WEBVTT

NOTE duration:"00:56:17.6400000"

NOTE recognizability:0.838

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NOTE Confidence: 0.768883635833333

00:00:00.000 --> 00:00:02.250 Real pleasure to introduce Doctor Ari

NOTE Confidence: 0.768883635833333

00:00:02.250 --> 00:00:04.680 Hakimi as today's Grand Round speaker.

NOTE Confidence: 0.768883635833333

00:00:04.680 --> 00:00:06.080 He's the an Associate Professor

NOTE Confidence: 0.768883635833333

00:00:06.080 --> 00:00:08.240 and Co leader of the Translational

NOTE Confidence: 0.768883635833333

00:00:08.240 --> 00:00:10.325 Kidney Cancer program and Memorial

NOTE Confidence: 0.768883635833333

00:00:10.325 --> 00:00:12.250 Sloan Kettering Cancer Center. Dr.

NOTE Confidence: 0.768883635833333

00:00:12.250 --> 00:00:13.750 Hakimi is a urologic surgeon who's

NOTE Confidence: 0.768883635833333

00:00:13.750 --> 00:00:15.598 focused on the care of patients

NOTE Confidence: 0.768883635833333

00:00:15.598 --> 00:00:16.639 with urologic malignancies,

NOTE Confidence: 0.768883635833333

00:00:16.640 --> 00:00:17.906 especially kidney tumors.

NOTE Confidence: 0.768883635833333

00:00:17.906 --> 00:00:20.438 He received his medical degree in

NOTE Confidence: 0.768883635833333

00:00:20.438 --> 00:00:22.182 residency training from Einstein

NOTE Confidence: 0.768883635833333

00:00:22.182 --> 00:00:24.080 College of Madison and completed

NOTE Confidence: 0.768883635833333

00:00:24.080 --> 00:00:25.680 his fellowship in Urologic Oncology,

NOTE Confidence: 0.768883635833333

00:00:25.680 --> 00:00:27.300 Oncology and Memorial Sloan

NOTE Confidence: 0.768883635833333

00:00:27.300 --> 00:00:28.515 Kettering Cancer Center.

NOTE Confidence: 0.768883635833333

00:00:28.520 --> 00:00:30.170 His research really aims to

NOTE Confidence: 0.768883635833333

00:00:30.170 --> 00:00:31.160 understand immune infiltration,

NOTE Confidence: 0.768883635833333

00:00:31.160 --> 00:00:33.015 inflammation in the tumor microenvironment

NOTE Confidence: 0.768883635833333

00:00:33.015 --> 00:00:35.372 in RCC and to identify novel

NOTE Confidence: 0.768883635833333

00:00:35.372 --> 00:00:37.124 therapeutic targets to overcome

NOTE Confidence: 0.768883635833333

00:00:37.124 --> 00:00:38.876 resistance to systemic therapy.

NOTE Confidence: 0.768883635833333

00:00:38.880 --> 00:00:40.840 His studies apply bulk single

NOTE Confidence: 0.768883635833333

00:00:40.840 --> 00:00:42.800 cell and spatial RNA sequencing,

NOTE Confidence: 0.768883635833333

00:00:42.800 --> 00:00:45.880 flow cytometry and immunogenomic analysis.

NOTE Confidence: 0.768883635833333

00:00:45.880 --> 00:00:47.740 Really to understand both patient

NOTE Confidence: 0.768883635833333

00:00:47.740 --> 00:00:49.600 samples and a novel immunocompetent

NOTE Confidence: 0.768883635833333

00:00:49.662 --> 00:00:51.540 kidney cancer mouse line that his

NOTE Confidence: 0.768883635833333

00:00:51.540 --> 00:00:53.335 lab has developed really has been

NOTE Confidence: 0.768883635833333

00:00:53.335 --> 00:00:55.036 a game game changer for the study

NOTE Confidence: 0.768883635833333

00:00:55.036 --> 00:00:56.844 of kidney cancer and particularly

NOTE Confidence: 0.768883635833333

00:00:56.844 --> 00:00:58.799 the immunobiology of kidney cancer.

NOTE Confidence: 0.768883635833333

00:00:58.800 --> 00:01:00.558 I followed Ari's work for many,

NOTE Confidence: 0.768883635833333

00:01:00.560 --> 00:01:02.208 many years now and to see him go

NOTE Confidence: 0.768883635833333

00:01:02.208 --> 00:01:04.139 from what was a rising star in kidney

NOTE Confidence: 0.768883635833333

00:01:04.139 --> 00:01:05.935 Cancer Research to now really one of

NOTE Confidence: 0.768883635833333

00:01:05.935 --> 00:01:07.720 the world leaders has been a pleasure.

NOTE Confidence: 0.768883635833333

00:01:07.720 --> 00:01:09.416 And it's a a body of work that

NOTE Confidence: 0.768883635833333

00:01:09.416 --> 00:01:10.240 I've tremendously admired.

NOTE Confidence: 0.768883635833333

00:01:10.240 --> 00:01:12.200 So it's really a pleasure to be able to walk.

NOTE Confidence: 0.768883635833333

00:01:12.200 --> 00:01:13.999 Welcome Doctor Akimi to grand rounds today.

NOTE Confidence: 0.868401695

00:01:20.670 --> 00:01:21.666 All right. Thank you so much.

NOTE Confidence: 0.868401695

00:01:21.670 --> 00:01:24.310 And it's really a pleasure to be here

NOTE Confidence: 0.868401695

00:01:24.310 --> 00:01:27.354 at Yale and especially I was especially

NOTE Confidence: 0.868401695

00:01:27.354 --> 00:01:30.480 enthusiastic come here because of David

NOTE Confidence: 0.868401695

00:01:30.566 --> 00:01:31.958 and I mean talk about rising stars.

NOTE Confidence: 0.868401695

00:01:31.960 --> 00:01:33.759 David is incredible and he's got great

NOTE Confidence: 0.868401695

00:01:33.759 --> 00:01:35.678 mentors here with with Harriet and others.

NOTE Confidence: 0.868401695

00:01:35.680 --> 00:01:38.677 And I think it's it's a real pleasure here.

NOTE Confidence: 0.868401695

00:01:38.680 --> 00:01:40.040 So that's my only disclosures,

NOTE Confidence: 0.868401695

00:01:40.040 --> 00:01:41.905 none of which is pertinent

NOTE Confidence: 0.868401695

00:01:41.905 --> 00:01:43.397 to this talk today.

NOTE Confidence: 0.868401695

00:01:43.400 --> 00:01:45.848 So I'll talk a little bit about the genetic,

NOTE Confidence: 0.868401695

00:01:45.848 --> 00:01:48.288 the genomic and genetic background

NOTE Confidence: 0.868401695

00:01:48.288 --> 00:01:49.752 of kidney cancer,

NOTE Confidence: 0.868401695

00:01:49.760 --> 00:01:51.548 in particular clear cell renal cell

NOTE Confidence: 0.868401695

00:01:51.548 --> 00:01:53.676 carcinoma which is the most common and

NOTE Confidence: 0.868401695

00:01:53.676 --> 00:01:55.434 aggressive form of kidney cancer but

NOTE Confidence: 0.868401695

00:01:55.434 --> 00:01:57.477 also one of the most immunoresponsive.

NOTE Confidence: 0.868401695

00:01:57.480 --> 00:01:59.223 We'll talk a little bit about the

NOTE Confidence: 0.868401695

00:01:59.223 --> 00:02:01.583 role of the micro environment as a

NOTE Confidence: 0.868401695

00:02:01.583 --> 00:02:03.434 predictive response and really focus

NOTE Confidence: 0.868401695

00:02:03.434 --> 00:02:05.582 on myeloid compartment which is one

NOTE Confidence: 0.868401695

00:02:05.582 --> 00:02:07.996 of my lab's interests a little bit

NOTE Confidence: 0.868401695

00:02:07.996 --> 00:02:10.024 from the genomic determinants of this

NOTE Confidence: 0.868401695

00:02:10.024 --> 00:02:12.317 and then some of the insights using

NOTE Confidence: 0.868401695

00:02:12.317 --> 00:02:14.530 both human and mouse strategies to

NOTE Confidence: 0.868401695

00:02:14.530 --> 00:02:17.440 understand this for for future targeting.

NOTE Confidence: 0.868401695

00:02:17.440 --> 00:02:20.450 So kidney cancer is about is the

NOTE Confidence: 0.868401695

00:02:20.450 --> 00:02:23.359 6th most common cancer overall or

NOTE Confidence: 0.868401695

00:02:23.360 --> 00:02:24.560 eighth most common cancer overall,

NOTE Confidence: 0.868401695

00:02:24.560 --> 00:02:26.080 6th most common in men.

NOTE Confidence: 0.868401695

00:02:26.080 --> 00:02:28.439 There's a 2 to one gender difference

NOTE Confidence: 0.868401695

00:02:28.440 --> 00:02:30.085 and we know that you know within

NOTE Confidence: 0.868401695

00:02:30.085 --> 00:02:31.279 the kidney there are many,

NOTE Confidence: 0.868401695

00:02:31.280 --> 00:02:33.212 many subtypes of kidney cancer and even

NOTE Confidence: 0.868401695

00:02:33.212 --> 00:02:35.716 if you just took the most common subtypes,

NOTE Confidence: 0.868401695

00:02:35.720 --> 00:02:37.256 they're very genetically different.

NOTE Confidence: 0.868401695

00:02:37.256 --> 00:02:39.880 Clear cell represents the most common form.

NOTE Confidence: 0.868401695

00:02:39.880 --> 00:02:42.512 About 6570% of all kidney tumors are

NOTE Confidence: 0.868401695

00:02:42.512 --> 00:02:45.020 a clear cell and we know the most

NOTE Confidence: 0.868401695

00:02:45.020 --> 00:02:47.160 about it from a genetic standpoint.

NOTE Confidence: 0.868401695

00:02:47.160 --> 00:02:47.961 But we also,

NOTE Confidence: 0.868401695

00:02:47.961 --> 00:02:49.296 there's also some very intriguing

NOTE Confidence: 0.868401695

00:02:49.296 --> 00:02:50.479 phenomenon that existed in it,

NOTE Confidence: 0.868401695

00:02:50.480 --> 00:02:52.020 particularly the amount of the

NOTE Confidence: 0.868401695

00:02:52.020 --> 00:02:52.636 immune response.

NOTE Confidence: 0.868401695

00:02:52.640 --> 00:02:54.558 And it's still not clear why these

NOTE Confidence: 0.868401695

00:02:54.558 --> 00:02:56.402 tumors are so immune infiltrated and

NOTE Confidence: 0.868401695

00:02:56.402 --> 00:02:58.642 and why they are so responsive to

NOTE Confidence: 0.868401695

00:02:58.701 --> 00:03:00.526 immunotherapy compared to other tumors

NOTE Confidence: 0.868401695

00:03:00.526 --> 00:03:02.780 that are much more highly mutated,

NOTE Confidence: 0.868401695

00:03:02.780 --> 00:03:05.106 for example like melanomas or or

NOTE Confidence: 0.868401695

00:03:05.106 --> 00:03:06.462 bladder lung cancers where you see

NOTE Confidence: 0.868401695

00:03:06.462 --> 00:03:08.478 a lot of mutations in those tumors.

NOTE Confidence: 0.868401695

00:03:08.480 --> 00:03:11.145 And probably you know everyone

NOTE Confidence: 0.868401695

00:03:11.145 --> 00:03:13.673 references TCGA papers initially in

NOTE Confidence: 0.868401695

00:03:13.673 --> 00:03:15.638 terms of the fundamental understanding.

NOTE Confidence: 0.868401695

00:03:15.640 --> 00:03:17.215 And I think some of the takeaways

NOTE Confidence: 0.868401695

00:03:17.215 --> 00:03:18.645 from this tumor from this analysis

NOTE Confidence: 0.868401695

00:03:18.645 --> 00:03:20.797 which is one of the first tumors to be

NOTE Confidence: 0.868401695

00:03:20.797 --> 00:03:22.177 profiled was that it's really dominated

NOTE Confidence: 0.868401695

00:03:22.177 --> 00:03:24.890 by a few driver mutations related to

NOTE Confidence: 0.868401695

00:03:24.890 --> 00:03:27.680 tumor suppressors On the 3P locus.

NOTE Confidence: 0.868401695

00:03:27.680 --> 00:03:28.916 There's not a lot of mutations.

NOTE Confidence: 0.868401695

00:03:28.920 --> 00:03:30.972 There's some copy number events that

NOTE Confidence: 0.868401695

00:03:30.972 --> 00:03:33.041 are really fundamental and maybe some

NOTE Confidence: 0.868401695

00:03:33.041 --> 00:03:34.955 of which are enriched in metastases.

NOTE Confidence: 0.868401695

00:03:34.960 --> 00:03:37.018 But there's not an obvious clue as

NOTE Confidence: 0.868401695

00:03:37.018 --> 00:03:39.564 to you know why these tumors retain

NOTE Confidence: 0.868401695

00:03:39.564 --> 00:03:41.554 such a high immune infiltration.

NOTE Confidence: 0.868401695

00:03:41.560 --> 00:03:43.756 We also know a little bit about what happens.

NOTE Confidence: 0.868401695

00:03:43.760 --> 00:03:46.202 Thanks to Seminole work from the

NOTE Confidence: 0.868401695

00:03:46.202 --> 00:03:47.612 Sanger Institute where they looked

NOTE Confidence: 0.868401695

00:03:47.612 --> 00:03:49.466 at what were the fundamental events

NOTE Confidence: 0.868401695

00:03:49.466 --> 00:03:51.470 that that are associated with clear

NOTE Confidence: 0.868401695

00:03:51.470 --> 00:03:53.319 cell nasal carcinoma development.

NOTE Confidence: 0.868401695

00:03:53.320 --> 00:03:55.868 And what this paper showed for the

NOTE Confidence: 0.868401695

00:03:55.868 --> 00:03:57.959 really the first time was that

NOTE Confidence: 0.868401695

00:03:57.960 --> 00:04:01.801 the loss of chromosome 3P1 arm is

NOTE Confidence: 0.868401695

00:04:01.801 --> 00:04:03.967 critical to the oncogenesis and then

NOTE Confidence: 0.868401695

00:04:03.967 --> 00:04:06.288 that's followed by VHL loss whether

NOTE Confidence: 0.868401695

00:04:06.288 --> 00:04:08.233 it's mutations or or methylation.

NOTE Confidence: 0.95925346

00:04:08.240 --> 00:04:10.599 But basically 90% of all clear cells

NOTE Confidence: 0.95925346

00:04:10.599 --> 00:04:13.330 have this and then eventually over time

NOTE Confidence: 0.95925346

00:04:13.330 --> 00:04:16.113 additional driver mutations are lost and that

NOTE Confidence: 0.95925346

00:04:16.113 --> 00:04:18.088 leads to different evolutionary subtypes.

NOTE Confidence: 0.95925346

00:04:18.088 --> 00:04:21.960 And in this paper Samara Trashlik and others

NOTE Confidence: 0.95925346

00:04:21.960 --> 00:04:25.075 came up with a relatively complex schema.

NOTE Confidence: 0.95925346

00:04:25.080 --> 00:04:26.988 But you know, fundamentally you can

NOTE Confidence: 0.95925346

00:04:26.988 --> 00:04:29.274 think about it as the tumors lose

NOTE Confidence: 0.95925346

00:04:29.274 --> 00:04:31.182 VHL and then they usually acquire

NOTE Confidence: 0.95925346

00:04:31.182 --> 00:04:33.360 one or two additional hits to form

NOTE Confidence: 0.95925346

00:04:33.360 --> 00:04:35.160 into sort of different trajectories.

NOTE Confidence: 0.95925346

00:04:35.160 --> 00:04:38.202 We know that tumors that lose PBM one and

NOTE Confidence: 0.95925346

00:04:38.202 --> 00:04:41.396 set D2 for example maybe more angiogenic,

NOTE Confidence: 0.95925346

00:04:41.400 --> 00:04:43.320 they may they may tend to be a

NOTE Confidence: 0.95925346

00:04:43.320 --> 00:04:45.160 little bit more indolent overall,

NOTE Confidence: 0.95925346

00:04:45.160 --> 00:04:47.314 maybe possibly more responsive to certain

NOTE Confidence: 0.95925346

00:04:47.314 --> 00:04:49.215 therapies like including even immunotherapy

NOTE Confidence: 0.95925346

00:04:49.215 --> 00:04:51.280 although that's not entirely clear.

NOTE Confidence: 0.95925346

00:04:51.280 --> 00:04:53.226 And then BAP one mutations which occurs

NOTE Confidence: 0.95925346

00:04:53.226 --> 00:04:55.376 well are are typically associated with

NOTE Confidence: 0.95925346

00:04:55.376 --> 00:04:57.466 more high grade aggressive proliferative

NOTE Confidence: 0.95925346

00:04:57.466 --> 00:05:00.157 tumor types and then you can have multiple

NOTE Confidence: 0.95925346

00:05:00.157 --> 00:05:01.840 clonal drivers which also represent a

NOTE Confidence: 0.95925346

00:05:01.840 --> 00:05:03.280 very aggressive form of kidney cancer.

NOTE Confidence: 0.95925346

00:05:03.280 --> 00:05:04.960 So we're starting to get a better

NOTE Confidence: 0.95925346

00:05:04.960 --> 00:05:06.680 framework for the underlying genomics,

NOTE Confidence: 0.95925346

00:05:06.680 --> 00:05:08.171 but none of this really has been

NOTE Confidence: 0.95925346

00:05:08.171 --> 00:05:09.400 shown to be targetable.

NOTE Confidence: 0.95925346

00:05:09.400 --> 00:05:11.680 So for years we just really started to

NOTE Confidence: 0.95925346

00:05:11.680 --> 00:05:13.678 understand what was driving kidney cancer,

NOTE Confidence: 0.95925346

00:05:13.680 --> 00:05:14.608 but we really didn't,

NOTE Confidence: 0.95925346

00:05:14.608 --> 00:05:16.000 wasn't giving us any further insights,

NOTE Confidence: 0.95925346

00:05:16.000 --> 00:05:17.160 weren't an oncogene that you

NOTE Confidence: 0.95925346

00:05:17.160 --> 00:05:18.320 could develop a target to.

NOTE Confidence: 0.95925346

00:05:18.320 --> 00:05:21.350 And while people are certainly working

NOTE Confidence: 0.95925346

00:05:21.350 --> 00:05:24.280 on epigenetic regulation and strategies,

NOTE Confidence: 0.95925346

00:05:24.280 --> 00:05:26.730 it's it's certainly not an obvious pathway

NOTE Confidence: 0.95925346

00:05:26.730 --> 00:05:29.357 forward in kidney cancer at least right now.

NOTE Confidence: 0.95925346

00:05:29.360 --> 00:05:30.360 And at the same time,

NOTE Confidence: 0.95925346

00:05:30.360 --> 00:05:31.764 we also knew clinically that that

NOTE Confidence: 0.95925346

00:05:31.764 --> 00:05:33.343 you know most of the targeted

NOTE Confidence: 0.95925346

00:05:33.343 --> 00:05:35.113 therapies were limited to the micro

NOTE Confidence: 0.95925346

00:05:35.113 --> 00:05:36.599 environment of the of the cancer.

NOTE Confidence: 0.95925346

00:05:36.600 --> 00:05:39.444 And really we've seen a tremendous

NOTE Confidence: 0.95925346

00:05:39.444 --> 00:05:41.385 growth in in outcomes and survival

NOTE Confidence: 0.95925346

00:05:41.385 --> 00:05:42.557 for kidney cancer patients.

NOTE Confidence: 0.95925346

00:05:42.560 --> 00:05:44.025 But it's all really focusing

NOTE Confidence: 0.95925346

00:05:44.025 --> 00:05:45.197 on the micro environment.

NOTE Confidence: 0.95925346

00:05:45.200 --> 00:05:46.256 So even back in,

NOTE Confidence: 0.95925346

00:05:46.256 --> 00:05:49.032 in the 90s when we were studying IL 2

NOTE Confidence: 0.95925346

00:05:49.032 --> 00:05:51.276 both in melanomas and kidney cancers,

NOTE Confidence: 0.95925346

00:05:51.280 --> 00:05:52.520 that was really the only

NOTE Confidence: 0.95925346

00:05:52.520 --> 00:05:53.760 treatment that seemed to work.

NOTE Confidence: 0.95925346

00:05:53.760 --> 00:05:56.280 We had tried all the chemotherapies

NOTE Confidence: 0.95925346

00:05:56.280 --> 00:05:58.116 you can imagine in the 80s,

NOTE Confidence: 0.95925346

00:05:58.120 --> 00:06:00.640 90s and you would see responses

NOTE Confidence: 0.95925346

00:06:00.640 --> 00:06:02.720 even 7 to 10% cures,

NOTE Confidence: 0.95925346

00:06:02.720 --> 00:06:03.920 but with very,

NOTE Confidence: 0.95925346

00:06:03.920 --> 00:06:05.920 very high toxicity in those

NOTE Confidence: 0.95925346

00:06:05.920 --> 00:06:07.720 populations and in those patients.

NOTE Confidence: 0.95925346

00:06:07.720 --> 00:06:10.485 And it wasn't until the advent of

NOTE Confidence: 0.95925346

00:06:10.485 --> 00:06:12.585 of really by work from Bill Kalin

NOTE Confidence: 0.95925346

00:06:12.585 --> 00:06:14.192 and others where we recognized the

NOTE Confidence: 0.95925346

00:06:14.192 --> 00:06:15.674 importance of Hifs that all these

NOTE Confidence: 0.95925346

00:06:15.674 --> 00:06:17.239 focus on VEGF had come around.

NOTE Confidence: 0.95925346

00:06:17.240 --> 00:06:20.320 And then it wasn't really until this

NOTE Confidence: 0.95925346

00:06:20.320 --> 00:06:22.504 notion of immunotherapy came around that

NOTE Confidence: 0.95925346

00:06:22.504 --> 00:06:24.520 we started to see this big revolution

NOTE Confidence: 0.95925346

00:06:24.520 --> 00:06:26.560 in terms of survival and outcomes.

NOTE Confidence: 0.95925346

00:06:26.560 --> 00:06:28.120 But it's all really focused on,

NOTE Confidence: 0.95925346

00:06:28.120 --> 00:06:31.160 on the micro environment.

NOTE Confidence: 0.95925346

00:06:31.160 --> 00:06:33.057 We know that you can take some

NOTE Confidence: 0.95925346

00:06:33.057 --> 00:06:34.992 of these genetic events that I

NOTE Confidence: 0.95925346

00:06:34.992 --> 00:06:36.732 mentioned earlier and risk stratify

NOTE Confidence: 0.95925346

00:06:36.732 --> 00:06:38.038 patients a little further.

NOTE Confidence: 0.95925346

00:06:38.040 --> 00:06:40.480 This is the work that we did several

NOTE Confidence: 0.95925346

00:06:40.480 --> 00:06:42.620 years ago now looking at the impact

NOTE Confidence: 0.95925346

00:06:42.620 --> 00:06:44.510 of some of these common mutations

NOTE Confidence: 0.95925346

00:06:44.568 --> 00:06:46.698 and outcomes for patients that were

NOTE Confidence: 0.95925346

00:06:46.698 --> 00:06:48.762 receiving VEGF therapy and it was

NOTE Confidence: 0.95925346

00:06:48.762 --> 00:06:50.688 you know prognostic maybe you could

NOTE Confidence: 0.95925346

00:06:50.688 --> 00:06:52.015 further stratify patients that

NOTE Confidence: 0.95925346

00:06:52.015 --> 00:06:53.590 were grouped into clinical risk

NOTE Confidence: 0.95925346

00:06:53.590 --> 00:06:55.519 groups by by common mutations.

NOTE Confidence: 0.908135683333334

00:06:55.520 --> 00:06:58.257 But it wasn't really telling us anything

NOTE Confidence: 0.908135683333334

00:06:58.257 --> 00:07:00.520 about the underlying immunobiology or

NOTE Confidence: 0.908135683333334

00:07:00.520 --> 00:07:02.000 angiogenic biology in these tumors.

NOTE Confidence: 0.908135683333334

00:07:02.000 --> 00:07:04.490 It was really more just a

NOTE Confidence: 0.908135683333334

00:07:04.490 --> 00:07:06.380 prognostic feature about it.

