
NOTE Confidence: 0.815105140209198
03:15:40.900 --> 03:15:43.258 It turns out that most cytokines
NOTE Confidence: 0.815105140209198
03:15:43.258 --> 03:15:46.247 that we give I'll to I'll 15 at 12,
NOTE Confidence: 0.815105140209198
03:15:46.250 --> 03:15:48.130 they don't really have selectivity
NOTE Confidence: 0.815105140209198
03:15:48.130 --> 03:15:49.634 toward these antigen experience
NOTE Confidence: 0.815105140209198
03:15:49.634 --> 03:15:50.899 management specific T cells,
NOTE Confidence: 0.815105140209198
03:15:50.900 --> 03:15:53.132 and so it was about this time at
NOTE Confidence: 0.815105140209198

03:15:53.132 --> 03:15:54.907 the single cell RNA sequencing
NOTE Confidence: 0.815105140209198

03:15:54.907 --> 03:15:56.822 revolution was coming to the
NOTE Confidence: 0.815105140209198

03:15:56.822 --> 03:15:58.760 foreign in Anderson's group.
NOTE Confidence: 0.815105140209198

03:15:58.760 --> 03:16:00.190 Publish this phenomenal paper where
NOTE Confidence: 0.815105140209198

03:16:00.190 --> 03:16:02.069 they perform single cell RNA sequencing
NOTE Confidence: 0.815105140209198

03:16:02.069 --> 03:16:03.677 on tumor infiltrating lymphocytes,
NOTE Confidence: 0.815105140209198

03:16:03.680 --> 03:16:05.552 and they were able to bioinformatic
NOTE Confidence: 0.815105140209198

03:16:05.552 --> 03:16:07.547 Lee extract AT cell activation score
NOTE Confidence: 0.815105140209198

03:16:07.547 --> 03:16:09.252 for every gene they've detected
NOTE Confidence: 0.815105140209198

03:16:09.252 --> 03:16:11.607 in the data set versus AT cell
NOTE Confidence: 0.815105140209198

03:16:11.607 --> 03:16:13.515 dysfunction score and what they found
NOTE Confidence: 0.815105140209198

03:16:13.520 --> 03:16:15.488 was that the best checkpoint targets
NOTE Confidence: 0.815105140209198

03:16:15.488 --> 03:16:17.779 the ones that you know of course,
NOTE Confidence: 0.815105140209198

03:16:17.780 --> 03:16:20.404 had so much success in the clinic PD,
NOTE Confidence: 0.815105140209198

03:16:20.410 --> 03:16:21.710 one seat away four,
NOTE Confidence: 0.815105140209198

03:16:21.710 --> 03:16:23.660 and a bunch of emerging targets

NOTE Confidence: 0.815105140209198
03:16:23.727 --> 03:16:25.641 that were on this upper right
NOTE Confidence: 0.815105140209198
03:16:25.641 --> 03:16:27.300 hand quadrant of the plot,
NOTE Confidence: 0.815105140209198
03:16:27.300 --> 03:16:29.382 meaning they were expressed in both
NOTE Confidence: 0.815105140209198
03:16:29.382 --> 03:16:31.269 activated and is Functional T cells.
NOTE Confidence: 0.815105140209198
03:16:31.270 --> 03:16:33.616 And that makes a lot of sense.
NOTE Confidence: 0.815105140209198
03:16:33.616 --> 03:16:35.466 These T cells will be activated
NOTE Confidence: 0.815105140209198
03:16:35.466 --> 03:16:36.936 because they're seeing tumor antigen
NOTE Confidence: 0.815105140209198
03:16:36.936 --> 03:16:38.419 and their dysfunctional because
NOTE Confidence: 0.815105140209198
03:16:38.419 --> 03:16:40.314 they're in the tumor microenvironment.
NOTE Confidence: 0.815105140209198
03:16:40.320 --> 03:16:41.990 Thought was a brilliant analysis.
NOTE Confidence: 0.815105140209198
03:16:41.990 --> 03:16:43.670 We wondered what about cytokines?
NOTE Confidence: 0.815105140209198
03:16:43.670 --> 03:16:45.791 And so we took their data and
NOTE Confidence: 0.815105140209198
03:16:45.791 --> 03:16:47.350 employed at every cytokine,
NOTE Confidence: 0.815105140209198
03:16:47.350 --> 03:16:49.215 receptor and pathway component that
NOTE Confidence: 0.815105140209198
03:16:49.215 --> 03:16:51.718 we could detect in the data set
NOTE Confidence: 0.815105140209198

03:16:51.718 --> 03:16:53.720 and to make a Long story short,
NOTE Confidence: 0.815105140209198

03:16:53.720 --> 03:16:55.730 would immediately jumped out at us.
NOTE Confidence: 0.815105140209198

03:16:55.730 --> 03:16:57.734 Was that the aisle 18 pathway
NOTE Confidence: 0.815105140209198

03:16:57.734 --> 03:16:58.736 was fairly unique,
NOTE Confidence: 0.815105140209198

03:16:58.740 --> 03:17:00.420 and then its receptor subunits,
NOTE Confidence: 0.815105140209198

03:17:00.420 --> 03:17:02.496 and even the cited kind itself.
NOTE Confidence: 0.815105140209198

03:17:02.500 --> 03:17:04.666 Or in that upper right hand
NOTE Confidence: 0.815105140209198

03:17:04.666 --> 03:17:06.110 quadrant of the plot,
NOTE Confidence: 0.815105140209198

03:17:06.110 --> 03:17:08.878 which made us think that that I lay
NOTE Confidence: 0.815105140209198

03:17:08.878 --> 03:17:11.955 team could be an open port on these T
NOTE Confidence: 0.815105140209198

03:17:11.955 --> 03:17:14.593 cells were trying to hack into them
NOTE Confidence: 0.815105140209198

03:17:14.593 --> 03:17:17.317 where we could deliver a selective message.
NOTE Confidence: 0.815105140209198

03:17:17.317 --> 03:17:19.202 More specifically to these antigen
NOTE Confidence: 0.815105140209198

03:17:19.202 --> 03:17:21.500 specific till as opposed to broad
NOTE Confidence: 0.815105140209198

03:17:21.500 --> 03:17:22.964 stimulation of lymphocytes that's
NOTE Confidence: 0.815105140209198

03:17:22.964 --> 03:17:24.962 known to cause cytokine release

NOTE Confidence: 0.815105140209198

03:17:24.962 --> 03:17:26.870 syndrome and unacceptable toxicity.

NOTE Confidence: 0.815105140209198

03:17:26.870 --> 03:17:29.222 So we actually first sought to confirm

NOTE Confidence: 0.815105140209198

03:17:29.222 --> 03:17:31.120 that the single scientist sequencing

NOTE Confidence: 0.815105140209198

03:17:31.120 --> 03:17:33.586 data with good old fashion flow

NOTE Confidence: 0.815105140209198

03:17:33.586 --> 03:17:35.970 cytometry and looking at mouse tumors,

NOTE Confidence: 0.815105140209198

03:17:35.970 --> 03:17:38.539 and what we found was that sure

NOTE Confidence: 0.815105140209198

03:17:38.539 --> 03:17:40.499 enough that the 18 Receptor

NOTE Confidence: 0.815105140209198

03:17:40.499 --> 03:17:42.030 was not very prevalent

NOTE Confidence: 0.771311640739441

03:17:42.030 --> 03:17:44.564 on T cells that were found in

NOTE Confidence: 0.771311640739441

03:17:44.564 --> 03:17:46.580 the periphery and the spleen,

NOTE Confidence: 0.771311640739441

03:17:46.580 --> 03:17:49.360 but the T cells in the tumor CD S in

NOTE Confidence: 0.771311640739441

03:17:49.437 --> 03:17:51.792 city force had abundantly upregulated

NOTE Confidence: 0.771311640739441

03:17:51.792 --> 03:17:54.919 I'll 18 Receptor and we also saw,

NOTE Confidence: 0.771311640739441

03:17:54.920 --> 03:17:57.155 as seen many times before, that.

NOTE Confidence: 0.771311640739441

03:17:57.155 --> 03:17:58.190 Natural killer cells,

NOTE Confidence: 0.771311640739441

03:17:58.190 --> 03:18:00.820 highly expressed al 18 receptor at baseline,
NOTE Confidence: 0.771311640739441

03:18:00.820 --> 03:18:03.046 so this is really a feature of
NOTE Confidence: 0.771311640739441

03:18:03.046 --> 03:18:04.938 innate capacity that T cells
NOTE Confidence: 0.771311640739441

03:18:04.938 --> 03:18:06.612 become antigen experienced. Again,
NOTE Confidence: 0.771311640739441

03:18:06.612 --> 03:18:09.508 the ability to respond to an 8 stimuli,
NOTE Confidence: 0.771311640739441

03:18:09.510 --> 03:18:11.682 in this case interleukin 18 and
NOTE Confidence: 0.771311640739441

03:18:11.682 --> 03:18:13.130 inconsistent with that idea.
NOTE Confidence: 0.771311640739441

03:18:13.130 --> 03:18:15.482 You can see that when you look
NOTE Confidence: 0.771311640739441

03:18:15.482 --> 03:18:17.315 within tumors that the cells
NOTE Confidence: 0.771311640739441

03:18:17.315 --> 03:18:19.200 that expressed the Allied Team
NOTE Confidence: 0.771311640739441

03:18:19.200 --> 03:18:21.121 Receptor it is exclusively found
NOTE Confidence: 0.771311640739441

03:18:21.121 --> 03:18:23.627 on the CD 44 very high cells,
NOTE Confidence: 0.771311640739441

03:18:23.630 --> 03:18:25.790 meaning that it really is marking
NOTE Confidence: 0.771311640739441

03:18:25.790 --> 03:18:27.650 those antigen experienced T cells.
NOTE Confidence: 0.771311640739441

03:18:27.650 --> 03:18:28.508 Within the tumor.
NOTE Confidence: 0.779286682605743

03:18:30.740 --> 03:18:33.440 So like I said, I only team it's

NOTE Confidence: 0.779286682605743
03:18:33.440 --> 03:18:35.140 an innate cytokinin just zooming
NOTE Confidence: 0.779286682605743
03:18:35.140 --> 03:18:37.653 out a little bit to give a little
NOTE Confidence: 0.779286682605743
03:18:37.653 --> 03:18:39.140 background on the biology.
NOTE Confidence: 0.779286682605743
03:18:39.140 --> 03:18:41.156 It's a member of the aisle.
NOTE Confidence: 0.779286682605743
03:18:41.160 --> 03:18:43.284 One family of static kinds which
NOTE Confidence: 0.779286682605743
03:18:43.284 --> 03:18:45.066 are essentially like alarm ends
NOTE Confidence: 0.779286682605743
03:18:45.066 --> 03:18:46.902 there made inside the cell in
NOTE Confidence: 0.779286682605743
03:18:46.902 --> 03:18:49.224 an inactive form with a with an
NOTE Confidence: 0.779286682605743
03:18:49.224 --> 03:18:50.904 inhibitory end terminal peptide that
NOTE Confidence: 0.779286682605743
03:18:50.904 --> 03:18:52.915 gets cleaved in removed by caspases
NOTE Confidence: 0.779286682605743
03:18:52.915 --> 03:18:54.255 downstream of the Inflammasome.
NOTE Confidence: 0.779286682605743
03:18:54.260 --> 03:18:56.332 Once these set of kinds of producing
NOTE Confidence: 0.779286682605743
03:18:56.332 --> 03:18:57.984 their mature form they exit
NOTE Confidence: 0.779286682605743
03:18:57.984 --> 03:18:59.739 the cell through a noncanonical
NOTE Confidence: 0.779286682605743
03:18:59.739 --> 03:19:01.218 secretion pathway that involves
NOTE Confidence: 0.779286682605743

03:19:01.218 --> 03:19:03.048 the formation of guests German.
NOTE Confidence: 0.779286682605743

03:19:03.050 --> 03:19:04.850 Wars in the cell membrane,
NOTE Confidence: 0.779286682605743

03:19:04.850 --> 03:19:06.902 then I'll 18 specifically signals by
NOTE Confidence: 0.779286682605743

03:19:06.902 --> 03:19:08.790 Hetero Dimerizing its receptor subunits.
NOTE Confidence: 0.779286682605743

03:19:08.790 --> 03:19:11.128 Eyelid team are Alpha and Alex nor
NOTE Confidence: 0.779286682605743

03:19:11.128 --> 03:19:13.459 beta to drive my TI88 signaling,
NOTE Confidence: 0.779286682605743

03:19:13.460 --> 03:19:15.335 which ultimately results in the
NOTE Confidence: 0.779286682605743

03:19:15.335 --> 03:19:18.625 activation of NF Kappa B and I got is
NOTE Confidence: 0.779286682605743

03:19:18.625 --> 03:19:20.635 pretty excited because the mighty 88.
NOTE Confidence: 0.779286682605743

03:19:20.640 --> 03:19:23.008 If you think about it is fairly orthogonal
NOTE Confidence: 0.779286682605743

03:19:23.008 --> 03:19:24.928 to most other immunotherapeutic agents
NOTE Confidence: 0.779286682605743

03:19:24.928 --> 03:19:27.454 that are currently in the clinic.
NOTE Confidence: 0.779286682605743

03:19:27.460 --> 03:19:29.980 Other side of clients or Jack stat.
NOTE Confidence: 0.779286682605743

03:19:29.980 --> 03:19:31.444 Other checkpoint pathways or
NOTE Confidence: 0.779286682605743

03:19:31.444 --> 03:19:33.274 item item TF super family.
NOTE Confidence: 0.779286682605743

03:19:33.280 --> 03:19:36.511 Traft rad so so my TI88 it's a powerful

NOTE Confidence: 0.779286682605743
03:19:36.511 --> 03:19:39.472 pathway in most 9088 coupled receptor
NOTE Confidence: 0.779286682605743
03:19:39.472 --> 03:19:41.992 agonists are not really competitive,
NOTE Confidence: 0.779286682605743
03:19:42.000 --> 03:19:43.672 compatible with systemic administration.
NOTE Confidence: 0.779286682605743
03:19:43.672 --> 03:19:46.800 You think about your TL are agonists,
NOTE Confidence: 0.779286682605743
03:19:46.800 --> 03:19:48.414 I'll one, etc.
NOTE Confidence: 0.779286682605743
03:19:48.414 --> 03:19:50.028 Like I said,
NOTE Confidence: 0.779286682605743
03:19:50.030 --> 03:19:51.795 You know it drives very
NOTE Confidence: 0.779286682605743
03:19:51.795 --> 03:19:52.854 strong signaling message,
NOTE Confidence: 0.779286682605743
03:19:52.860 --> 03:19:54.930 but the receptor is also expressed
NOTE Confidence: 0.779286682605743
03:19:54.930 --> 03:19:56.760 really on the right cells.
NOTE Confidence: 0.779286682605743
03:19:56.760 --> 03:19:59.584 That is to say a natural killer cells.
NOTE Confidence: 0.779286682605743
03:19:59.590 --> 03:20:01.708 Of course another innate lymphoid cells,
NOTE Confidence: 0.779286682605743
03:20:01.710 --> 03:20:04.006 but on an engine experience CD 8IN
NOTE Confidence: 0.779286682605743
03:20:04.006 --> 03:20:06.132 TH one cells and not importantly
NOTE Confidence: 0.779286682605743
03:20:06.132 --> 03:20:08.624 naive T cells but have not seen
NOTE Confidence: 0.779286682605743

03:20:08.697 --> 03:20:10.875 antigen or central memory T cells
NOTE Confidence: 0.779286682605743

03:20:10.875 --> 03:20:13.096 that have not seen antigen recently.
NOTE Confidence: 0.779286682605743

03:20:13.096 --> 03:20:15.011 There's also several reports that
NOTE Confidence: 0.779286682605743

03:20:15.011 --> 03:20:16.872 highlight team can inhibit the
NOTE Confidence: 0.779286682605743

03:20:16.872 --> 03:20:17.856 immunosuppressive function of
NOTE Confidence: 0.779286682605743

03:20:17.856 --> 03:20:19.496 T Reg or at least.
NOTE Confidence: 0.779286682605743

03:20:19.500 --> 03:20:21.550 Alter their programs away from
NOTE Confidence: 0.779286682605743

03:20:21.550 --> 03:20:22.780 immunosuppressive function and
NOTE Confidence: 0.779286682605743

03:20:22.780 --> 03:20:25.119 Tord a tissue repair phenotype.
NOTE Confidence: 0.779286682605743

03:20:25.120 --> 03:20:27.570 So all of these pieces of data
NOTE Confidence: 0.779286682605743

03:20:27.570 --> 03:20:29.160 together suggests that highlighting
NOTE Confidence: 0.779286682605743

03:20:29.160 --> 03:20:31.974 could be a really compelling agent
NOTE Confidence: 0.779286682605743

03:20:31.974 --> 03:20:34.375 as an immunotherapeutic both and
NOTE Confidence: 0.779286682605743

03:20:34.375 --> 03:20:36.223 immunogenic tumors through stimulating
NOTE Confidence: 0.779286682605743

03:20:36.223 --> 03:20:39.896 tumor reactive T cells as well as in
NOTE Confidence: 0.779286682605743

03:20:39.896 --> 03:20:42.620 in cold refractory tumors through the

NOTE Confidence: 0.779286682605743
03:20:42.719 --> 03:20:45.929 stimulation of natural killer cells.
NOTE Confidence: 0.779286682605743
03:20:45.930 --> 03:20:48.163 So we really floored to learn that
NOTE Confidence: 0.779286682605743
03:20:48.163 --> 03:20:50.577 that I liked Ben in the clinic
NOTE Confidence: 0.779286682605743
03:20:50.577 --> 03:20:53.121 before it was taken through phase two
NOTE Confidence: 0.779286682605743
03:20:53.121 --> 03:20:55.091 trials by GlaxoSmithKline and what
NOTE Confidence: 0.779286682605743
03:20:55.091 --> 03:20:57.386 they found was that for cytokines
NOTE Confidence: 0.779286682605743
03:20:57.386 --> 03:20:59.176 it was remarkably well tolerated.
NOTE Confidence: 0.779286682605743
03:20:59.180 --> 03:21:01.764 It could be given up to 2 milligrams
NOTE Confidence: 0.779286682605743
03:21:01.764 --> 03:21:04.188 per kilogram per day without treatment.
NOTE Confidence: 0.779286682605743
03:21:04.190 --> 03:21:04.904 Limiting toxicities.
NOTE Confidence: 0.779286682605743
03:21:04.904 --> 03:21:07.046 Very really astonishing for a cytokine.
NOTE Confidence: 0.779286682605743
03:21:07.050 --> 03:21:09.336 The problem was that it absolutely
NOTE Confidence: 0.779286682605743
03:21:09.336 --> 03:21:11.894 had no real efficacy to speak ofw
NOTE Confidence: 0.779286682605743
03:21:11.894 --> 03:21:13.494 on in the largest phase,
NOTE Confidence: 0.779286682605743
03:21:13.500 --> 03:21:15.636 two trial before 60 Melanoma patients,
NOTE Confidence: 0.779286682605743

03:21:15.640 --> 03:21:17.860 there was only one partial response.
NOTE Confidence: 0.779286682605743

03:21:17.860 --> 03:21:20.354 And I want to point out that these
NOTE Confidence: 0.779286682605743

03:21:20.354 --> 03:21:21.914 were not not just immunotherapy
NOTE Confidence: 0.779286682605743

03:21:21.914 --> 03:21:22.850 naive Melanoma patients,
NOTE Confidence: 0.779286682605743

03:21:22.850 --> 03:21:24.094 but actually treatment naive
NOTE Confidence: 0.779286682605743

03:21:24.094 --> 03:21:24.716 Melanoma patients.
NOTE Confidence: 0.779286682605743

03:21:24.720 --> 03:21:27.216 This study was done in the mid 2000s,
NOTE Confidence: 0.779286682605743

03:21:27.220 --> 03:21:29.596 so if there ever was a population we
NOTE Confidence: 0.779286682605743

03:21:29.596 --> 03:21:31.587 would expect to respond to therapy.
NOTE Confidence: 0.779286682605743

03:21:31.590 --> 03:21:32.538 This would be it.
NOTE Confidence: 0.779286682605743

03:21:32.538 --> 03:21:33.960 In this of course was a
NOTE Confidence: 0.821108937263489

03:21:34.020 --> 03:21:35.640 really disappointing result,
NOTE Confidence: 0.821108937263489

03:21:35.640 --> 03:21:37.700 and so the further development
NOTE Confidence: 0.821108937263489

03:21:37.700 --> 03:21:39.760 team has been largely curtailed.
NOTE Confidence: 0.821108937263489

03:21:39.760 --> 03:21:43.027 So this was a really striking paradox to us.
NOTE Confidence: 0.821108937263489

03:21:43.030 --> 03:21:44.905 How could this powerful cytokine

NOTE Confidence: 0.821108937263489
03:21:44.905 --> 03:21:47.526 hitting the right cells with the right
NOTE Confidence: 0.821108937263489
03:21:47.526 --> 03:21:49.913 message be so ineffective in the clinic?
NOTE Confidence: 0.821108937263489
03:21:49.920 --> 03:21:52.384 And so we dug into the data from
NOTE Confidence: 0.821108937263489
03:21:52.384 --> 03:21:54.485 these clinical studies that we found
NOTE Confidence: 0.821108937263489
03:21:54.485 --> 03:21:56.609 was that with repeated dosing of
NOTE Confidence: 0.821108937263489
03:21:56.677 --> 03:21:59.155 Islay team in these patients there
NOTE Confidence: 0.821108937263489
03:21:59.155 --> 03:22:01.181 was a waning pharmacodynamic effect.
NOTE Confidence: 0.821108937263489
03:22:01.181 --> 03:22:03.407 In this case, looking at Interferon
NOTE Confidence: 0.821108937263489
03:22:03.407 --> 03:22:05.169 Gamma released into the blood,
NOTE Confidence: 0.821108937263489
03:22:05.170 --> 03:22:07.246 I should say parenthetically the original
NOTE Confidence: 0.821108937263489
03:22:07.246 --> 03:22:09.969 name for all 18 was interferon gamma.
NOTE Confidence: 0.821108937263489
03:22:09.970 --> 03:22:12.502 Inducing factor which augurs well for
NOTE Confidence: 0.821108937263489
03:22:12.502 --> 03:22:14.605 immunotherapeutic but you can see
NOTE Confidence: 0.821108937263489
03:22:14.605 --> 03:22:16.681 that after what weekly dosing that
NOTE Confidence: 0.821108937263489
03:22:16.681 --> 03:22:19.102 many patients by 4 five 812 weeks
NOTE Confidence: 0.821108937263489

03:22:19.102 --> 03:22:21.070 had no increase in Interferon Gamma
NOTE Confidence: 0.821108937263489

03:22:21.070 --> 03:22:23.660 in the blood despite the fact that
NOTE Confidence: 0.821108937263489

03:22:23.660 --> 03:22:25.904 receiving the maximum dose of drug
NOTE Confidence: 0.821108937263489

03:22:25.904 --> 03:22:27.360 that decreased activity corresponds
NOTE Confidence: 0.821108937263489

03:22:27.360 --> 03:22:29.782 to a massive upregulation of a protein
NOTE Confidence: 0.821108937263489

03:22:29.782 --> 03:22:31.799 called Interleukin 18 binding protein.
NOTE Confidence: 0.821108937263489

03:22:31.800 --> 03:22:32.961 I'll 18 VP,
NOTE Confidence: 0.821108937263489

03:22:32.961 --> 03:22:35.283 which goes from single digit nanograms
NOTE Confidence: 0.821108937263489

03:22:35.283 --> 03:22:38.203 per mill in the blood to 10s to
NOTE Confidence: 0.821108937263489

03:22:38.203 --> 03:22:39.980 hundreds of nanograms per mill.
NOTE Confidence: 0.821108937263489

03:22:39.980 --> 03:22:41.105 In the blood.
NOTE Confidence: 0.821108937263489

03:22:41.105 --> 03:22:43.738 So this is a Ultra High Affinity
NOTE Confidence: 0.821108937263489

03:22:43.740 --> 03:22:45.972 soluble decoy receptor of I'll 18
NOTE Confidence: 0.821108937263489

03:22:45.972 --> 03:22:47.896 where it binds highlighting in
NOTE Confidence: 0.821108937263489

03:22:47.896 --> 03:22:49.384 sterically occludes its ability
NOTE Confidence: 0.821108937263489

03:22:49.384 --> 03:22:50.872 to engage the aisle.

NOTE Confidence: 0.821108937263489

03:22:50.880 --> 03:22:52.765 18 or Alpha Receptor highly

NOTE Confidence: 0.821108937263489

03:22:52.765 --> 03:22:53.519 overlapping interface,

NOTE Confidence: 0.821108937263489

03:22:53.520 --> 03:22:55.770 and I should also point out

NOTE Confidence: 0.821108937263489

03:22:55.770 --> 03:22:57.272 the importance of this.

NOTE Confidence: 0.821108937263489

03:22:57.272 --> 03:22:59.768 Gene is highlighted by the fact that

NOTE Confidence: 0.821108937263489

03:22:59.768 --> 03:23:02.040 the entire poxvirus family has stolen

NOTE Confidence: 0.821108937263489

03:23:02.040 --> 03:23:04.416 all ATP through horizontal gene transfer,

NOTE Confidence: 0.821108937263489

03:23:04.420 --> 03:23:06.634 and it's required for its virulence

NOTE Confidence: 0.821108937263489

03:23:06.634 --> 03:23:08.929 through escape from natural killer cells.

NOTE Confidence: 0.821108937263489

03:23:08.930 --> 03:23:11.190 So clearly the viruses have decided

NOTE Confidence: 0.821108937263489

03:23:11.190 --> 03:23:13.440 that this pathway is very important.

NOTE Confidence: 0.821108937263489

03:23:13.440 --> 03:23:17.115 This gene. Is a very effective one.

NOTE Confidence: 0.821108937263489

03:23:17.120 --> 03:23:17.804 You know,

NOTE Confidence: 0.821108937263489

03:23:17.804 --> 03:23:21.500 in our own biology I like team is is binding.

NOTE Confidence: 0.821108937263489

03:23:21.500 --> 03:23:23.000 Protein is upregulated downstream

NOTE Confidence: 0.821108937263489

03:23:23.000 --> 03:23:24.875 of Interferon Gamma where it
NOTE Confidence: 0.821108937263489

03:23:24.875 --> 03:23:26.610 completes a negative feedback loop.
NOTE Confidence: 0.821108937263489

03:23:26.610 --> 03:23:28.728 That's highly reminiscent of other side
NOTE Confidence: 0.821108937263489

03:23:28.728 --> 03:23:30.575 akinde sorry other immune checkpoints
NOTE Confidence: 0.821108937263489

03:23:30.575 --> 03:23:32.450 and concordant with that idea.
NOTE Confidence: 0.821108937263489

03:23:32.450 --> 03:23:35.005 If you look in that ECG data,
NOTE Confidence: 0.821108937263489

03:23:35.010 --> 03:23:37.030 there's a very strong correlation
NOTE Confidence: 0.821108937263489

03:23:37.030 --> 03:23:39.050 between 18 binding protein expression
NOTE Confidence: 0.821108937263489

03:23:39.110 --> 03:23:40.952 in other checkpoints that PD one
NOTE Confidence: 0.821108937263489

03:23:40.952 --> 03:23:43.039 ticket Tim three name your favorite.
NOTE Confidence: 0.821108937263489

03:23:43.040 --> 03:23:45.610 You'll see a high concordance.
NOTE Confidence: 0.821108937263489

03:23:45.610 --> 03:23:47.680 We looked ourselves, but you know,
NOTE Confidence: 0.821108937263489

03:23:47.680 --> 03:23:48.838 within human tumors,
NOTE Confidence: 0.821108937263489

03:23:48.838 --> 03:23:49.996 by immunohistochemical staining
NOTE Confidence: 0.821108937263489

03:23:49.996 --> 03:23:52.460 and what we found was that most
NOTE Confidence: 0.821108937263489

03:23:52.460 --> 03:23:54.182 tumors had at least punctate levels

NOTE Confidence: 0.821108937263489
03:23:54.182 --> 03:23:55.957 of staining on myeloid cells,
NOTE Confidence: 0.821108937263489
03:23:55.960 --> 03:23:57.690 typically macrophages in the tumor.
NOTE Confidence: 0.821108937263489
03:23:57.690 --> 03:23:59.410 But many types of cancer,
NOTE Confidence: 0.821108937263489
03:23:59.410 --> 03:24:01.135 including those that are not
NOTE Confidence: 0.821108937263489
03:24:01.135 --> 03:24:01.825 particularly Magenic,
NOTE Confidence: 0.821108937263489
03:24:01.830 --> 03:24:04.280 had extensive two to three plus levels
NOTE Confidence: 0.821108937263489
03:24:04.280 --> 03:24:05.969 of staining throughout the tumor.
NOTE Confidence: 0.821108937263489
03:24:05.970 --> 03:24:08.226 We also look systemically in the
NOTE Confidence: 0.821108937263489
03:24:08.226 --> 03:24:10.693 blood of cancer patients and what we
NOTE Confidence: 0.821108937263489
03:24:10.693 --> 03:24:12.866 found was that non small cell lung
NOTE Confidence: 0.821108937263489
03:24:12.866 --> 03:24:14.622 cancer patients have elevated levels
NOTE Confidence: 0.821108937263489
03:24:14.622 --> 03:24:16.740 of the binding protein at baseline.
NOTE Confidence: 0.821108937263489
03:24:16.740 --> 03:24:18.016 And these same patients,
NOTE Confidence: 0.821108937263489
03:24:18.016 --> 03:24:19.930 after treatment with anti PD one
NOTE Confidence: 0.821108937263489
03:24:19.992 --> 03:24:22.140 have further increases in the rally
NOTE Confidence: 0.821108937263489

03:24:22.140 --> 03:24:23.572 team binding protein levels.
NOTE Confidence: 0.821108937263489

03:24:23.580 --> 03:24:25.869 So all of this data together suggested
NOTE Confidence: 0.821108937263489

03:24:25.869 --> 03:24:28.351 that that maybe I'll a team would
NOTE Confidence: 0.821108937263489

03:24:28.351 --> 03:24:30.141 have worked well as immunotherapeutic
NOTE Confidence: 0.821108937263489

03:24:30.141 --> 03:24:32.197 but for this binding protein that's
NOTE Confidence: 0.821108937263489

03:24:32.197 --> 03:24:34.187 acting as a barrier to recombinantly
NOTE Confidence: 0.821108937263489

03:24:34.187 --> 03:24:35.228 18 amino therapy.
NOTE Confidence: 0.821108937263489

03:24:35.228 --> 03:24:38.021 And so it turns out my next door
NOTE Confidence: 0.821108937263489

03:24:38.021 --> 03:24:39.305 neighbor in the lab,
NOTE Confidence: 0.822734177112579

03:24:39.310 --> 03:24:41.188 Richard full Val their group had
NOTE Confidence: 0.822734177112579

03:24:41.188 --> 03:24:43.246 been working with our team binding
NOTE Confidence: 0.822734177112579

03:24:43.246 --> 03:24:45.466 protein knockout mouse for many years.
NOTE Confidence: 0.822734177112579

03:24:45.470 --> 03:24:48.286 So we obtain that that mouse from them.
NOTE Confidence: 0.822734177112579

03:24:48.290 --> 03:24:50.866 And graphs that with MC 38 tumors
NOTE Confidence: 0.822734177112579

03:24:50.866 --> 03:24:53.583 and compared it to the wild type
NOTE Confidence: 0.822734177112579

03:24:53.583 --> 03:24:55.881 litter mates and treated them with

NOTE Confidence: 0.822734177112579
03:24:55.963 --> 03:24:58.218 either sailing or eyelid team.
NOTE Confidence: 0.822734177112579
03:24:58.220 --> 03:25:00.596 And what we found was that
NOTE Confidence: 0.822734177112579
03:25:00.596 --> 03:25:01.784 just like impatience,
NOTE Confidence: 0.822734177112579
03:25:01.790 --> 03:25:03.725 wildtype Valley team has basically
NOTE Confidence: 0.822734177112579
03:25:03.725 --> 03:25:06.160 no activity to reduce tumor growth,
NOTE Confidence: 0.822734177112579
03:25:06.160 --> 03:25:08.470 inhibition or survival, whereas the mice
NOTE Confidence: 0.822734177112579
03:25:08.470 --> 03:25:10.520 that lacked alateen binding protein.
NOTE Confidence: 0.822734177112579
03:25:10.520 --> 03:25:13.696 Even though the tumor could still express it,
NOTE Confidence: 0.822734177112579
03:25:13.700 --> 03:25:16.094 did have a substantial increase in
NOTE Confidence: 0.822734177112579
03:25:16.094 --> 03:25:18.070 its sensitivity to wildstylez team.
NOTE Confidence: 0.822734177112579
03:25:18.070 --> 03:25:19.102 So this really.
NOTE Confidence: 0.822734177112579
03:25:19.102 --> 03:25:22.014 A confirmed to us that the binding protein
NOTE Confidence: 0.822734177112579
03:25:22.014 --> 03:25:25.024 was limiting the activity of violate team.
NOTE Confidence: 0.822734177112579
03:25:25.030 --> 03:25:27.892 So we wondered, what if we could take Kylie
NOTE Confidence: 0.822734177112579
03:25:27.892 --> 03:25:29.800 team binding protein of the equation?
NOTE Confidence: 0.822734177112579

03:25:29.800 --> 03:25:31.680 What if we can make a version of
NOTE Confidence: 0.822734177112579

03:25:31.680 --> 03:25:33.889 I'll 18 that was fully capable of
NOTE Confidence: 0.822734177112579

03:25:33.889 --> 03:25:35.564 engaging its receptor until but
NOTE Confidence: 0.822734177112579

03:25:35.630 --> 03:25:37.485 completely impervious to the binding
NOTE Confidence: 0.822734177112579

03:25:37.485 --> 03:25:39.792 protein that that's such a barrier
NOTE Confidence: 0.822734177112579

03:25:39.792 --> 03:25:41.600 to wild type violentine?
NOTE Confidence: 0.822734177112579

03:25:41.600 --> 03:25:43.832 So I should say this is a really
NOTE Confidence: 0.822734177112579

03:25:43.832 --> 03:25:45.105 tough engineering challenge because
NOTE Confidence: 0.822734177112579

03:25:45.105 --> 03:25:47.079 I'll 18 binds the binding protein
NOTE Confidence: 0.822734177112579

03:25:47.079 --> 03:25:48.800 and the receptor Alpha at.
NOTE Confidence: 0.822734177112579

03:25:48.800 --> 03:25:50.984 Like I said, a highly overlapping interface.
NOTE Confidence: 0.822734177112579

03:25:50.990 --> 03:25:53.055 But making matters worse is that the
NOTE Confidence: 0.822734177112579

03:25:53.055 --> 03:25:55.060 binding protein binds 10,000 times tighter,
NOTE Confidence: 0.822734177112579

03:25:55.060 --> 03:25:57.016 so we couldn't do what others
NOTE Confidence: 0.822734177112579

03:25:57.016 --> 03:25:59.128 have done with I'll two or L15.
NOTE Confidence: 0.822734177112579

03:25:59.130 --> 03:26:00.948 Or we can make selective mutations

NOTE Confidence: 0.822734177112579
03:26:00.948 --> 03:26:02.570 or regulation to a blade,
NOTE Confidence: 0.822734177112579
03:26:02.570 --> 03:26:04.754 one receptor interface and not the other.
NOTE Confidence: 0.822734177112579
03:26:04.760 --> 03:26:06.944 Very difficult to call your shot here.
NOTE Confidence: 0.822734177112579
03:26:06.950 --> 03:26:08.828 So our solution to this problem
NOTE Confidence: 0.822734177112579
03:26:08.828 --> 03:26:09.767 was was evolution.
NOTE Confidence: 0.822734177112579
03:26:09.770 --> 03:26:12.017 We use directed evolution with yeast display.
NOTE Confidence: 0.822734177112579
03:26:12.020 --> 03:26:13.710 To screen about 300 million
NOTE Confidence: 0.822734177112579
03:26:13.710 --> 03:26:15.400 variants of violate team mutated
NOTE Confidence: 0.822734177112579
03:26:15.459 --> 03:26:17.319 at that shared binding interface,
NOTE Confidence: 0.822734177112579
03:26:17.320 --> 03:26:19.348 and we selected for those clones
NOTE Confidence: 0.822734177112579
03:26:19.348 --> 03:26:21.549 that down the aisle 18 receptor.
NOTE Confidence: 0.822734177112579
03:26:21.550 --> 03:26:23.728 Whereas we counter selected against those
NOTE Confidence: 0.822734177112579
03:26:23.728 --> 03:26:26.489 that bound the binding protein and of course,
NOTE Confidence: 0.822734177112579
03:26:26.490 --> 03:26:28.175 repeated this process iteratively and
NOTE Confidence: 0.822734177112579
03:26:28.175 --> 03:26:31.030 what we saw as you monitor the selection
NOTE Confidence: 0.822734177112579

03:26:31.030 --> 03:26:33.910 process over round selection is that we see,
NOTE Confidence: 0.822734177112579

03:26:33.910 --> 03:26:36.388 you know that we're able to completely
NOTE Confidence: 0.822734177112579

03:26:36.388 --> 03:26:38.140 restore binding to the aisle.
NOTE Confidence: 0.822734177112579

03:26:38.140 --> 03:26:40.144 18 Alpha after Mutagen Ising this
NOTE Confidence: 0.822734177112579

03:26:40.144 --> 03:26:42.030 interface and selecting the variance.
NOTE Confidence: 0.822734177112579

03:26:42.030 --> 03:26:43.884 But we're able to completely prevent
NOTE Confidence: 0.822734177112579

03:26:43.884 --> 03:26:45.570 reactivity to the binding protein.
NOTE Confidence: 0.822734177112579

03:26:45.570 --> 03:26:45.895 Ultimately,
NOTE Confidence: 0.822734177112579

03:26:45.895 --> 03:26:48.832 you can see by the round five here where
NOTE Confidence: 0.822734177112579

03:26:48.832 --> 03:26:51.370 there's very strong binding to the R Alpha,
NOTE Confidence: 0.822734177112579

03:26:51.370 --> 03:26:52.650 none to the binding.
NOTE Confidence: 0.822734177112579

03:26:52.650 --> 03:26:55.548 Protein is a big contrast to the wild type.
NOTE Confidence: 0.822734177112579

03:26:55.550 --> 03:26:58.464 I'll 18 and we put these decoy resistant D.
NOTE Confidence: 0.822734177112579

03:26:58.464 --> 03:27:01.030 R18 variants onto NK cells in the dish.
NOTE Confidence: 0.822734177112579

03:27:01.030 --> 03:27:03.582 What we can see is they potently stimulate
NOTE Confidence: 0.822734177112579

03:27:03.582 --> 03:27:05.463 interferon gamma with equal or greater

NOTE Confidence: 0.822734177112579
03:27:05.463 --> 03:27:07.790 greater potency than wild type by lighting.
NOTE Confidence: 0.822734177112579
03:27:07.790 --> 03:27:09.716 But unlike wild set Valley team,
NOTE Confidence: 0.822734177112579
03:27:09.720 --> 03:27:10.713 they're entirely impervious
NOTE Confidence: 0.822734177112579
03:27:10.713 --> 03:27:12.037 to the decode receptor.
NOTE Confidence: 0.822734177112579
03:27:12.040 --> 03:27:13.294 Not at all.
NOTE Confidence: 0.822734177112579
03:27:13.294 --> 03:27:16.220 Inhibited by addition of the binding protein.
NOTE Confidence: 0.822734177112579
03:27:16.220 --> 03:27:16.978 And ultimately,
NOTE Confidence: 0.822734177112579
03:27:16.978 --> 03:27:19.252 we care about is what happens
NOTE Confidence: 0.822734177112579
03:27:19.252 --> 03:27:21.880 when we put this type of molecule
NOTE Confidence: 0.822734177112579
03:27:21.880 --> 03:27:23.736 into a preclinical tumor model.
NOTE Confidence: 0.822734177112579
03:27:23.736 --> 03:27:27.120 And so we started off with the tumor model.
NOTE Confidence: 0.822734177112579
03:27:27.120 --> 03:27:28.624 That's already been discussed
NOTE Confidence: 0.822734177112579
03:27:28.624 --> 03:27:30.128 quite a bit today.
NOTE Confidence: 0.822734177112579
03:27:30.130 --> 03:27:32.010 For for pretty obvious reasons,
NOTE Confidence: 0.822734177112579
03:27:32.010 --> 03:27:33.785 that's the Yammer Melanoma model
NOTE Confidence: 0.822734177112579

03:27:33.785 --> 03:27:35.560 that Marcus Lab created and
NOTE Confidence: 0.777021288871765

03:27:35.622 --> 03:27:37.572 what we found was completely
NOTE Confidence: 0.777021288871765

03:27:37.572 --> 03:27:39.522 consistent with our previous results.
NOTE Confidence: 0.777021288871765

03:27:39.530 --> 03:27:41.410 Completely consistent with Glaxo Smith,
NOTE Confidence: 0.777021288871765

03:27:41.410 --> 03:27:43.290 Kline saw in the clinic,
NOTE Confidence: 0.777021288871765

03:27:43.290 --> 03:27:45.185 wildstylez team does basically nothing
NOTE Confidence: 0.777021288871765

03:27:45.185 --> 03:27:47.869 in terms of tumor growth or survival.
NOTE Confidence: 0.777021288871765

03:27:47.870 --> 03:27:49.440 Where is the decoy resistant?
NOTE Confidence: 0.777021288871765

03:27:49.440 --> 03:27:51.162 I'll 18 had dramatic single agent
NOTE Confidence: 0.777021288871765

03:27:51.162 --> 03:27:53.055 activity that was able to produce
NOTE Confidence: 0.777021288871765

03:27:53.055 --> 03:27:54.775 very market tumor growth inhibition.
NOTE Confidence: 0.777021288871765

03:27:54.780 --> 03:27:56.664 In fact, it could clear established
NOTE Confidence: 0.777021288871765

03:27:56.664 --> 03:27:57.920 tumors in substantial fraction.
NOTE Confidence: 0.777021288871765

03:27:57.920 --> 03:27:59.936 The mice by itself to degree
NOTE Confidence: 0.777021288871765

03:27:59.936 --> 03:28:01.280 that was commensurate effect
NOTE Confidence: 0.777021288871765

03:28:01.345 --> 03:28:02.935 a bit better than NYPD one.

NOTE Confidence: 0.777021288871765
03:28:02.940 --> 03:28:03.780 In this model,
NOTE Confidence: 0.777021288871765
03:28:03.780 --> 03:28:05.460 and the two agents together produced
NOTE Confidence: 0.777021288871765
03:28:05.460 --> 03:28:07.335 a pretty brisk synergism, and,
NOTE Confidence: 0.777021288871765
03:28:07.335 --> 03:28:09.540 you know, not to belabor the point,
NOTE Confidence: 0.777021288871765
03:28:09.540 --> 03:28:11.661 but I just want to say briefly
NOTE Confidence: 0.777021288871765
03:28:11.661 --> 03:28:13.927 that we didn't just use one model.
NOTE Confidence: 0.777021288871765
03:28:13.930 --> 03:28:14.803 We use several,
NOTE Confidence: 0.777021288871765
03:28:14.803 --> 03:28:17.248 and we found that in multiple immuno genic
NOTE Confidence: 0.777021288871765
03:28:17.248 --> 03:28:19.354 models of various degrees of humanity.
NOTE Confidence: 0.777021288871765
03:28:19.360 --> 03:28:21.610 We confirm that the DRA team
NOTE Confidence: 0.777021288871765
03:28:21.610 --> 03:28:23.870 has that single agent activity,
NOTE Confidence: 0.777021288871765
03:28:23.870 --> 03:28:28.010 an synergism with anti PD one.
NOTE Confidence: 0.777021288871765
03:28:28.010 --> 03:28:30.854 So the timing of the mechanism a little bit.
NOTE Confidence: 0.777021288871765
03:28:30.860 --> 03:28:33.244 We first wanted to see what cells are
NOTE Confidence: 0.777021288871765
03:28:33.244 --> 03:28:35.515 required and it should come as no surprise
NOTE Confidence: 0.777021288871765

03:28:35.515 --> 03:28:38.150 that CD 8 cells were absolutely required.

NOTE Confidence: 0.777021288871765

03:28:38.150 --> 03:28:40.460 In these models there was a variable

NOTE Confidence: 0.777021288871765

03:28:40.460 --> 03:28:42.278 requirement for CD4 and NK cells,

NOTE Confidence: 0.777021288871765

03:28:42.280 --> 03:28:43.865 but clearly you know looking

NOTE Confidence: 0.777021288871765

03:28:43.865 --> 03:28:45.450 in the Rag deficient mouse,

NOTE Confidence: 0.777021288871765

03:28:45.450 --> 03:28:47.346 there was no activity of D,

NOTE Confidence: 0.777021288871765

03:28:47.350 --> 03:28:49.246 R18 or actually I should say,

NOTE Confidence: 0.777021288871765

03:28:49.250 --> 03:28:49.566 very,

NOTE Confidence: 0.777021288871765

03:28:49.566 --> 03:28:51.146 very slight tumor growth inhibition,

NOTE Confidence: 0.777021288871765

03:28:51.150 --> 03:28:53.341 but that we could we could restore

NOTE Confidence: 0.777021288871765

03:28:53.341 --> 03:28:55.269 that activity by giving T cells,

NOTE Confidence: 0.777021288871765

03:28:55.270 --> 03:28:57.489 and I think it's really interesting here.

NOTE Confidence: 0.777021288871765

03:28:57.490 --> 03:28:58.757 Is this particular study

NOTE Confidence: 0.777021288871765

03:28:58.757 --> 03:29:00.659 where we took a rag mouse.

NOTE Confidence: 0.777021288871765

03:29:00.660 --> 03:29:02.340 We adoptively transferred T cells.

NOTE Confidence: 0.777021288871765

03:29:02.340 --> 03:29:04.541 I'm from a wild type mouse.

