WEBVTT

NOTE duration:"01:02:01"

NOTE recognizability:0.816

NOTE language:en-us

NOTE Confidence: 0.708565115

00:00:00.000 --> 00:00:02.388 And so it's my great pleasure.

NOTE Confidence: 0.708565115

00:00:02.390 --> 00:00:03.332 I'm Marcus Bosenberg,

NOTE Confidence: 0.708565115

00:00:03.332 --> 00:00:06.413 I'm one of the Co leaders of the cancer

NOTE Confidence: 0.708565115

00:00:06.413 --> 00:00:08.456 immunology program and we're actually

NOTE Confidence: 0.708565115

00:00:08.456 --> 00:00:11.298 have our full House of a program

NOTE Confidence: 0.708565115

00:00:11.298 --> 00:00:14.550 Co leaders in person as we speak.

NOTE Confidence: 0.708565115

00:00:14.550 --> 00:00:16.950 So today's grand rounds speaker will

NOTE Confidence: 0.708565115

00:00:16.950 --> 00:00:18.900 be David Braun who's an assistant

NOTE Confidence: 0.708565115

00:00:18.958 --> 00:00:21.106 professor in the Department of Medicine

NOTE Confidence: 0.708565115

00:00:21.106 --> 00:00:23.160 and also has appointments in pathology

NOTE Confidence: 0.708565115

00:00:23.160 --> 00:00:25.127 and urology and is a Lewis Goodman

NOTE Confidence: 0.708565115

00:00:25.127 --> 00:00:27.298 and Alfred Gilman, Yale scholar.

NOTE Confidence: 0.708565115

00:00:27.298 --> 00:00:30.500 So he is also a member of.

NOTE Confidence: 0.708565115

00:00:30.500 --> 00:00:33.230 The Center for Molecular and Cellular

NOTE Confidence: 0.708565115

00:00:33.230 --> 00:00:35.885 Oncology that Marcus Musham leads at

NOTE Confidence: 0.708565115

00:00:35.885 --> 00:00:38.153 the Yellow Cancer Center and received

NOTE Confidence: 0.708565115

00:00:38.153 --> 00:00:40.722 his PhD in computational biology at

NOTE Confidence: 0.708565115

00:00:40.722 --> 00:00:44.016 NYU and his MD at Mount Sinai and was

NOTE Confidence: 0.708565115

00:00:44.016 --> 00:00:47.050 a resident in Boston and a fellow at

NOTE Confidence: 0.708565115

00:00:47.050 --> 00:00:49.600 Dana Farber prior to coming here.

NOTE Confidence: 0.708565115

00:00:49.600 --> 00:00:51.680 And we're very glad he's come to Yale.

NOTE Confidence: 0.708565115

00:00:51.680 --> 00:00:53.840 So David, as you will see,

NOTE Confidence: 0.708565115

00:00:53.840 --> 00:00:57.128 is covering a remarkably broad set of

NOTE Confidence: 0.708565115

00:00:57.128 --> 00:00:59.198 things related to cancer immunology,

NOTE Confidence: 0.708565115

00:00:59.200 --> 00:01:01.290 really focused initially on renal

NOTE Confidence: 0.708565115

00:01:01.290 --> 00:01:02.126 cell carcinoma.

NOTE Confidence: 0.708565115

00:01:02.130 --> 00:01:02.868 But you know,

NOTE Confidence: 0.708565115

00:01:02.868 --> 00:01:04.344 we'll see where that goes and

NOTE Confidence: 0.708565115

00:01:04.344 --> 00:01:06.250 we're super happy to have him here

NOTE Confidence: 0.708565115

00:01:06.250 --> 00:01:08.012 and have them associated with the

NOTE Confidence: 0.708565115

00:01:08.012 --> 00:01:08.978 cancer analogy program.

NOTE Confidence: 0.708565115

00:01:08.980 --> 00:01:10.500 And David, without further ado,

NOTE Confidence: 0.708565115

00:01:10.500 --> 00:01:13.440 we'll have to start.

NOTE Confidence: 0.708565115

00:01:13.440 --> 00:01:14.070 That's perfect.

NOTE Confidence: 0.853276494827586

00:01:16.640 --> 00:01:18.712 Thank you so much for the incredibly

NOTE Confidence: 0.853276494827586

00:01:18.712 --> 00:01:20.334 kind introduction and for that the

NOTE Confidence: 0.853276494827586

00:01:20.334 --> 00:01:22.195 chance to speak to you all here today

NOTE Confidence: 0.853276494827586

00:01:22.195 --> 00:01:24.059 and all the people on zoom as well.

NOTE Confidence: 0.853276494827586

00:01:24.060 --> 00:01:25.707 And So what I'm going to talk about today

NOTE Confidence: 0.853276494827586

00:01:25.707 --> 00:01:27.576 is some of the determinants of effective

NOTE Confidence: 0.853276494827586

00:01:27.576 --> 00:01:29.010 antitumor immunity in kidney cancer.

NOTE Confidence: 0.853276494827586

00:01:29.010 --> 00:01:29.978 And as Marcus mentioned,

NOTE Confidence: 0.853276494827586

00:01:29.978 --> 00:01:31.781 a lot of this is relevant specifically

NOTE Confidence: 0.853276494827586

00:01:31.781 --> 00:01:33.853 for kidney cancer and I see patients

NOTE Confidence: 0.853276494827586

00:01:33.853 --> 00:01:35.320 with kidney cancer at smilow.

NOTE Confidence: 0.853276494827586

00:01:35.320 --> 00:01:37.138 And so it's relevant for these,

NOTE Confidence: 0.853276494827586

00:01:37.140 --> 00:01:38.820 it's relevant for these

NOTE Confidence: 0.853276494827586

00:01:38.820 --> 00:01:39.660 patients specifically.

NOTE Confidence: 0.853276494827586

00:01:39.660 --> 00:01:41.660 But I hope as well that this could be used

NOTE Confidence: 0.853276494827586

00:01:41.716 --> 00:01:43.822 as a as a broader model of human tumor

NOTE Confidence: 0.853276494827586

00:01:43.822 --> 00:01:45.584 immunology that we might be able to learn.

NOTE Confidence: 0.853276494827586

00:01:45.590 --> 00:01:47.350 Uh, learn particularly neurologic

NOTE Confidence: 0.853276494827586

00:01:47.350 --> 00:01:49.550 mechanisms that might be applicable

NOTE Confidence: 0.853276494827586

00:01:49.550 --> 00:01:51.708 to other cancer types as well.

NOTE Confidence: 0.853276494827586

00:01:51.710 --> 00:01:53.870 Here my disclosure is not relevant

NOTE Confidence: 0.853276494827586

00:01:53.870 --> 00:01:55.678 for today's talk and so I usually

NOTE Confidence: 0.853276494827586

00:01:55.678 --> 00:01:57.315 like to start off with just a couple

NOTE Confidence: 0.853276494827586

00:01:57.315 --> 00:01:58.809 of patients just to highlight the

NOTE Confidence: 0.853276494827586

00:01:58.809 --> 00:01:59.929 challenges within kidney cancer.

NOTE Confidence: 0.853276494827586

00:01:59.930 --> 00:02:01.775 This is going to be true for a lot

NOTE Confidence: 0.853276494827586

00:02:01.775 --> 00:02:03.765 of solid tumors and particularly in

NOTE Confidence: 0.853276494827586

00:02:03.765 --> 00:02:05.145 the immune therapy era.

NOTE Confidence: 0.853276494827586

00:02:05.150 --> 00:02:05.874 So the first patient,

NOTE Confidence: 0.853276494827586

00:02:05.874 --> 00:02:06.960 these are two of my patients

NOTE Confidence: 0.853276494827586

00:02:07.001 --> 00:02:08.087 from the last couple of years.

NOTE Confidence: 0.853276494827586

00:02:08.090 --> 00:02:09.160 The first patient was a

NOTE Confidence: 0.853276494827586

00:02:09.160 --> 00:02:10.016 68 year old gentleman,

NOTE Confidence: 0.853276494827586

00:02:10.020 --> 00:02:12.364 had a fairly common age for kidney cancer,

NOTE Confidence: 0.853276494827586

00:02:12.370 --> 00:02:14.785 had metastatic clear cell kidney

NOTE Confidence: 0.853276494827586

00:02:14.785 --> 00:02:17.200 cancer that's the most common.

NOTE Confidence: 0.853276494827586

00:02:17.200 --> 00:02:18.080 Thank you.

NOTE Confidence: 0.853276494827586

00:02:18.080 --> 00:02:20.720 The most common histologic diagnosis of

NOTE Confidence: 0.853276494827586

00:02:20.720 --> 00:02:23.012 kidney cancer and had pretty widespread

NOTE Confidence: 0.853276494827586

00:02:23.012 --> 00:02:24.777 metastatic disease throughout the lungs.

NOTE Confidence: 0.853276494827586

00:02:24.780 --> 00:02:26.538 Lungs actually had a brain metastasis

NOTE Confidence: 0.853276494827586

00:02:26.538 --> 00:02:28.523 and so received a standard first

NOTE Confidence: 0.853276494827586

00:02:28.523 --> 00:02:30.035 line combination of checkpoint

NOTE Confidence: 0.853276494827586

00:02:30.035 --> 00:02:31.980 inhibitors and the volume animac.

NOTE Confidence: 0.853276494827586

00:02:31.980 --> 00:02:32.820 And for those that don't

NOTE Confidence: 0.853276494827586

00:02:32.820 --> 00:02:33.660 look at CC's every day,

NOTE Confidence: 0.853276494827586

00:02:33.660 --> 00:02:36.020 the primary tumor is outlined in red and

NOTE Confidence: 0.853276494827586

00:02:36.020 --> 00:02:38.758 we can see compared to prior to therapy,

NOTE Confidence: 0.853276494827586

00:02:38.760 --> 00:02:39.792 there's a tremendous shrinkage

NOTE Confidence: 0.853276494827586

00:02:39.792 --> 00:02:40.566 of that primary.

NOTE Confidence: 0.853276494827586

00:02:40.570 --> 00:02:41.671 There's basically resolution

NOTE Confidence: 0.853276494827586

00:02:41.671 --> 00:02:43.139 of all metastatic disease.

NOTE Confidence: 0.853276494827586

00:02:43.140 --> 00:02:44.358 The the primary,

NOTE Confidence: 0.853276494827586

00:02:44.358 --> 00:02:46.388 the residual primary was resected.

NOTE Confidence: 0.853276494827586

00:02:46.390 --> 00:02:48.286 And so this patient is free of disease,

NOTE Confidence: 0.853276494827586

00:02:48.290 --> 00:02:50.558 potentially cured of their disease has

NOTE Confidence: 0.853276494827586

00:02:50.558 --> 00:02:53.159 now been off therapy for over a year.

NOTE Confidence: 0.853276494827586

00:02:53.160 --> 00:02:54.472 That's in sharp contrast

NOTE Confidence: 0.853276494827586

00:02:54.472 --> 00:02:56.112 to a very similar patient,

NOTE Confidence: 0.853276494827586

00:02:56.120 --> 00:02:57.532 very similar demographic received

NOTE Confidence: 0.853276494827586

00:02:57.532 --> 00:02:59.650 the exact same therapy for the

NOTE Confidence: 0.853276494827586

00:02:59.709 --> 00:03:01.200 exact histologic diagnosis.

NOTE Confidence: 0.853276494827586

00:03:01.200 --> 00:03:02.256 But unfortunately the tumors

NOTE Confidence: 0.853276494827586

00:03:02.256 --> 00:03:03.576 did not respond to therapy.

NOTE Confidence: 0.853276494827586

00:03:03.580 --> 00:03:05.092 They all grew and despite this

NOTE Confidence: 0.853276494827586

00:03:05.092 --> 00:03:06.520 and subsequent lines of therapy,

NOTE Confidence: 0.853276494827586

00:03:06.520 --> 00:03:08.575 the patient passed away within

NOTE Confidence: 0.853276494827586

00:03:08.575 --> 00:03:10.219 eight months of diagnosis.

NOTE Confidence: 0.853276494827586

00:03:10.220 --> 00:03:11.858 And so it's it's cases like these,

NOTE Confidence: 0.853276494827586

00:03:11.860 --> 00:03:13.236 these extreme response phenotypes,

NOTE Confidence: 0.853276494827586

00:03:13.236 --> 00:03:15.722 the sort of promise of long standing

NOTE Confidence: 0.853276494827586

00:03:15.722 --> 00:03:17.166 durable responses and resistance

NOTE Confidence: 0.853276494827586

00:03:17.166 --> 00:03:19.339 that sort of drives the questions

NOTE Confidence: 0.853276494827586

00:03:19.339 --> 00:03:21.516 in in my lab and there's some

NOTE Confidence: 0.853276494827586

00:03:21.516 --> 00:03:22.648 peculiarities to kidney cancer.

NOTE Confidence: 0.853276494827586

00:03:22.648 --> 00:03:24.426 That on the scientific front has also

NOTE Confidence: 0.853276494827586

00:03:24.426 --> 00:03:26.288 been really interesting and fascinating.

NOTE Confidence: 0.853276494827586

00:03:26.290 --> 00:03:29.434 So historically we think of CDA T cell

NOTE Confidence: 0.853276494827586

00:03:29.434 --> 00:03:31.967 infiltration as being a positive thing,

NOTE Confidence: 0.853276494827586

00:03:31.970 --> 00:03:32.930 positive prognostic thing.

NOTE Confidence: 0.853276494827586

00:03:32.930 --> 00:03:34.210 They're main factor self

NOTE Confidence: 0.853276494827586

00:03:34.210 --> 00:03:35.670 or anti tumor immunity.

NOTE Confidence: 0.853276494827586

00:03:35.670 --> 00:03:37.358 So having a lot of them in the

NOTE Confidence: 0.853276494827586

00:03:37.358 --> 00:03:39.070 tumor is positive though historical

NOTE Confidence: 0.853276494827586

00:03:39.070 --> 00:03:41.070 exception is really kidney cancer

NOTE Confidence: 0.853276494827586

00:03:41.070 --> 00:03:43.290 where over time of the past 20

NOTE Confidence: 0.853276494827586

00:03:43.290 --> 00:03:45.124 years or so having a high degree

NOTE Confidence: 0.853276494827586

00:03:45.124 --> 00:03:47.504 of CD T cell infiltration has been

NOTE Confidence: 0.853276494827586

00:03:47.504 --> 00:03:49.315 associated with a worse prognosis

NOTE Confidence: 0.853276494827586

00:03:49.315 --> 00:03:51.940 really in contrast to just about every

NOTE Confidence: 0.833308110714286

00:03:52.009 --> 00:03:53.549 other solid tumor type.

NOTE Confidence: 0.833308110714286

00:03:53.550 --> 00:03:55.097 Further when we think of what our

NOTE Confidence: 0.833308110714286

00:03:55.097 --> 00:03:56.550 tumor types that typically responsive

NOTE Confidence: 0.833308110714286

00:03:56.550 --> 00:03:58.026 to new checkpoint inhibitors,

NOTE Confidence: 0.833308110714286

00:03:58.030 --> 00:03:59.190 we think of tumor types

NOTE Confidence: 0.833308110714286

00:03:59.190 --> 00:04:00.620 that are on the far end,

NOTE Confidence: 0.833308110714286

00:04:00.620 --> 00:04:02.246 the right end of this mutation

NOTE Confidence: 0.833308110714286

00:04:02.246 --> 00:04:04.068 spectrum that makes a lot of sense.

NOTE Confidence: 0.833308110714286

00:04:04.070 --> 00:04:06.542 We have tumors that have high

NOTE Confidence: 0.833308110714286

00:04:06.542 --> 00:04:08.381 mutation burdens, lots of neoantigens,

NOTE Confidence: 0.833308110714286

00:04:08.381 --> 00:04:10.066 so lots of potential antigenic

NOTE Confidence: 0.833308110714286

00:04:10.066 --> 00:04:11.759 targets for the immune system.

NOTE Confidence: 0.833308110714286

00:04:11.760 --> 00:04:13.506 They're potentially more likely to respond.

NOTE Confidence: 0.833308110714286

00:04:13.510 --> 00:04:15.988 So Melanoma, non small cell lung cancer,

NOTE Confidence: 0.833308110714286

00:04:15.990 --> 00:04:16.624 urothelial cancer,

NOTE Confidence: 0.833308110714286

00:04:16.624 --> 00:04:19.160 MSI colon cancer and then we see right

NOTE Confidence: 0.833308110714286

00:04:19.220 --> 00:04:21.089 in the middle is clear cell kidney

NOTE Confidence: 0.833308110714286

00:04:21.089 --> 00:04:23.230 cancer with a modest mutation burden.

NOTE Confidence: 0.833308110714286

00:04:23.230 --> 00:04:25.035 Pretty similar to glioblastoma or

NOTE Confidence: 0.833308110714286

00:04:25.035 --> 00:04:26.662 pancreatic cancer, ovarian cancer.

NOTE Confidence: 0.833308110714286

00:04:26.662 --> 00:04:28.917 Yet both historically and contemporarily,

NOTE Confidence: 0.833308110714286

00:04:28.920 --> 00:04:30.680 it's responsive to immune therapy.

NOTE Confidence: 0.833308110714286

00:04:30.680 --> 00:04:32.273 And so my hope is we might be able

NOTE Confidence: 0.833308110714286

00:04:32.273 --> 00:04:33.898 to learn a little bit about why,

NOTE Confidence: 0.833308110714286

00:04:33.900 --> 00:04:35.300 if we can figure out why this

NOTE Confidence: 0.833308110714286

00:04:35.300 --> 00:04:36.560 is responsive to immunotherapy,

NOTE Confidence: 0.833308110714286

00:04:36.560 --> 00:04:38.436 maybe we can apply those lessons elsewhere.

NOTE Confidence: 0.833308110714286

00:04:38.440 --> 00:04:40.288 And then also for those patients who

NOTE Confidence: 0.833308110714286

00:04:40.288 --> 00:04:42.560 aren't lucky to benefit from immune therapy,

NOTE Confidence: 0.833308110714286

00:04:42.560 --> 00:04:44.078 the current forms of immune therapy,

NOTE Confidence: 0.833308110714286

00:04:44.080 --> 00:04:46.125 can we understand mechanisms of

NOTE Confidence: 0.833308110714286

00:04:46.125 --> 00:04:48.170 resistance that can guide rational

NOTE Confidence: 0.833308110714286

00:04:48.234 --> 00:04:50.538 combinations of future therapies and so

NOTE Confidence: 0.833308110714286

00:04:50.538 --> 00:04:53.516 the framework that our lab really uses to.

NOTE Confidence: 0.833308110714286

00:04:53.516 --> 00:04:54.650 Answer these questions,

NOTE Confidence: 0.833308110714286

00:04:54.650 --> 00:04:56.258 what are the infiltrating immune cells

NOTE Confidence: 0.833308110714286

00:04:56.258 --> 00:04:58.000 and what are the antigenic targets

NOTE Confidence: 0.833308110714286

00:04:58.000 --> 00:05:00.149 in kidney cancer is a pretty simple

NOTE Confidence: 0.833308110714286

00:05:00.149 --> 00:05:01.658 framework and I've sort of outlined

NOTE Confidence: 0.833308110714286

00:05:01.658 --> 00:05:03.725 it here where we have a tumor cell,

NOTE Confidence: 0.833308110714286

00:05:03.725 --> 00:05:04.945 the kidney cancer cell,

NOTE Confidence: 0.833308110714286

00:05:04.950 --> 00:05:05.272 yeah,

NOTE Confidence: 0.833308110714286

00:05:05.272 --> 00:05:07.204 interacting with an infiltrating T cell

NOTE Confidence: 0.833308110714286

00:05:07.204 --> 00:05:09.755 and that takes place in the context

NOTE Confidence: 0.833308110714286

00:05:09.755 --> 00:05:11.283 of a heterogeneous microenvironment.

NOTE Confidence: 0.833308110714286

00:05:11.290 --> 00:05:13.840 And so with this really basic

NOTE Confidence: 0.833308110714286

00:05:13.840 --> 00:05:15.115 sort of worldview,

NOTE Confidence: 0.833308110714286

00:05:15.120 --> 00:05:16.982 we can begin to ask focus questions

NOTE Confidence: 0.833308110714286

00:05:16.982 --> 00:05:18.648 and these are the really the

NOTE Confidence: 0.833308110714286

00:05:18.648 --> 00:05:20.274 questions that end up guiding a

NOTE Confidence: 0.833308110714286

00:05:20.274 --> 00:05:22.068 lot of the projects in our lab.

NOTE Confidence: 0.833308110714286

00:05:22.070 --> 00:05:23.838 So the first is what are the genetic

NOTE Confidence: 0.833308110714286

00:05:23.838 --> 00:05:24.929 alterations in kidney cancer,

NOTE Confidence: 0.833308110714286

00:05:24.930 --> 00:05:27.114 how do they potentially impact immune

NOTE Confidence: 0.833308110714286

00:05:27.114 --> 00:05:28.967 infiltration into the tumor and

NOTE Confidence: 0.833308110714286

00:05:28.967 --> 00:05:30.983 ultimately how do those intersect or

NOTE Confidence: 0.833308110714286

00:05:30.983 --> 00:05:33.230 interplay to impact therapeutic response.

NOTE Confidence: 0.833308110714286

00:05:33.230 --> 00:05:34.958 What are those other immune cells

NOTE Confidence: 0.833308110714286

00:05:34.958 --> 00:05:37.062 with immune cells within the tumor

NOTE Confidence: 0.833308110714286

00:05:37.062 --> 00:05:39.808 microenvironment? How do they?

NOTE Confidence: 0.833308110714286

00:05:39.810 --> 00:05:42.912 Interact with T cells and impact

NOTE Confidence: 0.833308110714286

00:05:42.912 --> 00:05:43.946 cell phenotype.

NOTE Confidence: 0.833308110714286

00:05:43.950 --> 00:05:45.275 And finally when everything goes

NOTE Confidence: 0.833308110714286

00:05:45.275 --> 00:05:47.190 right and T cells are capable CD,

NOTE Confidence: 0.833308110714286

00:05:47.190 --> 00:05:49.134 T cells are capable of recognizing

NOTE Confidence: 0.833308110714286

00:05:49.134 --> 00:05:50.650 the tumor and eliminating it.

NOTE Confidence: 0.833308110714286

00:05:50.650 --> 00:05:52.348 What is it that it's recognizing.

NOTE Confidence: 0.833308110714286

00:05:52.350 --> 00:05:54.492 And so we know that at the heart of

NOTE Confidence: 0.833308110714286

00:05:54.492 --> 00:05:56.455 this interaction of antigen specific

NOTE Confidence: 0.833308110714286

00:05:56.455 --> 00:05:58.951 immunity is the tumor cells presenting

NOTE Confidence: 0.833308110714286

00:05:59.019 --> 00:06:01.305 antigenic peptides and MHC Class 1

NOTE Confidence: 0.833308110714286

00:06:01.305 --> 00:06:03.117 molecules being recognized by the

NOTE Confidence: 0.833308110714286

00:06:03.117 --> 00:06:05.126 cognate T cell receptor and for for

NOTE Confidence: 0.833308110714286

00:06:05.126 --> 00:06:07.166 this for kidney cancer and for most

NOTE Confidence: 0.833308110714286

00:06:07.166 --> 00:06:09.410 of their I would say solid tumors,

NOTE Confidence: 0.833308110714286

00:06:09.410 --> 00:06:10.785 we don't actually know what

NOTE Confidence: 0.833308110714286

00:06:10.785 --> 00:06:11.610 those antigens are.

NOTE Confidence: 0.833308110714286

00:06:11.610 --> 00:06:13.030 We know sometimes for high

NOTE Confidence: 0.833308110714286

00:06:13.030 --> 00:06:14.166 mutation burden tumors that.

NOTE Confidence: 0.833308110714286

00:06:14.170 --> 00:06:15.880 Can be classic in the antigens,

NOTE Confidence: 0.833308110714286

00:06:15.880 --> 00:06:17.355 but for things that are

NOTE Confidence: 0.833308110714286

00:06:17.355 --> 00:06:18.240 modest mutation burdens,

NOTE Confidence: 0.833308110714286

00:06:18.240 --> 00:06:19.600 tumors like kidney cancer,

NOTE Confidence: 0.833308110714286

00:06:19.600 --> 00:06:20.960 it's much less clear.

NOTE Confidence: 0.833308110714286

00:06:20.960 --> 00:06:23.032 And so these are the sort of three

NOTE Confidence: 0.833308110714286

00:06:23.032 --> 00:06:24.618 fundamental areas that the lab is

NOTE Confidence: 0.833308110714286

00:06:24.618 --> 00:06:25.888 currently working on and we'll

NOTE Confidence: 0.833308110714286

00:06:25.888 --> 00:06:27.439 kind of step through each one,

NOTE Confidence: 0.833308110714286

00:06:27.440 --> 00:06:28.940 maybe talking a little bit about

NOTE Confidence: 0.833308110714286

00:06:28.940 --> 00:06:29.940 some prior work over

NOTE Confidence: 0.862158939333333

00:06:29.990 --> 00:06:31.614 the last couple of years when I was

NOTE Confidence: 0.862158939333333

00:06:31.614 --> 00:06:33.249 back in in Boston and then some

NOTE Confidence: 0.862158939333333

00:06:33.249 --> 00:06:34.721 ongoing efforts now in the lab.

NOTE Confidence: 0.862158939333333

00:06:34.721 --> 00:06:37.049 So the first is really what are the

NOTE Confidence: 0.862158939333333

00:06:37.049 --> 00:06:39.004 mutations in kidney cancer that

NOTE Confidence: 0.862158939333333

00:06:39.004 --> 00:06:40.608 might impact immune infiltration

NOTE Confidence: 0.862158939333333

00:06:40.608 --> 00:06:42.639 and ultimately response to therapy.

NOTE Confidence: 0.862158939333333

00:06:42.640 --> 00:06:44.000 And I would say broadly,

NOTE Confidence: 0.862158939333333

00:06:44.000 --> 00:06:45.888 we use a lot of classic genomic techniques,

NOTE Confidence: 0.862158939333333

00:06:45.890 --> 00:06:47.078 whole exome sequencing,

NOTE Confidence: 0.862158939333333

00:06:47.078 --> 00:06:49.058 RNA sequencing to really approach

NOTE Confidence: 0.862158939333333

00:06:49.058 --> 00:06:49.850 these questions.

NOTE Confidence: 0.862158939333333

00:06:49.850 --> 00:06:51.222 And so a lot of the motivation

NOTE Confidence: 0.862158939333333

00:06:51.222 --> 00:06:52.654 for this came from an early study

NOTE Confidence: 0.862158939333333

00:06:52.654 --> 00:06:54.151 just a few years ago from Ellie

NOTE Confidence: 0.862158939333333

00:06:54.151 --> 00:06:55.639 van Allen's group at Dana Farber,

NOTE Confidence: 0.862158939333333

00:06:55.640 --> 00:06:57.784 where he looked at a small phase one

NOTE Confidence: 0.862158939333333

00:06:57.784 --> 00:06:59.999 trial of nivolumab in kidney cancer,

NOTE Confidence: 0.862158939333333

00:07:00.000 --> 00:07:02.072 the checkmate O 9 trial and it was

NOTE Confidence: 0.862158939333333

00:07:02.072 --> 00:07:04.453 only about 35 patients that had genomic

NOTE Confidence: 0.862158939333333

00:07:04.453 --> 00:07:06.472 data available, but for those 35.

NOTE Confidence: 0.862158939333333

00:07:06.472 --> 00:07:08.410 Patients asked a pretty simple question,

NOTE Confidence: 0.862158939333333

00:07:08.410 --> 00:07:10.566 what are the the mutations that are

NOTE Confidence: 0.862158939333333

00:07:10.566 --> 00:07:12.509 recurrent in kidney cancer among those

NOTE Confidence: 0.862158939333333

00:07:12.509 --> 00:07:14.742 35 patients and out of those recurrent

NOTE Confidence: 0.862158939333333

00:07:14.806 --> 00:07:16.766 mutations and that's on the X axis.

NOTE Confidence: 0.862158939333333

00:07:16.770 --> 00:07:18.760 And now those recurrent mutations

NOTE Confidence: 0.862158939333333

00:07:18.760 --> 00:07:20.352 which are actually significantly

NOTE Confidence: 0.862158939333333

00:07:20.352 --> 00:07:21.586 impacting response to therapy

NOTE Confidence: 0.862158939333333

00:07:21.586 --> 00:07:23.152 and that's on the Y axis.

NOTE Confidence: 0.862158939333333

00:07:23.160 --> 00:07:25.512 And we can see there's only one loss

NOTE Confidence: 0.862158939333333

00:07:25.512 --> 00:07:27.639 of function mutations in the Pfaff

NOTE Confidence: 0.862158939333333

00:07:27.639 --> 00:07:29.847 complex member PBR one was associated

NOTE Confidence: 0.862158939333333

00:07:29.911 --> 00:07:32.005 with improved response and we see

NOTE Confidence: 0.862158939333333

00:07:32.005 --> 00:07:34.300 the bottom also improve survival in

NOTE Confidence: 0.862158939333333

00:07:34.300 --> 00:07:36.970 this small cohort of 35 patients.