NOTE Confidence: 0.908135683333334

00:07:06.380 --> 00:07:09.030 So with this revolution of

NOTE Confidence: 0.908135683333334

00:07:09.030 --> 00:07:10.598 immunotherapies both by themselves

NOTE Confidence: 0.908135683333334

00:07:10.598 --> 00:07:12.674 and in combination with VEDF therapy,

NOTE Confidence: 0.908135683333334

00:07:12.680 --> 00:07:14.668 we've seen the the survival rate and

NOTE Confidence: 0.908135683333334

00:07:14.668 --> 00:07:16.558 the response rates go up dramatically.

NOTE Confidence: 0.908135683333334

00:07:16.560 --> 00:07:18.289 So you know the median survival when

NOTE Confidence: 0.908135683333334

00:07:18.289 --> 00:07:20.004 when I first started my training

NOTE Confidence: 0.908135683333334

00:07:20.004 --> 00:07:21.539 for metastatic kidney cancer was

NOTE Confidence: 0.908135683333334

00:07:21.539 --> 00:07:23.515 you know a year and a half or so

NOTE Confidence: 0.908135683333334

00:07:23.515 --> 00:07:25.091 and now we're pushing five years

NOTE Confidence: 0.908135683333334

00:07:25.091 --> 00:07:28.040 for for a lot of patients and and

NOTE Confidence: 0.908135683333334

00:07:28.040 --> 00:07:30.116 potentially curing some patients.

NOTE Confidence: 0.908135683333334

00:07:30.120 --> 00:07:32.024 And we there's a real need to

NOTE Confidence: 0.908135683333334

00:07:32.024 --> 00:07:33.607 understand why that's the case and

NOTE Confidence: 0.908135683333334

00:07:33.607 --> 00:07:35.252 how we can do better because we

NOTE Confidence: 0.908135683333334

00:07:35.309 --> 00:07:37.074 know that invariably most patients

NOTE Confidence: 0.908135683333334

00:07:37.074 --> 00:07:39.680 despite this high response rate will

NOTE Confidence: 0.908135683333334

00:07:39.680 --> 00:07:43.349 eventually develop resistance and you

NOTE Confidence: 0.908135683333334

00:07:43.349 --> 00:07:45.203 know understanding why that's the case

NOTE Confidence: 0.908135683333334

00:07:45.203 --> 00:07:47.118 requires you know good models to do.

NOTE Confidence: 0.908135683333334

00:07:47.120 --> 00:07:50.914 So we know that from an immunotherapy

NOTE Confidence: 0.908135683333334

00:07:50.914 --> 00:07:53.128 standpoint that it's not ATMB driven

NOTE Confidence: 0.908135683333334

00:07:53.128 --> 00:07:54.820 tumor at least not obviously and

NOTE Confidence: 0.908135683333334

00:07:54.880 --> 00:07:56.707 maybe you can break down the types

NOTE Confidence: 0.908135683333334

00:07:56.707 --> 00:07:58.399 of mutations a little bit more.

NOTE Confidence: 0.908135683333334

00:07:58.400 --> 00:08:00.045 I was just talking to David about

NOTE Confidence: 0.908135683333334

00:08:00.045 --> 00:08:01.480 this last night,

NOTE Confidence: 0.908135683333334

00:08:01.480 --> 00:08:03.520 but you know there's it's not obvious.

NOTE Confidence: 0.908135683333334

00:08:03.520 --> 00:08:04.625 There have been several attempts

NOTE Confidence: 0.908135683333334

00:08:04.625 --> 00:08:06.518 to look at TMB as a predictor for

NOTE Confidence: 0.908135683333334

00:08:06.518 --> 00:08:08.247 responses and most of the large clinical

NOTE Confidence: 0.908135683333334

00:08:08.300 --> 00:08:09.920 trials that have been performed that

NOTE Confidence: 0.908135683333334

00:08:09.920 --> 00:08:11.466 have have released their data have

NOTE Confidence: 0.908135683333334

00:08:11.466 --> 00:08:12.864 not shown this and certainly David

NOTE Confidence: 0.908135683333334

00:08:12.864 --> 00:08:14.479 has been on the forefront of this.

NOTE Confidence: 0.908135683333334

00:08:14.480 --> 00:08:16.230 But if you look across some of

NOTE Confidence: 0.908135683333334

00:08:16.230 --> 00:08:17.989 the major phase three trials that

NOTE Confidence: 0.908135683333334

00:08:17.989 --> 00:08:19.879 have at least released their data,

NOTE Confidence: 0.908135683333334

00:08:19.880 --> 00:08:21.704 there's not a really a signal at all

NOTE Confidence: 0.908135683333334

00:08:21.704 --> 00:08:23.239 with respect tumor mutation burden.

NOTE Confidence: 0.908135683333334

00:08:23.240 --> 00:08:25.844 We've looked in David and others have

NOTE Confidence: 0.908135683333334

00:08:25.844 --> 00:08:28.288 looked at whether mutations in PBM one

NOTE Confidence: 0.908135683333334

00:08:28.288 --> 00:08:30.580 or loss of nine P which is a common

NOTE Confidence: 0.908135683333334

00:08:30.580 --> 00:08:32.760 event in metastatic kidney cancers,

NOTE Confidence: 0.908135683333334

00:08:32.760 --> 00:08:34.288 whether that's associated with

NOTE Confidence: 0.908135683333334

00:08:34.288 --> 00:08:35.434 immune infiltration patterns.

NOTE Confidence: 0.908135683333334

00:08:35.440 --> 00:08:37.636 There may be some signals there.

NOTE Confidence: 0.908135683333334

00:08:37.640 --> 00:08:39.565 It's not a clear biomarker though and

NOTE Confidence: 0.908135683333334

00:08:39.565 --> 00:08:42.165 and that sort of has been lacking from a

NOTE Confidence: 0.908135683333334

00:08:42.165 --> 00:08:43.960 mutational and copy number standpoint.

NOTE Confidence: 0.908135683333334

00:08:43.960 --> 00:08:45.752 So I think one of the things that

NOTE Confidence: 0.908135683333334

00:08:45.752 --> 00:08:47.356 is unique about kidney cancer is

NOTE Confidence: 0.908135683333334

00:08:47.356 --> 00:08:49.369 that you know we've started to look

NOTE Confidence: 0.908135683333334

00:08:49.369 --> 00:08:51.199 many years ago now at transcriptomic

NOTE Confidence: 0.908135683333334

00:08:51.200 --> 00:08:52.708 predictors because the mutations

NOTE Confidence: 0.908135683333334

00:08:52.708 --> 00:08:54.970 are clearly and copy number of

NOTE Confidence: 0.908135683333334

00:08:55.033 --> 00:08:57.223 events are clearly not sufficient to

NOTE Confidence: 0.908135683333334

00:08:57.223 --> 00:08:59.515 determine who's going to respond at

NOTE Confidence: 0.908135683333334

00:08:59.515 --> 00:09:01.440 least from a biomarker standpoint.

NOTE Confidence: 0.908135683333334

00:09:01.440 --> 00:09:03.632 And you can just take a very simple

NOTE Confidence: 0.908135683333334

00:09:03.632 --> 00:09:05.514 metric of the uniqueness of kidney

NOTE Confidence: 0.908135683333334

00:09:05.514 --> 00:09:08.176 cancer and this I just plot out you

NOTE Confidence: 0.908135683333334

00:09:08.176 --> 00:09:09.916 know VEGFA and CD8 infiltration.

NOTE Confidence: 0.908135683333334

00:09:09.920 --> 00:09:11.320 This was an older slide,

NOTE Confidence: 0.908135683333334

00:09:11.320 --> 00:09:12.994 but I like showing it 'cause I think it

NOTE Confidence: 0.908135683333334

00:09:12.994 --> 00:09:14.556 shows the uniqueness of kidney cancer,

NOTE Confidence: 0.908135683333334

00:09:14.560 --> 00:09:15.102 clear cell,

NOTE Confidence: 0.908135683333334

00:09:15.102 --> 00:09:16.999 at least with respect to some of

NOTE Confidence: 0.908135683333334

00:09:16.999 --> 00:09:18.800 the micro environmental genes.

NOTE Confidence: 0.908135683333334

00:09:18.800 --> 00:09:21.200 And we know that they're just

NOTE Confidence: 0.908135683333334

00:09:21.200 --> 00:09:23.675 dominated by high infiltration of CD8

NOTE Confidence: 0.908135683333334

00:09:23.675 --> 00:09:25.675 cells and high angiogenic programs.

NOTE Confidence: 0.908135683333334

00:09:25.680 --> 00:09:27.479 So the question of course and this

NOTE Confidence: 0.908135683333334

00:09:27.479 --> 00:09:29.163 was shown across cancers and it's

NOTE Confidence: 0.908135683333334

00:09:29.163 --> 00:09:30.879 really distinct from its from the,

NOTE Confidence: 0.908135683333334

00:09:30.880 --> 00:09:32.240 from the normal tissue.

NOTE Confidence: 0.908135683333334

00:09:32.240 --> 00:09:35.240 If you look at for example lung cancers,

NOTE Confidence: 0.908135683333334

00:09:35.240 --> 00:09:35.542 many,

NOTE Confidence: 0.908135683333334

00:09:35.542 --> 00:09:37.656 much of the lung itself is very

NOTE Confidence: 0.908135683333334

00:09:37.656 --> 00:09:38.260 mean infiltrated

NOTE Confidence: 0.86279424625

00:09:38.320 --> 00:09:40.000 likely due to smoking or other

NOTE Confidence: 0.86279424625

00:09:40.000 --> 00:09:41.113 other carcinogenic features.

NOTE Confidence: 0.86279424625

00:09:41.113 --> 00:09:42.597 But the kidney itself,

NOTE Confidence: 0.86279424625

00:09:42.600 --> 00:09:44.150 the normal kidney is not

NOTE Confidence: 0.86279424625

00:09:44.150 --> 00:09:45.080 particularly mean infiltrated,

NOTE Confidence: 0.86279424625

00:09:45.080 --> 00:09:47.300 but the tumors are often very

NOTE Confidence: 0.86279424625

00:09:47.300 --> 00:09:48.040 dramatically infiltrated.

NOTE Confidence: 0.86279424625

00:09:48.040 --> 00:09:50.050 So there's something very distinct

NOTE Confidence: 0.86279424625

00:09:50.050 --> 00:09:52.060 about the actual tumor itself

NOTE Confidence: 0.86279424625

00:09:52.123 --> 00:09:54.098 rather than the underlying organ

NOTE Confidence: 0.86279424625

00:09:54.098 --> 00:09:56.073 that it's that's derived from.

NOTE Confidence: 0.86279424625

00:09:56.080 --> 00:09:58.352 This is work we did when when I

NOTE Confidence: 0.86279424625

00:09:58.352 --> 00:10:00.140 was just starting out and we we

NOTE Confidence: 0.86279424625

00:10:00.140 --> 00:10:02.384 you know we we we used immune

NOTE Confidence: 0.86279424625

00:10:02.384 --> 00:10:04.354 deconvolution strategies to show this.

NOTE Confidence: 0.86279424625

00:10:04.360 --> 00:10:07.535 You could take signatures for

NOTE Confidence: 0.86279424625

00:10:07.535 --> 00:10:10.530 T cells or for macrophages,

NOTE Confidence: 0.86279424625

00:10:10.530 --> 00:10:11.880 NK cells etcetera.

NOTE Confidence: 0.86279424625

00:10:11.880 --> 00:10:14.580 And you can start just deconvoluting

NOTE Confidence: 0.86279424625

00:10:14.653 --> 00:10:16.837 bulk RNA sequencing data and start

NOTE Confidence: 0.86279424625

00:10:16.837 --> 00:10:19.159 to try to understand where tumors

NOTE Confidence: 0.86279424625

00:10:19.160 --> 00:10:21.000 or particular samples might might

NOTE Confidence: 0.86279424625

00:10:21.000 --> 00:10:23.305 fall in a spectrum and and you

NOTE Confidence: 0.86279424625

00:10:23.305 --> 00:10:24.955 can use this to also subgroup.

NOTE Confidence: 0.86279424625

00:10:24.960 --> 00:10:26.912 So we use this strategy to kind of

NOTE Confidence: 0.86279424625

00:10:26.912 --> 00:10:28.555 think about tumor micro environmental

NOTE Confidence: 0.86279424625

00:10:28.555 --> 00:10:30.385 subgroups within kidney cancer and

NOTE Confidence: 0.86279424625

00:10:30.385 --> 00:10:32.294 this was our first attempt about

NOTE Confidence: 0.86279424625

00:10:32.294 --> 00:10:34.220 eight or nine years ago to look at you

NOTE Confidence: 0.86279424625

00:10:34.273 --> 00:10:35.978 know whether there's these enriched

NOTE Confidence: 0.86279424625

00:10:35.978 --> 00:10:38.000 groups and whether there's you know

NOTE Confidence: 0.86279424625

00:10:38.000 --> 00:10:39.680 other groups within kidney cancer.

NOTE Confidence: 0.86279424625

00:10:39.680 --> 00:10:41.760 Maybe that would sort of explain why you

NOTE Confidence: 0.86279424625

00:10:41.760 --> 00:10:43.497 see some some really great responses

NOTE Confidence: 0.86279424625

00:10:43.497 --> 00:10:45.771 in the streaming top And we we did

NOTE Confidence: 0.86279424625

00:10:45.771 --> 00:10:47.635 see that we saw you could clearly see

NOTE Confidence: 0.86279424625

00:10:47.640 --> 00:10:49.320 these T cell infiltrated clusters.

NOTE Confidence: 0.86279424625

00:10:49.320 --> 00:10:50.896 You could see at this point we really

NOTE Confidence: 0.86279424625

00:10:50.896 --> 00:10:52.079 didn't think about angiogenesis,

NOTE Confidence: 0.86279424625

00:10:52.080 --> 00:10:54.036 but in retrospect you know you've

NOTE Confidence: 0.86279424625

00:10:54.036 --> 00:10:55.655 seen angiogenic cluster and we'll

NOTE Confidence: 0.86279424625

00:10:55.655 --> 00:10:57.475 talk more about that in a minute.

NOTE Confidence: 0.86279424625

00:10:57.480 --> 00:10:59.580 And you know it did correlate with

NOTE Confidence: 0.86279424625

00:10:59.580 --> 00:11:01.440 certain genetic programs mostly

NOTE Confidence: 0.86279424625

00:11:01.440 --> 00:11:03.520 antigen presenting machinery programs.

NOTE Confidence: 0.86279424625

00:11:03.520 --> 00:11:06.600 So there was an up regulation of antigen

NOTE Confidence: 0.86279424625

00:11:06.600 --> 00:11:08.280 presenting machinery transcript,

NOTE Confidence: 0.86279424625

00:11:08.280 --> 00:11:10.023 but it wasn't clear still from this

NOTE Confidence: 0.86279424625

00:11:10.023 --> 00:11:11.918 point what was actually driving this.

NOTE Confidence: 0.86279424625

00:11:11.920 --> 00:11:15.200 We we looked at genetics,

NOTE Confidence: 0.86279424625

00:11:15.200 --> 00:11:16.550 common mutations and wasn't at

NOTE Confidence: 0.86279424625

00:11:16.550 --> 00:11:18.190 least obvious at the time when

NOTE Confidence: 0.86279424625

00:11:18.190 --> 00:11:19.355 we first did this study,

NOTE Confidence: 0.86279424625

00:11:19.360 --> 00:11:21.272 although that's evolved a bit and

NOTE Confidence: 0.86279424625

00:11:21.272 --> 00:11:23.144 that same approach was applied by

NOTE Confidence: 0.86279424625

00:11:23.144 --> 00:11:24.960 Genentech when they first published

NOTE Confidence: 0.86279424625

00:11:24.960 --> 00:11:26.796 and then analyze the EMOTION trial.

NOTE Confidence: 0.86279424625

00:11:26.800 --> 00:11:28.504 This was the first attempt to

NOTE Confidence: 0.86279424625

00:11:28.504 --> 00:11:30.280 combine VEGF and IO therapies.

NOTE Confidence: 0.86279424625

00:11:30.280 --> 00:11:33.240 They used tizolizumab and bevacizumab,

NOTE Confidence: 0.86279424625

00:11:33.240 --> 00:11:35.556 which is a VEGF monoclonal antibody.

NOTE Confidence: 0.86279424625

00:11:35.560 --> 00:11:36.164 And this,

NOTE Confidence: 0.86279424625

00:11:36.164 --> 00:11:37.976 this trial was negative in terms

NOTE Confidence: 0.86279424625

00:11:37.976 --> 00:11:39.800 of improving the standard of care,

NOTE Confidence: 0.86279424625

00:11:39.800 --> 00:11:41.016 but it was biomarker.

NOTE Confidence: 0.86279424625

00:11:41.016 --> 00:11:43.607 Biomarker Rich and I give a lot of

NOTE Confidence: 0.86279424625

00:11:43.607 --> 00:11:46.043 credit to Genentech for not only doing

NOTE Confidence: 0.86279424625

00:11:46.043 --> 00:11:47.978 phenomenal genomic work but also

NOTE Confidence: 0.86279424625

00:11:47.978 --> 00:11:49.878 making it all publicly available,

NOTE Confidence: 0.86279424625

00:11:49.880 --> 00:11:51.356 which is something that other companies

NOTE Confidence: 0.86279424625

00:11:51.356 --> 00:11:53.400 have have been a little reluctant to do.

NOTE Confidence: 0.86279424625

00:11:53.400 --> 00:11:54.534 So and maybe it was because it

NOTE Confidence: 0.86279424625

00:11:54.534 --> 00:11:55.280 was a negative study,

NOTE Confidence: 0.86279424625

00:11:55.280 --> 00:11:56.400 they were willing to share so much,

NOTE Confidence: 0.86279424625

00:11:56.400 --> 00:11:58.356 but it really was very helpful.

NOTE Confidence: 0.86279424625

00:11:58.360 --> 00:12:01.990 And David McDermott and others from

NOTE Confidence: 0.86279424625

00:12:01.990 --> 00:12:03.920 Boston performed really the first

NOTE Confidence: 0.86279424625

00:12:03.920 --> 00:12:05.900 type of analysis in the context

NOTE Confidence: 0.86279424625

00:12:05.965 --> 00:12:08.185 of systemic therapy to show that

NOTE Confidence: 0.86279424625

00:12:08.185 --> 00:12:09.665 these micro environmental groups

NOTE Confidence: 0.86279424625

00:12:09.728 --> 00:12:11.723 angiogenesis and T cell infiltration

NOTE Confidence: 0.86279424625

00:12:11.723 --> 00:12:13.718 and myeloid programs may stratify

NOTE Confidence: 0.86279424625

00:12:13.720 --> 00:12:15.720 patients into different groups but

NOTE Confidence: 0.86279424625

00:12:15.720 --> 00:12:17.720 also may associate with response.

NOTE Confidence: 0.86279424625

00:12:17.720 --> 00:12:19.560 And one thing I would point out I

NOTE Confidence: 0.86279424625

00:12:19.560 --> 00:12:21.306 think it it it's sort of logical

NOTE Confidence: 0.86279424625

00:12:21.306 --> 00:12:23.668 that a tumor that may have a lot of

NOTE Confidence: 0.86279424625

00:12:23.668 --> 00:12:25.276 T effector cells would respond well

NOTE Confidence: 0.832781635

00:12:25.280 --> 00:12:26.008 to amitotherapy.

NOTE Confidence: 0.832781635

00:12:26.008 --> 00:12:28.556 But you know what they also showed

NOTE Confidence: 0.832781635

00:12:28.556 --> 00:12:30.884 was that myeloid populations as as

NOTE Confidence: 0.832781635

00:12:30.884 --> 00:12:33.328 determined by again a gene program

NOTE Confidence: 0.832781635

00:12:33.328 --> 00:12:35.758 we're we're driving resistance also.

NOTE Confidence: 0.832781635

00:12:35.760 --> 00:12:37.832 So you could be AT effect or

NOTE Confidence: 0.832781635

00:12:37.832 --> 00:12:40.582 high tumor but if you had a high

NOTE Confidence: 0.832781635

00:12:40.582 --> 00:12:42.372 myeloid program it could supersede

NOTE Confidence: 0.832781635

00:12:42.444 --> 00:12:44.852 that impact and and and in fact

NOTE Confidence: 0.832781635

00:12:44.852 --> 00:12:46.496 actually show you know dramatically

NOTE Confidence: 0.832781635

00:12:46.496 --> 00:12:48.116 different responses in that context.

NOTE Confidence: 0.832781635

00:12:48.120 --> 00:12:50.184 So that really sort of laid the groundwork

NOTE Confidence: 0.832781635

00:12:50.184 --> 00:12:51.915 for not only the micro environment

NOTE Confidence: 0.832781635

00:12:51.915 --> 00:12:54.013 relevant but also it could it could

NOTE Confidence: 0.832781635

00:12:54.013 --> 00:12:55.843 predict responses and maybe give us

NOTE Confidence: 0.832781635

00:12:55.843 --> 00:12:57.740 some insight into into resistance.

NOTE Confidence: 0.832781635

00:12:57.740 --> 00:13:00.680 We applied that same strategy initially

NOTE Confidence: 0.832781635

00:13:00.680 --> 00:13:03.225 to just a VEGF cohort only and this was

NOTE Confidence: 0.832781635

00:13:03.225 --> 00:13:05.080 work that I did with with Bob Moecher,

NOTE Confidence: 0.832781635

00:13:05.080 --> 00:13:06.858 one of my mentors at at Sloan

NOTE Confidence: 0.832781635

00:13:06.858 --> 00:13:08.000 Kettering for many years.

NOTE Confidence: 0.832781635

00:13:08.000 --> 00:13:10.160 And this was just looking at

NOTE Confidence: 0.832781635

00:13:10.160 --> 00:13:12.400 the first trial that compared

NOTE Confidence: 0.832781635

00:13:12.400 --> 00:13:14.280 two different VEGF inhibitors.

NOTE Confidence: 0.832781635

00:13:14.280 --> 00:13:16.233 At the time we had really sunitinib

NOTE Confidence: 0.832781635

00:13:16.233 --> 00:13:18.920 and this was the first attempt to try

NOTE Confidence: 0.832781635

00:13:18.920 --> 00:13:21.158 a different strategy or a different

NOTE Confidence: 0.832781635

00:13:21.158 --> 00:13:23.391 VEGF inhibitor and you know it was

NOTE Confidence: 0.832781635

00:13:23.391 --> 00:13:25.518 really more to look at tolerability.

NOTE Confidence: 0.832781635

00:13:25.520 --> 00:13:27.278 There was no difference really in

NOTE Confidence: 0.832781635

00:13:27.280 --> 00:13:28.436 responses but actually Piszopinib

NOTE Confidence: 0.832781635

00:13:28.436 --> 00:13:30.574 but this you know showed a better

NOTE Confidence: 0.832781635

00:13:30.574 --> 00:13:31.998 toxicity profile for patients.

NOTE Confidence: 0.832781635

00:13:32.000 --> 00:13:33.440 So that became the standard of

NOTE Confidence: 0.832781635

00:13:33.440 --> 00:13:35.136 care ELISA Memorial for many years

NOTE Confidence: 0.832781635

00:13:35.136 --> 00:13:36.851 until obviously we developed next

NOTE Confidence: 0.832781635

00:13:36.851 --> 00:13:37.880 generations and immunotherapies.

NOTE Confidence: 0.832781635

00:13:37.880 --> 00:13:39.805 But at this time we took a

NOTE Confidence: 0.832781635

00:13:39.805 --> 00:13:40.355 transcriptomic approach.

NOTE Confidence: 0.832781635

00:13:40.360 --> 00:13:43.684 So we had microarray data from

NOTE Confidence: 0.832781635

00:13:43.684 --> 00:13:45.710 Novartis and we had looked at this

NOTE Confidence: 0.832781635

00:13:45.710 --> 00:13:47.356 question of whether you can identify

NOTE Confidence: 0.832781635

00:13:47.356 --> 00:13:49.491 subgroups and we found you know 4

NOTE Confidence: 0.832781635

00:13:49.491 --> 00:13:51.093 transcriptomic subgroups at the time

NOTE Confidence: 0.832781635

00:13:51.093 --> 00:13:52.953 they tended to really stratify patients.