NOTE Confidence: 0.777021288871765
03:29:04.541 --> 03:29:07.276 Is that that in itself is not enough
NOTE Confidence: 0.777021288871765
03:29:07.276 --> 03:29:10.048 to drive tumor clearance in these mice,
NOTE Confidence: 0.777021288871765
03:29:10.050 --> 03:29:12.080 but addition to the D R18 was
NOTE Confidence: 0.777021288871765
03:29:12.080 --> 03:29:13.926 able to enable those adoptively
NOTE Confidence: 0.777021288871765
03:29:13.926 --> 03:29:16.644 transferred cells to clear the tumors,
NOTE Confidence: 0.777021288871765
03:29:16.650 --> 03:29:18.804 and so I'm really hopeful actually
NOTE Confidence: 0.777021288871765
03:29:18.804 --> 03:29:21.054 that this data could provide a
NOTE Confidence: 0.777021288871765
03:29:21.054 --> 03:29:22.919 strong rationale to work with.
NOTE Confidence: 0.777021288871765
03:29:22.920 --> 03:29:24.650 People with my colleague Tristan
NOTE Confidence: 0.777021288871765
03:29:24.650 --> 03:29:26.380 parking and combine agents like
NOTE Confidence: 0.777021288871765
03:29:26.434 --> 03:29:28.180 I'll 18 Indy right inside the
NOTE Confidence: 0.777021288871765
03:29:28.180 --> 03:29:29.840 kinds with adoptive cell therapy.
NOTE Confidence: 0.777021288871765
03:29:29.840 --> 03:29:30.734 In any case,
NOTE Confidence: 0.777021288871765
03:29:30.734 --> 03:29:32.820 we're really curious to know what was
NOTE Confidence: 0.777021288871765
03:29:32.880 --> 03:29:34.878 going on mechanistically on the T
NOTE Confidence: 0.777021288871765

03:29:34.878 --> 03:29:37.060 cells and other immune cell populations
NOTE Confidence: 0.777021288871765

03:29:37.060 --> 03:29:39.015 after treatment with the R18.
NOTE Confidence: 0.777021288871765

03:29:39.020 --> 03:29:41.400 And so we perform single cell RNA
NOTE Confidence: 0.777021288871765

03:29:41.400 --> 03:29:43.428 sequencing of D, R18 treated tumors,
NOTE Confidence: 0.777021288871765

03:29:43.428 --> 03:29:45.780 and what we found was that compared
NOTE Confidence: 0.777021288871765

03:29:45.843 --> 03:29:47.859 to wild type or Saline treatment,
NOTE Confidence: 0.777021288871765

03:29:47.860 --> 03:29:50.142 that dear I team had elicited dramatic
NOTE Confidence: 0.777021288871765

03:29:50.142 --> 03:29:51.940 remodeling of the entire tumor.
NOTE Confidence: 0.777021288871765

03:29:51.940 --> 03:29:52.960 Immune macro environment,
NOTE Confidence: 0.777021288871765

03:29:52.960 --> 03:29:55.000 not just in T cells here,
NOTE Confidence: 0.777021288871765

03:29:55.000 --> 03:29:57.040 but also in the myeloid populations.
NOTE Confidence: 0.777021288871765

03:29:57.040 --> 03:29:59.364 We see the new appearance of a
NOTE Confidence: 0.777021288871765

03:29:59.364 --> 03:30:01.189 grainless site population even changes.
NOTE Confidence: 0.777021288871765

03:30:01.190 --> 03:30:01.832 In fibroblasts,
NOTE Confidence: 0.777021288871765

03:30:01.832 --> 03:30:03.758 but really we think that these
NOTE Confidence: 0.777021288871765

03:30:03.758 --> 03:30:05.393 changes are really being centrally

NOTE Confidence: 0.777021288871765
03:30:05.393 --> 03:30:07.563 driven by effects on the T cells.
NOTE Confidence: 0.777021288871765
03:30:07.570 --> 03:30:09.786 And so when you zoom in and the
NOTE Confidence: 0.777021288871765
03:30:09.786 --> 03:30:11.080 T cell clusters,
NOTE Confidence: 0.777021288871765
03:30:11.080 --> 03:30:13.033 what you see is that in wild
NOTE Confidence: 0.777021288871765
03:30:13.033 --> 03:30:14.910 type or Saline treated animal,
NOTE Confidence: 0.777021288871765
03:30:14.910 --> 03:30:16.940 the vast majority of the T cells
NOTE Confidence: 0.777021288871765
03:30:16.940 --> 03:30:18.740 are in this cluster tube,
NOTE Confidence: 0.777021288871765
03:30:18.740 --> 03:30:20.987 whereas in the D R18 treated animals
NOTE Confidence: 0.777021288871765
03:30:20.987 --> 03:30:23.199 the vast majority are in this cluster,
NOTE Confidence: 0.777021288871765
03:30:23.200 --> 03:30:24.770 one which is uniquely populated
NOTE Confidence: 0.777021288871765
03:30:24.770 --> 03:30:26.340 by the D R18 treated
NOTE Confidence: 0.78225189447403
03:30:26.407 --> 03:30:28.656 mice. I also want to point out that
NOTE Confidence: 0.78225189447403
03:30:28.656 --> 03:30:30.626 the writing also elicits a reasonable
NOTE Confidence: 0.78225189447403
03:30:30.626 --> 03:30:33.484 number of cells in this cluster. 5 here.
NOTE Confidence: 0.78225189447403
03:30:33.484 --> 03:30:35.626 And we actually analyze that the
NOTE Confidence: 0.78225189447403

03:30:35.626 --> 03:30:37.779 transcripts that define these clusters.
NOTE Confidence: 0.78225189447403

03:30:37.780 --> 03:30:40.588 What you see is that cluster two is
NOTE Confidence: 0.78225189447403

03:30:40.588 --> 03:30:43.659 defined by very high expression of talks,
NOTE Confidence: 0.78225189447403

03:30:43.660 --> 03:30:45.228 expression of exhaustion markers
NOTE Confidence: 0.78225189447403

03:30:45.228 --> 03:30:46.796 like CD244 and CD101.
NOTE Confidence: 0.78225189447403

03:30:46.800 --> 03:30:48.645 Very high expression of PD
NOTE Confidence: 0.78225189447403

03:30:48.645 --> 03:30:51.110 one and lag three and absent.
NOTE Confidence: 0.78225189447403

03:30:51.110 --> 03:30:52.442 Expression of costimulatory markers
NOTE Confidence: 0.78225189447403

03:30:52.442 --> 03:30:55.377 like CD 28 and I costs and concordantly
NOTE Confidence: 0.78225189447403

03:30:55.377 --> 03:30:57.562 decreased levels of effector cytokines
NOTE Confidence: 0.78225189447403

03:30:57.562 --> 03:30:59.718 and increased levels of immunosuppressive
NOTE Confidence: 0.78225189447403

03:30:59.718 --> 03:31:01.688 cytokines of TGF beta male.
NOTE Confidence: 0.78225189447403

03:31:01.690 --> 03:31:02.869 10 so really.
NOTE Confidence: 0.78225189447403

03:31:02.869 --> 03:31:05.620 We can say definitively that cluster 2.
NOTE Confidence: 0.78225189447403

03:31:05.620 --> 03:31:08.035 Is is the exhausted Lenny edge here.
NOTE Confidence: 0.78225189447403

03:31:08.040 --> 03:31:08.732 By contrast,

NOTE Confidence: 0.78225189447403

03:31:08.732 --> 03:31:11.155 cluster one is the exact opposite, right?

NOTE Confidence: 0.78225189447403

03:31:11.155 --> 03:31:13.225 And this is the DRT intercluster.

NOTE Confidence: 0.78225189447403

03:31:13.230 --> 03:31:13.575 Basically,

NOTE Confidence: 0.78225189447403

03:31:13.575 --> 03:31:15.645 no talks doesn't have those exhaustion.

NOTE Confidence: 0.78225189447403

03:31:15.650 --> 03:31:17.380 Markers instead has markers of

NOTE Confidence: 0.78225189447403

03:31:17.380 --> 03:31:18.418 T cell maturation.

NOTE Confidence: 0.78225189447403

03:31:18.420 --> 03:31:20.150 Cal RG1 I'll 18 receptors.

NOTE Confidence: 0.78225189447403

03:31:20.150 --> 03:31:22.334 The highest levels of Interferon Gamma and

NOTE Confidence: 0.78225189447403

03:31:22.334 --> 03:31:24.649 very high levels of costimulatory markers.

NOTE Confidence: 0.78225189447403

03:31:24.650 --> 03:31:27.154 So we would say that these are really

NOTE Confidence: 0.78225189447403

03:31:27.154 --> 03:31:29.489 a good example of that effect.

NOTE Confidence: 0.78225189447403

03:31:29.490 --> 03:31:30.531 Or Lenny Edge,

NOTE Confidence: 0.78225189447403

03:31:30.531 --> 03:31:32.952 and then that cluster five that I

NOTE Confidence: 0.78225189447403

03:31:32.952 --> 03:31:34.336 think is particularly interesting,

NOTE Confidence: 0.78225189447403

03:31:34.340 --> 03:31:36.839 has a little bit of PD one.

NOTE Confidence: 0.78225189447403

03:31:36.840 --> 03:31:39.480 As a little bit of a factor function,
NOTE Confidence: 0.78225189447403

03:31:39.480 --> 03:31:40.800 but importantly has intermediate
NOTE Confidence: 0.78225189447403

03:31:40.800 --> 03:31:42.120 levels of TCF seven,
NOTE Confidence: 0.78225189447403

03:31:42.120 --> 03:31:44.100 which encodes the gene product TCF.
NOTE Confidence: 0.78225189447403

03:31:44.100 --> 03:31:46.740 One hard to see in this heat map,
NOTE Confidence: 0.78225189447403

03:31:46.740 --> 03:31:48.720 but take my word for it,
NOTE Confidence: 0.78225189447403

03:31:48.720 --> 03:31:51.690 that there's there's a bit of yellow here in.
NOTE Confidence: 0.78225189447403

03:31:51.690 --> 03:31:53.320 This suggests that this population
NOTE Confidence: 0.78225189447403

03:31:53.320 --> 03:31:54.624 cluster five could represent
NOTE Confidence: 0.78225189447403

03:31:54.624 --> 03:31:56.070 that resource population that
NOTE Confidence: 0.78225189447403

03:31:56.070 --> 03:31:57.490 stem like precursor populations
NOTE Confidence: 0.78225189447403

03:31:57.490 --> 03:31:59.279 been talked about so much today,
NOTE Confidence: 0.78225189447403

03:31:59.280 --> 03:32:01.345 and so I'm not going to give
NOTE Confidence: 0.78225189447403

03:32:01.345 --> 03:32:03.039 too much background about those
NOTE Confidence: 0.78225189447403

03:32:03.039 --> 03:32:04.884 cells because Nick get raffia.
NOTE Confidence: 0.78225189447403

03:32:04.890 --> 03:32:06.238 Many others have already

NOTE Confidence: 0.78225189447403

03:32:06.238 --> 03:32:07.249 really discussed them.

NOTE Confidence: 0.78225189447403

03:32:07.250 --> 03:32:10.292 You know at much greater length than I could,

NOTE Confidence: 0.78225189447403

03:32:10.300 --> 03:32:13.012 but we really wanted to to look into

NOTE Confidence: 0.78225189447403

03:32:13.012 --> 03:32:15.247 the idea that that DRA team could be

NOTE Confidence: 0.78225189447403

03:32:15.247 --> 03:32:17.267 acting on this stem like population

NOTE Confidence: 0.78225189447403

03:32:17.267 --> 03:32:19.172 in Skewing the differentiation of

NOTE Confidence: 0.78225189447403

03:32:19.172 --> 03:32:21.403 these cells away from the exhausted

NOTE Confidence: 0.78225189447403

03:32:21.403 --> 03:32:23.515 Lenny Edge and Tord highly effective,

NOTE Confidence: 0.78225189447403

03:32:23.520 --> 03:32:25.220 highly effective effector Lenny edge.

NOTE Confidence: 0.78225189447403

03:32:25.220 --> 03:32:27.836 So we look by flow cytometry at the

NOTE Confidence: 0.78225189447403

03:32:27.836 --> 03:32:29.958 expression of talks in these cells,

NOTE Confidence: 0.78225189447403

03:32:29.960 --> 03:32:32.417 and what you can see is that Saline and

NOTE Confidence: 0.78225189447403

03:32:32.417 --> 03:32:34.467 wild type treated animals have high

NOTE Confidence: 0.78225189447403

03:32:34.467 --> 03:32:37.419 levels of talks on their initial experience.

NOTE Confidence: 0.78225189447403

03:32:37.420 --> 03:32:39.100 CD 44 high cells.

NOTE Confidence: 0.78225189447403

03:32:39.100 --> 03:32:40.780 Whereas with deer 18,
NOTE Confidence: 0.78225189447403

03:32:40.780 --> 03:32:43.208 that level is greatly decreased
NOTE Confidence: 0.78225189447403

03:32:43.210 --> 03:32:45.630 in concordance with that finding,
NOTE Confidence: 0.78225189447403

03:32:45.630 --> 03:32:48.070 we see that deer 18.
NOTE Confidence: 0.78225189447403

03:32:48.070 --> 03:32:49.638 Lymphocytes have the highest
NOTE Confidence: 0.78225189447403

03:32:49.638 --> 03:32:51.206 level of Poly functionality,
NOTE Confidence: 0.78225189447403

03:32:51.210 --> 03:32:54.354 meaning they don't just make 1 sided kind.
NOTE Confidence: 0.78225189447403

03:32:54.360 --> 03:32:56.320 That makes several interferon gamma,
NOTE Confidence: 0.78225189447403

03:32:56.320 --> 03:32:58.204 Tina Falfa, and grandson,
NOTE Confidence: 0.78225189447403

03:32:58.204 --> 03:33:00.559 so they're really quite active
NOTE Confidence: 0.78225189447403

03:33:00.559 --> 03:33:01.689 effector T cells.
NOTE Confidence: 0.78225189447403

03:33:01.690 --> 03:33:02.761 But you know,
NOTE Confidence: 0.78225189447403

03:33:02.761 --> 03:33:04.903 in addition to skewing the differentiation
NOTE Confidence: 0.78225189447403

03:33:04.903 --> 03:33:07.258 of these stem like precursor cells,
NOTE Confidence: 0.78225189447403

03:33:07.260 --> 03:33:09.850 we also wondered what was the effect
NOTE Confidence: 0.78225189447403

03:33:09.850 --> 03:33:12.079 on the frequency of these cells.

NOTE Confidence: 0.78225189447403

03:33:12.080 --> 03:33:13.838 Now we know that these cells

NOTE Confidence: 0.78225189447403

03:33:13.838 --> 03:33:15.010 are absolutely critical for

NOTE Confidence: 0.78225189447403

03:33:15.064 --> 03:33:16.530 immunotherapeutic responses,

NOTE Confidence: 0.78225189447403

03:33:16.530 --> 03:33:19.246 but the problem is that the checkpoint

NOTE Confidence: 0.78225189447403

03:33:19.246 --> 03:33:21.348 inhibition by itself and I just

NOTE Confidence: 0.78225189447403

03:33:21.348 --> 03:33:23.371 want to make a point that studies

NOTE Confidence: 0.78225189447403

03:33:23.445 --> 03:33:25.971 by Sadiki and others usually looked

NOTE Confidence: 0.78225189447403

03:33:25.971 --> 03:33:27.655 at combination of checkpoint

NOTE Confidence: 0.814510941505432

03:33:27.660 --> 03:33:29.886 with vaccination or CTA for blockade,

NOTE Confidence: 0.814510941505432

03:33:29.890 --> 03:33:31.398 which which will have

NOTE Confidence: 0.814510941505432

03:33:31.398 --> 03:33:32.529 other signaling effects.

NOTE Confidence: 0.814510941505432

03:33:32.530 --> 03:33:34.265 Particularly in in delivering a

NOTE Confidence: 0.814510941505432

03:33:34.265 --> 03:33:36.435 costimulatory signal but PD one blockade

NOTE Confidence: 0.814510941505432

03:33:36.435 --> 03:33:38.315 alone tends to actually consume.

NOTE Confidence: 0.814510941505432

03:33:38.320 --> 03:33:40.495 These cells were at least promote

NOTE Confidence: 0.814510941505432

03:33:40.495 --> 03:33:41.590 their terminal differentiation.
NOTE Confidence: 0.814510941505432

03:33:41.590 --> 03:33:44.155 This is what Nick hanging hanging script
NOTE Confidence: 0.814510941505432

03:33:44.155 --> 03:33:46.290 found, and also what we confirmed.
NOTE Confidence: 0.814510941505432

03:33:46.290 --> 03:33:48.342 Actually we found when we looked
NOTE Confidence: 0.814510941505432

03:33:48.342 --> 03:33:50.462 in tumors that were treated with
NOTE Confidence: 0.814510941505432

03:33:50.462 --> 03:33:52.856 anti PD one or Saline that there
NOTE Confidence: 0.814510941505432

03:33:52.856 --> 03:33:55.207 really wasn't a difference in the
NOTE Confidence: 0.814510941505432

03:33:55.207 --> 03:33:57.147 absolute numbers or frequency of
NOTE Confidence: 0.814510941505432

03:33:57.150 --> 03:33:58.960 these stem like precursor cells.
NOTE Confidence: 0.814510941505432

03:33:58.960 --> 03:34:00.755 Contrast at Dri team dramatically
NOTE Confidence: 0.814510941505432

03:34:00.755 --> 03:34:02.866 expanded the numbers and frequency of
NOTE Confidence: 0.814510941505432

03:34:02.866 --> 03:34:04.679 these of these precursor cells in the
NOTE Confidence: 0.814510941505432

03:34:04.679 --> 03:34:07.098 tumor by greater than an order of magnitude.
NOTE Confidence: 0.814510941505432

03:34:07.100 --> 03:34:07.712 And really,
NOTE Confidence: 0.814510941505432

03:34:07.712 --> 03:34:10.160 I think the MFI of the flow cytometry
NOTE Confidence: 0.814510941505432

03:34:10.230 --> 03:34:12.258 paints quite a picture that there's

NOTE Confidence: 0.814510941505432

03:34:12.258 --> 03:34:14.516 really more than a decade of staining

NOTE Confidence: 0.814510941505432

03:34:14.516 --> 03:34:16.803 of TCF one on these on the PD,

NOTE Confidence: 0.814510941505432

03:34:16.803 --> 03:34:17.742 one positive cells,

NOTE Confidence: 0.814510941505432

03:34:17.742 --> 03:34:19.620 and there are in the tumor,

NOTE Confidence: 0.814510941505432

03:34:19.620 --> 03:34:22.116 but I think Nick made a great point.

NOTE Confidence: 0.814510941505432

03:34:22.120 --> 03:34:22.748 Which is,

NOTE Confidence: 0.814510941505432

03:34:22.748 --> 03:34:23.376 you know,

NOTE Confidence: 0.814510941505432

03:34:23.376 --> 03:34:25.494 are these acting on the stem like

NOTE Confidence: 0.814510941505432

03:34:25.494 --> 03:34:27.222 cells in the tumor and maintaining

NOTE Confidence: 0.814510941505432

03:34:27.222 --> 03:34:29.008 their stemness or promoting them?

NOTE Confidence: 0.814510941505432

03:34:29.010 --> 03:34:31.082 Or is it acting upstream in the lymph

NOTE Confidence: 0.814510941505432

03:34:31.082 --> 03:34:33.524 node and we can't really pinpoint that

NOTE Confidence: 0.814510941505432

03:34:33.524 --> 03:34:35.384 particular distinction in our tumor,

NOTE Confidence: 0.814510941505432

03:34:35.390 --> 03:34:37.616 but I do want to point out,

NOTE Confidence: 0.814510941505432

03:34:37.620 --> 03:34:39.942 and I was inspired by Nick to put this

NOTE Confidence: 0.814510941505432

03:34:39.942 --> 03:34:42.378 in my talk at the last second that
NOTE Confidence: 0.814510941505432

03:34:42.378 --> 03:34:44.117 DRA team doesn't dramatically expand
NOTE Confidence: 0.814510941505432

03:34:44.117 --> 03:34:46.805 the frequency of these of these stem
NOTE Confidence: 0.814510941505432

03:34:46.805 --> 03:34:49.110 like cells within the draining lymph nodes.
NOTE Confidence: 0.814510941505432

03:34:49.110 --> 03:34:51.638 I think this provides good evidence for Nicks
NOTE Confidence: 0.814510941505432

03:34:51.638 --> 03:34:53.569 hypothesis that the draining lymph node,
NOTE Confidence: 0.814510941505432

03:34:53.570 --> 03:34:56.540 maybe that the prime target for
NOTE Confidence: 0.814510941505432

03:34:56.540 --> 03:34:58.520 checkpoint another immuno therapies.
NOTE Confidence: 0.814510941505432

03:34:58.520 --> 03:35:00.060 I'm going to switch gears
NOTE Confidence: 0.814510941505432

03:35:00.060 --> 03:35:02.000 and just say that you know,
NOTE Confidence: 0.814510941505432

03:35:02.000 --> 03:35:04.208 I told you earlier that that alley team
NOTE Confidence: 0.814510941505432

03:35:04.208 --> 03:35:06.100 receptors is actually most prevalent.
NOTE Confidence: 0.814510941505432

03:35:06.100 --> 03:35:08.476 Lee found in on NK cells and if you
NOTE Confidence: 0.814510941505432

03:35:08.476 --> 03:35:10.910 look in the blood and you stimulate
NOTE Confidence: 0.814510941505432

03:35:10.910 --> 03:35:13.369 peripheral blood PB MC with ally team.
NOTE Confidence: 0.814510941505432

03:35:13.370 --> 03:35:15.400 But by far and away the vast

NOTE Confidence: 0.814510941505432
03:35:15.400 --> 03:35:17.159 majority of cells that respond,
NOTE Confidence: 0.814510941505432
03:35:17.160 --> 03:35:19.113 ex vivo are natural killer cells and
NOTE Confidence: 0.814510941505432
03:35:19.113 --> 03:35:21.500 so that made us wonder if there were
NOTE Confidence: 0.814510941505432
03:35:21.500 --> 03:35:23.401 there were settings where we could
NOTE Confidence: 0.814510941505432
03:35:23.401 --> 03:35:25.555 leverage that activity and NK cells
NOTE Confidence: 0.814510941505432
03:35:25.555 --> 03:35:27.290 therapeutically in an obvious candidate
NOTE Confidence: 0.814510941505432
03:35:27.290 --> 03:35:29.565 for that type of approach would be.
NOTE Confidence: 0.814510941505432
03:35:29.570 --> 03:35:31.038 In that immune checkpoint
NOTE Confidence: 0.814510941505432
03:35:31.038 --> 03:35:32.873 resistance setting where loss of
NOTE Confidence: 0.814510941505432
03:35:32.873 --> 03:35:35.187 antigen presentation is one of the
NOTE Confidence: 0.814510941505432
03:35:35.187 --> 03:35:36.695 dominant mechanisms of resistance,
NOTE Confidence: 0.814510941505432
03:35:36.700 --> 03:35:39.884 and in fact it's really a common finding
NOTE Confidence: 0.814510941505432
03:35:39.884 --> 03:35:42.569 where reduced or absent image C Class one
NOTE Confidence: 0.814510941505432
03:35:42.569 --> 03:35:45.700 is found in a large fraction of tumors,
NOTE Confidence: 0.814510941505432
03:35:45.700 --> 03:35:47.575 even prior to any therapy
NOTE Confidence: 0.814510941505432

03:35:47.575 --> 03:35:49.450 just in the primary setting.
NOTE Confidence: 0.814510941505432

03:35:49.450 --> 03:35:51.320 Depending on the tumor type,
NOTE Confidence: 0.814510941505432

03:35:51.320 --> 03:35:55.540 can reach as high as 50% or so.
NOTE Confidence: 0.814510941505432

03:35:55.540 --> 03:35:58.474 Up now know the dog with me nology would
NOTE Confidence: 0.814510941505432

03:35:58.474 --> 03:36:01.846 be that if you have a large mass of class,
NOTE Confidence: 0.814510941505432

03:36:01.850 --> 03:36:03.510 one deficient cells that those
NOTE Confidence: 0.814510941505432

03:36:03.510 --> 03:36:04.838 cells would be resistant,
NOTE Confidence: 0.814510941505432

03:36:04.840 --> 03:36:06.495 those cells will be quickly
NOTE Confidence: 0.814510941505432

03:36:06.495 --> 03:36:07.819 cleared by NK cells.
NOTE Confidence: 0.814510941505432

03:36:07.820 --> 03:36:10.186 But in reality we know from from.
NOTE Confidence: 0.814510941505432

03:36:10.190 --> 03:36:12.955 From David relays work that these cells
NOTE Confidence: 0.814510941505432

03:36:12.955 --> 03:36:15.190 become rapidly exhausted in the tumor in,
NOTE Confidence: 0.814510941505432

03:36:15.190 --> 03:36:16.498 we essentially have found
NOTE Confidence: 0.814510941505432

03:36:16.498 --> 03:36:18.460 the same effect that NK cells
NOTE Confidence: 0.7414790391922

03:36:18.521 --> 03:36:20.897 within tumors have very little activity,
NOTE Confidence: 0.7414790391922

03:36:20.900 --> 03:36:23.399 and to make a Long story short,

NOTE Confidence: 0.7414790391922

03:36:23.400 --> 03:36:25.296 we found that we could reverse

NOTE Confidence: 0.7414790391922

03:36:25.296 --> 03:36:27.336 that phenotype and have promote NK

NOTE Confidence: 0.7414790391922

03:36:27.336 --> 03:36:29.121 cell responses against numerous and

NOTE Confidence: 0.7414790391922

03:36:29.121 --> 03:36:31.250 Macy class one deficient tumors.

NOTE Confidence: 0.7414790391922

03:36:31.250 --> 03:36:33.000 Different models where we deleted

NOTE Confidence: 0.7414790391922

03:36:33.000 --> 03:36:35.543 beta 2M or where the cells naturally

NOTE Confidence: 0.7414790391922

03:36:35.543 --> 03:36:37.721 lacked absent in terms of looking

NOTE Confidence: 0.7414790391922

03:36:37.721 --> 03:36:40.199 at the NK phenotypes that we see.

NOTE Confidence: 0.7414790391922

03:36:40.200 --> 03:36:42.550 Is that the I-18 treatment

NOTE Confidence: 0.7414790391922

03:36:42.550 --> 03:36:44.430 drives and queso Mac?

NOTE Confidence: 0.7414790391922

03:36:44.430 --> 03:36:47.155 Maturation again drives that NK

NOTE Confidence: 0.7414790391922

03:36:47.155 --> 03:36:48.790 cell polyfunctional phenotype.

NOTE Confidence: 0.7414790391922

03:36:48.790 --> 03:36:50.340 So just to wrap up,

NOTE Confidence: 0.7414790391922

03:36:50.340 --> 03:36:52.068 by hopefully I've shown you today

NOTE Confidence: 0.7414790391922

03:36:52.068 --> 03:36:54.157 that what makes the alley team pathway

NOTE Confidence: 0.7414790391922

03:36:54.157 --> 03:36:56.002 compelling is that the receptors
NOTE Confidence: 0.7414790391922

03:36:56.002 --> 03:36:58.083 really selective toward the right T
NOTE Confidence: 0.7414790391922

03:36:58.083 --> 03:36:59.980 cells as well as natural killer cells
NOTE Confidence: 0.7414790391922

03:36:59.980 --> 03:37:02.120 that it could be a great target.
NOTE Confidence: 0.7414790391922

03:37:02.120 --> 03:37:03.670 But for this binding protein,
NOTE Confidence: 0.7414790391922

03:37:03.670 --> 03:37:05.534 and if you can find ways to avoid
NOTE Confidence: 0.7414790391922

03:37:05.534 --> 03:37:07.492 the binding protein that that Alley
NOTE Confidence: 0.7414790391922

03:37:07.492 --> 03:37:09.282 Team receptor agonism is remarkably
NOTE Confidence: 0.7414790391922

03:37:09.282 --> 03:37:10.678 effective in particularly expanding
NOTE Confidence: 0.7414790391922

03:37:10.678 --> 03:37:12.967 the numbers of TCF one positive cells
NOTE Confidence: 0.7414790391922

03:37:12.970 --> 03:37:14.210 and Skewing their differentiation
NOTE Confidence: 0.7414790391922

03:37:14.210 --> 03:37:16.070 away from the exhaustive Lenny Edge.
NOTE Confidence: 0.7414790391922

03:37:16.070 --> 03:37:18.860 I just wanted to point out that you know,
NOTE Confidence: 0.7414790391922

03:37:18.860 --> 03:37:19.520 we're really.
NOTE Confidence: 0.7414790391922

03:37:19.520 --> 03:37:20.180 You know,
NOTE Confidence: 0.7414790391922

03:37:20.180 --> 03:37:21.830 motivated to briskly move this

NOTE Confidence: 0.7414790391922

03:37:21.830 --> 03:37:23.119 into clinical trials,

NOTE Confidence: 0.7414790391922

03:37:23.120 --> 03:37:25.647 particularly here at the Yale Cancer Center,

NOTE Confidence: 0.7414790391922

03:37:25.650 --> 03:37:28.546 where our phase one team is so accomplished.

NOTE Confidence: 0.7414790391922

03:37:28.550 --> 03:37:31.446 And so I thought I'd put this picture,

NOTE Confidence: 0.7414790391922

03:37:31.450 --> 03:37:33.484 which represents about half a kilogram

NOTE Confidence: 0.7414790391922

03:37:33.484 --> 03:37:35.789 of our lead DRA teen compound.

NOTE Confidence: 0.7414790391922

03:37:35.790 --> 03:37:38.317 It's now been produced under GNP conditions,

NOTE Confidence: 0.7414790391922

03:37:38.320 --> 03:37:41.240 and we should be able to start our

NOTE Confidence: 0.7414790391922

03:37:41.240 --> 03:37:44.118 first trial in the first half of 2021.

NOTE Confidence: 0.7414790391922

03:37:44.120 --> 03:37:46.660 So I just want to briefly acknowledge

NOTE Confidence: 0.7414790391922

03:37:46.660 --> 03:37:48.510 the people who were instrumental

NOTE Confidence: 0.7414790391922

03:37:48.510 --> 03:37:49.990 in driving this program.

NOTE Confidence: 0.7414790391922

03:37:49.990 --> 03:37:51.306 My Postdoc Ting Joe,

NOTE Confidence: 0.7414790391922

03:37:51.306 --> 03:37:53.798 who is just accepted a job at

NOTE Confidence: 0.7414790391922

03:37:53.798 --> 03:37:55.590 Westlake University in China,

NOTE Confidence: 0.7414790391922

03:37:55.590 --> 03:37:57.450 graduate student or L Weitzman,
NOTE Confidence: 0.7414790391922

03:37:57.450 --> 03:38:00.054 who's really actually in the Kiko slab,
NOTE Confidence: 0.7414790391922

03:38:00.060 --> 03:38:01.920 built Dembski who's a dermatology
NOTE Confidence: 0.7414790391922

03:38:01.920 --> 03:38:03.789 assistant professor, and of course,
NOTE Confidence: 0.7414790391922

03:38:03.789 --> 03:38:05.281 our stalwart collaborator Marcus
NOTE Confidence: 0.7414790391922

03:38:05.281 --> 03:38:07.189 bosenberg in numerous other collaborators
NOTE Confidence: 0.7414790391922

03:38:07.189 --> 03:38:09.004 here at Yale and elsewhere.
NOTE Confidence: 0.7414790391922

03:38:09.010 --> 03:38:10.147 So of course,
NOTE Confidence: 0.7414790391922

03:38:10.147 --> 03:38:12.042 acknowledge our funding sources and
NOTE Confidence: 0.7414790391922

03:38:12.042 --> 03:38:14.607 thank you so much for your attention.
NOTE Confidence: 0.825485289096832

03:38:16.840 --> 03:38:20.800 Great, thank you so much air and it's been
NOTE Confidence: 0.825485289096832

03:38:20.800 --> 03:38:24.320 a pleasure to actually see that story evolved
NOTE Confidence: 0.825485289096832

03:38:24.320 --> 03:38:27.840 since the first time that we've heard that
NOTE Confidence: 0.825485289096832

03:38:27.840 --> 03:38:30.920 there's a question from the audience. So
NOTE Confidence: 0.825485289096832

03:38:30.920 --> 03:38:33.560 do you think D R18 would
NOTE Confidence: 0.825485289096832

03:38:33.560 --> 03:38:37.520 be useful in lymphomas? Wear? My T 88 is

NOTE Confidence: 0.825485289096832

03:38:37.520 --> 03:38:39.720 mutated in such things as

NOTE Confidence: 0.825485289096832

03:38:39.720 --> 03:38:43.240 ABC diffuse, large B cell lymphoma, or in

NOTE Confidence: 0.825485289096832

03:38:43.240 --> 03:38:45.880 diseases like Walden store macro anemia.

NOTE Confidence: 0.8290194272995

03:38:46.950 --> 03:38:49.785 Right, yeah, you thank you for that

NOTE Confidence: 0.8290194272995

03:38:49.785 --> 03:38:53.206 question so you know I'm not really sure

NOTE Confidence: 0.8290194272995

03:38:53.206 --> 03:38:55.978 what the expression Valley Team receptor

NOTE Confidence: 0.8290194272995

03:38:55.978 --> 03:38:59.127 would be on the tumor cells in that case,

NOTE Confidence: 0.8290194272995

03:38:59.130 --> 03:39:01.797 and if it would be desirable actually

NOTE Confidence: 0.8290194272995

03:39:01.797 --> 03:39:03.999 to further stimulate those pathways.

NOTE Confidence: 0.8290194272995

03:39:04.000 --> 03:39:07.520 But in terms of thinking about the potential

NOTE Confidence: 0.8290194272995

03:39:07.520 --> 03:39:09.687 clinical indications for D R18 therapy,

NOTE Confidence: 0.8290194272995

03:39:09.690 --> 03:39:12.525 I think lymphoma is a good one.

NOTE Confidence: 0.8290194272995

03:39:12.530 --> 03:39:15.008 Maybe not in monotherapy, but in

NOTE Confidence: 0.8290194272995

03:39:15.008 --> 03:39:17.040 combination with tumor optimizing auto.

NOTE Confidence: 0.8290194272995

03:39:17.040 --> 03:39:19.320 Sing antibodies CD20 CD 19,

NOTE Confidence: 0.8290194272995

03:39:19.320 --> 03:39:22.141 where we know that I'll 18 can
NOTE Confidence: 0.8290194272995

03:39:22.141 --> 03:39:23.971 robustly stimulated antibody directed
NOTE Confidence: 0.8290194272995

03:39:23.971 --> 03:39:26.159 cell mediated cytotoxicity ADC.
NOTE Confidence: 0.8290194272995

03:39:26.160 --> 03:39:29.345 Also, we haven't looked at this yet,
NOTE Confidence: 0.8290194272995

03:39:29.350 --> 03:39:33.190 but I really want to would be to look at
NOTE Confidence: 0.8290194272995

03:39:33.293 --> 03:39:37.136 you know 18 agonism in combination with.
NOTE Confidence: 0.8290194272995

03:39:37.140 --> 03:39:38.532 T cell, engager, therapies,
NOTE Confidence: 0.8290194272995

03:39:38.532 --> 03:39:39.174 bites, etc,
NOTE Confidence: 0.8290194272995

03:39:39.174 --> 03:39:41.526 as well as in engineered T cell therapies
NOTE Confidence: 0.8290194272995

03:39:41.526 --> 03:39:43.960 that that potentially could be used in
NOTE Confidence: 0.8290194272995

03:39:43.960 --> 03:39:46.160 these types of hematologic malignancy's.
NOTE Confidence: 0.8290194272995

03:39:46.160 --> 03:39:49.342 So yeah, I don't know if I if I can really
NOTE Confidence: 0.8290194272995

03:39:49.342 --> 03:39:52.408 say much about the exact mutation here,
NOTE Confidence: 0.8290194272995

03:39:52.410 --> 03:39:54.626 but I do think that the tile 18
NOTE Confidence: 0.8290194272995

03:39:54.626 --> 03:39:56.949 could be useful in those pathway
NOTE Confidence: 0.8290194272995

03:39:56.949 --> 03:39:58.645 in in those malignancies.

NOTE Confidence: 0.795908570289612
03:40:02.570 --> 03:40:05.530 Ask questions. Yeah,
NOTE Confidence: 0.795908570289612
03:40:05.530 --> 03:40:08.682 so I was intrigued by your your engineering
NOTE Confidence: 0.795908570289612
03:40:08.682 --> 03:40:11.450 graph and this idea that it looked
NOTE Confidence: 0.795908570289612
03:40:11.450 --> 03:40:13.820 like maybe I'm just misreading it,
NOTE Confidence: 0.795908570289612
03:40:13.820 --> 03:40:17.089 but it looked like gaining that the.
NOTE Confidence: 0.795908570289612
03:40:17.090 --> 03:40:18.935 The initial contract may have
NOTE Confidence: 0.795908570289612
03:40:18.935 --> 03:40:21.195 had lower no affinity for I'll
NOTE Confidence: 0.795908570289612
03:40:21.195 --> 03:40:22.925 18 and the decoy receptor.
NOTE Confidence: 0.795908570289612
03:40:22.930 --> 03:40:25.352 What really changed was the gain of
NOTE Confidence: 0.795908570289612
03:40:25.352 --> 03:40:26.950 Receptor expressed receptor affinity.
NOTE Confidence: 0.795908570289612
03:40:26.950 --> 03:40:29.158 Is that very common when you
NOTE Confidence: 0.795908570289612
03:40:29.158 --> 03:40:30.630 do these kinds of.
NOTE Confidence: 0.795908570289612
03:40:30.630 --> 03:40:32.744 Engineering projects are usually go the other
NOTE Confidence: 0.82334840297699
03:40:32.750 --> 03:40:34.568 way. No, it's yeah, interesting question.
NOTE Confidence: 0.82334840297699
03:40:34.570 --> 03:40:35.778 Yeah, that's basically universal
NOTE Confidence: 0.82334840297699

03:40:35.778 --> 03:40:36.986 feature of directed evolution.
NOTE Confidence: 0.82334840297699

03:40:36.990 --> 03:40:38.560 'cause when you create these
NOTE Confidence: 0.82334840297699

03:40:38.560 --> 03:40:40.130 libraries were mutagen ising the
NOTE Confidence: 0.82334840297699

03:40:40.189 --> 03:40:41.839 heck out of the interface right?
NOTE Confidence: 0.82334840297699

03:40:41.840 --> 03:40:43.230 The average number of mutations
NOTE Confidence: 0.82334840297699

03:40:43.230 --> 03:40:45.479 here will be like 20 plus mutations.
NOTE Confidence: 0.82334840297699

03:40:45.480 --> 03:40:47.601 Now of course we widdle that down
NOTE Confidence: 0.82334840297699

03:40:47.601 --> 03:40:49.419 in our process, where there are
NOTE Confidence: 0.82334840297699

03:40:49.419 --> 03:40:51.540 only a handful of really good ones.
NOTE Confidence: 0.82334840297699

03:40:51.540 --> 03:40:53.675 But you can imagine of that 300
NOTE Confidence: 0.82334840297699

03:40:53.675 --> 03:40:55.479 million mutants that we start with.
NOTE Confidence: 0.82334840297699

03:40:55.480 --> 03:40:57.286 The vast majority are complete garbage.
NOTE Confidence: 0.82334840297699

03:40:57.290 --> 03:40:59.108 In fact, they're ruining the molecule.
NOTE Confidence: 0.82334840297699

03:40:59.110 --> 03:41:00.680 It may not even fold.
NOTE Confidence: 0.82334840297699

03:41:00.680 --> 03:41:03.400 If it does hold, it certainly doesn't bind,
NOTE Confidence: 0.82334840297699

03:41:03.400 --> 03:41:05.284 so that's actually what you don't

NOTE Confidence: 0.82334840297699

03:41:05.284 --> 03:41:07.739 see binding in that first round is

NOTE Confidence: 0.82334840297699

03:41:07.739 --> 03:41:09.520 because 99.99999% of the students

NOTE Confidence: 0.82334840297699

03:41:09.520 --> 03:41:11.220 in the library complete garbage,

NOTE Confidence: 0.82334840297699

03:41:11.220 --> 03:41:13.636 so that's why you know what we're really

NOTE Confidence: 0.82334840297699

03:41:13.636 --> 03:41:15.819 doing is we're selecting back the

NOTE Confidence: 0.82334840297699

03:41:15.819 --> 03:41:18.081 mutations that were were busy honing

NOTE Confidence: 0.82334840297699

03:41:18.144 --> 03:41:20.433 in the needles in the haystack that

NOTE Confidence: 0.82334840297699

03:41:20.433 --> 03:41:23.324 were present from that large source of.

NOTE Confidence: 0.82334840297699

03:41:23.324 --> 03:41:23.800 Straw,

NOTE Confidence: 0.82334840297699

03:41:23.800 --> 03:41:27.200 I guess that's not useful.

NOTE Confidence: 0.82334840297699

03:41:27.200 --> 03:41:27.540 Can

NOTE Confidence: 0.853207647800446

03:41:27.540 --> 03:41:30.220 I ask a follow up on that and

NOTE Confidence: 0.853207647800446

03:41:30.220 --> 03:41:32.372 that's whether or not it's fast?