NOTE Confidence: 0.862158939333333

00:07:36.970 --> 00:07:38.860 So really building off of this

NOTE Confidence: 0.862158939333333

00:07:38.860 --> 00:07:41.032 initial funding that we were through

NOTE Confidence: 0.862158939333333

00:07:41.032 --> 00:07:42.732 partnership with Bristol-Myers able

NOTE Confidence: 0.862158939333333

00:07:42.732 --> 00:07:44.765 to sequence not only the phase

NOTE Confidence: 0.862158939333333

00:07:44.765 --> 00:07:47.119 one data but the tumors from the

NOTE Confidence: 0.862158939333333

00:07:47.119 --> 00:07:49.159 phase two and phase three trials

NOTE Confidence: 0.862158939333333

00:07:49.159 --> 00:07:50.979 of nivolumab in kidney cancer.

NOTE Confidence: 0.862158939333333

00:07:50.980 --> 00:07:52.774 And looking specifically at the phase

NOTE Confidence: 0.862158939333333

00:07:52.774 --> 00:07:55.258 three trial which is the Checkmate O25 trial,

NOTE Confidence: 0.862158939333333

00:07:55.260 --> 00:07:57.059 we were able to confirm that yes,

NOTE Confidence: 0.862158939333333

00:07:57.060 --> 00:07:58.764 loss of function mutations and BM

NOTE Confidence: 0.862158939333333

00:07:58.764 --> 00:08:00.264 one were associated with improved

NOTE Confidence: 0.862158939333333

00:08:00.264 --> 00:08:02.118 response and in this case progression

NOTE Confidence: 0.862158939333333

00:08:02.118 --> 00:08:03.694 free and overall survival with

NOTE Confidence: 0.862158939333333

00:08:03.694 --> 00:08:05.189 nivolumab with immune therapy though

NOTE Confidence: 0.862158939333333

00:08:05.189 --> 00:08:07.380 we can see the effect size is fairly.

NOTE Confidence: 0.862158939333333

00:08:07.380 --> 00:08:07.610 Modest.

NOTE Confidence: 0.862158939333333

00:08:07.610 --> 00:08:08.760 So it's really, you know,

NOTE Confidence: 0.862158939333333

00:08:08.760 --> 00:08:10.104 it's something that's there,

NOTE Confidence: 0.862158939333333

00:08:10.104 --> 00:08:12.620 but it's certainly not the whole picture.

NOTE Confidence: 0.862158939333333

00:08:12.620 --> 00:08:14.503 And so this was a very focused

NOTE Confidence: 0.862158939333333

00:08:14.503 --> 00:08:15.860 sort of validation question,

NOTE Confidence: 0.862158939333333

00:08:15.860 --> 00:08:17.260 but we really want to look at

NOTE Confidence: 0.862158939333333

00:08:17.260 --> 00:08:18.640 this much more comprehensively.

NOTE Confidence: 0.862158939333333

00:08:18.640 --> 00:08:20.856 And So what we did was again in

NOTE Confidence: 0.862158939333333

00:08:20.856 --> 00:08:22.280 partnership with Bristol-Myers,

NOTE Confidence: 0.862158939333333

00:08:22.280 --> 00:08:23.495 we're fortunate to have access

NOTE Confidence: 0.862158939333333

00:08:23.495 --> 00:08:24.940 to tumors from the phase one,

NOTE Confidence: 0.862158939333333

00:08:24.940 --> 00:08:27.202 phase two and phase three trials

NOTE Confidence: 0.862158939333333

00:08:27.202 --> 00:08:29.260 of nivolumab in kidney cancer.

NOTE Confidence: 0.862158939333333

00:08:29.260 --> 00:08:30.676 The phase three trial is really

NOTE Confidence: 0.862158939333333

00:08:30.676 --> 00:08:32.557 the pivotal trial that led to the

NOTE Confidence: 0.862158939333333

00:08:32.557 --> 00:08:33.745 first checkpoint inhibitor approval

NOTE Confidence: 0.862158939333333

00:08:33.745 --> 00:08:34.636 within kidney cancer.

NOTE Confidence: 0.862158939333333

00:08:34.640 --> 00:08:36.140 And we're lucky to benefit as

NOTE Confidence: 0.862158939333333

00:08:36.140 --> 00:08:37.754 well from that phase three trial

NOTE Confidence: 0.862158939333333

00:08:37.754 --> 00:08:39.714 also having a control arm and mtor

NOTE Confidence: 0.862158939333333

00:08:39.714 --> 00:08:40.799 inhibitor of your elymus.

NOTE Confidence: 0.862158939333333

00:08:40.800 --> 00:08:42.249 And so we could see if there's

NOTE Confidence: 0.862158939333333

00:08:42.249 --> 00:08:44.047 anything that we find that might be

NOTE Confidence: 0.862158939333333

00:08:44.047 --> 00:08:45.462 associated with response or resistance.

NOTE Confidence: 0.862158939333333

00:08:45.470 --> 00:08:46.976 Is that something that's specific for

NOTE Confidence: 0.862158939333333

00:08:46.976 --> 00:08:48.566 immune therapy or is that something

NOTE Confidence: 0.862158939333333

00:08:48.566 --> 00:08:49.638 that's perhaps more prognostic

NOTE Confidence: 0.862158939333333

00:08:49.638 --> 00:08:51.369 that we see with old therapies,

NOTE Confidence: 0.862158939333333

00:08:51.370 --> 00:08:52.920 including one with an independent

NOTE Confidence: 0.862158939333333

00:08:52.920 --> 00:08:55.290 mechanism of action like an mtor inhibitor.

NOTE Confidence: 0.862158939333333

00:08:55.290 --> 00:08:57.048 So we performed whole exome sequencing,

NOTE Confidence: 0.862158939333333

00:08:57.050 --> 00:08:58.795 RNA sequencing and CD8 immunofluorescence

NOTE Confidence: 0.862158939333333

00:08:58.795 --> 00:09:00.966 to really look at the immune

NOTE Confidence: 0.862158939333333

00:09:00.966 --> 00:09:02.796 infiltration of the broad immune

NOTE Confidence: 0.862158939333333

00:09:02.796 --> 00:09:04.260 phenotype of these tumors.

NOTE Confidence: 0.865333130588235

00:09:04.260 --> 00:09:06.192 At the time this was the largest

NOTE Confidence: 0.865333130588235

00:09:06.192 --> 00:09:07.815 study of advanced kidney genetic

NOTE Confidence: 0.865333130588235

00:09:07.815 --> 00:09:09.665 study of advanced kidney cancer.

NOTE Confidence: 0.865333130588235

00:09:09.670 --> 00:09:12.070 The TCG which was really a foundational work

NOTE Confidence: 0.865333130588235

00:09:12.070 --> 00:09:14.247 really skews towards earlier stage tumors.

NOTE Confidence: 0.865333130588235

00:09:14.250 --> 00:09:16.682 Only around 10 to 15% of the kidney

NOTE Confidence: 0.865333130588235

00:09:16.682 --> 00:09:18.390 cancer tumors in TCG are advanced stage.

NOTE Confidence: 0.865333130588235

00:09:18.390 --> 00:09:20.190 And so by sequencing this we can really

NOTE Confidence: 0.865333130588235

00:09:20.190 --> 00:09:22.398 get an understanding of first the genetic

NOTE Confidence: 0.865333130588235

00:09:22.398 --> 00:09:24.481 landscape of advanced kidney cancer and

NOTE Confidence: 0.865333130588235

00:09:24.481 --> 00:09:26.407 there's some interesting findings in here,

NOTE Confidence: 0.865333130588235

00:09:26.410 --> 00:09:27.954 some enrichment and clinically

NOTE Confidence: 0.865333130588235

00:09:27.954 --> 00:09:29.112 unfavorable aggressive mutations

NOTE Confidence: 0.865333130588235

00:09:29.112 --> 00:09:30.760 and copy number variants,

NOTE Confidence: 0.865333130588235

00:09:30.760 --> 00:09:34.204 things like NF2 mutations, a loss of.

NOTE Confidence: 0.865333130588235

00:09:34.210 --> 00:09:35.197 Nine P 21.3,

NOTE Confidence: 0.865333130588235

00:09:35.197 --> 00:09:37.171 but really our our primary question

NOTE Confidence: 0.865333130588235

00:09:37.171 --> 00:09:39.225 was how does this ultimately

NOTE Confidence: 0.865333130588235

00:09:39.225 --> 00:09:41.300 impact response to immune therapy?

NOTE Confidence: 0.865333130588235

00:09:41.300 --> 00:09:43.460 And so the first thing we did was look

NOTE Confidence: 0.865333130588235

00:09:43.460 --> 00:09:46.262 at some of the classic markers of somatic

NOTE Confidence: 0.865333130588235

00:09:46.262 --> 00:09:48.315 alteration burden that is present in

NOTE Confidence: 0.865333130588235

00:09:48.315 --> 00:09:50.145 that we associate other tumor types

NOTE Confidence: 0.865333130588235

00:09:50.145 --> 00:09:52.100 in other tumor types response with.

NOTE Confidence: 0.865333130588235

00:09:52.100 --> 00:09:54.151 So we know that there's a Histology

NOTE Confidence: 0.865333130588235

00:09:54.151 --> 00:09:55.821 agnostic approval for the immunotherapy

NOTE Confidence: 0.865333130588235

00:09:55.821 --> 00:09:57.671 drug pembrolizumab based purely on

NOTE Confidence: 0.865333130588235

00:09:57.671 --> 00:10:00.243 mutation burden and we know that in many

NOTE Confidence: 0.865333130588235

00:10:00.243 --> 00:10:02.014 tumor types there's an association with

NOTE Confidence: 0.865333130588235

00:10:02.014 --> 00:10:04.138 high mutation burden response to therapy.

NOTE Confidence: 0.865333130588235

00:10:04.140 --> 00:10:05.260 And so for kidney cancer,

NOTE Confidence: 0.865333130588235

00:10:05.260 --> 00:10:07.396 we looked at total mutation burden,

NOTE Confidence: 0.865333130588235

00:10:07.400 --> 00:10:08.680 we inferred,

NOTE Confidence: 0.865333130588235

00:10:08.680 --> 00:10:11.240 neoantigen load we inferred.

NOTE Confidence: 0.865333130588235

00:10:11.240 --> 00:10:13.410 You want to drive from frameshift insertion,

NOTE Confidence: 0.865333130588235

00:10:13.410 --> 00:10:14.915 insertion deletions which create new

NOTE Confidence: 0.865333130588235

00:10:14.915 --> 00:10:16.765 open reading frames and no metric

NOTE Confidence: 0.865333130588235

00:10:16.765 --> 00:10:18.245 of somatic alteration burden was

NOTE Confidence: 0.865333130588235

00:10:18.245 --> 00:10:19.910 at all associated with response.

NOTE Confidence: 0.865333130588235

00:10:19.910 --> 00:10:21.772 So again this is in sharp contrast

NOTE Confidence: 0.865333130588235

00:10:21.772 --> 00:10:23.546 to Melanoma and non small cell

NOTE Confidence: 0.865333130588235

00:10:23.546 --> 00:10:25.076 lung cancer and bladder cancer.

NOTE Confidence: 0.865333130588235

00:10:25.080 --> 00:10:27.540 Here mutation burden really does not

NOTE Confidence: 0.865333130588235

00:10:27.540 --> 00:10:29.930 associate or predict response to therapy.

NOTE Confidence: 0.865333130588235

00:10:29.930 --> 00:10:32.072 When we then looked across each

NOTE Confidence: 0.865333130588235

00:10:32.072 --> 00:10:33.143 individual recurrent mutation

NOTE Confidence: 0.865333130588235

00:10:33.143 --> 00:10:35.478 and tried to see which one might

NOTE Confidence: 0.865333130588235

00:10:35.478 --> 00:10:37.135 be associated with resistance or

NOTE Confidence: 0.865333130588235

00:10:37.135 --> 00:10:39.067 response in this much expanded cohort,

NOTE Confidence: 0.865333130588235

00:10:39.070 --> 00:10:40.690 again we found only one in

NOTE Confidence: 0.865333130588235

00:10:40.690 --> 00:10:41.500 this pooled analysis.

NOTE Confidence: 0.865333130588235

00:10:41.500 --> 00:10:43.633 So again it was only PBR on one which

NOTE Confidence: 0.865333130588235

00:10:43.633 --> 00:10:45.484 is a very common mutation president

NOTE Confidence: 0.865333130588235

00:10:45.484 --> 00:10:48.164 perhaps up to 30 to 40% of of kidney

NOTE Confidence: 0.865333130588235

00:10:48.164 --> 00:10:49.952 cancer tumors that was associated with

NOTE Confidence: 0.865333130588235

00:10:49.952 --> 00:10:51.788 improved response and overall survival.

NOTE Confidence: 0.865333130588235

00:10:51.790 --> 00:10:53.224 And again here we really could

NOTE Confidence: 0.865333130588235

00:10:53.224 --> 00:10:54.890 benefit and see that this response,

NOTE Confidence: 0.865333130588235

00:10:54.890 --> 00:10:56.486 this impact on response and survival

NOTE Confidence: 0.865333130588235

00:10:56.486 --> 00:10:58.124 was unique to the patients tree

NOTE Confidence: 0.865333130588235

00:10:58.124 --> 00:10:59.690 with immune therapy and was not

NOTE Confidence: 0.865333130588235

00:10:59.690 --> 00:11:01.269 seen in patients treated with the

NOTE Confidence: 0.865333130588235

00:11:01.269 --> 00:11:04.330 control arm with an M Tor inhibitor.

NOTE Confidence: 0.865333130588235

00:11:04.330 --> 00:11:05.682 So that's uh mutations.

NOTE Confidence: 0.865333130588235

00:11:05.682 --> 00:11:07.710 What about the immune landscape and

NOTE Confidence: 0.865333130588235

00:11:07.767 --> 00:11:09.825 how that might impact kidney cancer?

NOTE Confidence: 0.865333130588235

00:11:09.830 --> 00:11:11.804 We know that prognostically having a lot

NOTE Confidence: 0.865333130588235

00:11:11.804 --> 00:11:14.086 of CDT cells might be a negative thing,

NOTE Confidence: 0.865333130588235

00:11:14.090 --> 00:11:16.190 but how does that impact response

NOTE Confidence: 0.865333130588235

00:11:16.190 --> 00:11:16.890 to immunotherapy?

NOTE Confidence: 0.865333130588235

00:11:16.890 --> 00:11:18.626 And so the first thing we did

NOTE Confidence: 0.865333130588235

00:11:18.626 --> 00:11:19.738 was characterize these tumors

NOTE Confidence: 0.865333130588235

00:11:19.738 --> 00:11:21.328 broadly into 3 immune phenotypes.

NOTE Confidence: 0.865333130588235

00:11:21.330 --> 00:11:23.194 And these are types you might be familiar

NOTE Confidence: 0.865333130588235

00:11:23.194 --> 00:11:24.631 with the classic immune infiltrated

NOTE Confidence: 0.865333130588235

00:11:24.631 --> 00:11:26.467 where there's lots of CDT cells,

NOTE Confidence: 0.865333130588235

00:11:26.470 --> 00:11:27.082 immune deserts,

NOTE Confidence: 0.865333130588235

00:11:27.082 --> 00:11:28.918 where there's a positive CDT cells

NOTE Confidence: 0.865333130588235

00:11:28.918 --> 00:11:30.827 and then in Munich excluded tumors

NOTE Confidence: 0.865333130588235

00:11:30.827 --> 00:11:32.693 where there's made perhaps lots of

NOTE Confidence: 0.865333130588235

00:11:32.748 --> 00:11:34.456 CDT cells lining up to the tumor.

NOTE Confidence: 0.865333130588235

00:11:34.460 --> 00:11:36.074 Urgent but really unable to infiltrate

NOTE Confidence: 0.865333130588235

00:11:36.074 --> 00:11:38.104 the tumor center and have a factor

NOTE Confidence: 0.865333130588235

00:11:38.104 --> 00:11:39.609 function that's a potential mechanism

NOTE Confidence: 0.865333130588235

00:11:39.609 --> 00:11:41.375 resistance and you know other solid

NOTE Confidence: 0.865333130588235

00:11:41.375 --> 00:11:43.043 tumor types including a common mechanism

NOTE Confidence: 0.918145438

00:11:43.050 --> 00:11:44.990 of resistance in bladder cancer.

NOTE Confidence: 0.918145438

00:11:44.990 --> 00:11:46.514 And so when we looked at

NOTE Confidence: 0.918145438

00:11:46.514 --> 00:11:47.530 our kidney cancer tumors,

NOTE Confidence: 0.918145438

00:11:47.530 --> 00:11:49.190 our advanced kidney cancer tumors,

NOTE Confidence: 0.918145438

00:11:49.190 --> 00:11:50.435 the first thing we observe

NOTE Confidence: 0.918145438

00:11:50.435 --> 00:11:51.680 was that immune occlusion is

NOTE Confidence: 0.918145438

00:11:51.730 --> 00:11:53.090 really not a common phenotype.

NOTE Confidence: 0.918145438

00:11:53.090 --> 00:11:55.792 It's not looking to be a predominant

NOTE Confidence: 0.918145438

00:11:55.792 --> 00:11:58.309 mechanism of resistance in in kidney cancer.

NOTE Confidence: 0.918145438

00:11:58.310 --> 00:12:00.030 We see here only about 5% of

NOTE Confidence: 0.918145438

00:12:00.030 --> 00:12:01.530 these tumors are Munich excluded.

NOTE Confidence: 0.918145438

00:12:01.530 --> 00:12:03.476 This is in contrast to some like

NOTE Confidence: 0.918145438

00:12:03.476 --> 00:12:04.956 bladder cancer where up to 50%

NOTE Confidence: 0.918145438

00:12:04.956 --> 00:12:06.260 of metastatic bladder cancers.

NOTE Confidence: 0.918145438

00:12:06.260 --> 00:12:08.588 Would have this immune exclusion phenotype.

NOTE Confidence: 0.918145438

00:12:08.590 --> 00:12:09.928 The other thing we can observe

NOTE Confidence: 0.918145438

00:12:09.928 --> 00:12:11.872 is by and large these are heavily

NOTE Confidence: 0.918145438

00:12:11.872 --> 00:12:12.868 CD8 infiltrated tumors.

NOTE Confidence: 0.918145438

00:12:12.870 --> 00:12:15.180 About 3/4 of these tumors are

NOTE Confidence: 0.918145438

00:12:15.180 --> 00:12:17.220 highly infiltrated by CDT cells.

NOTE Confidence: 0.918145438

00:12:17.220 --> 00:12:19.082 But again in contrast to a lot

NOTE Confidence: 0.918145438

00:12:19.082 --> 00:12:20.360 of other solid tumors,

NOTE Confidence: 0.918145438

00:12:20.360 --> 00:12:22.848 we're having a lot of CD T cells

NOTE Confidence: 0.918145438

00:12:22.848 --> 00:12:24.550 might positively impact response.

NOTE Confidence: 0.918145438

00:12:24.550 --> 00:12:26.391 Here it had no impact on response

NOTE Confidence: 0.918145438

00:12:26.391 --> 00:12:28.634 and survival and we can see that for

NOTE Confidence: 0.918145438

00:12:28.634 --> 00:12:30.029 patients I'm showing here treated

NOTE Confidence: 0.918145438

00:12:30.085 --> 00:12:31.585 with immune therapy that regardless

NOTE Confidence: 0.918145438

00:12:31.585 --> 00:12:33.796 of whether you had an immune excluded

NOTE Confidence: 0.918145438

00:12:33.796 --> 00:12:36.267 tumor and infiltrated tumor or desert tumor,

NOTE Confidence: 0.918145438

00:12:36.270 --> 00:12:38.391 all of those had roughly the same

NOTE Confidence: 0.918145438

00:12:38.391 --> 00:12:40.109 response to therapy and survival.

NOTE Confidence: 0.918145438

00:12:40.110 --> 00:12:42.384 And so looking at genetics alone

NOTE Confidence: 0.918145438

00:12:42.384 --> 00:12:44.330 you know didn't yield much.

NOTE Confidence: 0.918145438

00:12:44.330 --> 00:12:45.920 Looking at the immune phenotype

NOTE Confidence: 0.918145438

00:12:45.920 --> 00:12:47.907 alone really doesn't tell us which

NOTE Confidence: 0.918145438

00:12:47.907 --> 00:12:49.627 tumors are responsive to therapy.

NOTE Confidence: 0.918145438

00:12:49.630 --> 00:12:51.640 Is there perhaps some interaction

NOTE Confidence: 0.918145438

00:12:51.640 --> 00:12:53.455 or interplay between them and

NOTE Confidence: 0.918145438

00:12:53.455 --> 00:12:54.890 so the first thing we did was.

NOTE Confidence: 0.918145438

00:12:54.890 --> 00:12:55.228 Really,

NOTE Confidence: 0.918145438

00:12:55.228 --> 00:12:57.256 just look at among the infiltrated

NOTE Confidence: 0.918145438

00:12:57.256 --> 00:12:58.710 and non infiltrated tumors.

NOTE Confidence: 0.918145438

00:12:58.710 --> 00:13:00.440 Are there different mutational landscapes?

NOTE Confidence: 0.918145438

00:13:00.440 --> 00:13:02.168 Are there different driver mutations that

NOTE Confidence: 0.918145438

00:13:02.168 --> 00:13:04.167 might be present in one or the other?

NOTE Confidence: 0.918145438

00:13:04.170 --> 00:13:05.060 And the answer was yes.

NOTE Confidence: 0.918145438

00:13:05.060 --> 00:13:06.824 And here again it was only one that it

NOTE Confidence: 0.918145438

00:13:06.824 --> 00:13:08.666 was actually the immune desert tumors,

NOTE Confidence: 0.918145438

00:13:08.670 --> 00:13:10.746 the ones that lack CD infiltration

NOTE Confidence: 0.918145438

00:13:10.746 --> 00:13:12.872 that were really enriched for these

NOTE Confidence: 0.918145438

00:13:12.872 --> 00:13:14.912 clinically favorable CDA T cells that

NOTE Confidence: 0.918145438

00:13:14.912 --> 00:13:16.949 nearly half of those immune desert

NOTE Confidence: 0.918145438

00:13:16.949 --> 00:13:19.191 tumors had mutations in people on one,

NOTE Confidence: 0.918145438

00:13:19.191 --> 00:13:20.997 whereas less than 1/4 of the

NOTE Confidence: 0.918145438

00:13:20.997 --> 00:13:22.170 immune infiltrated ones did.

NOTE Confidence: 0.918145438

00:13:22.170 --> 00:13:23.187 So my mutations,

NOTE Confidence: 0.918145438

00:13:23.187 --> 00:13:25.221 we have enrichment of clinically favorable

NOTE Confidence: 0.918145438

00:13:25.221 --> 00:13:27.287 PR1 mutations within desert tumors.

NOTE Confidence: 0.918145438

00:13:27.290 --> 00:13:30.640 How about within infiltrated tumors,

NOTE Confidence: 0.918145438

00:13:30.640 --> 00:13:32.344 particularly looking at copy

NOTE Confidence: 0.918145438

00:13:32.344 --> 00:13:33.196 number alterations?

NOTE Confidence: 0.918145438

00:13:33.200 --> 00:13:35.120 And here there was a a different picture.

NOTE Confidence: 0.918145438

00:13:35.120 --> 00:13:37.283 There was actually a lot more copy

NOTE Confidence: 0.918145438

00:13:37.283 --> 00:13:38.651 number alterations within these

NOTE Confidence: 0.918145438

00:13:38.651 --> 00:13:39.809 infiltrated tumors potentially

NOTE Confidence: 0.918145438

00:13:39.809 --> 00:13:41.739 indicating these might be perhaps

NOTE Confidence: 0.918145438

00:13:41.739 --> 00:13:43.234 more chromosomally unstable having

NOTE Confidence: 0.918145438

00:13:43.234 --> 00:13:45.334 a higher copy number burden in

NOTE Confidence: 0.918145438

00:13:45.334 --> 00:13:47.050 general than non infiltrated tumors.

NOTE Confidence: 0.918145438

00:13:47.050 --> 00:13:49.740 And so we took a similar approach.

NOTE Confidence: 0.918145438

00:13:49.740 --> 00:13:51.820 We looked systematically which copy

NOTE Confidence: 0.918145438

00:13:51.820 --> 00:13:53.484 number alteration was associated

NOTE Confidence: 0.918145438

00:13:53.484 --> 00:13:55.238 with was increased and infiltrated

NOTE Confidence: 0.918145438

00:13:55.238 --> 00:13:57.500 tumors and that's on the X axis.

NOTE Confidence: 0.918145438

00:13:57.500 --> 00:13:59.383 And then out of those infiltrated tumors

NOTE Confidence: 0.918145438

00:13:59.383 --> 00:14:01.225 which copy number alteration might be

NOTE Confidence: 0.918145438

00:14:01.225 --> 00:14:02.870 associated with altered response or

NOTE Confidence: 0.918145438

00:14:02.870 --> 00:14:04.738 survival either positively or negatively.

NOTE Confidence: 0.918145438

00:14:04.740 --> 00:14:05.958 And that's on the Y axis.

NOTE Confidence: 0.918145438

00:14:05.960 --> 00:14:08.492 And again only one came out

NOTE Confidence: 0.918145438

00:14:08.492 --> 00:14:11.119 deletions of nine P 21.3 which

NOTE Confidence: 0.918145438

00:14:11.119 --> 00:14:13.142 contain genes like CDKN 2A,

NOTE Confidence: 0.918145438

00:14:13.142 --> 00:14:15.459 CDKN 2B M tap loss of function.

NOTE Confidence: 0.918145438

00:14:15.460 --> 00:14:17.994 The loss single copy loss of nine

NOTE Confidence: 0.918145438

00:14:18.000 --> 00:14:21.108 P 21.3 was associated with worse

NOTE Confidence: 0.918145438

00:14:21.108 --> 00:14:23.180 survival and worse response.

NOTE Confidence: 0.918145438

00:14:23.180 --> 00:14:24.950 And looking at whether this effect

NOTE Confidence: 0.918145438

00:14:24.950 --> 00:14:26.774 would really specific to NTP one

NOTE Confidence: 0.918145438

00:14:26.774 --> 00:14:28.538 treatment or a broad prognostic effect,

NOTE Confidence: 0.82571024375

00:14:28.540 --> 00:14:30.956 we could see that really loss of nine

NOTE Confidence: 0.82571024375

00:14:30.960 --> 00:14:32.892 P 21.3 within these infiltrated tumors

NOTE Confidence: 0.82571024375

00:14:32.892 --> 00:14:34.840 was associated with worse progression.

NOTE Confidence: 0.82571024375

00:14:34.840 --> 00:14:35.914 Green overall survival

NOTE Confidence: 0.82571024375

00:14:35.914 --> 00:14:37.704 really only with anti PD,

NOTE Confidence: 0.82571024375

00:14:37.710 --> 00:14:39.558 one treatment with immune therapy on

NOTE Confidence: 0.82571024375

00:14:39.558 --> 00:14:42.058 the left and not with mtor inhibition

NOTE Confidence: 0.82571024375

00:14:42.058 --> 00:14:45.550 of control arm shown on the right.

NOTE Confidence: 0.82571024375

00:14:45.550 --> 00:14:48.486 So what is it that's impacting this response?

NOTE Confidence: 0.82571024375

00:14:48.490 --> 00:14:51.703 Well, how is 9 P 21.3 actually acting to,

NOTE Confidence: 0.82571024375

00:14:51.710 --> 00:14:55.076 to lessen response to immune therapy?

NOTE Confidence: 0.82571024375

00:14:55.080 --> 00:14:56.350 That remains an open question.

NOTE Confidence: 0.82571024375

00:14:56.350 --> 00:14:58.358 We we took a a first look at

NOTE Confidence: 0.82571024375

00:14:58.358 --> 00:15:00.248 least some activated pathways by

NOTE Confidence: 0.82571024375

00:15:00.248 --> 00:15:02.605 integrating the RAC data and really

NOTE Confidence: 0.82571024375

00:15:02.605 --> 00:15:04.675 looking at which pathways might be

NOTE Confidence: 0.82571024375

00:15:04.675 --> 00:15:06.984 enriched in these nine P 21.3 tumors.

NOTE Confidence: 0.82571024375

00:15:06.984 --> 00:15:09.252 And there's some potentially initial hits.

NOTE Confidence: 0.82571024375

00:15:09.260 --> 00:15:12.062 There's certainly more angiogenesis

NOTE Confidence: 0.82571024375

00:15:12.062 --> 00:15:14.017 and hypoxia on those tumors.

NOTE Confidence: 0.82571024375

00:15:14.020 --> 00:15:15.672 There's definitely more increased

NOTE Confidence: 0.82571024375

00:15:15.672 --> 00:15:16.498 mtor signaling.

NOTE Confidence: 0.82571024375

00:15:16.500 --> 00:15:18.145 And so at least some initial hints

NOTE Confidence: 0.82571024375

00:15:18.145 --> 00:15:20.300 as to how these might be associated.

NOTE Confidence: 0.82571024375

00:15:20.300 --> 00:15:21.836 But there's a lot of mechanistic

NOTE Confidence: 0.82571024375

00:15:21.836 --> 00:15:23.439 work that still needs to be done.