NOTE Confidence: 0.832781635

00:13:52.960 --> 00:13:53.260 Again,

NOTE Confidence: 0.832781635

00:13:53.260 --> 00:13:55.360 all these patients received EDF first line,

NOTE Confidence: 0.832781635

00:13:55.360 --> 00:13:55.930 so clean,

NOTE Confidence: 0.832781635

00:13:55.930 --> 00:13:57.640 clean cohort and you could clearly

NOTE Confidence: 0.832781635

00:13:57.640 --> 00:13:59.638 see a difference in in groups.

NOTE Confidence: 0.832781635

00:13:59.640 --> 00:14:00.949 And there was a green group here

NOTE Confidence: 0.832781635

00:14:00.949 --> 00:14:02.469 that was very responsive and a red

NOTE Confidence: 0.832781635

00:14:02.469 --> 00:14:03.837 group that was very not responsive.

NOTE Confidence: 0.832781635

00:14:03.840 --> 00:14:05.240 And then there was these yellow and

NOTE Confidence: 0.832781635

00:14:05.240 --> 00:14:06.673 blue in the middle and the green

NOTE Confidence: 0.832781635

00:14:06.673 --> 00:14:08.172 group really had a lot of angiogenic

NOTE Confidence: 0.832781635

00:14:08.172 --> 00:14:09.948 program and that made sense, right?

NOTE Confidence: 0.832781635

00:14:09.948 --> 00:14:13.440 You know, if you have a lot of angiogenesis,

NOTE Confidence: 0.832781635

00:14:13.440 --> 00:14:14.850 it makes sense that you would

NOTE Confidence: 0.832781635

00:14:14.850 --> 00:14:15.555 respond very well.

NOTE Confidence: 0.832781635

00:14:15.560 --> 00:14:18.038 But the red group which was #4,

NOTE Confidence: 0.832781635

00:14:18.040 --> 00:14:19.840 that was the one that didn't respond well.

NOTE Confidence: 0.832781635

00:14:19.840 --> 00:14:21.560 They were actually the worst but they had

NOTE Confidence: 0.832781635

00:14:21.560 --> 00:14:23.320 the second highest amount of angiogenesis.

NOTE Confidence: 0.832781635

00:14:23.320 --> 00:14:24.398 So why why was that the case?

NOTE Confidence: 0.832781635

00:14:24.400 --> 00:14:26.878 Why didn't they stratify nicely by

NOTE Confidence: 0.832781635

00:14:26.880 --> 00:14:28.798 by angiogenic program and and when we

NOTE Confidence: 0.832781635

00:14:28.798 --> 00:14:30.640 compared that group to the other groups,

NOTE Confidence: 0.832781635

00:14:30.640 --> 00:14:32.383 we could see that it was really

NOTE Confidence: 0.832781635

00:14:32.383 --> 00:14:34.080 being dominated by a myeloid program.

NOTE Confidence: 0.832781635

00:14:34.080 --> 00:14:36.755 So despite having high angiogenic

NOTE Confidence: 0.832781635

00:14:36.755 --> 00:14:38.360 phenotype or transcript,

NOTE Confidence: 0.832781635

00:14:38.360 --> 00:14:40.856 they were they were reversing the

NOTE Confidence: 0.832781635

00:14:40.856 --> 00:14:43.617 response based on an infiltration of

NOTE Confidence: 0.832781635

00:14:43.617 --> 00:14:46.167 myeloid myeloids at least inferred

NOTE Confidence: 0.832781635

00:14:46.167 --> 00:14:49.382 by by microarray data.

NOTE Confidence: 0.832781635

00:14:49.382 --> 00:14:49.853 So,

NOTE Confidence: 0.832781635

00:14:49.853 --> 00:14:52.679 so that suggested that it could

NOTE Confidence: 0.832781635

00:14:52.680 --> 00:14:55.506 actually be driving a response overall

NOTE Confidence: 0.832781635

00:14:55.506 --> 00:14:58.353 and the micro environment may be

NOTE Confidence: 0.832781635

00:14:58.353 --> 00:15:01.135 useful in understanding biomarkers in in,

NOTE Confidence: 0.832781635

00:15:01.135 --> 00:15:03.075 in metastatic kidney cancer.

NOTE Confidence: 0.832781635

00:15:03.080 --> 00:15:04.106 And then actually this was something

NOTE Confidence: 0.832781635

00:15:04.106 --> 00:15:05.410 that we did and at the end and

NOTE Confidence: 0.832781635

00:15:05.410 --> 00:15:06.480 actually the my fellow at the time,

NOTE Confidence: 0.779711778333333

00:15:06.480 --> 00:15:07.392 one of the urology fellows at

NOTE Confidence: 0.779711778333333

00:15:07.392 --> 00:15:08.400 the time who was working in,

NOTE Confidence: 0.779711778333333

00:15:08.400 --> 00:15:09.816 in my group actually had the

NOTE Confidence: 0.779711778333333

00:15:09.816 --> 00:15:10.760 suggestion that we look,

NOTE Confidence: 0.779711778333333

00:15:10.760 --> 00:15:12.594 we kind of left them all together

NOTE Confidence: 0.779711778333333

00:15:12.594 --> 00:15:14.159 because there's open Evans Sunitnib,

NOTE Confidence: 0.779711778333333

00:15:14.160 --> 00:15:15.918 we're sort of both VEGF inhibitors.

NOTE Confidence: 0.779711778333333

00:15:15.920 --> 00:15:18.040 But we know that the TKIS target

NOTE Confidence: 0.779711778333333

00:15:18.040 --> 00:15:19.720 lots of different kinases,

NOTE Confidence: 0.779711778333333

00:15:19.720 --> 00:15:22.200 not they're not super specific

NOTE Confidence: 0.779711778333333

00:15:22.200 --> 00:15:24.678 and actually if you look at the

NOTE Confidence: 0.779711778333333

00:15:24.678 --> 00:15:26.240 macrophage and angiogenic groups,

NOTE Confidence: 0.779711778333333

00:15:26.240 --> 00:15:28.160 you could actually see that

NOTE Confidence: 0.779711778333333

00:15:28.160 --> 00:15:30.680 Pizzopinib has quite a different

NOTE Confidence: 0.779711778333333

00:15:30.680 --> 00:15:31.493 stratification than tsunitiv.

NOTE Confidence: 0.779711778333333

00:15:31.493 --> 00:15:33.390 This suggests to us we we didn't

NOTE Confidence: 0.779711778333333

00:15:33.436 --> 00:15:34.878 talk about too much in the paper,

NOTE Confidence: 0.779711778333333

00:15:34.880 --> 00:15:36.952 but it it really suggested that the

NOTE Confidence: 0.779711778333333

00:15:36.952 --> 00:15:38.896 targets of these TKIS may also actually

NOTE Confidence: 0.779711778333333

00:15:38.896 --> 00:15:40.480 be driving some of their responses.

NOTE Confidence: 0.779711778333333

00:15:40.480 --> 00:15:42.960 So some of these kinases are present on

NOTE Confidence: 0.779711778333333

00:15:42.960 --> 00:15:45.477 on immune cell populations for example.

NOTE Confidence: 0.779711778333333

00:15:45.480 --> 00:15:47.454 And the fact that these biomarkers

NOTE Confidence: 0.779711778333333

00:15:47.454 --> 00:15:49.136 were actually different with respect

NOTE Confidence: 0.779711778333333

00:15:49.136 --> 00:15:50.984 to the different Tkis was something

NOTE Confidence: 0.779711778333333

00:15:50.984 --> 00:15:52.958 that that we've now followed up on.

NOTE Confidence: 0.779711778333333

00:15:52.960 --> 00:15:54.766 And I think it's a really

NOTE Confidence: 0.779711778333333

00:15:54.766 --> 00:15:56.320 interesting finding that he made.

NOTE Confidence: 0.779711778333333

00:15:56.320 --> 00:15:58.245 And this just leads back to the

NOTE Confidence: 0.779711778333333

00:15:58.245 --> 00:15:59.977 same concept that what what Dave

NOTE Confidence: 0.779711778333333

00:15:59.977 --> 00:16:01.944 showed in in this in this beautiful

NOTE Confidence: 0.779711778333333

00:16:02.005 --> 00:16:03.883 paper from the from the Genentech

NOTE Confidence: 0.779711778333333

00:16:03.883 --> 00:16:06.150 study others have looked at micro

NOTE Confidence: 0.779711778333333

00:16:06.150 --> 00:16:07.710 environmental features in other

NOTE Confidence: 0.779711778333333

00:16:07.710 --> 00:16:09.344 in other more positive trials.

NOTE Confidence: 0.779711778333333

00:16:09.344 --> 00:16:09.920 So this,

NOTE Confidence: 0.779711778333333

00:16:09.920 --> 00:16:11.397 this was also sort of a negative,

NOTE Confidence: 0.779711778333333

00:16:11.400 --> 00:16:13.549 well not negative but has not has

NOTE Confidence: 0.779711778333333

00:16:13.549 --> 00:16:15.520 not been brought forward further.

NOTE Confidence: 0.779711778333333

00:16:15.520 --> 00:16:19.615 This was the Javelin 101 study again

NOTE Confidence: 0.779711778333333

00:16:19.615 --> 00:16:22.168 avolumab and exitinib again another

NOTE Confidence: 0.779711778333333

00:16:22.168 --> 00:16:26.145 combination of PD one and and and VEGF

NOTE Confidence: 0.779711778333333

00:16:26.145 --> 00:16:30.800 and they focused on a a lymphocytic

NOTE Confidence: 0.779711778333333

00:16:30.800 --> 00:16:33.620 signature identified 26 genes again

NOTE Confidence: 0.779711778333333

00:16:33.620 --> 00:16:36.120 specific signature for specific trial.

NOTE Confidence: 0.779711778333333

00:16:36.120 --> 00:16:37.752 Some of the challenges of these have been

NOTE Confidence: 0.779711778333333

00:16:37.752 --> 00:16:39.476 you know applying it to other data sets.

NOTE Confidence: 0.779711778333333

00:16:39.480 --> 00:16:42.350 But again you could see the the

NOTE Confidence: 0.779711778333333

00:16:42.350 --> 00:16:44.126 micro environmental features being

NOTE Confidence: 0.779711778333333

00:16:44.126 --> 00:16:46.038 associated with response here

NOTE Confidence: 0.779711778333333

00:16:46.040 --> 00:16:47.840 and suggesting you know that we

NOTE Confidence: 0.779711778333333

00:16:47.840 --> 00:16:49.719 could utilize this as a strategy.

NOTE Confidence: 0.779711778333333

00:16:49.720 --> 00:16:51.946 And then there have been subsequent

NOTE Confidence: 0.779711778333333

00:16:51.946 --> 00:16:55.304 efforts by by collaborative

NOTE Confidence: 0.779711778333333

00:16:55.304 --> 00:16:56.840 groups including Genentech again

NOTE Confidence: 0.779711778333333

00:16:56.840 --> 00:16:59.175 to integrate what we know about

NOTE Confidence: 0.779711778333333

00:16:59.175 --> 00:17:00.623 mutations and those evolutionary

NOTE Confidence: 0.779711778333333

00:17:00.623 --> 00:17:02.857 subtypes I showed you earlier into

NOTE Confidence: 0.779711778333333

00:17:02.857 --> 00:17:04.677 and the micro environmental feature.

NOTE Confidence: 0.779711778333333

00:17:04.680 --> 00:17:06.682 So if we have the micro environment

NOTE Confidence: 0.779711778333333

00:17:06.682 --> 00:17:08.878 and we know the genetics that are

NOTE Confidence: 0.779711778333333

00:17:08.880 --> 00:17:12.078 that arise as kidney cancers evolve,

NOTE Confidence: 0.779711778333333

00:17:12.080 --> 00:17:14.089 could they could they be sort of

NOTE Confidence: 0.779711778333333

00:17:14.089 --> 00:17:16.172 grouped together to form these kind

NOTE Confidence: 0.779711778333333

00:17:16.172 --> 00:17:17.720 of different molecular subgroups?

NOTE Confidence: 0.779711778333333

00:17:17.720 --> 00:17:19.352 And I think there's been some

NOTE Confidence: 0.779711778333333

00:17:19.352 --> 00:17:20.440 attempt to do this.

NOTE Confidence: 0.779711778333333

00:17:20.440 --> 00:17:21.600 I think it's improving,

NOTE Confidence: 0.779711778333333

00:17:21.600 --> 00:17:24.270 but you know you sort of have the sense

NOTE Confidence: 0.779711778333333

00:17:24.270 --> 00:17:26.160 that there are these different angiogenic,

NOTE Confidence: 0.779711778333333

00:17:26.160 --> 00:17:27.336 stromal and angiogenic alone.

NOTE Confidence: 0.779711778333333

00:17:27.336 --> 00:17:29.462 So some of these may have this

NOTE Confidence: 0.779711778333333

00:17:29.462 --> 00:17:31.292 myeloid phenotype that I showed you

NOTE Confidence: 0.779711778333333

00:17:31.292 --> 00:17:33.264 earlier and just a purely angiogenic

NOTE Confidence: 0.779711778333333

00:17:33.264 --> 00:17:35.076 tumor maybe the purely angiogenic

NOTE Confidence: 0.779711778333333

00:17:35.076 --> 00:17:37.290 tumors would respond really well to

NOTE Confidence: 0.779711778333333

00:17:37.349 --> 00:17:39.148 VEGF alone and those are tend to

NOTE Confidence: 0.779711778333333

00:17:39.148 --> 00:17:41.436 be the less aggressive tumors PBR 1

NOTE Confidence: 0.779711778333333

00:17:41.436 --> 00:17:43.228 mutated and then you have the ones

NOTE Confidence: 0.779711778333333

00:17:43.228 --> 00:17:44.515 that are myeloid and angiogenic

NOTE Confidence: 0.779711778333333

00:17:44.515 --> 00:17:45.930 and those actually don't respond

NOTE Confidence: 0.779711778333333

00:17:45.930 --> 00:17:48.100 at all to to VEGF inhibitors and

NOTE Confidence: 0.779711778333333

00:17:48.100 --> 00:17:49.200 then you have these proliferative

NOTE Confidence: 0.779711778333333

00:17:49.200 --> 00:17:50.320 ones and and other ones.

NOTE Confidence: 0.779711778333333

00:17:50.320 --> 00:17:52.042 So we're starting to get a sense

NOTE Confidence: 0.779711778333333

00:17:52.042 --> 00:17:53.920 that maybe you can subgroup kidney

NOTE Confidence: 0.779711778333333

00:17:53.920 --> 00:17:55.360 cancers into those features.

NOTE Confidence: 0.966443561111111

00:17:55.360 --> 00:17:57.115 And then came along this

NOTE Confidence: 0.966443561111111

00:17:57.115 --> 00:17:58.519 notion of single cell.

NOTE Confidence: 0.966443561111111

00:17:58.520 --> 00:18:00.680 And there have been a series of papers,

NOTE Confidence: 0.966443561111111

00:18:00.680 --> 00:18:01.760 one of which David LED,

NOTE Confidence: 0.966443561111111

00:18:01.760 --> 00:18:03.489 but that came out from the time

NOTE Confidence: 0.966443561111111

00:18:03.489 --> 00:18:05.338 because we had done all of all

NOTE Confidence: 0.966443561111111

00:18:05.338 --> 00:18:06.916 this work on bulk RNA sequencing.

NOTE Confidence: 0.966443561111111

00:18:06.920 --> 00:18:08.870 And as the fields across

NOTE Confidence: 0.966443561111111

00:18:08.870 --> 00:18:10.040 cancers have evolved,

NOTE Confidence: 0.966443561111111

00:18:10.040 --> 00:18:13.144 we started utilizing single cell to not only

NOTE Confidence: 0.966443561111111

00:18:13.144 --> 00:18:16.719 get a better sense of what was happening,

NOTE Confidence: 0.966443561111111

00:18:16.720 --> 00:18:18.382 but also really understand you know

NOTE Confidence: 0.966443561111111

00:18:18.382 --> 00:18:20.559 what are the specific features of these of,

NOTE Confidence: 0.966443561111111

00:18:20.560 --> 00:18:21.838 of the of the micro environment

NOTE Confidence: 0.966443561111111

00:18:21.838 --> 00:18:23.480 in a much more high resolution.

NOTE Confidence: 0.966443561111111

00:18:23.480 --> 00:18:24.894 So the advantage of bulk RNAC of

NOTE Confidence: 0.966443561111111

00:18:24.894 --> 00:18:26.200 course is that you can do big,

NOTE Confidence: 0.966443561111111

00:18:26.200 --> 00:18:28.350 big numbers of samples because

NOTE Confidence: 0.966443561111111

00:18:28.350 --> 00:18:29.640 it's relatively inexpensive.

NOTE Confidence: 0.966443561111111

00:18:29.640 --> 00:18:30.918 Single cell gives you deep dive,

NOTE Confidence: 0.966443561111111

00:18:30.920 --> 00:18:32.280 but often the cohorts were

NOTE Confidence: 0.966443561111111

00:18:32.280 --> 00:18:33.640 much more modest in size.

NOTE Confidence: 0.966443561111111

00:18:33.640 --> 00:18:34.625 So I think there's constantly

NOTE Confidence: 0.966443561111111

00:18:34.625 --> 00:18:36.079 a need to go back and forth.

NOTE Confidence: 0.966443561111111

00:18:36.080 --> 00:18:37.235 If you find a signal in one,

NOTE Confidence: 0.966443561111111

00:18:37.240 --> 00:18:38.680 you have to validate in the

NOTE Confidence: 0.966443561111111

00:18:38.680 --> 00:18:39.640 other so to speak.

NOTE Confidence: 0.966443561111111

00:18:39.640 --> 00:18:43.752 And so we we we did this in in

NOTE Confidence: 0.966443561111111

00:18:43.752 --> 00:18:45.866 clear cell focusing really on

NOTE Confidence: 0.966443561111111

00:18:45.866 --> 00:18:49.142 patients that had received just dual

NOTE Confidence: 0.966443561111111

00:18:49.142 --> 00:18:51.840 immunotherapy with PD1 and CTLA 4.

NOTE Confidence: 0.966443561111111

00:18:51.840 --> 00:18:54.756 We focused on 6 patients initially.

NOTE Confidence: 0.966443561111111

00:18:54.760 --> 00:18:57.240 When we did this together with Ming Lee,

NOTE Confidence: 0.966443561111111

00:18:57.240 --> 00:18:58.520 one of my immunology mentors,

NOTE Confidence: 0.966443561111111

00:18:58.520 --> 00:18:59.008 Christina Leslie,

NOTE Confidence: 0.966443561111111

00:18:59.008 --> 00:19:00.716 who's a computational biologist and a very,

NOTE Confidence: 0.966443561111111

00:19:00.720 --> 00:19:03.108 very talented graduate student at the

NOTE Confidence: 0.966443561111111

00:19:03.108 --> 00:19:06.112 time who's finishing his post doc at Harvard,

NOTE Confidence: 0.966443561111111

00:19:06.112 --> 00:19:07.360 now Shirag Krishna.

NOTE Confidence: 0.966443561111111

00:19:07.360 --> 00:19:10.461 And we looked at patients that had

NOTE Confidence: 0.966443561111111

00:19:10.461 --> 00:19:13.512 either were were high risk and not

NOTE Confidence: 0.966443561111111

00:19:13.512 --> 00:19:16.753 had not received PD one right away or

NOTE Confidence: 0.966443561111111

00:19:16.753 --> 00:19:21.030 versus ones that had had Ipinivo. Yeah.

NOTE Confidence: 0.966443561111111

00:19:21.030 --> 00:19:23.760 And were eventually went on to surgery.

NOTE Confidence: 0.966443561111111

00:19:23.760 --> 00:19:25.096 One of the unique things I I do

NOTE Confidence: 0.966443561111111

00:19:25.096 --> 00:19:26.790 as a surgeon is that we're able

NOTE Confidence: 0.966443561111111

00:19:26.790 --> 00:19:28.379 to get tissue after treatment and

NOTE Confidence: 0.966443561111111

00:19:28.379 --> 00:19:29.801 kidney cancer has evolved so much

NOTE Confidence: 0.966443561111111

00:19:29.801 --> 00:19:31.534 so because of the response rates

NOTE Confidence: 0.966443561111111

00:19:31.534 --> 00:19:33.224 now to upfront immunotherapy that

NOTE Confidence: 0.966443561111111

00:19:33.224 --> 00:19:35.390 most patients if they come in with

NOTE Confidence: 0.966443561111111

00:19:35.390 --> 00:19:36.825 metastatic disease will get upfront

NOTE Confidence: 0.966443561111111

00:19:36.878 --> 00:19:38.630 systemic therapy and then we're being

NOTE Confidence: 0.966443561111111

00:19:38.630 --> 00:19:40.643 asked to operate on them later on.

NOTE Confidence: 0.966443561111111

00:19:40.643 --> 00:19:42.610 So that gives us a unique opportunity

NOTE Confidence: 0.966443561111111

00:19:42.668 --> 00:19:44.398 to study tissue after treatment,

NOTE Confidence: 0.966443561111111

00:19:44.400 --> 00:19:46.176 which is something I think really

NOTE Confidence: 0.966443561111111

00:19:46.176 --> 00:19:47.870 unique to kidney cancer amongst many

NOTE Confidence: 0.966443561111111

00:19:47.870 --> 00:19:49.400 solid tumors we have this opportunity.

NOTE Confidence: 0.966443561111111

00:19:49.400 --> 00:19:51.262 So we were able to utilize that

NOTE Confidence: 0.966443561111111

00:19:51.262 --> 00:19:52.628 strategy here and this sort of

NOTE Confidence: 0.966443561111111

00:19:52.628 --> 00:19:54.172 gave us a broader sense and this

NOTE Confidence: 0.966443561111111

00:19:54.172 --> 00:19:55.672 has been replicated I think by

NOTE Confidence: 0.966443561111111

00:19:55.672 --> 00:19:57.063 many other single cell studies

NOTE Confidence: 0.966443561111111

00:19:57.063 --> 00:19:58.251 including David's really Seminole

NOTE Confidence: 0.966443561111111

00:19:58.251 --> 00:20:00.524 work in this and you can kind of

NOTE Confidence: 0.966443561111111

00:20:00.524 --> 00:20:02.440 get a sense of what's happening now.

NOTE Confidence: 0.966443561111111

00:20:02.440 --> 00:20:04.492 One of the things that's interesting

NOTE Confidence: 0.966443561111111

00:20:04.492 --> 00:20:07.084 about a quirk of single cell is that

NOTE Confidence: 0.966443561111111

00:20:07.084 --> 00:20:08.638 you know there's for those of you

NOTE Confidence: 0.966443561111111

00:20:08.638 --> 00:20:10.174 familiar with the technology is that

NOTE Confidence: 0.966443561111111

00:20:10.174 --> 00:20:11.944 you know there's generally at least if

NOTE Confidence: 0.966443561111111

00:20:11.944 --> 00:20:13.760 you do single cell and not single nucleus,

NOTE Confidence: 0.966443561111111

00:20:13.760 --> 00:20:15.790 you have to do some sort of

NOTE Confidence: 0.966443561111111

00:20:15.790 --> 00:20:17.520 sorting and a lot of the.

NOTE Confidence: 0.966443561111111

00:20:17.520 --> 00:20:18.704 Tumor cell populations actually

NOTE Confidence: 0.966443561111111

00:20:18.704 --> 00:20:20.480 die die off from that process.

NOTE Confidence: 0.966443561111111

00:20:20.480 --> 00:20:22.856 They're very fragile for some ironically

NOTE Confidence: 0.966443561111111

00:20:22.856 --> 00:20:25.443 and immune cells will often survive

NOTE Confidence: 0.966443561111111

00:20:25.443 --> 00:20:27.315 although you lose neutrophils.

NOTE Confidence: 0.966443561111111

00:20:27.320 --> 00:20:28.940 So kind of interesting quirk

NOTE Confidence: 0.966443561111111

00:20:28.940 --> 00:20:30.560 of any sort of single

NOTE Confidence: 0.910131814

00:20:30.628 --> 00:20:32.825 cell study that you do, you lose a

NOTE Confidence: 0.910131814

00:20:32.825 --> 00:20:34.235 lot of the cancer cell populations.