NOTE Confidence: 0.853207647800446

03:41:32.372 --> 03:41:35.179 If the mutation if there are mutations,

NOTE Confidence: 0.853207647800446

03:41:35.180 --> 03:41:37.080 now that you can identify,

NOTE Confidence: 0.853207647800446

03:41:37.080 --> 03:41:39.360 that may be in LA Team.
NOTE Confidence: 0.853207647800446

03:41:39.360 --> 03:41:41.502 Are there any patients that might
NOTE Confidence: 0.853207647800446

03:41:41.502 --> 03:41:43.798 have these kinds of mutations that
NOTE Confidence: 0.853207647800446

03:41:43.798 --> 03:41:46.577 would give them a phenotype like this?
NOTE Confidence: 0.816878736019135

03:41:47.180 --> 03:41:49.287 Yes, so in terms of you know
NOTE Confidence: 0.816878736019135

03:41:49.287 --> 03:41:50.890 mutations that patients might have.
NOTE Confidence: 0.816878736019135

03:41:50.890 --> 03:41:52.738 Where I like team would be
NOTE Confidence: 0.816878736019135

03:41:52.738 --> 03:41:53.662 naturally decour resistant.
NOTE Confidence: 0.816878736019135

03:41:53.670 --> 03:41:56.030 I highly doubt it just because it requires
NOTE Confidence: 0.816878736019135

03:41:56.030 --> 03:41:58.300 at least five mutations to get there.
NOTE Confidence: 0.816878736019135

03:41:58.300 --> 03:41:59.524 However, there are patients
NOTE Confidence: 0.816878736019135

03:41:59.524 --> 03:42:00.748 that have hypomorphic activity
NOTE Confidence: 0.816878736019135

03:42:00.748 --> 03:42:02.320 in El 18 binding protein.
NOTE Confidence: 0.816878736019135

03:42:02.320 --> 03:42:04.609 In fact, no Casanova just had a
NOTE Confidence: 0.816878736019135

03:42:04.609 --> 03:42:06.155 really interesting report of an
NOTE Confidence: 0.816878736019135

03:42:06.155 --> 03:42:07.919 11 year old girl sadly who passed

NOTE Confidence: 0.816878736019135
03:42:07.919 --> 03:42:09.926 away she had by allelic loss
NOTE Confidence: 0.816878736019135
03:42:09.926 --> 03:42:11.278 of violating binding protein.
NOTE Confidence: 0.816878736019135
03:42:11.280 --> 03:42:13.268 She was fine for most of her
NOTE Confidence: 0.816878736019135
03:42:13.268 --> 03:42:15.145 life until she got infected with
NOTE Confidence: 0.816878736019135
03:42:15.145 --> 03:42:17.770 Hepatitis A and she had to run away.
NOTE Confidence: 0.816878736019135
03:42:17.770 --> 03:42:18.721 Inflammation really highlights
NOTE Confidence: 0.816878736019135
03:42:18.721 --> 03:42:19.989 the important of these.
NOTE Confidence: 0.816878736019135
03:42:19.990 --> 03:42:21.184 Of these checkpoints,
NOTE Confidence: 0.816878736019135
03:42:21.184 --> 03:42:22.776 decor receptors negative feedback
NOTE Confidence: 0.816878736019135
03:42:22.776 --> 03:42:24.877 at protecting us in situations
NOTE Confidence: 0.816878736019135
03:42:24.877 --> 03:42:26.140 of extreme inflammation.
NOTE Confidence: 0.810822665691376
03:42:28.130 --> 03:42:29.640 Did you have question Pam?
NOTE Confidence: 0.810822665691376
03:42:29.640 --> 03:42:30.546 Go ahead. Yes,
NOTE Confidence: 0.810822665691376
03:42:30.546 --> 03:42:32.056 great talk really things phenomenal.
NOTE Confidence: 0.810822665691376
03:42:32.060 --> 03:42:34.476 Do you know if in your model if
NOTE Confidence: 0.810822665691376

03:42:34.476 --> 03:42:36.618 you use your I'll 18 agent with
NOTE Confidence: 0.810822665691376

03:42:36.618 --> 03:42:38.497 Anti Sitali 4 is that different
NOTE Confidence: 0.810822665691376

03:42:38.497 --> 03:42:40.651 than when you use it with anti
NOTE Confidence: 0.810822665691376

03:42:40.651 --> 03:42:42.367 PD one because I would expect
NOTE Confidence: 0.810822665691376

03:42:42.367 --> 03:42:44.795 it to be based on some of the
NOTE Confidence: 0.810822665691376

03:42:44.795 --> 03:42:46.360 mechanism mechanism to show but
NOTE Confidence: 0.810822665691376

03:42:46.429 --> 03:42:48.354 I don't know if you actually did
NOTE Confidence: 0.810822665691376

03:42:48.360 --> 03:42:48.964 those experiments.
NOTE Confidence: 0.810822665691376

03:42:48.964 --> 03:42:51.380 No we never did it and we should.
NOTE Confidence: 0.810822665691376

03:42:51.380 --> 03:42:54.098 I think the problem is that CTA forces two
NOTE Confidence: 0.810214579105377

03:42:54.100 --> 03:42:55.300 amazing in mouse models.
NOTE Confidence: 0.810214579105377

03:42:55.300 --> 03:42:56.840 Listening, he's happy to hear that,
NOTE Confidence: 0.810214579105377

03:42:56.840 --> 03:42:58.359 but I don't think that amazing 'cause
NOTE Confidence: 0.810214579105377

03:42:58.359 --> 03:43:00.080 we don't have all patients responding,
NOTE Confidence: 0.810214579105377

03:43:00.080 --> 03:43:01.746 so I can imagine that your design
NOTE Confidence: 0.810214579105377

03:43:01.746 --> 03:43:03.279 of your clinical trial would be

NOTE Confidence: 0.810214579105377
03:43:03.279 --> 03:43:04.803 anti patients who failed anti PD.
NOTE Confidence: 0.810214579105377
03:43:04.810 --> 03:43:06.930 One can now go on to get your anti PD
NOTE Confidence: 0.810214579105377
03:43:06.987 --> 03:43:09.045 one plus your L 18 targeting agents.
NOTE Confidence: 0.810214579105377
03:43:09.050 --> 03:43:10.765 So that would be the combination but
NOTE Confidence: 0.810214579105377
03:43:10.765 --> 03:43:12.517 it would be interesting to see an
NOTE Confidence: 0.810214579105377
03:43:12.517 --> 03:43:14.763 anti see Tilly for in the model if you
NOTE Confidence: 0.810214579105377
03:43:14.763 --> 03:43:16.513 could also do that with patients who
NOTE Confidence: 0.810214579105377
03:43:16.520 --> 03:43:18.123 failed Anti C telephone anti PD one
NOTE Confidence: 0.810214579105377
03:43:18.123 --> 03:43:19.499 because that would be spectacular.
NOTE Confidence: 0.810214579105377
03:43:19.500 --> 03:43:20.750 Yeah I think we think
NOTE Confidence: 0.807782232761383
03:43:20.750 --> 03:43:22.528 we need to pick the right syngeneic
NOTE Confidence: 0.807782232761383
03:43:22.528 --> 03:43:24.636 model to really test that but I'll just
NOTE Confidence: 0.807782232761383
03:43:24.636 --> 03:43:26.329 say briefly know Marcus move on but.
NOTE Confidence: 0.807782232761383
03:43:26.330 --> 03:43:27.900 We are working with your
NOTE Confidence: 0.807782232761383
03:43:27.900 --> 03:43:29.156 your colleague on Ming.
NOTE Confidence: 0.807782232761383

03:43:29.160 --> 03:43:31.408 At the phase one you did MBS MD
NOTE Confidence: 0.807782232761383

03:43:31.408 --> 03:43:33.547 Anderson to setup a clinical trial.
NOTE Confidence: 0.807782232761383

03:43:33.550 --> 03:43:35.720 One of the sites over there and
NOTE Confidence: 0.807782232761383

03:43:35.720 --> 03:43:37.948 so it would be really cool to
NOTE Confidence: 0.806815981864929

03:43:37.950 --> 03:43:39.475 think about how we can
NOTE Confidence: 0.806815981864929

03:43:39.475 --> 03:43:41.400 combine it with GTA4 as well.
NOTE Confidence: 0.806815981864929

03:43:41.400 --> 03:43:43.176 Actually Kelly has some models that
NOTE Confidence: 0.806815981864929

03:43:43.176 --> 03:43:45.406 will be useful for this where there's
NOTE Confidence: 0.806815981864929

03:43:45.406 --> 03:43:47.051 metastasis models for failure for
NOTE Confidence: 0.806815981864929

03:43:47.051 --> 03:43:49.248 both PD one plus CTA four blockade,
NOTE Confidence: 0.806815981864929

03:43:49.250 --> 03:43:52.076 which is what we commonly get to in Melanoma.
NOTE Confidence: 0.806815981864929

03:43:52.080 --> 03:43:53.958 So those will be useful models
NOTE Confidence: 0.806815981864929

03:43:53.960 --> 03:43:56.172 so I'd really like to thank Pam,
NOTE Confidence: 0.806815981864929

03:43:56.172 --> 03:43:57.460 Nick, Aaron. Great talks.
NOTE Confidence: 0.806815981864929

03:43:57.460 --> 03:43:58.146 Super exciting,
NOTE Confidence: 0.806815981864929

03:43:58.146 --> 03:44:00.204 this is when we were planning

NOTE Confidence: 0.806815981864929
03:44:00.204 --> 03:44:02.390 to start the next session. 5
NOTE Confidence: 0.866145253181458
03:44:02.390 --> 03:44:05.198 minutes 305 will go for the next session
NOTE Confidence: 0.866145253181458
03:44:05.200 --> 03:44:07.664 then thanks so much. Will see you
NOTE Confidence: 0.866145253181458
03:44:07.670 --> 03:44:10.130 guys in a couple of minutes and
NOTE Confidence: 0.866145253181458
03:44:10.130 --> 03:44:12.242 we've got two more great talks
NOTE Confidence: 0.866145253181458
03:44:12.242 --> 03:44:14.002 John where Emacs Krummel really
NOTE Confidence: 0.866145253181458
03:44:14.002 --> 03:44:15.757 really exciting stuff coming so
NOTE Confidence: 0.866145253181458
03:44:15.760 --> 03:44:17.878 come back and five minutes 305.
NOTE Confidence: 0.823767483234406
03:47:38.250 --> 03:47:40.406 IMAX and John John, if you can
NOTE Confidence: 0.823767483234406
03:47:40.406 --> 03:47:42.251 share your screen, I'm sure you're
NOTE Confidence: 0.823767483234406
03:47:42.251 --> 03:47:43.786 starting to do that anyway.
NOTE Confidence: 0.823767483234406
03:47:43.790 --> 03:47:47.240 That would be great. Thanks Pam.
NOTE Confidence: 0.861121296882629
03:47:49.590 --> 03:47:52.130 That should be good, right?
NOTE Confidence: 0.861121296882629
03:47:52.130 --> 03:47:55.180 It's perfect, just full screen it,
NOTE Confidence: 0.861121296882629
03:47:55.180 --> 03:47:58.750 and then we're good to go.
NOTE Confidence: 0.861121296882629

03:47:58.750 --> 03:48:01.766 It's like presenter mode for us,
NOTE Confidence: 0.861121296882629

03:48:01.766 --> 03:48:06.320 so there we go. How's that perfect?
NOTE Confidence: 0.861121296882629

03:48:06.320 --> 03:48:09.006 So I think it's a Friday afternoon
NOTE Confidence: 0.861121296882629

03:48:09.006 --> 03:48:11.308 and we're all looking to get,
NOTE Confidence: 0.861121296882629

03:48:11.310 --> 03:48:13.908 you know it's been a great day.
NOTE Confidence: 0.861121296882629

03:48:13.908 --> 03:48:16.690 A lot of lot of exciting stuff.
NOTE Confidence: 0.861121296882629

03:48:16.690 --> 03:48:18.832 I saw John at your listing
NOTE Confidence: 0.861121296882629

03:48:18.832 --> 03:48:21.299 in a lot of the talks,
NOTE Confidence: 0.861121296882629

03:48:21.300 --> 03:48:23.985 which is great sort of look a
NOTE Confidence: 0.861121296882629

03:48:23.985 --> 03:48:26.286 little bit like an old Ahmed
NOTE Confidence: 0.861121296882629

03:48:26.286 --> 03:48:28.206 lab meeting probably with Sue.
NOTE Confidence: 0.861121296882629

03:48:28.206 --> 03:48:30.125 Asking questions from a distance,
NOTE Confidence: 0.861121296882629

03:48:30.125 --> 03:48:31.280 you know, and
NOTE Confidence: 0.833384454250336

03:48:31.280 --> 03:48:32.429 a lot of
NOTE Confidence: 0.833384454250336

03:48:32.430 --> 03:48:33.579 lineages there from
NOTE Confidence: 0.833384454250336

03:48:33.580 --> 03:48:35.196 that point of view.

NOTE Confidence: 0.833384454250336

03:48:35.196 --> 03:48:37.190 But but anyway. Nick Joe,

NOTE Confidence: 0.833384454250336

03:48:37.190 --> 03:48:39.534 she will be moderating this session.

NOTE Confidence: 0.833384454250336

03:48:39.534 --> 03:48:41.469 Nick needs no introduction after

NOTE Confidence: 0.833384454250336

03:48:41.469 --> 03:48:43.838 his talk in the last session,

NOTE Confidence: 0.833384454250336

03:48:43.840 --> 03:48:46.186 so Nick fire away and let's

NOTE Confidence: 0.833384454250336

03:48:46.186 --> 03:48:48.750 get this going. Alright,

NOTE Confidence: 0.83854466676712

03:48:48.750 --> 03:48:50.310 thanks so much. So that's real

NOTE Confidence: 0.83854466676712

03:48:50.310 --> 03:48:52.468 honor to be able to induce the two

NOTE Confidence: 0.83854466676712

03:48:52.468 --> 03:48:54.737 people in this session to both my 2

NOTE Confidence: 0.83854466676712

03:48:54.737 --> 03:48:56.277 two heroes of line scientifically.

NOTE Confidence: 0.83854466676712

03:48:56.280 --> 03:48:58.632 And so I'm going to keep the introduction

NOTE Confidence: 0.83854466676712

03:48:58.632 --> 03:49:01.309 is very short so we can stay on time. John,

NOTE Confidence: 0.83854466676712

03:49:01.309 --> 03:49:03.820 we re I think most people in the audience.

NOTE Confidence: 0.83854466676712

03:49:03.820 --> 03:49:05.731 He needs no introduction has been a

NOTE Confidence: 0.83854466676712

03:49:05.731 --> 03:49:07.675 real thought leader in the field of

NOTE Confidence: 0.83854466676712

03:49:07.675 --> 03:49:09.015 trying to understand the mechanisms
NOTE Confidence: 0.83854466676712

03:49:09.015 --> 03:49:10.230 of T cell exhaustion.
NOTE Confidence: 0.83854466676712

03:49:10.230 --> 03:49:12.029 I'm just going to mention one thing
NOTE Confidence: 0.83854466676712

03:49:12.029 --> 03:49:14.042 that I noticed on his bio somewhere
NOTE Confidence: 0.83854466676712

03:49:14.042 --> 03:49:15.527 that he was actually appointed.
NOTE Confidence: 0.83854466676712

03:49:15.530 --> 03:49:17.518 He was actually named as one of
NOTE Confidence: 0.83854466676712

03:49:17.518 --> 03:49:19.540 the 37 under 36 at some point.
NOTE Confidence: 0.83854466676712

03:49:19.540 --> 03:49:22.032 I don't know how they get that
NOTE Confidence: 0.83854466676712

03:49:22.032 --> 03:49:23.100 very specific distinction,
NOTE Confidence: 0.83854466676712

03:49:23.100 --> 03:49:27.020 but that that is 1 claim to fame that he has.
NOTE Confidence: 0.83854466676712

03:49:27.020 --> 03:49:28.444 Of course many others.
NOTE Confidence: 0.83854466676712

03:49:28.444 --> 03:49:29.420 Many, many others.
NOTE Confidence: 0.83854466676712

03:49:29.420 --> 03:49:31.280 He's currently the chair of the
NOTE Confidence: 0.83854466676712

03:49:31.280 --> 03:49:32.723 Department of systems pharmacology
NOTE Confidence: 0.83854466676712

03:49:32.723 --> 03:49:33.875 and Translational Therapeutics
NOTE Confidence: 0.83854466676712

03:49:33.875 --> 03:49:36.223 at Penn and also the director

NOTE Confidence: 0.83854466676712

03:49:36.223 --> 03:49:38.048 of the Institute for immunology.

NOTE Confidence: 0.83854466676712

03:49:38.050 --> 03:49:40.186 So thanks for joining us to.

NOTE Confidence: 0.80652242898941

03:49:41.050 --> 03:49:43.386 And snacking and I guess like Aaron said,

NOTE Confidence: 0.80652242898941

03:49:43.390 --> 03:49:45.148 I'm definitely much older than 36

NOTE Confidence: 0.80652242898941

03:49:45.148 --> 03:49:47.202 at this point, but that's a whole

NOTE Confidence: 0.80652242898941

03:49:47.202 --> 03:49:48.667 different story about that one.

NOTE Confidence: 0.80652242898941

03:49:48.670 --> 03:49:51.009 Alright, So what I thought I would do

NOTE Confidence: 0.80652242898941

03:49:51.009 --> 03:49:53.045 is talk a little bit about some of

NOTE Confidence: 0.80652242898941

03:49:53.045 --> 03:49:54.897 our newer work trying to continue to

NOTE Confidence: 0.80652242898941

03:49:54.897 --> 03:49:56.181 understand the underlying molecular

NOTE Confidence: 0.80652242898941

03:49:56.181 --> 03:49:58.040 mechanisms of T cell exhaustion,

NOTE Confidence: 0.80652242898941

03:49:58.040 --> 03:49:59.510 so couple disclosures few things,

NOTE Confidence: 0.80652242898941

03:49:59.510 --> 03:50:01.561 but I don't think any of this

NOTE Confidence: 0.80652242898941

03:50:01.561 --> 03:50:02.440 is too relevant.

NOTE Confidence: 0.80652242898941

03:50:02.440 --> 03:50:04.198 What I'm going to talk about,

NOTE Confidence: 0.80652242898941

03:50:04.200 --> 03:50:06.544 so I'm not going to spend a lot
NOTE Confidence: 0.80652242898941

03:50:06.544 --> 03:50:08.006 of time in the introduction.
NOTE Confidence: 0.80652242898941

03:50:08.006 --> 03:50:10.638 There are a few simple points I want to
NOTE Confidence: 0.80652242898941

03:50:10.640 --> 03:50:13.000 make about the topic of T cell exhaustion.
NOTE Confidence: 0.80652242898941

03:50:13.000 --> 03:50:13.915 Over the years,
NOTE Confidence: 0.80652242898941

03:50:13.915 --> 03:50:15.745 we and many others studying T
NOTE Confidence: 0.80652242898941

03:50:15.745 --> 03:50:17.761 cell exhaustion in settings of
NOTE Confidence: 0.80652242898941

03:50:17.761 --> 03:50:19.409 chronic infection or cancer,
NOTE Confidence: 0.80652242898941

03:50:19.410 --> 03:50:20.478 or now autoimmunity,
NOTE Confidence: 0.80652242898941

03:50:20.480 --> 03:50:21.545 have, I think,
NOTE Confidence: 0.80652242898941

03:50:21.545 --> 03:50:23.780 come to the conclusion that exhausted
NOTE Confidence: 0.80652242898941

03:50:23.780 --> 03:50:26.064 T cells are distinct lineages that
NOTE Confidence: 0.80652242898941

03:50:26.064 --> 03:50:28.104 are as distinct from effector cells
NOTE Confidence: 0.80652242898941

03:50:28.104 --> 03:50:30.196 as memory cells or tissue resident
NOTE Confidence: 0.80652242898941

03:50:30.196 --> 03:50:32.218 memory or our other things and.
NOTE Confidence: 0.80652242898941

03:50:32.220 --> 03:50:33.644 And if that's true,

NOTE Confidence: 0.80652242898941
03:50:33.644 --> 03:50:35.780 then we can think about Therapeutics,
NOTE Confidence: 0.80652242898941
03:50:35.780 --> 03:50:37.916 the way an effector cell works.
NOTE Confidence: 0.80652242898941
03:50:37.920 --> 03:50:40.056 We have to think about Therapeutics,
NOTE Confidence: 0.80652242898941
03:50:40.060 --> 03:50:43.264 the way that they work on exhaust T cells.
NOTE Confidence: 0.80652242898941
03:50:43.270 --> 03:50:45.292 And so recently we've uncovered some
NOTE Confidence: 0.80652242898941
03:50:45.292 --> 03:50:47.099 of the transcriptional players in this,
NOTE Confidence: 0.80652242898941
03:50:47.100 --> 03:50:47.782 including talks,
NOTE Confidence: 0.80652242898941
03:50:47.782 --> 03:50:49.487 which lays down essentially the
NOTE Confidence: 0.80652242898941
03:50:49.487 --> 03:50:51.153 epigenetic tracks or the epigenetic
NOTE Confidence: 0.80652242898941
03:50:51.153 --> 03:50:52.633 program to divert exhausted T
NOTE Confidence: 0.80652242898941
03:50:52.633 --> 03:50:54.120 cells down that Lenny Edge,
NOTE Confidence: 0.80652242898941
03:50:54.120 --> 03:50:55.710 and actually a big role.
NOTE Confidence: 0.80652242898941
03:50:55.710 --> 03:50:57.600 What talks does is repressed the
NOTE Confidence: 0.80652242898941
03:50:57.600 --> 03:50:59.220 formation of terminal effector cells.
NOTE Confidence: 0.80652242898941
03:50:59.220 --> 03:51:01.446 It works in concert with TCF one,
NOTE Confidence: 0.80652242898941

03:51:01.450 --> 03:51:03.890 which of course has a role both in
NOTE Confidence: 0.80652242898941

03:51:03.890 --> 03:51:05.598 exhausted cells and memory cells.
NOTE Confidence: 0.80652242898941

03:51:05.600 --> 03:51:07.888 Although you can see a little bit of
NOTE Confidence: 0.80652242898941

03:51:07.888 --> 03:51:09.904 talks expression in some other cell
NOTE Confidence: 0.80652242898941

03:51:09.904 --> 03:51:11.980 populations and those other cell populations,
NOTE Confidence: 0.80652242898941

03:51:11.980 --> 03:51:13.960 when you get rid of talks.
NOTE Confidence: 0.80652242898941

03:51:13.960 --> 03:51:14.734 There's no effect,
NOTE Confidence: 0.80652242898941

03:51:14.734 --> 03:51:16.540 but if you get rid of talks,
NOTE Confidence: 0.80652242898941

03:51:16.540 --> 03:51:18.170 you simply don't get the
NOTE Confidence: 0.80652242898941

03:51:18.170 --> 03:51:19.474 lineages exhausted T cells.
NOTE Confidence: 0.80652242898941

03:51:19.480 --> 03:51:22.544 So we know a little bit about how this works.
NOTE Confidence: 0.80652242898941

03:51:22.544 --> 03:51:25.005 So first of all, why do we care?
NOTE Confidence: 0.80652242898941

03:51:25.005 --> 03:51:27.458 Of course, why do we care about this?
NOTE Confidence: 0.80652242898941

03:51:27.460 --> 03:51:27.767 Well,
NOTE Confidence: 0.80652242898941

03:51:27.767 --> 03:51:29.256 Raffi touching this little bit
NOTE Confidence: 0.80652242898941

03:51:29.256 --> 03:51:31.237 this morning and we care about this

NOTE Confidence: 0.80652242898941
03:51:31.237 --> 03:51:32.804 because exhausted T cells are at
NOTE Confidence: 0.80652242898941
03:51:32.804 --> 03:51:34.889 least one of the major cell populations
NOTE Confidence: 0.80652242898941
03:51:34.889 --> 03:51:37.283 responding to checkpoint blockade in humans,
NOTE Confidence: 0.80652242898941
03:51:37.290 --> 03:51:38.820 and probably more accurately, there.
NOTE Confidence: 0.80652242898941
03:51:38.820 --> 03:51:40.350 One of the major populations
NOTE Confidence: 0.80652242898941
03:51:40.350 --> 03:51:41.574 responding to P1 blockade.
NOTE Confidence: 0.80652242898941
03:51:41.580 --> 03:51:44.036 They may also respond to CTA for blockade,
NOTE Confidence: 0.80652242898941
03:51:44.040 --> 03:51:45.882 but there may be other cells
NOTE Confidence: 0.80652242898941
03:51:45.882 --> 03:51:47.110 involved there as well.
NOTE Confidence: 0.80652242898941
03:51:47.110 --> 03:51:48.266 So over the years,
NOTE Confidence: 0.80652242898941
03:51:48.266 --> 03:51:50.386 we and many others have examined the
NOTE Confidence: 0.80652242898941
03:51:50.386 --> 03:51:52.668 cells responding to PD one blockade using.
NOTE Confidence: 0.80652242898941
03:51:52.670 --> 03:51:54.260 Various forms of mean profiling
NOTE Confidence: 0.80652242898941
03:51:54.260 --> 03:51:56.896 and if you block the PD 1 pathway
NOTE Confidence: 0.80652242898941
03:51:56.896 --> 03:51:58.852 and then take the responding cells,
NOTE Confidence: 0.80652242898941

03:51:58.860 --> 03:52:01.142 look at them to try to understand
NOTE Confidence: 0.80652242898941

03:52:01.142 --> 03:52:02.120 what they are.
NOTE Confidence: 0.80652242898941

03:52:02.120 --> 03:52:04.136 The answer you get is that their
NOTE Confidence: 0.80652242898941

03:52:04.136 --> 03:52:06.495 share many of the same features as
NOTE Confidence: 0.80652242898941

03:52:06.495 --> 03:52:08.637 exhausted T cells from mouse models.
NOTE Confidence: 0.80652242898941

03:52:08.640 --> 03:52:10.292 So if you sort out the essentially
NOTE Confidence: 0.80652242898941

03:52:10.292 --> 03:52:12.211 the Ki 67 positive or the responding
NOTE Confidence: 0.80652242898941

03:52:12.211 --> 03:52:14.525 cells to PD one blockade in human
NOTE Confidence: 0.80652242898941

03:52:14.525 --> 03:52:16.079 Melanoma patients perform
NOTE Confidence: 0.80652242898941

03:52:16.079 --> 03:52:17.115 transcriptional profiling.
NOTE Confidence: 0.80652242898941

03:52:17.120 --> 03:52:19.619 What you find is that the underlying
NOTE Confidence: 0.80652242898941

03:52:19.619 --> 03:52:20.690 transcriptional program of
NOTE Confidence: 0.80987411737442

03:52:20.749 --> 03:52:22.194 these cells is most similar
NOTE Confidence: 0.80987411737442

03:52:22.194 --> 03:52:23.639 to an exhausted T cell.
NOTE Confidence: 0.80987411737442

03:52:23.640 --> 03:52:25.458 Yes, they re engage affecter biology
NOTE Confidence: 0.80987411737442

03:52:25.458 --> 03:52:27.449 when you block the PD 1 pathway.

NOTE Confidence: 0.80987411737442

03:52:27.450 --> 03:52:29.494 Yes, they turn effector genes back on.

NOTE Confidence: 0.80987411737442

03:52:29.500 --> 03:52:31.523 Yes they start Cliff rating but their

NOTE Confidence: 0.80987411737442

03:52:31.523 --> 03:52:33.640 broader wiring of what their cell identity

NOTE Confidence: 0.80987411737442

03:52:33.640 --> 03:52:35.768 is is actually much more related to

NOTE Confidence: 0.80987411737442

03:52:35.768 --> 03:52:37.700 exhausted T cells and effector T cells.

NOTE Confidence: 0.80987411737442

03:52:37.700 --> 03:52:40.337 We can see this in a variety of ways,

NOTE Confidence: 0.80987411737442

03:52:40.340 --> 03:52:42.338 and it's actually those exhausted T

NOTE Confidence: 0.80987411737442

03:52:42.338 --> 03:52:44.278 cells that correlate the most with

NOTE Confidence: 0.80987411737442

03:52:44.278 --> 03:52:46.182 the anti tumor response and we can

NOTE Confidence: 0.80987411737442

03:52:46.182 --> 03:52:47.820 find even in the peripheral blood

NOTE Confidence: 0.80987411737442

03:52:47.820 --> 03:52:50.009 some of the same T cell clones that

NOTE Confidence: 0.80987411737442

03:52:50.009 --> 03:52:52.060 you find in the tumors to Justin.

NOTE Confidence: 0.80987411737442

03:52:52.060 --> 03:52:54.460 What we see in the blood is actually.

NOTE Confidence: 0.80987411737442

03:52:54.460 --> 03:52:57.332 Playing a role in in the clinical response

NOTE Confidence: 0.80987411737442

03:52:57.332 --> 03:53:00.600 that we see and so from work from our group,

NOTE Confidence: 0.80987411737442

03:53:00.600 --> 03:53:02.288 but also many other groups,
NOTE Confidence: 0.80987411737442

03:53:02.288 --> 03:53:05.392 we know that exhausted T cells are the major
NOTE Confidence: 0.80987411737442

03:53:05.392 --> 03:53:07.751 responding cell type to PD one blockade.
NOTE Confidence: 0.80987411737442

03:53:07.760 --> 03:53:09.839 In humans we can identify exhausted T
NOTE Confidence: 0.80987411737442

03:53:09.839 --> 03:53:12.231 cells based on in humans Co expression
NOTE Confidence: 0.80987411737442

03:53:12.231 --> 03:53:14.031 patterns of inhibitory receptors is
NOTE Confidence: 0.80987411737442

03:53:14.031 --> 03:53:16.280 the easiest thing by flow cytometry,
NOTE Confidence: 0.80987411737442

03:53:16.280 --> 03:53:18.284 but we can confirm that transcriptionally
NOTE Confidence: 0.80987411737442

03:53:18.284 --> 03:53:20.369 and we now have good epigenetic
NOTE Confidence: 0.80987411737442

03:53:20.369 --> 03:53:21.737 data on human FINA,
NOTE Confidence: 0.80987411737442

03:53:21.740 --> 03:53:23.104 typically defined exhausted T
NOTE Confidence: 0.80987411737442

03:53:23.104 --> 03:53:25.150 cells than they actually are very,
NOTE Confidence: 0.80987411737442

03:53:25.150 --> 03:53:25.762 very distinctly.
NOTE Confidence: 0.80987411737442

03:53:25.762 --> 03:53:27.904 Exhausted at the epigenetic level as well,
NOTE Confidence: 0.80987411737442

03:53:27.910 --> 03:53:29.765 we can find some of these cells
NOTE Confidence: 0.80987411737442

03:53:29.765 --> 03:53:31.648 in the blood in some settings,

NOTE Confidence: 0.80987411737442

03:53:31.650 --> 03:53:33.743 rocky showed you this morning and head

NOTE Confidence: 0.80987411737442

03:53:33.743 --> 03:53:35.680 neck cancers are very hard to find.

NOTE Confidence: 0.80987411737442

03:53:35.680 --> 03:53:36.584 A blood in Melanoma.

NOTE Confidence: 0.80987411737442

03:53:36.584 --> 03:53:38.290 It's a little bit easier and allowing

NOTE Confidence: 0.80987411737442

03:53:38.290 --> 03:53:39.790 identifying which cell types are

NOTE Confidence: 0.80987411737442

03:53:39.790 --> 03:53:41.368 responding allows us to identify

NOTE Confidence: 0.80987411737442

03:53:41.368 --> 03:53:42.680 potential resistance mechanisms and

NOTE Confidence: 0.80987411737442

03:53:42.680 --> 03:53:45.136 their variety that I won't go into here,

NOTE Confidence: 0.80987411737442

03:53:45.136 --> 03:53:46.768 some of which are published in

NOTE Confidence: 0.80987411737442

03:53:46.768 --> 03:53:48.349 these papers and others here.

NOTE Confidence: 0.80987411737442

03:53:48.350 --> 03:53:50.350 Probably more expert in some

NOTE Confidence: 0.80987411737442

03:53:50.350 --> 03:53:52.670 of those things than I am.

NOTE Confidence: 0.80987411737442

03:53:52.670 --> 03:53:52.940 So,

NOTE Confidence: 0.80987411737442

03:53:52.940 --> 03:53:55.084 but to give a little bit more context

NOTE Confidence: 0.80987411737442

03:53:55.084 --> 03:53:57.180 on exhausted T cells and some of this,

NOTE Confidence: 0.80987411737442

03:53:57.180 --> 03:53:58.500 Raffi touched on this morning,
NOTE Confidence: 0.80987411737442

03:53:58.500 --> 03:54:00.885 and others have said along the way as well.
NOTE Confidence: 0.80987411737442

03:54:00.890 --> 03:54:02.834 I did want to touch in just a
NOTE Confidence: 0.80987411737442

03:54:02.834 --> 03:54:04.070 couple of key topics.
NOTE Confidence: 0.80987411737442

03:54:04.070 --> 03:54:04.610 So first,
NOTE Confidence: 0.80987411737442

03:54:04.610 --> 03:54:05.960 these are the cells responding
NOTE Confidence: 0.80987411737442

03:54:05.960 --> 03:54:07.250 to checkpoint blockade in humans,
NOTE Confidence: 0.80987411737442

03:54:07.250 --> 03:54:08.575 but they are epigenetically very
NOTE Confidence: 0.80987411737442

03:54:08.575 --> 03:54:09.900 distinct from other cell types.
NOTE Confidence: 0.80987411737442

03:54:09.900 --> 03:54:11.321 So this is just an example of
NOTE Confidence: 0.80987411737442

03:54:11.321 --> 03:54:12.587 studies that we published together
NOTE Confidence: 0.80987411737442

03:54:12.587 --> 03:54:14.405 with a study from McCain isgroup
NOTE Confidence: 0.80987411737442

03:54:14.405 --> 03:54:15.904 identifying the sort of epigenetic
NOTE Confidence: 0.80987411737442

03:54:15.904 --> 03:54:17.314 landscape of exhausted T cells,
NOTE Confidence: 0.80987411737442

03:54:17.320 --> 03:54:19.021 and there are a couple of very
NOTE Confidence: 0.80987411737442

03:54:19.021 --> 03:54:20.500 simple points from these studies,

NOTE Confidence: 0.80987411737442

03:54:20.500 --> 03:54:22.620 and since there are a couple years old,

NOTE Confidence: 0.80987411737442

03:54:22.620 --> 03:54:24.216 I just hit the high points.

NOTE Confidence: 0.80987411737442

03:54:24.220 --> 03:54:24.546 One,

NOTE Confidence: 0.80987411737442

03:54:24.546 --> 03:54:26.176 there are clear epigenetic distinctions

NOTE Confidence: 0.80987411737442

03:54:26.176 --> 03:54:28.495 and exhausted T cells that are markedly

NOTE Confidence: 0.80987411737442

03:54:28.495 --> 03:54:30.409 different from affecting memory T cells,

NOTE Confidence: 0.80987411737442

03:54:30.410 --> 03:54:31.890 including something like this

NOTE Confidence: 0.80987411737442

03:54:31.890 --> 03:54:33.370 and emblematic open chromatin

NOTE Confidence: 0.80987411737442

03:54:33.370 --> 03:54:35.297 region in the PD one locus PDC,

NOTE Confidence: 0.80987411737442

03:54:35.300 --> 03:54:36.528 one Locus Encoding Key,

NOTE Confidence: 0.80987411737442

03:54:36.528 --> 03:54:39.538 one that you only find and exhausted T cells.

NOTE Confidence: 0.80987411737442

03:54:39.540 --> 03:54:42.474 Or we now know regulatory T cells or TFH,

NOTE Confidence: 0.80987411737442

03:54:42.480 --> 03:54:44.110 all of which expresses very

NOTE Confidence: 0.80987411737442

03:54:44.110 --> 03:54:45.740 high levels of PD one.

NOTE Confidence: 0.80987411737442

03:54:45.740 --> 03:54:46.065 Overall,

NOTE Confidence: 0.80987411737442

03:54:46.065 --> 03:54:47.690 there are 18,000 open chromatin
NOTE Confidence: 0.80987411737442

03:54:47.690 --> 03:54:49.650 regions that differ from naive cells.
NOTE Confidence: 0.80987411737442

03:54:49.650 --> 03:54:53.150 A third of those are 6000 of those are unique
NOTE Confidence: 0.786481499671936

03:54:53.234 --> 03:54:54.870 to exhausted T cells.
NOTE Confidence: 0.786481499671936

03:54:54.870 --> 03:54:56.595 That's the same order of magnitude
NOTE Confidence: 0.786481499671936

03:54:56.595 --> 03:54:58.485 of difference that you have between
NOTE Confidence: 0.786481499671936

03:54:58.485 --> 03:55:00.510 a my Lloyd cell and a B cell,
NOTE Confidence: 0.786481499671936

03:55:00.510 --> 03:55:03.048 or between a B cell in a T cell,
NOTE Confidence: 0.786481499671936

03:55:03.050 --> 03:55:04.194 really indicating how distinct
NOTE Confidence: 0.786481499671936

03:55:04.194 --> 03:55:06.150 exhausted T cells are among the CDA,
NOTE Confidence: 0.786481499671936

03:55:06.150 --> 03:55:07.726 T cells, and so you can lay that
NOTE Confidence: 0.786481499671936

03:55:07.726 --> 03:55:09.319 out in principle component spacing
NOTE Confidence: 0.786481499671936

03:55:09.319 --> 03:55:11.599 the distance between the cells just
NOTE Confidence: 0.786481499671936

03:55:11.599 --> 03:55:13.198 illustrates that point I just made,
NOTE Confidence: 0.786481499671936

03:55:13.200 --> 03:55:13.678 but importantly,
NOTE Confidence: 0.786481499671936

03:55:13.678 --> 03:55:15.351 when you block the PD 1 pathway

NOTE Confidence: 0.786481499671936
03:55:15.351 --> 03:55:16.325 that epigenetic landscape
NOTE Confidence: 0.786481499671936
03:55:16.325 --> 03:55:17.705 doesn't change very much.
NOTE Confidence: 0.786481499671936
03:55:17.710 --> 03:55:18.670 In other words,
NOTE Confidence: 0.786481499671936
03:55:18.670 --> 03:55:20.270 despite the fact that you're
NOTE Confidence: 0.786481499671936
03:55:20.270 --> 03:55:20.910 reengaging transcriptional
NOTE Confidence: 0.786481499671936
03:55:20.957 --> 03:55:22.309 circuits of effector activity.
NOTE Confidence: 0.786481499671936
03:55:22.310 --> 03:55:24.010 Your epigenetic identity remains exhausted,
NOTE Confidence: 0.786481499671936
03:55:24.010 --> 03:55:26.390 so when that effect the PD one
NOTE Confidence: 0.786481499671936
03:55:26.390 --> 03:55:28.430 blockade wears off, which it does.
NOTE Confidence: 0.786481499671936
03:55:28.430 --> 03:55:30.470 Even if you continue to treat,
NOTE Confidence: 0.786481499671936
03:55:30.470 --> 03:55:32.170 the cell reverts to its
NOTE Confidence: 0.786481499671936
03:55:32.170 --> 03:55:33.190 essentially its identity,
NOTE Confidence: 0.786481499671936
03:55:33.190 --> 03:55:35.514 and its lifestyle is exhausted T cell
NOTE Confidence: 0.786481499671936
03:55:35.514 --> 03:55:37.496 rather than being converted into an
NOTE Confidence: 0.786481499671936
03:55:37.496 --> 03:55:40.092 effector or a memory cell or some other
NOTE Confidence: 0.786481499671936

03:55:40.092 --> 03:55:42.366 kind of more durable stuff population,
NOTE Confidence: 0.786481499671936

03:55:42.370 --> 03:55:44.410 and then I mentioned this already,
NOTE Confidence: 0.786481499671936

03:55:44.410 --> 03:55:46.450 but it's actually this transcription factor.
NOTE Confidence: 0.786481499671936

03:55:46.450 --> 03:55:48.730 This H MG Group transcription factor
NOTE Confidence: 0.786481499671936

03:55:48.730 --> 03:55:51.115 talks that actually programs the vast
NOTE Confidence: 0.786481499671936

03:55:51.115 --> 03:55:53.130 majority of the epigenetic changes
NOTE Confidence: 0.786481499671936

03:55:53.130 --> 03:55:54.870 associated with exhausted T cells.
NOTE Confidence: 0.786481499671936

03:55:54.870 --> 03:55:57.048 So I want to talk a little bit
NOTE Confidence: 0.786481499671936

03:55:57.048 --> 03:55:58.836 more about sort of the lineages
NOTE Confidence: 0.786481499671936

03:55:58.836 --> 03:56:00.491 development of exhausted T cells and
NOTE Confidence: 0.786481499671936

03:56:00.491 --> 03:56:02.129 this is a map kind of illustrating.
NOTE Confidence: 0.786481499671936

03:56:02.130 --> 03:56:02.666 Summarizing really,
NOTE Confidence: 0.786481499671936

03:56:02.666 --> 03:56:04.542 a lot of data in the field,
NOTE Confidence: 0.786481499671936

03:56:04.550 --> 03:56:05.936 but it kind of articulates this
NOTE Confidence: 0.786481499671936

03:56:05.936 --> 03:56:07.562 idea that early on after activation
NOTE Confidence: 0.786481499671936

03:56:07.562 --> 03:56:08.858 there are populations of.

NOTE Confidence: 0.786481499671936

03:56:08.860 --> 03:56:09.936 I'm sorry the terminology.

NOTE Confidence: 0.786481499671936

03:56:09.936 --> 03:56:11.550 This feels a little bit confusing.

NOTE Confidence: 0.786481499671936

03:56:11.550 --> 03:56:13.005 We call these the precursors

NOTE Confidence: 0.786481499671936

03:56:13.005 --> 03:56:14.460 because they are the precursors

NOTE Confidence: 0.786481499671936

03:56:14.516 --> 03:56:16.119 that can give rise to the memory.

NOTE Confidence: 0.786481499671936

03:56:16.120 --> 03:56:17.520 Lineages are the precursors that

NOTE Confidence: 0.786481499671936

03:56:17.520 --> 03:56:19.271 can give rise to the effectors

NOTE Confidence: 0.786481499671936

03:56:19.271 --> 03:56:21.017 and then the precursors that can

NOTE Confidence: 0.786481499671936

03:56:21.017 --> 03:56:22.898 give rise to exhausted T cells.

NOTE Confidence: 0.786481499671936

03:56:22.900 --> 03:56:25.348 We know that talks and TCF one play

NOTE Confidence: 0.786481499671936

03:56:25.348 --> 03:56:27.476 an important role here in determining

NOTE Confidence: 0.786481499671936

03:56:27.476 --> 03:56:30.360 which of these lineages the self goes down.

NOTE Confidence: 0.786481499671936

03:56:30.360 --> 03:56:32.394 And then once there's a commitment

NOTE Confidence: 0.786481499671936

03:56:32.394 --> 03:56:33.750 to the exhausted linkage,

NOTE Confidence: 0.786481499671936

03:56:33.750 --> 03:56:35.102 there are these exhausted.

NOTE Confidence: 0.786481499671936

03:56:35.102 --> 03:56:36.454 We call them progenitors.
NOTE Confidence: 0.786481499671936

03:56:36.460 --> 03:56:39.164 We identified them well over a decade ago.
NOTE Confidence: 0.786481499671936

03:56:39.170 --> 03:56:40.715 These cells that actually contain
NOTE Confidence: 0.786481499671936

03:56:40.715 --> 03:56:43.226 all of the ability to respond to PD
NOTE Confidence: 0.786481499671936

03:56:43.226 --> 03:56:44.741 one blockade those cells overtime
NOTE Confidence: 0.786481499671936

03:56:44.741 --> 03:56:46.586 in the response to persisting
NOTE Confidence: 0.786481499671936

03:56:46.586 --> 03:56:48.944 antigen can give rise to downstream
NOTE Confidence: 0.786481499671936

03:56:48.944 --> 03:56:50.644 populations of more term or
NOTE Confidence: 0.786481499671936

03:56:50.644 --> 03:56:51.622 terminally differentiated exhausted
NOTE Confidence: 0.786481499671936

03:56:51.622 --> 03:56:53.409 T cells including an intermediate.
NOTE Confidence: 0.786481499671936

03:56:53.410 --> 03:56:54.794 Population that expresses Tibetan
NOTE Confidence: 0.786481499671936

03:56:54.794 --> 03:56:56.524 circulates and then finally a
NOTE Confidence: 0.786481499671936

03:56:56.524 --> 03:56:57.832 terminal population that becomes
NOTE Confidence: 0.786481499671936

03:56:57.832 --> 03:56:59.656 resident in tumors or Ant issues.
NOTE Confidence: 0.786481499671936

03:56:59.660 --> 03:57:02.284 So the question for us is we wanted
NOTE Confidence: 0.786481499671936

03:57:02.290 --> 03:57:04.270 to understand more about this initial

NOTE Confidence: 0.786481499671936
03:57:04.270 --> 03:57:06.482 programming and we know that talks and
NOTE Confidence: 0.786481499671936
03:57:06.482 --> 03:57:09.199 TCF one do not explain the whole story,
NOTE Confidence: 0.786481499671936
03:57:09.200 --> 03:57:11.711 so we wanted to design a system to ask
NOTE Confidence: 0.786481499671936
03:57:11.711 --> 03:57:14.143 what else might be playing a key role
NOTE Confidence: 0.786481499671936
03:57:14.143 --> 03:57:16.297 in these fate decisions that determine
NOTE Confidence: 0.786481499671936
03:57:16.297 --> 03:57:19.069 the Lenny edge of exhausted T cells.
NOTE Confidence: 0.786481499671936
03:57:19.070 --> 03:57:20.708 So how do we discover novel
NOTE Confidence: 0.786481499671936
03:57:20.708 --> 03:57:21.800 regulators of this exhausted
NOTE Confidence: 0.786481499671936
03:57:21.856 --> 03:57:23.419 versus effector differentiation?
NOTE Confidence: 0.786481499671936
03:57:23.420 --> 03:57:25.380 Each choice at the beginning.
NOTE Confidence: 0.786481499671936
03:57:25.380 --> 03:57:26.156 And so,
NOTE Confidence: 0.786481499671936
03:57:26.156 --> 03:57:28.096 like Arlene and like others,
NOTE Confidence: 0.786481499671936
03:57:28.100 --> 03:57:28.490 city,
NOTE Confidence: 0.786481499671936
03:57:28.490 --> 03:57:29.660 Chen and others,
NOTE Confidence: 0.786481499671936
03:57:29.660 --> 03:57:30.440 Alex Marson,
NOTE Confidence: 0.786481499671936

03:57:30.440 --> 03:57:31.996 we've developed CRISPR screening
NOTE Confidence: 0.786481499671936

03:57:31.996 --> 03:57:34.330 system to try to identify some
NOTE Confidence: 0.773363888263702

03:57:34.396 --> 03:57:35.880 of those key regulators.
NOTE Confidence: 0.773363888263702

03:57:35.880 --> 03:57:38.214 Our system is a little bit
NOTE Confidence: 0.773363888263702

03:57:38.214 --> 03:57:39.378 different than Arlene's,
NOTE Confidence: 0.773363888263702

03:57:39.380 --> 03:57:41.624 but basically tries to achieve the
NOTE Confidence: 0.773363888263702

03:57:41.624 --> 03:57:44.440 same goals of doing in vivo screening.
NOTE Confidence: 0.773363888263702

03:57:44.440 --> 03:57:47.400 What we've done is use a cast 9
NOTE Confidence: 0.773363888263702

03:57:47.400 --> 03:57:50.142 transgenic mouse on LC MB specific 14
NOTE Confidence: 0.773363888263702

03:57:50.142 --> 03:57:52.610 background and into those P14 cells,
NOTE Confidence: 0.773363888263702

03:57:52.610 --> 03:57:54.190 we actually transducing retroviruses
NOTE Confidence: 0.773363888263702

03:57:54.190 --> 03:57:55.770 expressing the guide RNAs.
NOTE Confidence: 0.773363888263702

03:57:55.770 --> 03:57:58.157 And then put those retro virally transduced
NOTE Confidence: 0.773363888263702

03:57:58.157 --> 03:58:00.529 T cells back into infection match.
NOTE Confidence: 0.773363888263702

03:58:00.530 --> 03:58:02.948 My so we're doing the transduction
NOTE Confidence: 0.773363888263702

03:58:02.948 --> 03:58:05.380 and deletion using this in vitro

NOTE Confidence: 0.773363888263702
03:58:05.380 --> 03:58:08.005 incubation system and then we save an
NOTE Confidence: 0.773363888263702
03:58:08.005 --> 03:58:10.282 aliquot of those cells and then put
NOTE Confidence: 0.773363888263702
03:58:10.282 --> 03:58:12.974 the rest of them back into mice that
NOTE Confidence: 0.773363888263702
03:58:12.974 --> 03:58:15.170 are infected with the LCD Armstrong.
NOTE Confidence: 0.773363888263702
03:58:15.170 --> 03:58:17.725 Or else you clone 13 to get
NOTE Confidence: 0.773363888263702
03:58:17.725 --> 03:58:18.455 chronic infection,
NOTE Confidence: 0.773363888263702
03:58:18.460 --> 03:58:20.656 allow selection to occur in Vivo,
NOTE Confidence: 0.773363888263702
03:58:20.660 --> 03:58:22.880 which in our hands works several
NOTE Confidence: 0.773363888263702
03:58:22.880 --> 03:58:24.898 orders of magnitude more efficiently
NOTE Confidence: 0.773363888263702
03:58:24.898 --> 03:58:26.770 than in vitro selection.
NOTE Confidence: 0.773363888263702
03:58:26.770 --> 03:58:28.678 Isolate cells at various time points
NOTE Confidence: 0.773363888263702
03:58:28.678 --> 03:58:30.470 after that selection compared to the
NOTE Confidence: 0.773363888263702
03:58:30.470 --> 03:58:31.880 input to get a efficiency score.
NOTE Confidence: 0.773363888263702
03:58:31.880 --> 03:58:33.866 So we've done a few things here.
NOTE Confidence: 0.773363888263702
03:58:33.866 --> 03:58:35.872 This is all the work of a graduate
NOTE Confidence: 0.773363888263702

03:58:35.872 --> 03:58:36.988 student zeegen who actually
NOTE Confidence: 0.773363888263702

03:58:36.988 --> 03:58:38.926 just defended his thesis and our
NOTE Confidence: 0.773363888263702

