WEBVTT

NOTE duration: ”01:07:01.589”

NOTE Confidence: 0.6480881

00:00:00.160 --> 00:00:00.659 Buddy,

NOTE Confidence: 0.9767656

00:00:01.360 --> 00:00:02.820 thank you for being here.

NOTE Confidence: 0.9767656

00:00:02.960 --> 00:00:05.120 I'm, Barbara Burtness. I'm the

NOTE Confidence: 0.9767656

00:00:05.120 --> 00:00:07.040 associate director for translational science,

NOTE Confidence: 0.9767656

00:00:07.040 --> 00:00:08.320 and it's really my honor

NOTE Confidence: 0.9767656

00:00:08.320 --> 00:00:09.860 to be kicking off our,

NOTE Confidence: 0.96483535

00:00:11.440 --> 00:00:13.920 distinguished lecture series for, this

NOTE Confidence: 0.96483535

00:00:13.920 --> 00:00:14.559 year at the at the

NOTE Confidence: 0.96483535

00:00:14.559 --> 00:00:15.540 cancer center

NOTE Confidence: 0.9750827

00:00:15.915 --> 00:00:16.635 by having,

NOTE Confidence: 0.9817967

00:00:17.595 --> 00:00:19.035 the privilege of hosting doctor

NOTE Confidence: 0.9817967

00:00:19.035 --> 00:00:19.935 Rafi Ahmed.

NOTE Confidence: 0.9410149

00:00:20.475 --> 00:00:20.875 So,

NOTE Confidence: 0.9857077

00:00:22.235 --> 00:00:23.675 Rafi is a professor in

NOTE Confidence: 0.9857077

00:00:23.675 --> 00:00:25.195 the department of microbiology and

NOTE Confidence: 0.9857077

00:00:25.195 --> 00:00:26.654 immunology at Emory.

NOTE Confidence: 0.9710507

00:00:27.355 --> 00:00:29.195 He's also the, director of

NOTE Confidence: 0.9710507

00:00:29.195 --> 00:00:31.519 the Emory vaccine center, coleader

NOTE Confidence: 0.9710507

00:00:31.519 --> 00:00:33.520 of the cancer immunology research

NOTE Confidence: 0.9710507

00:00:33.520 --> 00:00:35.860 program at Winship Cancer Institute,

NOTE Confidence: 0.9710507

00:00:36.159 --> 00:00:38.320 and an investigator in the

NOTE Confidence: 0.9710507

00:00:38.320 --> 00:00:40.019 Emory Center for AIDS Research.

NOTE Confidence: 0.9971294

00:00:41.040 --> 00:00:42.019 He is really

NOTE Confidence: 0.84267205

00:00:42.320 --> 00:00:44.180 a pillar of the immunology

NOTE Confidence: 0.8795272

00:00:44.559 --> 00:00:45.059 revolution,

NOTE Confidence: 0.99982285

00:00:46.095 --> 00:00:47.155 that has impacted

NOTE Confidence: 0.9749569

00:00:47.534 --> 00:00:49.295 the the care of, cancer

NOTE Confidence: 0.9749569

00:00:49.295 --> 00:00:49.795 patients.

NOTE Confidence: 0.99044156

00:00:50.415 --> 00:00:50.915 He's,

NOTE Confidence: 0.95099586

00:00:51.855 --> 00:00:52.815 as I said, a professor

NOTE Confidence: 0.95099586

00:00:52.815 --> 00:00:54.115 in the department of microbiology

NOTE Confidence: 0.95099586

00:00:54.255 --> 00:00:55.695 and immunology, a member of

NOTE Confidence: 0.95099586

00:00:55.695 --> 00:00:56.755 the National Academy,

NOTE Confidence: 0.9996599

00:00:57.295 --> 00:00:59.155 and a world renowned immunologist.

NOTE Confidence: 0.9996112

00:00:59.510 --> 00:01:00.470 His work in the past

NOTE Confidence: 0.9996112

00:01:00.470 --> 00:01:02.170 decade has been highly influential

NOTE Confidence: 0.9822246

00:01:02.630 --> 00:01:04.250 in shaping our current understanding

NOTE Confidence: 0.9822246

00:01:04.310 --> 00:01:05.850 of memory t cell differentiation

NOTE Confidence: 0.96736586

00:01:06.150 --> 00:01:06.890 and antiviral

NOTE Confidence: 0.9825529

00:01:07.510 --> 00:01:08.810 t and b cell immunity.

NOTE Confidence: 0.9993474

00:01:09.670 --> 00:01:10.630 His goal is to use

NOTE Confidence: 0.9993474

00:01:10.630 --> 00:01:12.569 this information for vaccine development

NOTE Confidence: 0.9985607

00:01:13.025 --> 00:01:14.865 and insights into virally mediated

NOTE Confidence: 0.9985607

00:01:14.865 --> 00:01:15.365 cancers.

NOTE Confidence: 0.9956205

00:01:15.825 --> 00:01:17.104 A major area of focus

NOTE Confidence: 0.9956205

00:01:17.104 --> 00:01:18.485 for him has been identifying

NOTE Confidence: 0.9956205

00:01:18.545 --> 00:01:20.545 cellular molecules that regulate the

NOTE Confidence: 0.9956205

00:01:20.545 --> 00:01:21.765 generation and maintenance

NOTE Confidence: 0.91542906

00:01:22.145 --> 00:01:23.505 of CD eight and CD

NOTE Confidence: 0.91542906

00:01:23.505 --> 00:01:24.785 four T cell in humoral

NOTE Confidence: 0.91542906

00:01:24.785 --> 00:01:25.285 immunity.

NOTE Confidence: 0.955931

00:01:25.819 --> 00:01:27.420 One such molecule is mTOR

NOTE Confidence: 0.955931

00:01:27.420 --> 00:01:29.040 that his lab recently identified

NOTE Confidence: 0.955931

00:01:29.100 --> 00:01:30.159 as a major regulate

NOTE Confidence: 0.98555785

00:01:30.459 --> 00:01:32.619 regulator of memory CD eight

NOTE Confidence: 0.98555785

00:01:32.619 --> 00:01:33.680 T cell differentiation.

NOTE Confidence: 0.8994466

00:01:34.939 --> 00:01:36.540 Before we, get to hear

NOTE Confidence: 0.8994466

00:01:36.540 --> 00:01:37.420 him, and I I promise

NOTE Confidence: 0.8994466

00:01:37.420 --> 00:01:38.799 you he's a brilliant speaker,

NOTE Confidence: 0.8994466

00:01:38.939 --> 00:01:40.380 I do want to, have

NOTE Confidence: 0.8994466

00:01:40.380 --> 00:01:41.815 the opportunity to present a

NOTE Confidence: 0.8994466

00:01:41.815 --> 00:01:43.415 plaque to you. So when

NOTE Confidence: 0.8994466

00:01:43.415 --> 00:01:44.155 I come up?

NOTE Confidence: 0.95473963

00:01:48.455 --> 00:01:49.895 So this honors your your

NOTE Confidence: 0.95473963

00:01:49.895 --> 00:01:51.495 role as a distinguished lecturer

NOTE Confidence: 0.95473963

00:01:51.495 --> 00:01:52.695 here. Okay? Thank you for

NOTE Confidence: 0.95473963

00:01:52.695 --> 00:01:53.195 coming.

NOTE Confidence: 0.63510096

00:02:22.334 --> 00:02:23.955 It will it fall off?

NOTE Confidence: 0.7103906

00:02:28.710 --> 00:02:29.210 Yeah.

NOTE Confidence: 0.8468801

00:02:30.710 --> 00:02:31.610 Okay. Yeah.

NOTE Confidence: 0.9721737

00:02:32.790 --> 00:02:33.290 Okay.

NOTE Confidence: 0.7775911

00:02:44.044 --> 00:02:45.345 Ah, okay. Yeah. What I'm

NOTE Confidence: 0.9099511

00:02:46.825 --> 00:02:47.325 missing

NOTE Confidence: 0.31762865

00:02:48.805 --> 00:02:49.305 was

NOTE Confidence: 0.6944929

00:02:50.785 --> 00:02:51.285 glass.

NOTE Confidence: 0.996198

00:02:52.764 --> 00:02:53.725 Okay. Can you all hear

NOTE Confidence: 0.996198

00:02:53.725 --> 00:02:54.225 me?

NOTE Confidence: 0.924311

00:02:55.430 --> 00:02:56.550 Thank you, Barbara, for this,

NOTE Confidence: 0.924311

00:02:57.110 --> 00:02:58.550 very kind introduction and for

NOTE Confidence: 0.924311

00:02:58.550 --> 00:02:59.450 inviting me.

NOTE Confidence: 0.8550402

00:03:00.389 --> 00:03:01.430 Did we succeed on our

NOTE Confidence: 0.8550402

00:03:01.430 --> 00:03:02.470 third try or the fourth

NOTE Confidence: 0.8550402

00:03:02.470 --> 00:03:04.070 try? We we try to

NOTE Confidence: 0.8550402

00:03:04.070 --> 00:03:04.950 arrange the

NOTE Confidence: 0.97587377

00:03:05.270 --> 00:03:06.630 my seminar and something or

NOTE Confidence: 0.97587377

00:03:06.630 --> 00:03:07.590 the other happens. And I

NOTE Confidence: 0.97587377

00:03:07.590 --> 00:03:08.630 know, Barbara, that you have

NOTE Confidence: 0.97587377

00:03:08.630 --> 00:03:10.144 a flight to take, so

NOTE Confidence: 0.97587377

00:03:10.144 --> 00:03:11.345 please don't miss your flight

NOTE Confidence: 0.97587377

00:03:11.345 --> 00:03:12.385 because of me. Feel free

NOTE Confidence: 0.97587377

00:03:12.385 --> 00:03:13.125 to leave.

NOTE Confidence: 0.9826238

00:03:15.745 --> 00:03:17.025 Alright. So I'm gonna talk

NOTE Confidence: 0.9826238

00:03:17.025 --> 00:03:17.924 to you about,

NOTE Confidence: 0.9652633

00:03:19.264 --> 00:03:20.864 T cell exhaustion, and I

NOTE Confidence: 0.9652633

00:03:20.864 --> 00:03:22.305 thought I'd start by really

NOTE Confidence: 0.9652633

00:03:22.305 --> 00:03:23.205 asking the question,

NOTE Confidence: 0.9063569

00:03:23.584 --> 00:03:24.305 what what is T cell

NOTE Confidence: 0.9063569

00:03:24.305 --> 00:03:25.650 exhaustion? What does it really

NOTE Confidence: 0.9063569

00:03:25.650 --> 00:03:26.389 even mean?

NOTE Confidence: 0.99657446

00:03:27.650 --> 00:03:28.609 I think in the early

NOTE Confidence: 0.99657446

00:03:28.609 --> 00:03:29.109 days,

NOTE Confidence: 0.9814598

00:03:30.049 --> 00:03:31.650 there were very few labs

NOTE Confidence: 0.9814598

00:03:31.650 --> 00:03:32.689 that were studying T cell

NOTE Confidence: 0.9814598

00:03:32.689 --> 00:03:34.290 exhaustion. And although we didn't

NOTE Confidence: 0.9814598

00:03:34.290 --> 00:03:34.950 know everything,

NOTE Confidence: 0.9681345

00:03:35.409 --> 00:03:36.530 I think we kind of

NOTE Confidence: 0.9681345

00:03:36.530 --> 00:03:37.750 knew what we were doing.

NOTE Confidence: 0.9681345

00:03:38.015 --> 00:03:39.555 But this has become now

NOTE Confidence: 0.9681345

00:03:39.614 --> 00:03:41.715 a very important issue for

NOTE Confidence: 0.98248106

00:03:42.095 --> 00:03:43.855 in many areas, especially in

NOTE Confidence: 0.98248106

00:03:43.855 --> 00:03:44.355 cancer.

NOTE Confidence: 0.9733391

00:03:44.815 --> 00:03:45.614 And I think so I

NOTE Confidence: 0.9733391

00:03:45.614 --> 00:03:46.834 thought I'd spend if,

NOTE Confidence: 0.986033

00:03:47.855 --> 00:03:49.235 the first five, ten minutes

NOTE Confidence: 0.986033

00:03:49.295 --> 00:03:50.415 of the talk really kind

NOTE Confidence: 0.986033

00:03:50.415 --> 00:03:51.614 of taking you through,

NOTE Confidence: 0.99973655

00:03:52.175 --> 00:03:52.915 some historical

NOTE Confidence: 0.9867934

00:03:54.310 --> 00:03:55.850 observations that were made,

NOTE Confidence: 0.9902748

00:03:56.470 --> 00:03:58.250 that really first pointed out

NOTE Confidence: 0.99446625

00:03:58.790 --> 00:03:59.290 the

NOTE Confidence: 0.97862387

00:03:59.910 --> 00:04:01.770 the phenomena that during chronic

NOTE Confidence: 0.97862387

00:04:01.830 --> 00:04:02.730 viral infections,

NOTE Confidence: 0.9475987

00:04:03.350 --> 00:04:04.310 the t cells are not

NOTE Confidence: 0.9475987

00:04:04.310 --> 00:04:05.670 very functional. Just give you

NOTE Confidence: 0.9475987

00:04:05.670 --> 00:04:06.825 just a brief,

NOTE Confidence: 0.9831765

00:04:07.445 --> 00:04:08.965 summary of that and then

NOTE Confidence: 0.9831765

00:04:08.965 --> 00:04:10.005 bring you up to date

NOTE Confidence: 0.9831765

00:04:10.005 --> 00:04:11.285 in terms of what we

NOTE Confidence: 0.9831765

00:04:11.285 --> 00:04:12.345 currently mean,

NOTE Confidence: 0.98614895

00:04:12.645 --> 00:04:13.785 by t cell exhaustion.

NOTE Confidence: 0.99507946

00:04:14.405 --> 00:04:16.005 And then I will, spend

NOTE Confidence: 0.99507946

00:04:16.005 --> 00:04:16.745 some time

NOTE Confidence: 0.95166755

00:04:17.285 --> 00:04:17.785 describing,

NOTE Confidence: 0.95783615

00:04:19.380 --> 00:04:21.080 these very critical resource,

NOTE Confidence: 0.91123044

00:04:21.460 --> 00:04:22.900 CDAT cells or the stem

NOTE Confidence: 0.91123044

00:04:22.900 --> 00:04:23.639 like cells,

NOTE Confidence: 0.91235644

00:04:23.940 --> 00:04:25.720 which maintain CD eight responses

NOTE Confidence: 0.91235644

00:04:25.860 --> 00:04:26.360 during

NOTE Confidence: 0.98634106

00:04:26.740 --> 00:04:28.120 conditions of chronic infection.

NOTE Confidence: 0.9985541

00:04:28.820 --> 00:04:30.440 After that, I'll switch to,

NOTE Confidence: 0.99002606

00:04:31.380 --> 00:04:33.435 describing our recent work with

NOTE Confidence: 0.99002606

00:04:33.435 --> 00:04:35.035 HPV positive head and neck

NOTE Confidence: 0.99002606

00:04:35.035 --> 00:04:35.535 cancer.

NOTE Confidence: 0.97438055

00:04:35.995 --> 00:04:37.195 And if there is time,

NOTE Confidence: 0.97438055

00:04:37.195 --> 00:04:37.935 I'll present,

NOTE Confidence: 0.9991748

00:04:38.235 --> 00:04:39.515 a summary of our recent

NOTE Confidence: 0.9991748

00:04:39.515 --> 00:04:40.415 work with

NOTE Confidence: 0.94153756

00:04:40.955 --> 00:04:42.635 the combination therapy of PD

NOTE Confidence: 0.94153756

00:04:42.635 --> 00:04:44.235 one plus IL two. Yeah.

NOTE Confidence: 0.94153756

00:04:44.235 --> 00:04:45.435 But if I don't, Barbara,

NOTE Confidence: 0.94153756

00:04:45.435 --> 00:04:46.555 I can just stop after

NOTE Confidence: 0.94153756

00:04:46.555 --> 00:04:47.935 the HPV one. Yep.

NOTE Confidence: 0.9117421

00:04:48.315 --> 00:04:48.815 Yeah.

NOTE Confidence: 0.8762496

00:04:50.130 --> 00:04:51.010 So the question is what

NOTE Confidence: 0.8762496

00:04:51.010 --> 00:04:52.070 is T cell exhaustion?

NOTE Confidence: 0.9360435

00:04:53.090 --> 00:04:54.770 So the history of this

NOTE Confidence: 0.9360435

00:04:54.770 --> 00:04:57.330 really was started first, I

NOTE Confidence: 0.9360435

00:04:57.330 --> 00:04:58.550 would say, in the nineteen

NOTE Confidence: 0.81345624

00:04:59.250 --> 00:04:59.750 seventies,

NOTE Confidence: 0.9994118

00:05:00.450 --> 00:05:01.590 when people

NOTE Confidence: 0.9613289

00:05:01.895 --> 00:05:03.335 who were studying mouse models

NOTE Confidence: 0.9613289

00:05:03.335 --> 00:05:04.795 of chronic viral infection,

NOTE Confidence: 0.93496275

00:05:05.175 --> 00:05:06.635 in particular from LCMV,

NOTE Confidence: 0.97364014

00:05:07.255 --> 00:05:08.955 but also from mouse hepatitis

NOTE Confidence: 0.97364014

00:05:09.015 --> 00:05:11.015 virus and a strange virus

NOTE Confidence: 0.97364014

00:05:11.015 --> 00:05:12.235 called lactate dehydrogenase

NOTE Confidence: 0.9824094

00:05:12.615 --> 00:05:13.095 virus,

NOTE Confidence: 0.9607578

00:05:13.735 --> 00:05:14.535 which is also

NOTE Confidence: 0.9420921

00:05:15.169 --> 00:05:16.290 used to be. Now nobody

NOTE Confidence: 0.9420921

00:05:16.290 --> 00:05:17.169 uses it, but was a

NOTE Confidence: 0.9420921

00:05:17.169 --> 00:05:18.550 model for chronic infection.

NOTE Confidence: 0.9857835

00:05:18.930 --> 00:05:20.230 And there were these observations

NOTE Confidence: 0.9857835

00:05:20.449 --> 00:05:20.850 that,

NOTE Confidence: 0.95790124

00:05:21.970 --> 00:05:23.589 based on functional assays,

NOTE Confidence: 0.97949266

00:05:24.050 --> 00:05:25.169 that the t cells were

NOTE Confidence: 0.97949266

00:05:25.169 --> 00:05:26.930 not as responsive as one

NOTE Confidence: 0.97949266

00:05:26.930 --> 00:05:27.589 would expect.

NOTE Confidence: 0.9513587

00:05:28.635 --> 00:05:30.395 And interestingly, at that time,

NOTE Confidence: 0.9513587

00:05:30.395 --> 00:05:31.055 the major

NOTE Confidence: 0.9808876

00:05:31.835 --> 00:05:32.955 t cell assay that was

NOTE Confidence: 0.9808876

00:05:32.955 --> 00:05:34.714 used was chromium release, chromium

NOTE Confidence: 0.9808876

00:05:34.714 --> 00:05:36.075 fifty one release. And what

NOTE Confidence: 0.9808876

00:05:36.075 --> 00:05:37.435 was noticed was that when

NOTE Confidence: 0.9808876

00:05:37.435 --> 00:05:38.095 you took

NOTE Confidence: 0.97521156

00:05:38.555 --> 00:05:40.075 t cells or you took

NOTE Confidence: 0.97521156

00:05:40.075 --> 00:05:40.975 spleen cells

NOTE Confidence: 0.9922098

00:05:41.580 --> 00:05:43.419 from, during the acute phase

NOTE Confidence: 0.9922098

00:05:43.419 --> 00:05:44.160 of infection,

NOTE Confidence: 0.9632171

00:05:45.180 --> 00:05:46.460 there was good killing of

NOTE Confidence: 0.9632171

00:05:46.460 --> 00:05:48.139 the target cells, which these

NOTE Confidence: 0.9632171

00:05:48.139 --> 00:05:49.580 would be virally infected target

NOTE Confidence: 0.9632171

00:05:49.580 --> 00:05:51.260 cells. But when you took

NOTE Confidence: 0.9632171

00:05:51.260 --> 00:05:52.699 spleen cells from a chronically

NOTE Confidence: 0.9632171

00:05:52.699 --> 00:05:54.800 infected mouse, there was minimal

NOTE Confidence: 0.9277655

00:05:55.205 --> 00:05:56.025 chromium release,

NOTE Confidence: 0.9561167

00:05:56.325 --> 00:05:57.925 that is minimum killing. That

NOTE Confidence: 0.9561167

00:05:57.925 --> 00:05:59.705 really was the first beginning

NOTE Confidence: 0.9512879

00:06:00.085 --> 00:06:01.205 of those. And, of course,

NOTE Confidence: 0.9512879

00:06:01.205 --> 00:06:03.305 later on, cytokine assays

NOTE Confidence: 0.8597796

00:06:03.685 --> 00:06:05.305 also confirmed that.

NOTE Confidence: 0.9703038

00:06:06.085 --> 00:06:08.005 And then these observations made

NOTE Confidence: 0.9703038

00:06:08.005 --> 00:06:10.005 in mice, chronic infections were

NOTE Confidence: 0.9703038

00:06:10.005 --> 00:06:10.985 quickly extended

NOTE Confidence: 0.93981814

00:06:11.580 --> 00:06:13.500 to several human chronic viral

NOTE Confidence: 0.93981814

00:06:13.500 --> 00:06:14.000 infections.

NOTE Confidence: 0.98302835

00:06:14.940 --> 00:06:15.680 To HBV,

NOTE Confidence: 0.95284057

00:06:15.980 --> 00:06:17.180 people again found that,

NOTE Confidence: 0.83842546

00:06:19.339 --> 00:06:21.120 people people who are HBV

NOTE Confidence: 0.83842546

00:06:21.260 --> 00:06:23.100 carriers, again, it was difficult

NOTE Confidence: 0.83842546

00:06:23.100 --> 00:06:24.140 to detect good c d

NOTE Confidence: 0.83842546

00:06:24.140 --> 00:06:25.339 a t cell responses in

NOTE Confidence: 0.83842546

00:06:25.339 --> 00:06:27.185 the blood. But sim similar

NOTE Confidence: 0.83842546

00:06:27.245 --> 00:06:28.224 with HCV,

NOTE Confidence: 0.9319864

00:06:29.164 --> 00:06:30.625 some of the herpes viruses,

NOTE Confidence: 0.9319864

00:06:30.685 --> 00:06:32.525 and in particular HIV. Some

NOTE Confidence: 0.9319864

00:06:32.525 --> 00:06:34.224 of the early beautiful work

NOTE Confidence: 0.9319864

00:06:34.284 --> 00:06:35.164 done in human,

NOTE Confidence: 0.97207546

00:06:36.205 --> 00:06:38.384 infection showing, T cell dysfunction

NOTE Confidence: 0.97207546

00:06:38.525 --> 00:06:39.745 actually was in HIV.

NOTE Confidence: 0.8934351

00:06:40.750 --> 00:06:41.410 And then,

NOTE Confidence: 0.9438281

00:06:42.350 --> 00:06:43.650 we were at this stage.

NOTE Confidence: 0.9297236

00:06:44.350 --> 00:06:45.970 The question still remained.

NOTE Confidence: 0.9138325

00:06:48.669 --> 00:06:50.430 Is the decreased CDF T

NOTE Confidence: 0.9138325

00:06:50.430 --> 00:06:51.169 cell response

NOTE Confidence: 0.99021584

00:06:51.964 --> 00:06:53.085 that we are seeing by

NOTE Confidence: 0.99021584

00:06:53.085 --> 00:06:55.005 some functional assays, is this

NOTE Confidence: 0.99021584

00:06:55.005 --> 00:06:55.985 due to deletion

NOTE Confidence: 0.9623457

00:06:56.925 --> 00:06:58.545 of the virus specific cells,

NOTE Confidence: 0.9572462

00:06:59.565 --> 00:07:00.765 or are the t cells

NOTE Confidence: 0.9572462

00:07:00.765 --> 00:07:01.585 still present

NOTE Confidence: 0.99769616

00:07:02.125 --> 00:07:03.345 and truly dysfunctional?

NOTE Confidence: 0.91531783

00:07:04.210 --> 00:07:05.330 And this is an was

NOTE Confidence: 0.91531783

00:07:05.330 --> 00:07:07.190 an important question because often,

NOTE Confidence: 0.9810903

00:07:07.569 --> 00:07:08.610 it was thought that when

NOTE Confidence: 0.9810903

00:07:08.610 --> 00:07:09.590 we don't detect

NOTE Confidence: 0.971424

00:07:10.050 --> 00:07:12.050 a t cell response, that

NOTE Confidence: 0.971424

00:07:12.050 --> 00:07:13.569 either the t cell response

NOTE Confidence: 0.971424

00:07:13.569 --> 00:07:14.629 was never generated

NOTE Confidence: 0.96610576

00:07:15.169 --> 00:07:16.129 or the t cells had

NOTE Confidence: 0.96610576

00:07:16.129 --> 00:07:16.870 been deleted.

NOTE Confidence: 0.9758374

00:07:17.815 --> 00:07:19.255 And we should thank Mark

NOTE Confidence: 0.9758374

00:07:19.255 --> 00:07:20.395 Davis for the

NOTE Confidence: 0.9884499

00:07:20.775 --> 00:07:22.455 development of the MHC tetramer

NOTE Confidence: 0.9884499

00:07:22.455 --> 00:07:22.955 technology

NOTE Confidence: 0.94578606

00:07:23.735 --> 00:07:24.775 in this paper by John

NOTE Confidence: 0.94578606

00:07:24.775 --> 00:07:25.275 Altman,

NOTE Confidence: 0.68574286

00:07:25.575 --> 00:07:27.115 Michael, McKheiser, Williams,

NOTE Confidence: 0.9671697

00:07:27.655 --> 00:07:29.415 and Davis in Science in

NOTE Confidence: 0.9671697

00:07:29.415 --> 00:07:31.170 nineteen ninety six. This was

NOTE Confidence: 0.9671697

00:07:31.170 --> 00:07:32.690 a major breakthrough because this

NOTE Confidence: 0.9671697

00:07:32.690 --> 00:07:34.370 allowed us to, for the

NOTE Confidence: 0.9671697

00:07:34.370 --> 00:07:35.190 first time,

NOTE Confidence: 0.99246824

00:07:35.570 --> 00:07:37.350 to actually physically visualize,

NOTE Confidence: 0.91015047

00:07:38.050 --> 00:07:39.010 the t cell that we

NOTE Confidence: 0.91015047

00:07:39.010 --> 00:07:39.670 were studying.

NOTE Confidence: 0.91118366

00:07:40.050 --> 00:07:41.490 Not just a functional asset,

NOTE Confidence: 0.91118366

00:07:41.490 --> 00:07:42.450 but now actually you could

NOTE Confidence: 0.91118366

00:07:42.450 --> 00:07:43.030 see it.

NOTE Confidence: 0.95660424

00:07:43.330 --> 00:07:44.790 And this allowed actually

NOTE Confidence: 0.9282836

00:07:45.134 --> 00:07:46.595 our lab and Rob Zinkernagel's

NOTE Confidence: 0.9282836

00:07:46.895 --> 00:07:48.175 lab, and these were the

NOTE Confidence: 0.9282836

00:07:48.175 --> 00:07:50.414 papers published by Alan Zayak,

NOTE Confidence: 0.9282836

00:07:50.414 --> 00:07:51.535 who was a postdoc in

NOTE Confidence: 0.9282836

00:07:51.535 --> 00:07:53.134 the lab, and Gallimore was

NOTE Confidence: 0.9282836

00:07:53.134 --> 00:07:54.974 in Rob Zinkernagel's lab to

NOTE Confidence: 0.9282836

00:07:54.974 --> 00:07:57.395 show, that when you compare

NOTE Confidence: 0.9282836

00:07:57.534 --> 00:07:58.914 an acute infection,

NOTE Confidence: 0.7968294

00:07:59.330 --> 00:08:01.250 LCMV infection with the chronic

NOTE Confidence: 0.7968294

00:08:01.250 --> 00:08:02.310 LCMV infection,

NOTE Confidence: 0.9921693

00:08:03.410 --> 00:08:04.390 in both instances,

NOTE Confidence: 0.96885395

00:08:04.930 --> 00:08:06.770 you find tetramer positive cells.

NOTE Confidence: 0.96885395

00:08:06.770 --> 00:08:07.670 They are there.

NOTE Confidence: 0.9980638

00:08:08.050 --> 00:08:09.670 But when you do functional

NOTE Confidence: 0.9980638

00:08:09.730 --> 00:08:10.230 assays

NOTE Confidence: 0.87575597

00:08:10.770 --> 00:08:12.950 like ICS assay into cytokine

NOTE Confidence: 0.87575597

00:08:13.170 --> 00:08:14.710 or Elispod, then the functionality

NOTE Confidence: 0.97558105

00:08:15.465 --> 00:08:16.585 of those cells is much

NOTE Confidence: 0.97558105

00:08:16.585 --> 00:08:18.745 less. K? And this was

NOTE Confidence: 0.97558105

00:08:18.745 --> 00:08:20.365 the the clear first demonstration

NOTE Confidence: 0.97359973

00:08:20.985 --> 00:08:22.285 that the cells are present,

NOTE Confidence: 0.997483

00:08:22.825 --> 00:08:23.805 but that they

NOTE Confidence: 0.9170381

00:08:24.185 --> 00:08:25.785 lack or are not as

NOTE Confidence: 0.9170381

00:08:25.785 --> 00:08:27.625 functional as the memory cells

NOTE Confidence: 0.9170381

00:08:27.625 --> 00:08:29.065 or effector cells you get

NOTE Confidence: 0.9170381

00:08:29.065 --> 00:08:30.365 during acute infections.

NOTE Confidence: 0.88979685

00:08:31.000 --> 00:08:32.040 And, of course, this is

NOTE Confidence: 0.88979685

00:08:32.040 --> 00:08:33.740 very very quickly extended to

NOTE Confidence: 0.88979685

00:08:33.800 --> 00:08:35.420 human chronic viral infections

NOTE Confidence: 0.9969351

00:08:35.720 --> 00:08:37.260 and and to cancer.

NOTE Confidence: 0.9763739

00:08:39.240 --> 00:08:40.220 So then the

NOTE Confidence: 0.9701909

00:08:41.000 --> 00:08:42.679 next question that was addressed

NOTE Confidence: 0.9701909

00:08:42.679 --> 00:08:43.960 by us and by many

NOTE Confidence: 0.9701909

00:08:43.960 --> 00:08:45.320 other people in the in

NOTE Confidence: 0.9701909

00:08:45.320 --> 00:08:47.025 the in the field was,

NOTE Confidence: 0.9701909

00:08:47.025 --> 00:08:48.545 what is the gene expression

NOTE Confidence: 0.9701909

00:08:48.545 --> 00:08:49.045 profile

NOTE Confidence: 0.99956906

00:08:49.425 --> 00:08:50.165 of these

NOTE Confidence: 0.9980253

00:08:50.545 --> 00:08:51.765 exhausted cells

NOTE Confidence: 0.9699912

00:08:52.145 --> 00:08:54.065 versus the acute cells? It

NOTE Confidence: 0.9699912

00:08:54.065 --> 00:08:55.265 was shown that, actually, they're

NOTE Confidence: 0.9699912

00:08:55.265 --> 00:08:56.325 strikingly different.