NOTE Confidence: 0.910131814

00:20:34.240 --> 00:20:35.464 But we're able to kind of get a

NOTE Confidence: 0.910131814

00:20:35.464 --> 00:20:36.955 good sense of what's going on in the

NOTE Confidence: 0.910131814

00:20:36.955 --> 00:20:38.091 immune cell population and you get

NOTE Confidence: 0.910131814

00:20:38.091 --> 00:20:39.267 a general sense that and this has

NOTE Confidence: 0.910131814

00:20:39.267 --> 00:20:41.040 been replicated by our flow analysis

NOTE Confidence: 0.910131814

00:20:41.040 --> 00:20:43.544 over the many years that about 6040

NOTE Confidence: 0.910131814

00:20:43.544 --> 00:20:46.440 to 60% of the immune compartment is,

NOTE Confidence: 0.910131814

00:20:46.440 --> 00:20:48.904 is made-up of T cell and you have

NOTE Confidence: 0.910131814

00:20:48.904 --> 00:20:50.920 a good amount of Tams in this.

NOTE Confidence: 0.910131814

00:20:50.920 --> 00:20:53.440 And then a whole bunch of other

NOTE Confidence: 0.910131814

00:20:53.440 --> 00:20:55.312 populations including B cells and K

NOTE Confidence: 0.910131814

00:20:55.312 --> 00:20:57.240 cells and dendritic cell populations,

NOTE Confidence: 0.910131814

00:20:57.240 --> 00:20:59.858 but they're really dominated by these T

NOTE Confidence: 0.910131814

00:20:59.858 --> 00:21:02.996 cell and and and and and Tam populations

NOTE Confidence: 0.910131814

00:21:03.000 --> 00:21:04.362 and you could further phenotype them

NOTE Confidence: 0.910131814

00:21:04.362 --> 00:21:06.119 into you know and this has been done.

NOTE Confidence: 0.910131814

00:21:06.120 --> 00:21:06.648 You know,

NOTE Confidence: 0.910131814

00:21:06.648 --> 00:21:08.232 everyone's got their own slightly different

NOTE Confidence: 0.910131814

00:21:08.232 --> 00:21:09.768 way of of phenotyping populations,

NOTE Confidence: 0.910131814

00:21:09.768 --> 00:21:12.502 but this allows to sort of get a

NOTE Confidence: 0.910131814

00:21:12.502 --> 00:21:14.228 sense of what's happening, yeah,

NOTE Confidence: 0.910131814

00:21:14.228 --> 00:21:16.368 in both primary sensitivity and

NOTE Confidence: 0.910131814

00:21:16.368 --> 00:21:18.080 and primary resistant patients.

NOTE Confidence: 0.910131814

00:21:18.080 --> 00:21:20.264 And you know this one again we

NOTE Confidence: 0.910131814

00:21:20.264 --> 00:21:22.271 had epinivo resistant and a mixed

NOTE Confidence: 0.910131814

00:21:22.271 --> 00:21:23.956 response and a complete response,

NOTE Confidence: 0.910131814

00:21:23.960 --> 00:21:25.215 complete response patients are always

NOTE Confidence: 0.910131814

00:21:25.215 --> 00:21:26.722 interesting because why are we operating

NOTE Confidence: 0.910131814

00:21:26.722 --> 00:21:28.394 on them if they have a complete response?

NOTE Confidence: 0.910131814

00:21:28.400 --> 00:21:29.720 Well, when I say complete response,

NOTE Confidence: 0.910131814

00:21:29.720 --> 00:21:31.500 I mean that the tumor's

NOTE Confidence: 0.910131814

00:21:31.500 --> 00:21:33.280 mass itself is not viable.

NOTE Confidence: 0.910131814

00:21:33.280 --> 00:21:35.240 It's it's it, it there's a mass there,

NOTE Confidence: 0.910131814

00:21:35.240 --> 00:21:36.160 we we take it out.

NOTE Confidence: 0.910131814

00:21:36.160 --> 00:21:37.640 But actually under the microscope,

NOTE Confidence: 0.910131814

00:21:37.640 --> 00:21:38.740 there's no tumor left.

NOTE Confidence: 0.910131814

00:21:38.740 --> 00:21:40.115 It's just a conglomerate of

NOTE Confidence: 0.910131814

00:21:40.115 --> 00:21:42.680 immune cells and fibroblasts.

NOTE Confidence: 0.910131814

00:21:42.680 --> 00:21:44.185 And so that's kind of an interesting

NOTE Confidence: 0.910131814

00:21:44.185 --> 00:21:45.395 population to look at because

NOTE Confidence: 0.910131814

00:21:45.395 --> 00:21:46.439 what's what's residual there.

NOTE Confidence: 0.910131814

00:21:46.440 --> 00:21:48.690 And there we found these tissue

NOTE Confidence: 0.910131814

00:21:48.690 --> 00:21:50.622 resident T cell populations that

NOTE Confidence: 0.910131814

00:21:50.622 --> 00:21:53.708 were very abundant in the in the

NOTE Confidence: 0.910131814

00:21:53.708 --> 00:21:56.325 in the residual mass of the of the

NOTE Confidence: 0.910131814

00:21:56.325 --> 00:21:58.038 of that of that kidney even though

NOTE Confidence: 0.910131814

00:21:58.038 --> 00:21:59.879 it was there was no tumor left.

NOTE Confidence: 0.910131814

00:21:59.880 --> 00:22:01.338 And then we found within the

NOTE Confidence: 0.910131814

00:22:01.338 --> 00:22:02.610 patients that were not responding

NOTE Confidence: 0.910131814

00:22:02.610 --> 00:22:04.626 it really you know there was T cells

NOTE Confidence: 0.910131814

00:22:04.626 --> 00:22:06.411 there but it was really dominated

NOTE Confidence: 0.910131814

00:22:06.411 --> 00:22:07.595 by specific Tam populations.

NOTE Confidence: 0.910131814

00:22:07.600 --> 00:22:08.920 This was a primary resistant patient.

NOTE Confidence: 0.910131814

00:22:08.920 --> 00:22:10.994 He had had big tumor, big lymph nodes.

NOTE Confidence: 0.910131814

00:22:10.994 --> 00:22:12.601 We gave him a trial with Epinivo to

NOTE Confidence: 0.910131814

00:22:12.601 --> 00:22:14.033 see if that would help and it didn't.

NOTE Confidence: 0.910131814

00:22:14.040 --> 00:22:16.120 So we still end up operating on him,

NOTE Confidence: 0.910131814

00:22:16.120 --> 00:22:17.596 no response in the tumor whatsoever.

NOTE Confidence: 0.910131814

00:22:17.600 --> 00:22:19.532 And you could see this was really

NOTE Confidence: 0.910131814

00:22:19.532 --> 00:22:20.892 a Tam dominated tumor type.

NOTE Confidence: 0.910131814

00:22:20.892 --> 00:22:22.488 So it started giving us insights

NOTE Confidence: 0.910131814

00:22:22.488 --> 00:22:24.241 that really this may be associated

NOTE Confidence: 0.910131814

00:22:24.241 --> 00:22:25.117 again small numbers.

NOTE Confidence: 0.910131814

00:22:25.120 --> 00:22:26.506 So you really have to start building

NOTE Confidence: 0.910131814

00:22:26.506 --> 00:22:27.785 that out and you can develop

NOTE Confidence: 0.910131814

00:22:27.785 --> 00:22:29.075 signatures which is what we did.

NOTE Confidence: 0.910131814

00:22:29.080 --> 00:22:31.882 We actually took the single cell genes

NOTE Confidence: 0.910131814

00:22:31.882 --> 00:22:34.294 and from the different clusters and

NOTE Confidence: 0.910131814

00:22:34.294 --> 00:22:36.746 overlaid them on some of these genomic

NOTE Confidence: 0.910131814

00:22:36.746 --> 00:22:38.076 signatures that have been published.

NOTE Confidence: 0.910131814

00:22:38.080 --> 00:22:39.914 The javelin when I mentioned the the,

NOTE Confidence: 0.910131814

00:22:39.920 --> 00:22:40.247 the,

NOTE Confidence: 0.910131814

00:22:40.247 --> 00:22:42.536 the genomic ones from Genentech and we

NOTE Confidence: 0.910131814

00:22:42.536 --> 00:22:45.132 started saying like what are the actual

NOTE Confidence: 0.910131814

00:22:45.132 --> 00:22:46.636 populations that they're capturing.

NOTE Confidence: 0.910131814

00:22:46.640 --> 00:22:48.831 You get a better sense that there

NOTE Confidence: 0.910131814

00:22:48.831 --> 00:22:50.760 are some dominant Tam populations

NOTE Confidence: 0.910131814

00:22:50.760 --> 00:22:53.040 and that some of these populations

NOTE Confidence: 0.910131814

00:22:53.040 --> 00:22:54.416 may be potentially targetable.

NOTE Confidence: 0.910131814

00:22:54.416 --> 00:22:56.880 And I'll talk about that in in a

NOTE Confidence: 0.888787088181818

00:22:56.935 --> 00:22:58.838 moment. But I want to bring your

NOTE Confidence: 0.888787088181818

00:22:58.838 --> 00:23:00.760 attention to some of these adenosine

NOTE Confidence: 0.888787088181818

00:23:00.760 --> 00:23:02.515 signatures that were were published

NOTE Confidence: 0.888787088181818

00:23:02.515 --> 00:23:04.643 from an HUAR inhibitor which is

NOTE Confidence: 0.888787088181818

00:23:04.643 --> 00:23:06.521 something that has been shown to

NOTE Confidence: 0.888787088181818

00:23:06.521 --> 00:23:08.120 potentially shift Tam phenotypes.

NOTE Confidence: 0.888787088181818

00:23:08.120 --> 00:23:09.848 So, so this was sort of an interesting

NOTE Confidence: 0.888787088181818

00:23:09.848 --> 00:23:11.712 way for us to look at the data and

NOTE Confidence: 0.888787088181818

00:23:11.712 --> 00:23:13.164 you can develop signatures based on

NOTE Confidence: 0.888787088181818

00:23:13.164 --> 00:23:15.680 the single cell data and compare them

NOTE Confidence: 0.888787088181818

00:23:15.680 --> 00:23:18.695 to existing signatures to see if you

NOTE Confidence: 0.888787088181818

00:23:18.695 --> 00:23:20.750 could further stratify patients and

NOTE Confidence: 0.888787088181818

00:23:20.819 --> 00:23:23.052 responses across different different data

NOTE Confidence: 0.888787088181818

00:23:23.052 --> 00:23:25.160 sets And and we were able to do that.

NOTE Confidence: 0.888787088181818

00:23:25.160 --> 00:23:26.760 And then the question is also, well,

NOTE Confidence: 0.888787088181818

00:23:26.760 --> 00:23:29.400 is there a relationship between the

NOTE Confidence: 0.888787088181818

00:23:29.400 --> 00:23:31.844 underlying micro genetic micro environment

NOTE Confidence: 0.888787088181818

00:23:31.844 --> 00:23:34.994 and these specific immune micro environments?

NOTE Confidence: 0.888787088181818

00:23:35.000 --> 00:23:36.840 So I I showed you again on bulk,

NOTE Confidence: 0.888787088181818

00:23:36.840 --> 00:23:38.412 maybe there's these different

NOTE Confidence: 0.888787088181818

00:23:38.412 --> 00:23:39.198 sub classifications,

NOTE Confidence: 0.888787088181818

00:23:39.200 --> 00:23:40.624 but we also know there's a lot of

NOTE Confidence: 0.888787088181818

00:23:40.624 --> 00:23:41.762 heterogeneity in kidney tumors, right.

NOTE Confidence: 0.888787088181818

00:23:41.762 --> 00:23:43.940 So we know that if you took a kidney

NOTE Confidence: 0.888787088181818

00:23:44.005 --> 00:23:46.315 tumor and you sequence different regions,

NOTE Confidence: 0.888787088181818

00:23:46.320 --> 00:23:47.580 Charlie Swanton showed this many years

NOTE Confidence: 0.888787088181818

00:23:47.580 --> 00:23:49.478 ago in a famous paper New England Journal,

NOTE Confidence: 0.888787088181818

00:23:49.480 --> 00:23:50.542 intratumal heterogeneity exists.

NOTE Confidence: 0.888787088181818

00:23:50.542 --> 00:23:52.666 Does that same thing apply to

NOTE Confidence: 0.888787088181818

00:23:52.666 --> 00:23:54.478 the micro environment as well?

NOTE Confidence: 0.888787088181818

00:23:54.480 --> 00:23:55.860 And that's something of of course

NOTE Confidence: 0.888787088181818

00:23:55.860 --> 00:23:57.430 if you're going to develop a

NOTE Confidence: 0.888787088181818

00:23:57.430 --> 00:23:58.638 biomarker or suggest something,

NOTE Confidence: 0.888787088181818

00:23:58.640 --> 00:23:59.636 you have to think about that.

NOTE Confidence: 0.888787088181818

00:23:59.640 --> 00:24:01.504 And this is work that we did in

NOTE Confidence: 0.888787088181818

00:24:01.504 --> 00:24:02.893 collaboration with Illumina where we

NOTE Confidence: 0.888787088181818

00:24:02.893 --> 00:24:04.633 really thought about this question of,

NOTE Confidence: 0.888787088181818

00:24:04.640 --> 00:24:04.816 OK,

NOTE Confidence: 0.888787088181818

00:24:04.816 --> 00:24:06.224 now we have a good sense of what's

NOTE Confidence: 0.888787088181818

00:24:06.224 --> 00:24:07.560 going on in the micro environment.

NOTE Confidence: 0.888787088181818

00:24:07.560 --> 00:24:08.666 We have a good sense of what's

NOTE Confidence: 0.888787088181818

00:24:08.666 --> 00:24:09.617 going on in the underlying

NOTE Confidence: 0.888787088181818

00:24:09.617 --> 00:24:10.919 genomics and and how does that,

NOTE Confidence: 0.888787088181818

00:24:10.920 --> 00:24:13.320 how does that relate to the individual tumor.

NOTE Confidence: 0.888787088181818

00:24:13.320 --> 00:24:15.133 And one of the reasons why clinically

NOTE Confidence: 0.888787088181818

00:24:15.133 --> 00:24:16.509 that's interesting is 'cause if you

NOTE Confidence: 0.888787088181818

00:24:16.509 --> 00:24:18.805 look at at at data sets where the the

NOTE Confidence: 0.888787088181818

00:24:18.805 --> 00:24:20.598 primary tumor's still in place in

NOTE Confidence: 0.888787088181818

00:24:20.598 --> 00:24:22.410 the with the patient with metastatic

NOTE Confidence: 0.888787088181818

00:24:22.410 --> 00:24:23.760 disease and they get immunotherapy,

NOTE Confidence: 0.888787088181818

00:24:23.760 --> 00:24:25.320 often the Mets will respond well,

NOTE Confidence: 0.888787088181818

00:24:25.320 --> 00:24:26.795 but the primary tumors maybe

NOTE Confidence: 0.888787088181818

00:24:26.795 --> 00:24:27.912 only shrink modestly, right.

NOTE Confidence: 0.888787088181818

00:24:27.912 --> 00:24:28.840 So there's not a,

NOTE Confidence: 0.888787088181818

00:24:28.840 --> 00:24:31.038 there's not that same level of response.

NOTE Confidence: 0.888787088181818

00:24:31.040 --> 00:24:32.400 And one hypothesis is that,

NOTE Confidence: 0.888787088181818

00:24:32.400 --> 00:24:32.713 well,

NOTE Confidence: 0.888787088181818

00:24:32.713 --> 00:24:34.591 it's because the primary tumor is

NOTE Confidence: 0.888787088181818

00:24:34.591 --> 00:24:36.184 more clonally diverse and the Mets

NOTE Confidence: 0.888787088181818

00:24:36.184 --> 00:24:38.228 is just a a clone that was able to

NOTE Confidence: 0.888787088181818

00:24:38.228 --> 00:24:39.998 metastasize out that was selected for.

NOTE Confidence: 0.888787088181818

00:24:40.000 --> 00:24:42.392 So when you get a response in the

NOTE Confidence: 0.888787088181818

00:24:42.392 --> 00:24:44.314 Mets maybe it's because there's just

NOTE Confidence: 0.888787088181818

00:24:44.314 --> 00:24:45.399 a clone that's really responsive,

NOTE Confidence: 0.888787088181818

00:24:45.400 --> 00:24:46.723 but the primary may only have that

NOTE Confidence: 0.888787088181818

00:24:46.723 --> 00:24:48.389 clone in in part of it and sort

NOTE Confidence: 0.888787088181818

00:24:48.389 --> 00:24:49.439 of been our rationalization for

NOTE Confidence: 0.888787088181818

00:24:49.485 --> 00:24:50.700 continuing to operate on these

NOTE Confidence: 0.888787088181818

00:24:50.700 --> 00:24:52.314 patients because I tell them well

NOTE Confidence: 0.888787088181818

00:24:52.314 --> 00:24:54.678 a you know I like operating.

NOTE Confidence: 0.888787088181818

00:24:54.680 --> 00:24:56.660 But more more fundamentally it's

NOTE Confidence: 0.888787088181818

00:24:56.660 --> 00:24:58.862 actually because we think that you

NOTE Confidence: 0.888787088181818

00:24:58.862 --> 00:25:00.194 know we're we're removing the diverse,

NOTE Confidence: 0.888787088181818

00:25:00.200 --> 00:25:01.478 the biological diversity of them Even

NOTE Confidence: 0.888787088181818

00:25:01.478 --> 00:25:03.280 if they've had a good response up front,

NOTE Confidence: 0.888787088181818

00:25:03.280 --> 00:25:05.359 the chance for them to develop persistence

NOTE Confidence: 0.888787088181818

00:25:05.359 --> 00:25:07.955 down the road may come from from the primary.

NOTE Confidence: 0.888787088181818

00:25:07.960 --> 00:25:10.246 And so we tried to look at this with

NOTE Confidence: 0.888787088181818

00:25:10.246 --> 00:25:11.839 multi regional sequencing again

NOTE Confidence: 0.888787088181818

00:25:11.839 --> 00:25:13.959 relatively modest numbers but we

NOTE Confidence: 0.888787088181818

00:25:13.959 --> 00:25:16.007 we utilized the combinations of DNA

NOTE Confidence: 0.888787088181818

00:25:16.007 --> 00:25:18.177 and RNA and and TCR and different

NOTE Confidence: 0.888787088181818

00:25:18.177 --> 00:25:20.462 things within within tumors that

NOTE Confidence: 0.888787088181818

00:25:20.462 --> 00:25:22.290 had been exposed to

NOTE Confidence: 0.861487926363636

00:25:22.372 --> 00:25:24.164 immunotherapies as part of a

NOTE Confidence: 0.861487926363636

00:25:24.164 --> 00:25:25.560 trial that we ran and and others.

NOTE Confidence: 0.861487926363636

00:25:25.560 --> 00:25:27.990 And so we were able to look at the

NOTE Confidence: 0.861487926363636

00:25:27.990 --> 00:25:29.932 question of whether overall immune

NOTE Confidence: 0.861487926363636

00:25:29.932 --> 00:25:31.876 diversity is associated with,

NOTE Confidence: 0.861487926363636

00:25:31.880 --> 00:25:33.880 I'm sorry, overall genetic diversity

NOTE Confidence: 0.861487926363636

00:25:33.880 --> 00:25:35.880 is associated with particular micro

NOTE Confidence: 0.861487926363636

00:25:35.880 --> 00:25:36.867 micro environmental phenotypes.

NOTE Confidence: 0.861487926363636

00:25:36.867 --> 00:25:39.170 Indeed, we found at least in this

NOTE Confidence: 0.861487926363636

00:25:39.226 --> 00:25:41.368 study that if you were a very high lead

NOTE Confidence: 0.861487926363636

00:25:41.368 --> 00:25:43.080 diverse tumor from a genomic sample,

NOTE Confidence: 0.861487926363636

00:25:43.080 --> 00:25:44.280 you were more likely to be

NOTE Confidence: 0.861487926363636

00:25:44.280 --> 00:25:45.080 a myeloid high tumor,

NOTE Confidence: 0.861487926363636

00:25:45.080 --> 00:25:48.152 which was interesting and and vice

NOTE Confidence: 0.861487926363636

00:25:48.152 --> 00:25:51.022 versa with respect to some of the

NOTE Confidence: 0.861487926363636

00:25:51.022 --> 00:25:52.118 antigen presenting machinery genes.

NOTE Confidence: 0.861487926363636

00:25:52.120 --> 00:25:54.508 So the ITH tumors were actually

NOTE Confidence: 0.861487926363636

00:25:54.508 --> 00:25:57.068 lower with respect to the APM genes

NOTE Confidence: 0.861487926363636

00:25:57.068 --> 00:25:59.406 and actually if you took a specific

NOTE Confidence: 0.861487926363636

00:25:59.406 --> 00:26:02.020 tumor and you actually marked out

NOTE Confidence: 0.861487926363636

00:26:02.020 --> 00:26:03.792 the immune infiltration patterns,

NOTE Confidence: 0.861487926363636

00:26:03.800 --> 00:26:05.040 you could start seeing evolution

NOTE Confidence: 0.861487926363636

00:26:05.040 --> 00:26:06.032 within that same tumor.

NOTE Confidence: 0.861487926363636

00:26:06.040 --> 00:26:07.680 So this is an example of a of

NOTE Confidence: 0.861487926363636

00:26:07.680 --> 00:26:09.197 a tumor that was I TH high.

NOTE Confidence: 0.861487926363636

00:26:09.200 --> 00:26:11.131 It had a lot of intratumoral heterogeneity.

NOTE Confidence: 0.861487926363636

00:26:11.131 --> 00:26:14.448 It was AP Bear Monsanti 2 kind of

NOTE Confidence: 0.861487926363636

00:26:14.448 --> 00:26:15.664 micro environment or evolutionary

NOTE Confidence: 0.861487926363636

00:26:15.664 --> 00:26:17.787 subtype and we were able to look

NOTE Confidence: 0.861487926363636

00:26:17.787 --> 00:26:18.923 at individually in different

NOTE Confidence: 0.861487926363636

00:26:18.923 --> 00:26:20.479 regions of this tumor to see.

NOTE Confidence: 0.861487926363636

00:26:20.480 --> 00:26:22.013 We found that some of the regions

NOTE Confidence: 0.861487926363636

00:26:22.013 --> 00:26:23.498 were very T cell infiltrated at

NOTE Confidence: 0.861487926363636

00:26:23.498 --> 00:26:25.008 least by RNA and some of them

NOTE Confidence: 0.861487926363636

00:26:25.008 --> 00:26:25.918 were very mild and infiltrated.

NOTE Confidence: 0.861487926363636

00:26:25.920 --> 00:26:27.066 And we were actually able to

NOTE Confidence: 0.861487926363636

00:26:27.066 --> 00:26:28.357 track down like what were the

NOTE Confidence: 0.861487926363636

00:26:28.357 --> 00:26:29.567 individual genetic events that were

NOTE Confidence: 0.861487926363636

00:26:29.567 --> 00:26:30.959 occurring as this tumor developed.

NOTE Confidence: 0.861487926363636

00:26:30.960 --> 00:26:32.292 And you could see that, you know,

NOTE Confidence: 0.861487926363636

00:26:32.292 --> 00:26:33.596 as the tumor developed,

NOTE Confidence: 0.861487926363636

00:26:33.600 --> 00:26:35.968 there was loss of HLA and maybe some

NOTE Confidence: 0.861487926363636

00:26:35.968 --> 00:26:38.374 CDK into A&B loss which has been

NOTE Confidence: 0.861487926363636

00:26:38.374 --> 00:26:40.540 associated with a more immune desert

NOTE Confidence: 0.861487926363636

00:26:40.540 --> 00:26:42.640 or less immune infiltrated micro.