03:58:38.926 --> 03:58:40.766 collaborators in ways she has really
NOTE Confidence: 0.773363888263702

03:58:40.766 --> 03:58:42.398 helped us optimize the system and
NOTE Confidence: 0.773363888263702

03:58:42.398 --> 03:58:44.658 what we wanted to do first is actually
NOTE Confidence: 0.773363888263702

03:58:44.660 --> 03:58:46.362 go in with a focused library,
NOTE Confidence: 0.773363888263702

03:58:46.362 --> 03:58:48.066 so we can't do genome wide,
NOTE Confidence: 0.773363888263702

03:58:48.070 --> 03:58:49.690 and this to be transferred too
NOTE Confidence: 0.773363888263702

03:58:49.690 --> 03:58:51.479 many T cells in the system.
NOTE Confidence: 0.773363888263702

03:58:51.480 --> 03:58:52.900 You're turning your chronic infection,
NOTE Confidence: 0.773363888263702

03:58:52.900 --> 03:58:53.506 acute infection,
NOTE Confidence: 0.773363888263702

03:58:53.506 --> 03:58:55.021 so we're putting in numbers
NOTE Confidence: 0.773363888263702

03:58:55.021 --> 03:58:56.928 of T cells that allow us to.
NOTE Confidence: 0.773363888263702

03:58:56.930 --> 03:58:58.690 These are the normal pathogenesis
NOTE Confidence: 0.773363888263702

03:58:58.690 --> 03:59:01.119 of whatever the model is for using.
NOTE Confidence: 0.773363888263702

03:59:01.120 --> 03:59:03.824 In our case that allows us to do

NOTE Confidence: 0.773363888263702
03:59:03.824 --> 03:59:05.629 targets about 1:50 targets at
NOTE Confidence: 0.773363888263702
03:59:05.629 --> 03:59:08.093 once with a 5 guides for Target.
NOTE Confidence: 0.773363888263702
03:59:08.100 --> 03:59:09.204 In this case,
NOTE Confidence: 0.773363888263702
03:59:09.204 --> 03:59:10.676 we're targeting only transcription
NOTE Confidence: 0.773363888263702
03:59:10.676 --> 03:59:13.109 factors as sort of the key regulators
NOTE Confidence: 0.773363888263702
03:59:13.109 --> 03:59:14.373 of those fate choices,
NOTE Confidence: 0.773363888263702
03:59:14.380 --> 03:59:16.844 so we went with the Library of
NOTE Confidence: 0.773363888263702
03:59:16.844 --> 03:59:17.900 150 transcription factors.
NOTE Confidence: 0.773363888263702
03:59:17.900 --> 03:59:20.804 And so, like Arlene, we use PD one.
NOTE Confidence: 0.773363888263702
03:59:20.810 --> 03:59:23.904 Targeting is one of the positive controls.
NOTE Confidence: 0.773363888263702
03:59:23.910 --> 03:59:25.968 When you do this with the Library
NOTE Confidence: 0.773363888263702
03:59:25.968 --> 03:59:26.850 of transcription factors,
NOTE Confidence: 0.773363888263702
03:59:26.850 --> 03:59:28.614 a few negative controls and PD
NOTE Confidence: 0.773363888263702
03:59:28.614 --> 03:59:29.790 one is positive control.
NOTE Confidence: 0.773363888263702
03:59:29.790 --> 03:59:31.848 PD one comes out as the winner.
NOTE Confidence: 0.773363888263702

03:59:31.850 --> 03:59:32.436 Not surprisingly,
NOTE Confidence: 0.773363888263702

03:59:32.436 --> 03:59:34.487 it's when you get rid of P1,
NOTE Confidence: 0.773363888263702

03:59:34.490 --> 03:59:35.678 you massively, essentially Dearie,
NOTE Confidence: 0.773363888263702

03:59:35.678 --> 03:59:37.730 Press the response and get this very,
NOTE Confidence: 0.773363888263702

03:59:37.730 --> 03:59:39.488 very robust expansion of those cells,
NOTE Confidence: 0.773363888263702

03:59:39.490 --> 03:59:41.587 and then in fact we no longer use PD
NOTE Confidence: 0.773363888263702

03:59:41.587 --> 03:59:43.513 one because the number of sequencing
NOTE Confidence: 0.773363888263702

03:59:43.513 --> 03:59:45.836 reads devoted to PD one or library
NOTE Confidence: 0.773363888263702

03:59:45.836 --> 03:59:47.714 kind of swamps out other things.
NOTE Confidence: 0.773363888263702

03:59:47.720 --> 03:59:49.778 But we also find a lot of
NOTE Confidence: 0.773363888263702

03:59:49.778 --> 03:59:50.660 the expected players,
NOTE Confidence: 0.773363888263702

03:59:50.660 --> 03:59:52.876 so this is sort of the opposite of
NOTE Confidence: 0.773363888263702

03:59:52.876 --> 03:59:55.070 bill came and called the up screen.
NOTE Confidence: 0.773363888263702

03:59:55.070 --> 03:59:56.858 This is the loss of function.
NOTE Confidence: 0.773363888263702

03:59:56.860 --> 03:59:58.768 Of the 80 FIR 4C Myc,
NOTE Confidence: 0.773363888263702

03:59:58.770 --> 04:00:01.010 without which you simply can't get it,

NOTE Confidence: 0.773363888263702
04:00:01.010 --> 04:00:01.967 T cell response.
NOTE Confidence: 0.773363888263702
04:00:01.967 --> 04:00:04.200 These were nice positive controls to another.
NOTE Confidence: 0.773363888263702
04:00:04.200 --> 04:00:05.845 If we target these transcription
NOTE Confidence: 0.773363888263702
04:00:05.845 --> 04:00:07.821 factors that are important in the
NOTE Confidence: 0.773363888263702
04:00:07.821 --> 04:00:09.447 very earliest stages of a factor
NOTE Confidence: 0.773363888263702
04:00:09.447 --> 04:00:11.220 or activated T cell programming,
NOTE Confidence: 0.773363888263702
04:00:11.220 --> 04:00:12.496 essentially nothing happens when
NOTE Confidence: 0.773363888263702
04:00:12.496 --> 04:00:14.410 we lose them from the library.
NOTE Confidence: 0.773363888263702
04:00:14.410 --> 04:00:16.706 We also pulled out Tibet mid like 2
NOTE Confidence: 0.773363888263702
04:00:16.706 --> 04:00:19.022 and several others that have a key
NOTE Confidence: 0.773363888263702
04:00:19.022 --> 04:00:20.702 role in initiating the activated
NOTE Confidence: 0.816914141178131
04:00:20.763 --> 04:00:22.724 T cell response, but we were
NOTE Confidence: 0.816914141178131
04:00:22.724 --> 04:00:24.364 more interested in what happens
NOTE Confidence: 0.816914141178131
04:00:24.364 --> 04:00:26.526 on the up side of the screen.
NOTE Confidence: 0.816914141178131
04:00:26.530 --> 04:00:27.858 So what are the?
NOTE Confidence: 0.816914141178131

04:00:27.860 --> 04:00:29.210 Other things that appear to
NOTE Confidence: 0.816914141178131

04:00:29.210 --> 04:00:30.988 repress the response of T cells
NOTE Confidence: 0.816914141178131

04:00:30.988 --> 04:00:32.828 during chronic infection or the
NOTE Confidence: 0.816914141178131

04:00:32.828 --> 04:00:34.300 initial development of exhaustion,
NOTE Confidence: 0.816914141178131

04:00:34.300 --> 04:00:35.910 and there were clearly some
NOTE Confidence: 0.816914141178131

04:00:35.910 --> 04:00:36.879 other interesting transcription
NOTE Confidence: 0.816914141178131

04:00:36.880 --> 04:00:38.764 factors here smads left one we
NOTE Confidence: 0.816914141178131

04:00:38.764 --> 04:00:40.420 heard about earlier Rocky Mount.
NOTE Confidence: 0.816914141178131

04:00:40.420 --> 04:00:42.667 You can't tell from this normalized score,
NOTE Confidence: 0.816914141178131

04:00:42.670 --> 04:00:45.340 but this in vivo system allows us to
NOTE Confidence: 0.816914141178131

04:00:45.340 --> 04:00:47.410 obtain somewhere between 20 and 100
NOTE Confidence: 0.816914141178131

04:00:47.473 --> 04:00:49.543 fold enrichment so many fold better
NOTE Confidence: 0.816914141178131

04:00:49.543 --> 04:00:52.037 than what you would get in in vitro
NOTE Confidence: 0.816914141178131

04:00:52.037 --> 04:00:54.252 screen that has to do just with the
NOTE Confidence: 0.816914141178131

04:00:54.252 --> 04:00:56.464 in vivo T cell expansion that you
NOTE Confidence: 0.816914141178131

04:00:56.464 --> 04:00:59.131 get and giving you a little bit more.

NOTE Confidence: 0.816914141178131
04:00:59.131 --> 04:01:00.214 Resolution of this.
NOTE Confidence: 0.816914141178131
04:01:00.214 --> 04:01:03.700 You can see PD one smad TCF 7 talks all
NOTE Confidence: 0.816914141178131
04:01:03.700 --> 04:01:06.520 coming up on the upside of this screen.
NOTE Confidence: 0.816914141178131
04:01:06.520 --> 04:01:08.690 IRA Forebet Fmic and several
NOTE Confidence: 0.816914141178131
04:01:08.690 --> 04:01:10.426 others in the downside.
NOTE Confidence: 0.816914141178131
04:01:10.430 --> 04:01:12.620 So looking at this a little bit
NOTE Confidence: 0.816914141178131
04:01:12.620 --> 04:01:14.480 more again looking for things that
NOTE Confidence: 0.816914141178131
04:01:14.480 --> 04:01:16.082 seem to repress the response.
NOTE Confidence: 0.816914141178131
04:01:16.082 --> 04:01:17.339 There are some interesting
NOTE Confidence: 0.816914141178131
04:01:17.339 --> 04:01:18.278 transcription factors here,
NOTE Confidence: 0.816914141178131
04:01:18.280 --> 04:01:20.478 and the Icarus family in the end.
NOTE Confidence: 0.816914141178131
04:01:20.480 --> 04:01:21.134 Fat family.
NOTE Confidence: 0.816914141178131
04:01:21.134 --> 04:01:22.442 But actually this transcription
NOTE Confidence: 0.816914141178131
04:01:22.442 --> 04:01:24.379 factor fly one really caught our
NOTE Confidence: 0.816914141178131
04:01:24.379 --> 04:01:25.814 attention one because we just
NOTE Confidence: 0.816914141178131

04:01:25.820 --> 04:01:27.646 simply didn't know much about it,
NOTE Confidence: 0.816914141178131

04:01:27.646 --> 04:01:29.374 but too because it was actually
NOTE Confidence: 0.816914141178131

04:01:29.374 --> 04:01:30.840 the second most prominent.
NOTE Confidence: 0.816914141178131

04:01:30.840 --> 04:01:33.850 Hit in the screen after PD one.
NOTE Confidence: 0.816914141178131

04:01:33.850 --> 04:01:36.418 So what do we know about fly one?
NOTE Confidence: 0.816914141178131

04:01:36.420 --> 04:01:38.286 So fly one is Annette family
NOTE Confidence: 0.816914141178131

04:01:38.286 --> 04:01:39.530 transcription factor regulates matter
NOTE Confidence: 0.816914141178131

04:01:39.580 --> 04:01:41.230 poetic and Progenitor Cell Biology.
NOTE Confidence: 0.816914141178131

04:01:41.230 --> 04:01:43.071 In other systems it has a key
NOTE Confidence: 0.816914141178131

04:01:43.071 --> 04:01:45.090 role in AML tumor progression.
NOTE Confidence: 0.816914141178131

04:01:45.090 --> 04:01:46.980 Probably playing a role in the
NOTE Confidence: 0.816914141178131

04:01:46.980 --> 04:01:48.939 AML stem cell tumor stem cell.
NOTE Confidence: 0.816914141178131

04:01:48.940 --> 04:01:50.824 And there are genetic associations of
NOTE Confidence: 0.816914141178131

04:01:50.824 --> 04:01:53.110 fly one deficiency with lupus and psoriasis.
NOTE Confidence: 0.816914141178131

04:01:53.110 --> 04:01:55.036 I'm not sure I fully understand
NOTE Confidence: 0.816914141178131

04:01:55.036 --> 04:01:55.999 how that works,

NOTE Confidence: 0.816914141178131
04:01:56.000 --> 04:01:57.824 but it seems to play a role in
NOTE Confidence: 0.816914141178131
04:01:57.824 --> 04:01:59.635 some of the inflammation that
NOTE Confidence: 0.816914141178131
04:01:59.635 --> 04:02:01.780 accompanies both of these diseases.
NOTE Confidence: 0.816914141178131
04:02:01.780 --> 04:02:03.703 The place where this has been
NOTE Confidence: 0.816914141178131
04:02:03.703 --> 04:02:05.814 best studied is actually in this.
NOTE Confidence: 0.816914141178131
04:02:05.814 --> 04:02:07.644 Oncogene Fusion protein DWS fly.
NOTE Confidence: 0.816914141178131
04:02:07.650 --> 04:02:09.595 One mutation that drives Ewing
NOTE Confidence: 0.816914141178131
04:02:09.595 --> 04:02:11.151 sarcoma here what's interesting
NOTE Confidence: 0.816914141178131
04:02:11.151 --> 04:02:13.121 is fly one mediates chromatin
NOTE Confidence: 0.816914141178131
04:02:13.121 --> 04:02:15.016 remodeling in the tumor cells.
NOTE Confidence: 0.816914141178131
04:02:15.020 --> 04:02:17.054 Because the pryon domain of DWS
NOTE Confidence: 0.816914141178131
04:02:17.054 --> 04:02:19.336 essentially drags fly 12 regions of
NOTE Confidence: 0.816914141178131
04:02:19.336 --> 04:02:21.486 the genome where there shouldn't
NOTE Confidence: 0.816914141178131
04:02:21.486 --> 04:02:22.776 be chromatin rearrangement,
NOTE Confidence: 0.816914141178131
04:02:22.780 --> 04:02:25.496 and again ways that I think are
NOTE Confidence: 0.816914141178131

04:02:25.496 --> 04:02:26.660 still poorly understood,
NOTE Confidence: 0.816914141178131

04:02:26.660 --> 04:02:29.229 that actually plays a role in driving
NOTE Confidence: 0.816914141178131

04:02:29.229 --> 04:02:31.319 the oncogenesis of Ewing sarcoma,
NOTE Confidence: 0.816914141178131

04:02:31.320 --> 04:02:33.642 so that was interesting to us
NOTE Confidence: 0.816914141178131

04:02:33.642 --> 04:02:36.146 and suggested that a fly one was.
NOTE Confidence: 0.816914141178131

04:02:36.146 --> 04:02:38.150 Playing a role in chromatin remodeling,
NOTE Confidence: 0.816914141178131

04:02:38.150 --> 04:02:39.775 perhaps this was interesting to
NOTE Confidence: 0.816914141178131

04:02:39.775 --> 04:02:42.200 take a look at in CD8T cells.
NOTE Confidence: 0.816914141178131

04:02:42.200 --> 04:02:44.984 So we want to understand if we target
NOTE Confidence: 0.816914141178131

04:02:44.984 --> 04:02:47.072 only fly one, what would happen.
NOTE Confidence: 0.816914141178131

04:02:47.072 --> 04:02:49.856 So we chose two of the better guides,
NOTE Confidence: 0.816914141178131

04:02:49.860 --> 04:02:51.981 two 19360 and just wanted to confirm
NOTE Confidence: 0.816914141178131

04:02:51.981 --> 04:02:54.378 that they actually reduce protein expression.
NOTE Confidence: 0.816914141178131

04:02:54.380 --> 04:02:57.026 You can see that here and either
NOTE Confidence: 0.816914141178131

04:02:57.026 --> 04:02:59.094 Armstrong or clone 13 you get
NOTE Confidence: 0.816914141178131

04:02:59.094 --> 04:03:00.991 about an 80% reduction in protein

NOTE Confidence: 0.816914141178131
04:03:00.991 --> 04:03:02.726 and when you do that,
NOTE Confidence: 0.816914141178131
04:03:02.730 --> 04:03:04.584 you massively Dearie Press the initial
NOTE Confidence: 0.816914141178131
04:03:04.584 --> 04:03:06.910 response to acute LCD Armstrong infection.
NOTE Confidence: 0.816914141178131
04:03:06.910 --> 04:03:09.910 So you don't miss tenfold increase in the
NOTE Confidence: 0.816914141178131
04:03:09.910 --> 04:03:12.864 number of cells that they ate and a 15.
NOTE Confidence: 0.829770982265472
04:03:12.870 --> 04:03:15.750 When you look at what those cells look like,
NOTE Confidence: 0.829770982265472
04:03:15.750 --> 04:03:17.676 what you find is you've actually
NOTE Confidence: 0.829770982265472
04:03:17.676 --> 04:03:19.321 substantially increased portion of the
NOTE Confidence: 0.829770982265472
04:03:19.321 --> 04:03:21.086 response that expresses Cal, RG, one.
NOTE Confidence: 0.829770982265472
04:03:21.086 --> 04:03:23.230 So these now look like the more affecter
NOTE Confidence: 0.829770982265472
04:03:23.285 --> 04:03:25.115 like cells in Armstrong infection
NOTE Confidence: 0.829770982265472
04:03:25.115 --> 04:03:26.945 compared to the memory precursor.
NOTE Confidence: 0.829770982265472
04:03:26.950 --> 04:03:29.893 This is Day 15, so this is a pretty
NOTE Confidence: 0.829770982265472
04:03:29.893 --> 04:03:31.884 substantial increase in that killer
NOTE Confidence: 0.829770982265472
04:03:31.884 --> 04:03:34.266 T1 population at this time point.
NOTE Confidence: 0.829770982265472

04:03:34.270 --> 04:03:35.890 You can do the opposite,
NOTE Confidence: 0.829770982265472

04:03:35.890 --> 04:03:38.075 where if you overexpress fly one you
NOTE Confidence: 0.829770982265472

04:03:38.075 --> 04:03:39.845 actually repress the response just for
NOTE Confidence: 0.829770982265472

04:03:39.845 --> 04:03:41.270 the retroviral overexpression strategy
NOTE Confidence: 0.829770982265472

04:03:41.270 --> 04:03:44.309 can see that here at the eight word 815.
NOTE Confidence: 0.829770982265472

04:03:44.310 --> 04:03:46.690 Now what's interesting about this is that
NOTE Confidence: 0.829770982265472

04:03:46.690 --> 04:03:49.183 when you knockout fly one and you get
NOTE Confidence: 0.829770982265472

04:03:49.183 --> 04:03:51.120 this massive increase in cell numbers,
NOTE Confidence: 0.829770982265472

04:03:51.120 --> 04:03:53.070 you get this huge increasing
NOTE Confidence: 0.829770982265472

04:03:53.070 --> 04:03:54.240 the effective response.
NOTE Confidence: 0.829770982265472

04:03:54.240 --> 04:03:56.305 It looks like the memory precursor population
NOTE Confidence: 0.829770982265472

04:03:56.305 --> 04:03:58.200 decreases and it does proportionally,
NOTE Confidence: 0.829770982265472

04:03:58.200 --> 04:03:59.976 but the absolute number of these
NOTE Confidence: 0.829770982265472

04:03:59.976 --> 04:04:01.569 memory precursors does not change
NOTE Confidence: 0.829770982265472

04:04:01.569 --> 04:04:03.349 the numerical increase overall is
NOTE Confidence: 0.829770982265472

04:04:03.349 --> 04:04:05.130 essentially this affecter over sheet,

NOTE Confidence: 0.829770982265472

04:04:05.130 --> 04:04:07.786 so we wanted to ask what happened during

NOTE Confidence: 0.829770982265472

04:04:07.786 --> 04:04:09.769 chronic infection where that could be

NOTE Confidence: 0.829770982265472

04:04:09.769 --> 04:04:12.060 very valuable to have more effector cells,

NOTE Confidence: 0.829770982265472

04:04:12.060 --> 04:04:13.710 and indeed using different markers.

NOTE Confidence: 0.829770982265472

04:04:13.710 --> 04:04:17.670 Here CD 39 and Y 108 as a server for TCF one.

NOTE Confidence: 0.829770982265472

04:04:17.670 --> 04:04:19.650 You essentially see the same biology.

NOTE Confidence: 0.829770982265472

04:04:19.650 --> 04:04:21.960 That is when you target fly one,

NOTE Confidence: 0.829770982265472

04:04:21.960 --> 04:04:23.635 you push the response towards

NOTE Confidence: 0.829770982265472

04:04:23.635 --> 04:04:24.975 predominantly filling in this.

NOTE Confidence: 0.829770982265472

04:04:24.980 --> 04:04:27.074 Population of TCF negative or like

NOTE Confidence: 0.829770982265472

04:04:27.074 --> 04:04:29.255 108 negative CD 39 positive more

NOTE Confidence: 0.829770982265472

04:04:29.255 --> 04:04:31.391 affecter like cells in the early

NOTE Confidence: 0.829770982265472

04:04:31.391 --> 04:04:33.360 part of chronic infection.

NOTE Confidence: 0.829770982265472

04:04:33.360 --> 04:04:34.884 And that's just summarized

NOTE Confidence: 0.829770982265472

04:04:34.884 --> 04:04:36.027 over here numerically.

NOTE Confidence: 0.829770982265472

04:04:36.030 --> 04:04:38.648 On the right hand side again that's
NOTE Confidence: 0.829770982265472

04:04:38.648 --> 04:04:40.604 true proportionally for the increase
NOTE Confidence: 0.829770982265472

04:04:40.604 --> 04:04:42.509 in these affecter like cells,
NOTE Confidence: 0.829770982265472

04:04:42.510 --> 04:04:45.246 this decrease in the TCF rely 108 positive
NOTE Confidence: 0.829770982265472

04:04:45.246 --> 04:04:47.460 population is a proportional decrease.
NOTE Confidence: 0.829770982265472

04:04:47.460 --> 04:04:49.552 The absolute numbers actually
NOTE Confidence: 0.829770982265472

04:04:49.552 --> 04:04:50.598 remained constantly.
NOTE Confidence: 0.829770982265472

04:04:50.600 --> 04:04:53.150 So I wanted to understand what the underlying
NOTE Confidence: 0.823867082595825

04:04:53.150 --> 04:04:55.390 biology this was and if you do
NOTE Confidence: 0.823867082595825

04:04:55.390 --> 04:04:56.344 transcriptional profiling of
NOTE Confidence: 0.823867082595825

04:04:56.344 --> 04:04:57.934 these fly one deleted cells.
NOTE Confidence: 0.823867082595825

04:04:57.940 --> 04:05:00.508 What you find is a massive loss in
NOTE Confidence: 0.823867082595825

04:05:00.508 --> 04:05:01.781 the transcriptional signature of
NOTE Confidence: 0.823867082595825

04:05:01.781 --> 04:05:03.776 T cell exhaustion and a game in
NOTE Confidence: 0.823867082595825

04:05:03.776 --> 04:05:05.906 the signature of effector T cells,
NOTE Confidence: 0.823867082595825

04:05:05.910 --> 04:05:08.270 and you can sort of see this over

NOTE Confidence: 0.823867082595825

04:05:08.270 --> 04:05:10.702 here in the heat map where the jeans

NOTE Confidence: 0.823867082595825

04:05:10.702 --> 04:05:12.557 that are increasing expression on

NOTE Confidence: 0.823867082595825

04:05:12.557 --> 04:05:14.946 the bottom half is basically a who's

NOTE Confidence: 0.823867082595825

04:05:14.946 --> 04:05:17.078 who list of effector T cell biology

NOTE Confidence: 0.823867082595825

04:05:17.078 --> 04:05:19.304 including many of the Cal are molecules,

NOTE Confidence: 0.823867082595825

04:05:19.310 --> 04:05:20.970 CX3 CR 1, Tim 3.

NOTE Confidence: 0.823867082595825

04:05:20.970 --> 04:05:22.130 Taylor G1, Granzyme B.

NOTE Confidence: 0.823867082595825

04:05:22.130 --> 04:05:23.870 Whereas the jeans that are actually

NOTE Confidence: 0.823867082595825

04:05:23.924 --> 04:05:25.874 proportionally lower are some of the

NOTE Confidence: 0.823867082595825

04:05:25.874 --> 04:05:27.630 genes involved in progenitor biology,

NOTE Confidence: 0.823867082595825

04:05:27.630 --> 04:05:30.283 including TCF 7 ID 3 and others.

NOTE Confidence: 0.823867082595825

04:05:30.283 --> 04:05:33.758 Because supply one had a role

NOTE Confidence: 0.823867082595825

04:05:33.758 --> 04:05:36.136 in this EWS fly one.

NOTE Confidence: 0.823867082595825

04:05:36.136 --> 04:05:38.102 AKA Gene in regulating epigenetics

NOTE Confidence: 0.823867082595825

04:05:38.102 --> 04:05:40.790 wanted to look at the open chromatin

NOTE Confidence: 0.823867082595825

04:05:40.857 --> 04:05:43.090 landscape in the absence of fly one.
NOTE Confidence: 0.823867082595825

04:05:43.090 --> 04:05:47.060 And indeed if you do a taxi here the fly one.
NOTE Confidence: 0.823867082595825

04:05:47.060 --> 04:05:48.865 Deleted cells are very different
NOTE Confidence: 0.823867082595825

04:05:48.865 --> 04:05:49.948 from the control.
NOTE Confidence: 0.823867082595825

04:05:49.950 --> 04:05:52.838 If you map those changes to nearest gene.
NOTE Confidence: 0.823867082595825

04:05:52.840 --> 04:05:54.709 What you find is that a massive
NOTE Confidence: 0.823867082595825

04:05:54.709 --> 04:05:56.693 amount of this change actually occurs
NOTE Confidence: 0.823867082595825

04:05:56.693 --> 04:05:58.925 at genes related to the effector
NOTE Confidence: 0.823867082595825

04:05:58.925 --> 04:06:01.081 response you see increased chromatin
NOTE Confidence: 0.823867082595825

04:06:01.081 --> 04:06:03.231 Accessibility near genes and pathways
NOTE Confidence: 0.823867082595825

04:06:03.231 --> 04:06:05.122 involved in effector biology and
NOTE Confidence: 0.823867082595825

04:06:05.122 --> 04:06:06.574 a decrease relatively speaking.
NOTE Confidence: 0.823867082595825

04:06:06.580 --> 04:06:07.950 In chromatin Accessibility around genes
NOTE Confidence: 0.823867082595825

04:06:07.950 --> 04:06:10.199 that may be involved in progenitor biology,
NOTE Confidence: 0.823867082595825

04:06:10.200 --> 04:06:10.516 again,
NOTE Confidence: 0.823867082595825

04:06:10.516 --> 04:06:12.096 very similar lists of the

NOTE Confidence: 0.823867082595825
04:06:12.096 --> 04:06:13.829 jeans that are changed by RNA.
NOTE Confidence: 0.823867082595825
04:06:13.830 --> 04:06:15.642 If you look at the correlation
NOTE Confidence: 0.823867082595825
04:06:15.642 --> 04:06:16.548 between the two,
NOTE Confidence: 0.823867082595825
04:06:16.550 --> 04:06:18.056 there's a clear relationship you
NOTE Confidence: 0.823867082595825
04:06:18.056 --> 04:06:19.584 can look underneath this open
NOTE Confidence: 0.823867082595825
04:06:19.584 --> 04:06:21.114 chromatin to see what transcription
NOTE Confidence: 0.823867082595825
04:06:21.114 --> 04:06:22.589 factor binding sites may become.
NOTE Confidence: 0.823867082595825
04:06:22.590 --> 04:06:24.254 Less or more iaccessible.
NOTE Confidence: 0.823867082595825
04:06:24.254 --> 04:06:26.243 You lose Accessibility around sites.
NOTE Confidence: 0.823867082595825
04:06:26.243 --> 04:06:28.158 That combined, I RF molecules,
NOTE Confidence: 0.823867082595825
04:06:28.160 --> 04:06:30.080 particularly RF one and two,
NOTE Confidence: 0.823867082595825
04:06:30.080 --> 04:06:32.144 which may be interesting in terms
NOTE Confidence: 0.823867082595825
04:06:32.144 --> 04:06:34.027 of regulation of this exhausted
NOTE Confidence: 0.823867082595825
04:06:34.027 --> 04:06:36.217 T cell response by interference,
NOTE Confidence: 0.823867082595825
04:06:36.220 --> 04:06:38.602 but by far the biggest changes
NOTE Confidence: 0.823867082595825

04:06:38.602 --> 04:06:40.190 and increasing Accessibility at
NOTE Confidence: 0.823867082595825

04:06:40.255 --> 04:06:41.599 these sort of hybrid.
NOTE Confidence: 0.823867082595825

04:06:41.600 --> 04:06:44.042 Let's run sites massively increased in
NOTE Confidence: 0.823867082595825

04:06:44.042 --> 04:06:46.209 Accessibility when you remove fly one,
NOTE Confidence: 0.823867082595825

04:06:46.210 --> 04:06:48.954 so we wanted to understand the relationship
NOTE Confidence: 0.823867082595825

04:06:48.954 --> 04:06:51.577 of these changes to actually wear fly,
NOTE Confidence: 0.823867082595825

04:06:51.580 --> 04:06:53.148 one binds and performed,
NOTE Confidence: 0.823867082595825

04:06:53.148 --> 04:06:54.324 cut and run.
NOTE Confidence: 0.823867082595825

04:06:54.330 --> 04:06:56.214 Just to identify workflow is binding
NOTE Confidence: 0.823867082595825

04:06:56.214 --> 04:06:58.919 and then ask at those sites a water
NOTE Confidence: 0.823867082595825

04:06:58.919 --> 04:07:00.989 the sequences underneath those Ann B.
NOTE Confidence: 0.823867082595825

04:07:00.990 --> 04:07:02.988 How does that relate to the
NOTE Confidence: 0.823867082595825

04:07:02.988 --> 04:07:04.320 changes in chromatin Accessibility?
NOTE Confidence: 0.823867082595825

04:07:04.320 --> 04:07:05.993 And indeed we can find fly one
NOTE Confidence: 0.823867082595825

04:07:05.993 --> 04:07:07.789 binding at sites where chromatin
NOTE Confidence: 0.823867082595825

04:07:07.789 --> 04:07:09.319 becomes differentially accessible.

NOTE Confidence: 0.823867082595825
04:07:09.320 --> 04:07:10.800 The number one transcription
NOTE Confidence: 0.823867082595825
04:07:10.800 --> 04:07:12.650 factor binding sites under sites
NOTE Confidence: 0.823867082595825
04:07:12.650 --> 04:07:14.307 were fly one binds the fly,
NOTE Confidence: 0.823867082595825
04:07:14.310 --> 04:07:15.306 one binding site,
NOTE Confidence: 0.823867082595825
04:07:15.306 --> 04:07:16.966 although there are others here,
NOTE Confidence: 0.823867082595825
04:07:16.970 --> 04:07:18.640 including a runs binding site.
NOTE Confidence: 0.823867082595825
04:07:18.640 --> 04:07:20.300 What's interesting about this is
NOTE Confidence: 0.823867082595825
04:07:20.300 --> 04:07:22.302 that 78% of the places reply,
NOTE Confidence: 0.823867082595825
04:07:22.302 --> 04:07:24.984 one binds you see an increase in chromatin
NOTE Confidence: 0.823867082595825
04:07:24.984 --> 04:07:27.012 Accessibility when fly one is deleted.
NOTE Confidence: 0.823867082595825
04:07:27.020 --> 04:07:29.720 Suggesting that fly one is
NOTE Confidence: 0.823867082595825
04:07:29.720 --> 04:07:31.340 antagonizing chromatin Accessibility?
NOTE Confidence: 0.823867082595825
04:07:31.340 --> 04:07:33.566 Under those sites you find lots
NOTE Confidence: 0.823867082595825
04:07:33.566 --> 04:07:35.320 of effector genes close by.
NOTE Confidence: 0.823867082595825
04:07:35.320 --> 04:07:37.784 You do not find fly one binding at
NOTE Confidence: 0.823867082595825

04:07:37.784 --> 04:07:39.670 genes involved progenitor biology,
NOTE Confidence: 0.823867082595825

04:07:39.670 --> 04:07:42.201 So what this suggested to us was
NOTE Confidence: 0.823867082595825

04:07:42.201 --> 04:07:44.733 that fly one is playing a role
NOTE Confidence: 0.823867082595825

04:07:44.733 --> 04:07:46.182 in essentially safeguarding the
NOTE Confidence: 0.823867082595825

04:07:46.182 --> 04:07:46.904 effector response.
NOTE Confidence: 0.823867082595825

04:07:46.904 --> 04:07:47.987 The effector biology,
NOTE Confidence: 0.823867082595825

04:07:47.990 --> 04:07:50.162 so you don't have an overaggressive
NOTE Confidence: 0.823867082595825

04:07:50.162 --> 04:07:50.886 affective response,
NOTE Confidence: 0.823867082595825

04:07:50.890 --> 04:07:52.338 but actually has very
NOTE Confidence: 0.793176472187042

04:07:52.340 --> 04:07:54.144 little role in the transcriptional
NOTE Confidence: 0.793176472187042

04:07:54.144 --> 04:07:55.592 coordination of the genes
NOTE Confidence: 0.793176472187042

04:07:55.592 --> 04:07:57.040 involved in progenitor biology,
NOTE Confidence: 0.793176472187042

04:07:57.040 --> 04:07:59.469 which would be consistent with an increase
NOTE Confidence: 0.793176472187042

04:07:59.469 --> 04:08:01.696 in effector cells or Affecter lineage
NOTE Confidence: 0.793176472187042

04:08:01.696 --> 04:08:03.934 cells in acute and chronic infections.
NOTE Confidence: 0.793176472187042

04:08:03.940 --> 04:08:05.926 Without a loss of those progenitor,

NOTE Confidence: 0.793176472187042
04:08:05.930 --> 04:08:08.142 like cells for the cells will give
NOTE Confidence: 0.793176472187042
04:08:08.142 --> 04:08:10.579 rise to memory and exhausted T cells,
NOTE Confidence: 0.793176472187042
04:08:10.580 --> 04:08:11.948 so it's great fly,
NOTE Confidence: 0.793176472187042
04:08:11.948 --> 04:08:13.316 one repressive chromatin Accessibility
NOTE Confidence: 0.793176472187042
04:08:13.316 --> 04:08:14.559 binding effector like jeans,
NOTE Confidence: 0.793176472187042
04:08:14.560 --> 04:08:15.556 particularly those that
NOTE Confidence: 0.793176472187042
04:08:15.556 --> 04:08:17.216 will fly one runs motifs.
NOTE Confidence: 0.793176472187042
04:08:17.220 --> 04:08:19.180 Is there a connection between
NOTE Confidence: 0.793176472187042
04:08:19.180 --> 04:08:21.140 fly one and runx proteins?
NOTE Confidence: 0.793176472187042
04:08:21.140 --> 04:08:23.252 So we did an experiment to try to
NOTE Confidence: 0.793176472187042
04:08:23.252 --> 04:08:25.684 test this in the basic idea of this
NOTE Confidence: 0.793176472187042
04:08:25.684 --> 04:08:27.649 experiment was to delete fly one and
NOTE Confidence: 0.793176472187042
04:08:27.650 --> 04:08:29.168 enforce expression of the ranks.
NOTE Confidence: 0.793176472187042
04:08:29.168 --> 04:08:30.720 One or runs three.
NOTE Confidence: 0.793176472187042
04:08:30.720 --> 04:08:31.864 When you do this,
NOTE Confidence: 0.793176472187042

04:08:31.864 --> 04:08:33.014 we're using code transduction
NOTE Confidence: 0.793176472187042

04:08:33.014 --> 04:08:34.156 with two different retroviruses,
NOTE Confidence: 0.793176472187042

04:08:34.156 --> 04:08:36.137 one containing the guide to delete fly
NOTE Confidence: 0.793176472187042

04:08:36.137 --> 04:08:38.180 one and the other overexpressing runs three.
NOTE Confidence: 0.793176472187042

04:08:38.180 --> 04:08:39.722 You can just look at sort
NOTE Confidence: 0.793176472187042

04:08:39.722 --> 04:08:41.340 of the upper right quadrant.
NOTE Confidence: 0.793176472187042

04:08:41.340 --> 04:08:43.631 You do nothing about 10% of the response
NOTE Confidence: 0.793176472187042

04:08:43.631 --> 04:08:45.640 is double transduced with the empty vectors.
NOTE Confidence: 0.793176472187042

04:08:45.640 --> 04:08:47.080 If you overexpress runs three,
NOTE Confidence: 0.793176472187042

04:08:47.080 --> 04:08:48.802 you push a little bit better
NOTE Confidence: 0.793176472187042

04:08:48.802 --> 04:08:49.376 diesel expansion,
NOTE Confidence: 0.793176472187042

04:08:49.380 --> 04:08:50.810 and they're actually more killer.
NOTE Confidence: 0.793176472187042

04:08:50.810 --> 04:08:52.250 Do you want high cells?
NOTE Confidence: 0.793176472187042

04:08:52.250 --> 04:08:53.972 If you just delete fly one
NOTE Confidence: 0.793176472187042

04:08:53.972 --> 04:08:55.120 about the same effect,
NOTE Confidence: 0.793176472187042

04:08:55.120 --> 04:08:56.836 both in terms of numbers and

NOTE Confidence: 0.793176472187042
04:08:56.836 --> 04:08:57.694 also differentiation state.
NOTE Confidence: 0.793176472187042
04:08:57.700 --> 04:09:00.570 But if you do both things at the same time,
NOTE Confidence: 0.793176472187042
04:09:00.570 --> 04:09:02.418 you actually get at least an
NOTE Confidence: 0.793176472187042
04:09:02.418 --> 04:09:03.650 additive affect suggesting that.
NOTE Confidence: 0.793176472187042
04:09:03.650 --> 04:09:06.998 Removing fly one allows runx three
NOTE Confidence: 0.793176472187042
04:09:06.998 --> 04:09:09.230 to function more effectively.
NOTE Confidence: 0.793176472187042
04:09:09.230 --> 04:09:11.138 So fly one last cooperates with
NOTE Confidence: 0.793176472187042
04:09:11.138 --> 04:09:12.740 runs three overexpression to drive
NOTE Confidence: 0.793176472187042
04:09:12.740 --> 04:09:14.534 more of an effector expansion and
NOTE Confidence: 0.793176472187042
04:09:14.534 --> 04:09:16.422 effector response fly one seems to
NOTE Confidence: 0.793176472187042
04:09:16.422 --> 04:09:18.336 antagonize that should be runs three
NOTE Confidence: 0.793176472187042
04:09:18.336 --> 04:09:20.398 Accessibility and limit the effector program.
NOTE Confidence: 0.793176472187042
04:09:20.400 --> 04:09:21.990 There's some biology of Runx,
NOTE Confidence: 0.793176472187042
04:09:21.990 --> 04:09:24.216 one that I'm not coming into here,
NOTE Confidence: 0.793176472187042
04:09:24.220 --> 04:09:27.410 so this is the idea that you have only one,
NOTE Confidence: 0.793176472187042

04:09:27.410 --> 04:09:28.445 essentially safeguarding parts
NOTE Confidence: 0.793176472187042

04:09:28.445 --> 04:09:30.515 of the genome where runs three
NOTE Confidence: 0.793176472187042

04:09:30.515 --> 04:09:32.197 could bind when you remove fly,
NOTE Confidence: 0.793176472187042

04:09:32.200 --> 04:09:34.108 one runs three, has more Accessibility,
NOTE Confidence: 0.793176472187042

04:09:34.110 --> 04:09:35.064 can drive those,
NOTE Confidence: 0.793176472187042

04:09:35.064 --> 04:09:36.654 runs three dependent effector genes
NOTE Confidence: 0.765025615692139

04:09:36.660 --> 04:09:37.940 more effectively. So just
NOTE Confidence: 0.765025615692139

04:09:37.940 --> 04:09:38.900 in the last
NOTE Confidence: 0.773331236839295

04:09:38.900 --> 04:09:40.188 couple slides, of course.
NOTE Confidence: 0.773331236839295

04:09:40.188 --> 04:09:42.132 Want to address whether any of
NOTE Confidence: 0.773331236839295

04:09:42.132 --> 04:09:44.000 this matters at all? Of course.
NOTE Confidence: 0.773331236839295

04:09:44.000 --> 04:09:46.240 All goal of this is to see whether
NOTE Confidence: 0.773331236839295

04:09:46.305 --> 04:09:48.045 we can improve the efficiency
NOTE Confidence: 0.773331236839295

04:09:48.045 --> 04:09:49.785 of T cell responses during
NOTE Confidence: 0.773331236839295

04:09:49.854 --> 04:09:51.259 chronic infections and cancer.
NOTE Confidence: 0.773331236839295

04:09:51.260 --> 04:09:53.948 So let me just show you a couple

NOTE Confidence: 0.773331236839295
04:09:53.948 --> 04:09:55.828 of examples of how we tested
NOTE Confidence: 0.773331236839295
04:09:55.830 --> 04:09:57.460 this in models of infection,
NOTE Confidence: 0.773331236839295
04:09:57.460 --> 04:09:59.065 and so the simple experimental
NOTE Confidence: 0.773331236839295
04:09:59.065 --> 04:10:01.040 design here is we took mice,
NOTE Confidence: 0.773331236839295
04:10:01.040 --> 04:10:02.670 infected them with the pathogen,
NOTE Confidence: 0.773331236839295
04:10:02.670 --> 04:10:04.959 left them as you're just B6 mice.
NOTE Confidence: 0.773331236839295
04:10:04.960 --> 04:10:07.384 We either did not transfer any T cells
NOTE Confidence: 0.773331236839295
04:10:07.384 --> 04:10:09.056 we adoptively transferred in low
NOTE Confidence: 0.773331236839295
04:10:09.056 --> 04:10:11.054 numbers of P14 cells transduced with
NOTE Confidence: 0.773331236839295
04:10:11.054 --> 04:10:13.485 a control guide user cast 9014 cells.
NOTE Confidence: 0.773331236839295
04:10:13.490 --> 04:10:15.863 Or cast 9014 cells that actually had
NOTE Confidence: 0.773331236839295
04:10:15.863 --> 04:10:18.305 fly one targeted in all cases were
NOTE Confidence: 0.773331236839295
04:10:18.305 --> 04:10:20.000 using pathogens that express the
NOTE Confidence: 0.773331236839295
04:10:20.000 --> 04:10:22.328 GP 33 epitope matched to the P14,
NOTE Confidence: 0.773331236839295
04:10:22.330 --> 04:10:23.870 so we're putting in.
NOTE Confidence: 0.773331236839295

04:10:23.870 --> 04:10:25.410 So in chronic calcium,
NOTE Confidence: 0.773331236839295

04:10:25.410 --> 04:10:27.223 be putting in in grey just non
NOTE Confidence: 0.773331236839295

04:10:27.223 --> 04:10:29.121 targeted T cells gives us a little
NOTE Confidence: 0.773331236839295

04:10:29.121 --> 04:10:30.711 bit of a benefit because we're
NOTE Confidence: 0.773331236839295

04:10:30.767 --> 04:10:32.257 putting in diesel specific for
NOTE Confidence: 0.773331236839295

04:10:32.257 --> 04:10:34.312 the virus you see viral load go
NOTE Confidence: 0.773331236839295

04:10:34.312 --> 04:10:36.279 down and the Serum and liver and
NOTE Confidence: 0.773331236839295

04:10:36.279 --> 04:10:38.197 perhaps a little bit in the kidney.
NOTE Confidence: 0.773331236839295

04:10:38.200 --> 04:10:39.705 But when you actually delete fly one
NOTE Confidence: 0.773331236839295

04:10:39.705 --> 04:10:41.808 you see a substantially greater benefit.
NOTE Confidence: 0.773331236839295

04:10:41.810 --> 04:10:42.922 A controlling chronic infection
NOTE Confidence: 0.773331236839295

04:10:42.922 --> 04:10:43.756 because of loss.
NOTE Confidence: 0.773331236839295

04:10:43.760 --> 04:10:45.880 Apply one you do the same experiment in
NOTE Confidence: 0.773331236839295

04:10:45.880 --> 04:10:47.369 respiratory infection with influenza virus,
NOTE Confidence: 0.773331236839295

04:10:47.370 --> 04:10:49.155 where if you don't put in any
NOTE Confidence: 0.773331236839295

04:10:49.155 --> 04:10:51.173 T cells that might get sick in

NOTE Confidence: 0.773331236839295

04:10:51.173 --> 04:10:52.658 viral load is fairly high.

NOTE Confidence: 0.773331236839295

04:10:52.660 --> 04:10:54.876 You put in just non targeted T cells.

NOTE Confidence: 0.773331236839295

04:10:54.880 --> 04:10:57.220 Actually you do have a little bit of a

NOTE Confidence: 0.773331236839295

04:10:57.220 --> 04:10:59.128 benefit on pathogenesis and maybe a.

NOTE Confidence: 0.773331236839295

04:10:59.130 --> 04:11:00.066 Into viral control.

NOTE Confidence: 0.773331236839295

04:11:00.066 --> 04:11:01.314 Although it's not insignificant,

NOTE Confidence: 0.773331236839295

04:11:01.320 --> 04:11:02.416 you delete fly one.

NOTE Confidence: 0.773331236839295

04:11:02.416 --> 04:11:04.834 The mice are much healthier and you see

NOTE Confidence: 0.773331236839295

04:11:04.834 --> 04:11:06.634 substantial control of our replication.

NOTE Confidence: 0.773331236839295

04:11:06.640 --> 04:11:08.205 Interesting Lee in my still

NOTE Confidence: 0.773331236839295

04:11:08.205 --> 04:11:09.457 have high viral load.

NOTE Confidence: 0.773331236839295

04:11:09.460 --> 04:11:10.086 You see,

NOTE Confidence: 0.773331236839295

04:11:10.086 --> 04:11:11.338 actually much much greater

NOTE Confidence: 0.773331236839295

04:11:11.338 --> 04:11:12.590 expansion of the fly.