NOTE Confidence: 0.95312154

00:08:56.705 --> 00:08:58.225 The gene expression program of

NOTE Confidence: 0.95312154

00:08:58.225 --> 00:09:00.325 functional memory cells and exhausted

NOTE Confidence: 0.95312154

00:09:00.385 --> 00:09:02.110 cells is very different. This

NOTE Confidence: 0.95312154

00:09:02.110 --> 00:09:03.490 was work that John Biri

NOTE Confidence: 0.95312154

00:09:03.630 --> 00:09:04.130 did

NOTE Confidence: 0.9915459

00:09:04.670 --> 00:09:05.970 in in two thousand seven.

NOTE Confidence: 0.9915459

00:09:06.190 --> 00:09:07.550 Many other people followed up

NOTE Confidence: 0.9915459

00:09:07.550 --> 00:09:08.750 on it, extended it to

NOTE Confidence: 0.9915459

00:09:08.750 --> 00:09:10.770 humans. It was also shown

NOTE Confidence: 0.9915459

00:09:10.990 --> 00:09:12.910 that, PD one is a

NOTE Confidence: 0.9915459

00:09:12.910 --> 00:09:13.730 major regulator

NOTE Confidence: 0.9412406

00:09:14.350 --> 00:09:16.130 of the CDT cell exhaustion.

NOTE Confidence: 0.9940854

00:09:18.275 --> 00:09:19.315 And so at this time,

NOTE Confidence: 0.9940854

00:09:19.315 --> 00:09:20.995 basically, we knew that the

NOTE Confidence: 0.9940854

00:09:20.995 --> 00:09:22.215 gene expression profile

NOTE Confidence: 0.9998927

00:09:22.835 --> 00:09:23.495 of the

NOTE Confidence: 0.9987992

00:09:24.035 --> 00:09:26.035 exhausted cells was very different

NOTE Confidence: 0.9987992

00:09:26.035 --> 00:09:27.095 from what you see,

NOTE Confidence: 0.99955475

00:09:27.475 --> 00:09:28.934 in terms of memory cells.

NOTE Confidence: 0.9425588

00:09:29.280 --> 00:09:30.160 It was known that there

NOTE Confidence: 0.9425588

00:09:30.160 --> 00:09:31.600 are PD-one and also many

NOTE Confidence: 0.9425588

00:09:31.600 --> 00:09:32.100 other,

NOTE Confidence: 0.9417739

00:09:33.200 --> 00:09:34.900 inhibitory receptors that regulate,

NOTE Confidence: 0.8447542

00:09:35.680 --> 00:09:37.060 T cell, function.

NOTE Confidence: 0.998628

00:09:38.000 --> 00:09:38.500 But

NOTE Confidence: 0.94925416

00:09:38.960 --> 00:09:41.040 what was not known until

NOTE Confidence: 0.94925416

00:09:41.040 --> 00:09:42.160 about five years or so

NOTE Confidence: 0.94925416

00:09:42.480 --> 00:09:44.500 until twenty sixteen or so

NOTE Confidence: 0.9951065

00:09:44.885 --> 00:09:46.425 was really a clear definition

NOTE Confidence: 0.9998682

00:09:47.365 --> 00:09:48.184 of the different

NOTE Confidence: 0.9966578

00:09:49.365 --> 00:09:51.304 subsets which are there. So

NOTE Confidence: 0.9966578

00:09:51.445 --> 00:09:53.445 exhaustion wasn't a single cell

NOTE Confidence: 0.9966578

00:09:53.445 --> 00:09:54.425 that was functionally

NOTE Confidence: 0.7600874

00:09:54.804 --> 00:09:55.304 exhausted.

NOTE Confidence: 0.9149331

00:09:55.765 --> 00:09:56.505 But, basically,

NOTE Confidence: 0.99959785

00:09:56.964 --> 00:09:59.225 there was very interesting heterogeneity

NOTE Confidence: 0.99873835

00:10:00.590 --> 00:10:01.090 of

NOTE Confidence: 0.9917865

00:10:01.550 --> 00:10:03.070 the pool of exhausted t

NOTE Confidence: 0.9917865

00:10:03.070 --> 00:10:03.570 cells,

NOTE Confidence: 0.9960415

00:10:04.110 --> 00:10:05.330 in terms of the functionality.

NOTE Confidence: 0.9989255

00:10:06.350 --> 00:10:06.850 So

NOTE Confidence: 0.9954124

00:10:07.870 --> 00:10:09.070 this was work that was

NOTE Confidence: 0.9954124

00:10:09.070 --> 00:10:09.570 done

NOTE Confidence: 0.8240775

00:10:10.830 --> 00:10:12.190 in my lab by Sejgan

NOTE Confidence: 0.8240775

00:10:12.190 --> 00:10:13.730 I'm and also Uttschneider

NOTE Confidence: 0.9644346

00:10:14.110 --> 00:10:15.470 published a paper around the

NOTE Confidence: 0.9644346

00:10:15.470 --> 00:10:16.675 same at the same

NOTE Confidence: 0.88712955

00:10:17.054 --> 00:10:18.095 time, working with,

NOTE Confidence: 0.98854476

00:10:19.054 --> 00:10:20.514 Dietmar and and

NOTE Confidence: 0.6088581

00:10:20.815 --> 00:10:21.714 Werner Held.

NOTE Confidence: 0.959996

00:10:22.095 --> 00:10:23.135 And there was also a

NOTE Confidence: 0.959996

00:10:23.135 --> 00:10:24.755 paper by Lin and Yee.

NOTE Confidence: 0.959996

00:10:25.054 --> 00:10:26.334 These three papers came out

NOTE Confidence: 0.959996

00:10:26.334 --> 00:10:27.394 in twenty sixteen,

NOTE Confidence: 0.97381926

00:10:28.095 --> 00:10:29.154 and they defined,

NOTE Confidence: 0.9456393

00:10:29.670 --> 00:10:31.029 what I'll refer to as

NOTE Confidence: 0.9456393

00:10:31.029 --> 00:10:33.290 the stem like CDAT cells.

NOTE Confidence: 0.8730438

00:10:34.309 --> 00:10:35.910 These cells are also often

NOTE Confidence: 0.8730438

00:10:35.910 --> 00:10:38.230 referred to as, as t

NOTE Confidence: 0.8730438

00:10:38.230 --> 00:10:39.770 pect cells as

NOTE Confidence: 0.9667477

00:10:40.309 --> 00:10:42.230 standing for precursors of exhausted

NOTE Confidence: 0.9667477

00:10:42.230 --> 00:10:42.730 cells.

NOTE Confidence: 0.9672708

00:10:43.145 --> 00:10:44.045 And there are several

NOTE Confidence: 0.961292

00:10:44.665 --> 00:10:46.345 interesting features of this cell.

NOTE Confidence: 0.961292

00:10:46.345 --> 00:10:48.365 And, actually, my talk today

NOTE Confidence: 0.961292

00:10:48.425 --> 00:10:49.945 really is about this cell.

NOTE Confidence: 0.961292

00:10:49.945 --> 00:10:51.645 K? And I'll tell you

NOTE Confidence: 0.961292

00:10:51.865 --> 00:10:53.065 more about this also in

NOTE Confidence: 0.961292

00:10:53.065 --> 00:10:54.365 the context of HPV.

NOTE Confidence: 0.97836787

00:10:55.800 --> 00:10:57.100 So there were very unusual

NOTE Confidence: 0.97836787

00:10:57.160 --> 00:10:58.600 features of this cell. The

NOTE Confidence: 0.97836787

00:10:58.600 --> 00:11:00.120 first unusual feature was that

NOTE Confidence: 0.97836787

00:11:00.120 --> 00:11:00.860 even though

NOTE Confidence: 0.97388315

00:11:01.400 --> 00:11:02.059 this is

NOTE Confidence: 0.99245286

00:11:02.840 --> 00:11:03.960 in the conditions of a

NOTE Confidence: 0.99245286

00:11:03.960 --> 00:11:05.800 chronic infection, these cells are

NOTE Confidence: 0.99245286

00:11:05.800 --> 00:11:06.780 mostly quiescent.

NOTE Confidence: 0.9747804

00:11:07.835 --> 00:11:10.155 They're not rapidly dividing. There's

NOTE Confidence: 0.9747804

00:11:10.155 --> 00:11:11.455 some slow self renewal.

NOTE Confidence: 0.9649551

00:11:13.755 --> 00:11:16.155 And, also, their location was

NOTE Confidence: 0.9649551

00:11:16.155 --> 00:11:16.655 interesting.

NOTE Confidence: 0.9751074

00:11:17.115 --> 00:11:18.235 Even when you have a

NOTE Confidence: 0.9751074

00:11:18.235 --> 00:11:19.950 situation where virus is in

NOTE Confidence: 0.9751074

00:11:20.270 --> 00:11:22.350 multiple tissues with lymphoid and

NOTE Confidence: 0.9751074

00:11:22.350 --> 00:11:24.670 non lymphoid, these cells tend

NOTE Confidence: 0.9751074

00:11:24.670 --> 00:11:25.410 to be mostly

NOTE Confidence: 0.99212295

00:11:25.790 --> 00:11:26.929 in lymphoid tissues.

NOTE Confidence: 0.99826586

00:11:27.390 --> 00:11:29.010 And within the lymphoid tissues,

NOTE Confidence: 0.9544717

00:11:29.550 --> 00:11:30.590 they are in the t

NOTE Confidence: 0.9544717

00:11:30.590 --> 00:11:32.270 cell zones. And that's an

NOTE Confidence: 0.9544717

00:11:32.270 --> 00:11:33.950 interesting point because these cells

NOTE Confidence: 0.9544717

00:11:33.950 --> 00:11:35.650 express CXCR five,

NOTE Confidence: 0.9992717

00:11:36.084 --> 00:11:37.545 but they still don't

NOTE Confidence: 0.94343805

00:11:38.005 --> 00:11:39.045 go to where the b

NOTE Confidence: 0.94343805

00:11:39.045 --> 00:11:41.365 cells are. There's remaining more

NOTE Confidence: 0.94343805

00:11:41.365 --> 00:11:42.325 where the t cells are

NOTE Confidence: 0.94343805

00:11:42.325 --> 00:11:43.765 in from. So they are

NOTE Confidence: 0.94343805

00:11:43.765 --> 00:11:44.725 in the t cell zone,

NOTE Confidence: 0.948784

00:11:46.565 --> 00:11:48.964 and they're also resident. That

NOTE Confidence: 0.948784

00:11:48.964 --> 00:11:50.105 is they're not circulating.

NOTE Confidence: 0.9867752

00:11:50.760 --> 00:11:51.900 So this is the population

NOTE Confidence: 0.9867752

00:11:52.120 --> 00:11:53.100 that's within,

NOTE Confidence: 0.9832792

00:11:54.200 --> 00:11:55.480 the spleens and lymph nodes

NOTE Confidence: 0.9832792

00:11:55.480 --> 00:11:57.100 of a chronically infected mouse

NOTE Confidence: 0.9832792

00:11:57.160 --> 00:11:58.600 and has has been shown

NOTE Confidence: 0.9832792

00:11:58.600 --> 00:12:00.600 in humans. They're also in

NOTE Confidence: 0.9832792

00:12:00.600 --> 00:12:01.260 the tumor,

NOTE Confidence: 0.83643055

00:12:02.040 --> 00:12:02.540 environment.

NOTE Confidence: 0.96797925

00:12:02.920 --> 00:12:04.760 But, again, they are mostly,

NOTE Confidence: 0.8810461

00:12:06.504 --> 00:12:08.105 not proliferating and they are

NOTE Confidence: 0.8810461

00:12:08.105 --> 00:12:08.925 they are quiescent

NOTE Confidence: 0.803684

00:12:10.024 --> 00:12:11.165 and also resident.

NOTE Confidence: 0.8956081

00:12:12.264 --> 00:12:13.144 So what do these cells

NOTE Confidence: 0.8956081

00:12:13.144 --> 00:12:14.264 express? They, of course, express

NOTE Confidence: 0.8956081

00:12:14.264 --> 00:12:15.944 PD one because PD one

NOTE Confidence: 0.8956081

00:12:15.944 --> 00:12:16.444 as

NOTE Confidence: 0.97124034

00:12:17.304 --> 00:12:18.504 has been shown by many

NOTE Confidence: 0.97124034

00:12:18.504 --> 00:12:19.004 people

NOTE Confidence: 0.97880524

00:12:19.490 --> 00:12:20.690 is a marker that comes

NOTE Confidence: 0.97880524

00:12:20.690 --> 00:12:22.610 up upon TCR stimulation. If

NOTE Confidence: 0.97880524

00:12:22.610 --> 00:12:23.649 you take a naive T

NOTE Confidence: 0.97880524

00:12:23.649 --> 00:12:24.149 cell,

NOTE Confidence: 0.9510312

00:12:24.610 --> 00:12:25.990 you stimulate it

NOTE Confidence: 0.96929044

00:12:26.529 --> 00:12:27.750 in vivo or

NOTE Confidence: 0.92539775

00:12:28.370 --> 00:12:29.889 or in vitro within twenty

NOTE Confidence: 0.92539775

00:12:29.889 --> 00:12:30.929 four hours, p d one

NOTE Confidence: 0.92539775

00:12:30.929 --> 00:12:32.775 comes up. It's a marker

NOTE Confidence: 0.92539775

00:12:32.775 --> 00:12:34.375 that comes up immediately upon

NOTE Confidence: 0.92539775

00:12:34.375 --> 00:12:36.455 upon TCL activation. So these

NOTE Confidence: 0.92539775

00:12:36.455 --> 00:12:37.975 cells are seeing antigen. They're

NOTE Confidence: 0.92539775

00:12:37.975 --> 00:12:39.175 p they're p d one

NOTE Confidence: 0.92539775

00:12:39.175 --> 00:12:39.675 positive.

NOTE Confidence: 0.98261863

00:12:40.615 --> 00:12:42.075 But this stem like population

NOTE Confidence: 0.98261863

00:12:42.215 --> 00:12:44.155 also expresses TCF one

NOTE Confidence: 0.8446517

00:12:44.480 --> 00:12:46.260 and expresses BCL six,

NOTE Confidence: 0.9512468

00:12:47.440 --> 00:12:48.720 has high levels of post

NOTE Confidence: 0.9512468

00:12:48.720 --> 00:12:49.700 stimulatory molecules

NOTE Confidence: 0.8449009

00:12:50.720 --> 00:12:52.500 other than PD one and,

NOTE Confidence: 0.95663106

00:12:54.000 --> 00:12:55.200 and a little bit of,

NOTE Confidence: 0.95663106

00:12:55.440 --> 00:12:56.720 TIGIT that doesn't have too

NOTE Confidence: 0.95663106

00:12:56.720 --> 00:12:58.500 many other inhibitory receptors,

NOTE Confidence: 0.9960263

00:12:58.800 --> 00:12:59.540 these cells.

NOTE Confidence: 0.998387

00:13:02.054 --> 00:13:03.595 They have no effector molecules.

NOTE Confidence: 0.9873335

00:13:05.415 --> 00:13:07.255 They express interesting chemokines and

NOTE Confidence: 0.9873335

00:13:07.255 --> 00:13:08.235 chemokine receptors.

NOTE Confidence: 0.9734014

00:13:09.415 --> 00:13:10.695 They have CXCL five, so

NOTE Confidence: 0.9734014

00:13:10.695 --> 00:13:12.315 they respond to CXCL thirteen.

NOTE Confidence: 0.9734014

00:13:12.570 --> 00:13:14.090 But they also have sufficient

NOTE Confidence: 0.9734014

00:13:14.090 --> 00:13:16.110 amounts of, CCR seven

NOTE Confidence: 0.997886

00:13:16.570 --> 00:13:18.089 that they can respond to,

NOTE Confidence: 0.99531996

00:13:18.570 --> 00:13:20.510 CCL nineteen and twenty one.

NOTE Confidence: 0.9830738

00:13:20.970 --> 00:13:23.450 They express interesting chemokines that

NOTE Confidence: 0.9830738

00:13:23.450 --> 00:13:25.470 bring DCs around them.

NOTE Confidence: 0.9821285

00:13:25.804 --> 00:13:26.605 They're one of the few

NOTE Confidence: 0.9821285

00:13:26.605 --> 00:13:28.545 cells that express XCL one.

NOTE Confidence: 0.9821285

00:13:28.845 --> 00:13:30.144 XCL one attracts,

NOTE Confidence: 0.90039295

00:13:30.524 --> 00:13:32.384 CDC one. That's the XCLP

NOTE Confidence: 0.90039295

00:13:32.444 --> 00:13:33.725 positive DCs, so they are

NOTE Confidence: 0.90039295

00:13:33.725 --> 00:13:36.045 right, next to, so, basically,

NOTE Confidence: 0.90039295

00:13:36.045 --> 00:13:37.324 they've they have a nice

NOTE Confidence: 0.90039295

00:13:37.324 --> 00:13:39.005 niche that they've surrounded themselves

NOTE Confidence: 0.90039295

00:13:39.005 --> 00:13:39.505 with.

NOTE Confidence: 0.9977851

00:13:40.290 --> 00:13:41.890 And once and what these

NOTE Confidence: 0.9977851

00:13:41.890 --> 00:13:43.490 cells are doing is that

NOTE Confidence: 0.9977851

00:13:43.490 --> 00:13:44.309 at any

NOTE Confidence: 0.9451051

00:13:44.850 --> 00:13:46.230 in a slow rate,

NOTE Confidence: 0.98952836

00:13:46.610 --> 00:13:47.990 continuously, they're generating

NOTE Confidence: 0.9666517

00:13:48.690 --> 00:13:50.770 these transitory effector cells. So

NOTE Confidence: 0.9666517

00:13:50.770 --> 00:13:52.070 the step in this differentiation

NOTE Confidence: 0.9666517

00:13:52.210 --> 00:13:54.390 is downregulation of TCF one,

NOTE Confidence: 0.81911945

00:13:54.865 --> 00:13:56.885 up regulation of TIM3, TBET,

NOTE Confidence: 0.81911945

00:13:56.945 --> 00:13:57.845 they start proliferating,

NOTE Confidence: 0.98809224

00:13:59.025 --> 00:14:00.325 express effector molecules

NOTE Confidence: 0.875534

00:14:01.025 --> 00:14:02.385 and go out in the

NOTE Confidence: 0.875534

00:14:02.385 --> 00:14:02.885 circulation.

NOTE Confidence: 0.8733257

00:14:04.545 --> 00:14:06.405 And then eventually these cells

NOTE Confidence: 0.8733257

00:14:06.465 --> 00:14:07.205 will get

NOTE Confidence: 0.9322516

00:14:07.740 --> 00:14:09.100 what we call and others

NOTE Confidence: 0.9322516

00:14:09.100 --> 00:14:10.559 have called the termally differentiated,

NOTE Confidence: 0.9205704

00:14:11.500 --> 00:14:13.920 cells with minimal proliferative capacity.

NOTE Confidence: 0.9994629

00:14:14.380 --> 00:14:15.679 So if you look at

NOTE Confidence: 0.9705928

00:14:16.059 --> 00:14:16.780 to go back to my

NOTE Confidence: 0.9705928

00:14:16.780 --> 00:14:18.000 question, what is exhaustion?

NOTE Confidence: 0.9467575

00:14:18.540 --> 00:14:19.680 So, basically, exhaustion

NOTE Confidence: 0.99880475

00:14:20.060 --> 00:14:21.340 is all three of these

NOTE Confidence: 0.99880475

00:14:21.340 --> 00:14:23.120 cells at any given time.

NOTE Confidence: 0.996636

00:14:23.555 --> 00:14:24.995 The ratios of these three

NOTE Confidence: 0.996636

00:14:24.995 --> 00:14:25.735 can differ.

NOTE Confidence: 0.88491356

00:14:26.755 --> 00:14:28.435 Stem like cells usually are

NOTE Confidence: 0.88491356

00:14:28.435 --> 00:14:29.654 a very small percentage

NOTE Confidence: 0.9708474

00:14:30.035 --> 00:14:31.235 and only in the lymphoid

NOTE Confidence: 0.9708474

00:14:31.235 --> 00:14:32.755 tissue. They'll be about maybe

NOTE Confidence: 0.9708474

00:14:32.755 --> 00:14:34.194 ten to twenty percent in

NOTE Confidence: 0.9708474

00:14:34.194 --> 00:14:35.255 the lymphoid tissue.

NOTE Confidence: 0.9800755

00:14:35.610 --> 00:14:36.570 If you go to non

NOTE Confidence: 0.9800755

00:14:36.570 --> 00:14:38.670 lymphoid tissues, there's hardly any,

NOTE Confidence: 0.9800755

00:14:38.890 --> 00:14:39.930 less than one to five

NOTE Confidence: 0.9800755

00:14:39.930 --> 00:14:40.430 percent.

NOTE Confidence: 0.9165982

00:14:41.769 --> 00:14:43.690 Affector cells usually are also

NOTE Confidence: 0.9165982

00:14:43.690 --> 00:14:44.829 on the lower side,

NOTE Confidence: 0.97997093

00:14:45.610 --> 00:14:46.730 not a large number of

NOTE Confidence: 0.97997093

00:14:46.730 --> 00:14:47.230 them.

NOTE Confidence: 0.97067976

00:14:47.705 --> 00:14:49.145 Can be about twenty percent,

NOTE Confidence: 0.97067976

00:14:49.145 --> 00:14:51.065 ten percent, especially in a

NOTE Confidence: 0.97067976

00:14:51.065 --> 00:14:52.985 established long term chronic infection.

NOTE Confidence: 0.97067976

00:14:52.985 --> 00:14:54.365 They're only about ten percent.

NOTE Confidence: 0.9590094

00:14:55.625 --> 00:14:56.985 Most of it are these

NOTE Confidence: 0.9590094

00:14:56.985 --> 00:14:59.165 more differentiated exhausted cells.

NOTE Confidence: 0.97609854

00:14:59.465 --> 00:15:00.905 So when we and others

NOTE Confidence: 0.97609854

00:15:00.905 --> 00:15:02.105 in the past were looking

NOTE Confidence: 0.97609854

00:15:02.105 --> 00:15:03.150 at all three of these,

NOTE Confidence: 0.97609854

00:15:03.230 --> 00:15:03.950 because if you use a

NOTE Confidence: 0.97609854

00:15:03.950 --> 00:15:04.450 tetramer,

NOTE Confidence: 0.9378199

00:15:04.990 --> 00:15:06.190 you sought all three of

NOTE Confidence: 0.9378199

00:15:06.190 --> 00:15:06.850 these populations.

NOTE Confidence: 0.99021006

00:15:07.310 --> 00:15:08.610 We were mostly measuring

NOTE Confidence: 0.8981166

00:15:09.070 --> 00:15:10.690 this cell in terms of

NOTE Confidence: 0.8981166

00:15:10.910 --> 00:15:12.370 the image that we had.

NOTE Confidence: 0.93024874

00:15:12.750 --> 00:15:14.190 But there are clearly cells

NOTE Confidence: 0.93024874

00:15:14.190 --> 00:15:15.970 there which are too important

NOTE Confidence: 0.94451475

00:15:16.350 --> 00:15:17.010 and functional,

NOTE Confidence: 0.97000873

00:15:18.125 --> 00:15:19.645 and you have this effector

NOTE Confidence: 0.97000873

00:15:19.645 --> 00:15:20.865 cell that's being generated,

NOTE Confidence: 0.99444014

00:15:21.404 --> 00:15:22.925 and then you have this,

NOTE Confidence: 0.99444014

00:15:23.245 --> 00:15:24.145 terminal differentiation.

NOTE Confidence: 0.9996017

00:15:24.765 --> 00:15:25.805 So the answer to the

NOTE Confidence: 0.9996017

00:15:25.805 --> 00:15:26.865 question is that

NOTE Confidence: 0.9236147

00:15:27.325 --> 00:15:28.925 T cell exhaustion is actually

NOTE Confidence: 0.9236147

00:15:28.925 --> 00:15:29.425 a

NOTE Confidence: 0.9994757

00:15:29.805 --> 00:15:31.265 ongoing immune response.

NOTE Confidence: 0.9535675

00:15:32.150 --> 00:15:34.570 It is tightly, highly regulated

NOTE Confidence: 0.8505432

00:15:35.350 --> 00:15:36.810 by inhibitory receptors

NOTE Confidence: 0.96218586

00:15:37.350 --> 00:15:38.810 and also by the immunosuppressive

NOTE Confidence: 0.97462976

00:15:39.990 --> 00:15:42.330 myeloid cells that surround that.

NOTE Confidence: 0.97462976

00:15:42.550 --> 00:15:43.290 So it's

NOTE Confidence: 0.99640214

00:15:43.750 --> 00:15:45.610 suppression by the myeloid cells,

NOTE Confidence: 0.91991365

00:15:46.574 --> 00:15:48.014 inhibitory receptors on the t

NOTE Confidence: 0.91991365

00:15:48.014 --> 00:15:50.254 cells, plus probably some others

NOTE Confidence: 0.91991365

00:15:50.254 --> 00:15:52.574 keys inhibitory cytokines that are

NOTE Confidence: 0.91991365

00:15:52.574 --> 00:15:54.254 doing it. But it's active.

NOTE Confidence: 0.91991365

00:15:54.254 --> 00:15:55.875 It's active, and it's ongoing

NOTE Confidence: 0.9289439

00:15:56.334 --> 00:15:57.875 because you're always generating

NOTE Confidence: 0.98855203

00:15:58.254 --> 00:15:59.615 a low number of effector

NOTE Confidence: 0.98855203

00:15:59.615 --> 00:16:01.055 cells from that stem like

NOTE Confidence: 0.98855203

00:16:01.055 --> 00:16:01.555 population.

NOTE Confidence: 0.99256474

00:16:04.310 --> 00:16:05.610 And the key cell

NOTE Confidence: 0.97437125

00:16:06.070 --> 00:16:07.190 to maintain this,

NOTE Confidence: 0.9936226

00:16:07.830 --> 00:16:08.330 whole

NOTE Confidence: 0.9171983

00:16:08.790 --> 00:16:10.230 exhaustion program if you want

NOTE Confidence: 0.9171983

00:16:10.230 --> 00:16:11.830 to use that term is

NOTE Confidence: 0.9171983

00:16:11.830 --> 00:16:12.970 the p d one positive,

NOTE Confidence: 0.9171983

00:16:13.110 --> 00:16:14.630 Tc f one positive, Tox

NOTE Confidence: 0.9171983

00:16:14.630 --> 00:16:16.295 positive, and I prefer to

NOTE Confidence: 0.9171983

00:16:16.295 --> 00:16:18.075 use the term resource cell

NOTE Confidence: 0.9171983

00:16:18.215 --> 00:16:19.595 because this is the cell

NOTE Confidence: 0.9171983

00:16:19.735 --> 00:16:20.555 that's feeding

NOTE Confidence: 0.94702446

00:16:21.015 --> 00:16:22.455 the T cell response under

NOTE Confidence: 0.94702446

00:16:22.455 --> 00:16:24.375 condition of chronic infection. If

NOTE Confidence: 0.94702446

00:16:24.375 --> 00:16:25.655 you don't have the cell,

NOTE Confidence: 0.94702446

00:16:25.655 --> 00:16:27.415 the system just collapses. That

NOTE Confidence: 0.94702446

00:16:27.415 --> 00:16:29.579 is because the effector cells

NOTE Confidence: 0.94702446

00:16:29.579 --> 00:16:31.500 are short lived. They go

NOTE Confidence: 0.94702446

00:16:31.500 --> 00:16:33.579 further, become exhausted. Those cells

NOTE Confidence: 0.94702446

00:16:33.579 --> 00:16:36.079 also have a it's the

NOTE Confidence: 0.94529074

00:16:36.459 --> 00:16:38.300 the lifespan is very, is

NOTE Confidence: 0.94529074

00:16:38.300 --> 00:16:39.279 not very long.

NOTE Confidence: 0.97812426

00:16:40.535 --> 00:16:41.415 So what does p d

NOTE Confidence: 0.97812426

00:16:41.415 --> 00:16:42.535 one do? Basically, p d

NOTE Confidence: 0.97812426

00:16:42.535 --> 00:16:43.755 one changes the ratio

NOTE Confidence: 0.95556855

00:16:44.375 --> 00:16:45.274 of these cells.

NOTE Confidence: 0.99927396

00:16:45.894 --> 00:16:46.694 When you do p d

NOTE Confidence: 0.99927396

00:16:46.694 --> 00:16:48.535 one blockade, you get much

NOTE Confidence: 0.99927396

00:16:48.535 --> 00:16:49.514 faster differentiation

NOTE Confidence: 0.9517269

00:16:50.454 --> 00:16:51.574 of the stem like cells

NOTE Confidence: 0.9517269

00:16:51.574 --> 00:16:53.014 to give you more of

NOTE Confidence: 0.9517269

00:16:53.014 --> 00:16:54.235 these effective cells.

NOTE Confidence: 0.9999242

00:16:54.730 --> 00:16:55.710 So the main

NOTE Confidence: 0.96858805

00:16:56.090 --> 00:16:57.130 thing the p d one

NOTE Confidence: 0.96858805

00:16:57.130 --> 00:16:57.630 does

NOTE Confidence: 0.8935127

00:16:58.250 --> 00:17:00.030 in terms of changing the,

NOTE Confidence: 0.9497051

00:17:00.730 --> 00:17:01.850 is the it changes the

NOTE Confidence: 0.9497051

00:17:01.850 --> 00:17:02.970 ratio. That is, you get

NOTE Confidence: 0.9497051

00:17:02.970 --> 00:17:04.990 many more effector cells,

NOTE Confidence: 0.9810557

00:17:05.290 --> 00:17:07.450 which will contribute to the

NOTE Confidence: 0.9810557

00:17:07.450 --> 00:17:08.730 the killing of these target

NOTE Confidence: 0.9810557

00:17:08.730 --> 00:17:09.230 cells.

NOTE Confidence: 0.97688943

00:17:10.035 --> 00:17:11.715 And then, eventually, it will

NOTE Confidence: 0.97688943

00:17:11.715 --> 00:17:12.835 it will go into this

NOTE Confidence: 0.97688943

00:17:12.835 --> 00:17:13.335 thing.

NOTE Confidence: 0.9875486

00:17:17.555 --> 00:17:18.835 So when are these cells

NOTE Confidence: 0.9875486

00:17:18.835 --> 00:17:20.775 generated? Actually, fairly early

NOTE Confidence: 0.95086265

00:17:21.155 --> 00:17:22.675 in in the program. You

NOTE Confidence: 0.95086265

00:17:22.675 --> 00:17:24.515 get generation of these, stem

NOTE Confidence: 0.95086265

00:17:24.515 --> 00:17:25.175 like cells.

NOTE Confidence: 0.9798032

00:17:26.560 --> 00:17:27.520 And then, as I told

NOTE Confidence: 0.9798032

00:17:27.520 --> 00:17:28.640 you, this is what keeps

NOTE Confidence: 0.9798032

00:17:28.640 --> 00:17:30.180 the the engine going.

NOTE Confidence: 0.94652104

00:17:30.720 --> 00:17:32.320 The next, slide is just

NOTE Confidence: 0.94652104

00:17:32.320 --> 00:17:33.760 giving you a quick look

NOTE Confidence: 0.94652104

00:17:33.760 --> 00:17:35.300 at the gene expression program,

NOTE Confidence: 0.94652104

00:17:35.360 --> 00:17:37.600 again, published by many people

NOTE Confidence: 0.94652104

00:17:37.600 --> 00:17:38.800 multiple times. Just to give

NOTE Confidence: 0.94652104

00:17:38.800 --> 00:17:40.035 you a flavor of how

NOTE Confidence: 0.94652104

00:17:40.115 --> 00:17:41.395 these three cells differ in

NOTE Confidence: 0.94652104

00:17:41.395 --> 00:17:42.135 gene expression.