NOTE Confidence: 0.82571024375

00:15:23.440 --> 00:15:25.512 And so the initial model we put

NOTE Confidence: 0.82571024375

00:15:25.512 --> 00:15:27.192 forward for this is that yes,

NOTE Confidence: 0.82571024375

00:15:27.192 --> 00:15:29.236 in theory CD and infiltration should be

NOTE Confidence: 0.82571024375

00:15:29.236 --> 00:15:30.937 associated with better response to PD,

NOTE Confidence: 0.82571024375

00:15:30.940 --> 00:15:33.796 one therapy just like in other tumors.

NOTE Confidence: 0.82571024375

00:15:33.800 --> 00:15:35.333 But what we have here is overlying

NOTE Confidence: 0.82571024375

00:15:35.333 --> 00:15:36.479 the genetics of the tumor,

NOTE Confidence: 0.82571024375

00:15:36.480 --> 00:15:37.545 these non infiltrators.

NOTE Confidence: 0.82571024375

00:15:37.545 --> 00:15:39.320 Infiltrate tumors enriched for loss

NOTE Confidence: 0.82571024375

00:15:39.320 --> 00:15:41.180 of function P brown one mutations,

NOTE Confidence: 0.82571024375

00:15:41.180 --> 00:15:42.616 these clinically favorable mutations

NOTE Confidence: 0.82571024375

00:15:42.616 --> 00:15:45.196 that bring the response rates up and

NOTE Confidence: 0.82571024375

00:15:45.196 --> 00:15:47.066 the infiltrated tumors are enriched

NOTE Confidence: 0.82571024375

00:15:47.066 --> 00:15:48.562 for these clinically unfavorable

NOTE Confidence: 0.82571024375

00:15:48.620 --> 00:15:51.120 deletions of NI P 21.3 and again

NOTE Confidence: 0.82571024375

00:15:51.120 --> 00:15:53.270 dragging the response rates down.

NOTE Confidence: 0.82571024375

00:15:53.270 --> 00:15:55.313 And so this is the work that was done

NOTE Confidence: 0.82571024375

00:15:55.313 --> 00:15:57.367 now published a couple of years ago.

NOTE Confidence: 0.82571024375

00:15:57.370 --> 00:15:58.945 And while at the time this was

NOTE Confidence: 0.82571024375

00:15:58.945 --> 00:15:59.990 a large sequencing effort,

NOTE Confidence: 0.82571024375

00:15:59.990 --> 00:16:02.006 it was about 454 tumors that

NOTE Confidence: 0.82571024375

00:16:02.006 --> 00:16:03.350 underwent whole exome sequencing.

NOTE Confidence: 0.82571024375

00:16:03.350 --> 00:16:05.924 It turns out that that is only enough to

NOTE Confidence: 0.82571024375

00:16:05.924 --> 00:16:08.070 capture you essentially fairly common.

NOTE Confidence: 0.82571024375

00:16:08.070 --> 00:16:09.630 Mutations and kidney cancer that might

NOTE Confidence: 0.82571024375

00:16:09.630 --> 00:16:10.990 be associated with immune infiltration

NOTE Confidence: 0.82571024375

00:16:10.990 --> 00:16:12.880 or response that you actually need much,

NOTE Confidence: 0.82571024375

00:16:12.880 --> 00:16:14.482 much larger numbers to really saturate

NOTE Confidence: 0.82571024375

00:16:14.482 --> 00:16:16.472 and really get a better sense of

NOTE Confidence: 0.82571024375

00:16:16.472 --> 00:16:18.218 the full landscape of of genetic

NOTE Confidence: 0.82571024375

00:16:18.218 --> 00:16:19.580 alterations within kidney cancer.

NOTE Confidence: 0.82571024375

00:16:19.580 --> 00:16:21.694 And so in efforts that we're leading

NOTE Confidence: 0.82571024375

00:16:21.694 --> 00:16:23.520 together with Allie Van Allen's lab,

NOTE Confidence: 0.82571024375

00:16:23.520 --> 00:16:25.464 we've put together in our cohort

NOTE Confidence: 0.82571024375

00:16:25.464 --> 00:16:27.683 of just about 2000 patients that

NOTE Confidence: 0.82571024375

00:16:27.683 --> 00:16:29.818 were treated with immune therapy.

NOTE Confidence: 0.82571024375

00:16:29.820 --> 00:16:31.932 This is from a series of phase three

NOTE Confidence: 0.82571024375

00:16:31.932 --> 00:16:33.757 trials including that checkmate O25 trial,

NOTE Confidence: 0.82571024375

00:16:33.760 --> 00:16:35.960 but other more modern combination

NOTE Confidence: 0.82571024375

00:16:35.960 --> 00:16:38.160 therapies phase three trials of.

NOTE Confidence: 0.82571024375

00:16:38.160 --> 00:16:40.145 Pure immune checkpoint inhibitors like

NOTE Confidence: 0.82571024375

00:16:40.145 --> 00:16:42.752 the volume Applebaum lab or immune

NOTE Confidence: 0.82571024375

00:16:42.752 --> 00:16:44.968 therapy plus antiangiogenic inhibitors.

NOTE Confidence: 0.82571024375

00:16:44.970 --> 00:16:46.938 And the reason we're doing this is sort

NOTE Confidence: 0.82571024375

00:16:46.938 --> 00:16:48.632 of demonstrated by this simulated power

NOTE Confidence: 0.82571024375

00:16:48.632 --> 00:16:50.072 calculation which I've shown here,

NOTE Confidence: 0.82571024375

00:16:50.080 --> 00:16:51.754 which is basically for the number

NOTE Confidence: 0.82571024375

00:16:51.754 --> 00:16:53.669 of patients we have in our cohort,

NOTE Confidence: 0.82571024375

00:16:53.670 --> 00:16:55.588 which is shown on the X axis,

NOTE Confidence: 0.82571024375

00:16:55.590 --> 00:16:57.350 what frequency of mutation are

NOTE Confidence: 0.82571024375

00:16:57.350 --> 00:16:59.110 we actually powered to detect.

NOTE Confidence: 0.82571024375

00:16:59.110 --> 00:17:00.878 So if we look at our original paper

NOTE Confidence: 0.82571024375

00:17:00.878 --> 00:17:02.647 from a couple of years ago now,

NOTE Confidence: 0.82571024375

00:17:02.650 --> 00:17:04.444 we were actually powered to detect

NOTE Confidence: 0.82571024375

00:17:04.444 --> 00:17:06.524 exactly what we found things that are

NOTE Confidence: 0.82571024375

00:17:06.524 --> 00:17:08.463 really quite common in in this case.

NOTE Confidence: 0.82571024375

00:17:08.470 --> 00:17:09.076 Number one,

NOTE Confidence: 0.82571024375

00:17:09.076 --> 00:17:10.591 mutations was present in nearly

NOTE Confidence: 0.82571024375

00:17:10.591 --> 00:17:11.500 half of responsive

NOTE Confidence: 0.8098867

00:17:11.557 --> 00:17:13.132 patients and a little bit less than

NOTE Confidence: 0.8098867

00:17:13.132 --> 00:17:14.840 1/4 of non responsive patients,

NOTE Confidence: 0.8098867

00:17:14.840 --> 00:17:16.104 very, very common mutations.

NOTE Confidence: 0.8098867

00:17:16.104 --> 00:17:18.599 That's all that we were power to detect.

NOTE Confidence: 0.8098867

00:17:18.600 --> 00:17:20.824 Now that we have a much more substantial

NOTE Confidence: 0.8098867

00:17:20.824 --> 00:17:23.148 cohort of over 2000 out of which about

NOTE Confidence: 0.8098867

00:17:23.148 --> 00:17:25.180 1500 were treated with immune therapy,

NOTE Confidence: 0.8098867

00:17:25.180 --> 00:17:27.035 we're now powered to detect a much

NOTE Confidence: 0.8098867

00:17:27.035 --> 00:17:28.644 broader range of mutations that

NOTE Confidence: 0.8098867

00:17:28.644 --> 00:17:30.539 might impact response or resistance,

NOTE Confidence: 0.8098867

00:17:30.540 --> 00:17:31.850 things that might be present

NOTE Confidence: 0.8098867

00:17:31.850 --> 00:17:33.702 in as low as 5% of responders.

NOTE Confidence: 0.8098867

00:17:33.702 --> 00:17:35.599 And so really getting a much broader

NOTE Confidence: 0.8098867

00:17:35.599 --> 00:17:37.210 land idea of the genetic alterations

NOTE Confidence: 0.8098867

00:17:37.210 --> 00:17:39.320 and how they might be associated with.

NOTE Confidence: 0.8098867

00:17:39.320 --> 00:17:41.385 Resistance and so our our sort of

NOTE Confidence: 0.8098867

00:17:41.385 --> 00:17:42.990 questions driving this project are

NOTE Confidence: 0.8098867

00:17:42.990 --> 00:17:44.970 one just about kidney cancer genetics.

NOTE Confidence: 0.8098867

00:17:44.970 --> 00:17:46.734 What are the long tail of mutations,

NOTE Confidence: 0.8098867

00:17:46.740 --> 00:17:48.708 we know the the most common

NOTE Confidence: 0.8098867

00:17:48.708 --> 00:17:49.692 mutations from TGA,

NOTE Confidence: 0.8098867

00:17:49.700 --> 00:17:51.429 but what are the long tail of

NOTE Confidence: 0.8098867

00:17:51.429 --> 00:17:52.920 driver mutations and kidney cancer?

NOTE Confidence: 0.8098867

00:17:52.920 --> 00:17:54.720 Do those fall within common pathways

NOTE Confidence: 0.8098867

00:17:54.720 --> 00:17:56.943 that might actually lead us to better

NOTE Confidence: 0.8098867

00:17:56.943 --> 00:17:58.235 understand kidney cancer biology?

NOTE Confidence: 0.8098867

00:17:58.240 --> 00:18:00.277 What is the connection between the somatic

NOTE Confidence: 0.8098867

00:18:00.277 --> 00:18:01.780 alterations and immune infiltration?

NOTE Confidence: 0.8098867

00:18:01.780 --> 00:18:04.132 We saw some interactions between PT

NOTE Confidence: 0.8098867

00:18:04.132 --> 00:18:06.856 Barnum one or deletions of nine P 21.3,

NOTE Confidence: 0.8098867

00:18:06.856 --> 00:18:08.396 but again are there others?

NOTE Confidence: 0.8098867

00:18:08.400 --> 00:18:10.416 And then finally how do these intersect?

NOTE Confidence: 0.8098867

00:18:10.420 --> 00:18:14.146 Or interplay to ultimately impact response.

NOTE Confidence: 0.8098867

00:18:14.150 --> 00:18:16.226 So that's a large ongoing project,

NOTE Confidence: 0.8098867

00:18:16.230 --> 00:18:18.846 but I think the use of whole exome

NOTE Confidence: 0.8098867

00:18:18.846 --> 00:18:20.708 sequencing and an RNA sequencing

NOTE Confidence: 0.8098867

00:18:20.708 --> 00:18:22.988 is really applicable to answer a

NOTE Confidence: 0.8098867

00:18:22.988 --> 00:18:25.109 number of other focus questions.

NOTE Confidence: 0.8098867

00:18:25.110 --> 00:18:27.326 And I think as we think about these,

NOTE Confidence: 0.8098867

00:18:27.330 --> 00:18:28.410 it's also important.

NOTE Confidence: 0.8098867

00:18:28.410 --> 00:18:30.210 We're really obviously tumor focused,

NOTE Confidence: 0.8098867

00:18:30.210 --> 00:18:31.644 but also to integrate what's happening

NOTE Confidence: 0.8098867

00:18:31.644 --> 00:18:32.969 in the host immunity as well,

NOTE Confidence: 0.8098867

00:18:32.970 --> 00:18:34.594 for instance, soluble circulating,

NOTE Confidence: 0.8098867

00:18:34.594 --> 00:18:37.030 soluble factors in the plasma or

NOTE Confidence: 0.8098867

00:18:37.090 --> 00:18:39.090 circulating immune cells as well.

NOTE Confidence: 0.8098867

00:18:39.090 --> 00:18:40.863 And so just a little bit of a hint

NOTE Confidence: 0.8098867

00:18:40.863 --> 00:18:42.711 of some of the things that we've

NOTE Confidence: 0.8098867

00:18:42.711 --> 00:18:44.578 been working on over the past year.

NOTE Confidence: 0.8098867

00:18:44.580 --> 00:18:46.876 One is a partnership with Random McKay

NOTE Confidence: 0.8098867

00:18:46.876 --> 00:18:49.313 at sorry that should say UCSD who ran

NOTE Confidence: 0.8098867

00:18:49.313 --> 00:18:52.189 a phase two trial of a another immune

NOTE Confidence: 0.8098867

00:18:52.189 --> 00:18:54.554 therapy drug atezolizumab plus bevacizumab.

NOTE Confidence: 0.8098867

00:18:54.560 --> 00:18:56.264 This was actually non clear cell

NOTE Confidence: 0.8098867

00:18:56.264 --> 00:18:57.900 kidney cancer less common variants.

NOTE Confidence: 0.8098867

00:18:57.900 --> 00:19:00.028 And what we could we could see by

NOTE Confidence: 0.8098867

00:19:00.028 --> 00:19:02.198 looking at circulating factors by plasma

NOTE Confidence: 0.8098867

00:19:02.198 --> 00:19:04.556 cytokines that is actually a highly

NOTE Confidence: 0.8098867

00:19:04.623 --> 00:19:06.195 correlated module of inflammatory

NOTE Confidence: 0.8098867

00:19:06.195 --> 00:19:08.553 cytokines that are present in a

NOTE Confidence: 0.8098867

00:19:08.560 --> 00:19:10.582 variety of these patients with non

NOTE Confidence: 0.8098867

00:19:10.582 --> 00:19:13.114 clear cell disease and what we call

NOTE Confidence: 0.8098867

00:19:13.114 --> 00:19:14.589 the systemic inflammatory module.

NOTE Confidence: 0.8098867

00:19:14.589 --> 00:19:16.334 This was actually associated with

NOTE Confidence: 0.8098867

00:19:16.334 --> 00:19:18.198 worse response and worse survival

NOTE Confidence: 0.8098867

00:19:18.198 --> 00:19:19.428 within these patients.

NOTE Confidence: 0.795158911666667

00:19:21.670 --> 00:19:23.488 We've talked mostly about the genetics,

NOTE Confidence: 0.795158911666667

00:19:23.490 --> 00:19:25.389 but we know that the RNA sequencing can also

NOTE Confidence: 0.795158911666667

00:19:25.389 --> 00:19:27.380 be leveraged to really understand some of

NOTE Confidence: 0.795158911666667

00:19:27.380 --> 00:19:29.209 the molecular subtypes of kidney cancer.

NOTE Confidence: 0.795158911666667

00:19:29.210 --> 00:19:31.653 There was really nice work done from

NOTE Confidence: 0.795158911666667

00:19:31.653 --> 00:19:33.982 the Genentech group and work that was

NOTE Confidence: 0.795158911666667

00:19:33.982 --> 00:19:36.233 initially led by Bob Motzer and and

NOTE Confidence: 0.795158911666667

00:19:36.233 --> 00:19:38.718 Brian Reaney where they broke down kidney

NOTE Confidence: 0.795158911666667

00:19:38.718 --> 00:19:41.320 tumors from a phase three trial and kidney

NOTE Confidence: 0.795158911666667

00:19:41.320 --> 00:19:43.090 cancer into different molecular subtypes.

NOTE Confidence: 0.795158911666667

00:19:43.090 --> 00:19:45.094 And actually we're able to see

NOTE Confidence: 0.795158911666667

00:19:45.094 --> 00:19:46.801 differential response to therapies was

NOTE Confidence: 0.795158911666667

00:19:46.801 --> 00:19:48.685 actually predictive of whether a patient

NOTE Confidence: 0.795158911666667

00:19:48.685 --> 00:19:50.759 would respond to therapy A or therapy.

NOTE Confidence: 0.795158911666667

00:19:50.760 --> 00:19:52.776 Which is a really exciting sort of idea,

NOTE Confidence: 0.795158911666667

00:19:52.780 --> 00:19:55.005 biomarker driven selection of of

NOTE Confidence: 0.795158911666667

00:19:55.005 --> 00:19:57.780 therapy for patients with kidney cancer.

NOTE Confidence: 0.795158911666667

00:19:57.780 --> 00:19:59.628 However that was from patients treated

NOTE Confidence: 0.795158911666667

00:19:59.628 --> 00:20:01.819 with drugs that are not FDA approved.

NOTE Confidence: 0.795158911666667

00:20:01.820 --> 00:20:03.900 It was overall a negative phase three trial.

NOTE Confidence: 0.795158911666667

00:20:03.900 --> 00:20:06.300 And so in work led by Renee Maria

NOTE Confidence: 0.795158911666667

00:20:06.300 --> 00:20:08.746 Saliby in my lab we've actually used

NOTE Confidence: 0.795158911666667

00:20:08.746 --> 00:20:11.420 a random forest model to now classify

NOTE Confidence: 0.795158911666667

00:20:11.420 --> 00:20:13.880 tumors in a FDA approved regiment,

NOTE Confidence: 0.795158911666667

00:20:13.880 --> 00:20:15.826 a value map plus axitinib and actually

NOTE Confidence: 0.795158911666667

00:20:15.826 --> 00:20:17.635 look at whether these are associated

NOTE Confidence: 0.795158911666667

00:20:17.635 --> 00:20:19.791 with response or resistance in a really

NOTE Confidence: 0.795158911666667

00:20:19.851 --> 00:20:21.018 FDA approved. Measurement really.

NOTE Confidence: 0.795158911666667

00:20:21.018 --> 00:20:23.010 Can you use this for for treatment selection?

NOTE Confidence: 0.795158911666667

00:20:23.010 --> 00:20:25.380 The answer is probably not.

NOTE Confidence: 0.795158911666667

00:20:25.380 --> 00:20:25.928 And finally,

NOTE Confidence: 0.795158911666667

00:20:25.928 --> 00:20:28.120 we know that some patients as I showed

NOTE Confidence: 0.795158911666667

00:20:28.181 --> 00:20:30.185 not just respond to immune therapy

NOTE Confidence: 0.795158911666667

00:20:30.185 --> 00:20:32.060 but really have exceptional response.

NOTE Confidence: 0.795158911666667

00:20:32.060 --> 00:20:33.740 They really have long term durable

NOTE Confidence: 0.795158911666667

00:20:33.740 --> 00:20:35.584 response that goes on for years

NOTE Confidence: 0.795158911666667

00:20:35.584 --> 00:20:36.920 or tremendous tumor shrinkage.

NOTE Confidence: 0.795158911666667

00:20:36.920 --> 00:20:38.664 And so how can we learn what might

NOTE Confidence: 0.795158911666667

00:20:38.664 --> 00:20:40.346 drive not just responsive theory

NOTE Confidence: 0.795158911666667

00:20:40.346 --> 00:20:41.537 but exceptional response.

NOTE Confidence: 0.795158911666667

00:20:41.540 --> 00:20:43.466 And this is together with Suchat

NOTE Confidence: 0.795158911666667

00:20:43.466 --> 00:20:45.380 Shukla's lab at MD Anderson.

NOTE Confidence: 0.795158911666667

00:20:45.380 --> 00:20:47.179 We've partnered to look at a handful

NOTE Confidence: 0.795158911666667

00:20:47.179 --> 00:20:48.481 of these exceptional responders both

NOTE Confidence: 0.795158911666667

00:20:48.481 --> 00:20:50.154 from courts we have but also again

NOTE Confidence: 0.795158911666667

00:20:50.154 --> 00:20:51.980 in partnership with industry and are

NOTE Confidence: 0.795158911666667

00:20:51.980 --> 00:20:53.515 able to identify certain features,

NOTE Confidence: 0.795158911666667

00:20:53.520 --> 00:20:55.150 the presence of high clonal

NOTE Confidence: 0.795158911666667

00:20:55.150 --> 00:20:56.128 neoantigens and actually.

NOTE Confidence: 0.795158911666667

00:20:56.130 --> 00:20:57.930 A higher proportion of tertiary lymphoid

NOTE Confidence: 0.795158911666667

00:20:57.930 --> 00:21:00.121 structures they release seem to be associated

NOTE Confidence: 0.795158911666667

00:21:00.121 --> 00:21:01.385 with these exceptional responders,

NOTE Confidence: 0.795158911666667

00:21:01.390 --> 00:21:02.975 ones that really have response

NOTE Confidence: 0.795158911666667

00:21:02.975 --> 00:21:04.243 that lasts for years.

NOTE Confidence: 0.795158911666667

00:21:04.250 --> 00:21:05.201 And so overall,

NOTE Confidence: 0.795158911666667

00:21:05.201 --> 00:21:07.420 our lab is really focused on using

NOTE Confidence: 0.795158911666667

00:21:07.488 --> 00:21:10.064 a lot of these classic genomic and

NOTE Confidence: 0.795158911666667

00:21:10.064 --> 00:21:11.767 transcriptomic tools to understand

NOTE Confidence: 0.795158911666667

00:21:11.767 --> 00:21:13.899 response resistance to therapy.

NOTE Confidence: 0.795158911666667

00:21:13.900 --> 00:21:16.508 But we know these are sort of broad tools,

NOTE Confidence: 0.795158911666667

00:21:16.508 --> 00:21:17.918 classic genomic tools that to

NOTE Confidence: 0.795158911666667

00:21:17.918 --> 00:21:19.247 understand really what's happening

NOTE Confidence: 0.795158911666667

00:21:19.247 --> 00:21:20.912 in the tumor microenvironment and

NOTE Confidence: 0.795158911666667

00:21:20.912 --> 00:21:22.150 the tremendous heterogeneity both

NOTE Confidence: 0.795158911666667

00:21:22.150 --> 00:21:23.991 in T cell phenotypes but also in

NOTE Confidence: 0.795158911666667

00:21:23.991 --> 00:21:25.524 other cells with immune system,

NOTE Confidence: 0.795158911666667

00:21:25.524 --> 00:21:27.420 we need finer tools and that

NOTE Confidence: 0.795158911666667

00:21:27.487 --> 00:21:29.084 we've heavily relied on single

NOTE Confidence: 0.795158911666667

00:21:29.084 --> 00:21:30.714 cell RNA sequencing for this.

NOTE Confidence: 0.795158911666667

00:21:30.720 --> 00:21:32.848 And so our past work really asked a

NOTE Confidence: 0.795158911666667

00:21:32.848 --> 00:21:34.131 pretty basic question independent

NOTE Confidence: 0.795158911666667

00:21:34.131 --> 00:21:36.539 of therapy which was as you advance

NOTE Confidence: 0.795158911666667

00:21:36.539 --> 00:21:38.774 along disease stage as you go from

NOTE Confidence: 0.795158911666667

00:21:38.774 --> 00:21:40.584 a relatively normal kidney or at

NOTE Confidence: 0.795158911666667

00:21:40.584 --> 00:21:42.044 least non malignant kidney to

NOTE Confidence: 0.795158911666667

00:21:42.044 --> 00:21:43.360 early stage kidney cancer.

NOTE Confidence: 0.795158911666667

00:21:43.360 --> 00:21:44.750 To locally advanced kidney cancer,

NOTE Confidence: 0.795158911666667

00:21:44.750 --> 00:21:46.566 to metastatic kidney cancer,

NOTE Confidence: 0.795158911666667

00:21:46.566 --> 00:21:49.290 how does the immune microenvironment change?

NOTE Confidence: 0.795158911666667

00:21:49.290 --> 00:21:50.430 How do the T cells change?

NOTE Confidence: 0.795158911666667

00:21:50.430 --> 00:21:52.358 How do the myeloid cells change and are

NOTE Confidence: 0.795158911666667

00:21:52.358 --> 00:21:54.169 there any interactions between them?

NOTE Confidence: 0.795158911666667

00:21:54.170 --> 00:21:55.390 And to do this,

NOTE Confidence: 0.795158911666667

00:21:55.390 --> 00:21:56.915 we prospectively collected fresh tumor

NOTE Confidence: 0.795158911666667

00:21:56.915 --> 00:21:58.556 specimens from different patients with

NOTE Confidence: 0.795158911666667

00:21:58.556 --> 00:22:00.476 either early stage locally advanced or

NOTE Confidence: 0.747378448333333

00:22:00.524 --> 00:22:01.859 metastatic disease and perform single

NOTE Confidence: 0.747378448333333

00:22:01.859 --> 00:22:04.100 cell RNA in T cell TCR sequencing.

NOTE Confidence: 0.747378448333333

00:22:04.100 --> 00:22:07.250 Overall, we had a pretty good balance.

NOTE Confidence: 0.747378448333333

00:22:07.250 --> 00:22:08.948 We sequence about 165,000 cells from

NOTE Confidence: 0.747378448333333

00:22:08.948 --> 00:22:11.359 a little over a dozen patients heavily

NOTE Confidence: 0.747378448333333

00:22:11.359 --> 00:22:13.399 skewed towards sequencing the immune.

NOTE Confidence: 0.747378448333333

00:22:13.400 --> 00:22:14.980 Uh, the immune compartment

NOTE Confidence: 0.747378448333333

00:22:14.980 --> 00:22:16.165 of the microenvironment.

NOTE Confidence: 0.747378448333333

00:22:16.170 --> 00:22:17.786 And so now armed with this data set,

NOTE Confidence: 0.747378448333333

00:22:17.790 --> 00:22:19.734 we can begin to ask questions what are

NOTE Confidence: 0.747378448333333

00:22:19.734 --> 00:22:22.133 the T cell compartment look like and how

NOTE Confidence: 0.747378448333333

00:22:22.133 --> 00:22:24.195 does that evolve with progressive with

NOTE Confidence: 0.747378448333333

00:22:24.195 --> 00:22:26.481 advancing disease stage and ask similar

NOTE Confidence: 0.747378448333333

00:22:26.481 --> 00:22:29.278 questions of the myeloid compartment.

NOTE Confidence: 0.747378448333333

00:22:29.280 --> 00:22:30.530 For the T cell compartment,

NOTE Confidence: 0.747378448333333

00:22:30.530 --> 00:22:33.474 we can see heavy infiltration by CDT cells.

NOTE Confidence: 0.747378448333333

00:22:33.480 --> 00:22:35.412 Largely there's a huge component of

NOTE Confidence: 0.747378448333333

00:22:35.412 --> 00:22:36.700 terminally exhausted CD8T cells,

NOTE Confidence: 0.747378448333333

00:22:36.700 --> 00:22:38.804 but we see a variety of T cell

NOTE Confidence: 0.747378448333333

00:22:38.804 --> 00:22:40.057 phenotypes ranging from resident

NOTE Confidence: 0.747378448333333

00:22:40.057 --> 00:22:42.352 memory like cells to classic T regs.

NOTE Confidence: 0.747378448333333

00:22:42.352 --> 00:22:44.290 And so when we classify these

NOTE Confidence: 0.747378448333333

00:22:44.361 --> 00:22:46.179 different cell populations,

NOTE Confidence: 0.747378448333333

00:22:46.180 --> 00:22:49.072 these T cell clusters and organize

NOTE Confidence: 0.747378448333333

00:22:49.072 --> 00:22:51.480 them about organize them in a way

NOTE Confidence: 0.747378448333333

00:22:51.480 --> 00:22:53.296 to see which might be increase

NOTE Confidence: 0.747378448333333

00:22:53.296 --> 00:22:54.800 in advanced disease stage,

NOTE Confidence: 0.747378448333333

00:22:54.800 --> 00:22:56.592 we begin to see highlighted in red

NOTE Confidence: 0.747378448333333

00:22:56.592 --> 00:22:58.458 that there are few T cell clusters,

NOTE Confidence: 0.747378448333333

00:22:58.460 --> 00:22:59.856 few T cell populations.

NOTE Confidence: 0.747378448333333

00:22:59.856 --> 00:23:01.950 There really seems to be enriched

NOTE Confidence: 0.747378448333333

00:23:02.017 --> 00:23:03.549 in more advanced disease.

NOTE Confidence: 0.747378448333333

00:23:03.550 --> 00:23:04.910 Now, at least for me,

NOTE Confidence: 0.747378448333333

00:23:04.910 --> 00:23:06.462 it's a little bit unwieldy to look at

NOTE Confidence: 0.747378448333333

00:23:06.462 --> 00:23:08.068 so many different cell populations.

NOTE Confidence: 0.747378448333333

00:23:08.070 --> 00:23:10.464 And So what we did was brought more broadly,

NOTE Confidence: 0.747378448333333

00:23:10.470 --> 00:23:12.395 classify them just using standard

NOTE Confidence: 0.747378448333333

00:23:12.395 --> 00:23:13.165 hierarchical clustering.

NOTE Confidence: 0.747378448333333

00:23:13.170 --> 00:23:15.125 We can construct this dendrogram

NOTE Confidence: 0.747378448333333

00:23:15.125 --> 00:23:16.298 where transcriptionally related

NOTE Confidence: 0.747378448333333

00:23:16.298 --> 00:23:18.542 groups of cells are near each other

NOTE Confidence: 0.747378448333333

00:23:18.542 --> 00:23:20.415 on this dendrogram and once that

NOTE Confidence: 0.747378448333333

00:23:20.415 --> 00:23:22.485 transcriptionally different are far apart.