NOTE Confidence: 0.773331236839295

04:11:12.590 --> 04:11:15.082 One deleted T cells compared to control

NOTE Confidence: 0.773331236839295

04:11:15.082 --> 04:11:17.568 mice that had the same viral load.
NOTE Confidence: 0.773331236839295

04:11:17.570 --> 04:11:19.390 And then in systemic listeria
NOTE Confidence: 0.773331236839295

04:11:19.390 --> 04:11:20.118 monocytogenes infection,
NOTE Confidence: 0.773331236839295

04:11:20.120 --> 04:11:21.420 the stories the same,
NOTE Confidence: 0.773331236839295

04:11:21.420 --> 04:11:23.370 the mice do better when you
NOTE Confidence: 0.773331236839295

04:11:23.443 --> 04:11:25.768 actually delete fly one pathogen
NOTE Confidence: 0.773331236839295

04:11:25.768 --> 04:11:27.628 burden is substantially lower.
NOTE Confidence: 0.773331236839295

04:11:27.630 --> 04:11:28.196 So finally,
NOTE Confidence: 0.773331236839295

04:11:28.196 --> 04:11:30.164 what happens in a tumor setting where
NOTE Confidence: 0.773331236839295

04:11:30.164 --> 04:11:32.138 you might want to get tumor control.
NOTE Confidence: 0.773331236839295

04:11:32.140 --> 04:11:34.112 So in this case we did this.
NOTE Confidence: 0.773331236839295

04:11:34.112 --> 04:11:35.240 Actually rag two mice,
NOTE Confidence: 0.773331236839295

04:11:35.240 --> 04:11:36.650 so we could actually look
NOTE Confidence: 0.773331236839295

04:11:36.650 --> 04:11:37.778 at longer term affects,
NOTE Confidence: 0.773331236839295

04:11:37.780 --> 04:11:39.832 but you can do this also in B6 Mice
NOTE Confidence: 0.773331236839295

04:11:39.832 --> 04:11:41.881 and I'm happy to explain that a

NOTE Confidence: 0.773331236839295
04:11:41.881 --> 04:11:43.989 little bit more people are interested,
NOTE Confidence: 0.773331236839295
04:11:43.990 --> 04:11:45.957 but essentially you get the same answer.
NOTE Confidence: 0.773331236839295
04:11:45.960 --> 04:11:47.648 We established tumors and five days
NOTE Confidence: 0.773331236839295
04:11:47.650 --> 04:11:49.336 after the tumors have started growing,
NOTE Confidence: 0.773331236839295
04:11:49.340 --> 04:11:51.038 we do the same experiment putting
NOTE Confidence: 0.773331236839295
04:11:51.038 --> 04:11:53.280 in non control T cells or T cells
NOTE Confidence: 0.773331236839295
04:11:53.280 --> 04:11:55.193 that have fly one deleted and you
NOTE Confidence: 0.773331236839295
04:11:55.193 --> 04:11:56.927 can see that pretty much black
NOTE Confidence: 0.773331236839295
04:11:56.927 --> 04:11:58.100 and white answer that.
NOTE Confidence: 0.773331236839295
04:11:58.100 --> 04:11:59.000 Compared to T2,
NOTE Confidence: 0.773331236839295
04:11:59.000 --> 04:12:01.434 putting in just wild type T cells to
NOTE Confidence: 0.773331236839295
04:12:01.434 --> 04:12:03.408 control the tumor a little bit to
NOTE Confidence: 0.773331236839295
04:12:03.408 --> 04:12:05.840 fly one deleted tumors actually are
NOTE Confidence: 0.773331236839295
04:12:05.840 --> 04:12:08.325 substantially better control the fly one.
NOTE Confidence: 0.773331236839295
04:12:08.325 --> 04:12:09.905 Deleted T cells provide
NOTE Confidence: 0.773331236839295

04:12:09.905 --> 04:12:11.485 substantially better control of
NOTE Confidence: 0.773331236839295

04:12:11.485 --> 04:12:13.427 the tumor in these settings.
NOTE Confidence: 0.773331236839295

04:12:13.430 --> 04:12:16.150 So what I've shown you is this system,
NOTE Confidence: 0.838132619857788

04:12:16.150 --> 04:12:17.366 which we've turned optics,
NOTE Confidence: 0.838132619857788

04:12:17.366 --> 04:12:19.190 'cause everybody needs an acronym for
NOTE Confidence: 0.838132619857788

04:12:19.244 --> 04:12:20.908 their Christmas screening approach,
NOTE Confidence: 0.838132619857788

04:12:20.910 --> 04:12:22.610 is optimized for really focused,
NOTE Confidence: 0.838132619857788

04:12:22.610 --> 04:12:23.621 high resolution screens,
NOTE Confidence: 0.838132619857788

04:12:23.621 --> 04:12:26.378 gives us 20 to 100 fold resolution to
NOTE Confidence: 0.838132619857788

04:12:26.378 --> 04:12:28.730 understand the biology of T cell exhaustion.
NOTE Confidence: 0.838132619857788

04:12:28.730 --> 04:12:30.430 T cell differentiation in Vivo.
NOTE Confidence: 0.838132619857788

04:12:30.430 --> 04:12:33.328 We identified apply one as a key target and
NOTE Confidence: 0.838132619857788

04:12:33.328 --> 04:12:35.867 started to understand some of the biology.
NOTE Confidence: 0.838132619857788

04:12:35.870 --> 04:12:38.264 But there are also some other very
NOTE Confidence: 0.838132619857788

04:12:38.264 --> 04:12:39.610 interesting targets identified here,
NOTE Confidence: 0.838132619857788

04:12:39.610 --> 04:12:42.158 especially on the up side of the

NOTE Confidence: 0.838132619857788

04:12:42.158 --> 04:12:44.068 screen including Smad 2 EGRIR F2.

NOTE Confidence: 0.838132619857788

04:12:44.070 --> 04:12:46.914 One of the near 70 set or the newer

NOTE Confidence: 0.838132619857788

04:12:46.914 --> 04:12:49.668 are for a family members and ATF.

NOTE Confidence: 0.838132619857788

04:12:49.670 --> 04:12:51.770 Six loss of fly one enhances

NOTE Confidence: 0.838132619857788

04:12:51.770 --> 04:12:52.470 effector differentiation.

NOTE Confidence: 0.838132619857788

04:12:52.470 --> 04:12:53.124 But importantly,

NOTE Confidence: 0.838132619857788

04:12:53.124 --> 04:12:54.759 this occurs without compromising the

NOTE Confidence: 0.838132619857788

04:12:54.759 --> 04:12:56.320 memory or progenitor populations.

NOTE Confidence: 0.838132619857788

04:12:56.320 --> 04:12:58.472 So I think it's interesting to note that

NOTE Confidence: 0.838132619857788

04:12:58.472 --> 04:13:00.484 most of the other transcription factors

NOTE Confidence: 0.838132619857788

04:13:00.484 --> 04:13:03.126 that play this sort of toggling role

NOTE Confidence: 0.838132619857788

04:13:03.126 --> 04:13:05.416 between effector differentiation and memory,

NOTE Confidence: 0.838132619857788

04:13:05.420 --> 04:13:07.457 or effector and exhaustion when you delete

NOTE Confidence: 0.838132619857788

04:13:07.457 --> 04:13:09.619 them and promote effector differentiation,

NOTE Confidence: 0.838132619857788

04:13:09.620 --> 04:13:11.020 you actually lose the

NOTE Confidence: 0.838132619857788

04:13:11.020 --> 04:13:12.449 other lineages sells it.
NOTE Confidence: 0.838132619857788

04:13:12.449 --> 04:13:14.723 Sort of you can't have your
NOTE Confidence: 0.838132619857788

04:13:14.723 --> 04:13:16.549 cake and eat it too.
NOTE Confidence: 0.838132619857788

04:13:16.550 --> 04:13:18.560 This case will fly one deletion,
NOTE Confidence: 0.838132619857788

04:13:18.560 --> 04:13:20.905 since 51 seems to act as an
NOTE Confidence: 0.838132619857788

04:13:20.905 --> 04:13:21.910 effector lineages safeguard,
NOTE Confidence: 0.838132619857788

04:13:21.910 --> 04:13:23.685 rather than something that promotes
NOTE Confidence: 0.838132619857788

04:13:23.685 --> 04:13:25.105 the progenitor populations of
NOTE Confidence: 0.838132619857788

04:13:25.105 --> 04:13:26.268 exhausted or memory cells.
NOTE Confidence: 0.838132619857788

04:13:26.270 --> 04:13:28.382 We don't seem to have a loss of
NOTE Confidence: 0.838132619857788

04:13:28.382 --> 04:13:30.138 those key populations important
NOTE Confidence: 0.838132619857788

04:13:30.138 --> 04:13:31.878 for long-term immunity.
NOTE Confidence: 0.838132619857788

04:13:31.880 --> 04:13:34.872 The mechanism for fly one appears to be
NOTE Confidence: 0.838132619857788

04:13:34.872 --> 04:13:37.100 interacting with the access of Runx 3.
NOTE Confidence: 0.838132619857788

04:13:37.100 --> 04:13:39.218 Two genes involved in the effector
NOTE Confidence: 0.838132619857788

04:13:39.218 --> 04:13:41.398 biology and so removing fly one

NOTE Confidence: 0.838132619857788
04:13:41.398 --> 04:13:43.516 allows runs three to work more
NOTE Confidence: 0.838132619857788
04:13:43.516 --> 04:13:44.921 efficiently because it binds
NOTE Confidence: 0.838132619857788
04:13:44.921 --> 04:13:46.835 directly to fly one monks motifs.
NOTE Confidence: 0.838132619857788
04:13:46.840 --> 04:13:49.278 So we're working hard on using this
NOTE Confidence: 0.838132619857788
04:13:49.280 --> 04:13:51.270 information and the identification role
NOTE Confidence: 0.838132619857788
04:13:51.270 --> 04:13:53.618 for fly one and protective immunity
NOTE Confidence: 0.838132619857788
04:13:53.618 --> 04:13:55.978 to see whether we may be able to
NOTE Confidence: 0.838132619857788
04:13:55.978 --> 04:13:57.689 improve things like cellular therapies
NOTE Confidence: 0.838132619857788
04:13:57.689 --> 04:14:00.086 and car T cell models and other
NOTE Confidence: 0.838132619857788
04:14:00.086 --> 04:14:01.916 settings of adoptive cellular therapy.
NOTE Confidence: 0.838132619857788
04:14:01.920 --> 04:14:03.744 So stop here that you can.
NOTE Confidence: 0.838132619857788
04:14:03.744 --> 04:14:05.870 Is the student in the lab now.
NOTE Confidence: 0.838132619857788
04:14:05.870 --> 04:14:07.694 Postdoc is actually leaving to go
NOTE Confidence: 0.838132619857788
04:14:07.694 --> 04:14:09.520 to Brad Bernstein's lab very soon,
NOTE Confidence: 0.838132619857788
04:14:09.520 --> 04:14:11.645 who did all of this work in
NOTE Confidence: 0.838132619857788

04:14:11.645 --> 04:14:12.554 collaboration with you.
NOTE Confidence: 0.838132619857788

04:14:12.560 --> 04:14:13.406 My she's lab.
NOTE Confidence: 0.838132619857788

04:14:13.406 --> 04:14:14.534 Lots of collaborations with
NOTE Confidence: 0.838132619857788

04:14:14.534 --> 04:14:16.209 Shelly Burger on the epigenetics,
NOTE Confidence: 0.838132619857788

04:14:16.210 --> 04:14:16.776 Josephine Giles.
NOTE Confidence: 0.838132619857788

04:14:16.776 --> 04:14:19.040 Alex Wong played a role in some of
NOTE Confidence: 0.838132619857788

04:14:19.095 --> 04:14:21.015 the Melanoma work that I mentioned
NOTE Confidence: 0.838132619857788

04:14:21.015 --> 04:14:21.975 in the beginning.
NOTE Confidence: 0.838132619857788

04:14:21.980 --> 04:14:22.574 Omar, Coniston,
NOTE Confidence: 0.838132619857788

04:14:22.574 --> 04:14:24.356 all of the previous talks work
NOTE Confidence: 0.838132619857788

04:14:24.356 --> 04:14:26.050 with great collaborators in human
NOTE Confidence: 0.838132619857788

04:14:26.050 --> 04:14:27.795 Melanoma Melanoma side that I
NOTE Confidence: 0.838132619857788

04:14:27.795 --> 04:14:29.566 mentioned just in passing at the
NOTE Confidence: 0.838132619857788

04:14:29.566 --> 04:14:31.096 beginning and lots of thanks to
NOTE Confidence: 0.838132619857788

04:14:31.100 --> 04:14:33.326 a lot of the funding behind this.
NOTE Confidence: 0.838132619857788

04:14:33.330 --> 04:14:34.782 So stop there and happy to

NOTE Confidence: 0.838132619857788
04:14:34.782 --> 04:14:35.990 take questions at this time.
NOTE Confidence: 0.832812428474426
04:14:38.120 --> 04:14:39.893 Alright, Thanks John.
NOTE Confidence: 0.832812428474426
04:14:39.893 --> 04:14:43.440 So we have waiting for questions.
NOTE Confidence: 0.832812428474426
04:14:43.440 --> 04:14:46.990 I guess I wanted to ask
NOTE Confidence: 0.832812428474426
04:14:46.990 --> 04:14:49.940 about this question but I
NOTE Confidence: 0.832812428474426
04:14:49.940 --> 04:14:53.468 think this is an interesting idea
NOTE Confidence: 0.832812428474426
04:14:53.468 --> 04:14:57.795 and it's one of the areas that.
NOTE Confidence: 0.832812428474426
04:14:57.795 --> 04:15:00.708 Conceptually, it's very hard to put together,
NOTE Confidence: 0.832812428474426
04:15:00.710 --> 04:15:02.936 which is this idea of with the
NOTE Confidence: 0.832812428474426
04:15:02.936 --> 04:15:05.157 idea of stem like cells and
NOTE Confidence: 0.832812428474426
04:15:05.157 --> 04:15:07.527 trying to drive effector T cells.
NOTE Confidence: 0.832812428474426
04:15:07.530 --> 04:15:08.710 Always this trade off,
NOTE Confidence: 0.832812428474426
04:15:08.710 --> 04:15:11.322 and so you sort of have identified something
NOTE Confidence: 0.832812428474426
04:15:11.322 --> 04:15:14.402 here which may not have that trade off.
NOTE Confidence: 0.832812428474426
04:15:14.410 --> 04:15:16.480 And I like the mechanism potentially
NOTE Confidence: 0.832812428474426

04:15:16.480 --> 04:15:19.227 of being able to take the brakes off,
NOTE Confidence: 0.832812428474426

04:15:19.230 --> 04:15:20.169 but it does.
NOTE Confidence: 0.832812428474426

04:15:20.169 --> 04:15:21.734 It does suggest that these
NOTE Confidence: 0.832812428474426

04:15:21.734 --> 04:15:23.010 are different processes,
NOTE Confidence: 0.832812428474426

04:15:23.010 --> 04:15:25.418 especially as opposed to one process right?
NOTE Confidence: 0.832812428474426

04:15:25.420 --> 04:15:27.140 Like the that we've always.
NOTE Confidence: 0.832812428474426

04:15:27.140 --> 04:15:29.342 I guess I've always thought about
NOTE Confidence: 0.832812428474426

04:15:29.342 --> 04:15:31.837 the trade off as being you have
NOTE Confidence: 0.832812428474426

04:15:31.837 --> 04:15:34.049 to get one to get the other.
NOTE Confidence: 0.832812428474426

04:15:34.050 --> 04:15:35.550 That's that's what's going on.
NOTE Confidence: 0.832812428474426

04:15:35.550 --> 04:15:37.050 Or is it just a?
NOTE Confidence: 0.832812428474426

04:15:37.050 --> 04:15:38.550 Is there something more there
NOTE Confidence: 0.832812428474426

04:15:38.550 --> 04:15:39.450 than than I'm
NOTE Confidence: 0.840116739273071

04:15:39.450 --> 04:15:40.650 missing? I mean, that's
NOTE Confidence: 0.840116739273071

04:15:40.650 --> 04:15:42.750 what we think is happening and there
NOTE Confidence: 0.840116739273071

04:15:42.750 --> 04:15:44.338 are a couple different potential

NOTE Confidence: 0.840116739273071
04:15:44.338 --> 04:15:46.599 ways that that might play out and
NOTE Confidence: 0.840116739273071
04:15:46.599 --> 04:15:48.447 we don't have answers to this yet,
NOTE Confidence: 0.840116739273071
04:15:48.450 --> 04:15:50.250 but the simplest one is that fly
NOTE Confidence: 0.840116739273071
04:15:50.250 --> 04:15:52.040 one only plays a role after you've
NOTE Confidence: 0.840116739273071
04:15:52.040 --> 04:15:54.362 made that switch from whatever that
NOTE Confidence: 0.840116739273071
04:15:54.362 --> 04:15:55.523 progenitor precursor population
NOTE Confidence: 0.840116739273071
04:15:55.580 --> 04:15:57.146 is to the effector Lenny edge.
NOTE Confidence: 0.840116739273071
04:15:57.150 --> 04:15:59.250 Then in the effector Lenny edge fly,
NOTE Confidence: 0.840116739273071
04:15:59.250 --> 04:16:00.750 one is playing a role,
NOTE Confidence: 0.840116739273071
04:16:00.750 --> 04:16:01.954 probably to limit immunopathology.
NOTE Confidence: 0.840116739273071
04:16:01.954 --> 04:16:04.080 It just sort of restraining runs three.
NOTE Confidence: 0.840116739273071
04:16:04.080 --> 04:16:05.977 So we can start to test that.
NOTE Confidence: 0.840116739273071
04:16:05.980 --> 04:16:08.130 I mean, I think we really need to do to
NOTE Confidence: 0.840116739273071
04:16:08.194 --> 04:16:10.048 test that properly is do conditional
NOTE Confidence: 0.840116739273071
04:16:10.048 --> 04:16:12.508 deletion of fly one at later time points,
NOTE Confidence: 0.840116739273071

04:16:12.510 --> 04:16:14.478 so you know once you firmly established the
NOTE Confidence: 0.840116739273071

04:16:14.478 --> 04:16:16.048 exhausted lininger firmly established memory,
NOTE Confidence: 0.840116739273071

04:16:16.050 --> 04:16:16.827 then delete fly.
NOTE Confidence: 0.840116739273071

04:16:16.827 --> 04:16:19.040 Wanna make sure that there's not an impact.
NOTE Confidence: 0.840116739273071

04:16:19.040 --> 04:16:21.182 We also need to carry on some of these
NOTE Confidence: 0.840116739273071

04:16:21.182 --> 04:16:22.834 experiments a little bit longer and
NOTE Confidence: 0.840116739273071

04:16:22.834 --> 04:16:24.194 try to understand whether there's
NOTE Confidence: 0.840116739273071

04:16:24.241 --> 04:16:26.011 any long-term defect in memory or
NOTE Confidence: 0.840116739273071

04:16:26.011 --> 04:16:27.191 do re challenge experiments.
NOTE Confidence: 0.840116739273071

04:16:27.200 --> 04:16:29.104 We've not been able to do for
NOTE Confidence: 0.840116739273071

04:16:29.104 --> 04:16:29.920 some technical reasons.
NOTE Confidence: 0.840116739273071

04:16:29.920 --> 04:16:30.580 Right now,
NOTE Confidence: 0.840116739273071

04:16:30.580 --> 04:16:32.560 we're comfortable with sort of similar
NOTE Confidence: 0.840116739273071

04:16:32.560 --> 04:16:34.115 interpretation of that based on the
NOTE Confidence: 0.840116739273071

04:16:34.115 --> 04:16:36.029 data that we have that is just acting.
NOTE Confidence: 0.840116739273071

04:16:36.030 --> 04:16:36.732 Out of state,

NOTE Confidence: 0.840116739273071
04:16:36.732 --> 04:16:37.902 once you've already made the
NOTE Confidence: 0.840116739273071
04:16:37.902 --> 04:16:39.099 commitment to the effector Lenny
NOTE Confidence: 0.840116739273071
04:16:39.099 --> 04:16:40.702 edge and you could actually push the
NOTE Confidence: 0.840116739273071
04:16:40.751 --> 04:16:42.126 effector Lenny Edge even farther.
NOTE Confidence: 0.832057774066925
04:16:43.740 --> 04:16:45.390 So there's a couple of questions
NOTE Confidence: 0.832057774066925
04:16:45.390 --> 04:16:47.095 in the chat when I'm gonna
NOTE Confidence: 0.832057774066925
04:16:47.095 --> 04:16:48.733 ask is about the downsides to
NOTE Confidence: 0.832057774066925
04:16:48.740 --> 04:16:49.860 removing fly one. Yeah,
NOTE Confidence: 0.832057774066925
04:16:49.860 --> 04:16:51.645 so? I mean, there's always a downside
NOTE Confidence: 0.832057774066925
04:16:51.645 --> 04:16:53.190 to getting more effector cells,
NOTE Confidence: 0.832057774066925
04:16:53.190 --> 04:16:54.060 and that's immunopathology,
NOTE Confidence: 0.832057774066925
04:16:54.060 --> 04:16:56.090 and so this really depends on your
NOTE Confidence: 0.832057774066925
04:16:56.140 --> 04:16:57.918 setting and how much antigen there is.
NOTE Confidence: 0.832057774066925
04:16:57.920 --> 04:16:58.888 And things like that.
NOTE Confidence: 0.832057774066925
04:16:58.888 --> 04:17:00.949 And all the folks on the line who
NOTE Confidence: 0.832057774066925

04:17:00.949 --> 04:17:02.593 worked with LCD kind of understand
NOTE Confidence: 0.832057774066925

04:17:02.593 --> 04:17:04.728 how this might work and in the
NOTE Confidence: 0.832057774066925

04:17:04.728 --> 04:17:05.646 chronic infection experiments
NOTE Confidence: 0.832057774066925

04:17:05.646 --> 04:17:07.476 that I showed in one experiment,
NOTE Confidence: 0.832057774066925

04:17:07.476 --> 04:17:09.755 we actually had our cell numbers maybe 20
NOTE Confidence: 0.832057774066925

04:17:09.755 --> 04:17:11.818 or 30% higher than they should have been.
NOTE Confidence: 0.832057774066925

04:17:11.820 --> 04:17:12.690 And sure enough,
NOTE Confidence: 0.832057774066925

04:17:12.690 --> 04:17:13.850 we had lethal immunopathology.
NOTE Confidence: 0.832057774066925

04:17:13.850 --> 04:17:16.550 My cell had to be sacked because we lost,
NOTE Confidence: 0.832057774066925

04:17:16.550 --> 04:17:18.050 you know 3040% body weight.
NOTE Confidence: 0.832057774066925

04:17:18.050 --> 04:17:18.618 So yes,
NOTE Confidence: 0.832057774066925

04:17:18.618 --> 04:17:20.322 you do need to temper immunopathology
NOTE Confidence: 0.832057774066925

04:17:20.322 --> 04:17:22.081 and that does actually play role
NOTE Confidence: 0.832057774066925

04:17:22.081 --> 04:17:23.785 in humans in some settings and
NOTE Confidence: 0.832057774066925

04:17:23.839 --> 04:17:25.765 probably a subset of our kovid
NOTE Confidence: 0.832057774066925

04:17:25.765 --> 04:17:27.379 patients are experiencing some form

NOTE Confidence: 0.832057774066925
04:17:27.379 --> 04:17:29.353 of T cell mediated immune pathology
NOTE Confidence: 0.832057774066925
04:17:29.353 --> 04:17:31.247 where exactly the T cells fit in.
NOTE Confidence: 0.832057774066925
04:17:31.250 --> 04:17:33.050 There is a whole different conversation,
NOTE Confidence: 0.832057774066925
04:17:33.050 --> 04:17:37.330 so there is a downside if you're not careful.
NOTE Confidence: 0.832057774066925
04:17:37.330 --> 04:17:38.110 So sorry
NOTE Confidence: 0.800349652767181
04:17:38.110 --> 04:17:39.662 so the clarify John.
NOTE Confidence: 0.800349652767181
04:17:39.662 --> 04:17:41.662 So you're saying that there's
NOTE Confidence: 0.800349652767181
04:17:41.662 --> 04:17:43.274 a dose response relationship
NOTE Confidence: 0.800349652767181
04:17:43.274 --> 04:17:45.236 in terms of autoimmunity with
NOTE Confidence: 0.800349652767181
04:17:45.236 --> 04:17:47.420 with the fly one deleted cells.
NOTE Confidence: 0.800349652767181
04:17:47.420 --> 04:17:49.748 So if you give more adoptively
NOTE Confidence: 0.800349652767181
04:17:49.748 --> 04:17:52.070 transferred you see pathology. I would
NOTE Confidence: 0.800349652767181
04:17:52.070 --> 04:17:54.010 say it's a mythology, not
NOTE Confidence: 0.800349652767181
04:17:54.010 --> 04:17:56.803 autoimmunity. In this case and the way
NOTE Confidence: 0.800349652767181
04:17:56.803 --> 04:17:59.602 it manifests here is we can clearly see
NOTE Confidence: 0.800349652767181

04:17:59.602 --> 04:18:03.012 it in else MV because LCD is systemic and
NOTE Confidence: 0.800349652767181

04:18:03.012 --> 04:18:05.267 because there's an engine everywhere.
NOTE Confidence: 0.800349652767181

04:18:05.270 --> 04:18:07.610 You may see some of it.
NOTE Confidence: 0.800349652767181

04:18:07.610 --> 04:18:09.020 Infla if you're just on the
NOTE Confidence: 0.800349652767181

04:18:09.020 --> 04:18:10.589 wrong side of the Bell curve.
NOTE Confidence: 0.800349652767181

04:18:10.590 --> 04:18:12.760 But you're not going to see any of it really
NOTE Confidence: 0.800349652767181

04:18:12.819 --> 04:18:14.800 in this sort of Implantable tumor model,
NOTE Confidence: 0.800349652767181

04:18:14.800 --> 04:18:16.246 because the only place you have
NOTE Confidence: 0.800349652767181

04:18:16.246 --> 04:18:18.028 pathology would be in the tumor itself.
NOTE Confidence: 0.800349652767181

04:18:18.030 --> 04:18:19.506 That's one place the Antigen is,
NOTE Confidence: 0.800349652767181

04:18:19.510 --> 04:18:21.202 so the immunopathology risk actually can
NOTE Confidence: 0.800349652767181

04:18:21.202 --> 04:18:23.000 only really be evaluated when you also
NOTE Confidence: 0.800349652767181

04:18:23.000 --> 04:18:24.720 know where and how much energy you have.
NOTE Confidence: 0.800349652767181

04:18:24.720 --> 04:18:25.464 If it's systemic,
NOTE Confidence: 0.800349652767181

04:18:25.464 --> 04:18:27.200 the risk will be much higher than
NOTE Confidence: 0.797694444656372

04:18:27.200 --> 04:18:29.610 if it's local. OK, sorry,

NOTE Confidence: 0.797694444656372
04:18:29.610 --> 04:18:31.135 my zoom keeps cutting out
NOTE Confidence: 0.828332960605621
04:18:31.140 --> 04:18:31.752 and restarting,
NOTE Confidence: 0.828332960605621
04:18:31.752 --> 04:18:33.894 so I apologize if I missed something.
NOTE Confidence: 0.828332960605621
04:18:33.900 --> 04:18:35.718 There was one other question so
NOTE Confidence: 0.828332960605621
04:18:35.718 --> 04:18:38.178 I have to re open my chat that
NOTE Confidence: 0.828332960605621
04:18:38.180 --> 04:18:40.018 was there was about does removal
NOTE Confidence: 0.828332960605621
04:18:40.018 --> 04:18:41.548 of fly one Excel right?
NOTE Confidence: 0.828332960605621
04:18:41.550 --> 04:18:42.770 Resident memory development issue?
NOTE Confidence: 0.828332960605621
04:18:42.770 --> 04:18:43.990 Yeah yeah so great.
NOTE Confidence: 0.828332960605621
04:18:43.990 --> 04:18:45.218 I was actually just
NOTE Confidence: 0.828332960605621
04:18:45.220 --> 04:18:46.444 editing that paragraph of
NOTE Confidence: 0.828332960605621
04:18:46.444 --> 04:18:47.668 the paper this morning.
NOTE Confidence: 0.828332960605621
04:18:47.670 --> 04:18:49.500 So yeah, we actually think that
NOTE Confidence: 0.828332960605621
04:18:49.500 --> 04:18:51.818 this may be playing a role as well.
NOTE Confidence: 0.828332960605621
04:18:51.818 --> 04:18:54.106 Obviously runs three is a key role in
NOTE Confidence: 0.828332960605621

04:18:54.106 --> 04:18:56.178 resident memory and in some of the
NOTE Confidence: 0.828332960605621

04:18:56.178 --> 04:18:58.265 models that I showed you resident
NOTE Confidence: 0.828332960605621

04:18:58.265 --> 04:18:59.990 memory will play an important.
NOTE Confidence: 0.828332960605621

04:18:59.990 --> 04:19:01.887 Have an important role in protecting unity,
NOTE Confidence: 0.828332960605621

04:19:01.890 --> 04:19:03.780 especially that flew model that I showed.
NOTE Confidence: 0.828332960605621

04:19:03.780 --> 04:19:05.948 We actually don't know much about this yet,
NOTE Confidence: 0.828332960605621

04:19:05.950 --> 04:19:07.576 it's something that we're working on.
NOTE Confidence: 0.828332960605621

04:19:07.580 --> 04:19:09.449 We suspect that there will be an
NOTE Confidence: 0.828332960605621

04:19:09.449 --> 04:19:11.098 impact on resident memory as well,
NOTE Confidence: 0.828332960605621

04:19:11.100 --> 04:19:12.460 but we don't get it.
NOTE Confidence: 0.816081762313843

04:19:13.410 --> 04:19:14.590 Awesome, well thank you
NOTE Confidence: 0.816081762313843

04:19:14.590 --> 04:19:16.645 so much. John is real pleasure listening
NOTE Confidence: 0.816081762313843

04:19:16.645 --> 04:19:18.598 to you for the interest of time.
NOTE Confidence: 0.816081762313843

04:19:18.598 --> 04:19:21.210 I'm going to move on and it's a real
NOTE Confidence: 0.816081762313843

04:19:21.210 --> 04:19:23.106 pleasure also to introduce Max Promo.
NOTE Confidence: 0.816081762313843

04:19:23.110 --> 04:19:24.898 I'm not going to say much

NOTE Confidence: 0.816081762313843
04:19:24.898 --> 04:19:26.639 because of the interest of time,
NOTE Confidence: 0.816081762313843
04:19:26.640 --> 04:19:28.992 but there's a ton you could say about
NOTE Confidence: 0.816081762313843
04:19:28.992 --> 04:19:31.327 Max in terms of him having been sort
NOTE Confidence: 0.816081762313843
04:19:31.327 --> 04:19:33.990 of at the at the right places to be
NOTE Confidence: 0.816081762313843
04:19:33.990 --> 04:19:36.303 have a huge impact in terms of therapy.
NOTE Confidence: 0.816081762313843
04:19:36.303 --> 04:19:38.690 Was one of the first people to study.
NOTE Confidence: 0.816081762313843
04:19:38.690 --> 04:19:41.050 See till four in mice and really just
NOTE Confidence: 0.816081762313843
04:19:41.050 --> 04:19:43.478 has had a huge impact on the field.
NOTE Confidence: 0.816081762313843
04:19:43.480 --> 04:19:44.540 In his own lab,
NOTE Confidence: 0.816081762313843
04:19:44.540 --> 04:19:47.149 they've done a lot of just beautiful work,
NOTE Confidence: 0.816081762313843
04:19:47.150 --> 04:19:49.257 and I think that's the one thing
NOTE Confidence: 0.816081762313843
04:19:49.257 --> 04:19:50.820 that really stands out about.
NOTE Confidence: 0.816081762313843
04:19:50.820 --> 04:19:52.656 Max is work is always just
NOTE Confidence: 0.816081762313843
04:19:52.656 --> 04:19:53.268 amazingly beautiful.
NOTE Confidence: 0.816081762313843
04:19:53.270 --> 04:19:56.042 I can see in the back of his picture
NOTE Confidence: 0.816081762313843

04:19:56.042 --> 04:19:58.370 he's got one of his his, his.
NOTE Confidence: 0.816081762313843

04:19:58.370 --> 04:20:00.762 Images of a tumor or something
NOTE Confidence: 0.816081762313843

04:20:00.762 --> 04:20:02.130 in the back there.
NOTE Confidence: 0.816081762313843

04:20:02.130 --> 04:20:03.446 It's always beautiful work.
NOTE Confidence: 0.816081762313843

04:20:03.446 --> 04:20:05.890 So Max is the chair of sorry.
NOTE Confidence: 0.816081762313843

04:20:05.890 --> 04:20:08.333 Is the professor in the Department of
NOTE Confidence: 0.816081762313843

04:20:08.333 --> 04:20:10.422 pathology and he's a inaugural chair
NOTE Confidence: 0.816081762313843

04:20:10.422 --> 04:20:13.094 of the amino X initiative and it's real
NOTE Confidence: 0.816081762313843

04:20:13.094 --> 04:20:15.809 pleasure to have him to talk to them.
NOTE Confidence: 0.796269178390503

04:20:17.240 --> 04:20:19.634 Thanks Nick. In a room Mary yes great.
NOTE Confidence: 0.796269178390503

04:20:19.634 --> 04:20:21.755 Well I want to thank you Yale
NOTE Confidence: 0.796269178390503

04:20:21.755 --> 04:20:23.520 Cancer Center for setting this up.
NOTE Confidence: 0.796269178390503

04:20:23.520 --> 04:20:25.152 I'm hopeful that when Kovid is
NOTE Confidence: 0.796269178390503

04:20:25.152 --> 04:20:27.188 over that we can continue to learn
NOTE Confidence: 0.796269178390503

04:20:27.188 --> 04:20:29.253 how to do these kinds of meetings
NOTE Confidence: 0.796269178390503

04:20:29.319 --> 04:20:31.287 without flying all over the world.

NOTE Confidence: 0.796269178390503
04:20:31.290 --> 04:20:32.790 That's really useful for interactivity.
NOTE Confidence: 0.796269178390503
04:20:32.790 --> 04:20:34.578 I think for all of us,
NOTE Confidence: 0.796269178390503
04:20:34.580 --> 04:20:36.780 and we need to do figure out how
NOTE Confidence: 0.796269178390503
04:20:36.780 --> 04:20:39.069 to do this a little bit more,
NOTE Confidence: 0.796269178390503
04:20:39.070 --> 04:20:41.156 and obviously get the trainees involved too.
NOTE Confidence: 0.796269178390503
04:20:41.160 --> 04:20:43.673 But this has been great today in
NOTE Confidence: 0.796269178390503
04:20:43.673 --> 04:20:45.789 terms of moderating and the talks.
NOTE Confidence: 0.796269178390503
04:20:45.790 --> 04:20:47.614 So I'm going to tell us sort of
NOTE Confidence: 0.796269178390503
04:20:47.614 --> 04:20:49.704 a series of stories that feed on
NOTE Confidence: 0.796269178390503
04:20:49.704 --> 04:20:51.274 something that pointed out that
NOTE Confidence: 0.796269178390503
04:20:51.334 --> 04:20:53.389 we're really interested in how
NOTE Confidence: 0.796269178390503
04:20:53.389 --> 04:20:55.033 emerging behavior emergent behavior
NOTE Confidence: 0.796269178390503
04:20:55.033 --> 04:20:57.060 takes place in an immune system.
NOTE Confidence: 0.796269178390503
04:20:57.060 --> 04:20:58.670 It starts often with imaging
NOTE Confidence: 0.796269178390503
04:20:58.670 --> 04:21:00.280 to just ask what is,
NOTE Confidence: 0.796269178390503

04:21:00.280 --> 04:21:02.773 what do things look like an we do at
NOTE Confidence: 0.796269178390503

04:21:02.773 --> 04:21:05.279 the molecular level to look at how
NOTE Confidence: 0.796269178390503

04:21:05.279 --> 04:21:07.364 T solar separate act, for example,
NOTE Confidence: 0.796269178390503

04:21:07.364 --> 04:21:09.296 to understand how signaling gets going?
NOTE Confidence: 0.796269178390503

04:21:09.300 --> 04:21:11.226 We also look at, for example,
NOTE Confidence: 0.796269178390503

04:21:11.230 --> 04:21:13.288 how cells interact with one another in
NOTE Confidence: 0.796269178390503

04:21:13.288 --> 04:21:15.408 order to recognize and initiated response.
NOTE Confidence: 0.796269178390503

04:21:15.410 --> 04:21:17.100 And I just want to.
NOTE Confidence: 0.796269178390503

04:21:17.100 --> 04:21:17.928 Player quick movie.
NOTE Confidence: 0.796269178390503

04:21:17.928 --> 04:21:19.860 From that we're going to see in
NOTE Confidence: 0.796269178390503

04:21:19.920 --> 04:21:21.705 this T cell here that's in Green.
NOTE Confidence: 0.796269178390503

04:21:21.710 --> 04:21:23.502 It's probably not the way that you
NOTE Confidence: 0.796269178390503

04:21:23.502 --> 04:21:24.960 normally think of adi sailboat.
NOTE Confidence: 0.796269178390503

04:21:24.960 --> 04:21:26.976 If you do this kind of high resolution
NOTE Confidence: 0.796269178390503

04:21:26.976 --> 04:21:28.480 imaging called lattice light sheet,
NOTE Confidence: 0.796269178390503

04:21:28.480 --> 04:21:30.200 you see that what T cells do is

NOTE Confidence: 0.796269178390503
04:21:30.200 --> 04:21:31.934 they use these little finger like
NOTE Confidence: 0.796269178390503
04:21:31.934 --> 04:21:34.140 projections to probe the world to try
NOTE Confidence: 0.796269178390503
04:21:34.140 --> 04:21:35.800 to find peptide image, see complexes.
NOTE Confidence: 0.796269178390503
04:21:35.800 --> 04:21:37.150 And as this movie plays,
NOTE Confidence: 0.796269178390503
04:21:37.150 --> 04:21:38.776 the red is a dendritic cell,
NOTE Confidence: 0.796269178390503
04:21:38.780 --> 04:21:40.509 and you may think of a dendritic
NOTE Confidence: 0.796269178390503
04:21:40.509 --> 04:21:42.030 cells having these long dendrites.
NOTE Confidence: 0.796269178390503
04:21:42.030 --> 04:21:43.390 They're actually more like veils,
NOTE Confidence: 0.796269178390503
04:21:43.390 --> 04:21:45.231 and you can see them sweeping around
NOTE Confidence: 0.796269178390503
04:21:45.231 --> 04:21:47.182 the surface where the cell is probing
NOTE Confidence: 0.796269178390503
04:21:47.182 --> 04:21:48.562 and looking for package season.
NOTE Confidence: 0.796269178390503
04:21:48.570 --> 04:21:50.268 If you cut away that surface,
NOTE Confidence: 0.796269178390503
04:21:50.270 --> 04:21:52.167 one of the things you will appreciate
NOTE Confidence: 0.796269178390503
04:21:52.167 --> 04:21:53.810 is that the dendritic cell is
NOTE Confidence: 0.796269178390503
04:21:53.810 --> 04:21:55.963 doing as much of the work to font
NOTE Confidence: 0.796269178390503

04:21:55.963 --> 04:21:57.823 to be found to essentially wrap
NOTE Confidence: 0.796269178390503

04:21:57.823 --> 04:21:59.489 its membrane around the T cell.
NOTE Confidence: 0.796269178390503

04:21:59.489 --> 04:22:02.439 As the T cell is doing to probe the surface.
NOTE Confidence: 0.796269178390503

04:22:02.440 --> 04:22:04.138 So you see this incredible complementarity,
NOTE Confidence: 0.796269178390503

04:22:04.140 --> 04:22:06.148 and I think this is a nice movie
NOTE Confidence: 0.796269178390503

04:22:06.148 --> 04:22:07.540 to demonstrate the idea that
NOTE Confidence: 0.796269178390503

04:22:07.540 --> 04:22:09.208 immune systems and we think about
NOTE Confidence: 0.796269178390503

04:22:09.208 --> 04:22:10.928 them in cancer or partnerships,
NOTE Confidence: 0.796269178390503

04:22:10.930 --> 04:22:13.122 and the idea that one T cell is
NOTE Confidence: 0.796269178390503

04:22:13.122 --> 04:22:15.170 the source of all cure is lovely,
NOTE Confidence: 0.796269178390503

04:22:15.170 --> 04:22:17.172 and it certainly is the basis of
NOTE Confidence: 0.796269178390503

04:22:17.172 --> 04:22:18.579 our favourites Italy for work.
NOTE Confidence: 0.796269178390503

04:22:18.580 --> 04:22:20.980 NP1 and all these things that are followed,
NOTE Confidence: 0.796269178390503

04:22:20.980 --> 04:22:23.080 but really we do need to think
NOTE Confidence: 0.796269178390503

04:22:23.080 --> 04:22:24.622 about the partnerships that take
NOTE Confidence: 0.796269178390503

04:22:24.622 --> 04:22:26.380 place and that's you know, visual.

NOTE Confidence: 0.796269178390503
04:22:26.380 --> 04:22:27.580 You can visualize that.
NOTE Confidence: 0.796269178390503
04:22:27.580 --> 04:22:29.687 And I won't actually show any movies
NOTE Confidence: 0.796269178390503
04:22:29.687 --> 04:22:31.701 in the interest of time by thinking
NOTE Confidence: 0.796269178390503
04:22:31.701 --> 04:22:33.653 about how cells work in a multi
NOTE Confidence: 0.796269178390503
04:22:33.653 --> 04:22:35.928 cellular array and you can look for
NOTE Confidence: 0.796269178390503
04:22:35.928 --> 04:22:37.864 example tumors in black here and
NOTE Confidence: 0.796269178390503
04:22:37.864 --> 04:22:39.469 these are various different mileage
NOTE Confidence: 0.796269178390503
04:22:39.469 --> 04:22:41.179 populations and you can think about
NOTE Confidence: 0.796269178390503
04:22:41.179 --> 04:22:42.514 how they arrange themselves to
NOTE Confidence: 0.796269178390503
04:22:42.564 --> 04:22:44.370 create the biology want and then
NOTE Confidence: 0.796269178390503
04:22:44.370 --> 04:22:45.574 the final emergent behavior.
NOTE Confidence: 0.798586487770081
04:22:45.580 --> 04:22:47.080 The connection is clinical outcome.
NOTE Confidence: 0.798586487770081
04:22:47.080 --> 04:22:49.531 So in cancer we have. Feet, feet down.
NOTE Confidence: 0.798586487770081
04:22:49.531 --> 04:22:51.373 Answer of whether whether a patient
NOTE Confidence: 0.798586487770081
04:22:51.373 --> 04:22:53.362 lives or dies and it's really a
NOTE Confidence: 0.798586487770081

04:22:53.362 --> 04:22:54.809 dependent on the emergent behaviors
NOTE Confidence: 0.798586487770081

04:22:54.809 --> 04:22:56.651 of how the multi cellular systems
NOTE Confidence: 0.798586487770081

04:22:56.651 --> 04:22:58.772 are setting up and those in term.
NOTE Confidence: 0.798586487770081

04:22:58.772 --> 04:22:59.964 Obviously at the lovable.
NOTE Confidence: 0.798586487770081

04:22:59.970 --> 04:23:02.960 So before I go into the data from our lab,
NOTE Confidence: 0.798586487770081

04:23:02.960 --> 04:23:04.452 I want to do something
NOTE Confidence: 0.798586487770081

04:23:04.452 --> 04:23:05.644 that's a little different.
NOTE Confidence: 0.798586487770081

04:23:05.650 --> 04:23:07.396 Maybe from what people have done
NOTE Confidence: 0.798586487770081

04:23:07.396 --> 04:23:09.540 in this in this seminar so far,
NOTE Confidence: 0.798586487770081

04:23:09.540 --> 04:23:11.166 and that's to remind everybody that
NOTE Confidence: 0.798586487770081

04:23:11.166 --> 04:23:13.118 while we've been super focused on the
NOTE Confidence: 0.798586487770081

04:23:13.118 --> 04:23:14.473 benefits of checkpoint blockade and
NOTE Confidence: 0.798586487770081

04:23:14.473 --> 04:23:16.462 all the various different ideas that
NOTE Confidence: 0.798586487770081

04:23:16.462 --> 04:23:18.202 it's brought forward about immunology,
NOTE Confidence: 0.798586487770081

04:23:18.210 --> 04:23:20.040 the rest of the immune system.
NOTE Confidence: 0.798586487770081

04:23:20.040 --> 04:23:22.840 Has been tapped in a huge huge explosion.