NOTE Confidence: 0.89562255

00:17:43.155 --> 00:17:44.435 Again, all three so this

NOTE Confidence: 0.89562255

00:17:44.435 --> 00:17:46.675 is using a MHC class

NOTE Confidence: 0.89562255

00:17:46.675 --> 00:17:48.115 one tetramer to sort the

NOTE Confidence: 0.89562255

00:17:48.115 --> 00:17:49.395 antigen specific cells and then

NOTE Confidence: 0.89562255

00:17:49.395 --> 00:17:51.175 doing single cell RNA seq.

NOTE Confidence: 0.89562255

00:17:51.315 --> 00:17:52.440 You see these three subsets.

NOTE Confidence: 0.89562255

00:17:52.440 --> 00:17:53.559 You've got the stem, the

NOTE Confidence: 0.89562255

00:17:53.559 --> 00:17:55.080 transitory, and the more exhausted

NOTE Confidence: 0.89562255

00:17:55.080 --> 00:17:56.220 or the term we differentiate,

NOTE Confidence: 0.89562255

00:17:56.440 --> 00:17:57.980 all expressed p d one.

NOTE Confidence: 0.8935122

00:17:58.919 --> 00:18:00.220 All expressed stocks.

NOTE Confidence: 0.8865515

00:18:00.919 --> 00:18:02.359 Only the stem like cells

NOTE Confidence: 0.8865515

00:18:02.359 --> 00:18:03.659 expressed t c f one.

NOTE Confidence: 0.8865515

00:18:03.720 --> 00:18:04.700 These two don't.

NOTE Confidence: 0.9534422

00:18:05.164 --> 00:18:06.365 TEM three is expressed by

NOTE Confidence: 0.9534422

00:18:06.365 --> 00:18:07.825 these cells and not that,

NOTE Confidence: 0.9534422

00:18:07.965 --> 00:18:09.565 not the stem like. Again,

NOTE Confidence: 0.9534422

00:18:09.565 --> 00:18:11.024 thirty nine, another inhibitory

NOTE Confidence: 0.9596547

00:18:11.404 --> 00:18:13.005 marker expressed by the more

NOTE Confidence: 0.9596547

00:18:13.005 --> 00:18:14.605 differentiated cells and not by

NOTE Confidence: 0.9596547

00:18:14.605 --> 00:18:16.044 the stem like cell. I've

NOTE Confidence: 0.9596547

00:18:16.044 --> 00:18:17.804 spiked in here just what

NOTE Confidence: 0.9596547

00:18:17.804 --> 00:18:19.404 the gene expression program is

NOTE Confidence: 0.9596547

00:18:19.404 --> 00:18:21.460 of, naive cells. So naive

NOTE Confidence: 0.9596547

00:18:21.460 --> 00:18:22.260 cells, of course, have no

NOTE Confidence: 0.9596547

00:18:22.260 --> 00:18:23.140 p d one. They have

NOTE Confidence: 0.9596547

00:18:23.140 --> 00:18:24.020 no talks, but they have

NOTE Confidence: 0.9596547

00:18:24.020 --> 00:18:25.640 TCF one. In fact, every

NOTE Confidence: 0.9721361

00:18:26.100 --> 00:18:27.620 good t cell has TCF

NOTE Confidence: 0.9721361

00:18:27.620 --> 00:18:29.220 one. Memory cells have TCF

NOTE Confidence: 0.9721361

00:18:29.220 --> 00:18:29.720 one.

NOTE Confidence: 0.9081828

00:18:31.300 --> 00:18:32.420 The stem like cells have

NOTE Confidence: 0.9081828

00:18:32.420 --> 00:18:34.335 TCF one, and also you

NOTE Confidence: 0.9081828

00:18:34.335 --> 00:18:36.415 have Tcf one in all

NOTE Confidence: 0.9081828

00:18:36.415 --> 00:18:37.315 all naive cells.

NOTE Confidence: 0.871511

00:18:37.935 --> 00:18:39.055 PIM three and thirty nine

NOTE Confidence: 0.871511

00:18:39.055 --> 00:18:40.015 don't have it. I mean,

NOTE Confidence: 0.871511

00:18:40.015 --> 00:18:41.775 they've not not except the

NOTE Confidence: 0.871511

00:18:41.775 --> 00:18:43.215 naive cells. If you look

NOTE Confidence: 0.871511

00:18:43.215 --> 00:18:44.355 at effector molecules,

NOTE Confidence: 0.99211395

00:18:44.895 --> 00:18:46.835 effector molecules are not expressed

NOTE Confidence: 0.99211395

00:18:46.975 --> 00:18:48.310 by these cells. You have

NOTE Confidence: 0.99211395

00:18:48.310 --> 00:18:49.530 them in the differentiated

NOTE Confidence: 0.96325624

00:18:49.990 --> 00:18:52.330 transitory and exhausted. Again, granzyme

NOTE Confidence: 0.96325624

00:18:52.390 --> 00:18:54.150 b comes up. CD twenty

NOTE Confidence: 0.96325624

00:18:54.150 --> 00:18:55.430 eight is higher in these

NOTE Confidence: 0.96325624

00:18:55.430 --> 00:18:55.930 cells,

NOTE Confidence: 0.99553275

00:18:56.869 --> 00:18:57.369 and

NOTE Confidence: 0.9756943

00:18:57.830 --> 00:18:59.270 CD one twenty seven is

NOTE Confidence: 0.9756943

00:18:59.270 --> 00:19:00.630 expressed by the stem like

NOTE Confidence: 0.9756943

00:19:00.630 --> 00:19:02.285 cell. Again, CD one twenty

NOTE Confidence: 0.9756943

00:19:02.285 --> 00:19:03.905 seven, as is well recognized,

NOTE Confidence: 0.9756943

00:19:04.205 --> 00:19:05.965 is essential for long term

NOTE Confidence: 0.9756943

00:19:05.965 --> 00:19:07.585 survival of the t cell.

NOTE Confidence: 0.9756943

00:19:07.645 --> 00:19:09.265 IL seven signals are essential.

NOTE Confidence: 0.9756943

00:19:09.484 --> 00:19:10.365 So if you don't have

NOTE Confidence: 0.9756943

00:19:10.365 --> 00:19:11.744 CD one twenty seven,

NOTE Confidence: 0.9149552

00:19:12.045 --> 00:19:13.165 then a cell will not

NOTE Confidence: 0.9149552

00:19:13.165 --> 00:19:15.244 be persisting or surviving long

NOTE Confidence: 0.9149552

00:19:15.244 --> 00:19:16.240 term. And And it's the

NOTE Confidence: 0.9149552

00:19:16.240 --> 00:19:17.600 stem like cells that have

NOTE Confidence: 0.9149552

00:19:17.679 --> 00:19:18.960 and seven as do as

NOTE Confidence: 0.9149552

00:19:18.960 --> 00:19:20.080 naive cells, of course. And

NOTE Confidence: 0.9149552

00:19:20.080 --> 00:19:22.400 XCL one purely only made

NOTE Confidence: 0.9149552

00:19:22.400 --> 00:19:24.000 by these cells, not by

NOTE Confidence: 0.9149552

00:19:24.000 --> 00:19:25.200 these or by the naive

NOTE Confidence: 0.9149552

00:19:25.200 --> 00:19:25.700 cells.

NOTE Confidence: 0.9969222

00:19:29.695 --> 00:19:30.914 I want to spend a

NOTE Confidence: 0.9785803

00:19:31.534 --> 00:19:33.054 few minutes asking the question,

NOTE Confidence: 0.9785803

00:19:33.054 --> 00:19:34.595 are these stem like cells

NOTE Confidence: 0.9683957

00:19:35.455 --> 00:19:38.274 actually receiving TCR signals actively?

NOTE Confidence: 0.9173545

00:19:39.215 --> 00:19:40.254 And I've told you the

NOTE Confidence: 0.9173545

00:19:40.254 --> 00:19:41.294 express PD one, so it

NOTE Confidence: 0.9173545

00:19:41.294 --> 00:19:42.575 suggests that they might that

NOTE Confidence: 0.9173545

00:19:42.575 --> 00:19:43.619 that they should be. But

NOTE Confidence: 0.9173545

00:19:43.619 --> 00:19:45.000 then we ask this question

NOTE Confidence: 0.9173545

00:19:45.060 --> 00:19:45.560 more

NOTE Confidence: 0.8879073

00:19:46.020 --> 00:19:48.180 directly by using, node seventy

NOTE Confidence: 0.8879073

00:19:48.180 --> 00:19:48.680 seven

NOTE Confidence: 0.9392959

00:19:49.300 --> 00:19:49.800 reporter,

NOTE Confidence: 0.99437016

00:19:50.740 --> 00:19:51.240 cells.

NOTE Confidence: 0.9964069

00:19:52.500 --> 00:19:54.760 This is a transgenic mouse

NOTE Confidence: 0.8928003

00:19:55.300 --> 00:19:56.580 where the nodes if the

NOTE Confidence: 0.8928003

00:19:56.580 --> 00:19:58.695 cells get TCR signaling, expressed

NOTE Confidence: 0.8928003

00:19:58.695 --> 00:19:59.895 new seventy seven, which is

NOTE Confidence: 0.8928003

00:19:59.895 --> 00:20:01.195 downstream of TGA signaling,

NOTE Confidence: 0.9370718

00:20:01.815 --> 00:20:03.494 GFP will come up. So

NOTE Confidence: 0.9370718

00:20:03.494 --> 00:20:05.174 this shows you the new

NOTE Confidence: 0.9370718

00:20:05.174 --> 00:20:06.455 seventy seven staining in this

NOTE Confidence: 0.9370718

00:20:06.455 --> 00:20:07.414 case is where you're looking

NOTE Confidence: 0.9370718

00:20:07.414 --> 00:20:08.075 at GFP.

NOTE Confidence: 0.9926821

00:20:08.775 --> 00:20:09.975 So if you look at,

NOTE Confidence: 0.88601774

00:20:10.549 --> 00:20:11.750 a mouse that has cleared

NOTE Confidence: 0.88601774

00:20:11.750 --> 00:20:12.950 the infection and is a

NOTE Confidence: 0.88601774

00:20:12.950 --> 00:20:14.330 LCM b immune mouse,

NOTE Confidence: 0.9125139

00:20:14.710 --> 00:20:16.010 here's the tetramer staining.

NOTE Confidence: 0.93741703

00:20:16.390 --> 00:20:17.429 And, of course, these cells

NOTE Confidence: 0.93741703

00:20:17.429 --> 00:20:19.289 have neither new seventy seven,

NOTE Confidence: 0.97068673

00:20:19.590 --> 00:20:20.950 minimal to none, and they

NOTE Confidence: 0.97068673

00:20:20.950 --> 00:20:22.470 don't have PD one. But

NOTE Confidence: 0.97068673

00:20:22.470 --> 00:20:23.429 if you look at the

NOTE Confidence: 0.97068673

00:20:23.429 --> 00:20:26.175 antigen same specificity, antigen specific

NOTE Confidence: 0.97068673

00:20:26.175 --> 00:20:27.635 cell during chronic infection,

NOTE Confidence: 0.893392

00:20:28.015 --> 00:20:29.055 you see that they're all

NOTE Confidence: 0.893392

00:20:29.055 --> 00:20:30.434 new seventy seven positive,

NOTE Confidence: 0.9807111

00:20:30.975 --> 00:20:32.335 and they're all p d

NOTE Confidence: 0.9807111

00:20:32.335 --> 00:20:32.994 one positive.

NOTE Confidence: 0.99524933

00:20:33.615 --> 00:20:34.815 If you then ask the

NOTE Confidence: 0.99524933

00:20:34.815 --> 00:20:35.555 three subsets,

NOTE Confidence: 0.9891165

00:20:35.934 --> 00:20:36.835 the three clusters,

NOTE Confidence: 0.92029476

00:20:37.830 --> 00:20:39.669 and we can subdivide it

NOTE Confidence: 0.92029476

00:20:39.669 --> 00:20:41.109 into the the three clusters

NOTE Confidence: 0.92029476

00:20:41.109 --> 00:20:42.549 by using these MARCOS TIN

NOTE Confidence: 0.92029476

00:20:42.549 --> 00:20:43.590 three and CD one zero

NOTE Confidence: 0.92029476

00:20:43.590 --> 00:20:44.950 one, these are the stem

NOTE Confidence: 0.92029476

00:20:44.950 --> 00:20:46.390 like cells. These are the

NOTE Confidence: 0.92029476

00:20:46.390 --> 00:20:47.990 transitory effectors, and these are

NOTE Confidence: 0.92029476

00:20:47.990 --> 00:20:50.409 the more thermally differentiated cell.

NOTE Confidence: 0.92029476

00:20:50.644 --> 00:20:51.684 And then you ask that

NOTE Confidence: 0.92029476

00:20:51.764 --> 00:20:53.044 do Samsung's spinning. You see

NOTE Confidence: 0.92029476

00:20:53.044 --> 00:20:54.644 that all three of them,

NOTE Confidence: 0.92029476

00:20:54.644 --> 00:20:55.924 like, are node seventy seven

NOTE Confidence: 0.92029476

00:20:55.924 --> 00:20:56.424 positive.

NOTE Confidence: 0.93064773

00:20:57.125 --> 00:20:58.825 So even though these cells,

NOTE Confidence: 0.91021025

00:21:00.804 --> 00:21:01.845 this so all of these

NOTE Confidence: 0.91021025

00:21:01.845 --> 00:21:03.945 cells are getting TCR signals,

NOTE Confidence: 0.95894134

00:21:04.565 --> 00:21:05.065 continuously.

NOTE Confidence: 0.99943334

00:21:06.390 --> 00:21:07.430 But in spite of the

NOTE Confidence: 0.99943334

00:21:07.430 --> 00:21:08.470 fact that you're getting the

NOTE Confidence: 0.99943334

00:21:08.470 --> 00:21:09.369 TCR signals,

NOTE Confidence: 0.9982048

00:21:10.869 --> 00:21:11.369 the

NOTE Confidence: 0.9885671

00:21:11.910 --> 00:21:12.970 stem like cell

NOTE Confidence: 0.9831411

00:21:13.510 --> 00:21:14.490 is not dividing.

NOTE Confidence: 0.9990977

00:21:15.270 --> 00:21:17.210 There's only minimal proliferation.

NOTE Confidence: 0.9478822

00:21:18.085 --> 00:21:19.525 The transitory cell which have

NOTE Confidence: 0.9478822

00:21:19.525 --> 00:21:21.525 recently emerged from it are

NOTE Confidence: 0.9478822

00:21:21.525 --> 00:21:23.145 all mostly in cycle.

NOTE Confidence: 0.99861157

00:21:23.685 --> 00:21:25.225 So the recently emerging

NOTE Confidence: 0.9522086

00:21:25.765 --> 00:21:27.125 effector cells from the stem

NOTE Confidence: 0.9522086

00:21:27.125 --> 00:21:28.725 like cells at any given

NOTE Confidence: 0.9522086

00:21:28.725 --> 00:21:30.325 time, over fifty percent of

NOTE Confidence: 0.9522086

00:21:30.325 --> 00:21:31.705 them will be divided.

NOTE Confidence: 0.93839014

00:21:32.210 --> 00:21:33.330 Because they are just emerging

NOTE Confidence: 0.93839014

00:21:33.330 --> 00:21:34.070 from it.

NOTE Confidence: 0.9530759

00:21:34.770 --> 00:21:36.630 The terminally differentiated cells

NOTE Confidence: 0.9461245

00:21:37.330 --> 00:21:39.010 in terms of proliferation are

NOTE Confidence: 0.9461245

00:21:39.010 --> 00:21:39.910 truly exhausted.

NOTE Confidence: 0.9951821

00:21:40.450 --> 00:21:41.650 They have minimal to no

NOTE Confidence: 0.9951821

00:21:41.650 --> 00:21:42.150 capacity

NOTE Confidence: 0.9996446

00:21:42.530 --> 00:21:43.590 to further proliferate.

NOTE Confidence: 0.96394956

00:21:43.890 --> 00:21:44.930 They don't do that after

NOTE Confidence: 0.96394956

00:21:44.930 --> 00:21:45.910 PD one blockade.

NOTE Confidence: 0.96213555

00:21:46.215 --> 00:21:47.174 They don't do that after

NOTE Confidence: 0.96213555

00:21:47.174 --> 00:21:48.775 any cytokine that you give.

NOTE Confidence: 0.96213555

00:21:48.775 --> 00:21:49.835 So these are

NOTE Confidence: 0.8759632

00:21:50.135 --> 00:21:50.875 not divided.

NOTE Confidence: 0.99295753

00:21:52.375 --> 00:21:53.434 But this cell,

NOTE Confidence: 0.9999245

00:21:54.215 --> 00:21:55.034 which is

NOTE Confidence: 0.8117776

00:21:55.414 --> 00:21:56.475 very poorly potent

NOTE Confidence: 0.9858985

00:21:57.095 --> 00:21:58.875 and is able to divide

NOTE Confidence: 0.9858985

00:21:58.934 --> 00:22:00.135 after you give PD one

NOTE Confidence: 0.9858985

00:22:00.135 --> 00:22:01.595 blockade or other cytokine,

NOTE Confidence: 0.90379316

00:22:02.020 --> 00:22:03.859 under these conditions actually is

NOTE Confidence: 0.90379316

00:22:03.859 --> 00:22:04.359 quiescent.

NOTE Confidence: 0.99164313

00:22:07.140 --> 00:22:08.520 And then if you ask

NOTE Confidence: 0.92576474

00:22:09.220 --> 00:22:11.080 which cells express effector molecule,

NOTE Confidence: 0.98731965

00:22:12.660 --> 00:22:14.440 this stem cell expresses

NOTE Confidence: 0.8870585

00:22:15.184 --> 00:22:16.705 no granzyme b. Even though

NOTE Confidence: 0.8870585

00:22:16.705 --> 00:22:18.304 it's getting TCR signals, it

NOTE Confidence: 0.8870585

00:22:18.304 --> 00:22:20.225 expresses no granzyme b. The

NOTE Confidence: 0.8870585

00:22:20.225 --> 00:22:21.585 transducer cells, of course, have

NOTE Confidence: 0.8870585

00:22:21.585 --> 00:22:23.265 lot of granzyme b and,

NOTE Confidence: 0.98746496

00:22:23.825 --> 00:22:25.345 more exhausted cells also have

NOTE Confidence: 0.98746496

00:22:25.345 --> 00:22:26.244 granzyme b.

NOTE Confidence: 0.9995954

00:22:26.625 --> 00:22:27.984 So I find this quite

NOTE Confidence: 0.9995954

00:22:27.984 --> 00:22:28.484 fascinating

NOTE Confidence: 0.99954015

00:22:28.980 --> 00:22:30.760 that this cell is getting

NOTE Confidence: 0.8929847

00:22:31.300 --> 00:22:32.359 TCR signals,

NOTE Confidence: 0.91437966

00:22:33.859 --> 00:22:35.540 but and is it we

NOTE Confidence: 0.91437966

00:22:35.540 --> 00:22:36.900 know that this cell is

NOTE Confidence: 0.91437966

00:22:36.900 --> 00:22:38.580 functional to report and it

NOTE Confidence: 0.91437966

00:22:38.580 --> 00:22:39.780 can after you do the

NOTE Confidence: 0.91437966

00:22:39.780 --> 00:22:41.240 PDN blockade, it will

NOTE Confidence: 0.849642

00:22:41.540 --> 00:22:43.059 differentiate to give more transit

NOTE Confidence: 0.849642

00:22:43.059 --> 00:22:44.715 v cell. But in its

NOTE Confidence: 0.9955682

00:22:45.195 --> 00:22:46.015 own state,

NOTE Confidence: 0.98098785

00:22:46.955 --> 00:22:48.975 it does not express granzyme

NOTE Confidence: 0.98098785

00:22:49.034 --> 00:22:49.534 b.

NOTE Confidence: 0.9820122

00:22:51.195 --> 00:22:51.695 Basically,

NOTE Confidence: 0.95890087

00:22:51.994 --> 00:22:53.115 think of it as a

NOTE Confidence: 0.95890087

00:22:53.115 --> 00:22:54.095 TFH cell

NOTE Confidence: 0.8956101

00:22:54.475 --> 00:22:55.835 because the TFH so it

NOTE Confidence: 0.8956101

00:22:55.835 --> 00:22:57.135 has b c l six.

NOTE Confidence: 0.8956101

00:22:57.195 --> 00:22:58.575 It has, in some ways,

NOTE Confidence: 0.9995641

00:22:58.875 --> 00:22:59.375 hijacked

NOTE Confidence: 0.96504515

00:23:00.320 --> 00:23:02.160 some aspects of the TfH

NOTE Confidence: 0.96504515

00:23:02.160 --> 00:23:02.660 program.

NOTE Confidence: 0.92808723

00:23:03.359 --> 00:23:04.640 So when you have CD4

NOTE Confidence: 0.92808723

00:23:04.640 --> 00:23:06.000 cells that differentiate, you get

NOTE Confidence: 0.92808723

00:23:06.000 --> 00:23:06.500 Th1,

NOTE Confidence: 0.98644036

00:23:06.960 --> 00:23:07.859 you get TfH.

NOTE Confidence: 0.96372604

00:23:08.240 --> 00:23:10.020 The TfH cell, which has

NOTE Confidence: 0.9727861

00:23:10.720 --> 00:23:12.480 Bcl six, and so on,

NOTE Confidence: 0.9727861

00:23:12.480 --> 00:23:14.000 it shuts down the effector

NOTE Confidence: 0.9727861

00:23:14.000 --> 00:23:14.500 program.

NOTE Confidence: 0.92011786

00:23:15.674 --> 00:23:17.914 So TfH cells will never

NOTE Confidence: 0.92011786

00:23:17.914 --> 00:23:19.054 have effector molecules.

NOTE Confidence: 0.988499

00:23:19.434 --> 00:23:20.315 It's the t h one

NOTE Confidence: 0.988499

00:23:20.315 --> 00:23:21.674 cells that have it. So

NOTE Confidence: 0.988499

00:23:21.674 --> 00:23:23.294 the stem like cell has

NOTE Confidence: 0.988499

00:23:23.355 --> 00:23:25.455 taken some interesting aspect

NOTE Confidence: 0.9767227

00:23:26.075 --> 00:23:27.835 of that biology. It certainly

NOTE Confidence: 0.9767227

00:23:27.835 --> 00:23:29.215 is not a TfH cell.

NOTE Confidence: 0.9767227

00:23:29.280 --> 00:23:30.480 It doesn't even go near

NOTE Confidence: 0.9767227

00:23:30.480 --> 00:23:32.400 b cells. It's not involved

NOTE Confidence: 0.9767227

00:23:32.400 --> 00:23:33.619 in helping,

NOTE Confidence: 0.98765147

00:23:34.080 --> 00:23:35.440 b cells, but it has

NOTE Confidence: 0.98765147

00:23:35.440 --> 00:23:37.460 captured a very interesting aspect

NOTE Confidence: 0.9951437

00:23:37.920 --> 00:23:39.220 of TFA biology

NOTE Confidence: 0.9765789

00:23:39.840 --> 00:23:41.859 in its, differentiation program.

NOTE Confidence: 0.9279141

00:23:42.934 --> 00:23:44.135 And but when it then

NOTE Confidence: 0.9279141

00:23:44.135 --> 00:23:45.655 differentiates, you remove the PD

NOTE Confidence: 0.9279141

00:23:45.655 --> 00:23:47.195 one break. When it differentiates,

NOTE Confidence: 0.9935977

00:23:47.575 --> 00:23:48.635 now you get

NOTE Confidence: 0.9527181

00:23:49.015 --> 00:23:50.375 the the t h one

NOTE Confidence: 0.9527181

00:23:50.375 --> 00:23:51.415 type cells, which is your

NOTE Confidence: 0.9527181

00:23:51.415 --> 00:23:53.335 transitory effector cells, which express

NOTE Confidence: 0.9527181

00:23:53.335 --> 00:23:54.234 all the molecules

NOTE Confidence: 0.89736027

00:23:54.535 --> 00:23:55.975 that the cytotoxic t cell

NOTE Confidence: 0.89736027

00:23:55.975 --> 00:23:56.475 expresses.

NOTE Confidence: 0.98614025

00:23:57.150 --> 00:23:58.190 I think this is really

NOTE Confidence: 0.98614025

00:23:58.190 --> 00:23:58.690 quite,

NOTE Confidence: 0.98229665

00:24:00.590 --> 00:24:01.950 interesting biology for us to

NOTE Confidence: 0.98229665

00:24:01.950 --> 00:24:03.230 work out. So the stem

NOTE Confidence: 0.98229665

00:24:03.230 --> 00:24:04.130 cell niche,

NOTE Confidence: 0.9961707

00:24:05.869 --> 00:24:06.850 so this is

NOTE Confidence: 0.84330153

00:24:07.230 --> 00:24:08.850 not expressing these things

NOTE Confidence: 0.98671585

00:24:09.205 --> 00:24:11.125 is actually an active program.

NOTE Confidence: 0.98671585

00:24:11.125 --> 00:24:12.484 It's not a passive program.

NOTE Confidence: 0.98671585

00:24:12.484 --> 00:24:13.605 It's not due to lack

NOTE Confidence: 0.98671585

00:24:13.605 --> 00:24:15.305 of TCR stimulation,

NOTE Confidence: 0.96361977

00:24:15.685 --> 00:24:16.565 not due to lack of

NOTE Confidence: 0.96361977

00:24:16.565 --> 00:24:18.105 antigen. That is the program.

NOTE Confidence: 0.96361977

00:24:18.325 --> 00:24:20.025 That is the transcription program

NOTE Confidence: 0.96361977

00:24:20.165 --> 00:24:21.765 that changes after you remove

NOTE Confidence: 0.96361977

00:24:21.765 --> 00:24:22.965 the p d one break

NOTE Confidence: 0.96361977

00:24:22.965 --> 00:24:23.925 or can do it by

NOTE Confidence: 0.96361977

00:24:23.925 --> 00:24:24.630 some others,

NOTE Confidence: 0.99635065

00:24:25.190 --> 00:24:26.570 cytokines that you provide.

NOTE Confidence: 0.99598914

00:24:27.510 --> 00:24:28.710 Okay. So let me now

NOTE Confidence: 0.99598914

00:24:28.710 --> 00:24:29.350 get to,

NOTE Confidence: 0.71578604

00:24:30.390 --> 00:24:30.890 human,

NOTE Confidence: 0.9841334

00:24:31.670 --> 00:24:33.510 stem cells. Many people have

NOTE Confidence: 0.9841334

00:24:33.510 --> 00:24:34.330 shown this.

NOTE Confidence: 0.9693273

00:24:34.630 --> 00:24:36.230 Elegant studies done looking at

NOTE Confidence: 0.9693273

00:24:36.230 --> 00:24:36.730 neoantigen

NOTE Confidence: 0.96719426

00:24:37.030 --> 00:24:38.490 specific cells in melanoma,

NOTE Confidence: 0.9447179

00:24:39.030 --> 00:24:39.990 in many other,

NOTE Confidence: 0.95792

00:24:40.654 --> 00:24:42.014 cancer systems have shown that

NOTE Confidence: 0.95792

00:24:42.014 --> 00:24:43.774 you have these stem like

NOTE Confidence: 0.95792

00:24:43.774 --> 00:24:44.835 cells also

NOTE Confidence: 0.9654454

00:24:45.135 --> 00:24:45.375 in,

NOTE Confidence: 0.9912772

00:24:46.014 --> 00:24:47.154 in human cancer.

NOTE Confidence: 0.96153384

00:24:47.934 --> 00:24:49.375 We we have done shown

NOTE Confidence: 0.96153384

00:24:49.375 --> 00:24:50.894 this in lung cancer and

NOTE Confidence: 0.96153384

00:24:50.894 --> 00:24:51.955 head and neck cancer.

NOTE Confidence: 0.9409176

00:24:52.255 --> 00:24:53.774 I'll just show you couple

NOTE Confidence: 0.9409176

00:24:53.774 --> 00:24:55.315 of slides from lung cancer

NOTE Confidence: 0.96724796

00:24:56.390 --> 00:24:57.270 just to tell you that,

NOTE Confidence: 0.96724796

00:24:57.270 --> 00:24:58.730 yes, you find these cells,

NOTE Confidence: 0.8992977

00:24:59.510 --> 00:25:00.550 and this was the paper

NOTE Confidence: 0.8992977

00:25:00.550 --> 00:25:01.270 we published,

NOTE Confidence: 0.96838546

00:25:02.230 --> 00:25:03.110 last year, but I had

NOTE Confidence: 0.96838546

00:25:03.110 --> 00:25:04.710 also shown this in another

NOTE Confidence: 0.96838546

00:25:04.710 --> 00:25:05.530 paper earlier.

NOTE Confidence: 0.98171866

00:25:05.990 --> 00:25:07.430 But the more interesting thing

NOTE Confidence: 0.98171866

00:25:07.430 --> 00:25:08.490 from this study,

NOTE Confidence: 0.9863512

00:25:09.154 --> 00:25:10.274 in addition to showing the

NOTE Confidence: 0.9863512

00:25:10.274 --> 00:25:11.394 stem like cells in lung

NOTE Confidence: 0.9863512

00:25:11.394 --> 00:25:11.894 cancers,

NOTE Confidence: 0.9973543

00:25:12.914 --> 00:25:14.355 was the location of these

NOTE Confidence: 0.9973543

00:25:14.355 --> 00:25:14.855 cells

NOTE Confidence: 0.9928459

00:25:15.315 --> 00:25:16.615 within the lung cancer.

NOTE Confidence: 0.99763733

00:25:17.075 --> 00:25:18.434 So if you look in

NOTE Confidence: 0.99763733

00:25:18.434 --> 00:25:19.734 the lung cancer

NOTE Confidence: 0.90375304

00:25:20.195 --> 00:25:20.695 studies,

NOTE Confidence: 0.9317935

00:25:21.394 --> 00:25:22.195 in lung cancer,

NOTE Confidence: 0.9890326

00:25:22.595 --> 00:25:23.095 samples,

NOTE Confidence: 0.9862835

00:25:23.779 --> 00:25:25.299 these cells are not where

NOTE Confidence: 0.9862835

00:25:25.299 --> 00:25:27.220 the tumor is. They are

NOTE Confidence: 0.9862835

00:25:27.220 --> 00:25:28.359 away from the tumor.

NOTE Confidence: 0.9892362

00:25:28.899 --> 00:25:30.340 So on the tumor, you

NOTE Confidence: 0.9892362

00:25:30.340 --> 00:25:31.559 will find the more

NOTE Confidence: 0.94194794

00:25:31.859 --> 00:25:34.039 sector like cells, the transitory

NOTE Confidence: 0.94194794

00:25:34.179 --> 00:25:35.779 cells, and you find cells

NOTE Confidence: 0.94194794

00:25:35.779 --> 00:25:37.475 which are the more exhausted

NOTE Confidence: 0.94194794

00:25:37.615 --> 00:25:38.755 or terminally differentiated.