NOTE Confidence: 0.747378448333333

00:23:22.490 --> 00:23:24.470 And what we can see is now instead of,

NOTE Confidence: 0.747378448333333

00:23:24.470 --> 00:23:26.619 you know, 18 or 19 different clusters,

NOTE Confidence: 0.747378448333333

00:23:26.620 --> 00:23:28.657 we can see really 2 broad groups

NOTE Confidence: 0.747378448333333

00:23:28.657 --> 00:23:30.180 in red T cell CD.

NOTE Confidence: 0.747378448333333

00:23:30.180 --> 00:23:31.695 She sells that broadly have

NOTE Confidence: 0.747378448333333

00:23:31.695 --> 00:23:33.210 markers of T cell exhaustion,

NOTE Confidence: 0.747378448333333

00:23:33.210 --> 00:23:36.450 expression of talks, high expression,

NOTE Confidence: 0.747378448333333

00:23:36.450 --> 00:23:37.770 multiple inhibitory receptors

NOTE Confidence: 0.747378448333333

00:23:37.770 --> 00:23:39.530 and then everything else.

NOTE Confidence: 0.747378448333333

00:23:39.530 --> 00:23:40.562 All of the other T cells

NOTE Confidence: 0.747378448333333

00:23:40.562 --> 00:23:41.500 which are shown in blue,

NOTE Confidence: 0.747378448333333

00:23:41.500 --> 00:23:43.010 the non exhausted T cells.

NOTE Confidence: 0.747378448333333

00:23:43.010 --> 00:23:45.182 And now with this much more

NOTE Confidence: 0.747378448333333

00:23:45.182 --> 00:23:45.906 simplified definition,

NOTE Confidence: 0.747378448333333

00:23:45.910 --> 00:23:48.801 we can see a pretty striking pattern

NOTE Confidence: 0.747378448333333

00:23:48.801 --> 00:23:50.910 that terminally exhausted or exhausted

NOTE Confidence: 0.747378448333333

00:23:50.910 --> 00:23:52.582 CD8T cells progressively increase

NOTE Confidence: 0.747378448333333

00:23:52.582 --> 00:23:54.254 with advancing disease stage.

NOTE Confidence: 0.747378448333333

00:23:54.260 --> 00:23:55.256 They're essentially absent

NOTE Confidence: 0.747378448333333

00:23:55.256 --> 00:23:56.584 a normal kidney president,

NOTE Confidence: 0.747378448333333

00:23:56.590 --> 00:23:58.900 very low levels in early stage disease

NOTE Confidence: 0.747378448333333

00:23:58.900 --> 00:24:00.190 and progressively increasing more.

NOTE Confidence: 0.747378448333333

00:24:00.190 --> 00:24:02.590 Against disease stages and that

NOTE Confidence: 0.747378448333333

00:24:02.590 --> 00:24:05.441 we by contrast see relatively few

NOTE Confidence: 0.747378448333333

00:24:05.441 --> 00:24:07.764 non exhausted CD T cells with

NOTE Confidence: 0.747378448333333

00:24:07.764 --> 00:24:09.700 an advanced disease stage.

NOTE Confidence: 0.747378448333333

00:24:09.700 --> 00:24:11.176 So that's the T cell compartment.

NOTE Confidence: 0.747378448333333

00:24:11.180 --> 00:24:13.500 We have this progressive exhaustion

NOTE Confidence: 0.747378448333333

00:24:13.500 --> 00:24:15.356 with advancing disease stage.

NOTE Confidence: 0.747378448333333

00:24:15.360 --> 00:24:17.520 What about the myeloid compartment?

NOTE Confidence: 0.747378448333333

00:24:17.520 --> 00:24:18.800 And for the myeloid compartment,

NOTE Confidence: 0.747378448333333

00:24:18.800 --> 00:24:20.684 it's often harder to put these

NOTE Confidence: 0.747378448333333

00:24:20.684 --> 00:24:21.940 cells into discrete buckets.

NOTE Confidence: 0.747378448333333

00:24:21.940 --> 00:24:22.496 You know,

NOTE Confidence: 0.747378448333333

00:24:22.496 --> 00:24:24.720 for T cells were labeled them as either

NOTE Confidence: 0.747378448333333

00:24:24.784 --> 00:24:27.052 AT RAG or a CDA T cell that's exhausted.

NOTE Confidence: 0.747378448333333

00:24:27.060 --> 00:24:28.509 You put them in some of these

NOTE Confidence: 0.747378448333333

00:24:28.509 --> 00:24:29.560 discrete buckets or clusters.

NOTE Confidence: 0.747378448333333

00:24:29.560 --> 00:24:31.261 Myeloid cells as we know can exist

NOTE Confidence: 0.747378448333333

00:24:31.261 --> 00:24:32.844 much more along a phenotypic spectrum

NOTE Confidence: 0.747378448333333

00:24:32.844 --> 00:24:34.713 and so for this sort of analysis,

NOTE Confidence: 0.747378448333333

00:24:34.720 --> 00:24:37.275 for for this sort of continuous phenotype

NOTE Confidence: 0.747378448333333

00:24:37.275 --> 00:24:39.589 using a trajectory inference analysis.

NOTE Confidence: 0.747378448333333

00:24:39.590 --> 00:24:40.730 Is a really nice approach.

NOTE Confidence: 0.747378448333333

00:24:40.730 --> 00:24:42.278 It doesn't force you to put

NOTE Confidence: 0.747378448333333

00:24:42.278 --> 00:24:43.310 things into discrete buckets.

NOTE Confidence: 0.747378448333333

00:24:43.310 --> 00:24:45.626 It allows cells to exist on

NOTE Confidence: 0.747378448333333

00:24:45.626 --> 00:24:46.784 a phenotypic spectrum.

NOTE Confidence: 0.80934627625

00:24:46.790 --> 00:24:48.770 And so when we do that for our myeloid

NOTE Confidence: 0.80934627625

00:24:48.770 --> 00:24:50.798 cells we see a actually this interesting,

NOTE Confidence: 0.80934627625

00:24:50.800 --> 00:24:52.670 this nice interesting branching pattern,

NOTE Confidence: 0.80934627625

00:24:52.670 --> 00:24:53.760 which I think recapitulates a

NOTE Confidence: 0.80934627625

00:24:53.760 --> 00:24:55.250 lot of sort of known biology.

NOTE Confidence: 0.80934627625

00:24:55.250 --> 00:24:57.338 We have classic monocytes at the

NOTE Confidence: 0.80934627625

00:24:57.338 --> 00:24:59.476 root and then branching either into

NOTE Confidence: 0.80934627625

00:24:59.476 --> 00:25:01.522 non classical monocytes on the left

NOTE Confidence: 0.80934627625

00:25:01.522 --> 00:25:03.828 or into macrophages on the right.

NOTE Confidence: 0.80934627625

00:25:03.830 --> 00:25:05.580 And if we look at where these

NOTE Confidence: 0.80934627625

00:25:05.580 --> 00:25:06.990 individual cells are coming from,

NOTE Confidence: 0.80934627625

00:25:06.990 --> 00:25:08.645 those myeloid cells that are

NOTE Confidence: 0.80934627625

00:25:08.645 --> 00:25:09.969 present in normal kidney.

NOTE Confidence: 0.80934627625

00:25:09.970 --> 00:25:12.525 I should say normal with a caveat.

NOTE Confidence: 0.80934627625

00:25:12.530 --> 00:25:14.190 They're adjacent non malignant kidney.

NOTE Confidence: 0.80934627625

00:25:14.190 --> 00:25:15.522 So it's from a cancer patient

NOTE Confidence: 0.80934627625

00:25:15.522 --> 00:25:16.770 might not be totally normal,

NOTE Confidence: 0.80934627625

00:25:16.770 --> 00:25:18.646 but we see that they're largely classical

NOTE Confidence: 0.80934627625

00:25:18.646 --> 00:25:20.410 monocytes and non classical monocytes,

NOTE Confidence: 0.80934627625

00:25:20.410 --> 00:25:22.438 very few macrophages in

NOTE Confidence: 0.80934627625

00:25:22.438 --> 00:25:24.466 these non malignant kidneys.

NOTE Confidence: 0.80934627625

00:25:24.470 --> 00:25:26.094 Now if we look at myeloid cells

NOTE Confidence: 0.80934627625

00:25:26.094 --> 00:25:27.110 from different tumor types,

NOTE Confidence: 0.80934627625

00:25:27.110 --> 00:25:28.346 we see a very different pattern.

NOTE Confidence: 0.80934627625

00:25:28.350 --> 00:25:29.726 The first thing that might catch your eyes,

NOTE Confidence: 0.80934627625

00:25:29.730 --> 00:25:31.070 there's many more macrophages

NOTE Confidence: 0.80934627625

00:25:31.070 --> 00:25:32.745 that's the right-hand branch and

NOTE Confidence: 0.80934627625

00:25:32.745 --> 00:25:34.082 across different disease stages

NOTE Confidence: 0.80934627625

00:25:34.082 --> 00:25:35.978 there's just a lot more macrophages

NOTE Confidence: 0.80934627625

00:25:35.978 --> 00:25:37.507 than there are normal kidney.

NOTE Confidence: 0.80934627625

00:25:37.510 --> 00:25:39.950 But if we actually hone in on on.

NOTE Confidence: 0.80934627625

00:25:39.950 --> 00:25:41.132 That right branch,

NOTE Confidence: 0.80934627625

00:25:41.132 --> 00:25:43.496 we see again a different pattern

NOTE Confidence: 0.80934627625

00:25:43.500 --> 00:25:44.896 between early stage disease,

NOTE Confidence: 0.80934627625

00:25:44.896 --> 00:25:46.292 locally advanced and metastatic

NOTE Confidence: 0.80934627625

00:25:46.292 --> 00:25:47.740 and early stage disease.

NOTE Confidence: 0.80934627625

00:25:47.740 --> 00:25:49.228 Those myeloid cells,

NOTE Confidence: 0.80934627625

00:25:49.228 --> 00:25:51.708 those macrophages are heavily clustering.

NOTE Confidence: 0.80934627625

00:25:51.710 --> 00:25:53.790 Relatively early along that branch,

NOTE Confidence: 0.80934627625

00:25:53.790 --> 00:25:56.350 relatively early in that bifurcation.

NOTE Confidence: 0.80934627625

00:25:56.350 --> 00:25:56.972 By contrast,

NOTE Confidence: 0.80934627625

00:25:56.972 --> 00:25:58.838 locally advanced tumors are kind of

NOTE Confidence: 0.80934627625

00:25:58.838 --> 00:26:00.604 spread throughout that branch or spread

NOTE Confidence: 0.80934627625

00:26:00.604 --> 00:26:02.242 throughout what we call pseudo time.

NOTE Confidence: 0.80934627625

00:26:02.250 --> 00:26:03.480 And if you look at the

NOTE Confidence: 0.80934627625

00:26:03.480 --> 00:26:04.650 metastatic tumors at the bottom,

NOTE Confidence: 0.80934627625

00:26:04.650 --> 00:26:06.075 those macrophages are all the

NOTE Confidence: 0.80934627625

00:26:06.075 --> 00:26:08.290 way at the end of that branch,

NOTE Confidence: 0.80934627625

00:26:08.290 --> 00:26:10.225 all the way at the end of pseudo time.

NOTE Confidence: 0.80934627625

00:26:10.230 --> 00:26:11.987 And So what are the genes and

NOTE Confidence: 0.80934627625

00:26:11.987 --> 00:26:13.594 gene programs that are really

NOTE Confidence: 0.80934627625

00:26:13.594 --> 00:26:14.788 driving these trajectories?

NOTE Confidence: 0.80934627625

00:26:14.790 --> 00:26:16.558 It looks like a a switch from a

NOTE Confidence: 0.80934627625

00:26:16.558 --> 00:26:17.838 more pro inflammatory state to

NOTE Confidence: 0.80934627625

00:26:17.838 --> 00:26:19.990 a more ah as they use the term.

NOTE Confidence: 0.80934627625

00:26:19.990 --> 00:26:21.320 But an M2 like state,

NOTE Confidence: 0.80934627625

00:26:21.320 --> 00:26:23.704 an imperfect term but a a more immune

NOTE Confidence: 0.80934627625

00:26:23.704 --> 00:26:25.170 suppressive or pro tumorigenic state

NOTE Confidence: 0.80934627625

00:26:25.170 --> 00:26:27.491 that we see if we look at signatures

NOTE Confidence: 0.80934627625

00:26:27.491 --> 00:26:29.356 of a pro inflammatory signature

NOTE Confidence: 0.80934627625

00:26:29.356 --> 00:26:31.666 those are really those peak and are

NOTE Confidence: 0.80934627625

00:26:31.666 --> 00:26:33.570 really high early on in pseudo time

NOTE Confidence: 0.80934627625

00:26:33.628 --> 00:26:35.698 at that right hand branch where

NOTE Confidence: 0.80934627625

00:26:35.698 --> 00:26:37.370 those early stage macrophages are.

NOTE Confidence: 0.80934627625

00:26:37.370 --> 00:26:39.435 And by contrast we look in an

NOTE Confidence: 0.80934627625

00:26:39.435 --> 00:26:40.320 anti-inflammatory signature that

NOTE Confidence: 0.80934627625

00:26:40.377 --> 00:26:42.142 really peaks later corresponding to

NOTE Confidence: 0.80934627625

00:26:42.142 --> 00:26:43.554 where those metastatic macrophages

NOTE Confidence: 0.80934627625

00:26:43.554 --> 00:26:45.147 are if we look at individual.

NOTE Confidence: 0.80934627625

00:26:45.150 --> 00:26:46.474 Means prone flammatory genes,

NOTE Confidence: 0.80934627625

00:26:46.474 --> 00:26:48.644 aisle 1, beta TNF, aisle 6.

NOTE Confidence: 0.80934627625

00:26:48.644 --> 00:26:51.518 Those are all relatively absent in those

NOTE Confidence: 0.80934627625

00:26:51.518 --> 00:26:54.238 metastatic macrophages outlined in pink.

NOTE Confidence: 0.80934627625

00:26:54.240 --> 00:26:56.816 Whereas if we look at genes that

NOTE Confidence: 0.80934627625

00:26:56.816 --> 00:26:58.343 are typically associated with

NOTE Confidence: 0.80934627625

00:26:58.343 --> 00:27:00.118 this more M2 like phenotype,

NOTE Confidence: 0.80934627625

00:27:00.120 --> 00:27:02.815 things like C163 of the folate receptor,

NOTE Confidence: 0.80934627625

00:27:02.820 --> 00:27:05.385 those are significantly enriched expression

NOTE Confidence: 0.80934627625

00:27:05.385 --> 00:27:07.437 in those metastatic macrophages.

NOTE Confidence: 0.80934627625

00:27:07.440 --> 00:27:09.092 I should say not shown here those

NOTE Confidence: 0.80934627625

00:27:09.092 --> 00:27:10.613 really do express high levels of

NOTE Confidence: 0.80934627625

00:27:10.613 --> 00:27:12.137 complement genes as well and and

NOTE Confidence: 0.80934627625

00:27:12.137 --> 00:27:13.692 trimmed 2 which has been described

NOTE Confidence: 0.80934627625

00:27:13.692 --> 00:27:14.439 by other groups,

NOTE Confidence: 0.80934627625

00:27:14.440 --> 00:27:17.930 these trimmed 2 positive macrophages.

NOTE Confidence: 0.80934627625

00:27:17.930 --> 00:27:20.352 And so we've looked independently at T

NOTE Confidence: 0.80934627625

00:27:20.352 --> 00:27:22.230 cells independently and myeloid cells.

NOTE Confidence: 0.80934627625

00:27:22.230 --> 00:27:23.174 The natural question is,

NOTE Confidence: 0.80934627625

00:27:23.174 --> 00:27:24.590 are those independent events or are

NOTE Confidence: 0.80934627625

00:27:24.633 --> 00:27:26.085 they actually talking to one another?

NOTE Confidence: 0.948506981428571

00:27:26.090 --> 00:27:27.749 And to begin to look at this,

NOTE Confidence: 0.948506981428571

00:27:27.750 --> 00:27:29.970 we inferred cell cell interactions

NOTE Confidence: 0.948506981428571

00:27:29.970 --> 00:27:31.746 using the transcriptomic data.

NOTE Confidence: 0.948506981428571

00:27:31.750 --> 00:27:32.938 And the idea is fairly simple.

NOTE Confidence: 0.948506981428571

00:27:32.940 --> 00:27:34.524 We use a tool called cell phone DB,

NOTE Confidence: 0.948506981428571

00:27:34.530 --> 00:27:36.456 and the idea is if one group of cells

NOTE Confidence: 0.948506981428571

00:27:36.456 --> 00:27:38.329 is expressing a ligand and another

NOTE Confidence: 0.948506981428571

00:27:38.329 --> 00:27:40.645 group of cells is expressing the known

NOTE Confidence: 0.948506981428571

00:27:40.645 --> 00:27:42.285 receptor complex for that ligand,

NOTE Confidence: 0.948506981428571

00:27:42.290 --> 00:27:43.510 you might infer that they're

NOTE Confidence: 0.948506981428571

00:27:43.510 --> 00:27:45.110 interacting or talking to one another.

NOTE Confidence: 0.948506981428571

00:27:45.110 --> 00:27:46.886 And by randomly permuting the labels,

NOTE Confidence: 0.948506981428571

00:27:46.890 --> 00:27:48.246 you can actually get some statistics.

NOTE Confidence: 0.948506981428571

00:27:48.250 --> 00:27:49.804 And say, is this something that

NOTE Confidence: 0.948506981428571

00:27:49.804 --> 00:27:51.400 we expect more than by chance?

NOTE Confidence: 0.948506981428571

00:27:51.400 --> 00:27:52.968 And what's shown here is a heat map

NOTE Confidence: 0.948506981428571

00:27:52.968 --> 00:27:54.776 of the number of interactions between

NOTE Confidence: 0.948506981428571

00:27:54.776 --> 00:27:56.481 different cell populations and this

NOTE Confidence: 0.948506981428571

00:27:56.481 --> 00:27:58.416 couple different patterns you might see.

NOTE Confidence: 0.948506981428571

00:27:58.420 --> 00:28:00.534 There's the darker blue area that's an

NOTE Confidence: 0.948506981428571

00:28:00.534 --> 00:28:02.871 area of relatively low number of cell

NOTE Confidence: 0.948506981428571

00:28:02.871 --> 00:28:04.247 cell interactions between different

NOTE Confidence: 0.948506981428571

00:28:04.247 --> 00:28:06.633 cell types and that's between usually

NOTE Confidence: 0.948506981428571

00:28:06.633 --> 00:28:08.273 between different cell populations.

NOTE Confidence: 0.948506981428571

00:28:08.280 --> 00:28:09.855 In red in the upper left corner,

NOTE Confidence: 0.948506981428571

00:28:09.860 --> 00:28:12.296 you see a lot of interactions mostly

NOTE Confidence: 0.948506981428571

00:28:12.296 --> 00:28:14.360 between different myeloid cell populations.

NOTE Confidence: 0.948506981428571

00:28:14.360 --> 00:28:16.313 And then outlined in Black was a

NOTE Confidence: 0.948506981428571

00:28:16.313 --> 00:28:17.998 particular area that caught our eye,

NOTE Confidence: 0.948506981428571

00:28:18.000 --> 00:28:18.608 which are.

NOTE Confidence: 0.948506981428571

00:28:18.608 --> 00:28:20.432 High number of interactions between T

NOTE Confidence: 0.948506981428571

00:28:20.432 --> 00:28:22.511 cells and myeloid cells and when we zoom

NOTE Confidence: 0.948506981428571

00:28:22.511 --> 00:28:24.819 in and look on exactly what populations,

NOTE Confidence: 0.948506981428571

00:28:24.820 --> 00:28:27.256 it's actually these M2 like these trim

NOTE Confidence: 0.948506981428571

00:28:27.256 --> 00:28:28.696 2 positive macrophages interacting

NOTE Confidence: 0.948506981428571

00:28:28.696 --> 00:28:30.040 with these terminally exhausted

NOTE Confidence: 0.948506981428571

00:28:30.040 --> 00:28:32.469 CD T cells at a high degree.

NOTE Confidence: 0.948506981428571

00:28:32.470 --> 00:28:34.070 So these are inferred interactions.

NOTE Confidence: 0.948506981428571

00:28:34.070 --> 00:28:35.522 We obviously have to make sure

NOTE Confidence: 0.948506981428571

00:28:35.522 --> 00:28:36.490 they're actually present in

NOTE Confidence: 0.948506981428571

00:28:36.532 --> 00:28:37.696 the same in the same sample.

NOTE Confidence: 0.948506981428571

00:28:37.700 --> 00:28:39.044 They have to be in the same

NOTE Confidence: 0.948506981428571

00:28:39.044 --> 00:28:40.030 tumor to physically interact.

NOTE Confidence: 0.948506981428571

00:28:40.030 --> 00:28:41.542 And so we'll look at the relative

NOTE Confidence: 0.948506981428571

00:28:41.542 --> 00:28:43.140 proportion of these different populations.

NOTE Confidence: 0.948506981428571

00:28:43.140 --> 00:28:44.770 We can again see they're

NOTE Confidence: 0.948506981428571

00:28:44.770 --> 00:28:45.748 really highly correlated.

NOTE Confidence: 0.948506981428571

00:28:45.750 --> 00:28:47.022 That's a strong correlation

NOTE Confidence: 0.948506981428571

00:28:47.022 --> 00:28:48.930 between the presence of these CDT.

NOTE Confidence: 0.948506981428571

00:28:48.930 --> 00:28:51.435 Cells and these tumor associated

NOTE Confidence: 0.948506981428571

00:28:51.435 --> 00:28:52.437 macrophage populations.

NOTE Confidence: 0.948506981428571

00:28:52.440 --> 00:28:54.780 And So what are these interactions?

NOTE Confidence: 0.948506981428571

00:28:54.780 --> 00:28:56.145 They appear to be interactions

NOTE Confidence: 0.948506981428571

00:28:56.145 --> 00:28:57.510 that are bidirectional and really

NOTE Confidence: 0.948506981428571

00:28:57.562 --> 00:28:59.058 support these different phenotypes.

NOTE Confidence: 0.948506981428571

00:28:59.060 --> 00:29:00.648 So these tumor associated

NOTE Confidence: 0.948506981428571

00:29:00.648 --> 00:29:02.236 macrophages are producing ligands

NOTE Confidence: 0.948506981428571

00:29:02.236 --> 00:29:04.219 for inhibitory receptors on T cells,

NOTE Confidence: 0.948506981428571

00:29:04.220 --> 00:29:06.266 things we already know about and

NOTE Confidence: 0.948506981428571

00:29:06.266 --> 00:29:08.810 target like PD1 and PDL 2 for PD one,

NOTE Confidence: 0.948506981428571

00:29:08.810 --> 00:29:10.268 but things we don't yet target

NOTE Confidence: 0.948506981428571

00:29:10.268 --> 00:29:10.997 and kidney cancer,

NOTE Confidence: 0.948506981428571

00:29:11.000 --> 00:29:13.072 things like PVR and actin 2 for

NOTE Confidence: 0.948506981428571

00:29:13.072 --> 00:29:15.326 TIGIT ligands for Tim three and

NOTE Confidence: 0.948506981428571

00:29:15.326 --> 00:29:16.625 other inhibitory checkpoints.

NOTE Confidence: 0.948506981428571

00:29:16.630 --> 00:29:18.235 But it's not all myeloid

NOTE Confidence: 0.948506981428571

00:29:18.235 --> 00:29:19.519 cells inhibiting T cells,

NOTE Confidence: 0.948506981428571

00:29:19.520 --> 00:29:21.180 those T cells terminally exhausted

NOTE Confidence: 0.948506981428571

00:29:21.180 --> 00:29:23.284 CD T cells are also producing

NOTE Confidence: 0.948506981428571

00:29:23.284 --> 00:29:24.808 factors like myth or.

NOTE Confidence: 0.948506981428571

00:29:24.810 --> 00:29:25.116 Uh,

NOTE Confidence: 0.948506981428571

00:29:25.116 --> 00:29:25.422 CS,

NOTE Confidence: 0.948506981428571

00:29:25.422 --> 00:29:27.258 CSF one that support this more

NOTE Confidence: 0.948506981428571

00:29:27.258 --> 00:29:29.588 M2 like polarization and so it's

NOTE Confidence: 0.948506981428571

00:29:29.588 --> 00:29:31.648 really a bidirectional sort of

NOTE Confidence: 0.948506981428571

00:29:31.648 --> 00:29:34.130 immune circuit that seems to be

NOTE Confidence: 0.948506981428571

00:29:34.130 --> 00:29:36.125 present in advanced disease stages.

NOTE Confidence: 0.948506981428571

00:29:36.130 --> 00:29:37.846 This is of course all inferred

NOTE Confidence: 0.948506981428571

00:29:37.846 --> 00:29:38.704 from gene expression.

NOTE Confidence: 0.948506981428571

00:29:38.710 --> 00:29:40.526 So can we gain a little bit more

NOTE Confidence: 0.948506981428571

00:29:40.526 --> 00:29:42.017 confidence that this is this is true,

NOTE Confidence: 0.948506981428571

00:29:42.020 --> 00:29:43.556 this is real and we have a couple

NOTE Confidence: 0.948506981428571

00:29:43.556 --> 00:29:44.602 of different validation exercise

NOTE Confidence: 0.948506981428571

00:29:44.602 --> 00:29:45.830 I'll briefly go through.

NOTE Confidence: 0.948506981428571

00:29:45.830 --> 00:29:47.108 One is are these actually expressed

NOTE Confidence: 0.948506981428571

00:29:47.108 --> 00:29:48.735 at the surface of the protein level

NOTE Confidence: 0.948506981428571

00:29:48.735 --> 00:29:49.945 and these different populations and

NOTE Confidence: 0.948506981428571

00:29:49.945 --> 00:29:51.749 we can use flow cytometry to look at

NOTE Confidence: 0.948506981428571

00:29:51.749 --> 00:29:53.648 that are these actually present in the

NOTE Confidence: 0.948506981428571

00:29:53.648 --> 00:29:55.378 same tumors and physical proximity?

NOTE Confidence: 0.948506981428571

00:29:55.380 --> 00:29:56.844 In situ within the tumor itself

NOTE Confidence: 0.948506981428571

00:29:56.844 --> 00:29:57.820 and we can use

NOTE Confidence: 0.818132057

00:29:57.873 --> 00:29:59.019 Multiplex immunofluorescence and

NOTE Confidence: 0.818132057

00:29:59.019 --> 00:30:01.311 then ultimately is is actually true

NOTE Confidence: 0.818132057

00:30:01.311 --> 00:30:03.256 not just in this small discovery

NOTE Confidence: 0.818132057

00:30:03.256 --> 00:30:05.586 cohort but also more broadly in in

NOTE Confidence: 0.818132057

00:30:05.586 --> 00:30:07.626 other other larger patient cohorts.

NOTE Confidence: 0.818132057

00:30:07.630 --> 00:30:09.678 And so briefly to step through this is

NOTE Confidence: 0.818132057

00:30:09.678 --> 00:30:11.347 in partnership with Arlene Sharps lab.

NOTE Confidence: 0.818132057

00:30:11.350 --> 00:30:14.092 We looked at these different terminal

NOTE Confidence: 0.818132057

00:30:14.092 --> 00:30:16.355 exhaust C8T cell populations and CD

NOTE Confidence: 0.818132057

00:30:16.355 --> 00:30:17.799 163 positive macrophage populations

NOTE Confidence: 0.818132057

00:30:17.799 --> 00:30:20.141 and ask the question do the T cells

NOTE Confidence: 0.818132057

00:30:20.141 --> 00:30:21.845 express the ligands we think they

NOTE Confidence: 0.818132057

00:30:21.845 --> 00:30:23.770 should or the receptors we think they

NOTE Confidence: 0.818132057

00:30:23.770 --> 00:30:25.588 should and do the macrophages express?

NOTE Confidence: 0.818132057

00:30:25.590 --> 00:30:26.787 Well, I guess we think they should

NOTE Confidence: 0.818132057

00:30:26.787 --> 00:30:27.620 and the answer was yes,

NOTE Confidence: 0.818132057

00:30:27.620 --> 00:30:29.735 they do and they're higher

NOTE Confidence: 0.818132057

00:30:29.735 --> 00:30:31.427 in advanced disease stages.

NOTE Confidence: 0.818132057

00:30:31.430 --> 00:30:33.668 Partnering with Sabina Signer Ideas Lab

NOTE Confidence: 0.818132057

00:30:33.668 --> 00:30:34.787 performing Multiplex immunofluorescence,

NOTE Confidence: 0.818132057

00:30:34.790 --> 00:30:37.268 we looked at whether these myeloid cells,

NOTE Confidence: 0.818132057

00:30:37.268 --> 00:30:39.163 these CD 163 positive macrophages

NOTE Confidence: 0.818132057

00:30:39.163 --> 00:30:40.761 were actually physically interacting

NOTE Confidence: 0.818132057

00:30:40.761 --> 00:30:41.970 in advanced tumors.