NOTE Confidence: 0.798586487770081
04:23:22.840 --> 04:23:25.448 I would say that many of us sort
NOTE Confidence: 0.798586487770081
04:23:25.448 --> 04:23:27.740 of choose to ignore I suppose,
NOTE Confidence: 0.798586487770081
04:23:27.740 --> 04:23:29.833 and also give you a couple examples
NOTE Confidence: 0.798586487770081
04:23:29.833 --> 04:23:31.755 because the immune system is no
NOTE Confidence: 0.798586487770081
04:23:31.755 --> 04:23:33.360 longer our textbook immune system
NOTE Confidence: 0.798586487770081
04:23:33.360 --> 04:23:35.452 where we're thinking about the
NOTE Confidence: 0.798586487770081
04:23:35.452 --> 04:23:36.838 difference between vaccination.
NOTE Confidence: 0.798586487770081
04:23:36.840 --> 04:23:39.336 Where you get a huge sort of clearing
NOTE Confidence: 0.798586487770081
04:23:39.336 --> 04:23:40.811 response versus a tolerogenic
NOTE Confidence: 0.798586487770081
04:23:40.811 --> 04:23:42.786 response where you ignore things.
NOTE Confidence: 0.798586487770081
04:23:42.790 --> 04:23:44.890 So just to give one example,
NOTE Confidence: 0.798586487770081
04:23:44.890 --> 04:23:47.410 in the last 10 years we've come to
NOTE Confidence: 0.798586487770081
04:23:47.410 --> 04:23:49.984 realize that the immune system will be
NOTE Confidence: 0.798586487770081
04:23:49.984 --> 04:23:52.670 necessary for everyone in this zoom today.
NOTE Confidence: 0.798586487770081
04:23:52.670 --> 04:23:53.946 To remember this talk,
NOTE Confidence: 0.798586487770081

04:23:53.946 --> 04:23:55.860 namely the macrophages of the brain,
NOTE Confidence: 0.798586487770081

04:23:55.860 --> 04:23:57.455 the microglia are now known
NOTE Confidence: 0.798586487770081

04:23:57.455 --> 04:23:59.050 to be pruning your synapses,
NOTE Confidence: 0.798586487770081

04:23:59.050 --> 04:24:00.650 and that pruning is essential.
NOTE Confidence: 0.798586487770081

04:24:00.650 --> 04:24:02.564 If you don't have the complement
NOTE Confidence: 0.798586487770081

04:24:02.564 --> 04:24:03.840 proteins in the microglia.
NOTE Confidence: 0.798586487770081

04:24:03.840 --> 04:24:06.702 To do that you will not remember this today.
NOTE Confidence: 0.798586487770081

04:24:06.710 --> 04:24:09.254 That is not the immune system that we're
NOTE Confidence: 0.798586487770081

04:24:09.254 --> 04:24:11.170 thinking about in general in cancer,
NOTE Confidence: 0.798586487770081

04:24:11.170 --> 04:24:12.133 but we should.
NOTE Confidence: 0.798586487770081

04:24:12.133 --> 04:24:14.059 Another example of that would be
NOTE Confidence: 0.798586487770081

04:24:14.059 --> 04:24:15.958 obviously the rise of the microbiota.
NOTE Confidence: 0.798586487770081

04:24:15.960 --> 04:24:17.802 What you realize about that is
NOTE Confidence: 0.798586487770081

04:24:17.802 --> 04:24:19.746 that the immune system is not
NOTE Confidence: 0.798586487770081

04:24:19.746 --> 04:24:21.058 ignorant of the microbiota.
NOTE Confidence: 0.798586487770081

04:24:21.060 --> 04:24:23.020 It is really carefully curated at.

NOTE Confidence: 0.798586487770081
04:24:23.020 --> 04:24:25.474 To the extent that you have T cells
NOTE Confidence: 0.798586487770081
04:24:25.474 --> 04:24:26.986 against most of your microbiota,
NOTE Confidence: 0.798586487770081
04:24:26.986 --> 04:24:29.698 and then it chooses how to deal with that,
NOTE Confidence: 0.798586487770081
04:24:29.700 --> 04:24:31.210 and that's that's a theme,
NOTE Confidence: 0.798586487770081
04:24:31.210 --> 04:24:33.442 and I think we can also see with some
NOTE Confidence: 0.798586487770081
04:24:33.442 --> 04:24:35.686 of the things that John talked about
NOTE Confidence: 0.798586487770081
04:24:35.686 --> 04:24:38.159 and we think about exhausted T cells,
NOTE Confidence: 0.798586487770081
04:24:38.160 --> 04:24:40.001 will exhaustion one can argue is a
NOTE Confidence: 0.798586487770081
04:24:40.001 --> 04:24:42.088 way that you can quarantine things.
NOTE Confidence: 0.798586487770081
04:24:42.090 --> 04:24:43.872 You can have a response to
NOTE Confidence: 0.798586487770081
04:24:43.872 --> 04:24:45.410 something that is dialed back.
NOTE Confidence: 0.798586487770081
04:24:45.410 --> 04:24:47.898 Perhaps if you want to leave latent virus
NOTE Confidence: 0.798586487770081
04:24:47.898 --> 04:24:50.539 alone and I won't go through all of these,
NOTE Confidence: 0.798586487770081
04:24:50.540 --> 04:24:52.065 but obviously our tourist chlorosis
NOTE Confidence: 0.798586487770081
04:24:52.065 --> 04:24:53.590 now as a macrophage based.
NOTE Confidence: 0.798586487770081

04:24:53.590 --> 04:24:53.866 Disease,
NOTE Confidence: 0.798586487770081

04:24:53.866 --> 04:24:55.798 it used to be just about lipids,
NOTE Confidence: 0.798586487770081

04:24:55.800 --> 04:24:57.795 so the immune system is showing up
NOTE Confidence: 0.798586487770081

04:24:57.795 --> 04:24:59.939 everywhere and I use this as a cartoon.
NOTE Confidence: 0.798586487770081

04:24:59.940 --> 04:25:01.837 This is from a perspective that underground
NOTE Confidence: 0.798586487770081

04:25:01.837 --> 04:25:04.080 Omaha and I wrote for science last year,
NOTE Confidence: 0.798586487770081

04:25:04.080 --> 04:25:06.136 where we basically point out that in the
NOTE Confidence: 0.798586487770081

04:25:06.136 --> 04:25:08.185 past we might have thought about the
NOTE Confidence: 0.798586487770081

04:25:08.185 --> 04:25:10.482 new system that going from tolerance to
NOTE Confidence: 0.798586487770081

04:25:10.482 --> 04:25:12.397 immunity or tolerance to destruction.
NOTE Confidence: 0.798586487770081

04:25:12.400 --> 04:25:13.804 Those were the things that we
NOTE Confidence: 0.798586487770081

04:25:13.804 --> 04:25:15.060 thought about dialing so we're
NOTE Confidence: 0.798586487770081

04:25:15.060 --> 04:25:16.168 in Immuno Immuno Oncology.
NOTE Confidence: 0.798586487770081

04:25:16.170 --> 04:25:19.014 We're trying to get it to destroy the tumor.
NOTE Confidence: 0.798586487770081

04:25:19.020 --> 04:25:20.630 But what's emerging from all
NOTE Confidence: 0.798586487770081

04:25:20.630 --> 04:25:22.240 the things that I just

NOTE Confidence: 0.864533483982086

04:25:22.240 --> 04:25:24.900 told you about are these roles of the immune

NOTE Confidence: 0.864533483982086

04:25:24.900 --> 04:25:27.070 system that you could call accommodation.

NOTE Confidence: 0.864533483982086

04:25:27.070 --> 04:25:28.930 Immune system is made to accommodate

NOTE Confidence: 0.864533483982086

04:25:28.930 --> 04:25:30.930 all the needs of your organs,

NOTE Confidence: 0.864533483982086

04:25:30.930 --> 04:25:33.604 that many of them are not about

NOTE Confidence: 0.864533483982086

04:25:33.604 --> 04:25:34.750 defense to microorganisms.

NOTE Confidence: 0.864533483982086

04:25:34.750 --> 04:25:36.525 So Michigan management issue metabolism

NOTE Confidence: 0.864533483982086

04:25:36.525 --> 04:25:39.244 is one that many in this room in

NOTE Confidence: 0.864533483982086

04:25:39.244 --> 04:25:41.008 this zoom will know quite well.

NOTE Confidence: 0.864533483982086

04:25:41.010 --> 04:25:42.180 Assisting tissue development.

NOTE Confidence: 0.864533483982086

04:25:42.180 --> 04:25:44.660 T cells are important, for example,

NOTE Confidence: 0.864533483982086

04:25:44.660 --> 04:25:47.880 for memory, duct formation to take place.

NOTE Confidence: 0.864533483982086

04:25:47.880 --> 04:25:49.746 And all of these things again,

NOTE Confidence: 0.864533483982086

04:25:49.750 --> 04:25:51.920 create this backdrop of the immune system,

NOTE Confidence: 0.864533483982086

04:25:51.920 --> 04:25:54.100 by which we've said, Well, you start,

NOTE Confidence: 0.864533483982086

04:25:54.100 --> 04:25:56.555 you start to need to understand how T
NOTE Confidence: 0.864533483982086

04:25:56.555 --> 04:25:58.080 cell receptor specificity paired with
NOTE Confidence: 0.864533483982086

04:25:58.136 --> 04:26:00.008 particular cell types can create this.
NOTE Confidence: 0.864533483982086

04:26:00.010 --> 04:26:01.560 What we're going in archetype,
NOTE Confidence: 0.864533483982086

04:26:01.560 --> 04:26:03.632 and it's here defining that as a
NOTE Confidence: 0.864533483982086

04:26:03.632 --> 04:26:05.609 collection of cells and linked states,
NOTE Confidence: 0.864533483982086

04:26:05.610 --> 04:26:06.850 possibly across tissue types,
NOTE Confidence: 0.864533483982086

04:26:06.850 --> 04:26:07.780 almost certainly following.
NOTE Confidence: 0.864533483982086

04:26:07.780 --> 04:26:09.901 It'll evolutionary design that do all the
NOTE Confidence: 0.864533483982086

04:26:09.901 --> 04:26:12.139 things that I show in these hexagons.
NOTE Confidence: 0.864533483982086

04:26:12.140 --> 04:26:13.690 And there are many more,
NOTE Confidence: 0.864533483982086

04:26:13.690 --> 04:26:14.256 I'm sure.
NOTE Confidence: 0.864533483982086

04:26:14.256 --> 04:26:16.948 And so the idea of this is that this
NOTE Confidence: 0.864533483982086

04:26:16.948 --> 04:26:19.060 is a higher level of abstraction
NOTE Confidence: 0.864533483982086

04:26:19.060 --> 04:26:20.540 than a single cell,
NOTE Confidence: 0.864533483982086

04:26:20.540 --> 04:26:22.549 and it's a little lower than disease,

NOTE Confidence: 0.864533483982086

04:26:22.550 --> 04:26:24.545 so it's recurrent motif in immune system.

NOTE Confidence: 0.864533483982086

04:26:24.545 --> 04:26:26.839 And if we think about the immune system,

NOTE Confidence: 0.864533483982086

04:26:26.840 --> 04:26:29.000 then also in the term of even the

NOTE Confidence: 0.864533483982086

04:26:29.000 --> 04:26:30.837 elimination of host cells and cancer,

NOTE Confidence: 0.864533483982086

04:26:30.840 --> 04:26:31.816 there are almost certainly,

NOTE Confidence: 0.864533483982086

04:26:31.816 --> 04:26:33.639 and I will show you the evidence

NOTE Confidence: 0.864533483982086

04:26:33.639 --> 04:26:35.169 that there are certainly collections

NOTE Confidence: 0.864533483982086

04:26:35.169 --> 04:26:37.339 of cell types that work together as

NOTE Confidence: 0.864533483982086

04:26:37.339 --> 04:26:39.121 archetypes that creates the kinds of

NOTE Confidence: 0.864533483982086

04:26:39.121 --> 04:26:40.850 immunity we need for antitumor responses.

NOTE Confidence: 0.864533483982086

04:26:40.850 --> 04:26:42.566 So for example, CDA T cells,

NOTE Confidence: 0.864533483982086

04:26:42.570 --> 04:26:45.153 and I'll tell you bout CC ones

NOTE Confidence: 0.864533483982086

04:26:45.153 --> 04:26:46.870 in the first story.

NOTE Confidence: 0.864533483982086

04:26:46.870 --> 04:26:47.226 Alright,

NOTE Confidence: 0.864533483982086

04:26:47.226 --> 04:26:50.123 so this doesn't mention two too much today,

NOTE Confidence: 0.864533483982086

04:26:50.123 --> 04:26:52.720 but I'm going to introduce this idea
NOTE Confidence: 0.864533483982086

04:26:52.797 --> 04:26:55.437 that is really how we came into this.
NOTE Confidence: 0.864533483982086

04:26:55.440 --> 04:26:57.210 Came back into cancer immunology
NOTE Confidence: 0.864533483982086

04:26:57.210 --> 04:26:59.923 was that we started to look in the
NOTE Confidence: 0.864533483982086

04:26:59.923 --> 04:27:01.953 sort of early teens at what cells
NOTE Confidence: 0.864533483982086

04:27:02.021 --> 04:27:04.081 in the tumor micro environment
NOTE Confidence: 0.864533483982086

04:27:04.081 --> 04:27:06.141 are really the antigen presenting
NOTE Confidence: 0.864533483982086

04:27:06.150 --> 04:27:08.320 cells on which T cell responses can
NOTE Confidence: 0.864533483982086

04:27:08.320 --> 04:27:10.661 be built and Long story short was
NOTE Confidence: 0.864533483982086

04:27:10.661 --> 04:27:12.677 that when are Miranda Bros took
NOTE Confidence: 0.864533483982086

04:27:12.743 --> 04:27:14.808 apart the tumor micro environment
NOTE Confidence: 0.864533483982086

04:27:14.808 --> 04:27:16.873 from an oven expressing tumor?
NOTE Confidence: 0.864533483982086

04:27:16.880 --> 04:27:19.568 She found it really only see 103 CC,
NOTE Confidence: 0.864533483982086

04:27:19.570 --> 04:27:21.250 one Denver Dick cells were
NOTE Confidence: 0.864533483982086

04:27:21.250 --> 04:27:22.930 able to induce T cells.
NOTE Confidence: 0.864533483982086

04:27:22.930 --> 04:27:24.246 This is XVX vivo,

NOTE Confidence: 0.864533483982086

04:27:24.246 --> 04:27:26.220 so in vitro to express nurse

NOTE Confidence: 0.864533483982086

04:27:26.294 --> 04:27:28.443 77 to express the 69 and these

NOTE Confidence: 0.864533483982086

04:27:28.443 --> 04:27:30.658 are the same cells she showed.

NOTE Confidence: 0.864533483982086

04:27:30.660 --> 04:27:31.330 They were,

NOTE Confidence: 0.864533483982086

04:27:31.330 --> 04:27:33.340 for example the predominant producers vial.

NOTE Confidence: 0.864533483982086

04:27:33.340 --> 04:27:36.532 12 they have PD one PD L1 is

NOTE Confidence: 0.864533483982086

04:27:36.532 --> 04:27:38.329 very consistent with what?

NOTE Confidence: 0.864533483982086

04:27:38.330 --> 04:27:40.364 IRA Millman has recently shown about

NOTE Confidence: 0.864533483982086

04:27:40.364 --> 04:27:42.387 these cells being again the primary

NOTE Confidence: 0.864533483982086

04:27:42.387 --> 04:27:44.217 antigen presenting cell that you want

NOTE Confidence: 0.864533483982086

04:27:44.217 --> 04:27:46.749 to D repress with checkpoint blockade,

NOTE Confidence: 0.864533483982086

04:27:46.750 --> 04:27:49.102 'cause they're the ones that present

NOTE Confidence: 0.864533483982086

04:27:49.102 --> 04:27:51.334 an antigen effectively and this is

NOTE Confidence: 0.864533483982086

04:27:51.334 --> 04:27:53.413 led to a really a cottage industry.

NOTE Confidence: 0.864533483982086

04:27:53.420 --> 04:27:55.532 In Miranda's paper she showed the

NOTE Confidence: 0.864533483982086

04:27:55.532 --> 04:27:57.336 essentially the frequency of genius
NOTE Confidence: 0.864533483982086

04:27:57.336 --> 04:27:59.036 that define these cell types,
NOTE Confidence: 0.864533483982086

04:27:59.040 --> 04:28:01.422 help you understand who's going to
NOTE Confidence: 0.864533483982086

04:28:01.422 --> 04:28:03.995 respond or actually this is even just
NOTE Confidence: 0.864533483982086

04:28:03.995 --> 04:28:06.116 who is going to live in general.
NOTE Confidence: 0.864533483982086

04:28:06.120 --> 04:28:06.728 Psycho number,
NOTE Confidence: 0.864533483982086

04:28:06.728 --> 04:28:08.552 but also who responds to check
NOTE Confidence: 0.864533483982086

04:28:08.552 --> 04:28:10.550 one blockade and a lot of other
NOTE Confidence: 0.864533483982086

04:28:10.550 --> 04:28:11.885 people have communists have done
NOTE Confidence: 0.776196777820587

04:28:11.942 --> 04:28:13.302 in create incredible work and
NOTE Confidence: 0.776196777820587

04:28:13.302 --> 04:28:15.240 sort of filling in the details and
NOTE Confidence: 0.776196777820587

04:28:15.240 --> 04:28:16.665 and carrying this story further.
NOTE Confidence: 0.776196777820587

04:28:16.670 --> 04:28:18.356 So if you understand that you
NOTE Confidence: 0.776196777820587

04:28:18.356 --> 04:28:20.101 understand then why we got interested
NOTE Confidence: 0.776196777820587

04:28:20.101 --> 04:28:22.075 in the question of what are the,
NOTE Confidence: 0.776196777820587

04:28:22.080 --> 04:28:23.795 what are the allies that are

NOTE Confidence: 0.776196777820587
04:28:23.795 --> 04:28:25.500 of the allies of the allies?
NOTE Confidence: 0.776196777820587
04:28:25.500 --> 04:28:27.495 So in other words, what is this?
NOTE Confidence: 0.776196777820587
04:28:27.500 --> 04:28:29.780 What is the archetype of the CC one?
NOTE Confidence: 0.776196777820587
04:28:29.780 --> 04:28:32.060 Why are they there in some peoples tumors?
NOTE Confidence: 0.776196777820587
04:28:32.060 --> 04:28:33.698 What makes them and have my
NOTE Confidence: 0.776196777820587
04:28:33.698 --> 04:28:35.190 we get more of them?
NOTE Confidence: 0.776196777820587
04:28:35.190 --> 04:28:36.410 So we set up.
NOTE Confidence: 0.776196777820587
04:28:36.410 --> 04:28:38.866 A system about 5 six years ago we
NOTE Confidence: 0.776196777820587
04:28:38.866 --> 04:28:41.399 called UCSF in your profile or insist
NOTE Confidence: 0.776196777820587
04:28:41.399 --> 04:28:44.192 big initiative to get tumors from every
NOTE Confidence: 0.776196777820587
04:28:44.192 --> 04:28:46.387 possible cancer indication we can.
NOTE Confidence: 0.776196777820587
04:28:46.390 --> 04:28:48.287 And to do very uniform sampling of
NOTE Confidence: 0.776196777820587
04:28:48.287 --> 04:28:50.163 them and the basic sampling strategy
NOTE Confidence: 0.776196777820587
04:28:50.163 --> 04:28:52.167 is not so different from maybe
NOTE Confidence: 0.776196777820587
04:28:52.167 --> 04:28:54.238 the pipeline that John mentioned.
NOTE Confidence: 0.776196777820587

04:28:54.240 --> 04:28:56.148 Our own one involves and has
NOTE Confidence: 0.776196777820587

04:28:56.148 --> 04:28:58.160 involved for a very long time,
NOTE Confidence: 0.776196777820587

04:28:58.160 --> 04:28:59.800 flow cytometry at high dimensionality.
NOTE Confidence: 0.776196777820587

04:28:59.800 --> 04:29:01.756 And then we sort individual applications.
NOTE Confidence: 0.776196777820587

04:29:01.760 --> 04:29:03.716 Nowadays we're doing single cell sequencing,
NOTE Confidence: 0.776196777820587

04:29:03.720 --> 04:29:06.051 but in fact we get a lot more better
NOTE Confidence: 0.776196777820587

04:29:06.051 --> 04:29:08.335 data out of deep sequencing of
NOTE Confidence: 0.776196777820587

04:29:08.335 --> 04:29:10.295 populations just because single cell
NOTE Confidence: 0.776196777820587

04:29:10.358 --> 04:29:13.137 sequencing tends to be very shallow pursell.
NOTE Confidence: 0.776196777820587

04:29:13.140 --> 04:29:14.687 So with that data set we could
NOTE Confidence: 0.776196777820587

04:29:14.687 --> 04:29:16.507 answer to the question I just posed,
NOTE Confidence: 0.776196777820587

04:29:16.510 --> 04:29:17.956 which is what is the archetype
NOTE Confidence: 0.776196777820587

04:29:17.956 --> 04:29:18.920 of the CDC one?
NOTE Confidence: 0.776196777820587

04:29:18.920 --> 04:29:21.593 What are the other cells that go with it?
NOTE Confidence: 0.776196777820587

04:29:21.600 --> 04:29:23.967 The way we did that is we took on.
NOTE Confidence: 0.776196777820587

04:29:23.970 --> 04:29:25.608 This is just some Melanoma patients

NOTE Confidence: 0.776196777820587
04:29:25.608 --> 04:29:27.966 and we each dot is a patient and we
NOTE Confidence: 0.776196777820587
04:29:27.966 --> 04:29:29.756 ask their frequency of CC ones and
NOTE Confidence: 0.776196777820587
04:29:29.756 --> 04:29:31.597 then we said what genes expressed in
NOTE Confidence: 0.776196777820587
04:29:31.597 --> 04:29:33.048 the tumor microenvironment have a
NOTE Confidence: 0.776196777820587
04:29:33.048 --> 04:29:35.270 strong correlation with the CC 1 numbers.
NOTE Confidence: 0.776196777820587
04:29:35.270 --> 04:29:37.139 And the one that was of interest
NOTE Confidence: 0.776196777820587
04:29:37.139 --> 04:29:37.940 is the cytokine.
NOTE Confidence: 0.776196777820587
04:29:37.940 --> 04:29:38.888 It's actually a League,
NOTE Confidence: 0.776196777820587
04:29:38.888 --> 04:29:40.892 and on a cell surface I'm often not
NOTE Confidence: 0.776196777820587
04:29:40.892 --> 04:29:42.464 secrete is called flip through Ligon
NOTE Confidence: 0.776196777820587
04:29:42.464 --> 04:29:44.347 and the reason it's interesting for
NOTE Confidence: 0.776196777820587
04:29:44.350 --> 04:29:46.368 those that know is it's the it's the
NOTE Confidence: 0.776196777820587
04:29:46.368 --> 04:29:48.350 dominant thing that drives CC one production.
NOTE Confidence: 0.776196777820587
04:29:48.350 --> 04:29:49.860 And the reason that's interesting
NOTE Confidence: 0.776196777820587
04:29:49.860 --> 04:29:51.945 is because this is from the tumor
NOTE Confidence: 0.776196777820587

04:29:51.945 --> 04:29:53.758 and So what you're realizing is that
NOTE Confidence: 0.776196777820587

04:29:53.758 --> 04:29:55.675 in the tumor there is a cell type
NOTE Confidence: 0.776196777820587

04:29:55.675 --> 04:29:57.664 that is your friend that is making
NOTE Confidence: 0.776196777820587

04:29:57.664 --> 04:29:59.620 flips religion that is making these
NOTE Confidence: 0.776196777820587

04:29:59.684 --> 04:30:01.460 cells and you want these cells.
NOTE Confidence: 0.776196777820587

04:30:01.460 --> 04:30:04.364 So it just so happened we started that
NOTE Confidence: 0.776196777820587

04:30:04.364 --> 04:30:07.367 just started making flips religion Reporter.
NOTE Confidence: 0.776196777820587

04:30:07.370 --> 04:30:09.428 And this is follows of sort of
NOTE Confidence: 0.776196777820587

04:30:09.428 --> 04:30:11.380 model that Rich Loxley is made
NOTE Confidence: 0.776196777820587

04:30:11.380 --> 04:30:13.055 a cottage industry as well,
NOTE Confidence: 0.776196777820587

04:30:13.060 --> 04:30:15.265 and for all kinds of cool discoveries.
NOTE Confidence: 0.776196777820587

04:30:15.270 --> 04:30:16.248 And here, just.
NOTE Confidence: 0.776196777820587

04:30:16.248 --> 04:30:16.574 Essentially,
NOTE Confidence: 0.776196777820587

04:30:16.574 --> 04:30:18.750 that's really look like in Locust Dr.
NOTE Confidence: 0.776196777820587

04:30:18.750 --> 04:30:20.854 Zeti FP and what you find is that
NOTE Confidence: 0.776196777820587

04:30:20.854 --> 04:30:22.848 Indiana the tumor micro environment.

NOTE Confidence: 0.776196777820587
04:30:22.850 --> 04:30:24.746 There's really not a lot of
NOTE Confidence: 0.776196777820587
04:30:24.746 --> 04:30:26.010 expression by the Celtics.
NOTE Confidence: 0.776196777820587
04:30:26.010 --> 04:30:27.720 You might have thought would
NOTE Confidence: 0.776196777820587
04:30:27.720 --> 04:30:29.088 expressed literally the predominant
NOTE Confidence: 0.776196777820587
04:30:29.088 --> 04:30:30.440 one though is NK cells.
NOTE Confidence: 0.776196777820587
04:30:30.440 --> 04:30:32.379 And here's the full change of the
NOTE Confidence: 0.776196777820587
04:30:32.379 --> 04:30:34.548 Reporter in NK cells versus controls.
NOTE Confidence: 0.776196777820587
04:30:34.550 --> 04:30:36.155 You also find some expressions
NOTE Confidence: 0.776196777820587
04:30:36.155 --> 04:30:37.439 in CD4 and CD8.
NOTE Confidence: 0.776196777820587
04:30:37.440 --> 04:30:38.430 Long story short,
NOTE Confidence: 0.776196777820587
04:30:38.430 --> 04:30:40.410 when you look in tumors that
NOTE Confidence: 0.776196777820587
04:30:40.410 --> 04:30:42.468 are responsive to checkpoint,
NOTE Confidence: 0.776196777820587
04:30:42.470 --> 04:30:45.179 so these individual patients are in rows,
NOTE Confidence: 0.799794733524323
04:30:45.180 --> 04:30:47.110 columns here and cell populations
NOTE Confidence: 0.799794733524323
04:30:47.110 --> 04:30:49.434 are in rows here, you essentially
NOTE Confidence: 0.799794733524323

04:30:49.434 --> 04:30:51.369 code people that are responders.
NOTE Confidence: 0.799794733524323

04:30:51.370 --> 04:30:53.954 Awana nonresponders is 0 and you ask what
NOTE Confidence: 0.799794733524323

04:30:53.954 --> 04:30:56.019 cell population predicts responsiveness.
NOTE Confidence: 0.799794733524323

04:30:56.020 --> 04:30:58.778 The number one cell population with a
NOTE Confidence: 0.799794733524323

04:30:58.778 --> 04:31:01.816 really high P value are the CDC ones.
NOTE Confidence: 0.799794733524323

04:31:01.820 --> 04:31:04.466 So you want to have those and the number
NOTE Confidence: 0.799794733524323

04:31:04.466 --> 04:31:06.746 2 population that correlate's really
NOTE Confidence: 0.799794733524323

04:31:06.746 --> 04:31:09.608 strongly that those are NK cells.
NOTE Confidence: 0.799794733524323

04:31:09.610 --> 04:31:12.263 And many, many lines of evidence suggests
NOTE Confidence: 0.799794733524323

04:31:12.263 --> 04:31:14.668 now including work from Kitano racist,
NOTE Confidence: 0.799794733524323

04:31:14.670 --> 04:31:17.491 who's also that NK cells and CC
NOTE Confidence: 0.799794733524323

04:31:17.491 --> 04:31:19.756 ones existing kind of harmony
NOTE Confidence: 0.799794733524323

04:31:19.756 --> 04:31:22.176 in the tumor micro environment.
NOTE Confidence: 0.799794733524323

04:31:22.180 --> 04:31:24.628 But I bring this up also because if
NOTE Confidence: 0.799794733524323

04:31:24.628 --> 04:31:26.646 you're a sharp eye, you'll notice
NOTE Confidence: 0.799794733524323

04:31:26.646 --> 04:31:28.872 that some of the patients over here,

NOTE Confidence: 0.799794733524323
04:31:28.880 --> 04:31:30.788 even in this small data set,
NOTE Confidence: 0.799794733524323
04:31:30.790 --> 04:31:32.070 don't match this thing.
NOTE Confidence: 0.799794733524323
04:31:32.070 --> 04:31:33.350 I just told you.
NOTE Confidence: 0.799794733524323
04:31:33.350 --> 04:31:35.303 So there's 345 patients here that don't
NOTE Confidence: 0.799794733524323
04:31:35.303 --> 04:31:37.489 have that that archetype quite strongly,
NOTE Confidence: 0.799794733524323
04:31:37.490 --> 04:31:39.429 and what they have instead is they
NOTE Confidence: 0.799794733524323
04:31:39.429 --> 04:31:41.531 have a large number of CD4 cells
NOTE Confidence: 0.799794733524323
04:31:41.531 --> 04:31:43.337 and their concurrent CDC 2 here
NOTE Confidence: 0.799794733524323
04:31:43.401 --> 04:31:45.466 expressing BCA one dendritic cells.
NOTE Confidence: 0.799794733524323
04:31:45.470 --> 04:31:47.585 So it turns out that if you look at
NOTE Confidence: 0.799794733524323
04:31:47.585 --> 04:31:49.929 all responders to checkpoint blockade,
NOTE Confidence: 0.799794733524323
04:31:49.930 --> 04:31:52.036 you basically find that there are
NOTE Confidence: 0.799794733524323
04:31:52.036 --> 04:31:54.100 either of those that are high.
NOTE Confidence: 0.799794733524323
04:31:54.100 --> 04:31:55.815 PCA three in the cities he wants,
NOTE Confidence: 0.799794733524323
04:31:55.820 --> 04:31:57.724 or those that are high in the CZ
NOTE Confidence: 0.799794733524323

04:31:57.724 --> 04:31:58.998 one in the CC twos.
NOTE Confidence: 0.799794733524323

04:31:59.000 --> 04:32:00.715 So you either have a class of
NOTE Confidence: 0.771211683750153

04:32:00.720 --> 04:32:01.940 class one or Class 2
NOTE Confidence: 0.797308951616287

04:32:01.940 --> 04:32:05.180 immune response. That's the sign of my bread.
NOTE Confidence: 0.806008040904999

04:32:05.180 --> 04:32:06.915 Dough is ready just in
NOTE Confidence: 0.806008040904999

04:32:06.915 --> 04:32:08.303 case anybody is wondering.
NOTE Confidence: 0.806008040904999

04:32:08.310 --> 04:32:10.535 So this brings up this idea of Archetypes
NOTE Confidence: 0.806008040904999

04:32:10.535 --> 04:32:12.869 and I and I'm really just referencing.
NOTE Confidence: 0.806008040904999

04:32:12.870 --> 04:32:15.214 If you want to read more about these
NOTE Confidence: 0.806008040904999

04:32:15.214 --> 04:32:16.966 nature medicine paper where we describe
NOTE Confidence: 0.806008040904999

04:32:16.966 --> 04:32:19.250 what we call the type one archetype,
NOTE Confidence: 0.806008040904999

04:32:19.250 --> 04:32:20.984 that is NK cells that deliver
NOTE Confidence: 0.806008040904999

04:32:20.984 --> 04:32:22.836 flip through leg into CC ones
NOTE Confidence: 0.806008040904999

04:32:22.836 --> 04:32:24.416 in the tumor micro environment.
NOTE Confidence: 0.806008040904999

04:32:24.420 --> 04:32:26.464 Those the CDC ones then can activate
NOTE Confidence: 0.806008040904999

04:32:26.464 --> 04:32:28.374 and get to the draining lymph

NOTE Confidence: 0.806008040904999

04:32:28.374 --> 04:32:30.635 node where they activate CD8 CD S

NOTE Confidence: 0.806008040904999

04:32:30.702 --> 04:32:32.627 come back in an again CDC ones,

NOTE Confidence: 0.806008040904999

04:32:32.630 --> 04:32:35.276 and this is the This is the

NOTE Confidence: 0.806008040904999

04:32:35.276 --> 04:32:37.159 immune system that we want.

NOTE Confidence: 0.806008040904999

04:32:37.160 --> 04:32:38.570 However, there are also patients

NOTE Confidence: 0.806008040904999

04:32:38.570 --> 04:32:40.642 on which we can build an antitumor

NOTE Confidence: 0.806008040904999

04:32:40.642 --> 04:32:42.157 immune response that have a

NOTE Confidence: 0.806008040904999

04:32:42.157 --> 04:32:43.540 different kind of Dentrux.

NOTE Confidence: 0.806008040904999

04:32:43.540 --> 04:32:46.580 All this EC two that I just told you about,

NOTE Confidence: 0.806008040904999

04:32:46.580 --> 04:32:49.236 they can migrate to the lymph node activity

NOTE Confidence: 0.806008040904999

04:32:49.236 --> 04:32:51.138 fours seafort's go back to the tumor,

NOTE Confidence: 0.806008040904999

04:32:51.140 --> 04:32:53.205 but the key feature there is that

NOTE Confidence: 0.806008040904999

04:32:53.205 --> 04:32:55.685 the licensing of the CDC 2 is really

NOTE Confidence: 0.806008040904999

04:32:55.685 --> 04:32:57.220 regulated by regulatory T cells,

NOTE Confidence: 0.806008040904999

04:32:57.220 --> 04:32:59.372 and again I invite you to read that

NOTE Confidence: 0.806008040904999

04:32:59.372 --> 04:33:01.564 paper if you're interested and it brings
NOTE Confidence: 0.806008040904999

04:33:01.564 --> 04:33:04.154 up this idea that in the world now
NOTE Confidence: 0.806008040904999

04:33:04.154 --> 04:33:06.338 we have this antiviral sort of class.
NOTE Confidence: 0.806008040904999

04:33:06.340 --> 04:33:09.076 Two response C 4T cell stimulatory CDC twos.
NOTE Confidence: 0.806008040904999

04:33:09.080 --> 04:33:09.616 Macrophage phenotype,
NOTE Confidence: 0.806008040904999

04:33:09.616 --> 04:33:10.688 it's also interesting there,
NOTE Confidence: 0.806008040904999

04:33:10.690 --> 04:33:12.040 and these are CD4 based
NOTE Confidence: 0.806008040904999

04:33:12.040 --> 04:33:13.120 responders to checkpoint blockade.
NOTE Confidence: 0.806008040904999

04:33:13.120 --> 04:33:14.836 He said overall survival even without
NOTE Confidence: 0.806008040904999

04:33:14.836 --> 04:33:16.501 checkpoint blockade and you also have
NOTE Confidence: 0.806008040904999

04:33:16.501 --> 04:33:17.905 the ones that are more classically
NOTE Confidence: 0.806008040904999

04:33:17.905 --> 04:33:19.299 what you would have imagined.
NOTE Confidence: 0.806008040904999

04:33:19.300 --> 04:33:22.020 CDA T cells and then now the CDC ones in
NOTE Confidence: 0.806008040904999

04:33:22.089 --> 04:33:24.809 the NK cells as part of the partnership.
NOTE Confidence: 0.806008040904999

04:33:24.810 --> 04:33:26.906 The variant of this one that we defined.
NOTE Confidence: 0.806008040904999

04:33:26.910 --> 04:33:28.476 It's the regular regulated Class 2,

NOTE Confidence: 0.806008040904999

04:33:28.480 --> 04:33:30.648 and then there's kind of the rest of

NOTE Confidence: 0.806008040904999

04:33:30.648 --> 04:33:32.670 the world immune systems at large.

NOTE Confidence: 0.806008040904999

04:33:32.670 --> 04:33:34.974 What's more about this is that you can

NOTE Confidence: 0.806008040904999

04:33:34.974 --> 04:33:36.635 actually figure out the frequencies

NOTE Confidence: 0.806008040904999

04:33:36.635 --> 04:33:38.340 of these in different diseases,

NOTE Confidence: 0.806008040904999

04:33:38.340 --> 04:33:40.545 and it turns out that about 50%

NOTE Confidence: 0.806008040904999

04:33:40.550 --> 04:33:42.440 of Melanoma people respond to PD.

NOTE Confidence: 0.806008040904999

04:33:42.440 --> 04:33:44.638 One 2/3 of those have a class,

NOTE Confidence: 0.806008040904999

04:33:44.640 --> 04:33:48.640 one CDA response in less than 1/3 of the C4.

NOTE Confidence: 0.806008040904999

04:33:48.640 --> 04:33:50.040 In had net for example,

NOTE Confidence: 0.806008040904999

04:33:50.040 --> 04:33:51.570 though you really don't have a

NOTE Confidence: 0.806008040904999

04:33:51.570 --> 04:33:53.562 lot of class CD8T cells which you

NOTE Confidence: 0.806008040904999

04:33:53.562 --> 04:33:54.778 can build this response.

NOTE Confidence: 0.806008040904999

04:33:54.780 --> 04:33:55.016 OK,

NOTE Confidence: 0.806008040904999

04:33:55.016 --> 04:33:57.140 so this brings up this idea of what I'm

NOTE Confidence: 0.806008040904999

04:33:57.203 --> 04:33:59.237 going to call the reactive archetype,
NOTE Confidence: 0.806008040904999

04:33:59.240 --> 04:34:01.320 and this is from an image from a
NOTE Confidence: 0.806008040904999

04:34:01.320 --> 04:34:03.332 movie and in interest of time I'm
NOTE Confidence: 0.806008040904999

04:34:03.332 --> 04:34:05.380 just going to tell you what you,
NOTE Confidence: 0.806008040904999

04:34:05.380 --> 04:34:07.324 what you could see is that in blue
NOTE Confidence: 0.806008040904999

04:34:07.324 --> 04:34:09.411 there are T cells that here this
NOTE Confidence: 0.806008040904999

04:34:09.411 --> 04:34:10.956 is overexpressing tumor in black,
NOTE Confidence: 0.806008040904999

04:34:10.960 --> 04:34:12.992 blue or T cells that are swarming some
NOTE Confidence: 0.806008040904999

04:34:12.992 --> 04:34:14.867 dendritic cells that say reactive archetype.
NOTE Confidence: 0.806008040904999

04:34:14.870 --> 04:34:16.832 That's what we want but the
NOTE Confidence: 0.806008040904999

04:34:16.832 --> 04:34:18.654 dominant biology and tumor is tends
NOTE Confidence: 0.806008040904999

04:34:18.654 --> 04:34:20.446 to be CD 4T cells in CD 838,
NOTE Confidence: 0.806008040904999

04:34:20.450 --> 04:34:22.208 CDA T cells in this model.
NOTE Confidence: 0.806008040904999

04:34:22.210 --> 04:34:24.278 Swarming tumor associated macrophages.
NOTE Confidence: 0.806008040904999

04:34:24.278 --> 04:34:28.160 And if you find a lot of that,
NOTE Confidence: 0.806008040904999

04:34:28.160 --> 04:34:29.635 that's the majority of the

NOTE Confidence: 0.806008040904999
04:34:29.635 --> 04:34:31.110 mean system is doing OK.
NOTE Confidence: 0.806008040904999
04:34:31.110 --> 04:34:33.175 So why am I telling you that?
NOTE Confidence: 0.806008040904999
04:34:33.180 --> 04:34:35.540 So I'm going to tell you a very,
NOTE Confidence: 0.806008040904999
04:34:35.540 --> 04:34:36.425 very brief story.
NOTE Confidence: 0.806008040904999
04:34:36.425 --> 04:34:37.900 That's a very long story,
NOTE Confidence: 0.850976288318634
04:34:37.900 --> 04:34:40.300 and it's if I told its entire T of how
NOTE Confidence: 0.850976288318634
04:34:40.365 --> 04:34:42.789 we've been taking the data that I told
NOTE Confidence: 0.850976288318634
04:34:42.789 --> 04:34:44.979 you about it from Immuno Profiler.
NOTE Confidence: 0.850976288318634
04:34:44.980 --> 04:34:46.714 From all these different tumor types
NOTE Confidence: 0.850976288318634
04:34:46.714 --> 04:34:49.150 and doing the exact same thing I just
NOTE Confidence: 0.850976288318634
04:34:49.150 --> 04:34:50.980 mentioned you know flow cytometry sorting
NOTE Confidence: 0.850976288318634
04:34:51.035 --> 04:34:52.709 of populations and then just asking
NOTE Confidence: 0.850976288318634
04:34:52.709 --> 04:34:54.715 what is the immune landscape of tumors
NOTE Confidence: 0.850976288318634
04:34:54.715 --> 04:34:56.190 across all these different medications.
NOTE Confidence: 0.850976288318634
04:34:56.190 --> 04:34:58.733 So in one in one case you can just do
NOTE Confidence: 0.850976288318634

04:34:58.733 --> 04:35:00.703 this by the numbers and you can say
NOTE Confidence: 0.850976288318634

04:35:00.703 --> 04:35:02.719 if I do flow cytometry and I look at
NOTE Confidence: 0.850976288318634

04:35:02.780 --> 04:35:04.901 frequency of T cells or myeloid cells
NOTE Confidence: 0.850976288318634

04:35:04.901 --> 04:35:07.085 or stromal cells in tumors and I have
NOTE Confidence: 0.850976288318634

04:35:07.085 --> 04:35:08.670 my different tumor types down here,
NOTE Confidence: 0.850976288318634

04:35:08.670 --> 04:35:10.889 you can say for example like happen
NOTE Confidence: 0.850976288318634

04:35:10.889 --> 04:35:13.269 HC and kidney are very T cell rich.
NOTE Confidence: 0.850976288318634

04:35:13.270 --> 04:35:16.567 Kidneys also very mild, rich for example.
NOTE Confidence: 0.850976288318634

04:35:16.570 --> 04:35:17.983 But you know,
NOTE Confidence: 0.850976288318634

04:35:17.983 --> 04:35:21.280 for example that happens is quite low,
NOTE Confidence: 0.850976288318634

04:35:21.280 --> 04:35:24.437 relatively speaking. And you know in that.
NOTE Confidence: 0.850976288318634

04:35:24.440 --> 04:35:26.258 So there's there's a sensually you
NOTE Confidence: 0.850976288318634

04:35:26.258 --> 04:35:28.507 can do a waterfall plot to say what?
NOTE Confidence: 0.850976288318634

04:35:28.510 --> 04:35:30.274 What's the immune composition of various
NOTE Confidence: 0.850976288318634

04:35:30.274 --> 04:35:32.289 are consumers and what you'll notice is.
NOTE Confidence: 0.850976288318634

04:35:32.290 --> 04:35:34.386 Even though I said that in I'm referring

NOTE Confidence: 0.850976288318634
04:35:34.386 --> 04:35:36.369 to the means being stacked here,
NOTE Confidence: 0.850976288318634
04:35:36.370 --> 04:35:38.110 there's a tremendous amount of variety,
NOTE Confidence: 0.850976288318634
04:35:38.110 --> 04:35:40.301 even within a tumor type single tumor
NOTE Confidence: 0.850976288318634
04:35:40.301 --> 04:35:42.859 type in terms of whether they are tend to
NOTE Confidence: 0.850976288318634
04:35:42.859 --> 04:35:44.808 be high or low for different operations.
NOTE Confidence: 0.850976288318634
04:35:44.810 --> 04:35:46.882 So we started to take all of this
NOTE Confidence: 0.850976288318634
04:35:46.882 --> 04:35:48.878 data and do live and clustering.
NOTE Confidence: 0.850976288318634
04:35:48.880 --> 04:35:50.920 So this is a dimension reduction version.
NOTE Confidence: 0.850976288318634
04:35:50.920 --> 04:35:52.990 And if you just take the frequency
NOTE Confidence: 0.850976288318634
04:35:52.990 --> 04:35:53.920 of T cells.
NOTE Confidence: 0.850976288318634
04:35:53.920 --> 04:35:55.208 Myeloid cells overall not
NOTE Confidence: 0.850976288318634
04:35:55.208 --> 04:35:57.140 distinguishing any of them are stroma.
NOTE Confidence: 0.850976288318634
04:35:57.140 --> 04:35:59.114 You may already find 6 populations that
NOTE Confidence: 0.850976288318634
04:35:59.114 --> 04:36:01.340 are going to be the fundamental basis
NOTE Confidence: 0.850976288318634
04:36:01.340 --> 04:36:03.326 for since essentially what I'm going
NOTE Confidence: 0.850976288318634

04:36:03.381 --> 04:36:05.427 over 12 populations of dominant immune
NOTE Confidence: 0.850976288318634

04:36:05.427 --> 04:36:07.766 systems across all kinds of different tumors,
NOTE Confidence: 0.850976288318634

04:36:07.766 --> 04:36:09.698 and this is done in here.
NOTE Confidence: 0.850976288318634

04:36:09.700 --> 04:36:10.796 In our data set,
NOTE Confidence: 0.850976288318634

04:36:10.796 --> 04:36:13.252 we can take the markers of those and
NOTE Confidence: 0.850976288318634

04:36:13.252 --> 04:36:15.842 find the same populations in TGA ascentia
NOTE Confidence: 0.850976288318634

04:36:15.842 --> 04:36:18.706 you're seeing ones that are high for T cells,
NOTE Confidence: 0.850976288318634

04:36:18.710 --> 04:36:20.006 high for myeloid cells,
NOTE Confidence: 0.850976288318634

04:36:20.006 --> 04:36:22.260 looser stroma and various variations of this.
NOTE Confidence: 0.850976288318634

04:36:22.260 --> 04:36:23.870 Here there's two immune deserts.
NOTE Confidence: 0.850976288318634

04:36:23.870 --> 04:36:25.170 Those ultimately split into.
NOTE Confidence: 0.850976288318634

04:36:25.170 --> 04:36:27.120 And one further split will take
NOTE Confidence: 0.850976288318634

04:36:27.176 --> 04:36:28.910 place as we add some parameters,
NOTE Confidence: 0.850976288318634

04:36:28.910 --> 04:36:30.470 so that here's adding parameters.
NOTE Confidence: 0.850976288318634

04:36:30.470 --> 04:36:33.278 So we go to the point where we have,
NOTE Confidence: 0.850976288318634

04:36:33.280 --> 04:36:34.528 for example are dominant.