NOTE Confidence: 0.95752126

00:25:39.135 --> 00:25:41.054 The stem like cells are

NOTE Confidence: 0.95752126

00:25:41.054 --> 00:25:42.494 away from where the actual

NOTE Confidence: 0.95752126

00:25:42.494 --> 00:25:43.315 tumor is,

NOTE Confidence: 0.9789292

00:25:43.695 --> 00:25:44.815 and we found that some

NOTE Confidence: 0.9789292

00:25:44.815 --> 00:25:46.015 of them are actually in

NOTE Confidence: 0.9789292

00:25:46.015 --> 00:25:47.395 tertiary lymphoid structures

NOTE Confidence: 0.98442096

00:25:47.934 --> 00:25:48.915 within the tumor.

NOTE Confidence: 0.9561186

00:25:49.960 --> 00:25:51.400 And they're closer to the

NOTE Confidence: 0.9561186

00:25:51.400 --> 00:25:52.680 c d four t cells

NOTE Confidence: 0.9561186

00:25:52.680 --> 00:25:53.880 there than to the b

NOTE Confidence: 0.9561186

00:25:53.880 --> 00:25:54.380 cells.

NOTE Confidence: 0.9524987

00:25:55.800 --> 00:25:56.460 So, essentially,

NOTE Confidence: 0.9309927

00:25:58.119 --> 00:25:59.580 a similar kind of compartmentalization

NOTE Confidence: 0.97913873

00:26:00.600 --> 00:26:02.119 that we saw in the

NOTE Confidence: 0.97913873

00:26:02.119 --> 00:26:04.135 chronic viral infection model, that

NOTE Confidence: 0.97913873

00:26:04.135 --> 00:26:05.575 is they're not where the

NOTE Confidence: 0.97913873

00:26:05.575 --> 00:26:06.075 actual

NOTE Confidence: 0.98228145

00:26:06.615 --> 00:26:07.674 virally infected,

NOTE Confidence: 0.9678863

00:26:08.535 --> 00:26:09.734 cells are, but a little

NOTE Confidence: 0.9678863

00:26:09.734 --> 00:26:11.095 bit away from it. So,

NOTE Confidence: 0.9678863

00:26:11.095 --> 00:26:11.895 like, if you look in

NOTE Confidence: 0.9678863

00:26:11.895 --> 00:26:13.575 the spleen of these chronically

NOTE Confidence: 0.9678863

00:26:13.575 --> 00:26:14.554 infected mice,

NOTE Confidence: 0.9501596

00:26:14.855 --> 00:26:16.375 the major infection is in

NOTE Confidence: 0.9501596

00:26:16.375 --> 00:26:17.890 the red bulb of the

NOTE Confidence: 0.9501596

00:26:17.890 --> 00:26:18.470 f four

NOTE Confidence: 0.99222636

00:26:19.010 --> 00:26:20.790 eighty macrophages and other cells.

NOTE Confidence: 0.99222636

00:26:20.929 --> 00:26:21.890 These cells are in the

NOTE Confidence: 0.99222636

00:26:21.890 --> 00:26:22.790 t cell areas,

NOTE Confidence: 0.99283266

00:26:23.250 --> 00:26:24.950 but there isn't much infected

NOTE Confidence: 0.99283266

00:26:25.010 --> 00:26:25.510 cells.

NOTE Confidence: 0.9754566

00:26:26.290 --> 00:26:27.990 So they're hiding this beautiful

NOTE Confidence: 0.9754566

00:26:28.050 --> 00:26:29.650 niche that they have. It's

NOTE Confidence: 0.9754566

00:26:29.650 --> 00:26:31.270 keep it keeps them away

NOTE Confidence: 0.9754566

00:26:31.410 --> 00:26:33.055 from the major. It's just

NOTE Confidence: 0.9754566

00:26:33.055 --> 00:26:34.335 part of their whole program

NOTE Confidence: 0.9754566

00:26:34.335 --> 00:26:35.455 that keeps them there. It's

NOTE Confidence: 0.9754566

00:26:35.455 --> 00:26:36.275 when they differentiate

NOTE Confidence: 0.9870678

00:26:36.655 --> 00:26:37.615 that they will send the

NOTE Confidence: 0.9870678

00:26:37.615 --> 00:26:39.135 effectors out there. And then

NOTE Confidence: 0.9870678

00:26:39.135 --> 00:26:40.575 there was a beautiful paper,

NOTE Confidence: 0.9870678

00:26:40.575 --> 00:26:42.275 much nicer paper than ours,

NOTE Confidence: 0.9870509

00:26:43.215 --> 00:26:44.175 paper by,

NOTE Confidence: 0.7100959

00:26:44.575 --> 00:26:45.555 by Lee Hakowen,

NOTE Confidence: 0.8901572

00:26:47.059 --> 00:26:48.500 who did this published this

NOTE Confidence: 0.8901572

00:26:48.500 --> 00:26:49.000 paper,

NOTE Confidence: 0.9414897

00:26:49.540 --> 00:26:50.679 this this year.

NOTE Confidence: 0.9526272

00:26:51.299 --> 00:26:52.419 And in this one, he

NOTE Confidence: 0.9526272

00:26:52.419 --> 00:26:54.260 shows that again in lung

NOTE Confidence: 0.9526272

00:26:54.260 --> 00:26:54.760 cancer,

NOTE Confidence: 0.9698514

00:26:55.780 --> 00:26:56.660 if you look at the

NOTE Confidence: 0.9698514

00:26:56.660 --> 00:26:58.179 stem like cells, they are

NOTE Confidence: 0.9698514

00:26:58.179 --> 00:27:00.044 in what he calls stem

NOTE Confidence: 0.9698514

00:27:00.044 --> 00:27:02.144 immunity hubs, which are again

NOTE Confidence: 0.9698514

00:27:02.205 --> 00:27:03.484 removed from where the tumor

NOTE Confidence: 0.9698514

00:27:03.484 --> 00:27:05.404 is, and they're close to

NOTE Confidence: 0.9698514

00:27:05.404 --> 00:27:05.904 where

NOTE Confidence: 0.8238905

00:27:06.365 --> 00:27:07.325 the t cells are. In

NOTE Confidence: 0.8238905

00:27:07.325 --> 00:27:07.825 fact,

NOTE Confidence: 0.99062276

00:27:08.845 --> 00:27:10.205 he makes the analogy that

NOTE Confidence: 0.99062276

00:27:10.205 --> 00:27:11.644 these cells are found in

NOTE Confidence: 0.99062276

00:27:11.644 --> 00:27:12.144 areas

NOTE Confidence: 0.9808597

00:27:12.445 --> 00:27:14.044 that look like lymph node

NOTE Confidence: 0.9808597

00:27:14.044 --> 00:27:14.544 areas.

NOTE Confidence: 0.5940121

00:27:14.924 --> 00:27:15.300 K.

NOTE Confidence: 0.9855601

00:27:15.780 --> 00:27:16.980 And this is all within

NOTE Confidence: 0.9855601

00:27:16.980 --> 00:27:18.660 the lung tumor. He's not

NOTE Confidence: 0.9855601

00:27:18.660 --> 00:27:19.619 looking at a lymph node.

NOTE Confidence: 0.9855601

00:27:19.619 --> 00:27:20.820 He's looking right at the

NOTE Confidence: 0.9855601

00:27:20.820 --> 00:27:22.180 tumor. And we had done

NOTE Confidence: 0.9855601

00:27:22.180 --> 00:27:23.140 the same thing. We found

NOTE Confidence: 0.9855601

00:27:23.140 --> 00:27:24.580 that where you see the

NOTE Confidence: 0.9855601

00:27:24.580 --> 00:27:25.080 cancer,

NOTE Confidence: 0.96831286

00:27:25.619 --> 00:27:27.700 the tumor antigen, very few

NOTE Confidence: 0.96831286

00:27:27.700 --> 00:27:28.820 of these cells are there.

NOTE Confidence: 0.96831286

00:27:28.820 --> 00:27:30.500 They're always away to the

NOTE Confidence: 0.96831286

00:27:30.500 --> 00:27:31.000 side.

NOTE Confidence: 0.99845165

00:27:33.855 --> 00:27:35.215 Okay. Let me now go

NOTE Confidence: 0.99845165

00:27:35.215 --> 00:27:35.715 to,

NOTE Confidence: 0.9975128

00:27:36.654 --> 00:27:38.095 head and neck cancer. And

NOTE Confidence: 0.9975128

00:27:38.095 --> 00:27:39.135 one of the reasons we

NOTE Confidence: 0.9975128

00:27:39.135 --> 00:27:39.794 did this,

NOTE Confidence: 0.9688564

00:27:40.895 --> 00:27:42.654 Barbara, not because we knew

NOTE Confidence: 0.9688564

00:27:42.654 --> 00:27:43.775 anything about head and neck

NOTE Confidence: 0.9688564

00:27:43.775 --> 00:27:44.835 cancer, but because

NOTE Confidence: 0.98629135

00:27:45.375 --> 00:27:46.859 we wanted to look at

NOTE Confidence: 0.98629135

00:27:46.859 --> 00:27:48.859 antigen specific cells. Because in

NOTE Confidence: 0.98629135

00:27:48.859 --> 00:27:49.760 our lung studies,

NOTE Confidence: 0.8881286

00:27:50.460 --> 00:27:51.660 when you're looking at total

NOTE Confidence: 0.8881286

00:27:51.660 --> 00:27:52.160 cells,

NOTE Confidence: 0.98178554

00:27:52.619 --> 00:27:53.740 and we did not have

NOTE Confidence: 0.98178554

00:27:53.740 --> 00:27:55.020 the bandwidth to be doing

NOTE Confidence: 0.98178554

00:27:55.020 --> 00:27:58.060 the sequencing and identifying the

NOTE Confidence: 0.98178554

00:27:58.060 --> 00:28:00.320 precise mutation in each individual

NOTE Confidence: 0.98178554

00:28:00.380 --> 00:28:01.340 and doing it. So we

NOTE Confidence: 0.98178554

00:28:01.340 --> 00:28:02.355 said, let's go to

NOTE Confidence: 0.9940491

00:28:02.915 --> 00:28:04.375 a viral mediated cancer

NOTE Confidence: 0.927927

00:28:04.915 --> 00:28:06.195 where we could would be

NOTE Confidence: 0.927927

00:28:06.195 --> 00:28:07.655 easier for us to identify

NOTE Confidence: 0.9764458

00:28:08.355 --> 00:28:09.715 the epitopes which are being

NOTE Confidence: 0.9764458

00:28:09.715 --> 00:28:10.994 recognized, and then we can

NOTE Confidence: 0.9764458

00:28:10.994 --> 00:28:12.674 use tetramers and look at,

NOTE Confidence: 0.9858187

00:28:13.395 --> 00:28:14.994 HPV specific cells in the

NOTE Confidence: 0.9858187

00:28:14.994 --> 00:28:15.494 tumor.

NOTE Confidence: 0.98018426

00:28:16.429 --> 00:28:17.970 So we started out by

NOTE Confidence: 0.92459977

00:28:18.270 --> 00:28:20.669 collaborating with Nabil Saba and

NOTE Confidence: 0.92459977

00:28:20.669 --> 00:28:21.570 Mihir Patel

NOTE Confidence: 0.9485847

00:28:21.950 --> 00:28:23.309 and what they gave us

NOTE Confidence: 0.9485847

00:28:23.309 --> 00:28:24.609 was the following material.

NOTE Confidence: 0.9045748

00:28:25.710 --> 00:28:26.690 They gave us,

NOTE Confidence: 0.91865855

00:28:28.190 --> 00:28:29.230 in this study, we have

NOTE Confidence: 0.91865855

00:28:29.230 --> 00:28:30.270 now extended it and we

NOTE Confidence: 0.91865855

00:28:30.270 --> 00:28:31.090 have more data,

NOTE Confidence: 0.9952916

00:28:31.505 --> 00:28:32.865 But I'll share with you,

NOTE Confidence: 0.9952916

00:28:33.105 --> 00:28:34.485 some of our published work.

NOTE Confidence: 0.90926605

00:28:35.025 --> 00:28:36.225 So, basically, we had,

NOTE Confidence: 0.9998607

00:28:36.865 --> 00:28:38.085 seventeen patients

NOTE Confidence: 0.9526907

00:28:38.785 --> 00:28:40.385 who were HPV positive head

NOTE Confidence: 0.9526907

00:28:40.385 --> 00:28:41.905 and neck cancer patients. These

NOTE Confidence: 0.9526907

00:28:41.905 --> 00:28:44.210 were all treatment naive. By

NOTE Confidence: 0.9526907

00:28:44.210 --> 00:28:45.570 what I mean is that

NOTE Confidence: 0.9526907

00:28:45.570 --> 00:28:46.770 they had not had previous

NOTE Confidence: 0.9526907

00:28:46.770 --> 00:28:47.890 treatment. They had just been

NOTE Confidence: 0.9526907

00:28:47.890 --> 00:28:48.390 diagnosed

NOTE Confidence: 0.9739961

00:28:48.850 --> 00:28:49.890 as having head and neck

NOTE Confidence: 0.9739961

00:28:49.890 --> 00:28:50.390 cancer.

NOTE Confidence: 0.94888294

00:28:50.770 --> 00:28:52.290 And we I we got

NOTE Confidence: 0.94888294

00:28:52.290 --> 00:28:53.250 from them at the time

NOTE Confidence: 0.94888294

00:28:53.250 --> 00:28:54.950 of surgery, we got the

NOTE Confidence: 0.94888294

00:28:55.090 --> 00:28:56.310 sample of the blood,

NOTE Confidence: 0.9866665

00:28:57.034 --> 00:28:58.235 and we got the primary

NOTE Confidence: 0.9866665

00:28:58.235 --> 00:28:59.195 tumor, which you all know

NOTE Confidence: 0.9866665

00:28:59.195 --> 00:29:00.475 is in the tonsils. And

NOTE Confidence: 0.9866665

00:29:00.475 --> 00:29:01.774 then we also got,

NOTE Confidence: 0.96201986

00:29:02.315 --> 00:29:04.475 a metastatic lymph node. Not

NOTE Confidence: 0.96201986

00:29:04.475 --> 00:29:06.154 a draining lymph node, but

NOTE Confidence: 0.96201986

00:29:06.154 --> 00:29:08.015 a metastatic lymph node. Yeah.

NOTE Confidence: 0.97997826

00:29:08.875 --> 00:29:10.235 Now at this stage, we

NOTE Confidence: 0.97997826

00:29:10.235 --> 00:29:11.855 had no idea what

NOTE Confidence: 0.99598503

00:29:12.440 --> 00:29:13.580 responses these,

NOTE Confidence: 0.9815166

00:29:14.760 --> 00:29:15.900 individuals were making

NOTE Confidence: 0.979628

00:29:16.440 --> 00:29:17.480 in the tumor, and the

NOTE Confidence: 0.979628

00:29:17.480 --> 00:29:18.680 tumor material, as you know,

NOTE Confidence: 0.979628

00:29:18.680 --> 00:29:19.580 is very limited.

NOTE Confidence: 0.9995921

00:29:20.120 --> 00:29:21.320 So we first had to

NOTE Confidence: 0.9995921

00:29:21.320 --> 00:29:21.820 identify

NOTE Confidence: 0.9976476

00:29:22.600 --> 00:29:24.680 what potential epitopes were being

NOTE Confidence: 0.9976476

00:29:24.680 --> 00:29:27.180 seen by these seventeen patients.

NOTE Confidence: 0.9979099

00:29:27.904 --> 00:29:29.044 So what we did

NOTE Confidence: 0.99254966

00:29:29.424 --> 00:29:30.645 to address that issue,

NOTE Confidence: 0.9504472

00:29:31.105 --> 00:29:32.164 we did the following,

NOTE Confidence: 0.9922426

00:29:32.865 --> 00:29:34.465 experiment. So we took the

NOTE Confidence: 0.9922426

00:29:34.465 --> 00:29:35.424 blood from these,

NOTE Confidence: 0.9534753

00:29:36.304 --> 00:29:36.804 HNSCC,

NOTE Confidence: 0.999871

00:29:37.745 --> 00:29:38.245 patients

NOTE Confidence: 0.9782005

00:29:38.945 --> 00:29:40.705 and then expanded these cells

NOTE Confidence: 0.9782005

00:29:40.705 --> 00:29:41.924 for two weeks, basically

NOTE Confidence: 0.9831749

00:29:42.880 --> 00:29:45.140 expanding the cells in vitro.

NOTE Confidence: 0.9141486

00:29:45.679 --> 00:29:47.200 And we used, about two

NOTE Confidence: 0.9141486

00:29:47.200 --> 00:29:48.980 hundred fifty predicted HPV

NOTE Confidence: 0.9891276

00:29:49.360 --> 00:29:49.860 peptides.

NOTE Confidence: 0.9892283

00:29:50.320 --> 00:29:51.520 We, of course, included e

NOTE Confidence: 0.9892283

00:29:51.520 --> 00:29:52.880 six, e seven, which is

NOTE Confidence: 0.9892283

00:29:52.880 --> 00:29:54.799 the canonical oncogene. But we

NOTE Confidence: 0.9892283

00:29:54.799 --> 00:29:56.160 also included e two and

NOTE Confidence: 0.9892283

00:29:56.160 --> 00:29:57.805 e five because there were

NOTE Confidence: 0.9892283

00:29:57.805 --> 00:29:58.785 some reports

NOTE Confidence: 0.96105087

00:29:59.485 --> 00:30:00.925 saying that one can get

NOTE Confidence: 0.96105087

00:30:00.925 --> 00:30:02.605 CDH responses to e two

NOTE Confidence: 0.96105087

00:30:02.605 --> 00:30:03.565 and e five. These were

NOTE Confidence: 0.96105087

00:30:03.565 --> 00:30:05.405 not in tumor samples, but

NOTE Confidence: 0.96105087

00:30:05.405 --> 00:30:06.625 in people who were HPV

NOTE Confidence: 0.73565406

00:30:06.925 --> 00:30:07.425 positive.

NOTE Confidence: 0.97093797

00:30:07.965 --> 00:30:09.405 And, so we included e

NOTE Confidence: 0.97093797

00:30:09.405 --> 00:30:10.545 two and e five.

NOTE Confidence: 0.99043167

00:30:10.980 --> 00:30:12.760 And then expanded this population,

NOTE Confidence: 0.9278867

00:30:13.620 --> 00:30:14.260 looked at,

NOTE Confidence: 0.90292966

00:30:15.140 --> 00:30:16.500 reactivity if we could expand

NOTE Confidence: 0.90292966

00:30:16.500 --> 00:30:17.960 any cells from these individuals

NOTE Confidence: 0.89316756

00:30:18.500 --> 00:30:19.860 from the blood. We did

NOTE Confidence: 0.89316756

00:30:19.860 --> 00:30:21.700 first interferon gamma ELISpot, then

NOTE Confidence: 0.89316756

00:30:21.700 --> 00:30:22.440 did ICS.

NOTE Confidence: 0.9736757

00:30:22.740 --> 00:30:24.120 And then if the response

NOTE Confidence: 0.9736757

00:30:24.179 --> 00:30:25.300 was was good enough, we

NOTE Confidence: 0.9736757

00:30:25.300 --> 00:30:26.445 then went ahead

NOTE Confidence: 0.9938396

00:30:26.905 --> 00:30:28.845 and identified the precise tetramer.

NOTE Confidence: 0.9944321

00:30:30.025 --> 00:30:31.145 So here is an example

NOTE Confidence: 0.9944321

00:30:31.145 --> 00:30:32.025 of one of the good

NOTE Confidence: 0.9944321

00:30:32.025 --> 00:30:32.525 responders.

NOTE Confidence: 0.850525

00:30:32.985 --> 00:30:33.945 It's a very nice after

NOTE Confidence: 0.850525

00:30:33.945 --> 00:30:34.685 its expansion.

NOTE Confidence: 0.9534714

00:30:35.145 --> 00:30:36.505 We're looking now at the

NOTE Confidence: 0.9534714

00:30:36.505 --> 00:30:37.945 pool of peptides, all five

NOTE Confidence: 0.9534714

00:30:37.945 --> 00:30:38.825 of all four of them,

NOTE Confidence: 0.9534714

00:30:38.825 --> 00:30:39.945 all two fifty. We see

NOTE Confidence: 0.9534714

00:30:39.945 --> 00:30:40.685 nice response.

NOTE Confidence: 0.96369696

00:30:41.269 --> 00:30:42.870 By ICS, you see very

NOTE Confidence: 0.96369696

00:30:42.870 --> 00:30:43.269 nice,

NOTE Confidence: 0.83802414

00:30:44.629 --> 00:30:46.309 interferon gamma and tNF alpha

NOTE Confidence: 0.83802414

00:30:46.309 --> 00:30:46.809 production.

NOTE Confidence: 0.90849936

00:30:47.350 --> 00:30:49.029 And then by tetramer again,

NOTE Confidence: 0.90849936

00:30:49.029 --> 00:30:50.309 a very nice staining. This

NOTE Confidence: 0.90849936

00:30:50.309 --> 00:30:51.509 is the same tetramer, double

NOTE Confidence: 0.90849936

00:30:51.509 --> 00:30:53.289 tetramer staining. You see that.

NOTE Confidence: 0.97576916

00:30:54.525 --> 00:30:56.765 And, interestingly, all seventeen patients

NOTE Confidence: 0.97576916

00:30:56.765 --> 00:30:57.905 that we looked at

NOTE Confidence: 0.9864445

00:30:58.365 --> 00:30:59.105 were positive.

NOTE Confidence: 0.8472403

00:30:59.885 --> 00:31:00.845 So there is all of

NOTE Confidence: 0.8472403

00:31:00.845 --> 00:31:01.585 these individuals.

NOTE Confidence: 0.979671

00:31:02.045 --> 00:31:02.925 There was no one that

NOTE Confidence: 0.979671

00:31:02.925 --> 00:31:04.765 was negative. Some were higher,

NOTE Confidence: 0.979671

00:31:04.765 --> 00:31:05.965 some were lower in the

NOTE Confidence: 0.979671

00:31:05.965 --> 00:31:07.565 response, but all of them,

NOTE Confidence: 0.9632294

00:31:08.365 --> 00:31:09.345 gave us a response.

NOTE Confidence: 0.9638362

00:31:09.880 --> 00:31:11.000 That is, there was some

NOTE Confidence: 0.9638362

00:31:11.000 --> 00:31:12.440 low number of cells present

NOTE Confidence: 0.9638362

00:31:12.440 --> 00:31:13.559 in the blood that were

NOTE Confidence: 0.9638362

00:31:13.640 --> 00:31:14.700 that we could expand.

NOTE Confidence: 0.99708444

00:31:16.760 --> 00:31:17.720 And then we ended up

NOTE Confidence: 0.99708444

00:31:17.720 --> 00:31:18.940 identifying several,

NOTE Confidence: 0.9982185

00:31:19.720 --> 00:31:21.260 tetramers that we made.

NOTE Confidence: 0.9824663

00:31:21.975 --> 00:31:23.255 Note that e two and

NOTE Confidence: 0.9824663

00:31:23.255 --> 00:31:24.315 e five tetramers,

NOTE Confidence: 0.9430281

00:31:25.255 --> 00:31:26.615 there are several came responses

NOTE Confidence: 0.9430281

00:31:26.615 --> 00:31:27.575 came from e two and

NOTE Confidence: 0.9430281

00:31:27.575 --> 00:31:28.535 e five, some from e

NOTE Confidence: 0.9430281

00:31:28.535 --> 00:31:29.335 six. This is not by

NOTE Confidence: 0.9430281

00:31:29.335 --> 00:31:30.235 any means comprehensive.

NOTE Confidence: 0.9972692

00:31:30.695 --> 00:31:31.495 We had these,

NOTE Confidence: 0.92856055

00:31:32.054 --> 00:31:33.255 tetramers. So we used these

NOTE Confidence: 0.92856055

00:31:33.255 --> 00:31:33.755 tetramers.

NOTE Confidence: 0.9976526

00:31:34.375 --> 00:31:35.415 Now we could go back.

NOTE Confidence: 0.9976526

00:31:35.415 --> 00:31:36.554 We knew which individual

NOTE Confidence: 0.98481476

00:31:37.360 --> 00:31:38.880 was responding to which cell

NOTE Confidence: 0.98481476

00:31:38.880 --> 00:31:40.559 based on the expansion from

NOTE Confidence: 0.98481476

00:31:40.559 --> 00:31:41.519 the blood. So we can

NOTE Confidence: 0.98481476

00:31:41.519 --> 00:31:42.419 now go back

NOTE Confidence: 0.9852133

00:31:42.720 --> 00:31:44.399 and do the stain of

NOTE Confidence: 0.9852133

00:31:44.399 --> 00:31:45.380 the TILs themselves.

NOTE Confidence: 0.9813152

00:31:48.000 --> 00:31:49.519 And the results were really

NOTE Confidence: 0.9813152

00:31:49.679 --> 00:31:51.495 I never expected this. I

NOTE Confidence: 0.9813152

00:31:51.495 --> 00:31:53.035 did not expect to see

NOTE Confidence: 0.9877754

00:31:53.495 --> 00:31:54.795 that in these individuals,

NOTE Confidence: 0.98987275

00:31:55.735 --> 00:31:57.035 this is now no expansion.

NOTE Confidence: 0.9797202

00:31:57.575 --> 00:31:58.775 This is just staining the

NOTE Confidence: 0.9797202

00:31:58.775 --> 00:31:59.275 TILs,

NOTE Confidence: 0.9991312

00:32:00.135 --> 00:32:01.035 with the tetramer.

NOTE Confidence: 0.97714835

00:32:01.975 --> 00:32:03.415 So here is PD one

NOTE Confidence: 0.97714835

00:32:03.415 --> 00:32:05.175 on this axis, tetramer on

NOTE Confidence: 0.97714835

00:32:05.175 --> 00:32:07.070 this axis. This is a

NOTE Confidence: 0.9998691

00:32:08.090 --> 00:32:08.590 tetramer

NOTE Confidence: 0.9454275

00:32:09.130 --> 00:32:11.049 recognizing peptides one fifty one

NOTE Confidence: 0.9454275

00:32:11.049 --> 00:32:12.169 to one fifty eight from

NOTE Confidence: 0.9454275

00:32:12.169 --> 00:32:12.970 the e two. It's a

NOTE Confidence: 0.9454275

00:32:12.970 --> 00:32:13.950 o one restricted.

NOTE Confidence: 0.92333835

00:32:14.490 --> 00:32:15.870 And the primary tumor,

NOTE Confidence: 0.9788346

00:32:16.250 --> 00:32:17.950 and here's the metastatic tumor

NOTE Confidence: 0.7951786

00:32:18.675 --> 00:32:19.575 From the metastatic,

NOTE Confidence: 0.9213656

00:32:20.595 --> 00:32:22.035 the the the lymph node

NOTE Confidence: 0.9213656

00:32:22.035 --> 00:32:23.495 that also has the tumor,

NOTE Confidence: 0.9956199

00:32:23.795 --> 00:32:24.535 three percent

NOTE Confidence: 0.88211304

00:32:25.475 --> 00:32:26.775 point one percent.

NOTE Confidence: 0.98647326

00:32:27.315 --> 00:32:28.535 Here's another one,

NOTE Confidence: 0.99526995

00:32:28.835 --> 00:32:30.535 five percent, ten percent.

NOTE Confidence: 0.99964374

00:32:31.630 --> 00:32:33.090 It's really quite amazing

NOTE Confidence: 0.9990449

00:32:33.390 --> 00:32:34.130 that these

NOTE Confidence: 0.9838878

00:32:34.669 --> 00:32:36.510 treatment naive individuals who are

NOTE Confidence: 0.9838878

00:32:36.510 --> 00:32:37.570 coming in for surgery

NOTE Confidence: 0.9976317

00:32:38.270 --> 00:32:40.289 have such a vigorous response

NOTE Confidence: 0.9981838

00:32:40.750 --> 00:32:41.250 ongoing

NOTE Confidence: 0.9655573

00:32:41.870 --> 00:32:43.409 in their, in their tumor.

NOTE Confidence: 0.9467171

00:32:43.950 --> 00:32:44.669 This is a

NOTE Confidence: 0.9847303

00:32:47.534 --> 00:32:48.575 what if we use the

NOTE Confidence: 0.9847303

00:32:48.575 --> 00:32:49.934 same tetramer and look in

NOTE Confidence: 0.9847303

00:32:49.934 --> 00:32:50.595 the blood?

NOTE Confidence: 0.9983109

00:32:51.455 --> 00:32:52.355 Very low.

NOTE Confidence: 0.98071784

00:32:52.815 --> 00:32:54.835 The response is barely detectable.

NOTE Confidence: 0.86405116

00:32:55.855 --> 00:32:57.554 Yeah. Because, again,

NOTE Confidence: 0.98298424

00:32:59.190 --> 00:33:00.630 I didn't I didn't talk

NOTE Confidence: 0.98298424

00:33:00.630 --> 00:33:02.230 about this earlier, but the

NOTE Confidence: 0.98298424

00:33:02.389 --> 00:33:03.450 but in the,

NOTE Confidence: 0.9669934

00:33:04.389 --> 00:33:05.750 when you we did some

NOTE Confidence: 0.9669934

00:33:05.750 --> 00:33:07.049 parabiosis experiments

NOTE Confidence: 0.98075897

00:33:07.590 --> 00:33:09.350 in our chronic LCMV infection

NOTE Confidence: 0.98075897

00:33:09.350 --> 00:33:10.809 mice to see which cells

NOTE Confidence: 0.98075897

00:33:11.029 --> 00:33:11.909 are in the blood and

NOTE Confidence: 0.98075897

00:33:11.909 --> 00:33:12.809 which will actually

NOTE Confidence: 0.98953384

00:33:13.190 --> 00:33:15.355 migrate. It's only the transitory

NOTE Confidence: 0.98953384

00:33:15.495 --> 00:33:15.995 effectors

NOTE Confidence: 0.9968693

00:33:16.855 --> 00:33:18.134 that will come out. So

NOTE Confidence: 0.9968693

00:33:18.134 --> 00:33:20.315 the more differentiated cells

NOTE Confidence: 0.9869098

00:33:20.695 --> 00:33:22.294 are resident at the sites

NOTE Confidence: 0.9869098

00:33:22.294 --> 00:33:22.955 of infection,

NOTE Confidence: 0.9556904

00:33:23.575 --> 00:33:25.034 and the stem like cell

NOTE Confidence: 0.9996625

00:33:25.335 --> 00:33:26.075 is resident

NOTE Confidence: 0.98444414

00:33:26.615 --> 00:33:27.095 at the

NOTE Confidence: 0.76552963

00:33:31.880 --> 00:33:32.380 circulates

NOTE Confidence: 0.9811533

00:33:33.400 --> 00:33:34.299 are the recently

NOTE Confidence: 0.97108877

00:33:34.840 --> 00:33:36.780 generated effector like cells.

NOTE Confidence: 0.99907464

00:33:37.400 --> 00:33:38.860 So so it's not surprising

NOTE Confidence: 0.9879857

00:33:39.799 --> 00:33:41.225 that in the PBMC,

NOTE Confidence: 0.9601722

00:33:42.085 --> 00:33:42.965 there are very few it's

NOTE Confidence: 0.9601722

00:33:42.965 --> 00:33:44.725 not it's not zero because

NOTE Confidence: 0.9601722

00:33:44.725 --> 00:33:46.005 you know that's where we

NOTE Confidence: 0.9601722

00:33:46.005 --> 00:33:47.684 expanded these cells from. So

NOTE Confidence: 0.9601722

00:33:47.684 --> 00:33:48.805 we know that the cells

NOTE Confidence: 0.9601722

00:33:48.805 --> 00:33:50.165 were there, but when you

NOTE Confidence: 0.9601722

00:33:50.165 --> 00:33:51.145 do a stain,

NOTE Confidence: 0.98552907

00:33:51.605 --> 00:33:53.125 the frequency is very low.