NOTE Confidence: 0.818132057

00:30:41.970 --> 00:30:43.346 With these terminal exhausted

NOTE Confidence: 0.818132057

00:30:43.346 --> 00:30:45.410 T cells and again in multiple

NOTE Confidence: 0.818132057

00:30:45.473 --> 00:30:47.048 multiple metastatic tumors,

NOTE Confidence: 0.818132057

00:30:47.050 --> 00:30:48.815 we can see evidence for

NOTE Confidence: 0.818132057

00:30:48.815 --> 00:30:49.874 insight 2 interactions.

NOTE Confidence: 0.818132057

00:30:49.880 --> 00:30:51.380 And then finally looking

NOTE Confidence: 0.818132057

00:30:51.380 --> 00:30:52.880 at other external cohorts,

NOTE Confidence: 0.818132057

00:30:52.880 --> 00:30:55.154 we first looked at a previously

NOTE Confidence: 0.818132057

00:30:55.154 --> 00:30:56.990 published saitov cohort from Burn

NOTE Confidence: 0.818132057

00:30:56.990 --> 00:30:58.720 Bodenmiller's Group and re analyze

NOTE Confidence: 0.818132057

00:30:58.720 --> 00:31:00.800 that data to specifically look for

NOTE Confidence: 0.818132057

00:31:00.800 --> 00:31:02.576 our T cell and myeloid populations,

NOTE Confidence: 0.818132057

00:31:02.580 --> 00:31:03.836 our CD163 myeloid populations.

NOTE Confidence: 0.818132057

00:31:03.836 --> 00:31:05.720 And again could see this pattern

NOTE Confidence: 0.818132057

00:31:05.771 --> 00:31:07.775 where the proportion of these cells

NOTE Confidence: 0.818132057

00:31:07.775 --> 00:31:09.460 increase with advancing disease stage.

NOTE Confidence: 0.818132057

00:31:09.460 --> 00:31:11.650 And finally we derived a gene

NOTE Confidence: 0.818132057

00:31:11.650 --> 00:31:13.110 expression signature representing that

NOTE Confidence: 0.818132057

00:31:13.165 --> 00:31:14.429 interaction between those myeloid

NOTE Confidence: 0.818132057

00:31:14.429 --> 00:31:17.008 cells and T cells and use that gene

NOTE Confidence: 0.818132057

00:31:17.008 --> 00:31:18.563 signature to interrogate the TCA

NOTE Confidence: 0.818132057

00:31:18.563 --> 00:31:20.838 and again found this pattern of.

NOTE Confidence: 0.818132057

00:31:20.838 --> 00:31:22.622 Increasing signature of interaction

NOTE Confidence: 0.818132057

00:31:22.622 --> 00:31:24.380 with advancing disease stage.

NOTE Confidence: 0.818132057

00:31:24.380 --> 00:31:26.516 Now that we have this RNA seek signature,

NOTE Confidence: 0.818132057

00:31:26.520 --> 00:31:28.848 we actually ask the question is

NOTE Confidence: 0.818132057

00:31:28.848 --> 00:31:30.400 this interaction signature actually

NOTE Confidence: 0.818132057

00:31:30.463 --> 00:31:32.573 associated with worse outcomes with

NOTE Confidence: 0.818132057

00:31:32.573 --> 00:31:34.580 worse survival. And the answer was yes.

NOTE Confidence: 0.818132057

00:31:34.580 --> 00:31:36.722 If we look at the TCG a data having

NOTE Confidence: 0.818132057

00:31:36.722 --> 00:31:39.311 a high expression of this Tam to

NOTE Confidence: 0.818132057

00:31:39.311 --> 00:31:41.367 T cell interaction signature was

NOTE Confidence: 0.818132057

00:31:41.367 --> 00:31:43.235 really associated with worse

NOTE Confidence: 0.818132057

00:31:43.235 --> 00:31:44.636 overall survival overall.

NOTE Confidence: 0.818132057

00:31:44.640 --> 00:31:46.061 But again we have to be cautious

NOTE Confidence: 0.818132057

00:31:46.061 --> 00:31:47.456 that might just be because it's

NOTE Confidence: 0.818132057

00:31:47.456 --> 00:31:48.696 enriched in stage four disease.

NOTE Confidence: 0.818132057

00:31:48.700 --> 00:31:50.290 And so if we look specifically

NOTE Confidence: 0.818132057

00:31:50.290 --> 00:31:51.628 at those patients with stage

NOTE Confidence: 0.818132057

00:31:51.628 --> 00:31:52.996 four disease in the TCG a,

NOTE Confidence: 0.818132057

00:31:53.000 --> 00:31:54.090 again we see the same.

NOTE Confidence: 0.818132057

00:31:54.090 --> 00:31:55.200 Effect having a high number,

NOTE Confidence: 0.818132057

00:31:55.200 --> 00:31:56.860 higher number of those interactions

NOTE Confidence: 0.818132057

00:31:56.860 --> 00:31:58.520 associated with worse overall survival.

NOTE Confidence: 0.818132057

00:31:58.520 --> 00:32:00.554 And if we look at again our initial cohort,

NOTE Confidence: 0.818132057

00:32:00.560 --> 00:32:02.840 our checkmate cohort that we previously

NOTE Confidence: 0.818132057

00:32:02.840 --> 00:32:05.674 reported on again having a high expression

NOTE Confidence: 0.818132057

00:32:05.674 --> 00:32:07.754 of those that interaction signatures

NOTE Confidence: 0.818132057

00:32:07.754 --> 00:32:09.660 associated with a horse survival.

NOTE Confidence: 0.818132057

00:32:09.660 --> 00:32:11.496 And so the model we would put forward would

NOTE Confidence: 0.818132057

00:32:11.496 --> 00:32:13.354 be that with advancing disease stage we

NOTE Confidence: 0.818132057

00:32:13.354 --> 00:32:15.180 have this progressive T cell exhaustion,

NOTE Confidence: 0.818132057

00:32:15.180 --> 00:32:17.595 this switch to more M2 like this

NOTE Confidence: 0.818132057

00:32:17.595 --> 00:32:18.285 anti-inflammatory macrophage

NOTE Confidence: 0.818132057

00:32:18.285 --> 00:32:19.946 population and that critically in

NOTE Confidence: 0.818132057

00:32:19.946 --> 00:32:21.526 advanced disease states that they're

NOTE Confidence: 0.818132057

00:32:21.526 --> 00:32:22.997 really talking to one another,

NOTE Confidence: 0.818132057

00:32:23.000 --> 00:32:24.150 they're interacting in a way

NOTE Confidence: 0.818132057

00:32:24.150 --> 00:32:25.300 that we hope is therapeutically.

NOTE Confidence: 0.818132057

00:32:25.300 --> 00:32:27.400 Marketable.

NOTE Confidence: 0.818132057

00:32:27.400 --> 00:32:30.168 So up until now I've talked broadly about

NOTE Confidence: 0.818132057

00:32:30.168 --> 00:32:32.317 kidney cancer as if it's one entity,

NOTE Confidence: 0.818132057

00:32:32.320 --> 00:32:34.497 but I've been sort of misleading you.

NOTE Confidence: 0.818132057

00:32:34.500 --> 00:32:35.343 It's actually many,

NOTE Confidence: 0.818132057

00:32:35.343 --> 00:32:36.186 many different diseases.

NOTE Confidence: 0.818132057

00:32:36.190 --> 00:32:38.342 And So what we've been talking about is

NOTE Confidence: 0.818132057

00:32:38.342 --> 00:32:40.212 really clear cell kidney cancer which

NOTE Confidence: 0.818132057

00:32:40.212 --> 00:32:42.132 is shown here histologically which is

NOTE Confidence: 0.801564899

00:32:42.140 --> 00:32:43.420 looks clear under the microscope

NOTE Confidence: 0.801564899

00:32:43.420 --> 00:32:44.700 where it gets its name.

NOTE Confidence: 0.801564899

00:32:44.700 --> 00:32:47.238 But actually this is a host of over 20

NOTE Confidence: 0.801564899

00:32:47.238 --> 00:32:49.044 different disease with more entities

NOTE Confidence: 0.801564899

00:32:49.044 --> 00:32:50.869 being described each WHO update

NOTE Confidence: 0.801564899

00:32:50.869 --> 00:32:52.998 and there's a huge proportion of,

NOTE Confidence: 0.801564899

00:32:53.000 --> 00:32:54.630 I apologize, should be about

NOTE Confidence: 0.801564899

00:32:54.630 --> 00:32:56.688 25% non clear cell which is.

NOTE Confidence: 0.801564899

00:32:56.690 --> 00:32:58.010 So it was bad to be labeled by

NOTE Confidence: 0.801564899

00:32:58.010 --> 00:32:59.566 what you're not, but these are

NOTE Confidence: 0.801564899

00:32:59.566 --> 00:33:01.276 variant histologies of clear cell.

NOTE Confidence: 0.801564899

00:33:01.280 --> 00:33:03.824 The more common ones are papillary

NOTE Confidence: 0.801564899

00:33:03.824 --> 00:33:05.720 chromophobe accounts for about 5%

NOTE Confidence: 0.801564899

00:33:05.720 --> 00:33:07.580 rarer types including translocation

NOTE Confidence: 0.801564899

00:33:07.580 --> 00:33:09.905 and then hereditary forms including

NOTE Confidence: 0.801564899

00:33:09.905 --> 00:33:11.830 FH deficient really aggressive

NOTE Confidence: 0.801564899

00:33:11.830 --> 00:33:13.905 disease biology that often affects

NOTE Confidence: 0.801564899

00:33:13.905 --> 00:33:15.460 people in their 30s.

NOTE Confidence: 0.801564899

00:33:15.460 --> 00:33:17.100 And so while all of our efforts has

NOTE Confidence: 0.801564899

00:33:17.100 --> 00:33:18.879 been have been really focused on clear

NOTE Confidence: 0.801564899

00:33:18.879 --> 00:33:20.652 cell kidney cancer and that's where a

NOTE Confidence: 0.801564899

00:33:20.652 --> 00:33:22.252 lot of the clinical data is as well.

NOTE Confidence: 0.801564899

00:33:22.260 --> 00:33:24.549 We know that these non clear solver

NOTE Confidence: 0.801564899

00:33:24.549 --> 00:33:25.981 variants really aren't unmet

NOTE Confidence: 0.801564899

00:33:25.981 --> 00:33:27.557 clinical and scientific need.

NOTE Confidence: 0.801564899

00:33:27.560 --> 00:33:29.177 We really need to understand their biology.

NOTE Confidence: 0.801564899

00:33:29.180 --> 00:33:31.132 And how to treat them because most of

NOTE Confidence: 0.801564899

00:33:31.132 --> 00:33:32.539 their treatment is really extrapolated

NOTE Confidence: 0.801564899

00:33:32.539 --> 00:33:34.285 from our experience in clear cell.

NOTE Confidence: 0.801564899

00:33:34.290 --> 00:33:36.258 And so our first sort of approach to

NOTE Confidence: 0.801564899

00:33:36.258 --> 00:33:38.610 this is really in the chromophobe space.

NOTE Confidence: 0.801564899

00:33:38.610 --> 00:33:40.368 And so chromophobe is really are

NOTE Confidence: 0.801564899

00:33:40.368 --> 00:33:42.377 along a spectrum of these renal

NOTE Confidence: 0.801564899

00:33:42.377 --> 00:33:43.933 oncocytic neoplasms that range

NOTE Confidence: 0.801564899

00:33:43.933 --> 00:33:45.489 from pretty benign tumors,

NOTE Confidence: 0.801564899

00:33:45.490 --> 00:33:48.970 renal oncocytoma which never metastasize,

NOTE Confidence: 0.801564899

00:33:48.970 --> 00:33:51.325 I should say never virtually

NOTE Confidence: 0.801564899

00:33:51.325 --> 00:33:52.267 never metastasize.

NOTE Confidence: 0.801564899

00:33:52.270 --> 00:33:54.554 They really have limited

NOTE Confidence: 0.801564899

00:33:54.554 --> 00:33:56.267 genetic genomic alterations.

NOTE Confidence: 0.801564899

00:33:56.270 --> 00:33:58.492 Chromophobe is on the other end, are they?

NOTE Confidence: 0.801564899

00:33:58.492 --> 00:34:00.397 They are true malignant disease.

NOTE Confidence: 0.801564899

00:34:00.400 --> 00:34:02.130 They have multiple whole chromosome

NOTE Confidence: 0.801564899

00:34:02.130 --> 00:34:04.272 losses and then there's also these

NOTE Confidence: 0.801564899

00:34:04.272 --> 00:34:06.032 emerging entities in between low

NOTE Confidence: 0.801564899

00:34:06.032 --> 00:34:07.907 and high grade unconscious tumors

NOTE Confidence: 0.801564899

00:34:07.907 --> 00:34:10.242 which have variable potential to

NOTE Confidence: 0.801564899

00:34:10.242 --> 00:34:13.338 actually invade and metastasize.

NOTE Confidence: 0.801564899

00:34:13.340 --> 00:34:15.405 And so one of the key things

NOTE Confidence: 0.801564899

00:34:15.405 --> 00:34:17.035 about these chromophobe tumors is

NOTE Confidence: 0.801564899

00:34:17.035 --> 00:34:18.740 unlike clear cell kidney cancer,

NOTE Confidence: 0.801564899

00:34:18.740 --> 00:34:20.609 these don't do well with immune therapy.

NOTE Confidence: 0.801564899

00:34:20.610 --> 00:34:23.234 And so there's always going to be exceptions.

NOTE Confidence: 0.801564899

00:34:23.240 --> 00:34:25.305 But both in in clinical trial data

NOTE Confidence: 0.801564899

00:34:25.305 --> 00:34:27.213 of immune therapies where they've

NOTE Confidence: 0.801564899

00:34:27.213 --> 00:34:28.656 included chromophore patients,

NOTE Confidence: 0.801564899

00:34:28.660 --> 00:34:31.060 the response rate is typically less than 10%.

NOTE Confidence: 0.801564899

00:34:31.060 --> 00:34:33.420 And if we look at these chromophobe tumors,

NOTE Confidence: 0.801564899

00:34:33.420 --> 00:34:36.388 this is our own data partnership with the

NOTE Confidence: 0.801564899

00:34:36.388 --> 00:34:38.320 international Metastatic Database consortium,

NOTE Confidence: 0.801564899

00:34:38.320 --> 00:34:39.655 Danny hangs group at University

NOTE Confidence: 0.801564899

00:34:39.655 --> 00:34:41.679 of Alberta and we looked at now

NOTE Confidence: 0.801564899

00:34:41.679 --> 00:34:42.955 hundreds of patients treated

NOTE Confidence: 0.801564899

00:34:42.955 --> 00:34:44.231 with new checkpoint inhibitors.

NOTE Confidence: 0.801564899

00:34:44.240 --> 00:34:46.096 Real world data that are the clear cell

NOTE Confidence: 0.801564899

00:34:46.096 --> 00:34:48.220 or non or chromophobe and the chromophobe

NOTE Confidence: 0.801564899

00:34:48.220 --> 00:34:50.140 patients really don't do well here.

NOTE Confidence: 0.801564899

00:34:50.140 --> 00:34:53.526 This is in sharp contrast to in other

NOTE Confidence: 0.801564899

00:34:53.526 --> 00:34:55.038 treatment varieties chromophores typically

NOTE Confidence: 0.801564899

00:34:55.038 --> 00:34:57.342 shape a better disease prognosis and so

NOTE Confidence: 0.801564899

00:34:57.342 --> 00:34:59.370 really this is an area of unmet need.

NOTE Confidence: 0.801564899

00:34:59.370 --> 00:35:01.130 Why aren't chromophobe tumors

NOTE Confidence: 0.801564899

00:35:01.130 --> 00:35:02.890 responding to immune therapy.

NOTE Confidence: 0.801564899

00:35:02.890 --> 00:35:05.032 And so to begin to look at this and

NOTE Confidence: 0.801564899

00:35:05.032 --> 00:35:07.159 again these are rare tumor types we we

NOTE Confidence: 0.801564899

00:35:07.159 --> 00:35:09.807 were able to identify a handful of patients,

NOTE Confidence: 0.801564899

00:35:09.810 --> 00:35:11.570 about five patients that really

NOTE Confidence: 0.801564899

00:35:11.570 --> 00:35:12.978 represent this disease spectrum

NOTE Confidence: 0.801564899

00:35:12.978 --> 00:35:14.748 and again perform single cell.

NOTE Confidence: 0.801564899

00:35:14.750 --> 00:35:16.766 Kinda sequencing to look at the

NOTE Confidence: 0.801564899

00:35:16.766 --> 00:35:18.473 immune microenvironment and also the

NOTE Confidence: 0.801564899

00:35:18.473 --> 00:35:20.315 tumor and stromal components as well.

NOTE Confidence: 0.801564899

00:35:20.320 --> 00:35:21.720 And really our focus questions

NOTE Confidence: 0.801564899

00:35:21.720 --> 00:35:23.120 were why aren't these responding

NOTE Confidence: 0.801564899

00:35:23.170 --> 00:35:24.640 to immune therapies and going in.

NOTE Confidence: 0.801564899

00:35:24.640 --> 00:35:26.500 We had a couple of hypotheses.

NOTE Confidence: 0.801564899

00:35:26.500 --> 00:35:28.540 So one is maybe it's just a lack

NOTE Confidence: 0.801564899

00:35:28.540 --> 00:35:29.050 of immune

NOTE Confidence: 0.81162321

00:35:29.111 --> 00:35:30.518 infiltration. If you don't

NOTE Confidence: 0.81162321

00:35:30.518 --> 00:35:31.754 have cells there to begin with,

NOTE Confidence: 0.81162321

00:35:31.760 --> 00:35:34.448 then it's hard to get any immune response.

NOTE Confidence: 0.81162321

00:35:34.450 --> 00:35:36.664 The second is perhaps they're exhausted

NOTE Confidence: 0.81162321

00:35:36.664 --> 00:35:38.968 in ways that don't rely on PD1.

NOTE Confidence: 0.81162321

00:35:38.970 --> 00:35:41.274 So perhaps these have some severely

NOTE Confidence: 0.81162321

00:35:41.274 --> 00:35:43.516 exhausted or dysfunctional program that are

NOTE Confidence: 0.81162321

00:35:43.516 --> 00:35:45.326 really incapable of being reinvigorated

NOTE Confidence: 0.81162321

00:35:45.326 --> 00:35:47.549 by our current immune therapies.

NOTE Confidence: 0.81162321

00:35:47.550 --> 00:35:49.638 And the last possibility is maybe

NOTE Confidence: 0.81162321

00:35:49.638 --> 00:35:51.858 those are just bystander T cells

NOTE Confidence: 0.81162321

00:35:51.858 --> 00:35:53.778 where they're not actually infiltrated

NOTE Confidence: 0.81162321

00:35:53.778 --> 00:35:56.310 by tumor specific T cells that are

NOTE Confidence: 0.81162321

00:35:56.310 --> 00:35:58.290 required for true anti tumor efficacy.

NOTE Confidence: 0.81162321

00:35:58.290 --> 00:36:00.145 And so with these sort of focused

NOTE Confidence: 0.81162321

00:36:00.145 --> 00:36:01.814 hypotheses we can begin to look

NOTE Confidence: 0.81162321

00:36:01.814 --> 00:36:03.440 at these different areas and see

NOTE Confidence: 0.81162321

00:36:03.440 --> 00:36:04.857 which of them actually are.

NOTE Confidence: 0.81162321

00:36:04.860 --> 00:36:06.228 Able to chromophobe tumors.

NOTE Confidence: 0.81162321

00:36:06.228 --> 00:36:08.280 So the first is immuno filtration.

NOTE Confidence: 0.81162321

00:36:08.280 --> 00:36:10.716 Here we did very basic CD 45

NOTE Confidence: 0.81162321

00:36:10.716 --> 00:36:11.760 immunohistochemistry just to

NOTE Confidence: 0.81162321

00:36:11.824 --> 00:36:13.779 look at the immune infiltration,

NOTE Confidence: 0.81162321

00:36:13.780 --> 00:36:15.500 broad immune infiltration of these

NOTE Confidence: 0.81162321

00:36:15.500 --> 00:36:18.045 tumors and what we can see is on

NOTE Confidence: 0.81162321

00:36:18.045 --> 00:36:20.383 the right you see clear cell and the

NOTE Confidence: 0.81162321

00:36:20.383 --> 00:36:22.193 immunohistochemical stain for CD45.

NOTE Confidence: 0.81162321

00:36:22.193 --> 00:36:23.758 These are really heavily immune

NOTE Confidence: 0.81162321

00:36:23.758 --> 00:36:24.697 infiltrated T cells,

NOTE Confidence: 0.81162321

00:36:24.700 --> 00:36:26.450 immune infiltrated tumors as we

NOTE Confidence: 0.81162321

00:36:26.450 --> 00:36:28.200 saw in our previous study.

NOTE Confidence: 0.81162321

00:36:28.200 --> 00:36:30.500 By contrast these oncocytic neoplasms,

NOTE Confidence: 0.81162321

00:36:30.500 --> 00:36:32.600 oncocytoma is low grade oncocytic tumors,

NOTE Confidence: 0.81162321

00:36:32.600 --> 00:36:33.394 chromophobe tumors,

NOTE Confidence: 0.81162321

00:36:33.394 --> 00:36:36.173 these have really low degree of immunity.

NOTE Confidence: 0.81162321

00:36:36.180 --> 00:36:39.044 Centration and we can see that sort of

NOTE Confidence: 0.81162321

00:36:39.050 --> 00:36:41.150 characterized statistically on the right.

NOTE Confidence: 0.81162321

00:36:41.150 --> 00:36:42.886 And so that seems to be one problem.

NOTE Confidence: 0.81162321

00:36:42.890 --> 00:36:44.466 They just aren't a lot of immune cells.

NOTE Confidence: 0.81162321

00:36:44.470 --> 00:36:46.270 So we're going to improve immune

NOTE Confidence: 0.81162321

00:36:46.270 --> 00:36:47.470 responsiveness of these tumors.

NOTE Confidence: 0.81162321

00:36:47.470 --> 00:36:49.118 One will be driving,

NOTE Confidence: 0.81162321

00:36:49.118 --> 00:36:50.766 driving immune cells actually

NOTE Confidence: 0.81162321

00:36:50.766 --> 00:36:52.570 into the tumor itself.

NOTE Confidence: 0.81162321

00:36:52.570 --> 00:36:53.452 The second is,

NOTE Confidence: 0.81162321

00:36:53.452 --> 00:36:55.510 are these are these cells that are

NOTE Confidence: 0.81162321

00:36:55.570 --> 00:36:57.730 there just too exhausted to respond.

NOTE Confidence: 0.81162321

00:36:57.730 --> 00:36:59.626 And to begin to look at this weekend,

NOTE Confidence: 0.81162321

00:36:59.630 --> 00:36:59.861 look,

NOTE Confidence: 0.81162321

00:36:59.861 --> 00:37:01.709 turn to our single cell data and look

NOTE Confidence: 0.81162321

00:37:01.709 --> 00:37:03.819 to the CDA T cell populations and saw

NOTE Confidence: 0.81162321

00:37:03.819 --> 00:37:05.526 that they express markers of immune

NOTE Confidence: 0.81162321

00:37:05.526 --> 00:37:07.266 exhaustion and the transfer is no,

NOTE Confidence: 0.81162321

00:37:07.270 --> 00:37:08.686 those were not exhausted T cells.

NOTE Confidence: 0.81162321

00:37:08.690 --> 00:37:10.490 So if we look at clear cell which on the

NOTE Confidence: 0.81162321

00:37:10.540 --> 00:37:12.208 left versus chromophobe on the right,

NOTE Confidence: 0.81162321

00:37:12.210 --> 00:37:14.320 we see as we know the the ones in the

NOTE Confidence: 0.81162321

00:37:14.383 --> 00:37:16.747 clear cell tumors are often exhausted

NOTE Confidence: 0.81162321

00:37:16.747 --> 00:37:18.323 terminally exhausted CDT cells.

NOTE Confidence: 0.81162321

00:37:18.330 --> 00:37:20.192 That was not the case for chromophobe

NOTE Confidence: 0.81162321

00:37:20.192 --> 00:37:22.340 tumors and if we look now at the TCGA.

NOTE Confidence: 0.81162321

00:37:22.340 --> 00:37:22.690 Data,

NOTE Confidence: 0.81162321

00:37:22.690 --> 00:37:25.140 we see a very similar pattern that

NOTE Confidence: 0.81162321

00:37:25.140 --> 00:37:26.825 chromophobe tumors have relatively

NOTE Confidence: 0.81162321

00:37:26.825 --> 00:37:28.940 low levels of exhaustion markers,

NOTE Confidence: 0.81162321

00:37:28.940 --> 00:37:30.184 expression of exhaustion markers

NOTE Confidence: 0.81162321

00:37:30.184 --> 00:37:32.050 that's compared to clear cell disease.

NOTE Confidence: 0.81162321

00:37:32.050 --> 00:37:34.666 And so these are not exhausted T cells.

NOTE Confidence: 0.81162321

00:37:34.670 --> 00:37:36.278 They seem actually like they're cytotoxic.

NOTE Confidence: 0.81162321

00:37:36.280 --> 00:37:37.588 They they seem like they should

NOTE Confidence: 0.81162321

00:37:37.588 --> 00:37:38.024 be functional.

NOTE Confidence: 0.81162321

00:37:38.030 --> 00:37:39.140 The ones that are there,

NOTE Confidence: 0.81162321

00:37:39.140 --> 00:37:40.960 why aren't they actually doing the job.

NOTE Confidence: 0.81162321

00:37:40.960 --> 00:37:42.997 The last part is maybe they're not

NOTE Confidence: 0.81162321

00:37:42.997 --> 00:37:44.825 tumor specific and so there's ways

NOTE Confidence: 0.81162321

00:37:44.825 --> 00:37:46.607 to formally prove this by actually

NOTE Confidence: 0.81162321

00:37:46.607 --> 00:37:47.900 TCR sequencing these,

NOTE Confidence: 0.81162321

00:37:47.900 --> 00:37:49.735 reconstructing those TCR's and and

NOTE Confidence: 0.81162321

00:37:49.735 --> 00:37:51.203 testing for antitumor specificity.

NOTE Confidence: 0.81162321

00:37:51.210 --> 00:37:53.114 That's what needs to ultimately be done.

NOTE Confidence: 0.81162321

00:37:53.120 --> 00:37:54.928 Our first take out is is to use

NOTE Confidence: 0.81162321

00:37:54.928 --> 00:37:56.567 the single cell TCR data that we

NOTE Confidence: 0.81162321

00:37:56.567 --> 00:37:58.328 have to try to infer specifics and

NOTE Confidence: 0.81162321

00:37:58.328 --> 00:38:00.337 we did this in two different ways.

NOTE Confidence: 0.81162321

00:38:00.340 --> 00:38:03.236 One is by taking those TCR's and

NOTE Confidence: 0.81162321

00:38:03.236 --> 00:38:05.664 mapping them to known to TCR's.

NOTE Confidence: 0.81162321

00:38:05.664 --> 00:38:07.200 I've known viral specificity.

NOTE Confidence: 0.66308334

00:38:07.200 --> 00:38:09.115 Those are usually specific for

NOTE Confidence: 0.66308334

00:38:09.115 --> 00:38:11.620 things like CMB or EB or flu,

NOTE Confidence: 0.66308334

00:38:11.620 --> 00:38:12.668 common viruses that have

NOTE Confidence: 0.66308334

00:38:12.668 --> 00:38:14.240 nothing to do with these tumors.

NOTE Confidence: 0.66308334

00:38:14.240 --> 00:38:16.328 And we can see that the the T cells

NOTE Confidence: 0.66308334

00:38:16.328 --> 00:38:17.823 and chromophobe kidney cancer

NOTE Confidence: 0.66308334

00:38:17.823 --> 00:38:20.217 mapped out a much more significant

NOTE Confidence: 0.66308334

00:38:20.217 --> 00:38:22.124 degree to these viral specific.

NOTE Confidence: 0.66308334

00:38:22.124 --> 00:38:25.498 They have a viral specificity so much

NOTE Confidence: 0.66308334

00:38:25.498 --> 00:38:28.638 more likely to be bystander T cells.

NOTE Confidence: 0.66308334

00:38:28.640 --> 00:38:30.140 The other approach we used

NOTE Confidence: 0.66308334

00:38:30.140 --> 00:38:31.340 was to take signatures,

NOTE Confidence: 0.66308334

00:38:31.340 --> 00:38:33.060 gene expression signatures defined by

NOTE Confidence: 0.66308334

00:38:33.060 --> 00:38:35.379 both Kathy who's group but also Steve

NOTE Confidence: 0.66308334

00:38:35.380 --> 00:38:37.414 Rosenberg's group at the NCI that

NOTE Confidence: 0.66308334

00:38:37.414 --> 00:38:39.299 are signatures of tumor specificity

NOTE Confidence: 0.66308334

00:38:39.299 --> 00:38:40.706 including neoantigen specificity

NOTE Confidence: 0.66308334

00:38:40.706 --> 00:38:43.520 and see what that expression looks

NOTE Confidence: 0.66308334

00:38:43.589 --> 00:38:45.725 like in these different tumor types.