NOTE Confidence: 0.850976288318634
04:36:34.528 --> 04:36:36.088 This is using 6 features,
NOTE Confidence: 0.850976288318634
04:36:36.090 --> 04:36:37.334 T cells, myeloid cells,
NOTE Confidence: 0.850976288318634
04:36:37.334 --> 04:36:39.208 stromal cells, tregs, C4 CA ratio,
NOTE Confidence: 0.850976288318634
04:36:39.208 --> 04:36:40.768 and one that I'm forgetting.
NOTE Confidence: 0.850976288318634
04:36:40.770 --> 04:36:42.456 You find yourself sort of being
NOTE Confidence: 0.850976288318634
04:36:42.456 --> 04:36:44.668 able to divide the world up into
NOTE Confidence: 0.850976288318634
04:36:44.668 --> 04:36:46.388 eight archetypes of immune systems,
NOTE Confidence: 0.850976288318634
04:36:46.390 --> 04:36:49.470 and you can see the thing that I want to
NOTE Confidence: 0.850976288318634
04:36:49.549 --> 04:36:52.629 show you here is that when you go to 10,
NOTE Confidence: 0.850976288318634
04:36:52.630 --> 04:36:55.222 this is where you start to add in
NOTE Confidence: 0.850976288318634
04:36:55.222 --> 04:36:57.198 myeloid subsets and T cell subsets.
NOTE Confidence: 0.850976288318634
04:36:57.200 --> 04:36:59.186 That a lot of these basically
NOTE Confidence: 0.850976288318634
04:36:59.186 --> 04:37:00.510 keep their same track.
NOTE Confidence: 0.850976288318634
04:37:00.510 --> 04:37:01.172 So what.
NOTE Confidence: 0.850976288318634
04:37:01.172 --> 04:37:03.158 This is called a alluvial plot,
NOTE Confidence: 0.850976288318634

04:37:03.160 --> 04:37:05.140 and it basically like a River.
NOTE Confidence: 0.850976288318634

04:37:05.140 --> 04:37:07.644 It tracks where a patient was when you
NOTE Confidence: 0.850976288318634

04:37:07.644 --> 04:37:10.436 had it class by 6 features versus 10.
NOTE Confidence: 0.850976288318634

04:37:10.440 --> 04:37:12.750 So you see the majority of these
NOTE Confidence: 0.850976288318634

04:37:12.750 --> 04:37:14.787 perpetuate out to one just one
NOTE Confidence: 0.850976288318634

04:37:14.787 --> 04:37:17.055 future pen feature and you do create
NOTE Confidence: 0.801425576210022

04:37:17.123 --> 04:37:18.379 some sub sub phone.
NOTE Confidence: 0.801425576210022

04:37:18.380 --> 04:37:20.100 You always create subclasses
NOTE Confidence: 0.801425576210022

04:37:20.100 --> 04:37:22.250 when you add more features.
NOTE Confidence: 0.801425576210022

04:37:22.250 --> 04:37:24.074 But we like this 10 feature one at
NOTE Confidence: 0.801425576210022

04:37:24.074 --> 04:37:25.677 the moment and I'll tell you the
NOTE Confidence: 0.801425576210022

04:37:25.677 --> 04:37:27.330 reason why is that we get these.
NOTE Confidence: 0.801425576210022

04:37:27.330 --> 04:37:28.986 We give these things you can name immune
NOTE Confidence: 0.801425576210022

04:37:28.986 --> 04:37:30.567 rich CD 8 macrophage biased right?
NOTE Confidence: 0.801425576210022

04:37:30.570 --> 04:37:32.274 And that's based on all the
NOTE Confidence: 0.801425576210022

04:37:32.274 --> 04:37:33.760 different parameters told you about.

NOTE Confidence: 0.801425576210022
04:37:33.760 --> 04:37:35.419 But what's cool about that is that
NOTE Confidence: 0.801425576210022
04:37:35.419 --> 04:37:37.603 if you take other features like NK
NOTE Confidence: 0.801425576210022
04:37:37.603 --> 04:37:39.378 frequencies or plasma cell frequencies,
NOTE Confidence: 0.801425576210022
04:37:39.380 --> 04:37:40.860 or piece of frequencies using
NOTE Confidence: 0.801425576210022
04:37:40.860 --> 04:37:42.044 genes that represent those,
NOTE Confidence: 0.801425576210022
04:37:42.050 --> 04:37:43.975 you can see how well just using
NOTE Confidence: 0.801425576210022
04:37:43.975 --> 04:37:46.117 myeloid cells T regs and T cells
NOTE Confidence: 0.801425576210022
04:37:46.117 --> 04:37:47.373 already identify the ones.
NOTE Confidence: 0.801425576210022
04:37:47.380 --> 04:37:49.150 For example, that are NK rich,
NOTE Confidence: 0.801425576210022
04:37:49.150 --> 04:37:50.334 B cell, plasma rich,
NOTE Confidence: 0.801425576210022
04:37:50.334 --> 04:37:51.814 or just plain himself rich.
NOTE Confidence: 0.801425576210022
04:37:51.820 --> 04:37:53.766 So this is looking like the classes
NOTE Confidence: 0.801425576210022
04:37:53.766 --> 04:37:56.199 that you can find by just using a
NOTE Confidence: 0.801425576210022
04:37:56.199 --> 04:37:57.734 fairly small number of features.
NOTE Confidence: 0.801425576210022
04:37:57.740 --> 04:37:59.315 Define the dominant structure of
NOTE Confidence: 0.801425576210022

04:37:59.315 --> 04:38:01.293 immune system even in this populations
NOTE Confidence: 0.801425576210022

04:38:01.293 --> 04:38:03.028 that you didn't even count.
NOTE Confidence: 0.801425576210022

04:38:03.030 --> 04:38:04.908 Another way of looking at that
NOTE Confidence: 0.801425576210022

04:38:04.908 --> 04:38:06.440 is to just say OK.
NOTE Confidence: 0.801425576210022

04:38:06.440 --> 04:38:09.230 If I take the 12 different kinds of tumors,
NOTE Confidence: 0.801425576210022

04:38:09.230 --> 04:38:11.090 the Archetypes and I just ask
NOTE Confidence: 0.801425576210022

04:38:11.090 --> 04:38:12.330 about chemo kine expression.
NOTE Confidence: 0.801425576210022

04:38:12.330 --> 04:38:14.430 You can find that there is a
NOTE Confidence: 0.801425576210022

04:38:14.430 --> 04:38:16.360 cluster without us asking them to.
NOTE Confidence: 0.801425576210022

04:38:16.360 --> 04:38:17.600 They essentially cluster based
NOTE Confidence: 0.801425576210022

04:38:17.600 --> 04:38:19.460 on classes of chemo kines too.
NOTE Confidence: 0.801425576210022

04:38:19.460 --> 04:38:20.062 So again,
NOTE Confidence: 0.801425576210022

04:38:20.062 --> 04:38:21.868 the features of the tumor micro
NOTE Confidence: 0.801425576210022

04:38:21.868 --> 04:38:23.626 environment that come out of this
NOTE Confidence: 0.801425576210022

04:38:23.626 --> 04:38:25.001 suggests that we're really honing
NOTE Confidence: 0.801425576210022

04:38:25.001 --> 04:38:27.062 in on some fundamental chords of

NOTE Confidence: 0.801425576210022
04:38:27.062 --> 04:38:28.446 distinction and immune system,
NOTE Confidence: 0.801425576210022
04:38:28.450 --> 04:38:30.578 and this is the kind of ones
NOTE Confidence: 0.801425576210022
04:38:30.578 --> 04:38:32.169 that's coming up cool too.
NOTE Confidence: 0.801425576210022
04:38:32.170 --> 04:38:34.078 You take those same 12 archetypes.
NOTE Confidence: 0.801425576210022
04:38:34.080 --> 04:38:36.018 And you ask about gene expression
NOTE Confidence: 0.801425576210022
04:38:36.018 --> 04:38:37.310 in the tumor compartment,
NOTE Confidence: 0.801425576210022
04:38:37.310 --> 04:38:39.766 and you use some of the gene sort
NOTE Confidence: 0.801425576210022
04:38:39.766 --> 04:38:41.830 of expression modules like the ISG.
NOTE Confidence: 0.801425576210022
04:38:41.830 --> 04:38:44.737 This is by the way quite important in ours.
NOTE Confidence: 0.801425576210022
04:38:44.740 --> 04:38:46.355 Another covid studies butts in
NOTE Confidence: 0.801425576210022
04:38:46.355 --> 04:38:47.647 essence to associated genes,
NOTE Confidence: 0.801425576210022
04:38:47.650 --> 04:38:47.954 assassins,
NOTE Confidence: 0.801425576210022
04:38:47.954 --> 04:38:48.258 etc.
NOTE Confidence: 0.801425576210022
04:38:48.258 --> 04:38:51.117 And you can also see how the same populations
NOTE Confidence: 0.801425576210022
04:38:51.117 --> 04:38:53.637 tend to basically parse out based on
NOTE Confidence: 0.801425576210022

04:38:53.637 --> 04:38:56.038 what kind of jeans are in the tumor.
NOTE Confidence: 0.801425576210022

04:38:56.040 --> 04:38:58.120 And so this I think it brings us
NOTE Confidence: 0.801425576210022

04:38:58.120 --> 04:39:00.474 back to the idea that the immune
NOTE Confidence: 0.801425576210022

04:39:00.474 --> 04:39:02.750 system is just harnessing one of
NOTE Confidence: 0.801425576210022

04:39:02.750 --> 04:39:05.000 these programs that responds to
NOTE Confidence: 0.801425576210022

04:39:05.000 --> 04:39:06.800 various different gene expression.
NOTE Confidence: 0.801425576210022

04:39:06.800 --> 04:39:07.050 OK,
NOTE Confidence: 0.801425576210022

04:39:07.050 --> 04:39:09.038 so I'm going to move quickly into a
NOTE Confidence: 0.801425576210022

04:39:09.040 --> 04:39:11.315 technology story and then I'll be done.
NOTE Confidence: 0.801425576210022

04:39:11.320 --> 04:39:11.592 So.
NOTE Confidence: 0.801425576210022

04:39:11.592 --> 04:39:14.040 Many of us are in this mode right now
NOTE Confidence: 0.801425576210022

04:39:14.111 --> 04:39:16.577 of using the emerging technology of
NOTE Confidence: 0.801425576210022

04:39:16.577 --> 04:39:18.681 single cell sequencing for various
NOTE Confidence: 0.801425576210022

04:39:18.681 --> 04:39:20.991 different reasons and and one of
NOTE Confidence: 0.801425576210022

04:39:20.991 --> 04:39:23.046 those things that you get out of
NOTE Confidence: 0.801425576210022

04:39:23.046 --> 04:39:24.738 that we can just stay upfront is

NOTE Confidence: 0.801425576210022
04:39:24.738 --> 04:39:26.213 the ability to cluster populations
NOTE Confidence: 0.801425576210022
04:39:26.213 --> 04:39:28.245 of cells or patients or what have
NOTE Confidence: 0.801425576210022
04:39:28.245 --> 04:39:29.835 you based on dominant features that
NOTE Confidence: 0.801425576210022
04:39:29.835 --> 04:39:31.160 are maybe the computationally the
NOTE Confidence: 0.801425576210022
04:39:31.160 --> 04:39:32.220 biggest differences amongst them.
NOTE Confidence: 0.801425576210022
04:39:32.220 --> 04:39:34.870 And we do that and we get names of various.
NOTE Confidence: 0.801425576210022
04:39:34.870 --> 04:39:36.190 This is for myeloid cells,
NOTE Confidence: 0.801425576210022
04:39:36.190 --> 04:39:36.702 for example,
NOTE Confidence: 0.801425576210022
04:39:36.702 --> 04:39:38.750 from the six tumor and we get various
NOTE Confidence: 0.801425576210022
04:39:38.806 --> 04:39:40.216 different names of populations and
NOTE Confidence: 0.801425576210022
04:39:40.216 --> 04:39:42.170 with those we can do pretty cool
NOTE Confidence: 0.801425576210022
04:39:42.170 --> 04:39:44.770 analysis to look at how in one tumor to next.
NOTE Confidence: 0.801425576210022
04:39:44.770 --> 04:39:45.400 The lineages,
NOTE Confidence: 0.801425576210022
04:39:45.400 --> 04:39:47.290 for example going from the monocytes
NOTE Confidence: 0.801425576210022
04:39:47.343 --> 04:39:49.041 here in pink to the University
NOTE Confidence: 0.801425576210022

04:39:49.041 --> 04:39:50.173 of macrophages here in
NOTE Confidence: 0.79932545480274

04:39:50.226 --> 04:39:52.065 purple, are laid out on a
NOTE Confidence: 0.79932545480274

04:39:52.065 --> 04:39:53.237 trajectory and that's that's
NOTE Confidence: 0.79932545480274

04:39:53.237 --> 04:39:55.248 a very nice work of Trapnell,
NOTE Confidence: 0.79932545480274

04:39:55.250 --> 04:39:57.420 and many of us use these tools.
NOTE Confidence: 0.79932545480274

04:39:57.420 --> 04:39:59.184 So this is a nice way to
NOTE Confidence: 0.79932545480274

04:39:59.184 --> 04:40:00.830 find out the composition,
NOTE Confidence: 0.79932545480274

04:40:00.830 --> 04:40:02.380 but what are the partnerships?
NOTE Confidence: 0.79932545480274

04:40:02.380 --> 04:40:04.550 And this is kind of our interests,
NOTE Confidence: 0.79932545480274

04:40:04.550 --> 04:40:06.100 like how do we understand
NOTE Confidence: 0.798447012901306

04:40:06.100 --> 04:40:07.340 this in space? So
NOTE Confidence: 0.798447012901306

04:40:07.340 --> 04:40:08.270 we've been developing
NOTE Confidence: 0.798447012901306

04:40:08.270 --> 04:40:11.350 tools so that we can image tumor slice.
NOTE Confidence: 0.798447012901306

04:40:11.350 --> 04:40:13.492 Or any piece of tissue and watch
NOTE Confidence: 0.798447012901306

04:40:13.492 --> 04:40:15.723 how things behave and then ask what
NOTE Confidence: 0.798447012901306

04:40:15.723 --> 04:40:17.919 was each cell thinking. And I mean,

NOTE Confidence: 0.798447012901306
04:40:17.919 --> 04:40:20.110 thinking by the aspect of what RNA,
NOTE Confidence: 0.798447012901306
04:40:20.110 --> 04:40:21.362 where they expressing sort.
NOTE Confidence: 0.798447012901306
04:40:21.362 --> 04:40:23.240 It also could be a taxi,
NOTE Confidence: 0.798447012901306
04:40:23.240 --> 04:40:25.564 so I want to single cell sequencing
NOTE Confidence: 0.798447012901306
04:40:25.564 --> 04:40:27.489 analysis but we want to know
NOTE Confidence: 0.798447012901306
04:40:27.489 --> 04:40:29.491 going back to me to this slide,
NOTE Confidence: 0.798447012901306
04:40:29.500 --> 04:40:32.180 we want to know is this cell next to that
NOTE Confidence: 0.798447012901306
04:40:32.254 --> 04:40:35.134 sell and how are these cells spatially rate?
NOTE Confidence: 0.798447012901306
04:40:35.140 --> 04:40:36.960 So the trick that we figured out
NOTE Confidence: 0.798447012901306
04:40:36.960 --> 04:40:39.609 to do to do that is to essentially
NOTE Confidence: 0.798447012901306
04:40:39.609 --> 04:40:41.414 print barcodes onto onto cells.
NOTE Confidence: 0.798447012901306
04:40:41.420 --> 04:40:43.540 And the way we do that is we have an
NOTE Confidence: 0.798447012901306
04:40:43.603 --> 04:40:45.343 anchor oligonucleotide that can either
NOTE Confidence: 0.798447012901306
04:40:45.343 --> 04:40:48.499 be added to all your cells with an antibody,
NOTE Confidence: 0.798447012901306
04:40:48.500 --> 04:40:51.695 or for example all your cells with a link.
NOTE Confidence: 0.798447012901306

04:40:51.700 --> 04:40:53.278 And the key feature about this.
NOTE Confidence: 0.798447012901306

04:40:53.280 --> 04:40:54.610 Everybody from your DNA base
NOTE Confidence: 0.798447012901306

04:40:54.610 --> 04:40:56.509 pairing is that it has an overhang
NOTE Confidence: 0.798447012901306

04:40:56.509 --> 04:40:58.294 that is blocked by a photo cage.
NOTE Confidence: 0.798447012901306

04:40:58.300 --> 04:41:00.134 And that means that anything you might
NOTE Confidence: 0.798447012901306

04:41:00.134 --> 04:41:02.000 want to pair base pair with that.
NOTE Confidence: 0.798447012901306

04:41:02.000 --> 04:41:02.528 For example,
NOTE Confidence: 0.798447012901306

04:41:02.528 --> 04:41:04.640 if you brought in what is equivalently Inc,
NOTE Confidence: 0.798447012901306

04:41:04.640 --> 04:41:05.960 which is analogous nucleotide here,
NOTE Confidence: 0.798447012901306

04:41:05.960 --> 04:41:07.544 that has the 01 prime overhang
NOTE Confidence: 0.798447012901306

04:41:07.544 --> 04:41:08.600 to match the 01.
NOTE Confidence: 0.798447012901306

04:41:08.600 --> 04:41:10.434 It's not going to bind in less,
NOTE Confidence: 0.798447012901306

04:41:10.440 --> 04:41:11.760 we shine light on that.
NOTE Confidence: 0.798447012901306

04:41:11.760 --> 04:41:13.608 So if we shine light on this,
NOTE Confidence: 0.798447012901306

04:41:13.610 --> 04:41:15.430 these things are going to pop off
NOTE Confidence: 0.798447012901306

04:41:15.430 --> 04:41:17.309 and then we can print to that.

NOTE Confidence: 0.798447012901306
04:41:17.310 --> 04:41:19.102 And if we take advantage of the fact
NOTE Confidence: 0.798447012901306
04:41:19.102 --> 04:41:21.051 that in a microscope microscope is a
NOTE Confidence: 0.798447012901306
04:41:21.051 --> 04:41:22.860 spatial a system for spatial light.
NOTE Confidence: 0.798447012901306
04:41:22.860 --> 04:41:24.480 Direction right normally you would
NOTE Confidence: 0.798447012901306
04:41:24.480 --> 04:41:26.395 illuminate with a wide field light
NOTE Confidence: 0.798447012901306
04:41:26.395 --> 04:41:28.054 source in with blue here and here
NOTE Confidence: 0.798447012901306
04:41:28.054 --> 04:41:29.609 is the illumination source.
NOTE Confidence: 0.798447012901306
04:41:29.610 --> 04:41:32.130 If it's a mirror goes in and hits the
NOTE Confidence: 0.798447012901306
04:41:32.130 --> 04:41:34.105 sample and then you get fluorescence
NOTE Confidence: 0.798447012901306
04:41:34.105 --> 04:41:36.370 in that comes back to a camera.
NOTE Confidence: 0.798447012901306
04:41:36.370 --> 04:41:38.706 In this case we can add another light
NOTE Confidence: 0.798447012901306
04:41:38.706 --> 04:41:40.737 source that is actually itself printing
NOTE Confidence: 0.798447012901306
04:41:40.737 --> 04:41:43.220 light and therefore can I open up
NOTE Confidence: 0.798447012901306
04:41:43.220 --> 04:41:44.960 all the nucleotides for binding.
NOTE Confidence: 0.798447012901306
04:41:44.960 --> 04:41:47.004 And the way that works is you
NOTE Confidence: 0.798447012901306

04:41:47.004 --> 04:41:48.885 essentially use the same LCD projector
NOTE Confidence: 0.798447012901306

04:41:48.885 --> 04:41:51.090 chip that's in an LCD projector to
NOTE Confidence: 0.798447012901306

04:41:51.158 --> 04:41:53.302 turn on and off pixels that then turn
NOTE Confidence: 0.798447012901306

04:41:53.302 --> 04:41:55.616 them on and off in the samples space.
NOTE Confidence: 0.798447012901306

04:41:55.620 --> 04:41:57.685 And what we can do then is,
NOTE Confidence: 0.798447012901306

04:41:57.690 --> 04:41:58.292 for example,
NOTE Confidence: 0.798447012901306

04:41:58.292 --> 04:42:00.098 if we take a rectangular region
NOTE Confidence: 0.798447012901306

04:42:00.098 --> 04:42:02.129 as shown down here at the bottom,
NOTE Confidence: 0.798447012901306

04:42:02.130 --> 04:42:03.900 where every cell has the nucleotides
NOTE Confidence: 0.798447012901306

04:42:03.900 --> 04:42:04.785 added to it,
NOTE Confidence: 0.798447012901306

04:42:04.790 --> 04:42:06.542 we can selectively Uncage first here
NOTE Confidence: 0.798447012901306

04:42:06.542 --> 04:42:09.526 and add a die that's attached to a zip code.
NOTE Confidence: 0.798447012901306

04:42:09.530 --> 04:42:11.595 One of the zip code sequences here,
NOTE Confidence: 0.798447012901306

04:42:11.600 --> 04:42:13.382 that's blue, and then maybe use
NOTE Confidence: 0.798447012901306

04:42:13.382 --> 04:42:15.169 the middle on cage there at.
NOTE Confidence: 0.798447012901306

04:42:15.170 --> 04:42:17.067 Red uncaged them right now to green,

NOTE Confidence: 0.798447012901306
04:42:17.070 --> 04:42:18.974 and so we get something like this.
NOTE Confidence: 0.798447012901306
04:42:18.980 --> 04:42:21.077 This is by the way one of T cells
NOTE Confidence: 0.798447012901306
04:42:21.077 --> 04:42:23.056 in a couple and float around,
NOTE Confidence: 0.798447012901306
04:42:23.060 --> 04:42:24.608 which is why you see these
NOTE Confidence: 0.798447012901306
04:42:24.608 --> 04:42:26.050 cells that are off space,
NOTE Confidence: 0.798447012901306
04:42:26.050 --> 04:42:27.820 but in general you've now specially
NOTE Confidence: 0.798447012901306
04:42:27.820 --> 04:42:29.881 given a barcode to each of these
NOTE Confidence: 0.798447012901306
04:42:29.881 --> 04:42:31.519 regions and is the really cool
NOTE Confidence: 0.798447012901306
04:42:31.519 --> 04:42:33.265 thing here is you can do this
NOTE Confidence: 0.798447012901306
04:42:33.265 --> 04:42:34.660 in a chain reaction like the
NOTE Confidence: 0.798447012901306
04:42:34.660 --> 04:42:36.460 cooling of a PCR where if you if
NOTE Confidence: 0.787606775760651
04:42:36.518 --> 04:42:37.770 your oligonucleotide that you
NOTE Confidence: 0.787606775760651
04:42:37.770 --> 04:42:39.648 bring in is itself a caged.
NOTE Confidence: 0.787606775760651
04:42:39.650 --> 04:42:41.603 So instead of justice this piece that
NOTE Confidence: 0.787606775760651
04:42:41.603 --> 04:42:43.502 I just showed you in the previous
NOTE Confidence: 0.787606775760651

04:42:43.502 --> 04:42:45.400 the old one primes of code palie.
NOTE Confidence: 0.787606775760651

04:42:45.400 --> 04:42:46.516 You bring in something
NOTE Confidence: 0.787606775760651

04:42:46.516 --> 04:42:48.190 that has a new photo cage.
NOTE Confidence: 0.787606775760651

04:42:48.190 --> 04:42:50.414 Then you can do something like the following.
NOTE Confidence: 0.787606775760651

04:42:50.420 --> 04:42:52.010 Below you have a field of
NOTE Confidence: 0.787606775760651

04:42:52.010 --> 04:42:53.770 cells or a piece of tissue.
NOTE Confidence: 0.787606775760651

04:42:53.770 --> 04:42:55.070 You illuminate the left hand
NOTE Confidence: 0.787606775760651

04:42:55.070 --> 04:42:56.726 side only and you bring in
NOTE Confidence: 0.787606775760651

04:42:56.726 --> 04:42:58.226 unallocated get type for example,
NOTE Confidence: 0.787606775760651

04:42:58.230 --> 04:42:59.880 that's blue and so the right
NOTE Confidence: 0.787606775760651

04:42:59.880 --> 04:43:01.580 left hand side is now blue.
NOTE Confidence: 0.787606775760651

04:43:01.580 --> 04:43:03.700 Now you do 2 stripes like a bumblebee
NOTE Confidence: 0.787606775760651

04:43:03.700 --> 04:43:05.770 and you end up with four regions,
NOTE Confidence: 0.787606775760651

04:43:05.770 --> 04:43:07.723 so there's never got all of the
NOTE Confidence: 0.787606775760651

04:43:07.723 --> 04:43:09.390 nucleotide got read only got blue,
NOTE Confidence: 0.787606775760651

04:43:09.390 --> 04:43:11.542 only got blue red and you can do

NOTE Confidence: 0.787606775760651
04:43:11.542 --> 04:43:13.601 the same thing 50% and print only
NOTE Confidence: 0.787606775760651
04:43:13.601 --> 04:43:15.610 green and you end up with eight.
NOTE Confidence: 0.787606775760651
04:43:15.610 --> 04:43:17.218 So the formula for this in
NOTE Confidence: 0.787606775760651
04:43:17.218 --> 04:43:18.949 your math is 2 to the N,
NOTE Confidence: 0.787606775760651
04:43:18.950 --> 04:43:20.870 so you end up with like 256 different
NOTE Confidence: 0.787606775760651
04:43:20.870 --> 04:43:22.217 spatial regions that are highlighted
NOTE Confidence: 0.787606775760651
04:43:22.217 --> 04:43:23.577 by just eight print cycles.
NOTE Confidence: 0.787606775760651
04:43:23.580 --> 04:43:25.884 So that's a really fast way to do this,
NOTE Confidence: 0.787606775760651
04:43:25.890 --> 04:43:27.730 and this just shows you can do this
NOTE Confidence: 0.787606775760651
04:43:27.730 --> 04:43:29.490 pretty close to single cell resolution.
NOTE Confidence: 0.787606775760651
04:43:29.490 --> 04:43:30.770 Here we've got a region,
NOTE Confidence: 0.787606775760651
04:43:30.770 --> 04:43:32.294 for example is only ever printed
NOTE Confidence: 0.787606775760651
04:43:32.294 --> 04:43:33.860 in the bottom left with blue,
NOTE Confidence: 0.787606775760651
04:43:33.860 --> 04:43:36.011 so it's blue only and you can see that
NOTE Confidence: 0.787606775760651
04:43:36.011 --> 04:43:38.477 blue bar code is much higher in that region,
NOTE Confidence: 0.787606775760651

04:43:38.480 --> 04:43:39.765 and for example this one
NOTE Confidence: 0.787606775760651

04:43:39.765 --> 04:43:41.050 didn't ever get printed too,
NOTE Confidence: 0.787606775760651

04:43:41.050 --> 04:43:42.598 and all the variations in between.
NOTE Confidence: 0.787606775760651

04:43:42.600 --> 04:43:44.170 So these are basically identifiers
NOTE Confidence: 0.787606775760651

04:43:44.170 --> 04:43:46.120 of which cells came from where.
NOTE Confidence: 0.787606775760651

04:43:46.120 --> 04:43:47.872 And so the reason this There's
NOTE Confidence: 0.787606775760651

04:43:47.872 --> 04:43:49.361 a number of different ways
NOTE Confidence: 0.787606775760651

04:43:49.361 --> 04:43:50.945 that we've used this so far,
NOTE Confidence: 0.787606775760651

04:43:50.950 --> 04:43:52.938 and we're using it a lot more,
NOTE Confidence: 0.787606775760651

04:43:52.940 --> 04:43:54.500 but I'm going to just reference
NOTE Confidence: 0.787606775760651

04:43:54.500 --> 04:43:56.209 tumor volumes for a moment with
NOTE Confidence: 0.787606775760651

04:43:56.209 --> 04:43:58.045 reference to the idea of Archetypes,
NOTE Confidence: 0.787606775760651

04:43:58.050 --> 04:44:00.038 and also spatial temporal aspects of that.
NOTE Confidence: 0.787606775760651

04:44:00.040 --> 04:44:02.092 So this is a model that we've used a
NOTE Confidence: 0.787606775760651

04:44:02.092 --> 04:44:04.099 lot that is essentially putting tumors
NOTE Confidence: 0.787606775760651

04:44:04.099 --> 04:44:06.408 into mice that are cherry ova derived

NOTE Confidence: 0.787606775760651
04:44:06.408 --> 04:44:08.552 from our model that we made is PMT.
NOTE Confidence: 0.787606775760651
04:44:08.560 --> 04:44:10.174 It's a breast tumor model and
NOTE Confidence: 0.787606775760651
04:44:10.174 --> 04:44:11.959 goes into fat 14 days later.
NOTE Confidence: 0.787606775760651
04:44:11.960 --> 04:44:14.759 We can put in GOP level T1 cells that
NOTE Confidence: 0.787606775760651
04:44:14.759 --> 04:44:17.276 are against the over as we know.
NOTE Confidence: 0.787606775760651
04:44:17.280 --> 04:44:18.590 Four days later from that,
NOTE Confidence: 0.787606775760651
04:44:18.590 --> 04:44:20.102 we harvest and we the image
NOTE Confidence: 0.787606775760651
04:44:20.102 --> 04:44:21.719 of the tumor looks like this.
NOTE Confidence: 0.787606775760651
04:44:21.720 --> 04:44:23.298 So the border has lots and
NOTE Confidence: 0.787606775760651
04:44:23.298 --> 04:44:24.590 lots of details on it.
NOTE Confidence: 0.787606775760651
04:44:24.590 --> 04:44:26.298 The red tumor on the center is
NOTE Confidence: 0.787606775760651
04:44:26.298 --> 04:44:27.460 relatively sparse for Diesels,
NOTE Confidence: 0.787606775760651
04:44:27.460 --> 04:44:29.805 but still has T cells in there.
NOTE Confidence: 0.787606775760651
04:44:29.810 --> 04:44:31.376 And if we now barcode this,
NOTE Confidence: 0.787606775760651
04:44:31.380 --> 04:44:32.685 so the region that's highlighted
NOTE Confidence: 0.787606775760651

04:44:32.685 --> 04:44:33.990 with blue on the outside,
NOTE Confidence: 0.787606775760651

04:44:33.990 --> 04:44:35.740 we barcode that with one set of
NOTE Confidence: 0.787606775760651

04:44:35.740 --> 04:44:37.352 bar codes for a different set
NOTE Confidence: 0.787606775760651

04:44:37.352 --> 04:44:38.948 of bar codes on the inside.
NOTE Confidence: 0.787606775760651

04:44:38.950 --> 04:44:40.654 And we just do Disney and you sort
NOTE Confidence: 0.787606775760651

04:44:40.654 --> 04:44:42.328 of see all the different populations
NOTE Confidence: 0.787606775760651

04:44:42.328 --> 04:44:44.425 that you're used to and you start
NOTE Confidence: 0.787606775760651

04:44:44.425 --> 04:44:45.985 to see the beginnings of red,
NOTE Confidence: 0.787606775760651

04:44:45.990 --> 04:44:46.684 blue distinctions.
NOTE Confidence: 0.787606775760651

04:44:46.684 --> 04:44:49.113 You can really start to see those
NOTE Confidence: 0.787606775760651

04:44:49.113 --> 04:44:51.180 when you focus on the cell population.
NOTE Confidence: 0.787606775760651

04:44:51.180 --> 04:44:53.140 So here we pulled out the object
NOTE Confidence: 0.787606775760651

04:44:53.140 --> 04:44:54.989 or the collection of cells that
NOTE Confidence: 0.787606775760651

04:44:54.989 --> 04:44:56.499 represent T cells from this
NOTE Confidence: 0.789522469043732

04:44:56.554 --> 04:44:57.678 environment and you can
NOTE Confidence: 0.789522469043732

04:44:57.678 --> 04:44:59.083 see that the red cells,

NOTE Confidence: 0.789522469043732
04:44:59.090 --> 04:45:01.155 the ones on the inside or segregating
NOTE Confidence: 0.789522469043732
04:45:01.155 --> 04:45:02.890 pretty highly from the blue cells,
NOTE Confidence: 0.789522469043732
04:45:02.890 --> 04:45:04.276 and the difference between red cells
NOTE Confidence: 0.789522469043732
04:45:04.276 --> 04:45:06.058 and blue cells is exhaustion and
NOTE Confidence: 0.789522469043732
04:45:06.058 --> 04:45:07.267 terminal differentiation scores.
NOTE Confidence: 0.789522469043732
04:45:07.270 --> 04:45:09.559 And as best shown here where you
NOTE Confidence: 0.789522469043732
04:45:09.559 --> 04:45:11.411 basically compare blue cells to red
NOTE Confidence: 0.789522469043732
04:45:11.411 --> 04:45:13.884 cells in a volcano plot and some of the
NOTE Confidence: 0.789522469043732
04:45:13.884 --> 04:45:16.028 genes we just heard about from John C.
NOTE Confidence: 0.789522469043732
04:45:16.030 --> 04:45:18.685 F7 for example MIB and Slime family 6 R.
NOTE Confidence: 0.789522469043732
04:45:18.690 --> 04:45:20.706 Breast really in the outside region
NOTE Confidence: 0.789522469043732
04:45:20.706 --> 04:45:23.018 as cells for getting into the tumor.
NOTE Confidence: 0.789522469043732
04:45:23.020 --> 04:45:25.000 And as you go down differentiation
NOTE Confidence: 0.789522469043732
04:45:25.000 --> 04:45:27.348 pathways you see for example ID 2:05.
NOTE Confidence: 0.789522469043732
04:45:27.350 --> 04:45:29.300 If you other PD one being
NOTE Confidence: 0.789522469043732

04:45:29.300 --> 04:45:31.339 expressed highly as you go inward.
NOTE Confidence: 0.789522469043732

04:45:31.340 --> 04:45:32.684 So there's essentially starting
NOTE Confidence: 0.789522469043732

04:45:32.684 --> 04:45:34.700 to look like a gradient of
NOTE Confidence: 0.789522469043732

04:45:34.762 --> 04:45:36.847 exhaustion that permeates the tumor.
NOTE Confidence: 0.789522469043732

04:45:36.850 --> 04:45:38.898 And you can now because you have a
NOTE Confidence: 0.789522469043732

04:45:38.898 --> 04:45:41.101 whole data set you can rather gate
NOTE Confidence: 0.789522469043732

04:45:41.101 --> 04:45:42.726 on the monocytes and macrophages.
NOTE Confidence: 0.789522469043732

04:45:42.730 --> 04:45:44.714 And again you see now if you done
NOTE Confidence: 0.789522469043732

04:45:44.714 --> 04:45:46.688 that your object reduces to the
NOTE Confidence: 0.789522469043732

04:45:46.688 --> 04:45:48.100 monocytes and macrophages where
NOTE Confidence: 0.789522469043732

04:45:48.100 --> 04:45:50.080 now you can see that the red,
NOTE Confidence: 0.789522469043732

04:45:50.080 --> 04:45:52.138 red right hand side of this
NOTE Confidence: 0.789522469043732

04:45:52.138 --> 04:45:53.167 computationally generated Disney
NOTE Confidence: 0.789522469043732

04:45:53.167 --> 04:45:55.262 or Hue map represents all the cells
NOTE Confidence: 0.789522469043732

04:45:55.262 --> 04:45:57.185 came from the route from the center
NOTE Confidence: 0.789522469043732

04:45:57.185 --> 04:45:59.193 that left hand side has a lot more

NOTE Confidence: 0.789522469043732
04:45:59.193 --> 04:46:00.658 blue meaning from the margin.
NOTE Confidence: 0.789522469043732
04:46:00.660 --> 04:46:03.020 If you ask what this cell populations are,
NOTE Confidence: 0.789522469043732
04:46:03.020 --> 04:46:04.184 you see that C1,
NOTE Confidence: 0.789522469043732
04:46:04.184 --> 04:46:06.285 QA real high marker of Tams is
NOTE Confidence: 0.789522469043732
04:46:06.285 --> 04:46:07.715 on the right hand side.
NOTE Confidence: 0.789522469043732
04:46:07.720 --> 04:46:09.184 And Licensee, for example,
NOTE Confidence: 0.789522469043732
04:46:09.184 --> 04:46:11.380 big marker of early monocytes in
NOTE Confidence: 0.789522469043732
04:46:11.443 --> 04:46:13.571 the left hand side it allows you
NOTE Confidence: 0.789522469043732
04:46:13.571 --> 04:46:15.755 basically to say as you're going
NOTE Confidence: 0.789522469043732
04:46:15.755 --> 04:46:17.770 the trajectory from monocytes to
NOTE Confidence: 0.789522469043732
04:46:17.770 --> 04:46:18.942 tumor associated macrophages.
NOTE Confidence: 0.789522469043732
04:46:18.942 --> 04:46:21.476 This is how the spatial dimension goes.
NOTE Confidence: 0.789522469043732
04:46:21.480 --> 04:46:24.192 You go from being very much on the
NOTE Confidence: 0.789522469043732
04:46:24.192 --> 04:46:27.270 margin to being very much in the inside,
NOTE Confidence: 0.789522469043732
04:46:27.270 --> 04:46:29.720 so we're seeing kind of like a
NOTE Confidence: 0.789522469043732

04:46:29.720 --> 04:46:31.196 a coordinate differentiation of
NOTE Confidence: 0.789522469043732

04:46:31.196 --> 04:46:33.368 monocytes to Tams as we're seeing
NOTE Confidence: 0.789522469043732

04:46:33.368 --> 04:46:35.229 coordinate regulation of early entry.
NOTE Confidence: 0.789522469043732

04:46:35.230 --> 04:46:38.158 I think stem cells into the exhausted phase.
NOTE Confidence: 0.789522469043732

04:46:38.160 --> 04:46:40.086 The cool thing about this,
NOTE Confidence: 0.789522469043732

04:46:40.086 --> 04:46:42.018 just in just one hour.
NOTE Confidence: 0.815047025680542

04:46:44.080 --> 04:46:45.730 You can take multiple regions here.
NOTE Confidence: 0.815047025680542

04:46:45.730 --> 04:46:46.970 We've made four different concentric
NOTE Confidence: 0.815047025680542

04:46:46.970 --> 04:46:48.760 rings in a tumor micro environment,
NOTE Confidence: 0.815047025680542

04:46:48.760 --> 04:46:50.531 and you can find your favorite gene
NOTE Confidence: 0.815047025680542

04:46:50.531 --> 04:46:52.885 KLF two is as one of our favourites
NOTE Confidence: 0.815047025680542

04:46:52.885 --> 04:46:54.733 because it's almost always high on
NOTE Confidence: 0.815047025680542

04:46:54.733 --> 04:46:56.757 the inside of organs and low on the
NOTE Confidence: 0.815047025680542

04:46:56.757 --> 04:46:58.492 outside of organs and you can find
NOTE Confidence: 0.815047025680542

04:46:58.492 --> 04:47:00.308 other jeans that look like that and
NOTE Confidence: 0.815047025680542

04:47:00.308 --> 04:47:01.850 so that allows you to essentially

NOTE Confidence: 0.815047025680542
04:47:01.850 --> 04:47:03.711 to say what are the coordinate
NOTE Confidence: 0.815047025680542
04:47:03.711 --> 04:47:05.503 expression patterns in this cell type.
NOTE Confidence: 0.815047025680542
04:47:05.503 --> 04:47:07.447 But you can also now say what I
NOTE Confidence: 0.815047025680542
04:47:07.447 --> 04:47:09.218 wanna look for patterns that look
NOTE Confidence: 0.815047025680542
04:47:09.218 --> 04:47:11.309 like this in every other cell type.
NOTE Confidence: 0.815047025680542
04:47:11.310 --> 04:47:12.996 You can obviously look for the
NOTE Confidence: 0.815047025680542
04:47:12.996 --> 04:47:14.120 ones that are opposite.
NOTE Confidence: 0.815047025680542
04:47:14.120 --> 04:47:16.586 You can do that for other jeans like here,
NOTE Confidence: 0.815047025680542
04:47:16.590 --> 04:47:17.088 CR7 jeans.
NOTE Confidence: 0.815047025680542
04:47:17.088 --> 04:47:18.831 Again they tend to fall off as
NOTE Confidence: 0.815047025680542
04:47:18.831 --> 04:47:20.419 you go from inside outside,
NOTE Confidence: 0.815047025680542
04:47:20.420 --> 04:47:22.443 so this is really a discovery tool
NOTE Confidence: 0.815047025680542
04:47:22.443 --> 04:47:25.068 that starts to add to allow you to ask
NOTE Confidence: 0.815047025680542
04:47:25.068 --> 04:47:27.102 questions about how gene expression is
NOTE Confidence: 0.815047025680542
04:47:27.102 --> 04:47:29.207 coordinate Lee regulated over space.
NOTE Confidence: 0.815047025680542

04:47:29.210 --> 04:47:30.826 And I think the cool things that we're
NOTE Confidence: 0.815047025680542

04:47:30.826 --> 04:47:32.594 going to see about this is to ask
NOTE Confidence: 0.815047025680542

04:47:32.594 --> 04:47:33.850 what's special about these various
NOTE Confidence: 0.815047025680542

04:47:33.850 --> 04:47:35.158 different regions where different
NOTE Confidence: 0.815047025680542

04:47:35.158 --> 04:47:37.053 archetypes or different biology is pleasant.
NOTE Confidence: 0.815047025680542

04:47:37.053 --> 04:47:38.824 And in fact there's also to discover
NOTE Confidence: 0.815047025680542

04:47:38.824 --> 04:47:40.338 the Blacks, the famous black space.
NOTE Confidence: 0.815047025680542

04:47:40.338 --> 04:47:41.094 Whenever we image,
NOTE Confidence: 0.815047025680542

04:47:41.100 --> 04:47:42.864 we've chosen what we want to label,
NOTE Confidence: 0.815047025680542

04:47:42.870 --> 04:47:45.400 we don't label it, but we put Barcodes on it.
NOTE Confidence: 0.815047025680542

04:47:45.400 --> 04:47:48.039 We can find out what was there.
NOTE Confidence: 0.815047025680542

04:47:48.040 --> 04:47:50.992 So I need to think of Brazilian people
NOTE Confidence: 0.815047025680542

04:47:50.992 --> 04:47:53.938 for this, and this is a short list.
NOTE Confidence: 0.815047025680542

04:47:53.940 --> 04:47:57.270 John started the work that led to the CDC,
NOTE Confidence: 0.815047025680542

04:47:57.270 --> 04:47:59.846 one work of Miranda back in 2016,
NOTE Confidence: 0.815047025680542

04:47:59.850 --> 04:48:02.196 2014 McHale showed the CDC two

NOTE Confidence: 0.815047025680542
04:48:02.196 --> 04:48:04.166 archetype audriana Mahal was involved
NOTE Confidence: 0.815047025680542
04:48:04.166 --> 04:48:06.490 in a lot of the archetype work.
NOTE Confidence: 0.815047025680542
04:48:06.490 --> 04:48:07.192 In general.
NOTE Confidence: 0.815047025680542
04:48:07.192 --> 04:48:10.000 Kevin did the NK cell work is now
NOTE Confidence: 0.815047025680542
04:48:10.079 --> 04:48:12.029 at the hutch candid zips.
NOTE Confidence: 0.815047025680542
04:48:12.030 --> 04:48:14.676 Lexie did a lot of the dominant
NOTE Confidence: 0.815047025680542
04:48:14.676 --> 04:48:16.940 archetype work and it will see
NOTE Confidence: 0.815047025680542
04:48:16.940 --> 04:48:18.690 come out fairly soon and.
NOTE Confidence: 0.815047025680542
04:48:18.690 --> 04:48:21.834 Kyles are imaging at Expert in
NOTE Confidence: 0.815047025680542
04:48:21.834 --> 04:48:23.142 Vincent really coordinates all
NOTE Confidence: 0.815047025680542
04:48:23.142 --> 04:48:24.940 of the profiler and UX work,
NOTE Confidence: 0.815047025680542
04:48:24.940 --> 04:48:26.192 so thank you all.
NOTE Confidence: 0.815047025680542
04:48:26.192 --> 04:48:28.070 Thank you everybody for coming and
NOTE Confidence: 0.815047025680542
04:48:28.130 --> 04:48:29.972 general sticking with us to the
NOTE Confidence: 0.815047025680542
04:48:29.972 --> 04:48:31.200 end here and again,
NOTE Confidence: 0.815047025680542

04:48:31.200 --> 04:48:32.448 the moderators for really
NOTE Confidence: 0.815047025680542

04:48:32.448 --> 04:48:34.008 a great great news today.
NOTE Confidence: 0.847194373607636

04:48:34.660 --> 04:48:38.260 Thanks Max, I was really excellent talk.
NOTE Confidence: 0.847194373607636

04:48:38.260 --> 04:48:39.850 So we have one question.
NOTE Confidence: 0.847194373607636

04:48:39.850 --> 04:48:42.122 In the in the Q&A right now and
NOTE Confidence: 0.847194373607636

04:48:42.122 --> 04:48:44.476 I'll ask that and then I may
NOTE Confidence: 0.847194373607636

04:48:44.476 --> 04:48:46.181 have some questions as well.
NOTE Confidence: 0.847194373607636

04:48:46.190 --> 04:48:48.395 So the question comes from Adam Rubin,
NOTE Confidence: 0.847194373607636

04:48:48.400 --> 04:48:50.530 the question is.
NOTE Confidence: 0.847194373607636

04:48:50.530 --> 04:48:52.488 It is the CD8 CD.
NOTE Confidence: 0.847194373607636

04:48:52.488 --> 04:48:54.448 One interaction in the TI,
NOTE Confidence: 0.847194373607636

04:48:54.450 --> 04:48:56.610 me also engine specific are those
NOTE Confidence: 0.847194373607636

04:48:56.610 --> 04:48:58.760 CDC ones activated and migrating.
NOTE Confidence: 0.759216666221619

04:48:59.690 --> 04:49:02.427 Yeah, so it is antigen specific so
NOTE Confidence: 0.759216666221619

04:49:02.430 --> 04:49:05.592 if we take for example P14 cell and
NOTE Confidence: 0.759216666221619

04:49:05.592 --> 04:49:08.012 mix them together with the with

NOTE Confidence: 0.759216666221619
04:49:08.012 --> 04:49:10.250 the CDC ones from ANOVA tumor,
NOTE Confidence: 0.759216666221619
04:49:10.250 --> 04:49:11.810 there's there's no priming.
NOTE Confidence: 0.759216666221619
04:49:11.810 --> 04:49:14.154 There's no, there's no formation of
NOTE Confidence: 0.759216666221619
04:49:14.154 --> 04:49:16.109 a synapse that's above background,
NOTE Confidence: 0.759216666221619
04:49:16.110 --> 04:49:18.847 so I think that's there are key
NOTE Confidence: 0.759216666221619
04:49:18.847 --> 04:49:21.200 McCain gradients that bring in cells.
NOTE Confidence: 0.759216666221619
04:49:21.200 --> 04:49:23.486 This definitely CR5 Comic Con gradient
NOTE Confidence: 0.759216666221619
04:49:23.486 --> 04:49:25.889 that could bring cells towards that.
NOTE Confidence: 0.759216666221619
04:49:25.890 --> 04:49:27.840 I don't think the interactions
NOTE Confidence: 0.759216666221619
04:49:27.840 --> 04:49:29.778 that would be antigen nonspecific.
NOTE Confidence: 0.759216666221619
04:49:29.778 --> 04:49:32.100 And I think that Miriam basically
NOTE Confidence: 0.759216666221619
04:49:32.168 --> 04:49:34.232 has really opened up something that
NOTE Confidence: 0.759216666221619
04:49:34.232 --> 04:49:36.466 we showed and didn't spend a lot
NOTE Confidence: 0.759216666221619
04:49:36.466 --> 04:49:38.314 of detail to that the CDC ones,
NOTE Confidence: 0.759216666221619
04:49:38.320 --> 04:49:40.936 about 20% of them end up expressing CR7,
NOTE Confidence: 0.759216666221619

04:49:40.940 --> 04:49:43.187 and that's a maturation signal for them
NOTE Confidence: 0.759216666221619

04:49:43.187 --> 04:49:46.170 to go to the lymph node we focused on,
NOTE Confidence: 0.759216666221619

04:49:46.170 --> 04:49:48.162 that she's very much focused on
NOTE Confidence: 0.759216666221619

04:49:48.162 --> 04:49:50.418 the idea that when they do that,
NOTE Confidence: 0.759216666221619

04:49:50.420 --> 04:49:52.310 there are sort of being matured
NOTE Confidence: 0.759216666221619

04:49:52.310 --> 04:49:54.640 and she's focused on the fact that
NOTE Confidence: 0.759216666221619

04:49:54.640 --> 04:49:56.310 that also corresponds to them.
NOTE Confidence: 0.759216666221619

04:49:56.310 --> 04:49:57.940 I would say fairly modestly,
NOTE Confidence: 0.759216666221619

04:49:57.940 --> 04:49:59.800 but noticeably upregulating PD L1.
NOTE Confidence: 0.759216666221619

04:49:59.800 --> 04:50:01.678 And that the importance of that
NOTE Confidence: 0.759216666221619

04:50:01.678 --> 04:50:03.649 obviously comes to play with iris
NOTE Confidence: 0.759216666221619

04:50:03.649 --> 04:50:05.299 demonstration that the main cell
NOTE Confidence: 0.759216666221619

04:50:05.299 --> 04:50:07.428 that matters is the CDC one for PD.
NOTE Confidence: 0.759216666221619

04:50:07.430 --> 04:50:09.257 L1 and I think the reason for
NOTE Confidence: 0.759216666221619

04:50:09.257 --> 04:50:11.475 that is that the other sales just
NOTE Confidence: 0.759216666221619

04:50:11.475 --> 04:50:13.527 aren't expressing a lot of energy.