NOTE Confidence: 0.98552907

00:33:53.125 --> 00:33:55.100 I highlight this part because

NOTE Confidence: 0.98552907

00:33:55.320 --> 00:33:56.760 we often look at,

NOTE Confidence: 0.97764844

00:33:57.400 --> 00:33:59.080 new antigen specific cells, we

NOTE Confidence: 0.97764844

00:33:59.080 --> 00:34:00.120 want to look at tumor

NOTE Confidence: 0.97764844

00:34:00.120 --> 00:34:01.660 specific cells in the blood

NOTE Confidence: 0.97162235

00:34:02.280 --> 00:34:03.560 of somebody who's not had

NOTE Confidence: 0.97162235

00:34:03.560 --> 00:34:04.300 any treatment.

NOTE Confidence: 0.7767117

00:34:05.240 --> 00:34:05.740 That's

NOTE Confidence: 0.94850993

00:34:06.304 --> 00:34:07.105 it's not that they're not

NOTE Confidence: 0.94850993

00:34:07.105 --> 00:34:08.065 there, but you'll have to

NOTE Confidence: 0.94850993

00:34:08.065 --> 00:34:09.425 look very high. K? There'll

NOTE Confidence: 0.94850993

00:34:09.425 --> 00:34:10.385 be a very, very low

NOTE Confidence: 0.94850993

00:34:10.385 --> 00:34:10.885 frequency.

NOTE Confidence: 0.8717929

00:34:11.344 --> 00:34:12.725 So here are some example

NOTE Confidence: 0.97996217

00:34:13.105 --> 00:34:14.705 showing you the frequency of,

NOTE Confidence: 0.97996217

00:34:14.945 --> 00:34:16.625 about six six or seven

NOTE Confidence: 0.97996217

00:34:16.625 --> 00:34:17.525 different tetramers

NOTE Confidence: 0.8540947

00:34:18.065 --> 00:34:19.364 in different, individuals.

NOTE Confidence: 0.98517704

00:34:20.239 --> 00:34:21.599 And you can see that

NOTE Confidence: 0.98517704

00:34:21.599 --> 00:34:22.660 very high frequencies

NOTE Confidence: 0.9119678

00:34:23.359 --> 00:34:24.880 ranging from point one percent

NOTE Confidence: 0.9119678

00:34:24.880 --> 00:34:26.579 up sometimes even ten percent.

NOTE Confidence: 0.9119678

00:34:26.799 --> 00:34:27.859 But in the blood,

NOTE Confidence: 0.8650413

00:34:28.319 --> 00:34:30.079 by this approach, below detection,

NOTE Confidence: 0.8650413

00:34:30.079 --> 00:34:31.359 I. Bill below point or

NOTE Confidence: 0.8650413

00:34:31.359 --> 00:34:32.020 two percent.

NOTE Confidence: 0.89492637

00:34:32.719 --> 00:34:33.760 So a lot of cells

NOTE Confidence: 0.89492637

00:34:33.760 --> 00:34:35.299 in the tumor, k,

NOTE Confidence: 0.9878573

00:34:35.765 --> 00:34:37.045 but very few cells in

NOTE Confidence: 0.9878573

00:34:37.045 --> 00:34:38.745 the circulation, antigen specific.

NOTE Confidence: 0.9621724

00:34:39.765 --> 00:34:41.045 Okay. So the next question,

NOTE Confidence: 0.9621724

00:34:41.045 --> 00:34:42.165 of course, was, what do

NOTE Confidence: 0.9621724

00:34:42.165 --> 00:34:43.205 these cells look like? Do

NOTE Confidence: 0.9621724

00:34:43.205 --> 00:34:44.165 we have that stem like

NOTE Confidence: 0.9621724

00:34:44.165 --> 00:34:45.364 population? So we did single

NOTE Confidence: 0.9621724

00:34:45.364 --> 00:34:46.645 cell RNA seq, and the

NOTE Confidence: 0.9621724

00:34:46.645 --> 00:34:48.005 answer is yes. You again

NOTE Confidence: 0.9621724

00:34:48.005 --> 00:34:48.505 find

NOTE Confidence: 0.9488303

00:34:48.880 --> 00:34:51.219 within the tetramer sorted cells.

NOTE Confidence: 0.9488303

00:34:51.359 --> 00:34:52.820 Now this is all on

NOTE Confidence: 0.9919687

00:34:53.680 --> 00:34:54.739 getting the,

NOTE Confidence: 0.9739012

00:34:56.160 --> 00:34:57.920 the cells isolating them directly

NOTE Confidence: 0.9739012

00:34:57.920 --> 00:34:58.739 from the tumor

NOTE Confidence: 0.8073527

00:34:59.440 --> 00:34:59.920 and,

NOTE Confidence: 0.9396299

00:35:00.400 --> 00:35:01.520 and then doing single sign

NOTE Confidence: 0.9396299

00:35:01.520 --> 00:35:02.980 seq. And, again, you have

NOTE Confidence: 0.9396299

00:35:03.065 --> 00:35:04.665 the canonical cell here, which

NOTE Confidence: 0.9396299

00:35:04.665 --> 00:35:06.425 has TCF one. It's amazing

NOTE Confidence: 0.9396299

00:35:06.425 --> 00:35:07.645 that Xcl one

NOTE Confidence: 0.9951928

00:35:07.945 --> 00:35:09.165 always goes with them.

NOTE Confidence: 0.9479021

00:35:09.785 --> 00:35:11.065 It was just wasn't just

NOTE Confidence: 0.9479021

00:35:11.065 --> 00:35:11.965 a mouse phenomena.

NOTE Confidence: 0.9419711

00:35:12.345 --> 00:35:13.645 It every human,

NOTE Confidence: 0.9543284

00:35:14.105 --> 00:35:15.945 stem like cell defined by

NOTE Confidence: 0.9543284

00:35:15.945 --> 00:35:17.485 us or by the others

NOTE Confidence: 0.9543284

00:35:17.625 --> 00:35:19.109 have shown that XCL one

NOTE Confidence: 0.9543284

00:35:19.109 --> 00:35:20.549 is there. Again, this attracts

NOTE Confidence: 0.9543284

00:35:20.549 --> 00:35:22.069 CDC one. It's part of

NOTE Confidence: 0.9543284

00:35:22.069 --> 00:35:23.450 the niche that they create.

NOTE Confidence: 0.9197435

00:35:24.469 --> 00:35:24.969 And,

NOTE Confidence: 0.96346664

00:35:25.829 --> 00:35:27.269 again, no granzyme b in

NOTE Confidence: 0.96346664

00:35:27.269 --> 00:35:28.010 these cells.

NOTE Confidence: 0.9137443

00:35:29.349 --> 00:35:30.549 And you have LEF one,

NOTE Confidence: 0.9137443

00:35:30.549 --> 00:35:32.230 which is another transcription factor

NOTE Confidence: 0.9137443

00:35:32.230 --> 00:35:33.029 you see in these stem

NOTE Confidence: 0.9137443

00:35:33.029 --> 00:35:34.505 cells, more I l seven

NOTE Confidence: 0.9137443

00:35:34.505 --> 00:35:36.525 receptor over here, and, again,

NOTE Confidence: 0.9137443

00:35:36.665 --> 00:35:38.265 very little perforin and so

NOTE Confidence: 0.9137443

00:35:38.265 --> 00:35:38.765 on.

NOTE Confidence: 0.98466456

00:35:39.945 --> 00:35:41.145 So we found we looked

NOTE Confidence: 0.98466456

00:35:41.145 --> 00:35:42.205 at about fifteen

NOTE Confidence: 0.8975027

00:35:42.985 --> 00:35:44.045 or so tetrimers

NOTE Confidence: 0.9751608

00:35:44.745 --> 00:35:45.305 in different,

NOTE Confidence: 0.941847

00:35:46.580 --> 00:35:48.340 different per patients, and all

NOTE Confidence: 0.941847

00:35:48.340 --> 00:35:49.140 of them have the three

NOTE Confidence: 0.941847

00:35:49.140 --> 00:35:49.640 subsets.

NOTE Confidence: 0.97355556

00:35:50.180 --> 00:35:51.780 So the blue is the

NOTE Confidence: 0.97355556

00:35:51.780 --> 00:35:52.180 more,

NOTE Confidence: 0.9811836

00:35:53.700 --> 00:35:55.320 is the more exhausted subset.

NOTE Confidence: 0.9811836

00:35:55.380 --> 00:35:56.739 This was, in most cases,

NOTE Confidence: 0.9811836

00:35:56.739 --> 00:35:58.340 the highest number. But all

NOTE Confidence: 0.9811836

00:35:58.340 --> 00:35:59.320 of them had

NOTE Confidence: 0.98162526

00:35:59.835 --> 00:36:01.675 this transitory population, which is

NOTE Confidence: 0.98162526

00:36:01.675 --> 00:36:02.815 shown here in yellow,

NOTE Confidence: 0.95126206

00:36:03.435 --> 00:36:05.515 and also had the stem

NOTE Confidence: 0.95126206

00:36:05.515 --> 00:36:07.355 like population. So these three

NOTE Confidence: 0.95126206

00:36:07.355 --> 00:36:09.035 sub again, so in these

NOTE Confidence: 0.95126206

00:36:09.035 --> 00:36:10.234 head and neck cancer patients,

NOTE Confidence: 0.95126206

00:36:10.234 --> 00:36:11.675 you have an ongoing response

NOTE Confidence: 0.95126206

00:36:11.675 --> 00:36:12.960 there. You have the stem

NOTE Confidence: 0.95126206

00:36:12.960 --> 00:36:14.500 like cell is generating

NOTE Confidence: 0.99173045

00:36:14.880 --> 00:36:16.100 some effector cells

NOTE Confidence: 0.8764193

00:36:17.040 --> 00:36:18.239 and these are eventually getting

NOTE Confidence: 0.8764193

00:36:18.239 --> 00:36:19.760 glasses. It's a very active

NOTE Confidence: 0.8764193

00:36:19.760 --> 00:36:20.739 program ongoing.

NOTE Confidence: 0.9804398

00:36:21.360 --> 00:36:22.560 In this study, we also

NOTE Confidence: 0.9804398

00:36:22.560 --> 00:36:24.100 looked at the TCR sequences

NOTE Confidence: 0.9316983

00:36:24.640 --> 00:36:26.400 and the TCR sequences are

NOTE Confidence: 0.9316983

00:36:26.400 --> 00:36:26.900 shared.

NOTE Confidence: 0.96302867

00:36:27.364 --> 00:36:28.645 At least the major clonal

NOTE Confidence: 0.96302867

00:36:28.645 --> 00:36:30.005 types are shared between these

NOTE Confidence: 0.96302867

00:36:30.005 --> 00:36:32.505 three, again, establishing the lineage

NOTE Confidence: 0.96302867

00:36:32.565 --> 00:36:33.944 relationship between them.

NOTE Confidence: 0.9723425

00:36:34.645 --> 00:36:36.085 But and the other interesting

NOTE Confidence: 0.9723425

00:36:36.085 --> 00:36:37.785 finding was, in some cases,

NOTE Confidence: 0.99246126

00:36:38.325 --> 00:36:38.825 these

NOTE Confidence: 0.982693

00:36:39.930 --> 00:36:41.390 responses are very oligoclonal.

NOTE Confidence: 0.9982803

00:36:42.410 --> 00:36:44.170 In some cases, about fifty

NOTE Confidence: 0.9982803

00:36:44.170 --> 00:36:44.670 percent

NOTE Confidence: 0.8962211

00:36:45.369 --> 00:36:46.969 of the tetra deposits is

NOTE Confidence: 0.8962211

00:36:46.969 --> 00:36:48.890 very single clonal type. In

NOTE Confidence: 0.8962211

00:36:48.890 --> 00:36:49.930 others, a little bit more

NOTE Confidence: 0.8962211

00:36:49.930 --> 00:36:50.430 heterogeneity,

NOTE Confidence: 0.9961512

00:36:50.969 --> 00:36:51.950 but very oligoclonal.

NOTE Confidence: 0.9844188

00:36:52.864 --> 00:36:53.905 And I think you only

NOTE Confidence: 0.9844188

00:36:53.905 --> 00:36:54.885 see this oligochromality

NOTE Confidence: 0.96582234

00:36:55.825 --> 00:36:57.285 when you have long term

NOTE Confidence: 0.96582234

00:36:57.424 --> 00:36:59.265 chronic antigen stimulation, which has

NOTE Confidence: 0.96582234

00:36:59.265 --> 00:37:00.645 selected for certain TCRs.

NOTE Confidence: 0.73949265

00:37:01.025 --> 00:37:01.525 Yeah.

NOTE Confidence: 0.9178858

00:37:04.785 --> 00:37:06.005 Then we ask the question,

NOTE Confidence: 0.9671591

00:37:06.500 --> 00:37:08.040 are these stem like cells,

NOTE Confidence: 0.9453785

00:37:08.420 --> 00:37:09.700 the ones shown here in

NOTE Confidence: 0.9453785

00:37:09.700 --> 00:37:11.460 green, are these cells actually

NOTE Confidence: 0.9453785

00:37:11.460 --> 00:37:11.960 functional?

NOTE Confidence: 0.99913687

00:37:12.339 --> 00:37:14.119 Can we somehow demonstrate

NOTE Confidence: 0.99593335

00:37:14.420 --> 00:37:16.500 functionality in these cells? So

NOTE Confidence: 0.99593335

00:37:16.500 --> 00:37:17.559 for this, we

NOTE Confidence: 0.99129885

00:37:18.714 --> 00:37:20.015 we sorted the

NOTE Confidence: 0.92635983

00:37:20.875 --> 00:37:22.234 we we didn't use tetramer

NOTE Confidence: 0.92635983

00:37:22.234 --> 00:37:23.214 here because this

NOTE Confidence: 0.96470946

00:37:23.755 --> 00:37:25.194 the frequency is too low.

NOTE Confidence: 0.96470946

00:37:25.194 --> 00:37:25.994 We had to get as

NOTE Confidence: 0.96470946

00:37:25.994 --> 00:37:27.035 many cells as we could.

NOTE Confidence: 0.96470946

00:37:27.035 --> 00:37:27.755 We wanted to do the

NOTE Confidence: 0.96470946

00:37:27.755 --> 00:37:29.214 CTV labeling experiment.

NOTE Confidence: 0.9818207

00:37:30.234 --> 00:37:31.275 Frequency is not lower. The

NOTE Confidence: 0.9818207

00:37:31.275 --> 00:37:32.895 total numbers are not enough.

NOTE Confidence: 0.9818207

00:37:32.954 --> 00:37:34.500 So we enriched for this.

NOTE Confidence: 0.9818207

00:37:34.739 --> 00:37:36.500 So, basically, we did a

NOTE Confidence: 0.9818207

00:37:36.500 --> 00:37:37.400 sorting strategy

NOTE Confidence: 0.9669986

00:37:37.860 --> 00:37:39.140 that would enrich for where

NOTE Confidence: 0.9669986

00:37:39.140 --> 00:37:40.260 the stem like cells would

NOTE Confidence: 0.9669986

00:37:40.260 --> 00:37:41.540 be and where the more

NOTE Confidence: 0.9669986

00:37:41.540 --> 00:37:42.900 differentiated ones would be. So

NOTE Confidence: 0.9669986

00:37:42.900 --> 00:37:43.960 for this, we basically

NOTE Confidence: 0.9718506

00:37:44.260 --> 00:37:45.780 gated on PD one positive

NOTE Confidence: 0.9718506

00:37:45.780 --> 00:37:46.280 cells

NOTE Confidence: 0.8611691

00:37:46.900 --> 00:37:47.640 and then,

NOTE Confidence: 0.9963477

00:37:48.100 --> 00:37:48.600 used

NOTE Confidence: 0.94598025

00:37:49.905 --> 00:37:51.105 cells which were TIN three

NOTE Confidence: 0.94598025

00:37:51.105 --> 00:37:52.625 negative and CD thirty nine

NOTE Confidence: 0.94598025

00:37:52.625 --> 00:37:54.225 negative. So this would enrich

NOTE Confidence: 0.94598025

00:37:54.225 --> 00:37:55.445 for the stem like population,

NOTE Confidence: 0.944434

00:37:56.225 --> 00:37:57.505 and then the TIN three

NOTE Confidence: 0.944434

00:37:57.505 --> 00:37:59.185 positive, thirty nine positive would

NOTE Confidence: 0.944434

00:37:59.185 --> 00:38:00.885 enrich for the more differentiated

NOTE Confidence: 0.944434

00:38:00.945 --> 00:38:01.445 population.

NOTE Confidence: 0.90623313

00:38:01.905 --> 00:38:03.505 Then we culture these we

NOTE Confidence: 0.90623313

00:38:03.505 --> 00:38:04.005 we

NOTE Confidence: 0.9799838

00:38:04.530 --> 00:38:06.390 label the cells with CTV

NOTE Confidence: 0.9244607

00:38:07.010 --> 00:38:07.890 so we could look at,

NOTE Confidence: 0.9244607

00:38:08.130 --> 00:38:08.630 division

NOTE Confidence: 0.9219568

00:38:09.170 --> 00:38:11.489 and then stimulated them, but

NOTE Confidence: 0.9219568

00:38:11.489 --> 00:38:13.090 now we know exactly which

NOTE Confidence: 0.9219568

00:38:13.090 --> 00:38:14.150 peptide to use.

NOTE Confidence: 0.9398361

00:38:14.530 --> 00:38:15.830 So now we could stimulate

NOTE Confidence: 0.9398361

00:38:15.890 --> 00:38:17.350 with their Cognate peptide,

NOTE Confidence: 0.99926955

00:38:17.810 --> 00:38:18.610 and you can see the

NOTE Confidence: 0.99926955

00:38:18.610 --> 00:38:19.510 results here.

NOTE Confidence: 0.99991965

00:38:20.135 --> 00:38:20.635 So

NOTE Confidence: 0.9162459

00:38:21.015 --> 00:38:22.934 so we're looking here at

NOTE Confidence: 0.9162459

00:38:22.934 --> 00:38:23.755 at five days.

NOTE Confidence: 0.99219704

00:38:24.055 --> 00:38:25.255 After five days in culture,

NOTE Confidence: 0.99219704

00:38:25.255 --> 00:38:26.855 this is the unstimulated. There

NOTE Confidence: 0.99219704

00:38:26.855 --> 00:38:28.474 is no peptide stimulation.

NOTE Confidence: 0.99834174

00:38:29.255 --> 00:38:30.135 Here is the

NOTE Confidence: 0.9567286

00:38:32.150 --> 00:38:33.270 on this axis is the

NOTE Confidence: 0.9567286

00:38:33.270 --> 00:38:34.310 tetramer. Now we can stain

NOTE Confidence: 0.9567286

00:38:34.310 --> 00:38:35.590 with the tetramer. So even

NOTE Confidence: 0.9567286

00:38:35.590 --> 00:38:36.550 though we didn't sort with

NOTE Confidence: 0.9567286

00:38:36.550 --> 00:38:37.989 the tetramer, we now stain

NOTE Confidence: 0.9567286

00:38:37.989 --> 00:38:39.110 with the tetramers. We are

NOTE Confidence: 0.9567286

00:38:39.110 --> 00:38:40.790 truly looking at the antigen

NOTE Confidence: 0.9567286

00:38:40.790 --> 00:38:41.690 specific cells.

NOTE Confidence: 0.96993065

00:38:42.070 --> 00:38:43.590 And what you'd see here

NOTE Confidence: 0.96993065

00:38:43.590 --> 00:38:45.690 is that there's minimal proliferation

NOTE Confidence: 0.96993065

00:38:45.830 --> 00:38:46.810 without the peptide,

NOTE Confidence: 0.975134

00:38:48.114 --> 00:38:49.715 And here's the tetramer population

NOTE Confidence: 0.975134

00:38:49.715 --> 00:38:51.094 here. No division.

NOTE Confidence: 0.94660205

00:38:52.035 --> 00:38:53.315 And if you look now

NOTE Confidence: 0.94660205

00:38:53.315 --> 00:38:55.094 here after adding the peptide

NOTE Confidence: 0.89716923

00:38:55.635 --> 00:38:56.775 with the more differentiated

NOTE Confidence: 0.9895637

00:38:57.075 --> 00:38:57.575 cells,

NOTE Confidence: 0.99754333

00:38:57.955 --> 00:38:59.735 very minimal to no proliferation.

NOTE Confidence: 0.9754047

00:39:00.579 --> 00:39:02.260 Again, the proliferative capacity of

NOTE Confidence: 0.9754047

00:39:02.260 --> 00:39:03.940 these more exhausted cells is

NOTE Confidence: 0.9754047

00:39:03.940 --> 00:39:04.680 very minimal.

NOTE Confidence: 0.989171

00:39:04.980 --> 00:39:06.500 But look what happens here.

NOTE Confidence: 0.989171

00:39:06.500 --> 00:39:07.319 These cells

NOTE Confidence: 0.9548717

00:39:08.339 --> 00:39:09.319 proliferate beautifully.

NOTE Confidence: 0.9996411

00:39:10.099 --> 00:39:11.559 So they have this ability

NOTE Confidence: 0.9733357

00:39:11.940 --> 00:39:13.380 under the right conditions. You

NOTE Confidence: 0.9733357

00:39:13.380 --> 00:39:14.739 provide the peptide, and they

NOTE Confidence: 0.9733357

00:39:14.739 --> 00:39:16.285 will proliferate. You get very

NOTE Confidence: 0.9733357

00:39:16.285 --> 00:39:17.565 nice proliferation here. This is

NOTE Confidence: 0.9733357

00:39:17.565 --> 00:39:18.525 a summary of all the

NOTE Confidence: 0.9733357

00:39:18.525 --> 00:39:19.025 experiments

NOTE Confidence: 0.9754688

00:39:19.485 --> 00:39:21.665 that we did. Minimal proliferation

NOTE Confidence: 0.9754688

00:39:21.805 --> 00:39:23.645 of the more differentiated cells,

NOTE Confidence: 0.9754688

00:39:23.645 --> 00:39:24.864 but very nice proliferation,

NOTE Confidence: 0.9743486

00:39:25.805 --> 00:39:27.025 and CTV dilution

NOTE Confidence: 0.94746935

00:39:27.325 --> 00:39:28.705 of the stem like cells.

NOTE Confidence: 0.9890132

00:39:29.090 --> 00:39:30.210 And what happens now? Do

NOTE Confidence: 0.9890132

00:39:30.210 --> 00:39:31.810 they differentiate into effector like

NOTE Confidence: 0.9890132

00:39:31.810 --> 00:39:33.330 cell? Yes. They do. So

NOTE Confidence: 0.9890132

00:39:33.330 --> 00:39:34.390 if you now look

NOTE Confidence: 0.9766302

00:39:34.930 --> 00:39:36.050 after the if you now

NOTE Confidence: 0.9766302

00:39:36.050 --> 00:39:37.590 look at the stimulations,

NOTE Confidence: 0.86027014

00:39:38.210 --> 00:39:39.910 of how the markers change,

NOTE Confidence: 0.86027014

00:39:40.050 --> 00:39:41.350 TIM three comes up.

NOTE Confidence: 0.9922546

00:39:41.694 --> 00:39:43.234 Granzyme b comes up beautifully.

NOTE Confidence: 0.82522583

00:39:43.694 --> 00:39:44.674 K. See, before,

NOTE Confidence: 0.92221844

00:39:45.055 --> 00:39:46.255 there was no granzyme b

NOTE Confidence: 0.92221844

00:39:46.255 --> 00:39:47.855 in these cells. Granzyme b

NOTE Confidence: 0.92221844

00:39:47.855 --> 00:39:49.535 comes up. Three thirty nine

NOTE Confidence: 0.92221844

00:39:49.535 --> 00:39:50.355 comes up.

NOTE Confidence: 0.945972

00:39:50.734 --> 00:39:52.575 IL seven receptor was there,

NOTE Confidence: 0.945972

00:39:52.575 --> 00:39:54.114 goes down. K.

NOTE Confidence: 0.98321366

00:39:54.789 --> 00:39:56.150 So it and you can

NOTE Confidence: 0.98321366

00:39:56.150 --> 00:39:57.190 see that these cells had

NOTE Confidence: 0.98321366

00:39:57.190 --> 00:39:59.109 IL seven receptor. These cells

NOTE Confidence: 0.98321366

00:39:59.109 --> 00:40:00.630 didn't. K. As I've told

NOTE Confidence: 0.98321366

00:40:00.630 --> 00:40:01.829 you earlier, these cells don't

NOTE Confidence: 0.98321366

00:40:01.829 --> 00:40:03.589 survive that long. But after

NOTE Confidence: 0.98321366

00:40:03.589 --> 00:40:05.190 you generate the factors, IL

NOTE Confidence: 0.98321366

00:40:05.190 --> 00:40:07.185 seven receptor comes down. And,

NOTE Confidence: 0.98321366

00:40:07.185 --> 00:40:08.305 of course, over here, not

NOTE Confidence: 0.98321366

00:40:08.305 --> 00:40:09.445 a whole lot is happening

NOTE Confidence: 0.9334662

00:40:09.745 --> 00:40:10.864 except to point out that

NOTE Confidence: 0.9334662

00:40:10.864 --> 00:40:12.065 these cells were already TM

NOTE Confidence: 0.9334662

00:40:12.065 --> 00:40:13.825 three positive. These cells had

NOTE Confidence: 0.9334662

00:40:13.825 --> 00:40:15.344 granzyme b, whereas these cells

NOTE Confidence: 0.9334662

00:40:15.344 --> 00:40:16.005 did not.

NOTE Confidence: 0.9409487

00:40:17.185 --> 00:40:18.145 These cells had,

NOTE Confidence: 0.9973639

00:40:18.785 --> 00:40:19.525 you know,

NOTE Confidence: 0.98117256

00:40:21.980 --> 00:40:23.260 had thirty nine. These cells

NOTE Confidence: 0.98117256

00:40:23.260 --> 00:40:23.920 did not.

NOTE Confidence: 0.957832

00:40:26.300 --> 00:40:27.500 All of these cells are

NOTE Confidence: 0.957832

00:40:27.500 --> 00:40:29.020 RO. There's some confusion in

NOTE Confidence: 0.957832

00:40:29.020 --> 00:40:30.319 the literature that this

NOTE Confidence: 0.970485

00:40:30.619 --> 00:40:32.219 stem like cells are RA.

NOTE Confidence: 0.970485

00:40:32.219 --> 00:40:33.980 No. It's all RO, and

NOTE Confidence: 0.970485

00:40:33.980 --> 00:40:35.835 this is not the stem

NOTE Confidence: 0.970485

00:40:35.835 --> 00:40:37.515 like cells described after acute

NOTE Confidence: 0.970485

00:40:37.515 --> 00:40:38.015 infection.

NOTE Confidence: 0.949174

00:40:38.475 --> 00:40:39.755 Everything is RO because they've

NOTE Confidence: 0.949174

00:40:39.755 --> 00:40:41.195 all antigen experience. In fact,

NOTE Confidence: 0.949174

00:40:41.195 --> 00:40:42.094 they're seeing antigen.

NOTE Confidence: 0.97944736

00:40:42.875 --> 00:40:44.234 CD twenty five comes up

NOTE Confidence: 0.97944736

00:40:44.234 --> 00:40:44.734 beautifully

NOTE Confidence: 0.9974715

00:40:45.114 --> 00:40:45.614 after,

NOTE Confidence: 0.99976546

00:40:46.075 --> 00:40:46.575 this

NOTE Confidence: 0.94183755

00:40:47.675 --> 00:40:48.175 proliferation.

NOTE Confidence: 0.9677861

00:40:49.469 --> 00:40:51.250 And CD twenty eight,

NOTE Confidence: 0.9698756

00:40:51.710 --> 00:40:52.830 which I was pointing out

NOTE Confidence: 0.9698756

00:40:52.830 --> 00:40:54.350 earlier, is only the stem

NOTE Confidence: 0.9698756

00:40:54.350 --> 00:40:55.710 like cells that have CD

NOTE Confidence: 0.9698756

00:40:55.710 --> 00:40:57.390 twenty eight, and they require

NOTE Confidence: 0.9698756

00:40:57.390 --> 00:40:59.630 this costimetry signal for the

NOTE Confidence: 0.9698756

00:40:59.630 --> 00:41:00.989 expansion that you see after

NOTE Confidence: 0.9698756

00:41:00.989 --> 00:41:01.890 PD one blockade.

NOTE Confidence: 0.914505

00:41:02.205 --> 00:41:03.165 So it's the stem like

NOTE Confidence: 0.914505

00:41:03.165 --> 00:41:04.364 cells that have CD twenty

NOTE Confidence: 0.914505

00:41:04.364 --> 00:41:05.885 eight. And interestingly, they're retaining

NOTE Confidence: 0.914505

00:41:05.885 --> 00:41:07.185 it at least in this,

NOTE Confidence: 0.9470356

00:41:07.565 --> 00:41:08.685 in this, shot,

NOTE Confidence: 0.94225264

00:41:09.485 --> 00:41:10.685 after the shot in vitro

NOTE Confidence: 0.94225264

00:41:10.685 --> 00:41:11.185 stimulation.

NOTE Confidence: 0.8578342

00:41:11.645 --> 00:41:13.665 Whereas the more term differential

NOTE Confidence: 0.8578342

00:41:13.885 --> 00:41:15.165 actually never had much c

NOTE Confidence: 0.8578342

00:41:15.165 --> 00:41:16.545 twenty eight to begin with.

NOTE Confidence: 0.9837639

00:41:19.820 --> 00:41:21.260 Okay. So this is what

NOTE Confidence: 0.9837639

00:41:21.260 --> 00:41:21.739 I was,

NOTE Confidence: 0.9067361

00:41:22.140 --> 00:41:23.260 telling you where they are

NOTE Confidence: 0.9067361

00:41:23.260 --> 00:41:23.760 located.

NOTE Confidence: 0.99883246

00:41:24.380 --> 00:41:25.520 So this is now

NOTE Confidence: 0.9734623

00:41:26.140 --> 00:41:28.000 stain of a tumor,

NOTE Confidence: 0.9097335

00:41:29.900 --> 00:41:31.580 of the HPV tumor, and

NOTE Confidence: 0.9097335

00:41:31.580 --> 00:41:32.560 you can see that

NOTE Confidence: 0.9915339

00:41:33.055 --> 00:41:34.015 this is where the tumor

NOTE Confidence: 0.9915339

00:41:34.015 --> 00:41:35.315 is based on the cytokeratin

NOTE Confidence: 0.9915339

00:41:35.535 --> 00:41:36.035 staining.

NOTE Confidence: 0.90522826

00:41:37.614 --> 00:41:38.895 Lot of CD8 T cells

NOTE Confidence: 0.90522826

00:41:38.895 --> 00:41:39.715 in this tumor.