NOTE Confidence: 0.66308334

00:38:45.730 --> 00:38:47.938 And we can see for clear cell kidney

NOTE Confidence: 0.66308334

00:38:47.938 --> 00:38:50.184 cancer in red that those have a

NOTE Confidence: 0.66308334

00:38:50.184 --> 00:38:51.809 high degree of tumor specificity

NOTE Confidence: 0.66308334

00:38:51.869 --> 00:38:53.793 signature and for chromophobe

NOTE Confidence: 0.66308334

00:38:53.793 --> 00:38:55.236 that's substantially less.

NOTE Confidence: 0.66308334

00:38:55.240 --> 00:38:57.109 And so overall this is our first

NOTE Confidence: 0.66308334

00:38:57.109 --> 00:38:58.530 sort of attempt to really.

NOTE Confidence: 0.66308334

00:38:58.530 --> 00:39:00.000 Characterize what is an uncommon

NOTE Confidence: 0.66308334

00:39:00.000 --> 00:39:02.199 and rare tumor type and really try

NOTE Confidence: 0.66308334

00:39:02.199 --> 00:39:03.884 to understand it's immune biology.

NOTE Confidence: 0.66308334

00:39:03.890 --> 00:39:05.730 It looks like it has a lack of

NOTE Confidence: 0.66308334

00:39:05.730 --> 00:39:06.190 immune infiltration.

NOTE Confidence: 0.66308334

00:39:06.190 --> 00:39:08.510 It looks like the T cells that are

NOTE Confidence: 0.66308334

00:39:08.510 --> 00:39:10.540 there are probably fully functional

NOTE Confidence: 0.66308334

00:39:10.540 --> 00:39:12.845 but lack of tumor specificity.

NOTE Confidence: 0.66308334

00:39:12.850 --> 00:39:14.584 So that's the work we've we've

NOTE Confidence: 0.66308334

00:39:14.584 --> 00:39:16.317 largely done the work that was

NOTE Confidence: 0.66308334

00:39:16.317 --> 00:39:17.883 published last year and the work

NOTE Confidence: 0.66308334

00:39:17.883 --> 00:39:19.516 on on chromophobe tumors that's

NOTE Confidence: 0.66308334

00:39:19.516 --> 00:39:21.622 been really over the past year.

NOTE Confidence: 0.66308334

00:39:21.630 --> 00:39:23.174 But now what we want to do is

NOTE Confidence: 0.66308334

00:39:23.174 --> 00:39:24.340 move from just characterizing

NOTE Confidence: 0.66308334

00:39:24.340 --> 00:39:26.150 the disease biology to really

NOTE Confidence: 0.66308334

00:39:26.150 --> 00:39:27.691 understanding how these different

NOTE Confidence: 0.66308334

00:39:27.691 --> 00:39:29.299 tumor microenvironments might impact

NOTE Confidence: 0.66308334

00:39:29.299 --> 00:39:31.309 response or resistance if therapy.

NOTE Confidence: 0.66308334

00:39:31.310 --> 00:39:33.050 And ultimately how can we

NOTE Confidence: 0.66308334

00:39:33.050 --> 00:39:34.094 functionally evaluate these,

NOTE Confidence: 0.66308334

00:39:34.100 --> 00:39:35.591 how can we actually go from a

NOTE Confidence: 0.66308334

00:39:35.591 --> 00:39:36.874 laundry list of potential sell

NOTE Confidence: 0.66308334

00:39:36.874 --> 00:39:38.364 sell interactions to ones that

NOTE Confidence: 0.66308334

00:39:38.364 --> 00:39:39.625 actually might be therapeutically

NOTE Confidence: 0.66308334

00:39:39.625 --> 00:39:41.210 targetable in the clinic and

NOTE Confidence: 0.66308334

00:39:41.210 --> 00:39:43.130 that's really what the focus is.

NOTE Confidence: 0.66308334

00:39:43.130 --> 00:39:44.430 We've started this process,

NOTE Confidence: 0.66308334

00:39:44.430 --> 00:39:46.180 but over the next year.

NOTE Confidence: 0.66308334

00:39:46.180 --> 00:39:47.812 The sort of idea behind this

NOTE Confidence: 0.66308334

00:39:47.812 --> 00:39:48.900 is is shown here.

NOTE Confidence: 0.66308334

00:39:48.900 --> 00:39:50.769 This is a perspective we publish a

NOTE Confidence: 0.66308334

00:39:50.769 --> 00:39:52.667 couple of years ago now which is

NOTE Confidence: 0.66308334

00:39:52.667 --> 00:39:54.233 to really try to integrate these

NOTE Confidence: 0.66308334

00:39:54.240 --> 00:39:55.845 tumor biopsies for fresh tissue

NOTE Confidence: 0.66308334

00:39:55.845 --> 00:39:57.450 collection for single cell and

NOTE Confidence: 0.66308334

00:39:57.503 --> 00:39:59.159 sequencing into clinical trials.

NOTE Confidence: 0.66308334

00:39:59.160 --> 00:40:01.060 And obviously this is expensive,

NOTE Confidence: 0.66308334

00:40:01.060 --> 00:40:03.400 this is technically difficult

NOTE Confidence: 0.66308334

00:40:03.400 --> 00:40:05.155 this feasibility issues.

NOTE Confidence: 0.66308334

00:40:05.160 --> 00:40:06.448 But if you could do this even

NOTE Confidence: 0.66308334

00:40:06.448 --> 00:40:07.560 for a handful of patients,

NOTE Confidence: 0.66308334

00:40:07.560 --> 00:40:09.128 a small discovery cohort and really go

NOTE Confidence: 0.66308334

00:40:09.128 --> 00:40:10.996 into a lot of depth for small number

NOTE Confidence: 0.66308334

00:40:10.996 --> 00:40:12.418 of patients then you can actually

NOTE Confidence: 0.66308334

00:40:12.418 --> 00:40:14.021 learn some lessons like we did in

NOTE Confidence: 0.66308334

00:40:14.021 --> 00:40:16.520 our our prior work and try to then use more.

NOTE Confidence: 0.66308334

00:40:16.520 --> 00:40:17.716 Conventional tools,

NOTE Confidence: 0.66308334

00:40:17.716 --> 00:40:19.510 standard exome sequencing,

NOTE Confidence: 0.66308334

00:40:19.510 --> 00:40:20.706 RNA sequencing,

NOTE Confidence: 0.66308334

00:40:20.706 --> 00:40:21.304 immunofluorescence,

NOTE Confidence: 0.66308334

00:40:21.304 --> 00:40:22.500 amnestic chemistry,

NOTE Confidence: 0.66308334

00:40:22.500 --> 00:40:26.148 then try to apply that to a larger

NOTE Confidence: 0.66308334

00:40:26.148 --> 00:40:27.060 validation cohort.

NOTE Confidence: 0.66308334

00:40:27.060 --> 00:40:29.538 And so this is our our attempt,

NOTE Confidence: 0.66308334

00:40:29.540 --> 00:40:31.116 this is our basic schema that we try

NOTE Confidence: 0.66308334

00:40:31.116 --> 00:40:32.725 to take patients who are responsive

NOTE Confidence: 0.66308334

00:40:32.725 --> 00:40:34.471 and non responsive to immune therapy.

NOTE Confidence: 0.66308334

00:40:34.480 --> 00:40:36.181 We try to get biopsies before treatment

NOTE Confidence: 0.66308334

00:40:36.181 --> 00:40:38.417 as much as possible is often challenging.

NOTE Confidence: 0.66308334

00:40:38.420 --> 00:40:41.062 We try to get biopsies on treatment

NOTE Confidence: 0.66308334

00:40:41.062 --> 00:40:42.817 or at least that progression,

NOTE Confidence: 0.66308334

00:40:42.820 --> 00:40:45.540 very variable success on that.

NOTE Confidence: 0.66308334

00:40:45.540 --> 00:40:47.076 And then to perform single song

NOTE Confidence: 0.66308334

00:40:47.076 --> 00:40:48.432 RNA sequencing to really uncover

NOTE Confidence: 0.66308334

00:40:48.432 --> 00:40:50.118 what are the cell type differences,

NOTE Confidence: 0.801096541111111

00:40:50.120 --> 00:40:51.359 cellular composition differences,

NOTE Confidence: 0.801096541111111

00:40:51.359 --> 00:40:53.011 phenotypic differences and ultimately

NOTE Confidence: 0.801096541111111

00:40:53.011 --> 00:40:55.249 what are the differences in cell

NOTE Confidence: 0.801096541111111

00:40:55.249 --> 00:40:56.819 cell interactions and so we've.

NOTE Confidence: 0.801096541111111

00:40:56.820 --> 00:40:57.832 Uh Bin lucky again.

NOTE Confidence: 0.801096541111111

00:40:57.832 --> 00:40:59.350 This is through partnership with a

NOTE Confidence: 0.801096541111111

00:40:59.401 --> 00:41:00.949 number of academic collaborators,

NOTE Confidence: 0.801096541111111

00:41:00.950 --> 00:41:02.198 but also industry collaborators

NOTE Confidence: 0.801096541111111

00:41:02.198 --> 00:41:04.379 preparing to a number of phase two

NOTE Confidence: 0.801096541111111

00:41:04.379 --> 00:41:05.891 and phase three trials that we've

NOTE Confidence: 0.801096541111111

00:41:05.891 --> 00:41:07.469 been able to collect fresh tissue

NOTE Confidence: 0.801096541111111

00:41:07.469 --> 00:41:09.268 from a total of 96 tumors that

NOTE Confidence: 0.801096541111111

00:41:09.270 --> 00:41:11.070 were treated with immune therapy.

NOTE Confidence: 0.801096541111111

00:41:11.070 --> 00:41:12.554 And we've performed enzymatic

NOTE Confidence: 0.801096541111111

00:41:12.554 --> 00:41:14.409 association single cell RNA sequencing

NOTE Confidence: 0.801096541111111

00:41:14.409 --> 00:41:16.530 on these on these tumors really to

NOTE Confidence: 0.801096541111111

00:41:16.530 --> 00:41:18.129 understand what is the difference

NOTE Confidence: 0.801096541111111

00:41:18.129 --> 00:41:20.194 in the immune landscape between

NOTE Confidence: 0.801096541111111

00:41:20.194 --> 00:41:21.846 responsive and nonresponsive tumors.

NOTE Confidence: 0.801096541111111

00:41:21.850 --> 00:41:23.614 And we've put through a partnership

NOTE Confidence: 0.801096541111111

00:41:23.614 --> 00:41:25.372 with AKOYA began to look at

NOTE Confidence: 0.801096541111111

00:41:25.372 --> 00:41:26.938 what is the orientation of the.

NOTE Confidence: 0.801096541111111

00:41:26.940 --> 00:41:29.306 The physical location of these tumor types,

NOTE Confidence: 0.801096541111111

00:41:29.310 --> 00:41:31.338 these different immune populations in space

NOTE Confidence: 0.801096541111111

00:41:31.338 --> 00:41:33.210 using these high dimensional platforms.

NOTE Confidence: 0.801096541111111

00:41:33.210 --> 00:41:35.226 This is an example of of one of

NOTE Confidence: 0.801096541111111

00:41:35.226 --> 00:41:36.927 our tumors from a responsive

NOTE Confidence: 0.801096541111111

00:41:36.927 --> 00:41:38.807 patient showing actually a high,

NOTE Confidence: 0.801096541111111

00:41:38.810 --> 00:41:40.954 high number of traditional

NOTE Confidence: 0.801096541111111

00:41:40.954 --> 00:41:42.026 lymphoid structures.

NOTE Confidence: 0.801096541111111

00:41:42.030 --> 00:41:43.590 And so is this actually feasible,

NOTE Confidence: 0.801096541111111

00:41:43.590 --> 00:41:45.462 are we actually able to collect

NOTE Confidence: 0.801096541111111

00:41:45.462 --> 00:41:46.398 these cryopreserved specimens

NOTE Confidence: 0.801096541111111

00:41:46.398 --> 00:41:47.596 from different clinical trials

NOTE Confidence: 0.801096541111111

00:41:47.596 --> 00:41:49.549 and get viable cells out of this?

NOTE Confidence: 0.801096541111111

00:41:49.550 --> 00:41:51.370 So our first attempt at this was

NOTE Confidence: 0.801096541111111

00:41:51.370 --> 00:41:53.185 on a small number of patients

NOTE Confidence: 0.801096541111111

00:41:53.185 --> 00:41:54.810 was just on 13 patients.

NOTE Confidence: 0.801096541111111

00:41:54.810 --> 00:41:57.018 This is a collaboration with with

NOTE Confidence: 0.801096541111111

00:41:57.018 --> 00:41:59.084 Kathy still with MM Atkins at

NOTE Confidence: 0.801096541111111

00:41:59.084 --> 00:42:00.992 Georgetown and with Kelly St who

NOTE Confidence: 0.801096541111111

00:42:00.992 --> 00:42:02.995 runs a computational group at USC

NOTE Confidence: 0.801096541111111

00:42:02.995 --> 00:42:05.519 where we looked at the small number

NOTE Confidence: 0.801096541111111

00:42:05.519 --> 00:42:07.609 of cryopreserved tumors and said,

NOTE Confidence: 0.801096541111111

00:42:07.610 --> 00:42:09.970 are we able to get viable cells out of this?

NOTE Confidence: 0.801096541111111

00:42:09.970 --> 00:42:11.596 And the short answer was yes,

NOTE Confidence: 0.801096541111111

00:42:11.600 --> 00:42:13.264 that we're able to get actually really good.

NOTE Confidence: 0.801096541111111

00:42:13.270 --> 00:42:15.470 Representation of both tumor cells,

NOTE Confidence: 0.801096541111111

00:42:15.470 --> 00:42:17.690 immune cells and also stromal components

NOTE Confidence: 0.801096541111111

00:42:17.690 --> 00:42:19.799 and actually even with this small

NOTE Confidence: 0.801096541111111

00:42:19.799 --> 00:42:22.055 cord of end up being about 13 samples

NOTE Confidence: 0.801096541111111

00:42:22.118 --> 00:42:23.998 that were suitable for analysis.

NOTE Confidence: 0.801096541111111

00:42:24.000 --> 00:42:25.236 After passing quality control,

NOTE Confidence: 0.801096541111111

00:42:25.236 --> 00:42:27.979 we can actually begin to see are the

NOTE Confidence: 0.801096541111111

00:42:27.979 --> 00:42:29.635 differences in immune microenvironment

NOTE Confidence: 0.801096541111111

00:42:29.635 --> 00:42:31.720 between responsive and resistant tumors.

NOTE Confidence: 0.801096541111111

00:42:31.720 --> 00:42:33.556 And so again this is a

NOTE Confidence: 0.801096541111111

00:42:33.556 --> 00:42:34.474 trajectory inference analysis,

NOTE Confidence: 0.801096541111111

00:42:34.480 --> 00:42:35.800 this time it's for T cells.

NOTE Confidence: 0.801096541111111

00:42:35.800 --> 00:42:37.655 And again we see a branching structure,

NOTE Confidence: 0.801096541111111

00:42:37.660 --> 00:42:39.598 but here are fairly interesting one,

NOTE Confidence: 0.801096541111111

00:42:39.600 --> 00:42:41.648 one that starts with a root of naive

NOTE Confidence: 0.801096541111111

00:42:41.648 --> 00:42:43.964 T cells and branches either into

NOTE Confidence: 0.801096541111111

00:42:43.964 --> 00:42:45.384 terminally exhausted CD8T cells.

NOTE Confidence: 0.801096541111111

00:42:45.384 --> 00:42:47.560 Those are the same ones we saw in

NOTE Confidence: 0.801096541111111

00:42:47.623 --> 00:42:49.507 our our prior work across disease

NOTE Confidence: 0.801096541111111

00:42:49.507 --> 00:42:51.591 stages or to these still having

NOTE Confidence: 0.801096541111111

00:42:51.591 --> 00:42:53.496 an exhaustion phenotype but these

NOTE Confidence: 0.801096541111111

00:42:53.496 --> 00:42:56.630 slam F7 positive CD8T cells.

NOTE Confidence: 0.801096541111111

00:42:56.630 --> 00:42:57.491 And we look,

NOTE Confidence: 0.801096541111111

00:42:57.491 --> 00:42:59.213 when we look specifically at which

NOTE Confidence: 0.801096541111111

00:42:59.213 --> 00:43:01.158 immune populations are associated with

NOTE Confidence: 0.801096541111111

00:43:01.158 --> 00:43:03.163 resistance or with altered survival,

NOTE Confidence: 0.801096541111111

00:43:03.170 --> 00:43:05.322 it turns out that the slam of seven

NOTE Confidence: 0.801096541111111

00:43:05.322 --> 00:43:07.154 positive CDT cells again in this

NOTE Confidence: 0.801096541111111

00:43:07.154 --> 00:43:09.002 very small cohort only 13 patients,

NOTE Confidence: 0.801096541111111

00:43:09.010 --> 00:43:10.894 but associated with progressive

NOTE Confidence: 0.801096541111111

00:43:10.894 --> 00:43:13.249 disease and with worse progression

NOTE Confidence: 0.801096541111111

00:43:13.249 --> 00:43:15.190 free and overall survival.

NOTE Confidence: 0.801096541111111

00:43:15.190 --> 00:43:17.686 And so this is our sort of initial

NOTE Confidence: 0.801096541111111

00:43:17.686 --> 00:43:18.310 13 patients.

NOTE Confidence: 0.801096541111111

00:43:18.310 --> 00:43:20.290 We're now parsing through the sequencing

NOTE Confidence: 0.801096541111111

00:43:20.290 --> 00:43:22.501 data from our our 96 patients to

NOTE Confidence: 0.801096541111111

00:43:22.501 --> 00:43:24.884 really get a better handle on what are

NOTE Confidence: 0.801096541111111

00:43:24.884 --> 00:43:26.669 the different human populations that

NOTE Confidence: 0.801096541111111

00:43:26.669 --> 00:43:28.748 might exhibit this sort of behavior.

NOTE Confidence: 0.801096541111111

00:43:28.750 --> 00:43:30.154 But we also have to move

NOTE Confidence: 0.801096541111111

00:43:30.154 --> 00:43:30.856 beyond immune profiling.

NOTE Confidence: 0.801096541111111

00:43:30.860 --> 00:43:32.590 We might get a sense of what are the immune

NOTE Confidence: 0.807560435238095

00:43:32.631 --> 00:43:33.776 populations that are are relevant

NOTE Confidence: 0.807560435238095

00:43:33.776 --> 00:43:35.490 and what are the immune interactions,

NOTE Confidence: 0.807560435238095

00:43:35.490 --> 00:43:36.530 which could play a role.

NOTE Confidence: 0.807560435238095

00:43:36.530 --> 00:43:38.371 But we actually have to to nominate

NOTE Confidence: 0.807560435238095

00:43:38.371 --> 00:43:39.710 individual targets for the clinic.

NOTE Confidence: 0.807560435238095

00:43:39.710 --> 00:43:41.447 We actually have to be able to test this.

NOTE Confidence: 0.807560435238095

00:43:41.450 --> 00:43:43.166 And then kidney cancer is a

NOTE Confidence: 0.807560435238095

00:43:43.166 --> 00:43:44.650 unique opportunity to do this.

NOTE Confidence: 0.807560435238095

00:43:44.650 --> 00:43:46.148 Part of it is just purely practical.

NOTE Confidence: 0.807560435238095

00:43:46.150 --> 00:43:47.174 These are enormous tumors.

NOTE Confidence: 0.807560435238095

00:43:47.174 --> 00:43:49.067 You can have a 6 1/2 centimeter

NOTE Confidence: 0.807560435238095

00:43:49.067 --> 00:43:51.132 tumor that's a stage one tumor and

NOTE Confidence: 0.807560435238095

00:43:51.132 --> 00:43:53.109 it's not uncommon for these tumors

NOTE Confidence: 0.807560435238095

00:43:53.109 --> 00:43:55.107 to extend to exceed 10 centimeters.

NOTE Confidence: 0.807560435238095

00:43:55.110 --> 00:43:56.460 And so there's just lots of

NOTE Confidence: 0.807560435238095

00:43:56.460 --> 00:43:58.199 material to be able to extract

NOTE Confidence: 0.807560435238095

00:43:58.199 --> 00:43:59.378 individual immune populations.

NOTE Confidence: 0.807560435238095

00:43:59.380 --> 00:44:01.780 Individual tumor populations and

NOTE Confidence: 0.807560435238095

00:44:01.780 --> 00:44:03.478 actually functionally test which

NOTE Confidence: 0.807560435238095

00:44:03.478 --> 00:44:05.308 interactions might actually play a

NOTE Confidence: 0.807560435238095

00:44:05.308 --> 00:44:07.356 role and we've begun to do this.

NOTE Confidence: 0.807560435238095

00:44:07.360 --> 00:44:09.537 We've been able to take these primary

NOTE Confidence: 0.807560435238095

00:44:09.537 --> 00:44:12.000 tumors and I should mention Cat sudakin

NOTE Confidence: 0.807560435238095

00:44:12.000 --> 00:44:14.675 in the lab is really spearheaded this

NOTE Confidence: 0.807560435238095

00:44:14.675 --> 00:44:16.725 process of identifying patients as

NOTE Confidence: 0.807560435238095

00:44:16.725 --> 00:44:18.658 in collaboration with Mike Hurwitz

NOTE Confidence: 0.807560435238095

00:44:18.658 --> 00:44:20.962 who runs the Gu tumor bank with Debo

NOTE Confidence: 0.807560435238095

00:44:20.962 --> 00:44:22.569 Adeniran and Peter Humphrey and

NOTE Confidence: 0.807560435238095

00:44:22.569 --> 00:44:24.459 Pathology and Pat Kenny and Urology

NOTE Confidence: 0.807560435238095

00:44:24.520 --> 00:44:26.512 where we're able to routinely on

NOTE Confidence: 0.807560435238095

00:44:26.512 --> 00:44:28.062 just about every nephrectomy that's

NOTE Confidence: 0.807560435238095

00:44:28.062 --> 00:44:29.394 done at the at the hospital.

NOTE Confidence: 0.807560435238095

00:44:29.400 --> 00:44:29.855 Here,

NOTE Confidence: 0.807560435238095

00:44:29.855 --> 00:44:33.495 collect fresh tumor for this sort of work.

NOTE Confidence: 0.807560435238095

00:44:33.500 --> 00:44:35.215 And so we're able to extract both

NOTE Confidence: 0.807560435238095

00:44:35.215 --> 00:44:37.088 immune cells and tumor cells and for

NOTE Confidence: 0.807560435238095

00:44:37.088 --> 00:44:38.708 a subset of patients we're actually

NOTE Confidence: 0.807560435238095

00:44:38.761 --> 00:44:40.577 able to to grow out tumor cell lines.

NOTE Confidence: 0.807560435238095

00:44:40.580 --> 00:44:42.715 And so this is really a valuable

NOTE Confidence: 0.807560435238095

00:44:42.715 --> 00:44:44.535 resource for thinking about autologous

NOTE Confidence: 0.807560435238095

00:44:44.535 --> 00:44:46.635 coculture experiments with T cells.

NOTE Confidence: 0.807560435238095

00:44:46.640 --> 00:44:49.304 And so our sort of overall plan for

NOTE Confidence: 0.807560435238095

00:44:49.304 --> 00:44:51.318 functional validation is sort of two phases.

NOTE Confidence: 0.807560435238095

00:44:51.320 --> 00:44:53.162 One is a more reductionist approach

NOTE Confidence: 0.807560435238095

00:44:53.162 --> 00:44:55.576 and one is one that maybe perhaps

NOTE Confidence: 0.807560435238095

00:44:55.576 --> 00:44:57.446 recapitulates the contacts of the

NOTE Confidence: 0.807560435238095

00:44:57.446 --> 00:44:59.800 3D micro environment a bit better.

NOTE Confidence: 0.807560435238095

00:44:59.800 --> 00:45:00.700 The reductions to approach.

NOTE Confidence: 0.807560435238095

00:45:00.700 --> 00:45:02.525 Again this is led by a few people

NOTE Confidence: 0.807560435238095

00:45:02.525 --> 00:45:03.365 in the lab soaky.

NOTE Confidence: 0.807560435238095

00:45:03.370 --> 00:45:05.575 Uh Katrina and Hannah is to basically

NOTE Confidence: 0.807560435238095

00:45:05.575 --> 00:45:07.559 break this down into individual

NOTE Confidence: 0.807560435238095

00:45:07.559 --> 00:45:08.539 cell populations.

NOTE Confidence: 0.807560435238095

00:45:08.540 --> 00:45:10.565 So to associate those tumors

NOTE Confidence: 0.807560435238095

00:45:10.565 --> 00:45:12.185 into single cell suspension,

NOTE Confidence: 0.807560435238095

00:45:12.190 --> 00:45:14.030 isolate individual cell populations

NOTE Confidence: 0.807560435238095

00:45:14.030 --> 00:45:14.950 of interest,

NOTE Confidence: 0.807560435238095

00:45:14.950 --> 00:45:16.810 coculture just those populations of

NOTE Confidence: 0.807560435238095

00:45:16.810 --> 00:45:19.090 interest with a therapeutic drug with

NOTE Confidence: 0.807560435238095

00:45:19.090 --> 00:45:21.250 an inhibitor of a particular interaction.

NOTE Confidence: 0.807560435238095

00:45:21.250 --> 00:45:22.960 And then be able to measure

NOTE Confidence: 0.807560435238095

00:45:22.960 --> 00:45:24.740 changes in T cell function,

NOTE Confidence: 0.807560435238095

00:45:24.740 --> 00:45:27.630 basic flow cytometry for intracellular

NOTE Confidence: 0.807560435238095

00:45:27.630 --> 00:45:29.942 cytokine production collaboration assays,

NOTE Confidence: 0.807560435238095

00:45:29.950 --> 00:45:31.840 expression of cytotoxicity markers like

NOTE Confidence: 0.807560435238095

00:45:31.840 --> 00:45:34.540 granzyme and then we begun to implement.

NOTE Confidence: 0.807560435238095

00:45:34.540 --> 00:45:35.780 These model antigen systems

NOTE Confidence: 0.807560435238095

00:45:35.780 --> 00:45:38.012 where we have now T cells that

NOTE Confidence: 0.807560435238095

00:45:38.012 --> 00:45:39.866 we engineer with a specific TCR,

NOTE Confidence: 0.807560435238095

00:45:39.870 --> 00:45:40.647 TCR against NY,

NOTE Confidence: 0.807560435238095

00:45:40.647 --> 00:45:42.919 so one or against WT1 and we have

NOTE Confidence: 0.807560435238095

00:45:42.919 --> 00:45:44.894 tumor cells that express those

NOTE Confidence: 0.807560435238095

00:45:44.894 --> 00:45:46.474 antigens and express luciferase

NOTE Confidence: 0.807560435238095

00:45:46.534 --> 00:45:48.305 and we can actually now test have

NOTE Confidence: 0.807560435238095

00:45:48.305 --> 00:45:51.054 a a model antigen system for for

NOTE Confidence: 0.807560435238095

00:45:51.054 --> 00:45:53.583 testing these impact on cytotoxicity.

NOTE Confidence: 0.807560435238095

00:45:53.583 --> 00:45:54.094 Again,

NOTE Confidence: 0.807560435238095

00:45:54.094 --> 00:45:57.160 there's limitations of a reductionist model.

NOTE Confidence: 0.807560435238095

00:45:57.160 --> 00:45:59.106 And so in work that's done in

NOTE Confidence: 0.807560435238095

00:45:59.106 --> 00:46:00.260 collaboration actually now with

NOTE Confidence: 0.807560435238095

00:46:00.260 --> 00:46:01.868 AstraZeneca and and a lot of

NOTE Confidence: 0.807560435238095

00:46:01.868 --> 00:46:03.320 mentorship from from Marcus here,

NOTE Confidence: 0.807560435238095

00:46:03.320 --> 00:46:05.420 we also have begun to implement these

NOTE Confidence: 0.807560435238095

00:46:05.420 --> 00:46:07.389 tumor fragment models where we try

NOTE Confidence: 0.807560435238095

00:46:07.389 --> 00:46:09.074 to recapitulate the 3D microenvironment.

NOTE Confidence: 0.807560435238095

00:46:09.080 --> 00:46:10.455 We actually cut the tumor

NOTE Confidence: 0.807560435238095

00:46:10.455 --> 00:46:11.555 into these various fragments.

NOTE Confidence: 0.807560435238095

00:46:11.560 --> 00:46:13.716 We embed them in a collagen matrix.

NOTE Confidence: 0.807560435238095

00:46:13.720 --> 00:46:15.561 We float that in media where we

NOTE Confidence: 0.807560435238095

00:46:15.561 --> 00:46:16.350 can add various

NOTE Confidence: 0.817583681130435

00:46:16.414 --> 00:46:18.451 perturbations and we can see that over

NOTE Confidence: 0.817583681130435

00:46:18.451 --> 00:46:20.679 the course of its short-term culture,

NOTE Confidence: 0.817583681130435

00:46:20.680 --> 00:46:21.832 three to five days,

NOTE Confidence: 0.817583681130435

00:46:21.832 --> 00:46:23.560 we really can recapitulate the Histology,

NOTE Confidence: 0.817583681130435

00:46:23.560 --> 00:46:25.030 the architecture of these clear cell.