NOTE Confidence: 0.759216666221619
04:50:13.530 --> 04:50:16.580 So if you D repress PDL one on a macrophage,
NOTE Confidence: 0.759216666221619
04:50:16.580 --> 04:50:18.540 it wasn't really doing a lot for you
NOTE Confidence: 0.759216666221619
04:50:18.540 --> 04:50:20.849 anyway in terms of management presentation.
NOTE Confidence: 0.759216666221619
04:50:20.850 --> 04:50:23.900 So it's DL1 is most important on the C one,
NOTE Confidence: 0.759216666221619
04:50:23.900 --> 04:50:26.028 so that's kind of a long answer.
NOTE Confidence: 0.759216666221619
04:50:26.030 --> 04:50:27.635 The question there are definitely
NOTE Confidence: 0.759216666221619
04:50:27.635 --> 04:50:29.585 subpopulations of these we see the
NOTE Confidence: 0.759216666221619
04:50:29.585 --> 04:50:31.010 CR7 high population is likely.
NOTE Confidence: 0.759216666221619
04:50:31.010 --> 04:50:32.132 The ones that are just about
NOTE Confidence: 0.759216666221619
04:50:32.132 --> 04:50:33.370 to transit to the lymph node.
NOTE Confidence: 0.759216666221619
04:50:33.370 --> 04:50:35.143 But they may do something before they go to.
NOTE Confidence: 0.782402098178864
04:50:37.170 --> 04:50:41.788 Great so John has a question on the panel. A
NOTE Confidence: 0.832854449748993
04:50:41.790 --> 04:50:44.306 Max that was really cool.
NOTE Confidence: 0.832854449748993
04:50:44.306 --> 04:50:46.950 Great stuff, the question relates to these
NOTE Confidence: 0.832854449748993
04:50:46.950 --> 04:50:48.760 recent papers on interferon autoantibodies,
NOTE Confidence: 0.832854449748993

04:50:48.760 --> 04:50:50.938 interference genetics snips and things is,
NOTE Confidence: 0.832854449748993

04:50:50.940 --> 04:50:53.159 I think, really interesting and sets the
NOTE Confidence: 0.832854449748993

04:50:53.159 --> 04:50:55.785 stage for the fact that people might
NOTE Confidence: 0.832854449748993

04:50:55.785 --> 04:50:57.805 have auto antibodies against cytokines,
NOTE Confidence: 0.832854449748993

04:50:57.810 --> 04:50:58.446 including interferons.
NOTE Confidence: 0.832854449748993

04:50:58.446 --> 04:51:00.354 I think creates a whole new
NOTE Confidence: 0.832854449748993

04:51:00.354 --> 04:51:01.800 layer of possibilities,
NOTE Confidence: 0.832854449748993

04:51:01.800 --> 04:51:05.050 so do you see any things in the archetypes
NOTE Confidence: 0.832854449748993

04:51:05.050 --> 04:51:07.612 that it looked like you have segregation
NOTE Confidence: 0.832854449748993

04:51:07.612 --> 04:51:10.118 based on my SGS to some extent,
NOTE Confidence: 0.832854449748993

04:51:10.120 --> 04:51:12.402 but how much of that do you
NOTE Confidence: 0.832854449748993

04:51:12.402 --> 04:51:14.499 think relates to production or?
NOTE Confidence: 0.832854449748993

04:51:14.500 --> 04:51:16.100 Impacts the Archetypes. Yeah,
NOTE Confidence: 0.778503119945526

04:51:16.100 --> 04:51:18.170 well just briefly going to the
NOTE Confidence: 0.778503119945526

04:51:18.170 --> 04:51:20.093 Casanova paper we just submitted
NOTE Confidence: 0.778503119945526

04:51:20.093 --> 04:51:22.478 ours our longstanding kovid paper,

NOTE Confidence: 0.778503119945526
04:51:22.480 --> 04:51:25.728 and it turns out that I think, well,
NOTE Confidence: 0.778503119945526
04:51:25.728 --> 04:51:28.476 we show that every Sevier patient
NOTE Confidence: 0.778503119945526
04:51:28.476 --> 04:51:30.314 is generating autoantibodies that
NOTE Confidence: 0.778503119945526
04:51:30.314 --> 04:51:32.279 are against the IST phenotype.
NOTE Confidence: 0.778503119945526
04:51:32.280 --> 04:51:34.534 Not just the type one interferon itself,
NOTE Confidence: 0.778503119945526
04:51:34.540 --> 04:51:37.276 but many of them are against some sort of
NOTE Confidence: 0.778503119945526
04:51:37.276 --> 04:51:40.029 cell surface epitopes that are on my SGS,
NOTE Confidence: 0.778503119945526
04:51:40.030 --> 04:51:41.878 so there's a bigger story there
NOTE Confidence: 0.778503119945526
04:51:41.878 --> 04:51:43.503 that's covid related that's probably
NOTE Confidence: 0.778503119945526
04:51:43.503 --> 04:51:45.519 beyond the scope of today's meeting,
NOTE Confidence: 0.778503119945526
04:51:45.520 --> 04:51:47.921 but the one of the things that
NOTE Confidence: 0.778503119945526
04:51:47.921 --> 04:51:50.047 we're looking at is in the ISG.
NOTE Confidence: 0.778503119945526
04:51:50.050 --> 04:51:52.360 The tumors that show the ISG signature.
NOTE Confidence: 0.778503119945526
04:51:52.360 --> 04:51:53.062 Question is,
NOTE Confidence: 0.778503119945526
04:51:53.062 --> 04:51:55.519 is the source of that an ancient
NOTE Confidence: 0.778503119945526

04:51:55.519 --> 04:51:56.917 underlying viral infection and
NOTE Confidence: 0.778503119945526

04:51:56.917 --> 04:51:59.199 you can do that because when you
NOTE Confidence: 0.778503119945526

04:51:59.267 --> 04:52:01.507 sequence you get you can look and
NOTE Confidence: 0.778503119945526

04:52:01.507 --> 04:52:03.343 you align against all the known
NOTE Confidence: 0.778503119945526

04:52:03.343 --> 04:52:05.089 viruses you can find whether tumors
NOTE Confidence: 0.778503119945526

04:52:05.089 --> 04:52:06.944 have predominantly large amounts or
NOTE Confidence: 0.778503119945526

04:52:06.944 --> 04:52:09.206 particular subtypes of viruses in them.
NOTE Confidence: 0.778503119945526

04:52:09.210 --> 04:52:11.520 And you probably know that there was
NOTE Confidence: 0.778503119945526

04:52:11.520 --> 04:52:13.928 some nice papers this last year that
NOTE Confidence: 0.778503119945526

04:52:13.928 --> 04:52:15.950 show tumors with bacteria in them,
NOTE Confidence: 0.778503119945526

04:52:15.950 --> 04:52:18.099 and you know that that such that
NOTE Confidence: 0.778503119945526

04:52:18.099 --> 04:52:20.550 there's a much higher rate of ours
NOTE Confidence: 0.778503119945526

04:52:20.550 --> 04:52:22.370 are being residual E infected.
NOTE Confidence: 0.778503119945526

04:52:22.370 --> 04:52:24.056 But I think certainly was taught
NOTE Confidence: 0.778503119945526

04:52:24.056 --> 04:52:26.297 to us in textbooks we were taught
NOTE Confidence: 0.778503119945526

04:52:26.297 --> 04:52:27.709 about sterilizing immunity that

NOTE Confidence: 0.778503119945526
04:52:27.709 --> 04:52:29.539 when you finished an infection,
NOTE Confidence: 0.778503119945526
04:52:29.540 --> 04:52:32.148 you were back to being like a baby.
NOTE Confidence: 0.778503119945526
04:52:32.150 --> 04:52:34.425 You know bugs in you at all.
NOTE Confidence: 0.778503119945526
04:52:34.430 --> 04:52:36.721 And it's it's just not true, right?
NOTE Confidence: 0.778503119945526
04:52:36.721 --> 04:52:37.383 I mean,
NOTE Confidence: 0.778503119945526
04:52:37.383 --> 04:52:39.369 the fact that we can't find
NOTE Confidence: 0.778503119945526
04:52:39.369 --> 04:52:40.630 viruses in the blood,
NOTE Confidence: 0.778503119945526
04:52:40.630 --> 04:52:41.506 and you know,
NOTE Confidence: 0.778503119945526
04:52:41.506 --> 04:52:43.550 by PCR doesn't mean that there's not
NOTE Confidence: 0.778503119945526
04:52:43.616 --> 04:52:45.836 some transfer hanging around all over.
NOTE Confidence: 0.778503119945526
04:52:45.840 --> 04:52:48.448 So I think the SG might be interesting.
NOTE Confidence: 0.778503119945526
04:52:48.450 --> 04:52:51.122 Interesting one that it might be driven by
NOTE Confidence: 0.778503119945526
04:52:51.122 --> 04:52:53.379 residual tumor viruses that are in there.
NOTE Confidence: 0.778503119945526
04:52:53.380 --> 04:52:54.175 I don't know.
NOTE Confidence: 0.778503119945526
04:52:54.175 --> 04:52:55.500 Thanks for all your questions,
NOTE Confidence: 0.778503119945526

04:52:55.500 --> 04:52:57.620 'cause there's a lot of threads in there.
NOTE Confidence: 0.778503119945526

04:52:57.620 --> 04:52:58.680 The question of autoantibodies.
NOTE Confidence: 0.778503119945526

04:52:58.680 --> 04:53:00.005 And you did see it.
NOTE Confidence: 0.778503119945526

04:53:00.010 --> 04:53:01.546 Hopefully that one of the archetypes
NOTE Confidence: 0.778503119945526

04:53:01.546 --> 04:53:03.847 has a lot of plasma cells in it and
NOTE Confidence: 0.778503119945526

04:53:03.847 --> 04:53:05.698 you you showed that code with patients
NOTE Confidence: 0.778503119945526

04:53:05.698 --> 04:53:07.686 have a huge number of plasma glass,
NOTE Confidence: 0.778503119945526

04:53:07.690 --> 04:53:09.125 so that would be an interesting one
NOTE Confidence: 0.778503119945526

04:53:09.125 --> 04:53:11.123 to see whether those represent sort of
NOTE Confidence: 0.778503119945526

04:53:11.123 --> 04:53:12.459 continually production of autoantibodies.
NOTE Confidence: 0.778503119945526

04:53:12.460 --> 04:53:13.790 But we haven't done that.
NOTE Confidence: 0.778503119945526

04:53:13.790 --> 04:53:15.575 But we have the data set and
NOTE Confidence: 0.778503119945526

04:53:15.575 --> 04:53:17.230 we've had to share it, right?
NOTE Confidence: 0.80746058622996

04:53:17.230 --> 04:53:18.640 So Pam. I
NOTE Confidence: 0.812024593353271

04:53:18.640 --> 04:53:20.290 hate Max those great looking at
NOTE Confidence: 0.812024593353271

04:53:20.290 --> 04:53:22.009 your arch types based on the

NOTE Confidence: 0.812024593353271

04:53:22.009 --> 04:53:23.409 different tumors that you looked

NOTE Confidence: 0.812024593353271

04:53:23.409 --> 04:53:25.090 at where those primary tumors.

NOTE Confidence: 0.812024593353271

04:53:25.090 --> 04:53:27.124 Or did you also have access to

NOTE Confidence: 0.812024593353271

04:53:27.124 --> 04:53:28.564 metastatic lesions because you know

NOTE Confidence: 0.812024593353271

04:53:28.564 --> 04:53:30.054 the meta static micro environment

NOTE Confidence: 0.812024593353271

04:53:30.054 --> 04:53:31.782 may make a difference and I'm

NOTE Confidence: 0.812024593353271

04:53:31.782 --> 04:53:33.292 just wondering if the archtypes

NOTE Confidence: 0.812024593353271

04:53:33.292 --> 04:53:35.050 are really determined more by the

NOTE Confidence: 0.812024593353271

04:53:35.050 --> 04:53:36.515 primary colors themselves or to

NOTE Confidence: 0.812024593353271

04:53:36.515 --> 04:53:37.687 meta static micro environment.

NOTE Confidence: 0.784656882286072

04:53:38.530 --> 04:53:40.294 So the so the data I showed

NOTE Confidence: 0.784656882286072

04:53:40.294 --> 04:53:41.720 you is largely primaries.

NOTE Confidence: 0.784656882286072

04:53:41.720 --> 04:53:43.750 That does include some mid meta statics,

NOTE Confidence: 0.784656882286072

04:53:43.750 --> 04:53:45.200 but to your point there

NOTE Confidence: 0.784656882286072

04:53:45.200 --> 04:53:46.940 are things that seem to be.

NOTE Confidence: 0.784656882286072

04:53:46.940 --> 04:53:48.680 There's something when we take and
NOTE Confidence: 0.784656882286072

04:53:48.680 --> 04:53:50.420 you've done this answer to that.
NOTE Confidence: 0.784656882286072

04:53:50.420 --> 04:53:52.740 You take primaries and Mets from some people.
NOTE Confidence: 0.784656882286072

04:53:52.740 --> 04:53:54.190 They can look remarkably similar,
NOTE Confidence: 0.784656882286072

04:53:54.190 --> 04:53:55.624 but it's not a rule.
NOTE Confidence: 0.784656882286072

04:53:55.624 --> 04:53:57.542 It's clear that you can have some
NOTE Confidence: 0.784656882286072

04:53:57.542 --> 04:53:59.645 primaries in some Mets where the Met
NOTE Confidence: 0.784656882286072

04:53:59.645 --> 04:54:01.145 really diverges from the primary,
NOTE Confidence: 0.784656882286072

04:54:01.150 --> 04:54:03.580 and So what we did here is we basically
NOTE Confidence: 0.784656882286072

04:54:03.580 --> 04:54:05.630 treated the world as a garden's is
NOTE Confidence: 0.784656882286072

04:54:05.630 --> 04:54:07.240 like all garden variety tumors,
NOTE Confidence: 0.784656882286072

04:54:07.240 --> 04:54:09.050 whether their primaries or mats.
NOTE Confidence: 0.784656882286072

04:54:09.050 --> 04:54:10.470 Them into this analysis, right?
NOTE Confidence: 0.784656882286072

04:54:10.470 --> 04:54:11.890 So there's a separate question.
NOTE Confidence: 0.784656882286072

04:54:11.890 --> 04:54:13.310 One can answer, you know,
NOTE Confidence: 0.784656882286072

04:54:13.310 --> 04:54:14.876 like do primaries always look like

NOTE Confidence: 0.784656882286072

04:54:14.876 --> 04:54:16.719 their Mets or Mets liquor primary?

NOTE Confidence: 0.784656882286072

04:54:16.720 --> 04:54:19.544 And I think the answer is not always.

NOTE Confidence: 0.784656882286072

04:54:19.550 --> 04:54:21.338 I think it's probably dominantly true,

NOTE Confidence: 0.784656882286072

04:54:21.340 --> 04:54:23.050 but tissue tissue factors have a

NOTE Confidence: 0.784656882286072

04:54:23.050 --> 04:54:25.229 lot to do with things to write.

NOTE Confidence: 0.784656882286072

04:54:25.230 --> 04:54:27.996 If you go into the liver, you guys know.

NOTE Confidence: 0.784656882286072

04:54:27.996 --> 04:54:30.250 In Melanoma there's a big difference in

NOTE Confidence: 0.784656882286072

04:54:30.317 --> 04:54:32.373 going in along that what you have to

NOTE Confidence: 0.784656882286072

04:54:32.373 --> 04:54:34.795 do and what you have to immune system.

NOTE Confidence: 0.784656882286072

04:54:34.800 --> 04:54:37.900 You guys have in the first placement, OK.

NOTE Confidence: 0.784656882286072

04:54:37.900 --> 04:54:40.380 Yeah, I think I wanted to add to.

NOTE Confidence: 0.784656882286072

04:54:40.380 --> 04:54:42.550 That is whenever you have a tumor

NOTE Confidence: 0.784656882286072

04:54:42.550 --> 04:54:44.100 in any of those locations,

NOTE Confidence: 0.784656882286072

04:54:44.100 --> 04:54:46.219 it's mainly a failed immune response, right?

NOTE Confidence: 0.784656882286072

04:54:46.219 --> 04:54:48.550 So if there's still a tumor there an I

NOTE Confidence: 0.784656882286072

04:54:48.617 --> 04:54:50.633 think that's also sort of the beauty
NOTE Confidence: 0.784656882286072

04:54:50.633 --> 04:54:53.039 of some stuff than was talking about
NOTE Confidence: 0.784656882286072

04:54:53.039 --> 04:54:54.884 before about window of opportunity
NOTE Confidence: 0.784656882286072

04:54:54.884 --> 04:54:56.556 trials for you're actually giving
NOTE Confidence: 0.784656882286072

04:54:56.556 --> 04:54:58.176 therapies where you have responses
NOTE Confidence: 0.784656882286072

04:54:58.176 --> 04:54:59.600 that you can measure elsewhere,
NOTE Confidence: 0.784656882286072

04:54:59.600 --> 04:55:01.770 which we really have a hard time
NOTE Confidence: 0.784656882286072

04:55:01.770 --> 04:55:03.320 capturing in humans because those
NOTE Confidence: 0.784656882286072

04:55:03.320 --> 04:55:04.895 biopsies are not medically indicated
NOTE Confidence: 0.784656882286072

04:55:04.895 --> 04:55:07.039 and you have to pay for them,
NOTE Confidence: 0.784656882286072

04:55:07.040 --> 04:55:08.900 which I think MD Anderson's done
NOTE Confidence: 0.784656882286072

04:55:08.900 --> 04:55:11.130 a good job of trying to do.
NOTE Confidence: 0.784656882286072

04:55:11.130 --> 04:55:13.085 And we're trying to do this
NOTE Confidence: 0.784656882286072

04:55:13.085 --> 04:55:14.064 elsewhere as well,
NOTE Confidence: 0.784656882286072

04:55:14.064 --> 04:55:17.107 so I think keeping that in mind that if
NOTE Confidence: 0.784656882286072

04:55:17.107 --> 04:55:19.278 it's clinically indicated to remove a mass,

NOTE Confidence: 0.784656882286072
04:55:19.278 --> 04:55:21.244 it's usually not because the patient
NOTE Confidence: 0.784656882286072
04:55:21.244 --> 04:55:23.540 was doing so great that that you're
NOTE Confidence: 0.784656882286072
04:55:23.600 --> 04:55:25.800 trying to save the patient as result
NOTE Confidence: 0.784656882286072
04:55:25.800 --> 04:55:28.130 of that an it's 1 version of a
NOTE Confidence: 0.784656882286072
04:55:28.130 --> 04:55:30.359 failed response in a different issue,
NOTE Confidence: 0.784656882286072
04:55:30.360 --> 04:55:32.644 and I think that it's just useful
NOTE Confidence: 0.784656882286072
04:55:32.644 --> 04:55:34.275 to always annotate whatever the
NOTE Confidence: 0.784656882286072
04:55:34.275 --> 04:55:35.575 samples that you're getting,
NOTE Confidence: 0.784656882286072
04:55:35.580 --> 04:55:37.160 what they really represent is
NOTE Confidence: 0.784656882286072
04:55:37.160 --> 04:55:39.489 this in the middle of a response.
NOTE Confidence: 0.784656882286072
04:55:39.490 --> 04:55:42.422 Is this in the middle of a failed response?
NOTE Confidence: 0.784656882286072
04:55:42.422 --> 04:55:43.414 Is this on?
NOTE Confidence: 0.784656882286072
04:55:43.414 --> 04:55:45.074 Therapies does not run therapy,
NOTE Confidence: 0.784656882286072
04:55:45.080 --> 04:55:47.000 and all of those things matter.
NOTE Confidence: 0.784656882286072
04:55:47.000 --> 04:55:47.640 So I
NOTE Confidence: 0.835357785224915

04:55:47.640 --> 04:55:49.662 had a question about the archetypes

NOTE Confidence: 0.835357785224915

04:55:49.662 --> 04:55:51.377 and specifically this concept of

NOTE Confidence: 0.835357785224915

04:55:51.377 --> 04:55:53.243 whether or not you're defining there

NOTE Confidence: 0.835357785224915

04:55:53.243 --> 04:55:54.825 is different modules of function

NOTE Confidence: 0.835357785224915

04:55:54.825 --> 04:55:56.305 that the immune cells bring.

NOTE Confidence: 0.835357785224915

04:55:56.310 --> 04:55:58.910 So like the NK cell is not that

NOTE Confidence: 0.835357785224915

04:55:58.910 --> 04:56:00.478 different from a CD8T cell,

NOTE Confidence: 0.835357785224915

04:56:00.480 --> 04:56:02.106 and they kind of could bring

NOTE Confidence: 0.835357785224915

04:56:02.106 --> 04:56:04.247 the same thing is that is that

NOTE Confidence: 0.835357785224915

04:56:04.247 --> 04:56:06.227 really the concept there that the

NOTE Confidence: 0.835357785224915

04:56:06.227 --> 04:56:08.016 different cells are bringing in

NOTE Confidence: 0.835357785224915

04:56:08.016 --> 04:56:09.756 different modules and they're kind

NOTE Confidence: 0.835357785224915

04:56:09.756 --> 04:56:12.620 of interchangeable in a way?

NOTE Confidence: 0.772235453128815

04:56:12.620 --> 04:56:14.432 Well, it's a good question weather

NOTE Confidence: 0.772235453128815

04:56:14.432 --> 04:56:16.230 weather like a particular cell type

NOTE Confidence: 0.772235453128815

04:56:16.230 --> 04:56:17.832 can be substituted for another one

NOTE Confidence: 0.772235453128815
04:56:17.832 --> 04:56:19.629 and that then of course that comes
NOTE Confidence: 0.772235453128815
04:56:19.629 --> 04:56:21.418 down to how you define cell type.
NOTE Confidence: 0.772235453128815
04:56:21.418 --> 04:56:22.574 At some point lymphocytes
NOTE Confidence: 0.772235453128815
04:56:22.574 --> 04:56:24.130 would include NK cells at CDs,
NOTE Confidence: 0.772235453128815
04:56:24.130 --> 04:56:25.970 but then you can dive down and say
NOTE Confidence: 0.772235453128815
04:56:25.970 --> 04:56:28.029 only CD S in NK cells have cytolytic
NOTE Confidence: 0.772235453128815
04:56:28.029 --> 04:56:30.160 activity and so is cytolytic activity.
NOTE Confidence: 0.772235453128815
04:56:30.160 --> 04:56:32.752 The component of the archetype or is in
NOTE Confidence: 0.772235453128815
04:56:32.752 --> 04:56:34.840 lymphocytes or is it in case specific?
NOTE Confidence: 0.772235453128815
04:56:34.840 --> 04:56:36.814 You know the way that we've
NOTE Confidence: 0.772235453128815
04:56:36.814 --> 04:56:38.587 organized these has been based
NOTE Confidence: 0.772235453128815
04:56:38.587 --> 04:56:40.537 on very high level descriptors,
NOTE Confidence: 0.772235453128815
04:56:40.540 --> 04:56:43.375 and if it turns out you take enough of
NOTE Confidence: 0.772235453128815
04:56:43.375 --> 04:56:46.070 those and you end up with what look
NOTE Confidence: 0.772235453128815
04:56:46.070 --> 04:56:48.499 like pretty good class distinctions.
NOTE Confidence: 0.772235453128815

04:56:48.500 --> 04:56:49.355 That you know,
NOTE Confidence: 0.772235453128815

04:56:49.355 --> 04:56:50.495 predict other cell populations,
NOTE Confidence: 0.772235453128815

04:56:50.500 --> 04:56:51.716 whether they're interchangeable enough.
NOTE Confidence: 0.772235453128815

04:56:51.716 --> 04:56:53.847 I don't know that we have the
NOTE Confidence: 0.772235453128815

04:56:53.847 --> 04:56:55.646 statistical power of ask that right now.
NOTE Confidence: 0.772235453128815

04:56:55.650 --> 04:56:57.729 Like Are there like some NK cells
NOTE Confidence: 0.772235453128815

04:56:57.729 --> 04:56:59.939 that have caused one tumor in our 350.
NOTE Confidence: 0.772235453128815

04:56:59.940 --> 04:57:01.935 The tumors to get miss assigned and
NOTE Confidence: 0.772235453128815

04:57:01.935 --> 04:57:03.658 it really belongs in another one,
NOTE Confidence: 0.772235453128815

04:57:03.660 --> 04:57:05.886 because what the NK cell is doing
NOTE Confidence: 0.772235453128815

04:57:05.886 --> 04:57:08.068 in one tumor is different than
NOTE Confidence: 0.772235453128815

04:57:08.068 --> 04:57:10.372 what it was doing another tumor.
NOTE Confidence: 0.772235453128815

04:57:10.380 --> 04:57:11.385 But you know,
NOTE Confidence: 0.772235453128815

04:57:11.385 --> 04:57:13.396 I think those those things will
NOTE Confidence: 0.772235453128815

04:57:13.396 --> 04:57:14.690 have to be determined,
NOTE Confidence: 0.772235453128815

04:57:14.690 --> 04:57:16.930 and all we're trying to do here

NOTE Confidence: 0.772235453128815
04:57:16.998 --> 04:57:19.086 is to start a class distinction.
NOTE Confidence: 0.772235453128815
04:57:19.090 --> 04:57:19.734 Describer classes.
NOTE Confidence: 0.772235453128815
04:57:19.734 --> 04:57:21.666 I'm sure that if you started
NOTE Confidence: 0.772235453128815
04:57:21.666 --> 04:57:23.779 a new anchored on other ones,
NOTE Confidence: 0.772235453128815
04:57:23.780 --> 04:57:25.790 you might come to the same
NOTE Confidence: 0.772235453128815
04:57:25.790 --> 04:57:26.795 population somewhat differently,
NOTE Confidence: 0.772235453128815
04:57:26.800 --> 04:57:28.470 and sometimes you'll end up
NOTE Confidence: 0.772235453128815
04:57:28.470 --> 04:57:29.806 with an additional branch.
NOTE Confidence: 0.772235453128815
04:57:29.810 --> 04:57:31.490 The question about class distinctions,
NOTE Confidence: 0.772235453128815
04:57:31.490 --> 04:57:32.774 when does it matter?
NOTE Confidence: 0.772235453128815
04:57:32.774 --> 04:57:35.170 Like windows matter what the tumor hasn't?
NOTE Confidence: 0.772235453128815
04:57:35.170 --> 04:57:37.180 It was. Responsiveness is obviously key.
NOTE Confidence: 0.772235453128815
04:57:37.180 --> 04:57:37.696 One outcome.
NOTE Confidence: 0.772235453128815
04:57:37.696 --> 04:57:39.760 And we need to start it be coming
NOTE Confidence: 0.772235453128815
04:57:39.818 --> 04:57:41.666 at that from both sides as in OK?
NOTE Confidence: 0.772235453128815

04:57:41.670 --> 04:57:43.266 Who responds and then what are the
NOTE Confidence: 0.772235453128815

04:57:43.266 --> 04:57:44.709 sort of possible class structure out
NOTE Confidence: 0.772235453128815

04:57:44.709 --> 04:57:46.368 there and they start to match up.
NOTE Confidence: 0.772235453128815

04:57:46.370 --> 04:57:48.354 It will be when the wires hitting each
NOTE Confidence: 0.772235453128815

04:57:48.354 --> 04:57:50.365 other that we know that we got it right.
NOTE Confidence: 0.821840941905975

04:57:50.960 --> 04:57:52.815 Can I ask it? Maybe this is
NOTE Confidence: 0.821840941905975

04:57:52.815 --> 04:57:54.978 still to be determined as well,
NOTE Confidence: 0.821840941905975

04:57:54.980 --> 04:57:56.828 but the cells within a class?
NOTE Confidence: 0.821840941905975

04:57:56.830 --> 04:57:58.678 Are they all being targeted through
NOTE Confidence: 0.821840941905975

04:57:58.678 --> 04:58:00.224 targeting one? Or you know?
NOTE Confidence: 0.821840941905975

04:58:00.224 --> 04:58:02.456 So in terms of like therapy, right?
NOTE Confidence: 0.821840941905975

04:58:02.456 --> 04:58:05.464 So CTA for Axon cell a that then.
NOTE Confidence: 0.821840941905975

04:58:05.470 --> 04:58:07.820 Kicks off this whole class in that, so
NOTE Confidence: 0.829372465610504

04:58:07.820 --> 04:58:09.590 it's interesting question because I think
NOTE Confidence: 0.829372465610504

04:58:09.590 --> 04:58:11.690 the way I presented the way we
NOTE Confidence: 0.829372465610504

04:58:11.690 --> 04:58:13.700 think about this is that a tumor

NOTE Confidence: 0.829372465610504
04:58:13.700 --> 04:58:15.430 wouldn't be grown if it didn't
NOTE Confidence: 0.829372465610504
04:58:15.430 --> 04:58:16.855 have a dominant immune system
NOTE Confidence: 0.829372465610504
04:58:16.855 --> 04:58:18.699 that was supportive of the tumor.
NOTE Confidence: 0.829372465610504
04:58:18.700 --> 04:58:21.048 And yet, what we're trying to do when
NOTE Confidence: 0.829372465610504
04:58:21.050 --> 04:58:23.696 we're trying to get it to go is we're
NOTE Confidence: 0.829372465610504
04:58:23.696 --> 04:58:25.460 trying to harness the subdominant archetype.
NOTE Confidence: 0.829372465610504
04:58:25.460 --> 04:58:26.640 The population of cells
NOTE Confidence: 0.829372465610504
04:58:26.640 --> 04:58:28.398 that could work with us but
NOTE Confidence: 0.829372465610504
04:58:28.400 --> 04:58:29.870 aren't right, so that seems
NOTE Confidence: 0.829372465610504
04:58:29.870 --> 04:58:30.749 to be what
NOTE Confidence: 0.829372465610504
04:58:30.750 --> 04:58:32.220 we're doing with checkpoint blockade,
NOTE Confidence: 0.829372465610504
04:58:32.220 --> 04:58:33.400 is harnessing these populations
NOTE Confidence: 0.829372465610504
04:58:33.400 --> 04:58:35.540 of cells that could be doing good.
NOTE Confidence: 0.829372465610504
04:58:35.540 --> 04:58:37.268 But basically, the rest of the
NOTE Confidence: 0.829372465610504
04:58:37.268 --> 04:58:38.680 system is doing something bad.
NOTE Confidence: 0.829372465610504

04:58:38.680 --> 04:58:41.104 And so, So what are describing that dominant

NOTE Confidence: 0.829372465610504

04:58:41.104 --> 04:58:44.078 system is just saying what is the bulk mass

NOTE Confidence: 0.829372465610504

04:58:44.078 --> 04:58:46.409 action of the immune system look like?

NOTE Confidence: 0.829372465610504

04:58:46.410 --> 04:58:47.810 But that's really a different

NOTE Confidence: 0.829372465610504

04:58:47.810 --> 04:58:49.210 question than like, what else?

NOTE Confidence: 0.829372465610504

04:58:49.210 --> 04:58:51.170 Is there an Alpha often point to

NOTE Confidence: 0.829372465610504

04:58:51.170 --> 04:58:53.054 people this thing that everybody knows,

NOTE Confidence: 0.829372465610504

04:58:53.054 --> 04:58:55.520 and it isn't textbooks that if you take

NOTE Confidence: 0.829372465610504

04:58:55.520 --> 04:58:57.610 TH one and TH two is a class right?

NOTE Confidence: 0.829372465610504

04:58:57.610 --> 04:58:59.722 You can have gamma production or

NOTE Confidence: 0.829372465610504

04:58:59.722 --> 04:59:00.778 oil for production.

NOTE Confidence: 0.829372465610504

04:59:00.780 --> 04:59:03.279 If you look in any real lesion,

NOTE Confidence: 0.829372465610504

04:59:03.279 --> 04:59:05.637 it's never one or the other.

NOTE Confidence: 0.829372465610504

04:59:05.640 --> 04:59:07.260 You know, even when you're getting

NOTE Confidence: 0.829372465610504

04:59:07.260 --> 04:59:09.080 clearance and you've got lots of TH one,

NOTE Confidence: 0.829372465610504

04:59:09.080 --> 04:59:10.809 you will find TH two in there.

NOTE Confidence: 0.829372465610504

04:59:10.810 --> 04:59:12.511 And that's presumably because biology has at

NOTE Confidence: 0.829372465610504

04:59:12.511 --> 04:59:14.499 its heart the seeds of its own destruction.

NOTE Confidence: 0.829372465610504

04:59:14.500 --> 04:59:15.283 So we can.

NOTE Confidence: 0.829372465610504

04:59:15.283 --> 04:59:16.849 Basically then there might be a

NOTE Confidence: 0.829372465610504

04:59:16.849 --> 04:59:18.680 time when you want to be TH two,

NOTE Confidence: 0.829372465610504

04:59:18.680 --> 04:59:20.648 and so you keep the other guy around.

NOTE Confidence: 0.829372465610504

04:59:20.650 --> 04:59:21.880 And I think that's probably

NOTE Confidence: 0.829372465610504

04:59:21.880 --> 04:59:23.110 what we're trying to harness.

NOTE Confidence: 0.829372465610504

04:59:23.110 --> 04:59:24.586 And tumors were trying to harness

NOTE Confidence: 0.829372465610504

04:59:24.586 --> 04:59:25.570 the subdominant immune system.

NOTE Confidence: 0.829372465610504

04:59:25.570 --> 04:59:27.341 The tumor is managed to get mostly

NOTE Confidence: 0.829372465610504

04:59:27.341 --> 04:59:28.758 the mean system on its side,

NOTE Confidence: 0.829372465610504

04:59:28.760 --> 04:59:30.363 and we're trying to do is to

NOTE Confidence: 0.829372465610504

04:59:30.363 --> 04:59:31.720 grow that little tiny flower.

NOTE Confidence: 0.805318892002106

04:59:33.670 --> 04:59:35.777 Great, well this is an excellent talk.

NOTE Confidence: 0.805318892002106

04:59:35.780 --> 04:59:37.460 An excellent session with both John
NOTE Confidence: 0.805318892002106

04:59:37.460 --> 04:59:39.708 in and Max for speaking with that.
NOTE Confidence: 0.805318892002106

04:59:39.710 --> 04:59:41.220 I will conclude this session
NOTE Confidence: 0.805318892002106

04:59:41.220 --> 04:59:42.428 turned over to Marcus
NOTE Confidence: 0.805318892002106

04:59:42.430 --> 04:59:43.330 for concluding remarks.
NOTE Confidence: 0.848919570446014

04:59:44.050 --> 04:59:46.036 Thanks, I mean, what today really,
NOTE Confidence: 0.848919570446014

04:59:46.040 --> 04:59:48.427 really great talks all around and I
NOTE Confidence: 0.848919570446014

04:59:48.427 --> 04:59:51.000 really want to thank all of the speakers.
NOTE Confidence: 0.848919570446014

04:59:51.000 --> 04:59:52.984 So much for inspiring. We've had
NOTE Confidence: 0.848919570446014

04:59:52.984 --> 04:59:54.639 great attendance throughout the day,
NOTE Confidence: 0.848919570446014

04:59:54.640 --> 04:59:57.619 so it's made a huge impact primarily at Yale.
NOTE Confidence: 0.848919570446014

04:59:57.620 --> 04:59:59.940 But there are people from around the
NOTE Confidence: 0.848919570446014

04:59:59.940 --> 05:00:01.920 country who have been tuning in.
NOTE Confidence: 0.848919570446014

05:00:01.920 --> 05:00:03.244 Who had, you know,
NOTE Confidence: 0.848919570446014

05:00:03.244 --> 05:00:05.230 it's a good thing about finding
NOTE Confidence: 0.848919570446014

05:00:05.230 --> 05:00:08.880 things on the Internet. They

NOTE Confidence: 0.848919570446014
05:00:06.890 --> 05:00:07.880 can they can,
NOTE Confidence: 0.848919570446014
05:00:07.880 --> 05:00:08.879 you know, not
NOTE Confidence: 0.848919570446014
05:00:08.880 --> 05:00:10.860 zoom bomb, but sort of zoom
NOTE Confidence: 0.848919570446014
05:00:10.860 --> 05:00:11.850 bomb in a
NOTE Confidence: 0.848919570446014
05:00:11.850 --> 05:00:12.843 completely supported way.
NOTE Confidence: 0.848919570446014
05:00:12.843 --> 05:00:14.899 And I think that's great because.
NOTE Confidence: 0.848919570446014
05:00:14.900 --> 05:00:17.288 The goal of this is A to
NOTE Confidence: 0.848919570446014
05:00:17.288 --> 05:00:18.994 see where things are at,
NOTE Confidence: 0.848919570446014
05:00:18.994 --> 05:00:20.358 which is really spectacular.
NOTE Confidence: 0.848919570446014
05:00:20.360 --> 05:00:22.400 You think about 10 years ago?
NOTE Confidence: 0.848919570446014
05:00:22.400 --> 05:00:23.762 Well, Jim, you know,
NOTE Confidence: 0.848919570446014
05:00:23.762 --> 05:00:25.808 10 years ago was probably here,
NOTE Confidence: 0.848919570446014
05:00:25.810 --> 05:00:27.860 but you know, for and many
NOTE Confidence: 0.848919570446014
05:00:27.860 --> 05:00:29.906 others you know Max as well.
NOTE Confidence: 0.848919570446014
05:00:29.906 --> 05:00:31.950 Other folks were here as well,
NOTE Confidence: 0.848919570446014

05:00:31.950 --> 05:00:33.314 but the point is,
NOTE Confidence: 0.848919570446014

05:00:33.314 --> 05:00:35.360 is that where we were from
NOTE Confidence: 0.848919570446014

05:00:35.360 --> 05:00:37.066 a clinical point of view,
NOTE Confidence: 0.848919570446014

05:00:37.066 --> 05:00:38.770 and how household IO has
NOTE Confidence: 0.848919570446014

05:00:38.770 --> 05:00:39.790 become for everyone
NOTE Confidence: 0.850823104381561

05:00:39.790 --> 05:00:41.158 else. But I think
NOTE Confidence: 0.850823104381561

05:00:41.160 --> 05:00:42.520 if you really think
NOTE Confidence: 0.850823104381561

05:00:42.520 --> 05:00:44.890 about all the things you've heard today.
NOTE Confidence: 0.850823104381561

05:00:44.890 --> 05:00:46.470 There are so many unanswered
NOTE Confidence: 0.850823104381561

05:00:46.470 --> 05:00:48.654 questions that are still need to be
NOTE Confidence: 0.850823104381561

05:00:48.654 --> 05:00:50.526 addressed that we really don't know.
NOTE Confidence: 0.850823104381561

05:00:50.530 --> 05:00:51.770 These are really, really
NOTE Confidence: 0.88312029838562

05:00:51.770 --> 05:00:52.706 complicated questions. Cancers,
NOTE Confidence: 0.88312029838562

05:00:52.706 --> 05:00:53.954 complicated immunology is complicated.
NOTE Confidence: 0.88312029838562

05:00:53.960 --> 05:00:55.520 All of the subsets, things
NOTE Confidence: 0.88312029838562

05:00:55.520 --> 05:00:57.081 that we've been talking about.

NOTE Confidence: 0.88312029838562

05:00:57.081 --> 05:00:59.888 There's so much for all of the trainees to

NOTE Confidence: 0.88312029838562

05:00:59.890 --> 05:01:01.528 do out there to increase the

NOTE Confidence: 0.88312029838562

05:01:01.528 --> 05:01:03.055 number of patients that survive

NOTE Confidence: 0.88312029838562

05:01:03.055 --> 05:01:04.567 with immune based therapies,

NOTE Confidence: 0.88312029838562

05:01:04.570 --> 05:01:07.686 and I think that's at the end of the day.

NOTE Confidence: 0.88312029838562

05:01:07.686 --> 05:01:09.560 It's fun to understand all this,

NOTE Confidence: 0.88312029838562

05:01:09.560 --> 05:01:11.426 but what we're trying to do,

NOTE Confidence: 0.88312029838562

05:01:11.430 --> 05:01:13.928 I think in Part 2 is to save

NOTE Confidence: 0.88312029838562

05:01:13.930 --> 05:01:15.510 some lives along those lines.

NOTE Confidence: 0.88312029838562

05:01:15.510 --> 05:01:17.708 So I want to thank all of

NOTE Confidence: 0.88312029838562

05:01:17.710 --> 05:01:19.592 the speakers I want to thank

NOTE Confidence: 0.88312029838562

05:01:19.592 --> 05:01:20.848 especially alisa Matthews who

NOTE Confidence: 0.841283082962036

05:01:20.850 --> 05:01:22.734 was for the speakers. You obviously

NOTE Confidence: 0.841283082962036

05:01:22.734 --> 05:01:24.306 have met her in organizing,

NOTE Confidence: 0.841283082962036

05:01:24.306 --> 05:01:25.868 but the primary organizer from

NOTE Confidence: 0.841283082962036

05:01:25.870 --> 05:01:28.068 the El senor from you on Koleji.
NOTE Confidence: 0.841283082962036

05:01:28.070 --> 05:01:30.270 I want to thank the yell center,
NOTE Confidence: 0.841283082962036

05:01:30.270 --> 05:01:32.155 uh Cancer Center and Charlie Fuchs
NOTE Confidence: 0.841283082962036

05:01:32.155 --> 05:01:34.040 and let me know biology Department.
NOTE Confidence: 0.841283082962036

05:01:34.040 --> 05:01:36.235 With David Schatz also for supporting things.
NOTE Confidence: 0.841283082962036

05:01:36.235 --> 05:01:37.808 And it's a Friday afternoon.
NOTE Confidence: 0.841283082962036

05:01:37.808 --> 05:01:40.632 I hope all of you have a wonderful weekend.
NOTE Confidence: 0.841283082962036

05:01:40.632 --> 05:01:42.196 Thanks so much for participating.
NOTE Confidence: 0.841283082962036

05:01:42.196 --> 05:01:43.766 Thanks all of the folks
NOTE Confidence: 0.841283082962036

05:01:43.766 --> 05:01:45.700 again for being here all day.
NOTE Confidence: 0.841283082962036

05:01:45.700 --> 05:01:48.220 Thanks Max, I hope your air is better in
NOTE Confidence: 0.855198621749878

05:01:48.220 --> 05:01:49.340 San Francisco now than
NOTE Confidence: 0.855198621749878

05:01:49.340 --> 05:01:50.740 it was last time we
NOTE Confidence: 0.855198621749878

05:01:50.740 --> 05:01:53.820 talked. Seems like it is
NOTE Confidence: 0.855198621749878

05:01:52.140 --> 05:01:53.820 anyway. All thanks so much. Take
NOTE Confidence: 0.855198621749878

05:01:53.820 --> 05:01:59.000 care and have a great weekend. I buy thanks.