NOTE Confidence: 0.861487926363636

00:26:42.640 --> 00:26:44.116 So within the same tumor itself,

NOTE Confidence: 0.861487926363636

00:26:44.120 --> 00:26:45.686 you could see this evolution and

NOTE Confidence: 0.861487926363636

00:26:45.686 --> 00:26:47.501 that was correlating with the micro

NOTE Confidence: 0.861487926363636

00:26:47.501 --> 00:26:48.581 environmental features suggesting

NOTE Confidence: 0.861487926363636

00:26:48.581 --> 00:26:50.381 that there's this constant interplay

NOTE Confidence: 0.861487926363636

00:26:50.435 --> 00:26:52.163 And I think David has shown this and

NOTE Confidence: 0.861487926363636

00:26:52.163 --> 00:26:53.695 others have suggested this constant

NOTE Confidence: 0.861487926363636

00:26:53.695 --> 00:26:55.520 interplay between the underlying Genoma

NOTE Confidence: 0.861487926363636

00:26:55.520 --> 00:26:57.599 architecture of a tumor and what's actually,

NOTE Confidence: 0.861487926363636

00:26:57.600 --> 00:26:58.560 you know,

NOTE Confidence: 0.861487926363636

00:26:58.560 --> 00:27:00.288 underlying the response micro

NOTE Confidence: 0.861487926363636

00:27:00.288 --> 00:27:01.440 environmentally in that tumor.

NOTE Confidence: 0.861487926363636

00:27:01.440 --> 00:27:02.560 Obviously we don't fully tease

NOTE Confidence: 0.861487926363636

00:27:02.560 --> 00:27:03.880 out the mechanism here at all,

NOTE Confidence: 0.861487926363636

00:27:03.880 --> 00:27:06.925 but it begs the question that there's

NOTE Confidence: 0.861487926363636

00:27:06.925 --> 00:27:09.678 an opportunity here to to explore this

NOTE Confidence: 0.861487926363636

00:27:09.680 --> 00:27:11.360 and what about in in the metastatic question.

NOTE Confidence: 0.861487926363636

00:27:11.360 --> 00:27:12.240 So that was another

NOTE Confidence: 0.861487926363636

00:27:12.240 --> 00:27:13.560 question we had in the lab.

NOTE Confidence: 0.861487926363636

00:27:13.560 --> 00:27:15.331 So I've showed you everything in terms

NOTE Confidence: 0.861487926363636

00:27:15.331 --> 00:27:16.640 of treatment response potentially.

NOTE Confidence: 0.861487926363636

00:27:16.640 --> 00:27:18.832 But we also wanted to know are are

NOTE Confidence: 0.861487926363636

00:27:18.832 --> 00:27:20.640 these micro environmental groups

NOTE Confidence: 0.861487926363636

00:27:20.640 --> 00:27:23.005 also predicting or or associating

NOTE Confidence: 0.861487926363636

00:27:23.005 --> 00:27:24.230 with development of metastas,

NOTE Confidence: 0.861487926363636

00:27:24.230 --> 00:27:25.480 which is a different question,

NOTE Confidence: 0.861487926363636

00:27:25.480 --> 00:27:25.687 right.

NOTE Confidence: 0.861487926363636

00:27:25.687 --> 00:27:27.136 You know you could have a micro

NOTE Confidence: 0.861487926363636

00:27:27.136 --> 00:27:27.877 environment that's really

NOTE Confidence: 0.861487926363636

00:27:27.877 --> 00:27:29.037 important for treatment response,

NOTE Confidence: 0.861487926363636

00:27:29.040 --> 00:27:31.116 but it may not be associated

NOTE Confidence: 0.861487926363636

00:27:31.116 --> 00:27:32.154 with metastatic development.

NOTE Confidence: 0.861487926363636

00:27:32.160 --> 00:27:32.579 So,

NOTE Confidence: 0.861487926363636

00:27:32.579 --> 00:27:35.512 so David had had somewhat hinted at

NOTE Confidence: 0.861487926363636

00:27:35.512 --> 00:27:38.284 this with his work with with Ellie

NOTE Confidence: 0.861487926363636

00:27:38.284 --> 00:27:41.000 and Tony and others at Dana Farber

NOTE Confidence: 0.861487926363636

00:27:41.000 --> 00:27:42.953 and they showed it you know very

NOTE Confidence: 0.861487926363636

00:27:42.953 --> 00:27:44.731 elegantly in this paper that looked

NOTE Confidence: 0.861487926363636

00:27:44.731 --> 00:27:46.593 our paper focused on the advanced

NOTE Confidence: 0.861487926363636

00:27:46.593 --> 00:27:48.558 disease and and Ibidevo treated.

NOTE Confidence: 0.861487926363636

00:27:48.560 --> 00:27:51.944 But David's work was performing single

NOTE Confidence: 0.861487926363636

00:27:51.944 --> 00:27:54.476 cell sequencing on early locally

NOTE Confidence: 0.861487926363636

00:27:54.476 --> 00:27:55.856 advanced in metastatic tumors and

NOTE Confidence: 0.861487926363636

00:27:55.856 --> 00:27:58.029 at least in this work he showed this

NOTE Confidence: 0.861487926363636

00:27:58.029 --> 00:27:59.547 evidence of T cell exhaustion but

NOTE Confidence: 0.847979665555556

00:27:59.595 --> 00:28:01.311 also this shift in the macrophage

NOTE Confidence: 0.847979665555556

00:28:01.311 --> 00:28:03.040 polarity as tumors became more

NOTE Confidence: 0.847979665555556

00:28:03.040 --> 00:28:04.058 aggressive, more metastatic.

NOTE Confidence: 0.847979665555556

00:28:04.058 --> 00:28:06.361 So suggesting to us and others that

NOTE Confidence: 0.847979665555556

00:28:06.361 --> 00:28:09.087 you know maybe some of these Tams and

NOTE Confidence: 0.847979665555556

00:28:09.087 --> 00:28:10.918 and myeloid populations that were so,

NOTE Confidence: 0.847979665555556

00:28:10.920 --> 00:28:14.040 so, so driving responses are also

NOTE Confidence: 0.847979665555556

00:28:14.040 --> 00:28:15.900 associated with metastatic development.

NOTE Confidence: 0.847979665555556

00:28:15.900 --> 00:28:18.770 And so for this we again utilize

NOTE Confidence: 0.847979665555556

00:28:18.770 --> 00:28:20.967 our strategy with with going

NOTE Confidence: 0.847979665555556

00:28:20.967 --> 00:28:23.301 to clinical trials and and we

NOTE Confidence: 0.847979665555556

00:28:23.301 --> 00:28:24.886 worked with this adjuvant study.

NOTE Confidence: 0.847979665555556

00:28:24.886 --> 00:28:26.670 So this was one of the series of

NOTE Confidence: 0.847979665555556

00:28:26.718 --> 00:28:28.158 negative studies unfortunately,

NOTE Confidence: 0.847979665555556

00:28:28.160 --> 00:28:30.144 but again the benefit of having a lot

NOTE Confidence: 0.847979665555556

00:28:30.144 --> 00:28:32.001 of genomic data looking at whether

NOTE Confidence: 0.847979665555556

00:28:32.001 --> 00:28:33.957 giving it a VEGF inhibitor monotherapy.

NOTE Confidence: 0.847979665555556

00:28:33.960 --> 00:28:35.670 Again Pezopinib in this case was

NOTE Confidence: 0.847979665555556

00:28:35.670 --> 00:28:36.810 associated with better outcomes

NOTE Confidence: 0.847979665555556

00:28:36.861 --> 00:28:38.523 in patients with high risk non

NOTE Confidence: 0.847979665555556

00:28:38.523 --> 00:28:39.354 metastatic kidney cancer.

NOTE Confidence: 0.847979665555556

00:28:39.360 --> 00:28:41.184 All these patients in this trial

NOTE Confidence: 0.847979665555556

00:28:41.184 --> 00:28:42.400 had advanced kidney cancers.

NOTE Confidence: 0.847979665555556

00:28:42.400 --> 00:28:46.520 They had a high risk of relapse but

NOTE Confidence: 0.847979665555556

00:28:46.520 --> 00:28:48.088 but you know standard at the time

NOTE Confidence: 0.847979665555556

00:28:48.088 --> 00:28:50.005 was just to observe them and so there

NOTE Confidence: 0.847979665555556

00:28:50.005 --> 00:28:52.206 was a series of trials to see if you

NOTE Confidence: 0.847979665555556

00:28:52.206 --> 00:28:53.640 gave a VEGF inhibitor whether that

NOTE Confidence: 0.847979665555556

00:28:53.640 --> 00:28:56.600 actually was improved their survival.

NOTE Confidence: 0.847979665555556

00:28:56.600 --> 00:28:58.595 The vast majority of the studies were

NOTE Confidence: 0.847979665555556

00:28:58.595 --> 00:29:00.651 were -1 was sort of positive but no

NOTE Confidence: 0.847979665555556

00:29:00.651 --> 00:29:02.724 one has really adopted it and now

NOTE Confidence: 0.847979665555556

00:29:02.724 --> 00:29:04.960 we've moved on to immunotherapy but at

NOTE Confidence: 0.847979665555556

00:29:04.960 --> 00:29:07.040 this time this was a very interesting study.

NOTE Confidence: 0.847979665555556

00:29:07.040 --> 00:29:09.021 So we we compared we had microarray

NOTE Confidence: 0.847979665555556

00:29:09.021 --> 00:29:10.440 yet again from Novartis,

NOTE Confidence: 0.847979665555556

00:29:10.440 --> 00:29:12.720 we compared the the again all high risk.

NOTE Confidence: 0.847979665555556

00:29:12.720 --> 00:29:14.095 So they're they're you're sort

NOTE Confidence: 0.847979665555556

00:29:14.095 --> 00:29:15.470 of controlling for the potential

NOTE Confidence: 0.847979665555556

00:29:15.518 --> 00:29:16.958 tumor confounding features right.

NOTE Confidence: 0.847979665555556

00:29:16.960 --> 00:29:18.316 They're all high risk patients and

NOTE Confidence: 0.847979665555556

00:29:18.316 --> 00:29:19.763 we compared the ones that relapsed

NOTE Confidence: 0.847979665555556

00:29:19.763 --> 00:29:20.998 versus the ones that didn't.

NOTE Confidence: 0.847979665555556

00:29:21.000 --> 00:29:23.412 This is work that one of our one of

NOTE Confidence: 0.847979665555556

00:29:23.412 --> 00:29:26.166 our fellows LED and who who's now at

NOTE Confidence: 0.847979665555556

00:29:26.166 --> 00:29:27.928 Rochester with a surgeon scientist

NOTE Confidence: 0.847979665555556

00:29:27.928 --> 00:29:30.394 track their great guy Phil Rippolt

NOTE Confidence: 0.847979665555556

00:29:30.400 --> 00:29:32.784 with with Lynn Von from my lab who's

NOTE Confidence: 0.847979665555556

00:29:32.784 --> 00:29:34.828 a senior member now and we compared

NOTE Confidence: 0.847979665555556

00:29:34.828 --> 00:29:36.244 the the tumors that record versus

NOTE Confidence: 0.847979665555556

00:29:36.244 --> 00:29:38.115 didn't and we used an unbiased you know

NOTE Confidence: 0.847979665555556

00:29:38.115 --> 00:29:39.480 whole genome approach with with this.

NOTE Confidence: 0.847979665555556

00:29:39.480 --> 00:29:42.336 And so of course you saw things

NOTE Confidence: 0.847979665555556

00:29:42.336 --> 00:29:43.804 like EMT and mtor,

NOTE Confidence: 0.847979665555556

00:29:43.804 --> 00:29:45.268 which made sense to us because

NOTE Confidence: 0.847979665555556

00:29:45.268 --> 00:29:46.688 those are obviously very known

NOTE Confidence: 0.847979665555556

00:29:46.688 --> 00:29:47.964 and relevant oncogenic processes

NOTE Confidence: 0.847979665555556

00:29:47.964 --> 00:29:49.240 that that promote metastases.

NOTE Confidence: 0.847979665555556

00:29:49.240 --> 00:29:51.896 But we also saw a lot of immune

NOTE Confidence: 0.847979665555556

00:29:51.896 --> 00:29:54.048 inflammatory genes in particular Illinois

NOTE Confidence: 0.847979665555556

00:29:54.048 --> 00:29:57.192 6 and Jack in Stat 3 kind of stood out

NOTE Confidence: 0.847979665555556

00:29:57.192 --> 00:30:00.076 to us as being a driver of metastasis.

NOTE Confidence: 0.847979665555556

00:30:00.080 --> 00:30:00.400 Again,

NOTE Confidence: 0.847979665555556

00:30:00.400 --> 00:30:02.320 we applied the same single cell

NOTE Confidence: 0.847979665555556

00:30:02.320 --> 00:30:04.375 strategies what we had done before to

NOTE Confidence: 0.847979665555556

00:30:04.375 --> 00:30:06.410 see you know what are these myeloid

NOTE Confidence: 0.847979665555556

00:30:06.410 --> 00:30:08.520 inflammation and Illinois 6 pathways,

NOTE Confidence: 0.847979665555556

00:30:08.520 --> 00:30:09.876 what are they really converging on?

NOTE Confidence: 0.847979665555556

00:30:09.880 --> 00:30:13.500 And and and indeed it it showed a

NOTE Confidence: 0.847979665555556

00:30:13.500 --> 00:30:16.292 real enrichment in some of these tan

NOTE Confidence: 0.847979665555556

00:30:16.292 --> 00:30:18.271 populations that we had defined a

NOTE Confidence: 0.847979665555556

00:30:18.271 --> 00:30:20.799 little bit better with the single cell data.

NOTE Confidence: 0.847979665555556

00:30:20.800 --> 00:30:22.872 And suggesting that if you were a tumor

NOTE Confidence: 0.847979665555556

00:30:22.872 --> 00:30:25.116 that was myeloid high or adenosine high,

NOTE Confidence: 0.847979665555556

00:30:25.120 --> 00:30:26.716 similar overlapping signatures,

NOTE Confidence: 0.847979665555556

00:30:26.716 --> 00:30:30.440 you are more likely to develop metastasis.

NOTE Confidence: 0.847979665555556

00:30:30.440 --> 00:30:32.160 Again controlling for other features,

NOTE Confidence: 0.847979665555556

00:30:32.160 --> 00:30:34.036 all of the clinical and pathologic features.

NOTE Confidence: 0.847979665555556

00:30:34.040 --> 00:30:37.000 These are completely independent programs

NOTE Confidence: 0.847979665555556

00:30:37.000 --> 00:30:39.781 and you could show that if I mean if

NOTE Confidence: 0.847979665555556

00:30:39.781 --> 00:30:41.645 you were a AMSK inflammatory signature,

NOTE Confidence: 0.847979665555556

00:30:41.645 --> 00:30:43.990 which was a gene signature we developed

NOTE Confidence: 0.886790947272727

00:30:44.043 --> 00:30:46.304 from from the micro RAY data strongly

NOTE Confidence: 0.886790947272727

00:30:46.304 --> 00:30:48.224 overlapping with the myeloid signature

NOTE Confidence: 0.886790947272727

00:30:48.224 --> 00:30:50.677 from Genentech and others that you could

NOTE Confidence: 0.886790947272727

00:30:50.677 --> 00:30:52.393 take all these high risk patients.

NOTE Confidence: 0.886790947272727

00:30:52.400 --> 00:30:54.297 And really I mean it's pretty amazing

NOTE Confidence: 0.886790947272727

00:30:54.297 --> 00:30:56.120 to see curves like this separate out.

NOTE Confidence: 0.886790947272727

00:30:56.120 --> 00:30:57.560 But again all of these patients,

NOTE Confidence: 0.886790947272727

00:30:57.560 --> 00:30:59.660 this is a myeloid load tumor intermediate

NOTE Confidence: 0.886790947272727

00:30:59.660 --> 00:31:01.992 and then very high and you could

NOTE Confidence: 0.886790947272727

00:31:01.992 --> 00:31:03.360 see their survival probability.

NOTE Confidence: 0.886790947272727

00:31:03.360 --> 00:31:05.368 And then we were able to replicate this

NOTE Confidence: 0.886790947272727

00:31:05.368 --> 00:31:07.030 in multiple other data sets including

NOTE Confidence: 0.886790947272727

00:31:07.030 --> 00:31:08.968 from one of our former fellows who's

NOTE Confidence: 0.886790947272727

00:31:08.968 --> 00:31:10.662 at Moffett now and and again showing

NOTE Confidence: 0.886790947272727

00:31:10.662 --> 00:31:12.288 that if you were controlling for

NOTE Confidence: 0.886790947272727

00:31:12.288 --> 00:31:14.260 all these high risk features from

NOTE Confidence: 0.886790947272727

00:31:14.260 --> 00:31:15.640 a clinical pathologic standpoint,

NOTE Confidence: 0.886790947272727

00:31:15.640 --> 00:31:17.338 you you could still stratify patients

NOTE Confidence: 0.886790947272727

00:31:17.338 --> 00:31:20.412 by the risk of recurrence in that

NOTE Confidence: 0.886790947272727

00:31:20.412 --> 00:31:22.316 and it didn't seem to be associated

NOTE Confidence: 0.886790947272727

00:31:22.316 --> 00:31:23.800 much with the T cell response.

NOTE Confidence: 0.886790947272727

00:31:23.800 --> 00:31:25.624 So what was driving metastas is

NOTE Confidence: 0.886790947272727

00:31:25.624 --> 00:31:27.479 at least in this data set,

NOTE Confidence: 0.886790947272727

00:31:27.480 --> 00:31:28.920 but again it has been valid in others,

NOTE Confidence: 0.886790947272727

00:31:28.920 --> 00:31:31.314 was not really AT cell driven process.

NOTE Confidence: 0.886790947272727

00:31:31.320 --> 00:31:33.693 What was at least from a micro

NOTE Confidence: 0.886790947272727

00:31:33.693 --> 00:31:34.710 environmental standpoint promoting

NOTE Confidence: 0.886790947272727

00:31:34.762 --> 00:31:36.637 metastasis was was independent seen.

NOTE Confidence: 0.886790947272727

00:31:36.640 --> 00:31:38.306 We tried all the different T cell

NOTE Confidence: 0.886790947272727

00:31:38.306 --> 00:31:39.559 signatures that have been shown.

NOTE Confidence: 0.886790947272727

00:31:39.560 --> 00:31:41.400 We looked at IHC scores,

NOTE Confidence: 0.886790947272727

00:31:41.400 --> 00:31:43.590 we had IHC from CD8 infiltration

NOTE Confidence: 0.886790947272727

00:31:43.590 --> 00:31:44.320 patterns here.

NOTE Confidence: 0.886790947272727

00:31:44.320 --> 00:31:45.904 We were able to see if they were inflamed

NOTE Confidence: 0.886790947272727

00:31:45.904 --> 00:31:47.674 or excludeded and we really didn't see me.

NOTE Confidence: 0.886790947272727

00:31:47.680 --> 00:31:49.618 Maybe there's a signal with the

NOTE Confidence: 0.886790947272727

00:31:49.618 --> 00:31:51.506 desert that those are the tumors

NOTE Confidence: 0.886790947272727

00:31:51.506 --> 00:31:53.354 that have no T cells at all,

NOTE Confidence: 0.886790947272727

00:31:53.360 --> 00:31:55.448 but it wasn't clear at least that was

NOTE Confidence: 0.886790947272727

00:31:55.448 --> 00:31:57.199 that wasn't the clear driver here.

NOTE Confidence: 0.886790947272727

00:31:57.200 --> 00:31:59.160 It was really much more of the myeloid

NOTE Confidence: 0.886790947272727

00:31:59.160 --> 00:32:01.071 and Tam phenotypes and actually the

NOTE Confidence: 0.886790947272727

00:32:01.071 --> 00:32:02.776 angiogenic tumors that were low

NOTE Confidence: 0.886790947272727

00:32:02.776 --> 00:32:04.559 were also similarly associated,

NOTE Confidence: 0.886790947272727

00:32:04.560 --> 00:32:06.436 not quite as clean of a signal,

NOTE Confidence: 0.886790947272727

00:32:06.440 --> 00:32:07.959 but it's certainly it looks like if

NOTE Confidence: 0.886790947272727

00:32:07.959 --> 00:32:09.517 you're a low angiogenic tumor you're

NOTE Confidence: 0.886790947272727

00:32:09.517 --> 00:32:11.233 you're much more likely to recur.

NOTE Confidence: 0.886790947272727

00:32:11.240 --> 00:32:13.490 So this suggested that these micro

NOTE Confidence: 0.886790947272727

00:32:13.490 --> 00:32:14.990 environmental features also might

NOTE Confidence: 0.886790947272727

00:32:15.051 --> 00:32:16.511 be useful for adjuvant strategies

NOTE Confidence: 0.886790947272727

00:32:16.511 --> 00:32:18.756 and indeed a lot of the work now

NOTE Confidence: 0.886790947272727

00:32:18.756 --> 00:32:20.702 that's going forward in some of the

NOTE Confidence: 0.886790947272727

00:32:20.702 --> 00:32:22.735 newer adjuvant trials are factoring

NOTE Confidence: 0.886790947272727

00:32:22.735 --> 00:32:24.850 in things like these transcriptonic

NOTE Confidence: 0.886790947272727

00:32:24.850 --> 00:32:26.256 signatures into risk adapted models.

NOTE Confidence: 0.886790947272727

00:32:26.256 --> 00:32:28.357 And I think you know the future of

NOTE Confidence: 0.886790947272727

00:32:28.357 --> 00:32:29.822 course would would would incorporate

NOTE Confidence: 0.886790947272727

00:32:29.822 --> 00:32:31.745 some of these into selecting not only

NOTE Confidence: 0.886790947272727

00:32:31.745 --> 00:32:33.848 who's going to recur or not but maybe

NOTE Confidence: 0.886790947272727

00:32:33.848 --> 00:32:35.672 whether you give them a combination

NOTE Confidence: 0.886790947272727

00:32:35.672 --> 00:32:37.397 strategy or a single agent drug.

NOTE Confidence: 0.886790947272727

00:32:37.400 --> 00:32:38.198 But how can we test this.

NOTE Confidence: 0.886790947272727

00:32:38.200 --> 00:32:40.950 So ultimately you know I I show a lot of

NOTE Confidence: 0.886790947272727

00:32:41.026 --> 00:32:43.504 like nice kind of genomic correlative

NOTE Confidence: 0.886790947272727

00:32:43.504 --> 00:32:46.146 work and maybe some evolution of how

NOTE Confidence: 0.886790947272727

00:32:46.146 --> 00:32:48.622 we think about kidney cancer from a

NOTE Confidence: 0.886790947272727

00:32:48.622 --> 00:32:49.877 micro environmental and genomic standpoint,

NOTE Confidence: 0.886790947272727

00:32:49.880 --> 00:32:51.280 but really how do we test this.

NOTE Confidence: 0.886790947272727

00:32:51.280 --> 00:32:53.035 And so this is the challenge that I faced.

NOTE Confidence: 0.886790947272727

00:32:53.040 --> 00:32:54.657 I was kind of writing all these

NOTE Confidence: 0.886790947272727

00:32:54.657 --> 00:32:56.338 papers and thinking about this a lot

NOTE Confidence: 0.886790947272727

00:32:56.338 --> 00:32:57.748 and getting advice from mentors and

NOTE Confidence: 0.886790947272727

00:32:57.802 --> 00:32:59.475 everyone kept saying well you got to,

NOTE Confidence: 0.886790947272727

00:32:59.480 --> 00:33:00.041 you got to,

NOTE Confidence: 0.886790947272727

00:33:00.041 --> 00:33:01.920 you got to find a model that that works.

NOTE Confidence: 0.886790947272727

00:33:01.920 --> 00:33:03.888 And so you know we didn't have a

NOTE Confidence: 0.886790947272727

00:33:03.888 --> 00:33:06.155 lot of good models at the time and

NOTE Confidence: 0.886790947272727

00:33:06.160 --> 00:33:07.455 I'm going to talk about one we've

NOTE Confidence: 0.886790947272727

00:33:07.455 --> 00:33:08.010 we've developed a

NOTE Confidence: 0.803683961052632

00:33:08.053 --> 00:33:09.217 second which which I think is

NOTE Confidence: 0.803683961052632

00:33:09.217 --> 00:33:10.478 maybe even better, but I'm going

NOTE Confidence: 0.803683961052632

00:33:10.478 --> 00:33:12.408 to talk about the first one today.

NOTE Confidence: 0.803683961052632

00:33:12.408 --> 00:33:15.430 So. So you know there are some

NOTE Confidence: 0.803683961052632

00:33:15.430 --> 00:33:16.680 genetic models in kidney cancer.