NOTE Confidence: 0.817583681130435

00:46:25.030 --> 00:46:27.094 Consumers and preserve a lot of

NOTE Confidence: 0.817583681130435

00:46:27.094 --> 00:46:28.470 the immune microenvironment both

NOTE Confidence: 0.817583681130435

00:46:28.526 --> 00:46:30.136 T cell and myeloid components.

NOTE Confidence: 0.817583681130435

00:46:30.140 --> 00:46:31.344 And so with this we can actually

NOTE Confidence: 0.817583681130435

00:46:31.344 --> 00:46:32.616 use this to to actually function

NOTE Confidence: 0.817583681130435

00:46:32.616 --> 00:46:34.050 and validate some of these things.

NOTE Confidence: 0.817583681130435

00:46:34.050 --> 00:46:35.100 We've done some toy experiments,

NOTE Confidence: 0.817583681130435

00:46:35.100 --> 00:46:36.696 I'm showing one where we've added

NOTE Confidence: 0.817583681130435

00:46:36.696 --> 00:46:38.694 low dose or higher dose IL two and

NOTE Confidence: 0.817583681130435

00:46:38.694 --> 00:46:40.292 can show that we can impact the

NOTE Confidence: 0.817583681130435

00:46:40.292 --> 00:46:42.092 T cells that are there just as a

NOTE Confidence: 0.817583681130435

00:46:42.092 --> 00:46:43.380 initial sort of proof of concept.

NOTE Confidence: 0.817583681130435

00:46:43.380 --> 00:46:45.035 But now together with AstraZeneca

NOTE Confidence: 0.817583681130435

00:46:45.035 --> 00:46:47.087 really looking at some of these

NOTE Confidence: 0.817583681130435

00:46:47.087 --> 00:46:49.109 interactions that we found in our

NOTE Confidence: 0.817583681130435

00:46:49.109 --> 00:46:50.835 original cancer cell paper TIGIT

NOTE Confidence: 0.817583681130435

00:46:50.835 --> 00:46:52.480 and others and seeing whether

NOTE Confidence: 0.817583681130435

00:46:52.480 --> 00:46:54.088 inhibition of those inhibitory

NOTE Confidence: 0.817583681130435

00:46:54.088 --> 00:46:55.696 interactions might actually impact.

NOTE Confidence: 0.817583681130435

00:46:55.700 --> 00:46:58.560 Tumor killing and cell function.

NOTE Confidence: 0.817583681130435

00:46:58.560 --> 00:47:00.792 And so that second piece is really the

NOTE Confidence: 0.817583681130435

00:47:00.792 --> 00:47:02.177 tumor microenvironment and how that

NOTE Confidence: 0.817583681130435

00:47:02.177 --> 00:47:03.737 changes with advancing disease stage and

NOTE Confidence: 0.817583681130435

00:47:03.737 --> 00:47:05.872 now how we can use that to understand

NOTE Confidence: 0.817583681130435

00:47:05.872 --> 00:47:07.164 response and resistance to therapy.

NOTE Confidence: 0.817583681130435

00:47:07.164 --> 00:47:08.928 The final aspect of our lab focuses

NOTE Confidence: 0.817583681130435

00:47:08.928 --> 00:47:10.730 on is really trying to identify

NOTE Confidence: 0.817583681130435

00:47:10.730 --> 00:47:12.496 what are the relevant antigens in

NOTE Confidence: 0.817583681130435

00:47:12.496 --> 00:47:13.828 kidney cancer and how we might

NOTE Confidence: 0.817583681130435

00:47:13.828 --> 00:47:15.162 be able to therapeutically target

NOTE Confidence: 0.817583681130435

00:47:15.162 --> 00:47:16.817 them with antigen directed therapy.

NOTE Confidence: 0.817583681130435

00:47:16.820 --> 00:47:18.416 And in order to do this,

NOTE Confidence: 0.817583681130435

00:47:18.420 --> 00:47:19.995 in my mind we need sort of two pieces.

NOTE Confidence: 0.817583681130435

00:47:20.000 --> 00:47:21.326 We need a toolkit of experimental

NOTE Confidence: 0.817583681130435

00:47:21.326 --> 00:47:22.910 toolkit to do this and the other

NOTE Confidence: 0.817583681130435

00:47:22.910 --> 00:47:24.212 is we actually need the samples.

NOTE Confidence: 0.817583681130435

00:47:24.220 --> 00:47:25.744 And so the experimental tool toolkit

NOTE Confidence: 0.817583681130435

00:47:25.744 --> 00:47:27.572 is I would say both computational

NOTE Confidence: 0.817583681130435

00:47:27.572 --> 00:47:28.709 and physical tools.

NOTE Confidence: 0.817583681130435

00:47:28.710 --> 00:47:30.600 Computational tools includes

NOTE Confidence: 0.817583681130435

00:47:30.600 --> 00:47:32.490 better antigen prediction,

NOTE Confidence: 0.817583681130435

00:47:32.490 --> 00:47:34.818 the ability to infer not just

NOTE Confidence: 0.817583681130435

00:47:34.818 --> 00:47:36.370 neoantigens but things like

NOTE Confidence: 0.817583681130435

00:47:36.438 --> 00:47:38.820 expression endogenous retroviruses.

NOTE Confidence: 0.817583681130435

00:47:38.820 --> 00:47:40.670 Physical tools for antigen detection.

NOTE Confidence: 0.817583681130435

00:47:40.670 --> 00:47:42.992 These are immuno epidemics where we

NOTE Confidence: 0.817583681130435

00:47:42.992 --> 00:47:44.540 can actually immunoprecipitate off

NOTE Confidence: 0.817583681130435

00:47:44.602 --> 00:47:46.540 Class 1 molecules from tumor cells,

NOTE Confidence: 0.817583681130435

00:47:46.540 --> 00:47:49.006 elute peptide and and actually physically

NOTE Confidence: 0.817583681130435

00:47:49.006 --> 00:47:52.009 detect the presence of individual peptides.

NOTE Confidence: 0.817583681130435

00:47:52.010 --> 00:47:53.810 This was done in collaboration with

NOTE Confidence: 0.817583681130435

00:47:53.810 --> 00:47:55.600 Steve Carr's group at the Broad.

NOTE Confidence: 0.817583681130435

00:47:55.600 --> 00:47:57.413 And then TCR tools and these are

NOTE Confidence: 0.817583681130435

00:47:57.413 --> 00:47:58.520 now pretty established tools,

NOTE Confidence: 0.817583681130435

00:47:58.520 --> 00:47:59.948 tools for single cell TCR sequencing

NOTE Confidence: 0.817583681130435

00:47:59.948 --> 00:48:01.439 where we know the full alpha,

NOTE Confidence: 0.817583681130435

00:48:01.440 --> 00:48:03.620 beta paired TT cell sequence,

NOTE Confidence: 0.817583681130435

00:48:03.620 --> 00:48:06.588 but also the ability to then reconstruct

NOTE Confidence: 0.817583681130435

00:48:06.588 --> 00:48:09.448 them in primary healthy T cells and

NOTE Confidence: 0.817583681130435

00:48:09.448 --> 00:48:11.036 actually probe their specificity.

NOTE Confidence: 0.817583681130435

00:48:11.040 --> 00:48:13.296 So we do have a good toolkit for

NOTE Confidence: 0.817583681130435

00:48:13.296 --> 00:48:15.094 antigen discovery now we need the

NOTE Confidence: 0.817583681130435

00:48:15.094 --> 00:48:16.852 samples and I think clinical trials,

NOTE Confidence: 0.817583681130435

00:48:16.860 --> 00:48:18.610 particularly early phase clinical trials

NOTE Confidence: 0.817583681130435

00:48:18.610 --> 00:48:20.672 are really wonderful platform to be

NOTE Confidence: 0.817583681130435

00:48:20.672 --> 00:48:22.513 able to do this really in-depth analysis.

NOTE Confidence: 0.817583681130435

00:48:22.520 --> 00:48:24.184 And so I'm going to give a little

NOTE Confidence: 0.817583681130435

00:48:24.184 --> 00:48:25.640 bit of a vignette of work.

NOTE Confidence: 0.817583681130435

00:48:25.640 --> 00:48:27.068 That's wrapping up from my time

NOTE Confidence: 0.817583681130435

00:48:27.068 --> 00:48:27.782 at Dana Farber.

NOTE Confidence: 0.817583681130435

00:48:27.790 --> 00:48:28.830 This is a clinical trial,

NOTE Confidence: 0.817583681130435

00:48:28.830 --> 00:48:30.685 a phase one trial that led together

NOTE Confidence: 0.817583681130435

00:48:30.685 --> 00:48:32.814 with Tony Sherry and Patrick OTT of

NOTE Confidence: 0.817583681130435

00:48:32.814 --> 00:48:34.098 neoantigen vaccination in kidney

NOTE Confidence: 0.817583681130435

00:48:34.098 --> 00:48:35.943 cancer that I think has some

NOTE Confidence: 0.817583681130435

00:48:35.943 --> 00:48:37.383 interesting findings in of itself,

NOTE Confidence: 0.817583681130435

00:48:37.390 --> 00:48:38.578 but really also serves I think,

NOTE Confidence: 0.817583681130435

00:48:38.580 --> 00:48:40.692 as a platform for answering some

NOTE Confidence: 0.817583681130435

00:48:40.692 --> 00:48:41.748 of these questions.

NOTE Confidence: 0.817583681130435

00:48:41.750 --> 00:48:43.838 So this was a a trial that took

NOTE Confidence: 0.817583681130435

00:48:43.838 --> 00:48:45.877 stage three or stage four patients

NOTE Confidence: 0.817583681130435

00:48:45.877 --> 00:48:46.969 with kidney cancer.

NOTE Confidence: 0.817583681130435

00:48:46.970 --> 00:48:48.596 They had to be fully resected

NOTE Confidence: 0.817583681130435

00:48:48.596 --> 00:48:49.680 at the time of

NOTE Confidence: 0.86685781

00:48:49.746 --> 00:48:51.899 surgery. So they had no evidence of disease

NOTE Confidence: 0.86685781

00:48:51.899 --> 00:48:53.928 and these were clear cell only and we

NOTE Confidence: 0.86685781

00:48:53.928 --> 00:48:55.767 treated 5 patients, vaccine or local.

NOTE Confidence: 0.86685781

00:48:55.767 --> 00:48:57.921 Pipeline maps or ctla 4 inhibitor

NOTE Confidence: 0.86685781

00:48:57.921 --> 00:49:00.227 given at the vaccine site or vaccine

NOTE Confidence: 0.86685781

00:49:00.227 --> 00:49:02.215 alone and the basic process we

NOTE Confidence: 0.86685781

00:49:02.215 --> 00:49:04.195 would take their tumor and then

NOTE Confidence: 0.86685781

00:49:04.200 --> 00:49:05.898 normal cells would take their blood,

NOTE Confidence: 0.86685781

00:49:05.900 --> 00:49:07.076 perform whole exome sequencing

NOTE Confidence: 0.86685781

00:49:07.076 --> 00:49:08.840 and RNA sequencing on the tumor.

NOTE Confidence: 0.86685781

00:49:08.840 --> 00:49:11.120 We'd identify tumor specific mutations,

NOTE Confidence: 0.86685781

00:49:11.120 --> 00:49:13.025 we ensure that they're actually

NOTE Confidence: 0.86685781

00:49:13.025 --> 00:49:14.930 expressed that the RNA level

NOTE Confidence: 0.86685781

00:49:15.000 --> 00:49:17.440 we'd use some of our tools that I

NOTE Confidence: 0.86685781

00:49:17.440 --> 00:49:19.412 just described to infer what are

NOTE Confidence: 0.86685781

00:49:19.412 --> 00:49:21.356 likely to be HLA binding peptide,

NOTE Confidence: 0.86685781

00:49:21.360 --> 00:49:23.784 so likely to be antigens and then we'd

NOTE Confidence: 0.86685781

00:49:23.784 --> 00:49:25.995 actually get together in a spin a room.

NOTE Confidence: 0.86685781

00:49:26.000 --> 00:49:27.930 And turn it over zoom,

NOTE Confidence: 0.86685781

00:49:27.930 --> 00:49:29.799 but we get together as an epitope

NOTE Confidence: 0.86685781

00:49:29.799 --> 00:49:31.210 selection board to actually pick

NOTE Confidence: 0.86685781

00:49:31.210 --> 00:49:32.872 which of the mutations we want

NOTE Confidence: 0.86685781

00:49:32.872 --> 00:49:34.408 to target and design synthetic

NOTE Confidence: 0.86685781

00:49:34.408 --> 00:49:35.948 long peptides anywhere between 20

NOTE Confidence: 0.86685781

00:49:35.948 --> 00:49:39.125 to 25 more typically in order to

NOTE Confidence: 0.86685781

00:49:39.125 --> 00:49:41.169 actually physically synthesize them.

NOTE Confidence: 0.86685781

00:49:41.170 --> 00:49:43.600 We then partnered with a GMP

NOTE Confidence: 0.86685781

00:49:43.600 --> 00:49:45.220 peptide manufacturer to actually

NOTE Confidence: 0.86685781

00:49:45.294 --> 00:49:48.396 synthesize these peptides up to 20

NOTE Confidence: 0.86685781

00:49:48.396 --> 00:49:49.947 representing different neoantigens,

NOTE Confidence: 0.86685781

00:49:49.950 --> 00:49:51.750 pulled that together with an immune

NOTE Confidence: 0.86685781

00:49:51.750 --> 00:49:53.958 adjuvant Poly ICLC and then that

NOTE Confidence: 0.86685781

00:49:53.958 --> 00:49:55.968 delivered that to the patient.

NOTE Confidence: 0.86685781

00:49:55.970 --> 00:49:59.310 We treated 9 patients overall.

NOTE Confidence: 0.86685781

00:49:59.310 --> 00:50:01.158 It's the sort of standard demographics

NOTE Confidence: 0.86685781

00:50:01.158 --> 00:50:02.790 you'd expect for kidney cancer.

NOTE Confidence: 0.86685781

00:50:02.790 --> 00:50:03.874 Majority were stage three.

NOTE Confidence: 0.86685781

00:50:03.874 --> 00:50:05.500 There were a couple of stage

NOTE Confidence: 0.86685781

00:50:05.554 --> 00:50:06.638 four patients as well.

NOTE Confidence: 0.86685781

00:50:06.640 --> 00:50:08.944 And in every patient we were able to to

NOTE Confidence: 0.86685781

00:50:08.944 --> 00:50:11.177 identify enough mutations to actually target.

NOTE Confidence: 0.86685781

00:50:11.180 --> 00:50:13.130 So median of 13 unique mutations

NOTE Confidence: 0.86685781

00:50:13.130 --> 00:50:14.430 were targeted per patient

NOTE Confidence: 0.86685781

00:50:14.487 --> 00:50:15.999 with 15 different peptides.

NOTE Confidence: 0.86685781

00:50:16.000 --> 00:50:17.463 Kidney tumors have a lot more frameshift

NOTE Confidence: 0.86685781

00:50:17.463 --> 00:50:19.046 mutations than a lot of other tumor types.

NOTE Confidence: 0.86685781

00:50:19.050 --> 00:50:20.280 So we're able to target a

NOTE Confidence: 0.86685781

00:50:20.280 --> 00:50:21.100 lot of frame shifts.

NOTE Confidence: 0.86685781

00:50:21.100 --> 00:50:21.919 I think interestingly,

NOTE Confidence: 0.86685781

00:50:21.919 --> 00:50:23.830 we're actually able to target in the

NOTE Confidence: 0.86685781

00:50:23.882 --> 00:50:25.596 majority of patients actually driver

NOTE Confidence: 0.86685781

00:50:25.596 --> 00:50:27.168 mutations within kidney cancer.

NOTE Confidence: 0.86685781

00:50:27.170 --> 00:50:29.081 And it turns out those when we

NOTE Confidence: 0.86685781

00:50:29.081 --> 00:50:31.365 look back ends up being the most

NOTE Confidence: 0.86685781

00:50:31.365 --> 00:50:33.084 immunogenic immunogenic peptides,

NOTE Confidence: 0.86685781

00:50:33.084 --> 00:50:37.176 the ones that represent driver mutations.

NOTE Confidence: 0.86685781

00:50:37.180 --> 00:50:39.105 And I hesitate to like talk about

NOTE Confidence: 0.86685781

00:50:39.105 --> 00:50:41.514 any sort of clinical data here just

NOTE Confidence: 0.86685781

00:50:41.514 --> 00:50:43.414 because it's it's nine patients,

NOTE Confidence: 0.86685781

00:50:43.420 --> 00:50:44.108 but they're,

NOTE Confidence: 0.86685781

00:50:44.108 --> 00:50:44.452 yeah,

NOTE Confidence: 0.86685781

00:50:44.452 --> 00:50:46.860 at least encouraging that was certainly safe.

NOTE Confidence: 0.86685781

00:50:46.860 --> 00:50:47.320 No one,

NOTE Confidence: 0.86685781

00:50:47.320 --> 00:50:48.930 everyone did well on the trial and

NOTE Confidence: 0.86685781

00:50:48.930 --> 00:50:50.697 there have been no clinical relapses,

NOTE Confidence: 0.86685781

00:50:50.700 --> 00:50:52.730 I would say in this population probably

NOTE Confidence: 0.86685781

00:50:52.730 --> 00:50:54.668 at this point somewhere around 1/3

NOTE Confidence: 0.86685781

00:50:54.668 --> 00:50:56.678 third to half might have relapsed.

NOTE Confidence: 0.86685781

00:50:56.680 --> 00:50:59.182 And so the fact that there have been no

NOTE Confidence: 0.86685781

00:50:59.182 --> 00:51:01.656 disease recurrences is at least encouraging.

NOTE Confidence: 0.86685781

00:51:01.660 --> 00:51:02.074 But again,

NOTE Confidence: 0.86685781

00:51:02.074 --> 00:51:03.730 a big part of this was really the

NOTE Confidence: 0.86685781

00:51:03.780 --> 00:51:05.240 Biospecimen collection and these

NOTE Confidence: 0.86685781

00:51:05.240 --> 00:51:06.917 were really generous patients that

NOTE Confidence: 0.86685781

00:51:06.917 --> 00:51:08.436 went through a lot for this trial.

NOTE Confidence: 0.86685781

00:51:08.440 --> 00:51:10.320 And so for each of these patients and

NOTE Confidence: 0.86685781

00:51:10.320 --> 00:51:12.388 they went through the vaccination itself,

NOTE Confidence: 0.86685781

00:51:12.390 --> 00:51:13.896 which were five priming doses of

NOTE Confidence: 0.86685781

00:51:13.896 --> 00:51:15.634 the course of three weeks and two

NOTE Confidence: 0.86685781

00:51:15.634 --> 00:51:17.420 booster shots at week 12 and week 20.

NOTE Confidence: 0.86685781

00:51:17.420 --> 00:51:18.895 They had multiple skin biopsies

NOTE Confidence: 0.86685781

00:51:18.895 --> 00:51:20.729 prior to and after vaccination to

NOTE Confidence: 0.86685781

00:51:20.729 --> 00:51:22.274 look at whether they infiltrated

NOTE Confidence: 0.86685781

00:51:22.274 --> 00:51:23.800 immune populations within the skin.

NOTE Confidence: 0.86685781

00:51:23.800 --> 00:51:25.837 We obviously have the tumor tissue itself,

NOTE Confidence: 0.86685781

00:51:25.840 --> 00:51:27.382 but we need lots of circulating

NOTE Confidence: 0.86685781

00:51:27.382 --> 00:51:29.486 blood cells as well to perform immune

NOTE Confidence: 0.86685781

00:51:29.486 --> 00:51:31.532 monitoring and so we perform leukapheresis.

NOTE Confidence: 0.782859847894737

00:51:31.540 --> 00:51:33.712 Often required a central line placement

NOTE Confidence: 0.782859847894737

00:51:33.712 --> 00:51:36.315 before and after treatment and weeks here and

NOTE Confidence: 0.782859847894737

00:51:36.315 --> 00:51:39.292 week 16 and pretty regular 200ML blood draws,

NOTE Confidence: 0.782859847894737

00:51:39.292 --> 00:51:41.428 regular 200ML blood draws,

NOTE Confidence: 0.782859847894737

00:51:41.430 --> 00:51:45.007 really look at what are the circulating

NOTE Confidence: 0.782859847894737

00:51:45.007 --> 00:51:46.738 immune populations and our questions,

NOTE Confidence: 0.782859847894737

00:51:46.738 --> 00:51:48.654 we're really trying to look kind of end

NOTE Confidence: 0.782859847894737

00:51:48.654 --> 00:51:50.358 to end what's happening at the skin as

NOTE Confidence: 0.782859847894737

00:51:50.358 --> 00:51:51.814 we move to the circulating immune system.

NOTE Confidence: 0.782859847894737

00:51:51.820 --> 00:51:53.650 Ultimately are we getting tumor reactivity,

NOTE Confidence: 0.782859847894737

00:51:53.650 --> 00:51:54.990 it's nice to get reactivity

NOTE Confidence: 0.782859847894737

00:51:54.990 --> 00:51:56.062 against the vaccine itself,

NOTE Confidence: 0.782859847894737

00:51:56.070 --> 00:51:57.810 but it's actually not impacting

NOTE Confidence: 0.782859847894737

00:51:57.810 --> 00:51:58.506 tumor reactivity.

NOTE Confidence: 0.782859847894737

00:51:58.510 --> 00:51:59.690 We haven't done too much.

NOTE Confidence: 0.782859847894737

00:51:59.690 --> 00:52:01.550 We haven't actually been helpful.

NOTE Confidence: 0.782859847894737

00:52:01.550 --> 00:52:03.166 And so just to briefly walk through this,

NOTE Confidence: 0.782859847894737

00:52:03.170 --> 00:52:04.892 this is what a typical this

NOTE Confidence: 0.782859847894737

00:52:04.892 --> 00:52:05.753 actually patient one.

NOTE Confidence: 0.782859847894737

00:52:05.760 --> 00:52:08.328 So this is the prior vaccine scars and

NOTE Confidence: 0.782859847894737

00:52:08.328 --> 00:52:10.746 what what the vaccine site looks like

NOTE Confidence: 0.782859847894737

00:52:10.746 --> 00:52:13.260 two to three days after vaccination

NOTE Confidence: 0.782859847894737

00:52:13.260 --> 00:52:16.280 we can perform enzymatic dissociation,

NOTE Confidence: 0.782859847894737

00:52:16.280 --> 00:52:18.986 CD45 isolation and single cell RNA

NOTE Confidence: 0.782859847894737

00:52:18.986 --> 00:52:20.790 sequencing identifying really high

NOTE Confidence: 0.782859847894737

00:52:20.855 --> 00:52:23.597 populations of myeloid and lymphoid cells.

NOTE Confidence: 0.782859847894737

00:52:23.600 --> 00:52:26.036 And this is work in progress,

NOTE Confidence: 0.782859847894737

00:52:26.040 --> 00:52:27.720 but we actually see some fairly

NOTE Confidence: 0.782859847894737

00:52:27.720 --> 00:52:29.152 interesting changes in both the

NOTE Confidence: 0.782859847894737

00:52:29.152 --> 00:52:30.736 myeloid cell and T cell population.

NOTE Confidence: 0.782859847894737

00:52:30.740 --> 00:52:32.378 I would say predominantly it happens.

NOTE Confidence: 0.782859847894737

00:52:32.380 --> 00:52:33.032 With vaccination,

NOTE Confidence: 0.782859847894737

00:52:33.032 --> 00:52:34.662 we're not seeing huge differences

NOTE Confidence: 0.782859847894737

00:52:34.662 --> 00:52:36.538 with the addition of epilimnion map.

NOTE Confidence: 0.782859847894737

00:52:36.540 --> 00:52:39.137 Moving on to the circulating immune system,

NOTE Confidence: 0.782859847894737

00:52:39.140 --> 00:52:40.620 really the workhorse for this

NOTE Confidence: 0.782859847894737

00:52:40.620 --> 00:52:42.100 was interferon gamma Ellie spots.

NOTE Confidence: 0.782859847894737

00:52:42.100 --> 00:52:43.773 These are taking peripheral T cells out

NOTE Confidence: 0.782859847894737

00:52:43.773 --> 00:52:46.088 out of a patient peripheral blood cells,

NOTE Confidence: 0.782859847894737

00:52:46.090 --> 00:52:47.798 putting them into a dish and stimulating

NOTE Confidence: 0.782859847894737

00:52:47.798 --> 00:52:49.417 them with the same vaccine peptides

NOTE Confidence: 0.782859847894737

00:52:49.417 --> 00:52:51.097 and seeing whether those T cells

NOTE Confidence: 0.782859847894737

00:52:51.097 --> 00:52:52.782 release interferon gamma as a marker

NOTE Confidence: 0.782859847894737

00:52:52.782 --> 00:52:54.385 of antigen reactivity and would see

NOTE Confidence: 0.782859847894737

00:52:54.385 --> 00:52:55.855 it week one prior to vaccination.

NOTE Confidence: 0.782859847894737

00:52:55.860 --> 00:52:58.116 Basically none of the neoantigen pools,

NOTE Confidence: 0.782859847894737

00:52:58.120 --> 00:53:01.074 the 1st 4 rows had any reactivity,

NOTE Confidence: 0.782859847894737

00:53:01.080 --> 00:53:03.936 but we get pretty strong reactivity

NOTE Confidence: 0.782859847894737

00:53:03.940 --> 00:53:06.614 with vaccination and that when we do.

NOTE Confidence: 0.782859847894737

00:53:06.620 --> 00:53:08.198 Close cytometry and it's Cellular said

NOTE Confidence: 0.782859847894737

00:53:08.198 --> 00:53:10.184 to kind of standing we actually see that

NOTE Confidence: 0.782859847894737

00:53:10.184 --> 00:53:11.858 these are not largely polyfunctional,

NOTE Confidence: 0.782859847894737

00:53:11.858 --> 00:53:15.890 that they T cells not only produce interferon

NOTE Confidence: 0.782859847894737

00:53:15.970 --> 00:53:18.746 gamma but things like aisle 2 and TNF.

NOTE Confidence: 0.782859847894737

00:53:18.750 --> 00:53:19.554 And finally,

NOTE Confidence: 0.782859847894737

00:53:19.554 --> 00:53:21.564 moving beyond just vaccine reactivity,

NOTE Confidence: 0.782859847894737

00:53:21.570 --> 00:53:23.376 are we getting actually tumor reactivity.

NOTE Confidence: 0.782859847894737

00:53:23.380 --> 00:53:25.342 And So what we can do is again take

NOTE Confidence: 0.782859847894737

00:53:25.342 --> 00:53:27.247 some of these post vaccine T cells,

NOTE Confidence: 0.782859847894737

00:53:27.250 --> 00:53:29.350 stimulate them with one of our vaccine

NOTE Confidence: 0.782859847894737

00:53:29.350 --> 00:53:31.529 peptides in this case against a driver

NOTE Confidence: 0.782859847894737

00:53:31.529 --> 00:53:33.761 mutation PR one and then coculture with

NOTE Confidence: 0.782859847894737

00:53:33.761 --> 00:53:35.451 that same patients autologous tumor

NOTE Confidence: 0.782859847894737

00:53:35.451 --> 00:53:38.271 and see whether those PBR one specific

NOTE Confidence: 0.782859847894737

00:53:38.271 --> 00:53:40.706 T cells actually recognize tumor.

NOTE Confidence: 0.782859847894737

00:53:40.710 --> 00:53:42.048 And the answer is, is yes,

NOTE Confidence: 0.782859847894737

00:53:42.050 --> 00:53:43.580 that we are able to actually

NOTE Confidence: 0.782859847894737

00:53:43.580 --> 00:53:44.345 get tumor reactivity.

NOTE Confidence: 0.782859847894737

00:53:44.350 --> 00:53:45.350 It's not for all patients,

NOTE Confidence: 0.782859847894737

00:53:45.350 --> 00:53:46.772 but for the majority of patients

NOTE Confidence: 0.782859847894737

00:53:46.772 --> 00:53:48.619 we're able to get evidence of tumor.

NOTE Confidence: 0.782859847894737

00:53:48.620 --> 00:53:50.000 The activity with vaccination and

NOTE Confidence: 0.782859847894737

00:53:50.000 --> 00:53:51.999 so really this is our our first

NOTE Confidence: 0.782859847894737

00:53:51.999 --> 00:53:53.685 sort of attempt at an antigen

NOTE Confidence: 0.782859847894737

00:53:53.685 --> 00:53:55.208 directed therapy and kidney cancer,

NOTE Confidence: 0.782859847894737

00:53:55.210 --> 00:53:56.690 but I think neoantigens are

NOTE Confidence: 0.782859847894737

00:53:56.690 --> 00:53:58.170 a good place to start.

NOTE Confidence: 0.782859847894737

00:53:58.170 --> 00:53:59.214 But I think those are clearly

NOTE Confidence: 0.782859847894737

00:53:59.214 --> 00:54:00.569 not going to be the whole story.