NOTE Confidence: 0.96258044

00:41:41.535 --> 00:41:42.495 And if you look at

NOTE Confidence: 0.96258044

00:41:42.495 --> 00:41:43.935 PD one, pretty much all

NOTE Confidence: 0.96258044

00:41:43.935 --> 00:41:45.135 of them or most of

NOTE Confidence: 0.96258044

00:41:45.135 --> 00:41:46.895 them expressing PD one. This

NOTE Confidence: 0.96258044

00:41:46.895 --> 00:41:48.819 is the CD eight. There's

NOTE Confidence: 0.96258044

00:41:48.819 --> 00:41:50.180 the PD one. And now

NOTE Confidence: 0.96258044

00:41:50.180 --> 00:41:51.559 you look at TCF one.

NOTE Confidence: 0.92762834

00:41:52.500 --> 00:41:53.559 This they're here.

NOTE Confidence: 0.9988856

00:41:54.339 --> 00:41:56.420 This is where there was

NOTE Confidence: 0.9988856

00:41:56.420 --> 00:41:57.559 no tumor.

NOTE Confidence: 0.98024416

00:41:58.500 --> 00:41:59.640 Again, they segregate.

NOTE Confidence: 0.9764102

00:42:00.099 --> 00:42:01.540 They're not where the tumor

NOTE Confidence: 0.9764102

00:42:01.540 --> 00:42:02.040 is.

NOTE Confidence: 0.99898034

00:42:02.344 --> 00:42:03.545 Their progeny will go to

NOTE Confidence: 0.99898034

00:42:03.545 --> 00:42:05.164 the tumor, but these cells

NOTE Confidence: 0.99898034

00:42:05.385 --> 00:42:06.844 will be in these niches.

NOTE Confidence: 0.9873076

00:42:11.464 --> 00:42:13.085 So let me conclude this

NOTE Confidence: 0.9873076

00:42:13.144 --> 00:42:13.644 and

NOTE Confidence: 0.9813697

00:42:14.360 --> 00:42:15.320 and kind of end on

NOTE Confidence: 0.9813697

00:42:15.320 --> 00:42:15.960 a couple of,

NOTE Confidence: 0.96204865

00:42:16.600 --> 00:42:17.980 next steps that we're doing.

NOTE Confidence: 0.96204865

00:42:18.120 --> 00:42:19.420 So, basically, we've identified

NOTE Confidence: 0.9382552

00:42:19.960 --> 00:42:21.800 three transcriptionally distinct states of

NOTE Confidence: 0.9382552

00:42:21.800 --> 00:42:23.880 HPV specific CDT cells. And

NOTE Confidence: 0.9382552

00:42:23.880 --> 00:42:24.760 I didn't show you this

NOTE Confidence: 0.9382552

00:42:24.760 --> 00:42:25.560 data, but this is in

NOTE Confidence: 0.9382552

00:42:25.560 --> 00:42:27.344 our published paper. And they

NOTE Confidence: 0.9382552

00:42:27.344 --> 00:42:28.945 share the TCR. The same

NOTE Confidence: 0.9382552

00:42:28.945 --> 00:42:29.925 TCR chronotype

NOTE Confidence: 0.978872

00:42:30.225 --> 00:42:31.185 is found in all three

NOTE Confidence: 0.978872

00:42:31.185 --> 00:42:31.685 subsets.

NOTE Confidence: 0.9974481

00:42:32.065 --> 00:42:33.905 Again, consistent with showing that

NOTE Confidence: 0.9974481

00:42:33.905 --> 00:42:34.965 one is generating,

NOTE Confidence: 0.9943095

00:42:35.745 --> 00:42:36.785 to give rise to the

NOTE Confidence: 0.9943095

00:42:36.785 --> 00:42:38.305 other. And I've shown you

NOTE Confidence: 0.9943095

00:42:38.305 --> 00:42:39.285 functional evidence,

NOTE Confidence: 0.93973416

00:42:39.905 --> 00:42:41.265 also because you you have

NOTE Confidence: 0.93973416

00:42:41.265 --> 00:42:41.425 this,

NOTE Confidence: 0.9107137

00:42:42.730 --> 00:42:43.850 this thing happening based on

NOTE Confidence: 0.9107137

00:42:43.850 --> 00:42:45.530 atria chronotype being shared. But

NOTE Confidence: 0.9107137

00:42:45.530 --> 00:42:46.489 this is the more important

NOTE Confidence: 0.9107137

00:42:46.489 --> 00:42:46.989 point.

NOTE Confidence: 0.9496887

00:42:47.290 --> 00:42:49.230 The cellular machinery, essentially,

NOTE Confidence: 0.8919193

00:42:50.489 --> 00:42:51.450 I e the PD one

NOTE Confidence: 0.8919193

00:42:51.450 --> 00:42:53.210 positive stem like or resource

NOTE Confidence: 0.8919193

00:42:53.210 --> 00:42:54.890 cells that are required for

NOTE Confidence: 0.8919193

00:42:54.890 --> 00:42:56.250 response to PD one pathway

NOTE Confidence: 0.8919193

00:42:56.250 --> 00:42:57.915 blockade, they exist in these

NOTE Confidence: 0.8919193

00:42:57.915 --> 00:42:59.215 h three positive hNSCC,

NOTE Confidence: 0.9958346

00:43:00.155 --> 00:43:00.655 patients

NOTE Confidence: 0.8083866

00:43:01.114 --> 00:43:01.614 pretreatment,

NOTE Confidence: 0.9963577

00:43:02.475 --> 00:43:03.995 suggesting that PD one adjuvant

NOTE Confidence: 0.9963577

00:43:03.995 --> 00:43:05.135 therapy could be,

NOTE Confidence: 0.9994921

00:43:05.675 --> 00:43:06.895 an effective treatment.

NOTE Confidence: 0.9599438

00:43:07.675 --> 00:43:09.515 The other interesting finding here

NOTE Confidence: 0.9599438

00:43:09.515 --> 00:43:10.015 was,

NOTE Confidence: 0.9931029

00:43:10.640 --> 00:43:11.920 although the study is limited

NOTE Confidence: 0.9931029

00:43:12.080 --> 00:43:13.200 by limited, I mean, we

NOTE Confidence: 0.9931029

00:43:13.200 --> 00:43:14.580 don't have hundreds of patients.

NOTE Confidence: 0.99880284

00:43:15.120 --> 00:43:16.480 We found that e two

NOTE Confidence: 0.99880284

00:43:16.480 --> 00:43:17.460 and e five

NOTE Confidence: 0.96135503

00:43:18.400 --> 00:43:19.300 were the dominant

NOTE Confidence: 0.9174945

00:43:19.760 --> 00:43:21.860 targets, in particular, e two.

NOTE Confidence: 0.95350933

00:43:22.160 --> 00:43:23.280 E two is a major

NOTE Confidence: 0.95350933

00:43:23.280 --> 00:43:23.745 target.

NOTE Confidence: 0.9399478

00:43:24.145 --> 00:43:25.745 And this finding of ours

NOTE Confidence: 0.9399478

00:43:25.745 --> 00:43:27.105 has been subsequent in the

NOTE Confidence: 0.9399478

00:43:27.105 --> 00:43:28.225 last since our paper came

NOTE Confidence: 0.9399478

00:43:28.225 --> 00:43:29.345 out, two more papers have

NOTE Confidence: 0.9399478

00:43:29.345 --> 00:43:30.705 come out showing the same

NOTE Confidence: 0.9399478

00:43:30.705 --> 00:43:31.205 thing.

NOTE Confidence: 0.9908606

00:43:31.585 --> 00:43:33.045 E two is a dominant

NOTE Confidence: 0.88328195

00:43:33.825 --> 00:43:35.205 antigen in HPV.

NOTE Confidence: 0.99953604

00:43:38.900 --> 00:43:39.400 And

NOTE Confidence: 0.9853924

00:43:40.180 --> 00:43:41.299 and so far, there have

NOTE Confidence: 0.9853924

00:43:41.299 --> 00:43:42.520 been some very

NOTE Confidence: 0.97194487

00:43:43.219 --> 00:43:45.539 lot of experiments done using

NOTE Confidence: 0.97194487

00:43:45.539 --> 00:43:46.819 e six and e seven

NOTE Confidence: 0.97194487

00:43:46.819 --> 00:43:47.319 vaccines

NOTE Confidence: 0.9739944

00:43:48.020 --> 00:43:49.539 that have gone into many

NOTE Confidence: 0.9739944

00:43:49.539 --> 00:43:51.219 clinical trials, both for cervical

NOTE Confidence: 0.9739944

00:43:51.219 --> 00:43:52.795 cancer and maybe some for

NOTE Confidence: 0.9739944

00:43:52.875 --> 00:43:53.594 but but most of this

NOTE Confidence: 0.9739944

00:43:53.594 --> 00:43:54.875 has been focused on cervical

NOTE Confidence: 0.9739944

00:43:54.875 --> 00:43:56.395 cancer, maybe some also head

NOTE Confidence: 0.9739944

00:43:56.395 --> 00:43:58.315 and neck. But but we

NOTE Confidence: 0.9739944

00:43:58.315 --> 00:43:59.915 would strongly recommend that if

NOTE Confidence: 0.9739944

00:43:59.915 --> 00:44:00.795 you want to do a

NOTE Confidence: 0.9739944

00:44:00.795 --> 00:44:01.855 therapeutic vaccination

NOTE Confidence: 0.9976748

00:44:02.715 --> 00:44:03.995 of either head and neck

NOTE Confidence: 0.9976748

00:44:03.995 --> 00:44:04.815 cancer patients,

NOTE Confidence: 0.9682996

00:44:05.500 --> 00:44:06.380 especially for head and neck

NOTE Confidence: 0.9682996

00:44:06.380 --> 00:44:07.340 cancer patients where we have

NOTE Confidence: 0.9682996

00:44:07.340 --> 00:44:09.020 this data that e two

NOTE Confidence: 0.9682996

00:44:09.020 --> 00:44:10.219 and e five should also

NOTE Confidence: 0.9682996

00:44:10.219 --> 00:44:11.500 be part of the vaccine,

NOTE Confidence: 0.9682996

00:44:11.500 --> 00:44:12.320 in particular,

NOTE Confidence: 0.9926818

00:44:13.020 --> 00:44:13.900 e two, which is a

NOTE Confidence: 0.9926818

00:44:13.900 --> 00:44:15.600 very, very dominant antigen.

NOTE Confidence: 0.9540484

00:44:18.594 --> 00:44:19.395 So I want to kind

NOTE Confidence: 0.9540484

00:44:19.395 --> 00:44:20.435 of end with couple of

NOTE Confidence: 0.9540484

00:44:20.515 --> 00:44:21.795 oh, so this was our

NOTE Confidence: 0.9540484

00:44:21.795 --> 00:44:23.475 paper published by today. But

NOTE Confidence: 0.9540484

00:44:23.475 --> 00:44:25.255 I didn't say anything about

NOTE Confidence: 0.95634663

00:44:25.635 --> 00:44:26.995 our second paper that was

NOTE Confidence: 0.95634663

00:44:26.995 --> 00:44:28.675 published with it, which looked

NOTE Confidence: 0.95634663

00:44:28.675 --> 00:44:30.594 at b cell responses to

NOTE Confidence: 0.95634663

00:44:30.594 --> 00:44:31.094 HBV

NOTE Confidence: 0.92615366

00:44:31.475 --> 00:44:32.295 in the tumor,

NOTE Confidence: 0.96696717

00:44:33.410 --> 00:44:35.010 and they are also very

NOTE Confidence: 0.96696717

00:44:35.010 --> 00:44:35.510 strong.

NOTE Confidence: 0.9976269

00:44:36.050 --> 00:44:37.350 So within the tumor,

NOTE Confidence: 0.98029226

00:44:37.730 --> 00:44:39.650 we find HPV specific memory

NOTE Confidence: 0.98029226

00:44:39.650 --> 00:44:40.390 b cells.

NOTE Confidence: 0.95002663

00:44:41.170 --> 00:44:43.170 We have antibody secreting cells.

NOTE Confidence: 0.95002663

00:44:43.170 --> 00:44:44.290 That is, there are plasma

NOTE Confidence: 0.95002663

00:44:44.290 --> 00:44:46.150 cells right in the tumor,

NOTE Confidence: 0.95002663

00:44:46.425 --> 00:44:48.425 which are secreting antibody to,

NOTE Confidence: 0.9615684

00:44:49.465 --> 00:44:51.065 e six, e seven, and

NOTE Confidence: 0.9615684

00:44:51.065 --> 00:44:52.105 e two, and e five.

NOTE Confidence: 0.9615684

00:44:52.105 --> 00:44:53.405 So there's a lot of,

NOTE Confidence: 0.95406425

00:44:53.864 --> 00:44:55.645 active b cell response ongoing.

NOTE Confidence: 0.99631447

00:44:56.825 --> 00:44:57.545 So these are

NOTE Confidence: 0.9965047

00:44:58.370 --> 00:44:59.190 to use the

NOTE Confidence: 0.90755844

00:44:59.489 --> 00:45:00.690 the the term heart, these

NOTE Confidence: 0.90755844

00:45:00.690 --> 00:45:02.070 are very, very immunologically

NOTE Confidence: 0.9336563

00:45:02.530 --> 00:45:03.670 active, tumors.

NOTE Confidence: 0.9416775

00:45:04.210 --> 00:45:05.330 Both b cell and t

NOTE Confidence: 0.9416775

00:45:05.330 --> 00:45:06.630 cell response is ongoing,

NOTE Confidence: 0.9957235

00:45:07.090 --> 00:45:07.810 to multiple,

NOTE Confidence: 0.8867586

00:45:09.090 --> 00:45:10.850 HPV antigens with, at least

NOTE Confidence: 0.8867586

00:45:10.850 --> 00:45:11.650 for the end, for the

NOTE Confidence: 0.8867586

00:45:11.650 --> 00:45:12.150 CDH,

NOTE Confidence: 0.9995425

00:45:12.505 --> 00:45:13.325 real dominance

NOTE Confidence: 0.97297466

00:45:13.625 --> 00:45:14.825 of, of e two in

NOTE Confidence: 0.97297466

00:45:14.825 --> 00:45:15.645 this response.

NOTE Confidence: 0.98109674

00:45:16.025 --> 00:45:17.565 So what we have started

NOTE Confidence: 0.98109674

00:45:17.705 --> 00:45:18.744 now, and I was talking

NOTE Confidence: 0.98109674

00:45:18.744 --> 00:45:20.105 to Barbara about this,

NOTE Confidence: 0.9717859

00:45:20.665 --> 00:45:21.965 a very small study,

NOTE Confidence: 0.9479337

00:45:22.344 --> 00:45:23.405 and this is ongoing,

NOTE Confidence: 0.93149555

00:45:25.270 --> 00:45:26.390 Took us forever to get

NOTE Confidence: 0.93149555

00:45:26.390 --> 00:45:27.510 it going, but we have

NOTE Confidence: 0.93149555

00:45:27.510 --> 00:45:29.190 a small study that's being

NOTE Confidence: 0.93149555

00:45:29.190 --> 00:45:31.590 done by Mihir Patel and

NOTE Confidence: 0.93149555

00:45:31.590 --> 00:45:33.350 Nabil Saba. It base basically,

NOTE Confidence: 0.93149555

00:45:33.350 --> 00:45:33.910 it's an adjuvant,

NOTE Confidence: 0.9201145

00:45:35.830 --> 00:45:37.270 study where we we are

NOTE Confidence: 0.9201145

00:45:37.270 --> 00:45:37.770 giving

NOTE Confidence: 0.9771131

00:45:40.025 --> 00:45:41.405 head and neck cancer patients,

NOTE Confidence: 0.9387257

00:45:42.745 --> 00:45:44.105 two doses of,

NOTE Confidence: 0.9467014

00:45:45.145 --> 00:45:46.344 anti PD one that we

NOTE Confidence: 0.9467014

00:45:46.344 --> 00:45:48.765 got from Roche from Genentech,

NOTE Confidence: 0.9748232

00:45:49.305 --> 00:45:50.125 and Roche.

NOTE Confidence: 0.94805974

00:45:50.585 --> 00:45:52.185 So they will get before

NOTE Confidence: 0.94805974

00:45:52.185 --> 00:45:53.485 they have their surgery,

NOTE Confidence: 0.9983805

00:45:54.105 --> 00:45:55.565 they will get two

NOTE Confidence: 0.8903087

00:45:56.400 --> 00:45:58.420 infusions of anti PDL one,

NOTE Confidence: 0.9977219

00:45:59.280 --> 00:46:00.160 and then they will go

NOTE Confidence: 0.9977219

00:46:00.160 --> 00:46:01.059 in for the surgery.

NOTE Confidence: 0.927325

00:46:01.359 --> 00:46:02.819 We've been collecting blood,

NOTE Confidence: 0.9996101

00:46:03.119 --> 00:46:04.099 from these patients.

NOTE Confidence: 0.9694093

00:46:04.640 --> 00:46:05.680 The plan is to have

NOTE Confidence: 0.9694093

00:46:05.680 --> 00:46:07.200 twenty patients who will get,

NOTE Confidence: 0.9736023

00:46:07.680 --> 00:46:09.520 PDL one treatment prior to

NOTE Confidence: 0.9736023

00:46:09.520 --> 00:46:09.839 their,

NOTE Confidence: 0.92988425

00:46:10.515 --> 00:46:12.434 to their surgery and, and

NOTE Confidence: 0.92988425

00:46:12.434 --> 00:46:14.035 radiation treatment and so on.

NOTE Confidence: 0.92988425

00:46:14.035 --> 00:46:15.815 K. And so far, seven

NOTE Confidence: 0.92988425

00:46:15.875 --> 00:46:17.174 patients have been enrolled,

NOTE Confidence: 0.7686185

00:46:17.555 --> 00:46:18.055 and,

NOTE Confidence: 0.8633965

00:46:18.515 --> 00:46:20.454 basically, blood is being collected

NOTE Confidence: 0.7433632

00:46:21.394 --> 00:46:21.894 pretreatment.

NOTE Confidence: 0.94861007

00:46:23.440 --> 00:46:25.040 Pre infusion of the PD

NOTE Confidence: 0.94861007

00:46:25.040 --> 00:46:26.560 one, we'll get one blood

NOTE Confidence: 0.94861007

00:46:26.560 --> 00:46:28.080 sample. And then after that,

NOTE Confidence: 0.94861007

00:46:28.080 --> 00:46:28.880 and then at the time

NOTE Confidence: 0.94861007

00:46:28.880 --> 00:46:30.320 of surgery, we'll get the

NOTE Confidence: 0.94861007

00:46:30.320 --> 00:46:31.840 tissue sample as well as

NOTE Confidence: 0.94861007

00:46:31.840 --> 00:46:32.500 the blood.

NOTE Confidence: 0.9946371

00:46:33.680 --> 00:46:35.600 So seven have been recruited

NOTE Confidence: 0.9946371

00:46:35.600 --> 00:46:36.820 into the thing already.

NOTE Confidence: 0.95040584

00:46:37.655 --> 00:46:38.855 Two of them have actually

NOTE Confidence: 0.95040584

00:46:38.855 --> 00:46:40.234 completed their regimen.

NOTE Confidence: 0.961858

00:46:40.935 --> 00:46:42.214 And the early data is

NOTE Confidence: 0.961858

00:46:42.214 --> 00:46:43.815 only n of two, but

NOTE Confidence: 0.961858

00:46:43.815 --> 00:46:45.815 both these patients have shown

NOTE Confidence: 0.961858

00:46:45.815 --> 00:46:46.474 a pathological

NOTE Confidence: 0.8861264

00:46:46.775 --> 00:46:47.275 response,

NOTE Confidence: 0.9637852

00:46:48.454 --> 00:46:50.135 within this month of, anti

NOTE Confidence: 0.9637852

00:46:50.135 --> 00:46:51.960 PDL one treatment. We haven't

NOTE Confidence: 0.9637852

00:46:51.960 --> 00:46:53.180 done the T cell analysis

NOTE Confidence: 0.9637852

00:46:53.239 --> 00:46:54.520 yet because we have the

NOTE Confidence: 0.9637852

00:46:54.520 --> 00:46:55.719 samples there. We first need

NOTE Confidence: 0.9637852

00:46:55.719 --> 00:46:56.380 to identify.

NOTE Confidence: 0.9989399

00:46:57.000 --> 00:46:57.800 We need to do what

NOTE Confidence: 0.9989399

00:46:57.800 --> 00:46:58.840 we did with the previous

NOTE Confidence: 0.9989399

00:46:58.840 --> 00:46:59.340 time

NOTE Confidence: 0.9759023

00:46:59.960 --> 00:47:01.260 and see, what

NOTE Confidence: 0.92158455

00:47:01.560 --> 00:47:02.840 they're responding to. But here

NOTE Confidence: 0.92158455

00:47:02.840 --> 00:47:03.739 I have a prediction.

NOTE Confidence: 0.9776303

00:47:04.120 --> 00:47:05.320 Now we will see more

NOTE Confidence: 0.9776303

00:47:05.320 --> 00:47:06.414 cells in the blood is

NOTE Confidence: 0.9776303

00:47:06.414 --> 00:47:07.154 my prediction.

NOTE Confidence: 0.9339583

00:47:08.015 --> 00:47:09.134 Because they have gotten the

NOTE Confidence: 0.9339583

00:47:09.134 --> 00:47:10.914 anti PDL one, treatment,

NOTE Confidence: 0.9401347

00:47:11.375 --> 00:47:13.055 blood these effector cells should

NOTE Confidence: 0.9401347

00:47:13.055 --> 00:47:14.194 come out into the blood.

NOTE Confidence: 0.9401347

00:47:14.414 --> 00:47:15.535 Now we will see cells

NOTE Confidence: 0.9401347

00:47:15.535 --> 00:47:16.414 in the blood. That's my

NOTE Confidence: 0.9401347

00:47:16.414 --> 00:47:16.914 prediction.

NOTE Confidence: 0.79346824

00:47:18.510 --> 00:47:19.010 And,

NOTE Confidence: 0.922815

00:47:20.110 --> 00:47:21.150 so that's where we are,

NOTE Confidence: 0.922815

00:47:21.150 --> 00:47:22.290 and I'll keep you posted.

NOTE Confidence: 0.922815

00:47:22.350 --> 00:47:23.310 And this is my I

NOTE Confidence: 0.922815

00:47:23.310 --> 00:47:24.590 will stop after the next

NOTE Confidence: 0.922815

00:47:24.590 --> 00:47:25.630 one. I'm just gonna skip

NOTE Confidence: 0.922815

00:47:25.630 --> 00:47:26.610 dial two. Okay?

NOTE Confidence: 0.83256394

00:47:27.150 --> 00:47:28.130 And then then

NOTE Confidence: 0.9986401

00:47:28.750 --> 00:47:29.489 so we

NOTE Confidence: 0.9264059

00:47:30.030 --> 00:47:31.070 so far, it's been all

NOTE Confidence: 0.9264059

00:47:31.070 --> 00:47:31.890 head and neck,

NOTE Confidence: 0.9182284

00:47:32.355 --> 00:47:32.795 and,

NOTE Confidence: 0.9497931

00:47:33.235 --> 00:47:34.935 but I've been in discussions

NOTE Confidence: 0.9497931

00:47:35.075 --> 00:47:37.175 with several people about

NOTE Confidence: 0.9505611

00:47:38.275 --> 00:47:39.715 maybe trying to do something

NOTE Confidence: 0.9505611

00:47:39.715 --> 00:47:40.215 similar

NOTE Confidence: 0.9775458

00:47:40.675 --> 00:47:42.435 in cervical cancer. The question

NOTE Confidence: 0.9775458

00:47:42.435 --> 00:47:44.275 is, in cervical cancer, is

NOTE Confidence: 0.9775458

00:47:44.275 --> 00:47:45.155 it going to be all

NOTE Confidence: 0.9775458

00:47:45.155 --> 00:47:46.614 e six, e seven only?

NOTE Confidence: 0.9775458

00:47:46.910 --> 00:47:48.110 Will you also have e

NOTE Confidence: 0.9775458

00:47:48.110 --> 00:47:49.570 two and e five responses

NOTE Confidence: 0.9775458

00:47:49.790 --> 00:47:51.390 in cervical cancer or not?

NOTE Confidence: 0.9775458

00:47:51.390 --> 00:47:52.430 So we are just starting

NOTE Confidence: 0.9775458

00:47:52.430 --> 00:47:53.650 a collaboration. Actually,

NOTE Confidence: 0.9428831

00:47:54.270 --> 00:47:55.390 I'm also going to India

NOTE Confidence: 0.9428831

00:47:55.390 --> 00:47:56.750 next week, okay, for for

NOTE Confidence: 0.9428831

00:47:56.750 --> 00:47:57.570 this. So,

NOTE Confidence: 0.9615347

00:47:58.510 --> 00:48:00.614 so it it's we're lucky

NOTE Confidence: 0.9615347

00:48:00.614 --> 00:48:01.355 that we,

NOTE Confidence: 0.9130438

00:48:02.055 --> 00:48:03.735 the Emory vaccine center at,

NOTE Confidence: 0.95342255

00:48:05.015 --> 00:48:06.135 has a lab at a

NOTE Confidence: 0.95342255

00:48:06.135 --> 00:48:07.815 very nice institute there called

NOTE Confidence: 0.95342255

00:48:07.815 --> 00:48:08.315 ICGV.

NOTE Confidence: 0.98649466

00:48:10.055 --> 00:48:11.255 So we have a and

NOTE Confidence: 0.98649466

00:48:11.255 --> 00:48:12.375 we've had this lab for

NOTE Confidence: 0.98649466

00:48:12.375 --> 00:48:14.160 many years. Our focus actually

NOTE Confidence: 0.98649466

00:48:14.160 --> 00:48:15.520 has been on dengue dengue

NOTE Confidence: 0.98649466

00:48:15.520 --> 00:48:16.420 virus infection.

NOTE Confidence: 0.96912783

00:48:17.440 --> 00:48:18.820 But now we are starting,

NOTE Confidence: 0.96912783

00:48:19.119 --> 00:48:20.420 we will start a program

NOTE Confidence: 0.96912783

00:48:20.480 --> 00:48:20.800 on,

NOTE Confidence: 0.9941703

00:48:21.440 --> 00:48:21.940 HPV

NOTE Confidence: 0.9573144

00:48:22.239 --> 00:48:24.000 cervical cancer, and this will

NOTE Confidence: 0.9573144

00:48:24.000 --> 00:48:25.599 be in collaboration with, one

NOTE Confidence: 0.9573144

00:48:25.599 --> 00:48:26.719 of the largest and the

NOTE Confidence: 0.9573144

00:48:26.719 --> 00:48:28.475 best hospitals in India, the

NOTE Confidence: 0.9573144

00:48:28.475 --> 00:48:29.935 AIMS Hospital in New Delhi.

NOTE Confidence: 0.88992417

00:48:30.475 --> 00:48:31.995 So, hopefully, in the next,

NOTE Confidence: 0.9714864

00:48:33.275 --> 00:48:34.555 few years, we will have

NOTE Confidence: 0.9714864

00:48:34.555 --> 00:48:36.735 some data on what responses

NOTE Confidence: 0.9714864

00:48:36.875 --> 00:48:38.255 look like in HPV

NOTE Confidence: 0.99391276

00:48:38.555 --> 00:48:40.575 positive cervical cancer patients.

NOTE Confidence: 0.838021

00:48:40.875 --> 00:48:41.935 K. I will

NOTE Confidence: 0.849079

00:48:42.770 --> 00:48:44.790 skip the IL two part.

NOTE Confidence: 0.99935323

00:48:47.410 --> 00:48:48.710 I should skip it. Right?

NOTE Confidence: 0.89064765

00:48:50.210 --> 00:48:51.089 I have time. Okay. I'll

NOTE Confidence: 0.89064765

00:48:51.089 --> 00:48:51.989 go through it quickly.

NOTE Confidence: 0.9609099

00:48:54.954 --> 00:48:55.915 Most of it is published,

NOTE Confidence: 0.9609099

00:48:55.915 --> 00:48:56.635 but it's it's I think

NOTE Confidence: 0.9609099

00:48:56.635 --> 00:48:58.234 it's relevant because there's some

NOTE Confidence: 0.9609099

00:48:58.234 --> 00:48:58.974 IL two.

NOTE Confidence: 0.94744587

00:49:00.075 --> 00:49:00.575 Okay.

NOTE Confidence: 0.996141

00:49:02.395 --> 00:49:03.515 Alright. So I will go

NOTE Confidence: 0.996141

00:49:03.515 --> 00:49:04.815 through this quickly. So

NOTE Confidence: 0.9939045

00:49:05.515 --> 00:49:06.875 so this I'm switching now

NOTE Confidence: 0.9939045

00:49:06.875 --> 00:49:09.614 to, rational design of, immunotherapy.

NOTE Confidence: 0.9642837

00:49:10.260 --> 00:49:11.380 So as I've mentioned to

NOTE Confidence: 0.9642837

00:49:11.380 --> 00:49:12.500 you, there are three of

NOTE Confidence: 0.9642837

00:49:12.500 --> 00:49:13.960 these subsets there.

NOTE Confidence: 0.9974891

00:49:14.260 --> 00:49:15.300 So what can we do

NOTE Confidence: 0.9974891

00:49:15.300 --> 00:49:16.580 to increase the number of

NOTE Confidence: 0.9974891

00:49:16.580 --> 00:49:17.560 stem like cells?

NOTE Confidence: 0.9829113

00:49:18.260 --> 00:49:19.540 Can we do something to

NOTE Confidence: 0.9829113

00:49:19.540 --> 00:49:21.219 change the quality of the

NOTE Confidence: 0.9829113

00:49:21.219 --> 00:49:22.840 effector cells that we get?

NOTE Confidence: 0.9662005

00:49:23.585 --> 00:49:24.864 And probably the hardest thing,

NOTE Confidence: 0.9662005

00:49:24.864 --> 00:49:26.325 can we do something to,

NOTE Confidence: 0.8253335

00:49:27.984 --> 00:49:29.904 get those truly terribly different

NOTE Confidence: 0.8253335

00:49:29.904 --> 00:49:30.805 to do something?

NOTE Confidence: 0.99472237

00:49:31.744 --> 00:49:32.244 But

NOTE Confidence: 0.91291463

00:49:32.625 --> 00:49:33.664 what I wanna talk to

NOTE Confidence: 0.91291463

00:49:33.664 --> 00:49:35.184 you today a bit I

NOTE Confidence: 0.91291463

00:49:35.184 --> 00:49:36.864 l two is improving the

NOTE Confidence: 0.91291463

00:49:36.864 --> 00:49:38.500 quality of vector cells. I

NOTE Confidence: 0.91291463

00:49:38.500 --> 00:49:39.460 l two doesn't do much

NOTE Confidence: 0.91291463

00:49:39.460 --> 00:49:40.760 in terms of expanding

NOTE Confidence: 0.98597264

00:49:41.140 --> 00:49:41.880 stem cells,

NOTE Confidence: 0.94570225

00:49:42.180 --> 00:49:43.480 and it doesn't do anything

NOTE Confidence: 0.94570225

00:49:43.540 --> 00:49:45.160 on the more differentiated cells.

NOTE Confidence: 0.94570225

00:49:45.380 --> 00:49:46.340 So I l two doesn't

NOTE Confidence: 0.94570225

00:49:46.340 --> 00:49:47.940 do anything with, with the

NOTE Confidence: 0.94570225

00:49:47.940 --> 00:49:48.440 cell.