NOTE Confidence: 0.803683961052632

00:33:16.680 --> 00:33:18.682 The, the one that was was used

NOTE Confidence: 0.803683961052632

00:33:18.682 --> 00:33:20.503 really until this time was really

NOTE Confidence: 0.803683961052632

00:33:20.503 --> 00:33:22.822 the Renka model which is for those

NOTE Confidence: 0.803683961052632

00:33:22.822 --> 00:33:24.877 of you familiar it spontaneously

NOTE Confidence: 0.803683961052632

00:33:24.880 --> 00:33:28.368 arose in a valve C mouse which is

NOTE Confidence: 0.803683961052632

00:33:28.368 --> 00:33:30.164 immunocompetent mouse and it was called

NOTE Confidence: 0.803683961052632

00:33:30.164 --> 00:33:31.319 the renal cortical Adam carcinoma.

NOTE Confidence: 0.803683961052632

00:33:31.320 --> 00:33:33.035 Back then we we really had very

NOTE Confidence: 0.803683961052632

00:33:33.040 --> 00:33:34.570 limited understanding but it has

NOTE Confidence: 0.803683961052632

00:33:34.570 --> 00:33:36.378 been profiled now and we know

NOTE Confidence: 0.803683961052632

00:33:36.378 --> 00:33:37.963 that it's not a VHL driven tumor.

NOTE Confidence: 0.803683961052632

00:33:37.963 --> 00:33:40.190 So VHL as I showed you earlier is is

NOTE Confidence: 0.803683961052632

00:33:40.190 --> 00:33:41.636 the fundamental event in in clear

NOTE Confidence: 0.803683961052632

00:33:41.636 --> 00:33:43.411 cell you have to have a VHL mutation

NOTE Confidence: 0.803683961052632

00:33:43.411 --> 00:33:47.715 to be a clear cell really and and so,

NOTE Confidence: 0.803683961052632

00:33:47.715 --> 00:33:50.240 so it was used forever.

NOTE Confidence: 0.803683961052632

00:33:50.240 --> 00:33:51.864 GEM models of course we know the

NOTE Confidence: 0.803683961052632

00:33:51.864 --> 00:33:53.500 genetics so why can't we just use

NOTE Confidence: 0.803683961052632

00:33:53.500 --> 00:33:55.141 gems and there are there are many

NOTE Confidence: 0.803683961052632

00:33:55.141 --> 00:33:56.665 many GEM models you can probably

NOTE Confidence: 0.803683961052632

00:33:56.665 --> 00:33:58.720 find six or seven out there.

NOTE Confidence: 0.803683961052632

00:33:58.720 --> 00:34:01.318 They're often from mixed mixed backgrounds.

NOTE Confidence: 0.803683961052632

00:34:01.320 --> 00:34:04.000 They have a very long tumor initiation time,

NOTE Confidence: 0.803683961052632

00:34:04.000 --> 00:34:06.400 very low lower tumor petitrins

NOTE Confidence: 0.803683961052632

00:34:06.400 --> 00:34:08.641 compared to other gems and they're

NOTE Confidence: 0.803683961052632

00:34:08.641 --> 00:34:10.243 very hard to transplant and often

NOTE Confidence: 0.803683961052632

00:34:10.243 --> 00:34:11.725 they develop cystic renal failure

NOTE Confidence: 0.803683961052632

00:34:11.725 --> 00:34:13.623 because when you knock out even in

NOTE Confidence: 0.803683961052632

00:34:13.623 --> 00:34:16.800 a KSP specific or Cree specific

NOTE Confidence: 0.803683961052632

00:34:16.800 --> 00:34:19.080 kidney specific fashion you will,

NOTE Confidence: 0.803683961052632

00:34:19.080 --> 00:34:20.290 you'll often develop cystic renal

NOTE Confidence: 0.803683961052632

00:34:20.290 --> 00:34:22.285 failure which is what you see in in

NOTE Confidence: 0.803683961052632

00:34:22.285 --> 00:34:23.515 people with hereditary kidney cancers.

NOTE Confidence: 0.803683961052632

00:34:23.520 --> 00:34:24.830 Many of them especially with

NOTE Confidence: 0.803683961052632

00:34:24.830 --> 00:34:25.878 VHL will develop many,

NOTE Confidence: 0.803683961052632

00:34:25.880 --> 00:34:27.120 many cysts in their kidney

NOTE Confidence: 0.803683961052632

00:34:27.120 --> 00:34:28.112 in addition to tumors.

NOTE Confidence: 0.803683961052632

00:34:28.120 --> 00:34:28.500 So,

NOTE Confidence: 0.803683961052632

00:34:28.500 --> 00:34:31.160 so it's hard to use those models.

NOTE Confidence: 0.803683961052632

00:34:31.160 --> 00:34:33.442 So we teamed up with Scott Lowe

NOTE Confidence: 0.803683961052632

00:34:33.442 --> 00:34:35.681 together and Scott Lowe is for those

NOTE Confidence: 0.803683961052632

00:34:35.681 --> 00:34:37.959 of you not familiar with him is very,

NOTE Confidence: 0.803683961052632

00:34:37.959 --> 00:34:39.354 very compass scientists at Memorial

NOTE Confidence: 0.803683961052632

00:34:39.354 --> 00:34:41.511 and does a lot of mouse engineering

NOTE Confidence: 0.803683961052632

00:34:41.511 --> 00:34:43.485 beautiful ways and we used an

NOTE Confidence: 0.803683961052632

00:34:43.485 --> 00:34:44.942 electroporation strategy at the time

NOTE Confidence: 0.803683961052632

00:34:44.942 --> 00:34:46.886 which would allowed us to deliver guides.

NOTE Confidence: 0.803683961052632

00:34:46.886 --> 00:34:48.842 We focused on a actually interesting

NOTE Confidence: 0.803683961052632

00:34:48.842 --> 00:34:50.700 combination of genes which are not

NOTE Confidence: 0.803683961052632

00:34:50.700 --> 00:34:52.080 super common in kidney cancer,

NOTE Confidence: 0.803683961052632

00:34:52.080 --> 00:34:53.578 but they define and I'll show you

NOTE Confidence: 0.803683961052632

00:34:53.578 --> 00:34:55.068 in a minute some of the myeloid

NOTE Confidence: 0.803683961052632

00:34:55.068 --> 00:34:56.676 phenotypes which is one of the

NOTE Confidence: 0.803683961052632

00:34:56.676 --> 00:34:58.547 reasons why we focus on it is there

NOTE Confidence: 0.803683961052632

00:34:58.547 --> 00:35:00.299 also happen to be a very nice gem

NOTE Confidence: 0.803683961052632

00:35:00.299 --> 00:35:02.214 from Ian Frus group in in Germany.

NOTE Confidence: 0.803683961052632

00:35:02.214 --> 00:35:04.536 It's time that utilize VHRB and

NOTE Confidence: 0.803683961052632

00:35:04.536 --> 00:35:07.230 P53 and showed very nicely a gem

NOTE Confidence: 0.803683961052632

00:35:07.230 --> 00:35:08.811 that which we had been using in the

NOTE Confidence: 0.803683961052632

00:35:08.811 --> 00:35:10.086 lab for many years and I'll show

NOTE Confidence: 0.803683961052632

00:35:10.086 --> 00:35:11.560 you some of that work in a minute.

NOTE Confidence: 0.803683961052632

00:35:11.560 --> 00:35:13.546 But we had utilized this strategy

NOTE Confidence: 0.803683961052632

00:35:13.546 --> 00:35:15.543 because a because Scott had utilizing

NOTE Confidence: 0.803683961052632

00:35:15.543 --> 00:35:17.692 P53 in a lot of different tumour

NOTE Confidence: 0.803683961052632

00:35:17.692 --> 00:35:19.632 models and he had very good guides

NOTE Confidence: 0.803683961052632

00:35:19.632 --> 00:35:21.013 for and very good strategies,

NOTE Confidence: 0.803683961052632

00:35:21.013 --> 00:35:23.011 but also because of the genetic

NOTE Confidence: 0.803683961052632

00:35:23.011 --> 00:35:24.776 combination and also because of

NOTE Confidence: 0.803683961052632

00:35:24.776 --> 00:35:25.838 the myeloid phenotypes.

NOTE Confidence: 0.803683961052632

00:35:25.840 --> 00:35:27.828 This was sort of our strategy at

NOTE Confidence: 0.803683961052632

00:35:27.828 --> 00:35:29.765 the time and this was not trivial

NOTE Confidence: 0.803683961052632

00:35:29.765 --> 00:35:31.842 because we had VHL as the backbone

NOTE Confidence: 0.803683961052632

00:35:31.842 --> 00:35:33.798 and that that that makes cells

NOTE Confidence: 0.803683961052632

00:35:33.798 --> 00:35:35.879 very tricky to add additional guys.

NOTE Confidence: 0.803683961052632

00:35:35.880 --> 00:35:37.752 For some reason when when you

NOTE Confidence: 0.803683961052632

00:35:37.752 --> 00:35:39.000 when you knockout VHL

NOTE Confidence: 0.93650505

00:35:39.000 --> 00:35:40.510 in vitro the cells don't

NOTE Confidence: 0.93650505

00:35:40.510 --> 00:35:41.718 tolerate it very well.

NOTE Confidence: 0.93650505

00:35:41.720 --> 00:35:43.800 They they senesce they they.

NOTE Confidence: 0.93650505

00:35:43.800 --> 00:35:45.792 And so this was about a year and

NOTE Confidence: 0.93650505

00:35:45.792 --> 00:35:47.760 a half of work that Lynn did.

NOTE Confidence: 0.93650505

00:35:47.760 --> 00:35:49.368 And eventually though we were able

NOTE Confidence: 0.93650505

00:35:49.368 --> 00:35:51.232 to develop a tumor that we could

NOTE Confidence: 0.93650505

00:35:51.232 --> 00:35:52.714 transplant and we were able to

NOTE Confidence: 0.93650505

00:35:52.714 --> 00:35:54.082 show transcriptomically that this

NOTE Confidence: 0.93650505

00:35:54.082 --> 00:35:55.852 matched into that myeloid high

NOTE Confidence: 0.93650505

00:35:55.852 --> 00:35:57.804 group that that Bob Moitzer and

NOTE Confidence: 0.93650505

00:35:57.804 --> 00:35:59.359 others from Genentech had shown

NOTE Confidence: 0.93650505

00:35:59.360 --> 00:36:01.118 to be critical for that cluster.

NOTE Confidence: 0.93650505

00:36:01.120 --> 00:36:02.812 The the, the very aggressive one

NOTE Confidence: 0.93650505

00:36:02.812 --> 00:36:04.982 that seems to be resistant to to

NOTE Confidence: 0.93650505

00:36:04.982 --> 00:36:06.599 vegif and I can show you here

NOTE Confidence: 0.93650505

00:36:06.599 --> 00:36:08.424 you know this was that cluster

NOTE Confidence: 0.93650505

00:36:08.424 --> 00:36:10.030 here it's P53 enriched 30%.

NOTE Confidence: 0.93650505

00:36:10.030 --> 00:36:12.010 Again P53 is not commonly seen

NOTE Confidence: 0.93650505

00:36:12.010 --> 00:36:13.960 in localized kidney cancer,

NOTE Confidence: 0.93650505

00:36:13.960 --> 00:36:15.556 but if you look at metastatic

NOTE Confidence: 0.93650505

00:36:15.556 --> 00:36:16.990 cohorts it's about between 10

NOTE Confidence: 0.93650505

00:36:16.990 --> 00:36:19.195 and 30% of those will have them.

NOTE Confidence: 0.93650505

00:36:19.200 --> 00:36:21.168 And so this is really the

NOTE Confidence: 0.93650505

00:36:21.168 --> 00:36:22.152 stromal proliferative cluster.

NOTE Confidence: 0.93650505

00:36:22.160 --> 00:36:26.720 When you do flow cytology analysis on it,

NOTE Confidence: 0.93650505

00:36:26.720 --> 00:36:28.946 they they're very macrophage and rich

NOTE Confidence: 0.93650505

00:36:28.946 --> 00:36:31.876 tumors and they have AP 53 program.

NOTE Confidence: 0.93650505

00:36:31.880 --> 00:36:33.120 When you look at transcriptomics,

NOTE Confidence: 0.93650505

00:36:33.120 --> 00:36:34.680 it's very similar to that group.

NOTE Confidence: 0.93650505

00:36:34.680 --> 00:36:36.423 And as I mentioned there was this

NOTE Confidence: 0.93650505

00:36:36.423 --> 00:36:37.948 adenosine signature that we saw which

NOTE Confidence: 0.93650505

00:36:37.948 --> 00:36:39.158 overlap with the myeloid sector.

NOTE Confidence: 0.93650505

00:36:39.160 --> 00:36:39.521 This,

NOTE Confidence: 0.93650505

00:36:39.521 --> 00:36:42.048 this actually came from this paper that

NOTE Confidence: 0.93650505

00:36:42.048 --> 00:36:46.158 was published in from UCSF from Fong ET al.

NOTE Confidence: 0.93650505

00:36:46.160 --> 00:36:47.860 In combination with with Corvis

NOTE Confidence: 0.93650505

00:36:47.860 --> 00:36:50.006 which is a biotech company.

NOTE Confidence: 0.93650505

00:36:50.006 --> 00:36:53.384 And they had developed an adenosine

NOTE Confidence: 0.93650505

00:36:53.384 --> 00:36:56.357 2 receptor blockade therapy for

NOTE Confidence: 0.93650505

00:36:56.357 --> 00:36:57.625 patients with metastatic kidney

NOTE Confidence: 0.93650505

00:36:57.625 --> 00:36:59.210 cancer that were treatment refractory

NOTE Confidence: 0.93650505

00:36:59.254 --> 00:37:00.682 and they had developed a signature

NOTE Confidence: 0.93650505

00:37:00.682 --> 00:37:02.336 which which was very much overlapping

NOTE Confidence: 0.93650505

00:37:02.336 --> 00:37:03.636 with this myeloid signature.

NOTE Confidence: 0.93650505

00:37:03.640 --> 00:37:05.120 So this gave us the thought of OK,

NOTE Confidence: 0.93650505

00:37:05.120 --> 00:37:07.656 well we showed that this myeloid program is

NOTE Confidence: 0.93650505

00:37:07.656 --> 00:37:09.880 so important for metastasis development.

NOTE Confidence: 0.93650505

00:37:09.880 --> 00:37:12.196 Maybe if we targeted this adenosine

NOTE Confidence: 0.93650505

00:37:12.196 --> 00:37:14.480 pathway this could abrogate metastasis.

NOTE Confidence: 0.93650505

00:37:14.480 --> 00:37:16.720 And So what Lynn did in her model

NOTE Confidence: 0.93650505

00:37:16.720 --> 00:37:18.865 when she developed it was was

NOTE Confidence: 0.93650505

00:37:18.865 --> 00:37:20.755 stored sort of started testing

NOTE Confidence: 0.93650505

00:37:20.760 --> 00:37:22.040 CP1444 is this adenosine inhibitor.

NOTE Confidence: 0.93650505

00:37:22.040 --> 00:37:23.680 And we were able to show that you

NOTE Confidence: 0.93650505

00:37:23.680 --> 00:37:25.231 get this dramatic abrogation of

NOTE Confidence: 0.93650505

00:37:25.231 --> 00:37:27.036 metastasis doesn't fully control it,

NOTE Confidence: 0.93650505

00:37:27.040 --> 00:37:30.008 but the the number of Mets and the

NOTE Confidence: 0.93650505

00:37:30.008 --> 00:37:31.528 development of Mets is abrogated

NOTE Confidence: 0.93650505

00:37:31.528 --> 00:37:33.140 quite dramatically using a myeloid

NOTE Confidence: 0.93650505

00:37:33.140 --> 00:37:34.775 depletion strategy or a specific

NOTE Confidence: 0.93650505

00:37:34.775 --> 00:37:35.756 myeloid depletion strategy.

NOTE Confidence: 0.93650505

00:37:35.760 --> 00:37:36.760 It doesn't deplete all Tams,

NOTE Confidence: 0.93650505

00:37:36.760 --> 00:37:38.650 but it does shift the phenotype of

NOTE Confidence: 0.93650505

00:37:38.650 --> 00:37:40.879 some of the Tams quite dramatically

NOTE Confidence: 0.93650505

00:37:40.880 --> 00:37:43.448 suggesting perhaps that this could be

NOTE Confidence: 0.93650505

00:37:43.448 --> 00:37:46.199 a strategy and utilizing a mouse model.

NOTE Confidence: 0.93650505

00:37:46.200 --> 00:37:47.160 In the background of all this,

NOTE Confidence: 0.93650505

00:37:47.160 --> 00:37:49.944 we've also you know really been

NOTE Confidence: 0.93650505

00:37:49.944 --> 00:37:53.068 thinking about how to utilize the

NOTE Confidence: 0.93650505

00:37:53.068 --> 00:37:56.238 micro environment to study resistance.

NOTE Confidence: 0.93650505

00:37:56.240 --> 00:37:57.761 And so again we had to go back to

NOTE Confidence: 0.93650505

00:37:57.761 --> 00:37:59.844 a mouse model and I I showed this

NOTE Confidence: 0.93650505

00:37:59.844 --> 00:38:01.319 engineering model which we developed.

NOTE Confidence: 0.93650505

00:38:01.320 --> 00:38:02.360 But we're in the background of all this.

NOTE Confidence: 0.93650505

00:38:02.360 --> 00:38:04.136 For many years we had been utilizing

NOTE Confidence: 0.93650505

00:38:04.136 --> 00:38:06.768 this gem and we we utilize this

NOTE Confidence: 0.93650505

00:38:06.768 --> 00:38:08.840 gem from Ian Frue ET all this.

NOTE Confidence: 0.93650505

00:38:08.840 --> 00:38:12.288 Again this was a KSP, sorry Cree,

NOTE Confidence: 0.93650505

00:38:12.288 --> 00:38:16.925 ERT 2 KSP 1 Flocks mouse that had lost VHL,

NOTE Confidence: 0.93650505

00:38:16.925 --> 00:38:18.140 PT3 and RB.

NOTE Confidence: 0.93650505

00:38:18.140 --> 00:38:20.570 They develop pretty nice clear cell

NOTE Confidence: 0.93650505

00:38:20.652 --> 00:38:23.430 tumors and we utilize this model to to

NOTE Confidence: 0.93650505

00:38:23.430 --> 00:38:25.719 actually study some of these questions.

NOTE Confidence: 0.8089033575

00:38:25.720 --> 00:38:27.865 We want to understand what's

NOTE Confidence: 0.8089033575

00:38:27.865 --> 00:38:30.603 happening with both PD1 and VEGF

NOTE Confidence: 0.8089033575

00:38:30.603 --> 00:38:33.158 therapies alone and in combination.

NOTE Confidence: 0.8089033575

00:38:33.160 --> 00:38:34.868 Again I showed you the the real

NOTE Confidence: 0.8089033575

00:38:34.868 --> 00:38:36.745 the relevance of this from a

NOTE Confidence: 0.8089033575

00:38:36.745 --> 00:38:37.837 predicting response standpoint.

NOTE Confidence: 0.8089033575

00:38:37.840 --> 00:38:40.248 And so we first looked at these

NOTE Confidence: 0.8089033575

00:38:40.248 --> 00:38:42.547 tumors genomic this is this is

NOTE Confidence: 0.8089033575

00:38:42.547 --> 00:38:44.537 unpublished data but hopefully will

NOTE Confidence: 0.8089033575

00:38:44.537 --> 00:38:46.956 be submitted in the next few months.

NOTE Confidence: 0.8089033575

00:38:46.960 --> 00:38:48.928 So, so we we started looking at these

NOTE Confidence: 0.8089033575

00:38:48.928 --> 00:38:50.726 KVPR tumors that had from this Ian

NOTE Confidence: 0.8089033575

00:38:50.726 --> 00:38:52.455 fruit model again validating the fact

NOTE Confidence: 0.8089033575

00:38:52.455 --> 00:38:54.080 that they are really representative

NOTE Confidence: 0.8089033575

00:38:54.080 --> 00:38:56.524 of this myeloid high tumor that I had

NOTE Confidence: 0.8089033575

00:38:56.524 --> 00:38:58.400 shown you earlier from from Bob's work.

NOTE Confidence: 0.8089033575

00:38:58.400 --> 00:39:00.266 This is again showing RNA sequencing

NOTE Confidence: 0.8089033575

00:39:00.266 --> 00:39:02.382 from from from many tumors that we

NOTE Confidence: 0.8089033575

00:39:02.382 --> 00:39:04.286 have from these mice and that they

NOTE Confidence: 0.8089033575

00:39:04.343 --> 00:39:06.282 overlap very nicely with the the myeloid

NOTE Confidence: 0.8089033575

00:39:06.282 --> 00:39:10.640 high PV 3 driven tumors in in human.

NOTE Confidence: 0.8089033575

00:39:10.640 --> 00:39:12.560 And we started treating these mice

NOTE Confidence: 0.8089033575

00:39:12.560 --> 00:39:14.428 and really focusing on a combination

NOTE Confidence: 0.8089033575

00:39:14.428 --> 00:39:16.780 strategy which I think is near to dear

NOTE Confidence: 0.8089033575

00:39:16.843 --> 00:39:18.716 Harriet from her from work in Melanoma.

NOTE Confidence: 0.8089033575

00:39:18.720 --> 00:39:21.952 But we we utilized linvanib and and PD

NOTE Confidence: 0.8089033575

00:39:21.952 --> 00:39:23.998 one in combination for a few reasons.

NOTE Confidence: 0.8089033575

00:39:24.000 --> 00:39:25.344 One we were very interested in levanim

NOTE Confidence: 0.8089033575

00:39:25.344 --> 00:39:27.137 and PD one comma that that has the

NOTE Confidence: 0.8089033575

00:39:27.137 --> 00:39:28.077 highest overall response rate.

NOTE Confidence: 0.8089033575

00:39:28.080 --> 00:39:29.998 If you look at the clinical trials,

NOTE Confidence: 0.8089033575

00:39:30.000 --> 00:39:32.639 it's about 75% of patients will have

NOTE Confidence: 0.8089033575

00:39:32.640 --> 00:39:34.117 a first line response which is really,

NOTE Confidence: 0.8089033575

00:39:34.120 --> 00:39:38.798 really incredible and and also we

NOTE Confidence: 0.8089033575

00:39:38.798 --> 00:39:40.874 know that Lenva has potentially a

NOTE Confidence: 0.8089033575

00:39:40.874 --> 00:39:42.983 lot of micro environmental targets

NOTE Confidence: 0.8089033575

00:39:42.983 --> 00:39:45.636 beyond just veg F So so we're very

NOTE Confidence: 0.8089033575

00:39:45.636 --> 00:39:47.070 interested in this question and we

NOTE Confidence: 0.8089033575

00:39:47.123 --> 00:39:48.796 utilized a sort of a mouse clinical

NOTE Confidence: 0.8089033575

00:39:48.796 --> 00:39:49.800 trial from this work.

NOTE Confidence: 0.8089033575

00:39:49.800 --> 00:39:53.755 We also included though ACSF 1 inhibitor

NOTE Confidence: 0.8089033575

00:39:53.760 --> 00:39:56.289 BLZ 945 to see if if we just broadly

NOTE Confidence: 0.8089033575

00:39:56.289 --> 00:39:58.038 depleting Tam's would be helpful.

NOTE Confidence: 0.8089033575

00:39:58.040 --> 00:40:00.376 And I should note that CSF one and

NOTE Confidence: 0.8089033575

00:40:00.376 --> 00:40:02.108 our inhibitors have been have been

NOTE Confidence: 0.8089033575

00:40:02.108 --> 00:40:03.478 a DUD in the clinic.

NOTE Confidence: 0.8089033575

00:40:03.480 --> 00:40:04.760 Primarily because they they tend

NOTE Confidence: 0.8089033575

00:40:04.760 --> 00:40:06.460 to deplete lots of Tams and Tams

NOTE Confidence: 0.8089033575

00:40:06.460 --> 00:40:07.956 can be good and they can be bad.

NOTE Confidence: 0.8089033575

00:40:07.960 --> 00:40:09.738 So we don't really we we weren't

NOTE Confidence: 0.8089033575

00:40:09.738 --> 00:40:11.239 really didn't really know what to

NOTE Confidence: 0.8089033575

00:40:11.239 --> 00:40:12.849 expect here and I'll just show some

NOTE Confidence: 0.8089033575

00:40:12.898 --> 00:40:14.312 of that data and we did single

NOTE Confidence: 0.8089033575

00:40:14.312 --> 00:40:16.920 cell on pretty much all of these

NOTE Confidence: 0.8089033575

00:40:16.920 --> 00:40:18.864 mice that we developed tumors from

NOTE Confidence: 0.8089033575

00:40:18.864 --> 00:40:19.836 in different categories.