NOTE Confidence: 0.782859847894737

00:54:00.570 --> 00:54:02.166 And kidney cancer we know that

NOTE Confidence: 0.782859847894737

00:54:02.166 --> 00:54:03.538 there's not an association between

NOTE Confidence: 0.782859847894737

00:54:03.538 --> 00:54:05.104 as I showed high neoantigens and

NOTE Confidence: 0.782859847894737

00:54:05.104 --> 00:54:06.310 and response to therapy.

NOTE Confidence: 0.782859847894737

00:54:06.310 --> 00:54:09.362 So we have to look beyond this

NOTE Confidence: 0.782859847894737

00:54:09.362 --> 00:54:10.670 initial neoantigen focused

NOTE Confidence: 0.842992571818182

00:54:10.670 --> 00:54:12.326 world and really look at other

NOTE Confidence: 0.842992571818182

00:54:12.326 --> 00:54:13.750 sources of antigens as well.

NOTE Confidence: 0.842992571818182

00:54:13.750 --> 00:54:15.682 And very briefly this is work large

NOTE Confidence: 0.842992571818182

00:54:15.682 --> 00:54:17.152 in collaboration with Bill Kaylan's

NOTE Confidence: 0.842992571818182

00:54:17.152 --> 00:54:18.637 Group and Steve Carr's group.

NOTE Confidence: 0.842992571818182

00:54:18.640 --> 00:54:20.894 We're using the same cohort of patients,

NOTE Confidence: 0.842992571818182

00:54:20.900 --> 00:54:23.006 the same tumors to actually look

NOTE Confidence: 0.842992571818182

00:54:23.006 --> 00:54:24.410 at endogenous retroviruses as

NOTE Confidence: 0.842992571818182

00:54:24.472 --> 00:54:26.059 potential antigenic targets.

NOTE Confidence: 0.842992571818182

00:54:26.060 --> 00:54:27.194 These are ones that are aberrantly

NOTE Confidence: 0.842992571818182

00:54:27.194 --> 00:54:28.779 expressed in a few different tumor types,

NOTE Confidence: 0.842992571818182

00:54:28.780 --> 00:54:31.062 but specifically kidney cancer has a high

NOTE Confidence: 0.842992571818182

00:54:31.062 --> 00:54:33.380 expression of these endogenous retroviruses.

NOTE Confidence: 0.842992571818182

00:54:33.380 --> 00:54:35.620 So we can again use our computational

NOTE Confidence: 0.842992571818182

00:54:35.620 --> 00:54:37.180 tools to predict antigens,

NOTE Confidence: 0.842992571818182

00:54:37.180 --> 00:54:39.184 potential ER derived antigens and use

NOTE Confidence: 0.842992571818182

00:54:39.184 --> 00:54:41.383 mass spec based approach to actually

NOTE Confidence: 0.842992571818182

00:54:41.383 --> 00:54:42.999 physically detect those antigens.

NOTE Confidence: 0.842992571818182

00:54:43.000 --> 00:54:44.860 And in this first patient,

NOTE Confidence: 0.842992571818182

00:54:44.860 --> 00:54:47.317 this patient 110 from our original trial,

NOTE Confidence: 0.842992571818182

00:54:47.320 --> 00:54:49.210 we see that there were seven ERV.

NOTE Confidence: 0.842992571818182

00:54:49.210 --> 00:54:50.745 Derived peptides that were present

NOTE Confidence: 0.842992571818182

00:54:50.745 --> 00:54:52.941 on tumor but on a normal normal

NOTE Confidence: 0.842992571818182

00:54:52.941 --> 00:54:55.349 tissue and when we take one of those,

NOTE Confidence: 0.842992571818182

00:54:55.350 --> 00:54:57.120 the one highlighted in pink and

NOTE Confidence: 0.842992571818182

00:54:57.120 --> 00:54:59.095 actually test those for reactivity in

NOTE Confidence: 0.842992571818182

00:54:59.095 --> 00:55:01.309 peripheral blood cells from that patient,

NOTE Confidence: 0.842992571818182

00:55:01.310 --> 00:55:03.256 we can see that those that patients

NOTE Confidence: 0.842992571818182

00:55:03.256 --> 00:55:04.927 actually capable of mounting a low

NOTE Confidence: 0.842992571818182

00:55:04.927 --> 00:55:06.761 level but a response to that peptide.

NOTE Confidence: 0.842992571818182

00:55:06.770 --> 00:55:08.604 So just a initial proof of concept

NOTE Confidence: 0.842992571818182

00:55:08.604 --> 00:55:10.268 that these RV's can actually be

NOTE Confidence: 0.842992571818182

00:55:10.268 --> 00:55:12.179 antigenic and now we can actually do

NOTE Confidence: 0.842992571818182

00:55:12.233 --> 00:55:13.858 this much more systematically look

NOTE Confidence: 0.842992571818182

00:55:13.858 --> 00:55:16.222 across all patients and all of their

NOTE Confidence: 0.842992571818182

00:55:16.222 --> 00:55:17.686 endogenous retroviruses that are

NOTE Confidence: 0.842992571818182

00:55:17.686 --> 00:55:19.960 presented and look for antigenicity.

NOTE Confidence: 0.842992571818182

00:55:19.960 --> 00:55:21.706 Again, these are very focused approaches.

NOTE Confidence: 0.842992571818182

00:55:21.710 --> 00:55:24.878 These are specific hypothesis,

NOTE Confidence: 0.842992571818182

00:55:24.878 --> 00:55:25.670 neoantigen.

NOTE Confidence: 0.842992571818182

00:55:25.670 --> 00:55:26.778 Uh or endogenous retroviruses,

NOTE Confidence: 0.842992571818182

00:55:26.778 --> 00:55:29.422 the last thing we want to do is ultimately

NOTE Confidence: 0.842992571818182

00:55:29.422 --> 00:55:30.977 build systems and collaborate with

NOTE Confidence: 0.842992571818182

00:55:30.977 --> 00:55:32.898 with groups that are interested in

NOTE Confidence: 0.842992571818182

00:55:32.898 --> 00:55:34.453 more broad antigen discovery efforts

NOTE Confidence: 0.842992571818182

00:55:34.453 --> 00:55:36.150 for things that we're not thinking of.

NOTE Confidence: 0.842992571818182

00:55:36.150 --> 00:55:37.686 And so we recently entered a

NOTE Confidence: 0.842992571818182

00:55:37.686 --> 00:55:38.710 partnership with Remedy Bio,

NOTE Confidence: 0.842992571818182

00:55:38.710 --> 00:55:41.200 a biotech company based in Ireland,

NOTE Confidence: 0.842992571818182

00:55:41.200 --> 00:55:43.348 which has a a novel platform,

NOTE Confidence: 0.842992571818182

00:55:43.350 --> 00:55:45.354 a nano reactor platform that actually

NOTE Confidence: 0.842992571818182

00:55:45.354 --> 00:55:47.051 allows you to coculture individual

NOTE Confidence: 0.842992571818182

00:55:47.051 --> 00:55:49.158 T cells and tumor cells within each

NOTE Confidence: 0.842992571818182

00:55:49.158 --> 00:55:50.150 of these wells,

NOTE Confidence: 0.842992571818182

00:55:50.150 --> 00:55:51.968 but actually measure which of those

NOTE Confidence: 0.842992571818182

00:55:51.968 --> 00:55:53.610 wells are reactive to tumors,

NOTE Confidence: 0.842992571818182

00:55:53.610 --> 00:55:55.955 use a pneumatic system to extract viable.

NOTE Confidence: 0.842992571818182

00:55:55.960 --> 00:55:57.472 These cells tumor reactive T cells

NOTE Confidence: 0.842992571818182

00:55:57.472 --> 00:55:59.518 and be able to sequence their TCR,

NOTE Confidence: 0.842992571818182

00:55:59.520 --> 00:56:01.686 so really be able to understand

NOTE Confidence: 0.842992571818182

00:56:01.686 --> 00:56:03.509 much more systematically what is

NOTE Confidence: 0.842992571818182

00:56:03.509 --> 00:56:05.079 the repertoire of tumor reactive

NOTE Confidence: 0.842992571818182

00:56:05.079 --> 00:56:06.810 T cells in kidney cancer.

NOTE Confidence: 0.842992571818182

00:56:06.810 --> 00:56:08.994 And so overall our kind of hope with

NOTE Confidence: 0.842992571818182

00:56:08.994 --> 00:56:11.201 this branch of the lab is really to

NOTE Confidence: 0.842992571818182

00:56:11.201 --> 00:56:13.069 move beyond our classic tools for

NOTE Confidence: 0.842992571818182

00:56:13.069 --> 00:56:14.914 immunomodulation to add the steering

NOTE Confidence: 0.842992571818182

00:56:14.914 --> 00:56:16.966 wheels rather than only looking at

NOTE Confidence: 0.842992571818182

00:56:16.966 --> 00:56:18.526 the inhibitory checkpoints or the

NOTE Confidence: 0.842992571818182

00:56:18.526 --> 00:56:20.555 the sort of go signals for your

NOTE Confidence: 0.842992571818182

00:56:20.555 --> 00:56:22.250 immune cells to actually be able

NOTE Confidence: 0.842992571818182

00:56:22.250 --> 00:56:24.287 to add a component of an antigen

NOTE Confidence: 0.842992571818182

00:56:24.287 --> 00:56:26.169 directed therapy really focus on

NOTE Confidence: 0.842992571818182

00:56:26.169 --> 00:56:27.468 HLA restricted antigens.

NOTE Confidence: 0.842992571818182

00:56:27.470 --> 00:56:29.166 And that's where the model for the lab,

NOTE Confidence: 0.842992571818182

00:56:29.170 --> 00:56:31.210 it's been a busy but a great year.

NOTE Confidence: 0.842992571818182

00:56:31.210 --> 00:56:33.429 That's been a wonderful, a wonderful time.

NOTE Confidence: 0.842992571818182

00:56:33.430 --> 00:56:34.800 I felt incredibly welcome here

NOTE Confidence: 0.842992571818182

00:56:34.800 --> 00:56:36.787 at Yale and been lucky to have

NOTE Confidence: 0.842992571818182

00:56:36.787 --> 00:56:38.461 remarkably energetic and and and kind

NOTE Confidence: 0.842992571818182

00:56:38.461 --> 00:56:40.350 group of people joined the lab and

NOTE Confidence: 0.842992571818182

00:56:40.350 --> 00:56:42.082 really focus on sort of this model

NOTE Confidence: 0.842992571818182

00:56:42.082 --> 00:56:43.468 that we start with the patient.

NOTE Confidence: 0.842992571818182

00:56:43.470 --> 00:56:46.190 We try to learn things from their tumor,

NOTE Confidence: 0.842992571818182

00:56:46.190 --> 00:56:47.198 from their immune system.

NOTE Confidence: 0.842992571818182

00:56:47.198 --> 00:56:48.710 We have a lot to go

NOTE Confidence: 0.819177374545455

00:56:48.769 --> 00:56:51.595 and a lot of open questions about sell sell

NOTE Confidence: 0.819177374545455

00:56:51.595 --> 00:56:52.948 interactions and about antigenic targets,

NOTE Confidence: 0.819177374545455

00:56:52.948 --> 00:56:54.860 but always with an eye to try to

NOTE Confidence: 0.819177374545455

00:56:54.912 --> 00:56:56.647 bring that into improved diagnostics,

NOTE Confidence: 0.819177374545455

00:56:56.650 --> 00:56:57.601 actually improve therapeutics.

NOTE Confidence: 0.819177374545455

00:56:57.601 --> 00:57:00.167 And try to bring that back into early

NOTE Confidence: 0.819177374545455

00:57:00.167 --> 00:57:02.239 phase trials like I showed with our

NOTE Confidence: 0.819177374545455

00:57:02.239 --> 00:57:03.847 neoantigen trial and then to continually

NOTE Confidence: 0.819177374545455

00:57:03.847 --> 00:57:05.676 iterate to try to get a little bit

NOTE Confidence: 0.819177374545455

00:57:05.676 --> 00:57:07.027 better each time that we do this.

NOTE Confidence: 0.819177374545455

00:57:07.030 --> 00:57:08.066 And so with that,

NOTE Confidence: 0.819177374545455

00:57:08.066 --> 00:57:09.620 thank you again for the opportunity

NOTE Confidence: 0.819177374545455

00:57:09.671 --> 00:57:11.085 to speak and a lot of people,

NOTE Confidence: 0.819177374545455

00:57:11.090 --> 00:57:12.710 both my lab and collaborators,

NOTE Confidence: 0.819177374545455

00:57:12.710 --> 00:57:14.445 but most importantly the patients

NOTE Confidence: 0.819177374545455

00:57:14.445 --> 00:57:15.486 and their families.

NOTE Confidence: 0.819177374545455

00:57:15.490 --> 00:57:16.910 And this time I'm happy

NOTE Confidence: 0.819177374545455

00:57:16.910 --> 00:57:18.046 to take some questions.

NOTE Confidence: 0.6855213275

00:57:24.640 --> 00:57:26.760 Alright, just one question.

NOTE Confidence: 0.76040465

00:57:32.920 --> 00:57:35.068 In general, most of them are.

NOTE Confidence: 0.787722142

00:57:39.180 --> 00:57:41.970 There must be some difference. Responded.

NOTE Confidence: 0.8806778

00:57:44.940 --> 00:57:45.740 Yeah.

NOTE Confidence: 0.640314086666667

00:57:48.010 --> 00:57:50.926 The CDA looks great based on

NOTE Confidence: 0.640314086666667

00:57:50.930 --> 00:57:52.198 responding to non response.

NOTE Confidence: 0.774150805714286

00:57:55.030 --> 00:57:56.383 Within infiltrated tumors,

NOTE Confidence: 0.774150805714286

00:57:56.383 --> 00:57:58.187 it's a good question.

NOTE Confidence: 0.774150805714286

00:57:58.190 --> 00:58:00.020 I think that's where our sort

NOTE Confidence: 0.774150805714286

00:58:00.020 --> 00:58:01.852 of larger collection of this 90

NOTE Confidence: 0.774150805714286

00:58:01.852 --> 00:58:03.508 single cell sequence of 96 tumors

NOTE Confidence: 0.774150805714286

00:58:03.508 --> 00:58:05.387 will I think be very helpful.

NOTE Confidence: 0.774150805714286

00:58:05.390 --> 00:58:07.586 If I were to answer this six months ago,

NOTE Confidence: 0.774150805714286

00:58:07.590 --> 00:58:08.952 I would have said it's it's

NOTE Confidence: 0.774150805714286

00:58:08.952 --> 00:58:10.463 going to be impacted largely by

NOTE Confidence: 0.774150805714286

00:58:10.463 --> 00:58:11.848 the myeloid component as well.

NOTE Confidence: 0.774150805714286

00:58:11.850 --> 00:58:13.146 And I think that's still is

NOTE Confidence: 0.774150805714286

00:58:13.146 --> 00:58:14.530 probably true that we kind of

NOTE Confidence: 0.774150805714286

00:58:14.530 --> 00:58:15.934 showed in our original study that

NOTE Confidence: 0.774150805714286

00:58:15.934 --> 00:58:17.311 even though we're we're thinking

NOTE Confidence: 0.774150805714286

00:58:17.311 --> 00:58:18.746 that we're measuring CDT cells,

NOTE Confidence: 0.774150805714286

00:58:18.750 --> 00:58:20.748 likely what we're actually capturing is

NOTE Confidence: 0.774150805714286

00:58:20.748 --> 00:58:22.080 interactions between those terminally

NOTE Confidence: 0.774150805714286

00:58:22.130 --> 00:58:23.690 exhausted CDT cells and the myeloid.

NOTE Confidence: 0.774150805714286

00:58:23.690 --> 00:58:24.791 Component and that.

NOTE Confidence: 0.774150805714286

00:58:24.791 --> 00:58:25.158 Historically,

NOTE Confidence: 0.774150805714286

00:58:25.158 --> 00:58:27.700 we've only targeted 11 branch of that.

NOTE Confidence: 0.774150805714286

00:58:27.700 --> 00:58:29.282 We've only targeted the T cell compartment

NOTE Confidence: 0.774150805714286

00:58:29.282 --> 00:58:30.850 and not the myeloid compartment.

NOTE Confidence: 0.774150805714286

00:58:30.850 --> 00:58:31.942 I think that's going to be

NOTE Confidence: 0.774150805714286

00:58:31.942 --> 00:58:32.840 one big piece of it.

NOTE Confidence: 0.774150805714286

00:58:32.840 --> 00:58:34.520 The second piece which was we

NOTE Confidence: 0.774150805714286

00:58:34.520 --> 00:58:36.285 weren't expecting to find is this

NOTE Confidence: 0.774150805714286

00:58:36.285 --> 00:58:37.760 particular phenotype of slam of

NOTE Confidence: 0.774150805714286

00:58:37.760 --> 00:58:39.284 seven positive CDT cells that

NOTE Confidence: 0.774150805714286

00:58:39.284 --> 00:58:40.734 requires a lot of validation

NOTE Confidence: 0.774150805714286

00:58:40.734 --> 00:58:42.072 both that they're actually real,

NOTE Confidence: 0.774150805714286

00:58:42.072 --> 00:58:43.920 but then that they have a functional role.

NOTE Confidence: 0.774150805714286

00:58:43.920 --> 00:58:45.012 I think that's going to be the

NOTE Confidence: 0.774150805714286

00:58:45.012 --> 00:58:45.880 other sort of component.

NOTE Confidence: 0.774150805714286

00:58:45.880 --> 00:58:47.692 Are there different actually the cell

NOTE Confidence: 0.774150805714286

00:58:47.692 --> 00:58:49.259 phone even though they're broadly

NOTE Confidence: 0.774150805714286

00:58:49.259 --> 00:58:51.436 infiltrated by similar numbers of CDT cells,

NOTE Confidence: 0.774150805714286

00:58:51.440 --> 00:58:53.449 are those CDT cells of a different

NOTE Confidence: 0.774150805714286

00:58:53.449 --> 00:58:55.309 phenotype that actually might be perturbed?

NOTE Confidence: 0.774150805714286

00:58:55.310 --> 00:58:57.238 In some way and one nice thing is

NOTE Confidence: 0.774150805714286

00:58:57.238 --> 00:58:59.513 there are even you know FDA approved

NOTE Confidence: 0.774150805714286

00:58:59.513 --> 00:59:01.480 antibodies like elotuzumab for slim F7.

NOTE Confidence: 0.774150805714286

00:59:01.480 --> 00:59:04.024 So one can see actually a pathway those

NOTE Confidence: 0.774150805714286

00:59:04.024 --> 00:59:06.300 end up being true to to the clinic.

NOTE Confidence: 0.774150805714286

00:59:06.300 --> 00:59:07.658 So that's that's kind of ongoing work.

NOTE Confidence: 0.774150805714286

00:59:07.660 --> 00:59:09.460 Now actually a rotation student in

NOTE Confidence: 0.774150805714286

00:59:09.460 --> 00:59:11.184 the lab is putting some of seven

NOTE Confidence: 0.774150805714286

00:59:11.184 --> 00:59:13.163 into some of these T cells and we're

NOTE Confidence: 0.774150805714286

00:59:13.163 --> 00:59:14.903 actually seeing whether this impacts

NOTE Confidence: 0.774150805714286

00:59:14.903 --> 00:59:15.947 cytokine production proliferation,

NOTE Confidence: 0.774150805714286

00:59:15.950 --> 00:59:16.500 tumor killing.

NOTE Confidence: 0.7731182

00:59:20.150 --> 00:59:25.780 Yeah. Ohh. And. 27.

NOTE Confidence: 0.70971655

00:59:33.350 --> 00:59:33.780 Thank you.

NOTE Confidence: 0.792454042

00:59:38.800 --> 00:59:40.070 Yeah, it's a great question.

NOTE Confidence: 0.792454042

00:59:40.070 --> 00:59:42.646 So the question was just about the

NOTE Confidence: 0.792454042

00:59:42.646 --> 00:59:44.137 stromal component fibroblasts and

NOTE Confidence: 0.792454042

00:59:44.137 --> 00:59:45.819 other stromal and kidney can't

NOTE Confidence: 0.792454042

00:59:45.819 --> 00:59:47.877 strictly anthelion cells as well which

NOTE Confidence: 0.792454042

00:59:47.877 --> 00:59:49.848 these are heavily vascular tumors.

NOTE Confidence: 0.792454042

00:59:49.850 --> 00:59:51.596 I would say our first study

NOTE Confidence: 0.792454042

00:59:51.596 --> 00:59:52.990 really didn't we weren't we,

NOTE Confidence: 0.792454042

00:59:52.990 --> 00:59:54.404 we really didn't look at it at

NOTE Confidence: 0.792454042

00:59:54.404 --> 00:59:55.676 all because our protocol really

NOTE Confidence: 0.792454042

00:59:55.676 --> 00:59:56.908 enriched for immune cells.

NOTE Confidence: 0.792454042

00:59:56.910 --> 00:59:59.350 I think now with not only the chromophobe,

NOTE Confidence: 0.792454042

00:59:59.350 --> 01:00:00.496 the Chromophobe project,

NOTE Confidence: 0.792454042

01:00:00.496 --> 01:00:03.616 but also this these you know larger 96

NOTE Confidence: 0.792454042

01:00:03.616 --> 01:00:05.854 samples we actually much more broadly.

NOTE Confidence: 0.792454042

01:00:05.860 --> 01:00:06.880 Capture cancer,

NOTE Confidence: 0.792454042

01:00:06.880 --> 01:00:09.430 associated fibroblasts and epithelial cells.

NOTE Confidence: 0.792454042

01:00:09.430 --> 01:00:10.934 I will say that first 13 patients we

NOTE Confidence: 0.792454042

01:00:10.934 --> 01:00:12.438 didn't see any that were specifically

NOTE Confidence: 0.792454042

01:00:12.438 --> 01:00:13.526 associated with response or

NOTE Confidence: 0.792454042

01:00:13.526 --> 01:00:14.950 resistance in this very broad look.

NOTE Confidence: 0.792454042

01:00:14.950 --> 01:00:16.495 But that obviously doesn't mean

NOTE Confidence: 0.792454042

01:00:16.495 --> 01:00:18.040 they're not important actually driving

NOTE Confidence: 0.792454042

01:00:18.090 --> 01:00:19.548 either T cell or myeloid biology.

NOTE Confidence: 0.792454042

01:00:19.550 --> 01:00:20.817 And so that's something that I think

NOTE Confidence: 0.792454042

01:00:20.817 --> 01:00:22.328 we need to look into in more depth,

NOTE Confidence: 0.792454042

01:00:22.330 --> 01:00:23.290 but we don't have,

NOTE Confidence: 0.792454042

01:00:23.290 --> 01:00:24.730 we don't know quite yet but

NOTE Confidence: 0.792454042

01:00:24.784 --> 01:00:25.880 actually now I think.

NOTE Confidence: 0.792454042

01:00:25.880 --> 01:00:26.022 Yeah.

NOTE Confidence: 0.792454042

01:00:26.022 --> 01:00:27.016 Now we actually have the tools that

NOTE Confidence: 0.792454042

01:00:27.016 --> 01:00:27.980 I would be able to look at it.

NOTE Confidence: 0.885148

01:00:32.720 --> 01:00:33.020 You know.

NOTE Confidence: 0.688550993333333

01:00:35.680 --> 01:00:38.716 Really the only type that sold?

NOTE Confidence: 0.688550993333333

01:00:38.720 --> 01:00:40.668 Obesity and commonly treated

NOTE Confidence: 0.688550993333333

01:00:40.668 --> 01:00:42.129 with cycling inhibitors.

NOTE Confidence: 0.688550993333333

01:00:42.130 --> 01:00:44.188 I'm wondering if you have any hints

NOTE Confidence: 0.688550993333333

01:00:44.188 --> 01:00:46.570 in your data as to the role of

NOTE Confidence: 0.688550993333333

01:00:46.570 --> 01:00:48.132 metabolism in the micro environment.

NOTE Confidence: 0.688550993333333

01:00:48.132 --> 01:00:49.334 Yeah, it's a great question.

NOTE Confidence: 0.688550993333333

01:00:49.334 --> 01:00:50.439 The shortening I'll give is,

NOTE Confidence: 0.688550993333333

01:00:50.440 --> 01:00:51.800 is not yet, but I'd love to be

NOTE Confidence: 0.688550993333333

01:00:51.800 --> 01:00:53.417 able to support it and look at

NOTE Confidence: 0.688550993333333

01:00:53.417 --> 01:00:54.647 it because it's some fascinating

NOTE Confidence: 0.688550993333333

01:00:54.697 --> 01:00:56.215 parts about kidney cancer as well.

NOTE Confidence: 0.688550993333333

01:00:56.220 --> 01:00:58.005 So there's something where even

NOTE Confidence: 0.688550993333333

01:00:58.005 --> 01:00:59.790 though it's you're more likely

NOTE Confidence: 0.688550993333333

01:00:59.852 --> 01:01:01.442 to get it the the incidence

NOTE Confidence: 0.688550993333333

01:01:01.442 --> 01:01:03.080 is higher in obese patients.

NOTE Confidence: 0.688550993333333

01:01:03.080 --> 01:01:04.586 Those patients who are obese who

NOTE Confidence: 0.688550993333333

01:01:04.586 --> 01:01:05.940 have metastatic disease do better.

NOTE Confidence: 0.688550993333333

01:01:05.940 --> 01:01:07.384 Something called the obesity

NOTE Confidence: 0.688550993333333

01:01:07.384 --> 01:01:08.828 paradox within kidney cancer.

NOTE Confidence: 0.688550993333333

01:01:08.830 --> 01:01:10.084 And we know that there's some

NOTE Confidence: 0.688550993333333

01:01:10.084 --> 01:01:11.560 hints that these are in general

NOTE Confidence: 0.688550993333333

01:01:11.560 --> 01:01:12.756 are really metabolically active.

NOTE Confidence: 0.688550993333333

01:01:12.760 --> 01:01:14.150 There's really excellent work from

NOTE Confidence: 0.688550993333333

01:01:14.150 --> 01:01:15.540 Jeff Rathmell and Jim Rathman's

NOTE Confidence: 0.688550993333333

01:01:15.583 --> 01:01:17.431 group that looked at what are the the

NOTE Confidence: 0.688550993333333

01:01:17.431 --> 01:01:18.732 primary consumers of for instance

NOTE Confidence: 0.688550993333333

01:01:18.732 --> 01:01:20.047 glucose and the micro environment.

NOTE Confidence: 0.688550993333333

01:01:20.050 --> 01:01:21.667 And since that's not the tumor cells,

NOTE Confidence: 0.688550993333333

01:01:21.670 --> 01:01:23.290 it turns out it's mostly the

NOTE Confidence: 0.688550993333333

01:01:23.290 --> 01:01:24.759 myeloid compartment that's a primary

NOTE Confidence: 0.688550993333333

01:01:24.759 --> 01:01:26.087 drive the primary consumer.

NOTE Confidence: 0.688550993333333

01:01:26.090 --> 01:01:28.583 But T cells are are still consuming a lot.

NOTE Confidence: 0.688550993333333

01:01:28.590 --> 01:01:30.170 How those actually ultimately I

NOTE Confidence: 0.688550993333333

01:01:30.170 --> 01:01:32.230 think impact the function of T cells,

NOTE Confidence: 0.688550993333333

01:01:32.230 --> 01:01:34.239 I think we haven't looked at all,

NOTE Confidence: 0.688550993333333

01:01:34.240 --> 01:01:35.797 but it would be great to be able to

NOTE Confidence: 0.688550993333333

01:01:35.797 --> 01:01:37.156 explore especially with some of these

NOTE Confidence: 0.688550993333333

01:01:37.156 --> 01:01:38.869 models where we're you know have them in.

NOTE Confidence: 0.688550993333333

01:01:38.870 --> 01:01:40.268 Really nutrient rich,

NOTE Confidence: 0.688550993333333

01:01:40.268 --> 01:01:42.598 metabolically favorable conditions and xvo

NOTE Confidence: 0.688550993333333

01:01:42.598 --> 01:01:45.036 actually would be nice to recapitulate

NOTE Confidence: 0.688550993333333

01:01:45.036 --> 01:01:46.836 some of the nutrient limitations

NOTE Confidence: 0.688550993333333

01:01:46.836 --> 01:01:49.149 that are present in the tumor itself.

NOTE Confidence: 0.688550993333333

01:01:49.150 --> 01:01:51.430 Yes.

NOTE Confidence: 0.688550993333333

01:01:51.430 --> 01:01:52.354 Well, thank you,

NOTE Confidence: 0.688550993333333

01:01:52.354 --> 01:01:52.662 David.

NOTE Confidence: 0.688550993333333

01:01:52.662 --> 01:01:54.914 I thank you all for also coming

NOTE Confidence: 0.688550993333333

01:01:54.914 --> 01:01:56.954 here in person and we'll look

NOTE Confidence: 0.688550993333333

01:01:56.954 --> 01:01:59.128 forward to grand rounds next week.

NOTE Confidence: 0.688550993333333

01:01:59.130 --> 01:02:00.999 Thanks so much.