NOTE Confidence: 0.9979996

00:49:48.740 --> 00:49:50.260 But what we found is

NOTE Confidence: 0.9979996

00:49:50.260 --> 00:49:50.760 that

NOTE Confidence: 0.97770196

00:49:52.505 --> 00:49:53.805 that when you combine

NOTE Confidence: 0.8525744

00:49:55.065 --> 00:49:56.605 IL two with PD one,

NOTE Confidence: 0.8525744

00:49:56.825 --> 00:49:58.285 and this was, published,

NOTE Confidence: 0.9950935

00:49:58.745 --> 00:50:00.045 a couple of years back,

NOTE Confidence: 0.9950935

00:50:00.105 --> 00:50:01.485 that we see a dramatic

NOTE Confidence: 0.9998561

00:50:02.105 --> 00:50:02.605 change

NOTE Confidence: 0.99328923

00:50:03.545 --> 00:50:05.005 in the transcriptional

NOTE Confidence: 0.9997359

00:50:05.385 --> 00:50:05.885 program

NOTE Confidence: 0.94194186

00:50:06.239 --> 00:50:07.619 of the effector cells.

NOTE Confidence: 0.97920597

00:50:10.480 --> 00:50:11.840 Basically, what we see is

NOTE Confidence: 0.97920597

00:50:11.840 --> 00:50:12.960 that when you do,

NOTE Confidence: 0.9758043

00:50:13.440 --> 00:50:14.640 actually, let me go to

NOTE Confidence: 0.9758043

00:50:14.640 --> 00:50:14.960 the

NOTE Confidence: 0.9614249

00:50:15.520 --> 00:50:16.320 let me go to this.

NOTE Confidence: 0.9614249

00:50:16.320 --> 00:50:17.119 Yeah. Let me go to

NOTE Confidence: 0.9614249

00:50:17.119 --> 00:50:18.719 this slide. Okay. So, basically,

NOTE Confidence: 0.9614249

00:50:18.719 --> 00:50:20.320 this is what the previous,

NOTE Confidence: 0.9614249

00:50:20.640 --> 00:50:22.315 data shows you, that when

NOTE Confidence: 0.9614249

00:50:22.315 --> 00:50:24.335 you do with an untreated,

NOTE Confidence: 0.99604976

00:50:25.675 --> 00:50:26.175 situation,

NOTE Confidence: 0.919992

00:50:26.875 --> 00:50:27.915 you have the stem like

NOTE Confidence: 0.919992

00:50:27.915 --> 00:50:29.215 cells, you have the transitory

NOTE Confidence: 0.919992

00:50:29.275 --> 00:50:30.795 effector cells, and you have

NOTE Confidence: 0.919992

00:50:30.795 --> 00:50:32.415 the term you differentiated. So

NOTE Confidence: 0.919992

00:50:32.555 --> 00:50:33.594 after you do PD one

NOTE Confidence: 0.919992

00:50:33.594 --> 00:50:34.094 blockade,

NOTE Confidence: 0.9804221

00:50:34.475 --> 00:50:35.835 you get many more of

NOTE Confidence: 0.9804221

00:50:35.835 --> 00:50:37.059 these cells, k, which eventually

NOTE Confidence: 0.9804221

00:50:37.059 --> 00:50:39.140 will go here. But when

NOTE Confidence: 0.9804221

00:50:39.140 --> 00:50:39.880 we did

NOTE Confidence: 0.9251296

00:50:40.180 --> 00:50:41.940 PD one blockade plus IL

NOTE Confidence: 0.9251296

00:50:41.940 --> 00:50:43.960 two, we totally changed

NOTE Confidence: 0.99963987

00:50:44.579 --> 00:50:45.079 the

NOTE Confidence: 0.96997005

00:50:45.380 --> 00:50:47.079 the program of these cells.

NOTE Confidence: 0.96997005

00:50:47.299 --> 00:50:49.160 So these stem like cells

NOTE Confidence: 0.8548553

00:50:50.275 --> 00:50:52.135 are have tremendous pluripotency,

NOTE Confidence: 0.95741713

00:50:52.835 --> 00:50:53.955 that is they're not fate

NOTE Confidence: 0.95741713

00:50:53.955 --> 00:50:55.475 locked into the kind of

NOTE Confidence: 0.95741713

00:50:55.475 --> 00:50:56.915 effectors they will get. So

NOTE Confidence: 0.95741713

00:50:56.915 --> 00:50:58.455 this creates another opportunity,

NOTE Confidence: 0.95280087

00:50:58.995 --> 00:51:00.755 not only to just get

NOTE Confidence: 0.95280087

00:51:00.755 --> 00:51:02.055 more of the blue cells,

NOTE Confidence: 0.95280087

00:51:02.260 --> 00:51:04.120 but also to change their

NOTE Confidence: 0.95280087

00:51:04.180 --> 00:51:06.280 transcriptional trajectory and epigenetically

NOTE Confidence: 0.9350322

00:51:06.900 --> 00:51:08.340 get much better effector cells.

NOTE Confidence: 0.9350322

00:51:08.340 --> 00:51:09.880 And that's what PD one

NOTE Confidence: 0.9350322

00:51:09.940 --> 00:51:12.120 plus IL two combination therapy

NOTE Confidence: 0.9350322

00:51:12.180 --> 00:51:13.620 does. Not only do you

NOTE Confidence: 0.9350322

00:51:13.620 --> 00:51:15.714 get many more cells, but

NOTE Confidence: 0.9350322

00:51:15.714 --> 00:51:16.375 they are transcriptionally

NOTE Confidence: 0.99752426

00:51:16.915 --> 00:51:17.734 and epigenetically

NOTE Confidence: 0.9835153

00:51:18.435 --> 00:51:19.255 very distinct.

NOTE Confidence: 0.9935296

00:51:19.714 --> 00:51:20.675 And what do they look

NOTE Confidence: 0.9935296

00:51:20.675 --> 00:51:22.035 like now? Now they start

NOTE Confidence: 0.9935296

00:51:22.035 --> 00:51:24.535 looking more like effector cells

NOTE Confidence: 0.9935296

00:51:24.755 --> 00:51:25.815 that you generate

NOTE Confidence: 0.9979588

00:51:26.114 --> 00:51:27.655 during an acute infection.

NOTE Confidence: 0.99562424

00:51:29.000 --> 00:51:29.960 So I think that this

NOTE Confidence: 0.99562424

00:51:29.960 --> 00:51:30.859 offers really

NOTE Confidence: 0.95313555

00:51:31.480 --> 00:51:32.859 very interesting opportunities

NOTE Confidence: 0.9997918

00:51:33.160 --> 00:51:34.700 in terms of further manipulating

NOTE Confidence: 0.98359853

00:51:35.000 --> 00:51:36.219 that stem like population.

NOTE Confidence: 0.9702074

00:51:39.640 --> 00:51:41.160 So then this was the

NOTE Confidence: 0.9702074

00:51:41.160 --> 00:51:42.460 part that was,

NOTE Confidence: 0.95744705

00:51:43.835 --> 00:51:44.795 at least, to me, more

NOTE Confidence: 0.95744705

00:51:44.795 --> 00:51:46.154 interesting, but I think more

NOTE Confidence: 0.95744705

00:51:46.154 --> 00:51:46.654 problematic

NOTE Confidence: 0.94398737

00:51:47.114 --> 00:51:47.934 for the field,

NOTE Confidence: 0.989467

00:51:48.394 --> 00:51:50.255 k, is what we found

NOTE Confidence: 0.9951317

00:51:51.434 --> 00:51:53.194 in our the qualifier is

NOTE Confidence: 0.9951317

00:51:53.194 --> 00:51:53.934 that this

NOTE Confidence: 0.90816694

00:51:54.394 --> 00:51:55.914 is a mouse model. Okay?

NOTE Confidence: 0.90816694

00:51:55.914 --> 00:51:57.355 What what we found is

NOTE Confidence: 0.90816694

00:51:57.355 --> 00:51:57.855 that

NOTE Confidence: 0.9277241

00:51:58.260 --> 00:51:59.560 CD twenty five engagement

NOTE Confidence: 0.99903476

00:52:01.380 --> 00:52:02.200 was important.

NOTE Confidence: 0.97452384

00:52:02.580 --> 00:52:03.460 As you all know, the

NOTE Confidence: 0.97452384

00:52:03.460 --> 00:52:04.520 trimeric receptor

NOTE Confidence: 0.9900722

00:52:04.900 --> 00:52:05.300 is,

NOTE Confidence: 0.9384964

00:52:06.020 --> 00:52:07.239 is the alpha chain,

NOTE Confidence: 0.96943223

00:52:07.620 --> 00:52:08.980 there's the beta chain, and

NOTE Confidence: 0.96943223

00:52:08.980 --> 00:52:10.580 there's the gamma chain. The

NOTE Confidence: 0.96943223

00:52:10.580 --> 00:52:12.200 signaling is through the beta

NOTE Confidence: 0.96943223

00:52:12.260 --> 00:52:13.640 and the gamma chain.

NOTE Confidence: 0.9424092

00:52:14.555 --> 00:52:15.594 The alpha chain, which is

NOTE Confidence: 0.9424092

00:52:15.594 --> 00:52:16.734 CD twenty five,

NOTE Confidence: 0.9884887

00:52:17.194 --> 00:52:19.035 forms the trimeric receptor. The

NOTE Confidence: 0.9884887

00:52:19.035 --> 00:52:20.734 affinity of the trimeric receptor

NOTE Confidence: 0.9884887

00:52:20.875 --> 00:52:22.575 is long orders more

NOTE Confidence: 0.99625957

00:52:23.035 --> 00:52:24.795 than the affinity of beta

NOTE Confidence: 0.99625957

00:52:24.795 --> 00:52:25.535 and gamma.

NOTE Confidence: 0.90674096

00:52:26.474 --> 00:52:27.855 And our results

NOTE Confidence: 0.8709982

00:52:28.619 --> 00:52:30.059 were that if we use,

NOTE Confidence: 0.99482995

00:52:30.779 --> 00:52:31.660 so we did three kind

NOTE Confidence: 0.99482995

00:52:31.660 --> 00:52:32.400 of experiments.

NOTE Confidence: 0.853078

00:52:33.259 --> 00:52:34.960 One was if we,

NOTE Confidence: 0.9755196

00:52:36.700 --> 00:52:37.180 if we do

NOTE Confidence: 0.98007786

00:52:37.819 --> 00:52:39.420 if we if we use

NOTE Confidence: 0.98007786

00:52:39.420 --> 00:52:41.519 a cytokine that was mutated,

NOTE Confidence: 0.97102475

00:52:42.215 --> 00:52:43.175 that is did not have

NOTE Confidence: 0.97102475

00:52:43.175 --> 00:52:45.255 binding to the alpha chain,

NOTE Confidence: 0.97102475

00:52:45.255 --> 00:52:47.255 we actually saw no synergy

NOTE Confidence: 0.97102475

00:52:47.255 --> 00:52:48.614 at all. In fact, that

NOTE Confidence: 0.97102475

00:52:48.614 --> 00:52:50.215 that basically, it was the

NOTE Confidence: 0.97102475

00:52:50.215 --> 00:52:51.975 sync effect. It just went

NOTE Confidence: 0.97102475

00:52:51.975 --> 00:52:53.175 and bound every T cell

NOTE Confidence: 0.97102475

00:52:53.175 --> 00:52:54.075 that was there,

NOTE Confidence: 0.9687798

00:52:54.455 --> 00:52:55.755 k, and was not targeted

NOTE Confidence: 0.9687798

00:52:55.815 --> 00:52:56.315 properly.

NOTE Confidence: 0.99682945

00:52:57.219 --> 00:52:58.760 And then we also showed

NOTE Confidence: 0.99682945

00:52:58.900 --> 00:52:59.860 that if you do c

NOTE Confidence: 0.99682945

00:52:59.860 --> 00:53:00.920 twenty five blockade,

NOTE Confidence: 0.99900943

00:53:01.940 --> 00:53:03.000 then the synergy

NOTE Confidence: 0.9205926

00:53:03.380 --> 00:53:04.980 was totally gone. That is

NOTE Confidence: 0.9205926

00:53:04.980 --> 00:53:06.760 using wild type l two

NOTE Confidence: 0.9205926

00:53:06.900 --> 00:53:08.040 and then doing blockade,

NOTE Confidence: 0.97908485

00:53:09.060 --> 00:53:10.120 completely gone.

NOTE Confidence: 0.64052784

00:53:10.420 --> 00:53:10.920 K.

NOTE Confidence: 0.9751619

00:53:11.565 --> 00:53:13.244 That the the critical way

NOTE Confidence: 0.9751619

00:53:13.244 --> 00:53:14.765 that cytokine was working was

NOTE Confidence: 0.9751619

00:53:14.765 --> 00:53:16.625 binding to the trimeric receptor.

NOTE Confidence: 0.6315821

00:53:17.085 --> 00:53:17.585 K.

NOTE Confidence: 0.917276

00:53:21.165 --> 00:53:22.685 We will skip. Yeah. Again,

NOTE Confidence: 0.917276

00:53:22.685 --> 00:53:23.484 this is what I told

NOTE Confidence: 0.917276

00:53:23.484 --> 00:53:25.005 you. But but there are

NOTE Confidence: 0.917276

00:53:25.005 --> 00:53:26.204 ways out of it. That

NOTE Confidence: 0.917276

00:53:26.204 --> 00:53:28.060 is you can still use

NOTE Confidence: 0.9521442

00:53:28.460 --> 00:53:29.180 so as I told you

NOTE Confidence: 0.9521442

00:53:29.180 --> 00:53:30.540 to, and also that I

NOTE Confidence: 0.9521442

00:53:30.540 --> 00:53:32.140 skipped data. Twenty five comes

NOTE Confidence: 0.9521442

00:53:32.140 --> 00:53:33.339 up very quickly on the

NOTE Confidence: 0.9521442

00:53:33.339 --> 00:53:34.940 antigen specific cells in vivo

NOTE Confidence: 0.9521442

00:53:34.940 --> 00:53:36.480 after this combination therapy.

NOTE Confidence: 0.97318006

00:53:38.540 --> 00:53:40.460 Twenty five blockade abrogates this

NOTE Confidence: 0.97318006

00:53:40.460 --> 00:53:40.960 effect.

NOTE Confidence: 0.9884781

00:53:41.325 --> 00:53:42.685 But if you target it

NOTE Confidence: 0.9884781

00:53:42.765 --> 00:53:43.885 so we also did a

NOTE Confidence: 0.9884781

00:53:43.885 --> 00:53:44.785 study using,

NOTE Confidence: 0.74577975

00:53:45.645 --> 00:53:46.944 a a,

NOTE Confidence: 0.9675349

00:53:47.565 --> 00:53:49.325 molecule from Roche, which was

NOTE Confidence: 0.9675349

00:53:49.325 --> 00:53:50.864 an anti PD one antibody,

NOTE Confidence: 0.96950823

00:53:51.885 --> 00:53:53.100 which on which there was

NOTE Confidence: 0.96950823

00:53:53.260 --> 00:53:54.220 IL two. This was the

NOTE Confidence: 0.96950823

00:53:54.220 --> 00:53:56.140 mutated IL two, and this

NOTE Confidence: 0.96950823

00:53:56.140 --> 00:53:57.600 works also quite well.

NOTE Confidence: 0.9618411

00:53:57.980 --> 00:54:00.000 K. So now you're targeting

NOTE Confidence: 0.9618411

00:54:00.060 --> 00:54:01.020 it to the cells of

NOTE Confidence: 0.9618411

00:54:01.020 --> 00:54:02.700 interest, and then you see,

NOTE Confidence: 0.9618411

00:54:02.940 --> 00:54:04.640 you see an effect. K.

NOTE Confidence: 0.9926324

00:54:05.100 --> 00:54:06.720 And that was published there.

NOTE Confidence: 0.95243734

00:54:07.805 --> 00:54:08.925 So where do we stand

NOTE Confidence: 0.95243734

00:54:08.925 --> 00:54:10.445 now with with IL two

NOTE Confidence: 0.95243734

00:54:10.445 --> 00:54:12.125 therapy? So I think if

NOTE Confidence: 0.95243734

00:54:12.125 --> 00:54:12.945 you use,

NOTE Confidence: 0.93581915

00:54:13.965 --> 00:54:14.625 and, unfortunately,

NOTE Confidence: 0.9714223

00:54:15.245 --> 00:54:17.105 the failure of many cytokine,

NOTE Confidence: 0.9713719

00:54:17.965 --> 00:54:19.565 IL two cytokines is consistent

NOTE Confidence: 0.9713719

00:54:19.565 --> 00:54:20.465 with our findings,

NOTE Confidence: 0.9985645

00:54:20.845 --> 00:54:21.585 is that

NOTE Confidence: 0.99871427

00:54:22.059 --> 00:54:23.579 if you use a free

NOTE Confidence: 0.99871427

00:54:23.579 --> 00:54:24.079 cytokine

NOTE Confidence: 0.8107216

00:54:24.380 --> 00:54:25.599 that is just the cytokine,

NOTE Confidence: 0.99937636

00:54:26.140 --> 00:54:27.200 but that's mutated

NOTE Confidence: 0.95285875

00:54:27.579 --> 00:54:29.420 in the alpha chain to

NOTE Confidence: 0.95285875

00:54:29.420 --> 00:54:30.859 binding to c twenty five,

NOTE Confidence: 0.95285875

00:54:30.859 --> 00:54:33.099 it's unlikely to work. And

NOTE Confidence: 0.95285875

00:54:33.099 --> 00:54:33.599 several

NOTE Confidence: 0.9980265

00:54:34.695 --> 00:54:35.335 phase one

NOTE Confidence: 0.94865435

00:54:36.215 --> 00:54:37.975 several phase three clinical trials

NOTE Confidence: 0.94865435

00:54:37.975 --> 00:54:38.635 have failed.

NOTE Confidence: 0.9908579

00:54:39.255 --> 00:54:39.755 When

NOTE Confidence: 0.91833544

00:54:40.055 --> 00:54:41.415 a free cytokine is being

NOTE Confidence: 0.91833544

00:54:41.415 --> 00:54:41.915 used

NOTE Confidence: 0.9289848

00:54:42.215 --> 00:54:43.495 and the CD twenty five,

NOTE Confidence: 0.9289848

00:54:43.495 --> 00:54:45.515 either the either by pegylation,

NOTE Confidence: 0.9067872

00:54:45.895 --> 00:54:47.575 you you block signal binding,

NOTE Confidence: 0.9067872

00:54:47.575 --> 00:54:48.555 which was the nectar

NOTE Confidence: 0.75397813

00:54:48.989 --> 00:54:49.650 IL two.

NOTE Confidence: 0.97323203

00:54:50.030 --> 00:54:51.310 And other IL twos where

NOTE Confidence: 0.97323203

00:54:51.310 --> 00:54:52.610 this was, mutated,

NOTE Confidence: 0.9532972

00:54:52.989 --> 00:54:54.510 they have either stopped after

NOTE Confidence: 0.9532972

00:54:54.510 --> 00:54:55.330 phase one,

NOTE Confidence: 0.931111

00:54:56.510 --> 00:54:57.250 or have,

NOTE Confidence: 0.948271

00:54:57.870 --> 00:54:59.890 unfortunately, gone further and stopped

NOTE Confidence: 0.948271

00:55:00.030 --> 00:55:00.530 later.

NOTE Confidence: 0.99052

00:55:01.425 --> 00:55:03.105 But targeted therapy is one

NOTE Confidence: 0.99052

00:55:03.105 --> 00:55:04.545 option, and this many people

NOTE Confidence: 0.99052

00:55:04.545 --> 00:55:05.765 are using this now.

NOTE Confidence: 0.907157

00:55:06.305 --> 00:55:07.665 Some are using CD eight

NOTE Confidence: 0.907157

00:55:07.665 --> 00:55:08.165 targeting,

NOTE Confidence: 0.948727

00:55:08.785 --> 00:55:09.905 but probably the PD one

NOTE Confidence: 0.948727

00:55:09.905 --> 00:55:11.045 targeting is better.

NOTE Confidence: 0.9747994

00:55:11.425 --> 00:55:12.945 And, currently, there is a

NOTE Confidence: 0.9747994

00:55:12.945 --> 00:55:15.265 clinical trial that Regeneron is

NOTE Confidence: 0.9747994

00:55:15.265 --> 00:55:15.765 doing

NOTE Confidence: 0.93203217

00:55:16.200 --> 00:55:17.580 where they are also using

NOTE Confidence: 0.93203217

00:55:17.880 --> 00:55:19.000 a p d one targeted,

NOTE Confidence: 0.93203217

00:55:19.000 --> 00:55:20.460 but they're using wild type.

NOTE Confidence: 0.9567306

00:55:21.080 --> 00:55:21.820 So Regeneron,

NOTE Confidence: 0.98681265

00:55:22.520 --> 00:55:23.880 they just started a clinical

NOTE Confidence: 0.98681265

00:55:23.880 --> 00:55:25.239 trial in lung cancer and

NOTE Confidence: 0.98681265

00:55:25.239 --> 00:55:26.219 also other cancer.

NOTE Confidence: 0.9733197

00:55:26.599 --> 00:55:28.460 They're using what we did,

NOTE Confidence: 0.8873545

00:55:28.760 --> 00:55:29.880 but with the wild type

NOTE Confidence: 0.8873545

00:55:29.880 --> 00:55:30.700 l two.

NOTE Confidence: 0.97533715

00:55:31.055 --> 00:55:32.335 And, actually, that might even

NOTE Confidence: 0.97533715

00:55:32.335 --> 00:55:33.475 be better. Yeah.

NOTE Confidence: 0.98697585

00:55:33.775 --> 00:55:35.055 The issue with wild type

NOTE Confidence: 0.98697585

00:55:35.055 --> 00:55:35.695 I l two is the

NOTE Confidence: 0.98697585

00:55:35.695 --> 00:55:36.835 toxicity issue.

NOTE Confidence: 0.9968041

00:55:37.375 --> 00:55:38.175 But I think if it's

NOTE Confidence: 0.9968041

00:55:38.175 --> 00:55:38.995 more targeted,

NOTE Confidence: 0.92646927

00:55:39.375 --> 00:55:40.575 it can probably be regulate

NOTE Confidence: 0.92646927

00:55:40.735 --> 00:55:41.935 it can be better. But

NOTE Confidence: 0.92646927

00:55:41.935 --> 00:55:42.675 in addition,

NOTE Confidence: 0.94197714

00:55:43.190 --> 00:55:45.350 there's also now regulated IL

NOTE Confidence: 0.94197714

00:55:45.350 --> 00:55:46.470 twos being used. That is

NOTE Confidence: 0.94197714

00:55:46.470 --> 00:55:48.170 they will only become active

NOTE Confidence: 0.9620101

00:55:48.550 --> 00:55:49.989 after they engage with PD

NOTE Confidence: 0.9620101

00:55:49.989 --> 00:55:51.350 one. That will bring in

NOTE Confidence: 0.9620101

00:55:51.350 --> 00:55:53.370 another safety aspect to it.

NOTE Confidence: 0.9620101

00:55:53.510 --> 00:55:54.810 So I think that this

NOTE Confidence: 0.99929774

00:55:55.605 --> 00:55:56.965 field is going to see

NOTE Confidence: 0.99929774

00:55:56.965 --> 00:55:58.344 a lot of interesting data.

NOTE Confidence: 0.9628809

00:55:59.685 --> 00:56:00.805 IL two is, as I

NOTE Confidence: 0.9628809

00:56:00.805 --> 00:56:01.844 put in the first bullet

NOTE Confidence: 0.9628809

00:56:01.844 --> 00:56:03.285 point here, it is the

NOTE Confidence: 0.9628809

00:56:03.285 --> 00:56:05.305 key cytokine for effective differentiation.

NOTE Confidence: 0.9979209

00:56:06.085 --> 00:56:07.465 There is no other cytokine

NOTE Confidence: 0.9979209

00:56:07.605 --> 00:56:08.505 that we have

NOTE Confidence: 0.99985856

00:56:08.810 --> 00:56:09.710 that is better

NOTE Confidence: 0.9822919

00:56:10.010 --> 00:56:11.770 in terms of generating good

NOTE Confidence: 0.9822919

00:56:11.770 --> 00:56:12.270 effectors.

NOTE Confidence: 0.97223884

00:56:13.130 --> 00:56:14.330 In our mouse model, we

NOTE Confidence: 0.97223884

00:56:14.330 --> 00:56:15.609 have tried many, many different

NOTE Confidence: 0.97223884

00:56:15.609 --> 00:56:16.750 combination therapies,

NOTE Confidence: 0.99893504

00:56:17.930 --> 00:56:19.210 and the one that's the

NOTE Confidence: 0.99893504

00:56:19.210 --> 00:56:20.030 most superior

NOTE Confidence: 0.89729196

00:56:20.410 --> 00:56:22.190 is the IL two plus

NOTE Confidence: 0.89729196

00:56:22.250 --> 00:56:23.070 p d one.

NOTE Confidence: 0.92886484

00:56:23.715 --> 00:56:24.995 So I think that the

NOTE Confidence: 0.92886484

00:56:24.995 --> 00:56:26.114 field will now, I think,

NOTE Confidence: 0.92886484

00:56:26.114 --> 00:56:27.075 is in a in a

NOTE Confidence: 0.92886484

00:56:27.075 --> 00:56:27.975 place where,

NOTE Confidence: 0.9577753

00:56:28.995 --> 00:56:30.435 some attention is being paid

NOTE Confidence: 0.9577753

00:56:30.435 --> 00:56:31.715 to targeting the I l

NOTE Confidence: 0.9577753

00:56:31.715 --> 00:56:33.255 two and not just using

NOTE Confidence: 0.9577753

00:56:33.315 --> 00:56:34.275 free I l two that

NOTE Confidence: 0.9577753

00:56:34.275 --> 00:56:35.475 doesn't bind c d twenty

NOTE Confidence: 0.9577753

00:56:35.475 --> 00:56:36.595 five. That basically is a

NOTE Confidence: 0.9577753

00:56:36.595 --> 00:56:37.095 washout

NOTE Confidence: 0.97281265

00:56:37.580 --> 00:56:40.000 because every cell has the

NOTE Confidence: 0.97281265

00:56:40.140 --> 00:56:41.260 beta and the gamma chain,

NOTE Confidence: 0.9401454

00:56:42.620 --> 00:56:43.660 chain. So it binds to

NOTE Confidence: 0.9401454

00:56:43.660 --> 00:56:44.400 every cell.

NOTE Confidence: 0.96344376

00:56:44.860 --> 00:56:46.380 It's just a major sync

NOTE Confidence: 0.96344376

00:56:46.380 --> 00:56:47.820 effect. I think that strategy

NOTE Confidence: 0.96344376

00:56:47.820 --> 00:56:48.960 is pretty much gone.

NOTE Confidence: 0.99679685

00:56:49.340 --> 00:56:50.000 But targeting

NOTE Confidence: 0.9865286

00:56:50.300 --> 00:56:51.600 is a is a real,

NOTE Confidence: 0.74000615

00:56:52.460 --> 00:56:52.960 possibility,

NOTE Confidence: 0.99957883

00:56:53.435 --> 00:56:55.035 and then additional safety can

NOTE Confidence: 0.99957883

00:56:55.035 --> 00:56:55.855 come by

NOTE Confidence: 0.94889784

00:56:56.315 --> 00:56:57.755 regulating it so that it

NOTE Confidence: 0.94889784

00:56:57.755 --> 00:56:59.515 only becomes active after it

NOTE Confidence: 0.94889784

00:56:59.515 --> 00:57:00.555 binds PD one. So I

NOTE Confidence: 0.94889784

00:57:00.555 --> 00:57:02.234 think it's a exciting time

NOTE Confidence: 0.94889784

00:57:02.234 --> 00:57:03.135 for these studies.

NOTE Confidence: 0.9885485

00:57:03.675 --> 00:57:05.695 So to end my talk

NOTE Confidence: 0.9885485

00:57:05.969 --> 00:57:07.410 on the stem like chronic

NOTE Confidence: 0.9885485

00:57:07.410 --> 00:57:07.910 cells,

NOTE Confidence: 0.93481374

00:57:08.210 --> 00:57:09.250 I showed you data on

NOTE Confidence: 0.93481374

00:57:09.250 --> 00:57:10.230 the chronic infection

NOTE Confidence: 0.91522104

00:57:10.770 --> 00:57:12.290 and in cancer, both human

NOTE Confidence: 0.91522104

00:57:12.290 --> 00:57:13.570 and many people, others have

NOTE Confidence: 0.91522104

00:57:13.570 --> 00:57:14.770 shown this, but also in

NOTE Confidence: 0.91522104

00:57:14.770 --> 00:57:15.270 autoimmunity.

NOTE Confidence: 0.9594574

00:57:15.969 --> 00:57:17.330 So now there are several

NOTE Confidence: 0.9594574

00:57:17.330 --> 00:57:18.790 papers that have come out

NOTE Confidence: 0.9594574

00:57:19.025 --> 00:57:19.845 that in autoimmunity,

NOTE Confidence: 0.83620465

00:57:20.625 --> 00:57:22.645 also you have this subset.

NOTE Confidence: 0.81916153

00:57:23.825 --> 00:57:25.025 Part which which part of

NOTE Confidence: 0.81916153

00:57:25.025 --> 00:57:26.485 the t s seventeen pathway

NOTE Confidence: 0.9288236

00:57:26.865 --> 00:57:28.385 would be something bad. But,

NOTE Confidence: 0.9288236

00:57:28.385 --> 00:57:29.925 again, you need the cell.

NOTE Confidence: 0.9781646

00:57:30.305 --> 00:57:31.425 The key message here is

NOTE Confidence: 0.9781646

00:57:31.425 --> 00:57:32.945 that without the cell, you

NOTE Confidence: 0.9781646

00:57:32.945 --> 00:57:33.925 cannot maintain

NOTE Confidence: 0.9754782

00:57:34.310 --> 00:57:35.670 the t cell response, whether

NOTE Confidence: 0.9754782

00:57:35.670 --> 00:57:37.030 it's for good or it's

NOTE Confidence: 0.9754782

00:57:37.030 --> 00:57:38.869 for bad. This cell is

NOTE Confidence: 0.9754782

00:57:38.869 --> 00:57:40.710 absolutely essential to keep the

NOTE Confidence: 0.9754782

00:57:40.710 --> 00:57:41.609 engine going.

NOTE Confidence: 0.9887402

00:57:42.790 --> 00:57:44.170 So a lot of wonderful

NOTE Confidence: 0.9887402

00:57:44.310 --> 00:57:45.270 people in the lab. I

NOTE Confidence: 0.9887402

00:57:45.270 --> 00:57:46.310 mentioned their names when I

NOTE Confidence: 0.9887402

00:57:46.310 --> 00:57:47.290 was there discussing

NOTE Confidence: 0.92916834

00:57:47.694 --> 00:57:49.454 great collaboration on, head and

NOTE Confidence: 0.92916834

00:57:49.454 --> 00:57:50.974 neck cancer with Naveed Saba

NOTE Confidence: 0.92916834

00:57:50.974 --> 00:57:52.655 and Meeha Patel and many

NOTE Confidence: 0.92916834

00:57:52.655 --> 00:57:53.155 wonderful,

NOTE Confidence: 0.9991683

00:57:54.015 --> 00:57:54.994 external collaborators.

NOTE Confidence: 0.9992596

00:57:55.295 --> 00:57:56.035 Thank you.

NOTE Confidence: 0.9004572

00:58:05.240 --> 00:58:06.460 There are questions.