NOTE Confidence: 0.8089033575

00:40:19.840 --> 00:40:21.240 And we and we this to this,

NOTE Confidence: 0.8089033575

00:40:21.240 --> 00:40:23.115 this model actually is quite

NOTE Confidence: 0.8089033575

00:40:23.115 --> 00:40:24.880 sensitive to linvatinib and actually

NOTE Confidence: 0.8089033575

00:40:24.880 --> 00:40:26.480 the combination is is pretty

NOTE Confidence: 0.8089033575

00:40:26.480 --> 00:40:27.400 dramatically responsive here.

NOTE Confidence: 0.8089033575

00:40:27.400 --> 00:40:29.500 But they don't respond at all to

NOTE Confidence: 0.8089033575

00:40:29.500 --> 00:40:30.905 PD1 and actually CSF ONE inhibitors

NOTE Confidence: 0.8089033575

00:40:30.905 --> 00:40:32.200 don't really do anything at all.

NOTE Confidence: 0.8089033575

00:40:32.200 --> 00:40:36.076 So we were then also able to take

NOTE Confidence: 0.8089033575

00:40:36.080 --> 00:40:38.198 early responders and resistant and and

NOTE Confidence: 0.8089033575

00:40:38.198 --> 00:40:40.080 actually start comparing them as well.

NOTE Confidence: 0.8089033575

00:40:40.080 --> 00:40:41.928 So we can look at the impacts on

NOTE Confidence: 0.8089033575

00:40:41.928 --> 00:40:43.743 the micro environment from these

NOTE Confidence: 0.8089033575

00:40:43.743 --> 00:40:45.463 different treatment strategies alone

NOTE Confidence: 0.8089033575

00:40:45.463 --> 00:40:47.756 in combination and in resistance and

NOTE Confidence: 0.8089033575

00:40:47.756 --> 00:40:49.640 in sensitivity which is which is

NOTE Confidence: 0.8089033575

00:40:49.640 --> 00:40:51.234 really I think something you want to do.

NOTE Confidence: 0.8089033575

00:40:51.240 --> 00:40:52.766 And we could take single cell data

NOTE Confidence: 0.8089033575

00:40:52.766 --> 00:40:54.212 from this same strategy that we

NOTE Confidence: 0.8089033575

00:40:54.212 --> 00:40:55.706 applied before and start looking at

NOTE Confidence: 0.8089033575

00:40:55.706 --> 00:40:56.946 the differences between responders

NOTE Confidence: 0.8089033575

00:40:56.946 --> 00:40:58.836 and non responders between ones that

NOTE Confidence: 0.8089033575

00:40:58.836 --> 00:41:01.773 are in combination or or alone and

NOTE Confidence: 0.8089033575

00:41:01.773 --> 00:41:03.797 get a sense of what's really driving us.

NOTE Confidence: 0.917395440833333

00:41:03.800 --> 00:41:05.642 You know one of the interesting

NOTE Confidence: 0.917395440833333

00:41:05.642 --> 00:41:07.415 things about this single cell data

NOTE Confidence: 0.917395440833333

00:41:07.415 --> 00:41:09.102 set was that we actually had a

NOTE Confidence: 0.917395440833333

00:41:09.102 --> 00:41:10.998 lot of neutrophil populations and

NOTE Confidence: 0.917395440833333

00:41:11.000 --> 00:41:12.278 we don't really know their role.

NOTE Confidence: 0.917395440833333

00:41:12.280 --> 00:41:14.212 I mean there's been some really nice

NOTE Confidence: 0.917395440833333

00:41:14.212 --> 00:41:16.143 work from Taha Murgoob and Jed Walchak

NOTE Confidence: 0.917395440833333

00:41:16.143 --> 00:41:18.360 recently on the on on on neutrophils

NOTE Confidence: 0.917395440833333

00:41:18.360 --> 00:41:21.760 roles in in immunotherapy strategies.

NOTE Confidence: 0.917395440833333

00:41:21.760 --> 00:41:22.308 So it's an emergency,

NOTE Confidence: 0.917395440833333

00:41:22.308 --> 00:41:23.312 but I'm not going to talk about

NOTE Confidence: 0.917395440833333

00:41:23.312 --> 00:41:23.916 that too much today,

NOTE Confidence: 0.917395440833333

00:41:23.920 --> 00:41:25.649 but it was a striking finding here

NOTE Confidence: 0.917395440833333

00:41:25.649 --> 00:41:27.603 and we could further subtype the

NOTE Confidence: 0.917395440833333

00:41:27.603 --> 00:41:29.139 macrophage clusters within here

NOTE Confidence: 0.917395440833333

00:41:29.139 --> 00:41:30.880 and understand what's happening.

NOTE Confidence: 0.917395440833333

00:41:30.880 --> 00:41:32.736 It's a, it's a very Tam dominated tumor

NOTE Confidence: 0.917395440833333

00:41:32.736 --> 00:41:34.999 type as I mentioned with the P53 and RB.

NOTE Confidence: 0.862237040454545

00:41:37.400 --> 00:41:39.098 And we can actually further stratify

NOTE Confidence: 0.862237040454545

00:41:39.098 --> 00:41:40.978 them and to understand what's actually

NOTE Confidence: 0.862237040454545

00:41:40.978 --> 00:41:43.054 happening in the context of both

NOTE Confidence: 0.862237040454545

00:41:43.054 --> 00:41:44.520 therapeutic sensitivity and resistance.

NOTE Confidence: 0.862237040454545

00:41:44.520 --> 00:41:46.446 And you can start to see that certain Tams

NOTE Confidence: 0.862237040454545

00:41:46.446 --> 00:41:48.413 are associated with response and certain

NOTE Confidence: 0.862237040454545

00:41:48.413 --> 00:41:50.113 Tams are associated with resistance.

NOTE Confidence: 0.862237040454545

00:41:50.120 --> 00:41:52.118 So even though if you just deplete all Tams,

NOTE Confidence: 0.862237040454545

00:41:52.120 --> 00:41:53.956 you would actually lose that effect.

NOTE Confidence: 0.862237040454545

00:41:53.960 --> 00:41:55.202 But actually if you understood which

NOTE Confidence: 0.862237040454545

00:41:55.202 --> 00:41:56.332 Tams which tumor associated macrophages

NOTE Confidence: 0.862237040454545

00:41:56.332 --> 00:41:57.677 are actually associated with response,

NOTE Confidence: 0.862237040454545

00:41:57.680 --> 00:41:58.920 these Angio hide Tams,

NOTE Confidence: 0.862237040454545

00:41:58.920 --> 00:42:00.780 Tams that are producing angiogenic genes

NOTE Confidence: 0.862237040454545

00:42:00.829 --> 00:42:02.949 which maybe have been reflected by some of

NOTE Confidence: 0.862237040454545

00:42:02.949 --> 00:42:05.156 those Angio bulk RNA sequencing data earlier,

NOTE Confidence: 0.862237040454545

00:42:05.160 --> 00:42:06.400 they're actually associated with response.

NOTE Confidence: 0.862237040454545

00:42:06.400 --> 00:42:07.264 Whereas other Tams,

NOTE Confidence: 0.862237040454545

00:42:07.264 --> 00:42:08.704 maybe those myeloid high Angio

NOTE Confidence: 0.862237040454545

00:42:08.704 --> 00:42:10.705 hide tumors that don't respond are

NOTE Confidence: 0.862237040454545

00:42:10.705 --> 00:42:12.077 actually associated with resistance.

NOTE Confidence: 0.862237040454545

00:42:12.080 --> 00:42:14.504 So now we can start getting further into

NOTE Confidence: 0.862237040454545

00:42:14.504 --> 00:42:16.760 the phenotypes of these Tams and and

NOTE Confidence: 0.862237040454545

00:42:16.760 --> 00:42:18.355 the context of treatment strategies.

NOTE Confidence: 0.862237040454545

00:42:18.360 --> 00:42:19.680 And for the sake of time,

NOTE Confidence: 0.862237040454545

00:42:19.680 --> 00:42:20.718 I won't talk about the neutrophils,

NOTE Confidence: 0.862237040454545

00:42:20.720 --> 00:42:23.620 but it is another story and we

NOTE Confidence: 0.862237040454545

00:42:23.620 --> 00:42:25.570 can actually use neutrophils to

NOTE Confidence: 0.862237040454545

00:42:25.570 --> 00:42:27.440 associate again further responses.

NOTE Confidence: 0.862237040454545

00:42:27.440 --> 00:42:29.231 So perhaps there's a a major role for them

NOTE Confidence: 0.862237040454545

00:42:29.231 --> 00:42:31.000 and I don't have time to talk about it.

NOTE Confidence: 0.862237040454545

00:42:31.000 --> 00:42:31.994 But then then of course you have

NOTE Confidence: 0.862237040454545

00:42:31.994 --> 00:42:33.077 to go back to the human right,

NOTE Confidence: 0.862237040454545

00:42:33.080 --> 00:42:34.438 because I showed you something in mouse.

NOTE Confidence: 0.862237040454545

00:42:34.440 --> 00:42:36.170 But are there analogous populations

NOTE Confidence: 0.862237040454545

00:42:36.170 --> 00:42:37.733 in human post treatment, right,

NOTE Confidence: 0.862237040454545

00:42:37.733 --> 00:42:38.598 Because if you're going to,

NOTE Confidence: 0.862237040454545

00:42:38.600 --> 00:42:40.238 you can cure lots of mice,

NOTE Confidence: 0.862237040454545

00:42:40.240 --> 00:42:41.955 but you don't know if if those,

NOTE Confidence: 0.862237040454545

00:42:41.960 --> 00:42:44.840 if those populations are are

NOTE Confidence: 0.862237040454545

00:42:44.840 --> 00:42:46.544 relevant to human biology and that's

NOTE Confidence: 0.862237040454545

00:42:46.544 --> 00:42:48.080 a major challenge for immuno,

NOTE Confidence: 0.862237040454545

00:42:48.080 --> 00:42:50.855 immuno genomic studies or immunologies

NOTE Confidence: 0.862237040454545

00:42:50.855 --> 00:42:53.075 immunotherapy related studies because

NOTE Confidence: 0.862237040454545

00:42:53.080 --> 00:42:55.908 of course the mouse and the human micro

NOTE Confidence: 0.862237040454545

00:42:55.908 --> 00:42:57.516 environments are can be quite different.

NOTE Confidence: 0.862237040454545

00:42:57.520 --> 00:43:00.598 So that requires post treatment tissue.

NOTE Confidence: 0.862237040454545

00:43:00.600 --> 00:43:01.398 So how do you do that?

NOTE Confidence: 0.862237040454545

00:43:01.400 --> 00:43:03.944 So that's you know some of the beauty

NOTE Confidence: 0.862237040454545

00:43:03.944 --> 00:43:06.716 about going back and forth in in my group.

NOTE Confidence: 0.862237040454545

00:43:06.716 --> 00:43:08.960 So this is work that was led by

NOTE Confidence: 0.862237040454545

00:43:08.960 --> 00:43:10.625 Steven Reese who's graduating from

NOTE Confidence: 0.862237040454545

00:43:10.625 --> 00:43:11.957 our program this year.

NOTE Confidence: 0.862237040454545

00:43:11.960 --> 00:43:14.021 He's spent a year with me in the lab

NOTE Confidence: 0.862237040454545

00:43:14.021 --> 00:43:16.681 and a whole whole including a lot of

NOTE Confidence: 0.862237040454545

00:43:16.681 --> 00:43:18.506 very talented pathologists and research

NOTE Confidence: 0.862237040454545

00:43:18.506 --> 00:43:20.446 pathologists and of course Christina

NOTE Confidence: 0.862237040454545

00:43:20.446 --> 00:43:22.676 Leslie from the Computational Biology.

NOTE Confidence: 0.862237040454545

00:43:22.680 --> 00:43:24.066 And we and we we took all these patients

NOTE Confidence: 0.862237040454545

00:43:24.066 --> 00:43:25.597 that we've been operating on over the years.

NOTE Confidence: 0.862237040454545

00:43:25.600 --> 00:43:27.622 Now we started to define them

NOTE Confidence: 0.862237040454545

00:43:27.622 --> 00:43:29.770 into categories right of of early

NOTE Confidence: 0.862237040454545

00:43:29.770 --> 00:43:31.600 response of a complete response,

NOTE Confidence: 0.862237040454545

00:43:31.600 --> 00:43:33.520 partial response and and no response.

NOTE Confidence: 0.862237040454545

00:43:33.520 --> 00:43:36.008 These are patients that Pat operates

NOTE Confidence: 0.862237040454545

00:43:36.008 --> 00:43:38.560 on all the time and and I operate on

NOTE Confidence: 0.862237040454545

00:43:38.560 --> 00:43:40.296 quite a bit and these are patients

NOTE Confidence: 0.862237040454545

00:43:40.296 --> 00:43:41.791 that that are post immunotherapy

NOTE Confidence: 0.862237040454545

00:43:41.791 --> 00:43:43.720 now which is a new new frontier.

NOTE Confidence: 0.862237040454545

00:43:43.720 --> 00:43:45.770 A lot of our surgery now is now in the

NOTE Confidence: 0.862237040454545

00:43:45.832 --> 00:43:48.152 in the post IO space that gives you a very,

NOTE Confidence: 0.862237040454545

00:43:48.160 --> 00:43:50.015 very unique opportunity to actually

NOTE Confidence: 0.862237040454545

00:43:50.015 --> 00:43:51.870 study what's happening both within

NOTE Confidence: 0.862237040454545

00:43:51.925 --> 00:43:52.879 and across tumors.

NOTE Confidence: 0.862237040454545

00:43:52.880 --> 00:43:55.664 And so this this is allows us to

NOTE Confidence: 0.862237040454545

00:43:55.664 --> 00:43:57.963 assemble cohorts of patients that have

NOTE Confidence: 0.862237040454545

00:43:57.963 --> 00:44:00.480 been exposed to IO therapy alone to

NOTE Confidence: 0.862237040454545

00:44:00.480 --> 00:44:03.925 IOTKI therapy and we have some with

NOTE Confidence: 0.862237040454545

00:44:03.925 --> 00:44:06.158 just TKLO but that's really not done anymore.

NOTE Confidence: 0.862237040454545

00:44:06.160 --> 00:44:06.502 So,

NOTE Confidence: 0.862237040454545

00:44:06.502 --> 00:44:08.554 so essentially we can look at

NOTE Confidence: 0.862237040454545

00:44:08.554 --> 00:44:09.580 responses both defined

NOTE Confidence: 0.827261062727272

00:44:09.647 --> 00:44:11.112 clinically, radiographically but

NOTE Confidence: 0.827261062727272

00:44:11.112 --> 00:44:12.696 also pathologically and understand

NOTE Confidence: 0.827261062727272

00:44:12.696 --> 00:44:14.915 are there what are the populations

NOTE Confidence: 0.827261062727272

00:44:14.915 --> 00:44:16.938 in human and are they analogous to

NOTE Confidence: 0.827261062727272

00:44:16.938 --> 00:44:19.151 the mouse of course which is you know

NOTE Confidence: 0.827261062727272

00:44:19.151 --> 00:44:21.272 something that I you know really want

NOTE Confidence: 0.827261062727272

00:44:21.272 --> 00:44:24.520 to do what we really want to focus on.

NOTE Confidence: 0.827261062727272

00:44:24.520 --> 00:44:26.092 And so you can start defining

NOTE Confidence: 0.827261062727272

00:44:26.092 --> 00:44:26.878 this different ways.

NOTE Confidence: 0.827261062727272

00:44:26.880 --> 00:44:27.984 This hasn't been,

NOTE Confidence: 0.827261062727272

00:44:27.984 --> 00:44:29.638 there's not an official Canon

NOTE Confidence: 0.827261062727272

00:44:29.638 --> 00:44:31.474 here on how to do this.

NOTE Confidence: 0.827261062727272

00:44:31.480 --> 00:44:33.384 It's sort of been adopted a lot from

NOTE Confidence: 0.827261062727272

00:44:33.384 --> 00:44:34.934 the Melanoma literature about how

NOTE Confidence: 0.827261062727272

00:44:34.934 --> 00:44:36.634 to define true pathologic response.

NOTE Confidence: 0.827261062727272

00:44:36.640 --> 00:44:37.936 A lot of us have looked at you

NOTE Confidence: 0.827261062727272

00:44:37.936 --> 00:44:38.811 know complete response where

NOTE Confidence: 0.827261062727272

00:44:38.811 --> 00:44:40.076 there's no residual viable tumor,

NOTE Confidence: 0.827261062727272

00:44:40.080 --> 00:44:42.055 RVT, residual viable tumor or

NOTE Confidence: 0.827261062727272

00:44:42.055 --> 00:44:43.240 near complete response.

NOTE Confidence: 0.827261062727272

00:44:43.240 --> 00:44:44.770 And those patients actually if you

NOTE Confidence: 0.827261062727272

00:44:44.770 --> 00:44:46.679 if you take their their kidneys out

NOTE Confidence: 0.827261062727272

00:44:46.680 --> 00:44:48.435 we we showed and and we'll show in in

NOTE Confidence: 0.827261062727272

00:44:48.435 --> 00:44:50.436 our paper that you know they have really,

NOTE Confidence: 0.827261062727272

00:44:50.440 --> 00:44:52.078 really durable responses you know many,

NOTE Confidence: 0.827261062727272

00:44:52.080 --> 00:44:53.796 many years without even off therapy.

NOTE Confidence: 0.827261062727272

00:44:53.800 --> 00:44:55.528 So that's a it's a good biomarker for

NOTE Confidence: 0.827261062727272

00:44:55.528 --> 00:44:57.157 how they're going to do down the road.

NOTE Confidence: 0.827261062727272

00:44:57.160 --> 00:44:58.630 And then you can have these partial

NOTE Confidence: 0.827261062727272

00:44:58.630 --> 00:44:59.904 responses where they have this in

NOTE Confidence: 0.827261062727272

00:44:59.904 --> 00:45:01.297 between and you have these non responses

NOTE Confidence: 0.827261062727272

00:45:01.341 --> 00:45:02.955 where there's really no treatment response.

NOTE Confidence: 0.827261062727272

00:45:02.960 --> 00:45:04.710 You can see it all within the

NOTE Confidence: 0.827261062727272

00:45:04.710 --> 00:45:06.879 tumor and you could do single cell

NOTE Confidence: 0.827261062727272

00:45:06.879 --> 00:45:08.569 sequencing on these cohorts and

NOTE Confidence: 0.827261062727272

00:45:08.569 --> 00:45:10.152 start to get obviously in the human.

NOTE Confidence: 0.827261062727272

00:45:10.152 --> 00:45:12.030 You still see a lot more T cells as

NOTE Confidence: 0.827261062727272

00:45:12.030 --> 00:45:13.395 I showed you earlier from the work

NOTE Confidence: 0.827261062727272

00:45:13.439 --> 00:45:14.999 that we did and what David has done.

NOTE Confidence: 0.827261062727272

00:45:15.000 --> 00:45:16.953 But you can see these tan populations

NOTE Confidence: 0.827261062727272

00:45:16.953 --> 00:45:19.278 here and then you can overlay work that.

NOTE Confidence: 0.827261062727272

00:45:19.280 --> 00:45:20.320 Andrew Corners,

NOTE Confidence: 0.827261062727272

00:45:20.320 --> 00:45:23.491 who's an MD medical oncology fellow

NOTE Confidence: 0.827261062727272

00:45:23.491 --> 00:45:26.060 working with Ming Lee has done

NOTE Confidence: 0.827261062727272

00:45:26.060 --> 00:45:27.320 a lot of this work now.

NOTE Confidence: 0.827261062727272

00:45:27.320 --> 00:45:29.280 And we can start seeing what are

NOTE Confidence: 0.827261062727272

00:45:29.280 --> 00:45:30.740 the differences between the IO only

NOTE Confidence: 0.827261062727272

00:45:30.740 --> 00:45:32.264 and the IOTKI and the untreated

NOTE Confidence: 0.827261062727272

00:45:32.264 --> 00:45:34.280 populations in terms of the single cell,

NOTE Confidence: 0.827261062727272

00:45:34.280 --> 00:45:35.968 again post treatment populations

NOTE Confidence: 0.827261062727272

00:45:35.968 --> 00:45:38.924 and we can start focusing on some

NOTE Confidence: 0.827261062727272

00:45:38.924 --> 00:45:41.042 of these same populations that we

NOTE Confidence: 0.827261062727272

00:45:41.042 --> 00:45:43.670 saw that and then we can actually

NOTE Confidence: 0.827261062727272

00:45:43.670 --> 00:45:45.550 overlay the mouse Tam signatures

NOTE Confidence: 0.827261062727272

00:45:45.550 --> 00:45:47.800 onto these populations to see other

NOTE Confidence: 0.827261062727272

00:45:47.800 --> 00:45:49.601 analogous populations and are they

NOTE Confidence: 0.827261062727272

00:45:49.601 --> 00:45:50.933 associated with resistance and

NOTE Confidence: 0.827261062727272

00:45:50.933 --> 00:45:52.642 response both within the tumors

NOTE Confidence: 0.827261062727272

00:45:52.642 --> 00:45:54.277 and across the different regions.

NOTE Confidence: 0.827261062727272

00:45:54.280 --> 00:45:56.120 And that's sort of where we're focusing now.

NOTE Confidence: 0.827261062727272

00:45:56.120 --> 00:45:57.800 And so we can further substratify

NOTE Confidence: 0.827261062727272

00:45:57.800 --> 00:45:59.838 the Tams just like I showed you in

NOTE Confidence: 0.827261062727272

00:45:59.838 --> 00:46:01.931 the mouse and to see are the TKII

NOTE Confidence: 0.827261062727272

00:46:01.931 --> 00:46:03.953 iOS really depleting some of these.

NOTE Confidence: 0.827261062727272

00:46:03.960 --> 00:46:05.703 This is just looking at them broadly

NOTE Confidence: 0.827261062727272

00:46:05.703 --> 00:46:07.000 without looking at resistance.

NOTE Confidence: 0.827261062727272

00:46:07.000 --> 00:46:09.128 But you can start seeing that that the

NOTE Confidence: 0.827261062727272

00:46:09.128 --> 00:46:11.016 the different populations are being

NOTE Confidence: 0.827261062727272

00:46:11.016 --> 00:46:13.224 affected in different ways by the

NOTE Confidence: 0.827261062727272

00:46:13.224 --> 00:46:15.052 different treatments in maybe similar ways,

NOTE Confidence: 0.827261062727272

00:46:15.052 --> 00:46:16.144 but I'm sure different

NOTE Confidence: 0.827261062727272

00:46:16.144 --> 00:46:17.678 ways as well as the mouse.

NOTE Confidence: 0.827261062727272

00:46:17.680 --> 00:46:19.388 But hopefully that will help us hone

NOTE Confidence: 0.827261062727272

00:46:19.388 --> 00:46:21.068 in on what are the most relevant

NOTE Confidence: 0.827261062727272

00:46:21.068 --> 00:46:22.676 targets to try in the mouse.

NOTE Confidence: 0.827261062727272

00:46:22.680 --> 00:46:24.040 And you can see this if you focus

NOTE Confidence: 0.827261062727272

00:46:24.040 --> 00:46:25.464 on one of the M0 signatures from

NOTE Confidence: 0.827261062727272

00:46:25.464 --> 00:46:26.720 the mouse that I showed you,

NOTE Confidence: 0.827261062727272

00:46:26.720 --> 00:46:28.440 that Cape, that GEM mouse.

NOTE Confidence: 0.827261062727272

00:46:28.440 --> 00:46:30.798 You can see that there's clearly

NOTE Confidence: 0.827261062727272

00:46:30.798 --> 00:46:32.952 differences in terms of the

NOTE Confidence: 0.827261062727272

00:46:32.952 --> 00:46:34.479 TKIO combination patients

NOTE Confidence: 0.716195541052632

00:46:34.480 --> 00:46:35.936 and in in the upper tail and the

NOTE Confidence: 0.716195541052632

00:46:35.936 --> 00:46:37.600 lower tail on this platter actually

NOTE Confidence: 0.716195541052632

00:46:37.600 --> 00:46:39.160 associating with resistance and response.