NOTE Confidence: 0.85851777

00:58:07.480 --> 00:58:07.980 Yes.

NOTE Confidence: 0.91681606

00:58:08.440 --> 00:58:09.560 So thank you for the

NOTE Confidence: 0.91681606

00:58:09.560 --> 00:58:09.960 talk.

NOTE Confidence: 0.7425093

00:58:10.920 --> 00:58:12.040 You mentioned that it's sub

NOTE Confidence: 0.7425093

00:58:12.040 --> 00:58:13.240 vector cells that connect the

NOTE Confidence: 0.7425093

00:58:13.240 --> 00:58:13.980 stem cells

NOTE Confidence: 0.738261

00:58:14.440 --> 00:58:16.220 to the tumor differentiated cells,

NOTE Confidence: 0.8755413

00:58:28.265 --> 00:58:29.325 Ah, that's a good question.

NOTE Confidence: 0.9277207

00:58:29.750 --> 00:58:31.190 My we don't have direct

NOTE Confidence: 0.9277207

00:58:31.190 --> 00:58:32.470 evidence for that. K? It's

NOTE Confidence: 0.9277207

00:58:32.470 --> 00:58:34.010 a very good question. K?

NOTE Confidence: 0.9277207

00:58:34.069 --> 00:58:36.329 Whether they move before they

NOTE Confidence: 0.9277207

00:58:36.550 --> 00:58:37.050 differentiate,

NOTE Confidence: 0.9838293

00:58:37.430 --> 00:58:39.290 my prediction would be that,

NOTE Confidence: 0.98689467

00:58:40.470 --> 00:58:42.230 they start differentiating before they

NOTE Confidence: 0.98689467

00:58:42.230 --> 00:58:43.910 move because that program keeps

NOTE Confidence: 0.98689467

00:58:43.910 --> 00:58:44.650 them there.

NOTE Confidence: 0.9862139

00:58:45.165 --> 00:58:46.125 The the,

NOTE Confidence: 0.97119963

00:58:47.245 --> 00:58:49.565 the chemokine receptors change. So

NOTE Confidence: 0.97119963

00:58:49.565 --> 00:58:50.785 I think it's the differentiation

NOTE Confidence: 0.97119963

00:58:51.005 --> 00:58:52.225 step that then

NOTE Confidence: 0.9294558

00:58:52.605 --> 00:58:53.965 brings them out. And the

NOTE Confidence: 0.9294558

00:58:53.965 --> 00:58:55.485 key difference actually is down

NOTE Confidence: 0.9294558

00:58:55.485 --> 00:58:56.605 regulation of t c f

NOTE Confidence: 0.9294558

00:58:56.605 --> 00:58:58.500 one. And then TBET comes

NOTE Confidence: 0.9294558

00:58:58.500 --> 00:58:59.540 up. All these other things

NOTE Confidence: 0.9294558

00:58:59.540 --> 00:59:01.300 come up. So but some

NOTE Confidence: 0.9294558

00:59:01.380 --> 00:59:03.240 the initial signals for differentiation

NOTE Confidence: 0.9294558

00:59:03.380 --> 00:59:05.080 are happening in those hubs.

NOTE Confidence: 0.9294558

00:59:05.220 --> 00:59:06.500 K? But then once they

NOTE Confidence: 0.9294558

00:59:06.500 --> 00:59:08.020 differentiate, part of the program

NOTE Confidence: 0.9294558

00:59:08.020 --> 00:59:09.315 is you go out, which

NOTE Confidence: 0.9294558

00:59:09.474 --> 00:59:10.595 actually is not that different

NOTE Confidence: 0.9294558

00:59:10.595 --> 00:59:11.795 from what happens to a

NOTE Confidence: 0.9294558

00:59:11.795 --> 00:59:13.635 naive cell after infection or

NOTE Confidence: 0.9294558

00:59:13.635 --> 00:59:14.135 vaccination.

NOTE Confidence: 0.9505999

00:59:14.755 --> 00:59:16.595 K? The initial signals are

NOTE Confidence: 0.9505999

00:59:16.595 --> 00:59:18.035 in the lymph node in

NOTE Confidence: 0.9505999

00:59:18.035 --> 00:59:19.474 the t cell zones. Once

NOTE Confidence: 0.9505999

00:59:19.474 --> 00:59:20.915 they become effect like cells,

NOTE Confidence: 0.9505999

00:59:20.915 --> 00:59:21.895 they will come out.

NOTE Confidence: 0.7827157

00:59:26.940 --> 00:59:28.100 Before we talk Thank you.

NOTE Confidence: 0.7827157

00:59:28.220 --> 00:59:29.500 I was wondering about the

NOTE Confidence: 0.7827157

00:59:29.500 --> 00:59:31.340 tumor like mitogenics that we

NOTE Confidence: 0.7827157

00:59:31.340 --> 00:59:32.460 see. Do you also look

NOTE Confidence: 0.7827157

00:59:32.460 --> 00:59:34.380 at other cytotoxic effectors like

NOTE Confidence: 0.7827157

00:59:34.380 --> 00:59:35.660 natural killer cells? Are there

NOTE Confidence: 0.7827157

00:59:35.660 --> 00:59:36.780 a then new line stem

NOTE Confidence: 0.7827157

00:59:36.780 --> 00:59:37.280 cell?

NOTE Confidence: 0.93282324

00:59:37.795 --> 00:59:39.475 Yeah. We've been very focused

NOTE Confidence: 0.93282324

00:59:39.475 --> 00:59:40.995 on we've even been ignoring

NOTE Confidence: 0.93282324

00:59:40.995 --> 00:59:42.135 CD four cells.

NOTE Confidence: 0.9771899

00:59:42.995 --> 00:59:44.435 So we've been very focused

NOTE Confidence: 0.9771899

00:59:44.435 --> 00:59:45.735 on because, again, the,

NOTE Confidence: 0.94821453

00:59:47.955 --> 00:59:49.495 the tumor sample is small,

NOTE Confidence: 0.94821453

00:59:49.555 --> 00:59:50.515 the number of things we

NOTE Confidence: 0.94821453

00:59:50.515 --> 00:59:51.540 can do. So we've been

NOTE Confidence: 0.94821453

00:59:51.540 --> 00:59:53.060 very, very focused. But Andreas

NOTE Confidence: 0.94821453

00:59:53.060 --> 00:59:53.780 Wieland, who,

NOTE Confidence: 0.9673621

00:59:55.300 --> 00:59:56.420 was involved in both of

NOTE Confidence: 0.9673621

00:59:56.420 --> 00:59:57.620 these studies, he's on the

NOTE Confidence: 0.9673621

00:59:57.620 --> 00:59:59.620 faculty at Ohio State now,

NOTE Confidence: 0.9673621

00:59:59.620 --> 01:00:01.080 and he's putting a focus

NOTE Confidence: 0.9673621

01:00:01.220 --> 01:00:02.660 on CD four t cells

NOTE Confidence: 0.9673621

01:00:02.660 --> 01:00:03.640 and b cells.

NOTE Confidence: 0.968542

01:00:04.935 --> 01:00:05.915 Can I ask you,

NOTE Confidence: 0.9078687

01:00:06.695 --> 01:00:07.815 this work was all done

NOTE Confidence: 0.9078687

01:00:07.815 --> 01:00:09.895 in treatment naive Yes? All

NOTE Confidence: 0.9078687

01:00:09.895 --> 01:00:10.775 done into yes.

NOTE Confidence: 0.37761426

01:00:11.175 --> 01:00:11.675 Cancer.

NOTE Confidence: 0.8297212

01:00:12.135 --> 01:00:13.015 Yes. If you know, in

NOTE Confidence: 0.8297212

01:00:13.015 --> 01:00:14.055 head neck cancer, a big

NOTE Confidence: 0.8297212

01:00:14.055 --> 01:00:15.335 problem is that we've removed

NOTE Confidence: 0.8297212

01:00:15.335 --> 01:00:16.775 all the lymph nodes in

NOTE Confidence: 0.8297212

01:00:16.775 --> 01:00:17.915 in many of our patients.

NOTE Confidence: 0.99946177

01:00:18.215 --> 01:00:18.715 Yes.

NOTE Confidence: 0.9790511

01:00:20.960 --> 01:00:22.160 And yet I think from

NOTE Confidence: 0.9790511

01:00:22.160 --> 01:00:23.040 what you were showing us

NOTE Confidence: 0.9790511

01:00:23.040 --> 01:00:24.240 in lung cancer and and

NOTE Confidence: 0.9790511

01:00:24.240 --> 01:00:25.040 from the fact that we

NOTE Confidence: 0.9790511

01:00:25.040 --> 01:00:26.800 see responses in people with

NOTE Confidence: 0.9790511

01:00:26.800 --> 01:00:28.020 recurrent disease,

NOTE Confidence: 0.95820934

01:00:28.640 --> 01:00:30.800 I assume that the effector

NOTE Confidence: 0.95820934

01:00:30.800 --> 01:00:32.180 t cells that we generate

NOTE Confidence: 0.95820934

01:00:32.240 --> 01:00:32.980 with pembrolizumab

NOTE Confidence: 0.8970315

01:00:33.280 --> 01:00:34.815 in a recurrent Yeah. Patient

NOTE Confidence: 0.8970315

01:00:34.815 --> 01:00:36.015 also Yeah. I know that

NOTE Confidence: 0.8970315

01:00:36.015 --> 01:00:36.895 you're raising a very

NOTE Confidence: 0.9930695

01:00:37.535 --> 01:00:38.035 well,

NOTE Confidence: 0.958572

01:00:38.335 --> 01:00:39.454 you're raising a very important

NOTE Confidence: 0.958572

01:00:39.454 --> 01:00:41.135 question is that when you

NOTE Confidence: 0.958572

01:00:41.135 --> 01:00:41.875 do surgery,

NOTE Confidence: 0.99866664

01:00:43.055 --> 01:00:44.255 and you remove all the

NOTE Confidence: 0.99866664

01:00:44.255 --> 01:00:45.075 lymph nodes,

NOTE Confidence: 0.97202224

01:00:45.855 --> 01:00:46.895 how many of these stem

NOTE Confidence: 0.97202224

01:00:46.895 --> 01:00:48.415 like cells are remaining? I

NOTE Confidence: 0.97202224

01:00:48.415 --> 01:00:49.375 don't know the answer for

NOTE Confidence: 0.97202224

01:00:49.375 --> 01:00:51.520 that. You probably are removing

NOTE Confidence: 0.97202224

01:00:51.740 --> 01:00:52.720 a lot of them.

NOTE Confidence: 0.9596452

01:00:53.580 --> 01:00:54.460 But So I think it's

NOTE Confidence: 0.9596452

01:00:54.460 --> 01:00:55.980 very you can't leave the

NOTE Confidence: 0.9596452

01:00:55.980 --> 01:00:57.180 lymph nodes there because for

NOTE Confidence: 0.9596452

01:00:57.180 --> 01:00:59.100 obvious reasons, but you are,

NOTE Confidence: 0.9596452

01:00:59.100 --> 01:00:59.660 I think,

NOTE Confidence: 0.96672356

01:01:00.220 --> 01:01:01.740 because where are these cells

NOTE Confidence: 0.96672356

01:01:01.740 --> 01:01:02.700 as far as we know?

NOTE Confidence: 0.96672356

01:01:02.700 --> 01:01:04.160 They're in the tumor

NOTE Confidence: 0.9990767

01:01:04.655 --> 01:01:06.115 within these niches that,

NOTE Confidence: 0.99209726

01:01:06.734 --> 01:01:07.474 you know,

NOTE Confidence: 0.8557678

01:01:08.335 --> 01:01:09.454 Neil had to find and

NOTE Confidence: 0.8557678

01:01:09.454 --> 01:01:10.575 other people and we have

NOTE Confidence: 0.8557678

01:01:10.575 --> 01:01:11.075 shown,

NOTE Confidence: 0.9349396

01:01:12.015 --> 01:01:13.135 and they're in the draining

NOTE Confidence: 0.9349396

01:01:13.135 --> 01:01:14.815 nodes. That's been shown by

NOTE Confidence: 0.9349396

01:01:14.815 --> 01:01:15.555 many people.

NOTE Confidence: 0.9247858

01:01:16.255 --> 01:01:17.615 So if when you remove

NOTE Confidence: 0.9247858

01:01:17.615 --> 01:01:18.435 both compartments,

NOTE Confidence: 0.99562764

01:01:19.299 --> 01:01:21.299 you certainly are reducing the

NOTE Confidence: 0.99562764

01:01:21.299 --> 01:01:22.440 number of those cells.

NOTE Confidence: 0.91155034

01:01:22.980 --> 01:01:24.180 The the lung cancer that

NOTE Confidence: 0.91155034

01:01:24.180 --> 01:01:24.980 I told you, that was

NOTE Confidence: 0.91155034

01:01:24.980 --> 01:01:26.019 not there was no surgery.

NOTE Confidence: 0.91155034

01:01:26.019 --> 01:01:27.299 That was people getting PD

NOTE Confidence: 0.91155034

01:01:27.299 --> 01:01:28.359 one blockade.

NOTE Confidence: 0.9766186

01:01:29.779 --> 01:01:30.819 I'm just saying that there

NOTE Confidence: 0.9766186

01:01:30.819 --> 01:01:32.339 must be I'm I'm wondering

NOTE Confidence: 0.9766186

01:01:32.339 --> 01:01:33.299 if there's a process that

NOTE Confidence: 0.9766186

01:01:33.299 --> 01:01:35.205 recruits these TCS TCS one

NOTE Confidence: 0.9766186

01:01:35.205 --> 01:01:37.845 positive cells into Yeah. Right.

NOTE Confidence: 0.9766186

01:01:37.845 --> 01:01:38.965 Right. Right. So that brings

NOTE Confidence: 0.9766186

01:01:38.965 --> 01:01:40.565 up interesting questions about how

NOTE Confidence: 0.9766186

01:01:40.565 --> 01:01:42.245 do you in that setting,

NOTE Confidence: 0.9766186

01:01:42.245 --> 01:01:43.685 how do you increase the

NOTE Confidence: 0.9766186

01:01:43.685 --> 01:01:45.305 the frequency? I mean, one,

NOTE Confidence: 0.9507607

01:01:45.845 --> 01:01:47.625 thing would be therapeutic vaccination.

NOTE Confidence: 0.94841564

01:01:48.450 --> 01:01:50.050 And, hopefully, there's still some

NOTE Confidence: 0.94841564

01:01:50.050 --> 01:01:51.670 naive cells with that TCRs,

NOTE Confidence: 0.9726498

01:01:52.130 --> 01:01:53.190 which can be recruited.

NOTE Confidence: 0.97371995

01:01:53.730 --> 01:01:54.930 And I don't think it

NOTE Confidence: 0.97371995

01:01:54.930 --> 01:01:55.810 would be that all of

NOTE Confidence: 0.97371995

01:01:55.810 --> 01:01:56.770 the cells would be gone

NOTE Confidence: 0.97371995

01:01:56.770 --> 01:01:57.650 from the lymph nodes that

NOTE Confidence: 0.97371995

01:01:57.650 --> 01:01:59.010 you removed. K? So I

NOTE Confidence: 0.97371995

01:01:59.010 --> 01:02:00.130 think you may then need

NOTE Confidence: 0.97371995

01:02:00.130 --> 01:02:02.070 to provide some

NOTE Confidence: 0.9981091

01:02:02.450 --> 01:02:02.950 vaccination

NOTE Confidence: 0.9992674

01:02:03.250 --> 01:02:03.750 strategy

NOTE Confidence: 0.8852918

01:02:04.345 --> 01:02:05.565 for increasing their numbers.

NOTE Confidence: 0.9479532

01:02:06.025 --> 01:02:07.305 Yep. Numbers, I think, do

NOTE Confidence: 0.9479532

01:02:07.305 --> 01:02:08.345 go down after you do

NOTE Confidence: 0.9479532

01:02:08.345 --> 01:02:08.845 it.

NOTE Confidence: 0.93689495

01:02:09.385 --> 01:02:10.665 I can't imagine them not

NOTE Confidence: 0.93689495

01:02:10.665 --> 01:02:12.105 going down, right, because you're

NOTE Confidence: 0.93689495

01:02:12.105 --> 01:02:13.785 removing the reservoirs with these

NOTE Confidence: 0.93689495

01:02:13.785 --> 01:02:14.605 cells there.

NOTE Confidence: 0.9617792

01:02:30.805 --> 01:02:32.245 There probably are more states.

NOTE Confidence: 0.9617792

01:02:32.245 --> 01:02:33.365 Okay. I'm sure that somebody

NOTE Confidence: 0.9617792

01:02:33.365 --> 01:02:35.285 will find subsets of effectors

NOTE Confidence: 0.9617792

01:02:35.285 --> 01:02:36.885 and subsets of stem, but

NOTE Confidence: 0.9617792

01:02:36.885 --> 01:02:38.505 these are the three canonical,

NOTE Confidence: 0.99543244

01:02:39.045 --> 01:02:40.185 subsets. Yes.

NOTE Confidence: 0.9052336

01:02:47.490 --> 01:02:48.869 It's also talks positive.

NOTE Confidence: 0.97435784

01:02:49.569 --> 01:02:50.069 Yeah.

NOTE Confidence: 0.94017786

01:03:00.335 --> 01:03:02.175 It's happening continuously because when

NOTE Confidence: 0.94017786

01:03:02.175 --> 01:03:02.675 these

NOTE Confidence: 0.9962115

01:03:04.015 --> 01:03:04.915 cells are differentiating,

NOTE Confidence: 0.96616226

01:03:05.615 --> 01:03:06.815 they're giving rise to the

NOTE Confidence: 0.96616226

01:03:06.815 --> 01:03:08.335 effector cells, which remain, I

NOTE Confidence: 0.96616226

01:03:08.335 --> 01:03:09.810 think, good for several we

NOTE Confidence: 0.96616226

01:03:09.810 --> 01:03:10.790 don't know exactly.

NOTE Confidence: 0.9624089

01:03:11.090 --> 01:03:11.830 Might be

NOTE Confidence: 0.946598

01:03:12.530 --> 01:03:13.810 days or weeks they'll be

NOTE Confidence: 0.946598

01:03:13.810 --> 01:03:14.310 there,

NOTE Confidence: 0.90520144

01:03:15.330 --> 01:03:16.310 and then eventually,

NOTE Confidence: 0.88921756

01:03:16.690 --> 01:03:17.970 they will go to that

NOTE Confidence: 0.88921756

01:03:17.970 --> 01:03:19.810 terminal differential state. There's some

NOTE Confidence: 0.88921756

01:03:19.810 --> 01:03:21.090 people who think that they

NOTE Confidence: 0.88921756

01:03:21.090 --> 01:03:21.830 might be,

NOTE Confidence: 0.9956234

01:03:23.105 --> 01:03:24.244 depending on the environment,

NOTE Confidence: 0.96201783

01:03:24.545 --> 01:03:26.065 they might be generating more

NOTE Confidence: 0.96201783

01:03:26.065 --> 01:03:28.085 of the exhausted cells immediately.

NOTE Confidence: 0.9765348

01:03:28.944 --> 01:03:30.224 But our data would is

NOTE Confidence: 0.9765348

01:03:30.224 --> 01:03:32.224 more consistent with the, you

NOTE Confidence: 0.9765348

01:03:32.224 --> 01:03:33.744 know, it going through a

NOTE Confidence: 0.9765348

01:03:33.744 --> 01:03:34.244 early

NOTE Confidence: 0.99077654

01:03:34.560 --> 01:03:36.320 functional stage before they become

NOTE Confidence: 0.99077654

01:03:36.320 --> 01:03:38.100 exhausted, but both are possible.

NOTE Confidence: 0.9150241

01:03:38.800 --> 01:03:38.880 Yep.

NOTE Confidence: 0.98704934

01:03:40.240 --> 01:03:41.540 So in terms of

NOTE Confidence: 0.90227365

01:03:45.120 --> 01:03:46.880 when is each thing happening,

NOTE Confidence: 0.90227365

01:03:46.880 --> 01:03:47.380 once

NOTE Confidence: 0.98704654

01:03:48.285 --> 01:03:49.565 the system has kind of

NOTE Confidence: 0.98704654

01:03:49.565 --> 01:03:50.845 set in, basically, you have

NOTE Confidence: 0.98704654

01:03:50.845 --> 01:03:52.065 all three of these cells.

NOTE Confidence: 0.91807973

01:03:53.085 --> 01:03:54.204 Are you asking the question

NOTE Confidence: 0.91807973

01:03:54.204 --> 01:03:55.665 when are stem cells generated?

NOTE Confidence: 0.88549006

01:04:02.910 --> 01:04:03.790 Oh, the if they don't

NOTE Confidence: 0.88549006

01:04:03.790 --> 01:04:05.330 respond to therapy, then,

NOTE Confidence: 0.9949322

01:04:06.270 --> 01:04:07.630 many things could be wrong.

NOTE Confidence: 0.9400505

01:04:08.350 --> 01:04:09.390 You know, the tumor could

NOTE Confidence: 0.9400505

01:04:09.390 --> 01:04:10.510 be more aggressive. But from

NOTE Confidence: 0.9400505

01:04:10.510 --> 01:04:12.109 a t cell side, I

NOTE Confidence: 0.9400505

01:04:12.109 --> 01:04:13.470 think when a patient doesn't

NOTE Confidence: 0.9400505

01:04:13.470 --> 01:04:13.970 respond,

NOTE Confidence: 0.9971554

01:04:14.350 --> 01:04:15.250 I think the

NOTE Confidence: 0.9222082

01:04:15.565 --> 01:04:16.605 number of t cells to

NOTE Confidence: 0.9222082

01:04:16.605 --> 01:04:18.145 begin with are very low.

NOTE Confidence: 0.96107996

01:04:19.245 --> 01:04:20.605 See, PD one does not

NOTE Confidence: 0.96107996

01:04:20.605 --> 01:04:22.145 create any new t cell.

NOTE Confidence: 0.9991884

01:04:22.925 --> 01:04:23.905 None of the checkpoint,

NOTE Confidence: 0.9849659

01:04:24.925 --> 01:04:26.765 blockade strategies create a new

NOTE Confidence: 0.9849659

01:04:26.765 --> 01:04:28.445 t cell. They are trying

NOTE Confidence: 0.9849659

01:04:28.445 --> 01:04:28.945 to

NOTE Confidence: 0.9703363

01:04:29.559 --> 01:04:30.059 provide,

NOTE Confidence: 0.99974334

01:04:31.319 --> 01:04:32.140 more differentiation

NOTE Confidence: 0.99821275

01:04:32.440 --> 01:04:33.819 from an existing cell.

NOTE Confidence: 0.925637

01:04:35.640 --> 01:04:37.400 Take one last question maybe

NOTE Confidence: 0.925637

01:04:37.400 --> 01:04:38.920 from Brenda Emu, and then

NOTE Confidence: 0.925637

01:04:38.920 --> 01:04:39.799 would would it be okay

NOTE Confidence: 0.925637

01:04:39.799 --> 01:04:40.599 if people come up with

NOTE Confidence: 0.925637

01:04:40.680 --> 01:04:41.480 Oh, yeah. I'll just I'll

NOTE Confidence: 0.925637

01:04:41.480 --> 01:04:43.500 still I'll be I'll yeah.

NOTE Confidence: 0.9469135

01:04:55.275 --> 01:04:56.315 Is there something in the

NOTE Confidence: 0.9469135

01:04:56.315 --> 01:04:57.915 premalignant stage that there's a

NOTE Confidence: 0.9469135

01:04:57.915 --> 01:04:59.910 difference that that some patients

NOTE Confidence: 0.9469135

01:04:59.970 --> 01:05:01.410 lose some Yeah. That's a

NOTE Confidence: 0.9469135

01:05:01.410 --> 01:05:02.450 very good question. Again, in

NOTE Confidence: 0.9469135

01:05:02.450 --> 01:05:03.730 terms of how their initial

NOTE Confidence: 0.9469135

01:05:03.730 --> 01:05:05.650 responses were, how many cells

NOTE Confidence: 0.9469135

01:05:05.650 --> 01:05:07.030 were made. So

NOTE Confidence: 0.8693364

01:05:07.970 --> 01:05:09.330 and then, also, the question,

NOTE Confidence: 0.8693364

01:05:09.330 --> 01:05:10.450 when do you generate these

NOTE Confidence: 0.8693364

01:05:10.450 --> 01:05:11.825 stem? We have a full

NOTE Confidence: 0.8693364

01:05:11.825 --> 01:05:13.285 story on that. That's okay.

NOTE Confidence: 0.7365348

01:05:13.825 --> 01:05:15.444 But they're generated very early.

NOTE Confidence: 0.94460773

01:05:15.984 --> 01:05:17.825 Very early. So in actually,

NOTE Confidence: 0.94460773

01:05:17.825 --> 01:05:19.025 the so I would say

NOTE Confidence: 0.94460773

01:05:19.025 --> 01:05:20.005 that in the HPV

NOTE Confidence: 0.7920115

01:05:20.385 --> 01:05:20.885 infection,

NOTE Confidence: 0.9582919

01:05:21.505 --> 01:05:23.585 that this cell cell, which

NOTE Confidence: 0.9582919

01:05:23.585 --> 01:05:24.885 has some of these characteristics,

NOTE Confidence: 0.9947379

01:05:25.530 --> 01:05:26.970 would have been generated very

NOTE Confidence: 0.9947379

01:05:26.970 --> 01:05:28.350 early during the infection.

NOTE Confidence: 0.56128037

01:05:32.170 --> 01:05:32.990 It's status.

NOTE Confidence: 0.99542695

01:05:33.530 --> 01:05:35.530 If the antigen clears, then

NOTE Confidence: 0.99542695

01:05:35.530 --> 01:05:36.570 it will not have this

NOTE Confidence: 0.99542695

01:05:36.570 --> 01:05:37.070 phenotype.

NOTE Confidence: 0.95068294

01:05:37.530 --> 01:05:39.130 It'll then start looking more

NOTE Confidence: 0.95068294

01:05:39.130 --> 01:05:40.685 like a memory cell. K.

NOTE Confidence: 0.95068294

01:05:40.745 --> 01:05:42.045 But this cell population

NOTE Confidence: 0.93612427

01:05:42.505 --> 01:05:44.125 is generated very early,

NOTE Confidence: 0.9209333

01:05:45.545 --> 01:05:46.985 and, that's a paper that's

NOTE Confidence: 0.9209333

01:05:46.985 --> 01:05:48.105 coming out. I I didn't

NOTE Confidence: 0.9209333

01:05:48.105 --> 01:05:49.065 wanna include that talk in

NOTE Confidence: 0.9209333

01:05:49.065 --> 01:05:49.565 here.

NOTE Confidence: 0.9385032

01:05:49.945 --> 01:05:51.465 Let's see. But it's really

NOTE Confidence: 0.9385032

01:05:51.465 --> 01:05:52.745 quite nice because the immune

NOTE Confidence: 0.9385032

01:05:52.745 --> 01:05:53.725 system is actually

NOTE Confidence: 0.98903227

01:05:54.440 --> 01:05:56.520 preparing for generating that cell

NOTE Confidence: 0.98903227

01:05:56.520 --> 01:05:58.220 before even knowing the outcome.

NOTE Confidence: 0.98966086

01:05:59.560 --> 01:06:00.440 I mean, the paper that

NOTE Confidence: 0.98966086

01:06:00.440 --> 01:06:01.560 we have in press, and

NOTE Confidence: 0.98966086

01:06:01.560 --> 01:06:02.380 that would be

NOTE Confidence: 0.9639225

01:06:02.680 --> 01:06:04.200 a different seminar, is that

NOTE Confidence: 0.9639225

01:06:04.200 --> 01:06:06.140 even in the acute infection

NOTE Confidence: 0.9639225

01:06:06.280 --> 01:06:06.780 setting,

NOTE Confidence: 0.9785811

01:06:07.865 --> 01:06:09.484 you generate the cell population

NOTE Confidence: 0.9785811

01:06:09.545 --> 01:06:10.444 in small numbers.

NOTE Confidence: 0.9492821

01:06:12.265 --> 01:06:13.464 Because at that time, you

NOTE Confidence: 0.9492821

01:06:13.464 --> 01:06:14.665 don't know is the infection

NOTE Confidence: 0.9492821

01:06:14.665 --> 01:06:15.785 going to be chronic or

NOTE Confidence: 0.9492821

01:06:15.785 --> 01:06:17.645 acute. So there's this very

NOTE Confidence: 0.9492821

01:06:17.704 --> 01:06:18.605 early preparation

NOTE Confidence: 0.9629983

01:06:18.905 --> 01:06:20.744 by generating this, so this

NOTE Confidence: 0.9629983

01:06:20.744 --> 01:06:21.565 fake decision

NOTE Confidence: 0.89684844

01:06:21.944 --> 01:06:23.280 to give you the cell,

NOTE Confidence: 0.89684844

01:06:23.520 --> 01:06:24.980 which is, again, I emphasize

NOTE Confidence: 0.89684844

01:06:25.120 --> 01:06:26.260 Granzyme b negative

NOTE Confidence: 0.95172834

01:06:26.720 --> 01:06:28.500 and having the TFH flavor

NOTE Confidence: 0.95172834

01:06:28.720 --> 01:06:29.940 happens very quickly

NOTE Confidence: 0.942315

01:06:30.240 --> 01:06:31.460 within the first week.

NOTE Confidence: 0.9630546

01:06:31.760 --> 01:06:33.140 And this cell is there

NOTE Confidence: 0.9630546

01:06:33.360 --> 01:06:34.720 even in the acute infant.

NOTE Confidence: 0.9630546

01:06:34.720 --> 01:06:35.680 Then you look later, it's

NOTE Confidence: 0.9630546

01:06:35.680 --> 01:06:36.960 gone. It's become part of

NOTE Confidence: 0.9630546

01:06:36.960 --> 01:06:38.000 the pool of the central

NOTE Confidence: 0.9630546

01:06:38.000 --> 01:06:38.980 memory cells.

NOTE Confidence: 0.9917076

01:06:39.335 --> 01:06:39.974 We don't know how much

NOTE Confidence: 0.9917076

01:06:39.974 --> 01:06:41.015 of that contributes to it,

NOTE Confidence: 0.9917076

01:06:41.015 --> 01:06:42.234 but that cell is gone.

NOTE Confidence: 0.9917076

01:06:42.295 --> 01:06:43.575 If you but but if

NOTE Confidence: 0.9917076

01:06:43.575 --> 01:06:44.634 the chronic infection

NOTE Confidence: 0.99709207

01:06:45.015 --> 01:06:45.515 ensues,

NOTE Confidence: 0.9990459

01:06:46.055 --> 01:06:47.095 then that is the key

NOTE Confidence: 0.9990459

01:06:47.095 --> 01:06:48.394 cell maintaining it.

NOTE Confidence: 0.940425

01:06:49.015 --> 01:06:50.234 So I think the HPV,

NOTE Confidence: 0.940425

01:06:50.295 --> 01:06:51.174 what you're asking is, I

NOTE Confidence: 0.940425

01:06:51.174 --> 01:06:52.454 think this cell was generated

NOTE Confidence: 0.940425

01:06:52.454 --> 01:06:53.674 when they first got,

NOTE Confidence: 0.99967134

01:06:54.375 --> 01:06:54.875 infected.

NOTE Confidence: 0.9603553

01:06:58.574 --> 01:06:59.774 Thank you so much. Thank

NOTE Confidence: 0.9603553

01:06:59.774 --> 01:07:00.274 you.