NOTE Confidence: 0.716195541052632

00:46:39.160 --> 00:46:41.351 So you get a sense that maybe

NOTE Confidence: 0.716195541052632

00:46:41.351 --> 00:46:42.819 these populations are relevant

NOTE Confidence: 0.716195541052632

00:46:42.819 --> 00:46:44.054 across you know species.

NOTE Confidence: 0.716195541052632

00:46:44.054 --> 00:46:45.860 So that I think is sort of

NOTE Confidence: 0.716195541052632

00:46:45.924 --> 00:46:48.080 where we're headed. So overall

NOTE Confidence: 0.866673109375

00:46:50.160 --> 00:46:51.876 my conclusions really are that RNA

NOTE Confidence: 0.866673109375

00:46:51.876 --> 00:46:53.020 signatures and immune response

NOTE Confidence: 0.866673109375

00:46:53.072 --> 00:46:54.440 are really the the useful ones.

NOTE Confidence: 0.866673109375

00:46:54.440 --> 00:46:56.132 Clinically I showed you sort of

NOTE Confidence: 0.866673109375

00:46:56.132 --> 00:46:57.846 the genetic recap of kidney cancers

NOTE Confidence: 0.866673109375

00:46:57.846 --> 00:46:59.701 and how it might relate to some

NOTE Confidence: 0.866673109375

00:46:59.701 --> 00:47:01.439 of these microviomal feature.

NOTE Confidence: 0.866673109375

00:47:01.440 --> 00:47:03.337 But that's really what we have from

NOTE Confidence: 0.866673109375

00:47:03.337 --> 00:47:05.883 a from a predictive and prognostic

NOTE Confidence: 0.866673109375

00:47:05.883 --> 00:47:07.945 standpoint and maybe it'll help us

NOTE Confidence: 0.866673109375

00:47:07.945 --> 00:47:09.149 select adjuvant treatment strategies

NOTE Confidence: 0.866673109375

00:47:09.149 --> 00:47:10.520 down the road for patients,

NOTE Confidence: 0.866673109375

00:47:10.520 --> 00:47:12.896 certainly pick the high risk patients

NOTE Confidence: 0.866673109375

00:47:12.896 --> 00:47:15.550 a little bit better perhaps the the

NOTE Confidence: 0.866673109375

00:47:15.550 --> 00:47:17.080 phenotype seems to be enriched in

NOTE Confidence: 0.866673109375

00:47:17.080 --> 00:47:19.105 the in the map in the metastatic

NOTE Confidence: 0.866673109375

00:47:19.105 --> 00:47:21.992 setting and particularly post IO.

NOTE Confidence: 0.866673109375

00:47:21.992 --> 00:47:24.005 And and maybe this this cross

NOTE Confidence: 0.866673109375

00:47:24.005 --> 00:47:25.779 analysis will allow us to prioritize

NOTE Confidence: 0.866673109375

00:47:25.779 --> 00:47:27.897 targets to test pre clinically and

NOTE Confidence: 0.866673109375

00:47:27.897 --> 00:47:29.706 then hopefully bring them out to

NOTE Confidence: 0.866673109375

00:47:29.706 --> 00:47:31.316 the to the clinic now that more

NOTE Confidence: 0.866673109375

00:47:31.320 --> 00:47:33.225 and more companies are interested

NOTE Confidence: 0.866673109375

00:47:33.225 --> 00:47:35.130 in in targeting tan populations

NOTE Confidence: 0.866673109375

00:47:35.194 --> 00:47:36.718 with different inhibitors.

NOTE Confidence: 0.866673109375

00:47:36.720 --> 00:47:38.632 And I want to obviously thank my funding

NOTE Confidence: 0.866673109375

00:47:38.632 --> 00:47:40.912 and of course, members of my lab,

NOTE Confidence: 0.866673109375

00:47:40.912 --> 00:47:42.992 Ming Lee's lab, the urology department,

NOTE Confidence: 0.866673109375

00:47:42.992 --> 00:47:44.712 Christina Leslie from computational biology

NOTE Confidence: 0.866673109375

00:47:44.712 --> 00:47:46.958 and all the medical colleges I work with,

NOTE Confidence: 0.866673109375

00:47:46.960 --> 00:47:47.815 particularly Doctor Mozer,

NOTE Confidence: 0.866673109375

00:47:47.815 --> 00:47:50.279 who's been a wonderful mentor to me for many,

NOTE Confidence: 0.866673109375

00:47:50.280 --> 00:47:51.920 many years.

NOTE Confidence: 0.866673109375

00:47:51.920 --> 00:47:52.852 Thank you so much.

NOTE Confidence: 0.866673109375

00:47:52.852 --> 00:47:54.800 And I'll have you answer any questions.

NOTE Confidence: 0.591752427777778

00:48:08.580 --> 00:48:09.304 Thanks, Ari.

NOTE Confidence: 0.591752427777778

00:48:09.304 --> 00:48:11.838 That was a real Tour de force.

NOTE Confidence: 0.591752427777778

00:48:11.840 --> 00:48:14.000 I have a question about the

NOTE Confidence: 0.591752427777778

00:48:14.000 --> 00:48:15.440 complexity of your clustering.

NOTE Confidence: 0.591752427777778

00:48:15.440 --> 00:48:19.260 So I I noted that you had 21 clusters of

NOTE Confidence: 0.591752427777778

00:48:19.358 --> 00:48:21.960 myeloid cells in one of your figures,

NOTE Confidence: 0.591752427777778

00:48:21.960 --> 00:48:24.912 I believe it was one of the mouse figures.

NOTE Confidence: 0.591752427777778

00:48:24.920 --> 00:48:29.880 Yeah. Well so that's sort of the art and the

NOTE Confidence: 0.591752427777778

00:48:29.880 --> 00:48:31.840 the dark art of of single cell sequencing.

NOTE Confidence: 0.591752427777778

00:48:31.840 --> 00:48:33.610 You could, you can cluster any

NOTE Confidence: 0.591752427777778

00:48:33.610 --> 00:48:36.217 way you want and you can set your

NOTE Confidence: 0.591752427777778

00:48:36.217 --> 00:48:38.020 parameters quite differently. So yeah,

NOTE Confidence: 0.591752427777778

00:48:38.020 --> 00:48:41.599 and this is all all my Lloyd populations,

NOTE Confidence: 0.591752427777778

00:48:41.600 --> 00:48:42.359 you're absolutely right.

NOTE Confidence: 0.591752427777778

00:48:42.359 --> 00:48:45.077 So one of the things we do then of course is,

NOTE Confidence: 0.591752427777778

00:48:45.080 --> 00:48:47.798 is then go back with my immunology

NOTE Confidence: 0.591752427777778

00:48:47.798 --> 00:48:48.834 colleagues and actually start

NOTE Confidence: 0.591752427777778

00:48:48.834 --> 00:48:50.239 to think about what are the,

NOTE Confidence: 0.591752427777778

00:48:50.240 --> 00:48:52.400 what are what are really representing

NOTE Confidence: 0.591752427777778

00:48:52.400 --> 00:48:53.882 unique populations versus just

NOTE Confidence: 0.591752427777778

00:48:53.882 --> 00:48:56.126 slicing and dicing single cell data

NOTE Confidence: 0.591752427777778

00:48:56.126 --> 00:48:58.198 in more and more complex ways.

NOTE Confidence: 0.591752427777778

00:48:58.200 --> 00:49:00.615 And we try to validate them by

NOTE Confidence: 0.591752427777778

00:49:00.615 --> 00:49:02.448 flow and to look at really the

NOTE Confidence: 0.591752427777778

00:49:02.448 --> 00:49:03.440 the dominant populations there.

NOTE Confidence: 0.591752427777778

00:49:03.440 --> 00:49:05.246 So it's just that this is just

NOTE Confidence: 0.591752427777778

00:49:05.246 --> 00:49:07.537 sort of an early iteration of of

NOTE Confidence: 0.591752427777778

00:49:07.537 --> 00:49:09.352 what would be real clustering.

NOTE Confidence: 0.591752427777778

00:49:09.360 --> 00:49:10.200 No, I get it and it's,

NOTE Confidence: 0.591752427777778

00:49:10.200 --> 00:49:11.500 it is really complicated

NOTE Confidence: 0.591752427777778

00:49:11.500 --> 00:49:12.800 before treatment on treatment.

NOTE Confidence: 0.591752427777778

00:49:12.800 --> 00:49:14.330 But my other question is spatially

NOTE Confidence: 0.591752427777778

00:49:14.330 --> 00:49:16.012 are some of the clusters uniquely

NOTE Confidence: 0.591752427777778

00:49:16.012 --> 00:49:18.119 positioned in a certain area of the

NOTE Confidence: 0.591752427777778

00:49:18.119 --> 00:49:19.757 large tumours that's in humans,

NOTE Confidence: 0.591752427777778

00:49:19.760 --> 00:49:20.960 I guess is where I'm interested.

NOTE Confidence: 0.591752427777778

00:49:20.960 --> 00:49:21.456 Yeah, yeah.

NOTE Confidence: 0.591752427777778

00:49:21.456 --> 00:49:21.704 So,

NOTE Confidence: 0.591752427777778

00:49:21.704 --> 00:49:23.440 so in that same cohort that I

NOTE Confidence: 0.591752427777778

00:49:23.496 --> 00:49:25.036 showed you that we're doing,

NOTE Confidence: 0.591752427777778

00:49:25.040 --> 00:49:28.240 we're working with Heartland Jackson

NOTE Confidence: 0.591752427777778

00:49:28.240 --> 00:49:31.120 who's at who's in Toronto who's

NOTE Confidence: 0.591752427777778

00:49:31.120 --> 00:49:32.960 spatial mass cytometry kind of person.

NOTE Confidence: 0.591752427777778

00:49:32.960 --> 00:49:35.600 We developed from the single cell

NOTE Confidence: 0.591752427777778

00:49:35.600 --> 00:49:37.720 data a series of of populations

NOTE Confidence: 0.591752427777778

00:49:37.720 --> 00:49:40.120 really relying on most of the human.

NOTE Confidence: 0.591752427777778

00:49:40.120 --> 00:49:41.954 So we we took a conglomerate of

NOTE Confidence: 0.591752427777778

00:49:41.954 --> 00:49:43.332 the different single cell studies

NOTE Confidence: 0.591752427777778

00:49:43.332 --> 00:49:45.201 that David has done and others have

NOTE Confidence: 0.591752427777778

00:49:45.201 --> 00:49:47.115 done and kind of come up with like

NOTE Confidence: 0.591752427777778

00:49:47.115 --> 00:49:49.048 a meta analysis of what are the

NOTE Confidence: 0.591752427777778

00:49:49.048 --> 00:49:50.920 key markers of the different Tam

NOTE Confidence: 0.591752427777778

00:49:50.985 --> 00:49:52.935 populations to reduce it down to

NOTE Confidence: 0.591752427777778

00:49:52.935 --> 00:49:55.600 maybe five or six that might you know,

NOTE Confidence: 0.591752427777778

00:49:55.600 --> 00:49:58.470 you tag a Tam by you know CD 68 or

NOTE Confidence: 0.591752427777778

00:49:58.470 --> 00:49:59.995 something else and then you can add

NOTE Confidence: 0.591752427777778

00:49:59.995 --> 00:50:01.339 a few additional markers and then

NOTE Confidence: 0.591752427777778

00:50:01.339 --> 00:50:02.797 look at the spatial orientation

NOTE Confidence: 0.591752427777778

00:50:02.797 --> 00:50:03.757 in these contexts.

NOTE Confidence: 0.591752427777778

00:50:03.760 --> 00:50:06.118 So we're we're taking all these

NOTE Confidence: 0.591752427777778

00:50:06.120 --> 00:50:07.830 regions both within tumors and

NOTE Confidence: 0.591752427777778

00:50:07.830 --> 00:50:09.855 across tumors and and reducing it

NOTE Confidence: 0.591752427777778

00:50:09.855 --> 00:50:11.115 down to probably a core.

NOTE Confidence: 0.591752427777778

00:50:11.120 --> 00:50:12.195 And I think ultimately from

NOTE Confidence: 0.591752427777778

00:50:12.195 --> 00:50:12.840 a biomarker standpoint,

NOTE Confidence: 0.591752427777778

00:50:12.840 --> 00:50:15.108 you want to kind of just be able to

NOTE Confidence: 0.591752427777778

00:50:15.108 --> 00:50:16.595 choose a particular Tam or particular

NOTE Confidence: 0.591752427777778

00:50:16.595 --> 00:50:18.383 T cell that would be relevant and

NOTE Confidence: 0.591752427777778

00:50:18.383 --> 00:50:20.147 just reduce it to a couple quick

NOTE Confidence: 0.591752427777778

00:50:20.147 --> 00:50:21.531 stains that a pathologist could

NOTE Confidence: 0.591752427777778

00:50:21.531 --> 00:50:23.868 hopefully do as opposed to have to do

NOTE Confidence: 0.591752427777778

00:50:23.868 --> 00:50:25.638 fancy and very expensive sequencing.

NOTE Confidence: 0.591752427777778

00:50:25.640 --> 00:50:27.842 So absolutely thinking about the same

NOTE Confidence: 0.591752427777778

00:50:27.842 --> 00:50:29.919 same questions that you bring up.

NOTE Confidence: 0.591752427777778

00:50:29.920 --> 00:50:30.688 Thank you.

NOTE Confidence: 0.591752427777778

00:50:30.688 --> 00:50:32.160 I guess I haven't

NOTE Confidence: 0.642265273333333

00:50:34.840 --> 00:50:36.640 not. I got an unrelated 1

NOTE Confidence: 0.642265273333333

00:50:36.640 --> 00:50:38.960 unrelated the mouse cell line.

NOTE Confidence: 0.642265273333333

00:50:38.960 --> 00:50:40.796 So thank you for sending us and sharing that.

NOTE Confidence: 0.642265273333333

00:50:40.800 --> 00:50:42.599 Of course, the cell line with us.

NOTE Confidence: 0.642265273333333

00:50:42.600 --> 00:50:44.328 You're planning on making additional ones

NOTE Confidence: 0.642265273333333

00:50:44.328 --> 00:50:45.833 with different genetic proteins. Yeah.

NOTE Confidence: 0.642265273333333

00:50:45.833 --> 00:50:47.864 So that's real community service, yes.

NOTE Confidence: 0.642265273333333

00:50:47.864 --> 00:50:50.176 Yeah. So, so we, yeah, we are doing,

NOTE Confidence: 0.642265273333333

00:50:50.176 --> 00:50:52.116 we have a VHLBA P1 CD can to be,

NOTE Confidence: 0.642265273333333

00:50:52.120 --> 00:50:54.542 which is a more common combination and

NOTE Confidence: 0.642265273333333

00:50:54.542 --> 00:50:58.340 that one is a sarcomatoid tumor perfectly

NOTE Confidence: 0.642265273333333

00:50:58.340 --> 00:51:02.600 responds well to CTLA 4 very nicely.

NOTE Confidence: 0.642265273333333

00:51:02.600 --> 00:51:05.652 So that one yeah we'll be hopefully

NOTE Confidence: 0.642265273333333

00:51:05.652 --> 00:51:07.530 that's that papers you know we're

NOTE Confidence: 0.642265273333333

00:51:07.586 --> 00:51:09.279 finishing up this that work but

NOTE Confidence: 0.642265273333333

00:51:09.279 --> 00:51:11.050 that I think that will be something

NOTE Confidence: 0.642265273333333

00:51:11.101 --> 00:51:12.865 that people find more exciting just

NOTE Confidence: 0.642265273333333

00:51:12.865 --> 00:51:14.560 because of the common genetics.

NOTE Confidence: 0.642265273333333

00:51:14.560 --> 00:51:17.010 In fact when I presented this one

NOTE Confidence: 0.642265273333333

00:51:17.010 --> 00:51:19.360 initially Bill very Bill Kalin very,

NOTE Confidence: 0.642265273333333

00:51:19.360 --> 00:51:21.106 very astutely said you know that's

NOTE Confidence: 0.642265273333333

00:51:21.106 --> 00:51:23.120 not a very common genetic study.

NOTE Confidence: 0.642265273333333

00:51:23.120 --> 00:51:24.758 I'm like yeah but that's it's a

NOTE Confidence: 0.642265273333333

00:51:24.758 --> 00:51:26.584 common one for the for the bad

NOTE Confidence: 0.642265273333333

00:51:26.584 --> 00:51:27.914 tumors that don't respond well.

NOTE Confidence: 0.642265273333333

00:51:27.920 --> 00:51:30.980 So so this one is is a much more

NOTE Confidence: 0.642265273333333

00:51:30.980 --> 00:51:33.644 common genetic subtype and I it's a

NOTE Confidence: 0.642265273333333

00:51:33.644 --> 00:51:34.799 challenge of doing anything engineering.

NOTE Confidence: 0.642265273333333

00:51:34.800 --> 00:51:37.666 We tried of course all the the more

NOTE Confidence: 0.642265273333333

00:51:37.666 --> 00:51:40.384 common mutations as has Bill and

NOTE Confidence: 0.642265273333333

00:51:40.384 --> 00:51:42.604 others you know Crisp bring out PBR

NOTE Confidence: 0.642265273333333

00:51:42.604 --> 00:51:44.744 and what the tumors just don't grow

NOTE Confidence: 0.642265273333333

00:51:44.744 --> 00:51:47.155 well and they're very hard so the the

NOTE Confidence: 0.642265273333333

00:51:47.155 --> 00:51:49.800 nice clear cells are hard to engineer.

NOTE Confidence: 0.642265273333333

00:51:49.800 --> 00:51:52.187 The bad ones that don't look super

NOTE Confidence: 0.642265273333333

00:51:52.187 --> 00:51:54.669 clear cell but have they retain the CA

NOTE Confidence: 0.642265273333333

00:51:54.669 --> 00:51:57.281 9 and hip one at least don't don't look

NOTE Confidence: 0.642265273333333

00:51:57.281 --> 00:51:59.480 you know those are the ones that grow.

NOTE Confidence: 0.642265273333333

00:51:59.480 --> 00:52:01.070 It's it's a challenge of any

NOTE Confidence: 0.642265273333333

00:52:01.070 --> 00:52:01.600 syngeneic system.

NOTE Confidence: 0.642265273333333

00:52:01.600 --> 00:52:03.769 So that's why you know you can rely on

NOTE Confidence: 0.642265273333333

00:52:03.769 --> 00:52:06.033 gems but gems are just hard to to treat.

NOTE Confidence: 0.642265273333333

00:52:06.040 --> 00:52:07.440 So limitation of the field

NOTE Confidence: 0.81871223

00:52:10.880 --> 00:52:11.280 sure.

NOTE Confidence: 0.754209888571428

00:52:15.240 --> 00:52:17.416 Thank you. So so really great work in

NOTE Confidence: 0.754209888571428

00:52:17.416 --> 00:52:19.520 terms of single cell transcriptomics and

NOTE Confidence: 0.754209888571428

00:52:19.520 --> 00:52:22.120 even profiling and site off and such.

NOTE Confidence: 0.754209888571428

00:52:22.120 --> 00:52:24.502 But ultimately the biomarker should be

NOTE Confidence: 0.754209888571428

00:52:24.502 --> 00:52:26.939 translated into clinic and should be

NOTE Confidence: 0.754209888571428

00:52:26.939 --> 00:52:29.279 easily performed and reputable and cheap.

NOTE Confidence: 0.754209888571428

00:52:29.280 --> 00:52:31.716 So how do you envision translating these,

NOTE Confidence: 0.754209888571428

00:52:31.720 --> 00:52:33.520 yeah, into the clinic? That's great.

NOTE Confidence: 0.754209888571428

00:52:33.520 --> 00:52:35.040 So a couple couple ways.

NOTE Confidence: 0.754209888571428

00:52:35.040 --> 00:52:36.048 And I think we're thinking about

NOTE Confidence: 0.754209888571428

00:52:36.048 --> 00:52:36.920 this a few different ways.

NOTE Confidence: 0.754209888571428

00:52:36.920 --> 00:52:40.552 So one of course is where obviously

NOTE Confidence: 0.754209888571428

00:52:40.552 --> 00:52:42.920 reducing it to a few markers that might

NOTE Confidence: 0.754209888571428

00:52:42.975 --> 00:52:44.781 stand for the most relevant populations

NOTE Confidence: 0.754209888571428

00:52:44.781 --> 00:52:47.120 and maybe it's a combination of Tams,

NOTE Confidence: 0.754209888571428

00:52:47.120 --> 00:52:49.214 maybe some neutrophils and some CDA

NOTE Confidence: 0.754209888571428

00:52:49.214 --> 00:52:50.959 populations that might ultimately come

NOTE Confidence: 0.754209888571428

00:52:50.959 --> 00:52:52.996 up with a very straightforward IHC panel.

NOTE Confidence: 0.754209888571428

00:52:53.000 --> 00:52:54.776 The other thing of course is that what

NOTE Confidence: 0.754209888571428

00:52:54.776 --> 00:52:56.740 a lot of people are thinking about

NOTE Confidence: 0.754209888571428

00:52:56.740 --> 00:52:58.559 is digital pathology and sort of AI.

NOTE Confidence: 0.754209888571428

00:52:58.560 --> 00:53:02.248 So if you can define groups of tumors

NOTE Confidence: 0.754209888571428

00:53:02.248 --> 00:53:04.130 transcriptionally and then you you

NOTE Confidence: 0.754209888571428

00:53:04.130 --> 00:53:06.130 put it into some model where you have

NOTE Confidence: 0.754209888571428

00:53:06.130 --> 00:53:08.460 the scan slide scanned in and and put

NOTE Confidence: 0.754209888571428

00:53:08.460 --> 00:53:09.920 through a machine learning platform.

NOTE Confidence: 0.754209888571428

00:53:09.920 --> 00:53:11.462 You could maybe even digitally say

NOTE Confidence: 0.754209888571428

00:53:11.462 --> 00:53:13.355 this is this tumor has this feature

NOTE Confidence: 0.754209888571428

00:53:13.355 --> 00:53:14.710 even though the pathologist has

NOTE Confidence: 0.754209888571428

00:53:14.710 --> 00:53:16.278 no idea what they're seeing,

NOTE Confidence: 0.754209888571428

00:53:16.280 --> 00:53:17.920 but the the model does.

NOTE Confidence: 0.754209888571428

00:53:17.920 --> 00:53:18.416 And so for that,

NOTE Confidence: 0.754209888571428

00:53:18.416 --> 00:53:19.520 you know and I know a lot of

NOTE Confidence: 0.754209888571428

00:53:19.520 --> 00:53:20.315 people are working on this,

NOTE Confidence: 0.754209888571428

00:53:20.320 --> 00:53:21.846 but we you know for that same

NOTE Confidence: 0.754209888571428

00:53:21.846 --> 00:53:23.118 Novartis study where I showed you,

NOTE Confidence: 0.754209888571428

00:53:23.120 --> 00:53:25.352 we showed that the myeloid phenotype

NOTE Confidence: 0.754209888571428

00:53:25.352 --> 00:53:26.840 is associated with recurrence.

NOTE Confidence: 0.754209888571428

00:53:26.840 --> 00:53:28.238 We're working with group at Dartmouth

NOTE Confidence: 0.754209888571428

00:53:28.238 --> 00:53:29.839 that has a machine learning model.

NOTE Confidence: 0.754209888571428

00:53:29.840 --> 00:53:31.200 We have all the transcriptomic,

NOTE Confidence: 0.754209888571428

00:53:31.200 --> 00:53:33.296 We have the the slides sent from Novartis

NOTE Confidence: 0.754209888571428

00:53:33.296 --> 00:53:35.236 which is like 12 terabytes of data.

NOTE Confidence: 0.754209888571428

00:53:35.240 --> 00:53:35.958 They high,

NOTE Confidence: 0.754209888571428

00:53:35.958 --> 00:53:38.112 high resolution scanned all the slides

NOTE Confidence: 0.754209888571428

00:53:38.112 --> 00:53:40.344 from that trial and we've given them

NOTE Confidence: 0.754209888571428

00:53:40.344 --> 00:53:41.488 the micro environmental subgroups

NOTE Confidence: 0.754209888571428

00:53:41.488 --> 00:53:42.878 and strategies and they're trying to

NOTE Confidence: 0.754209888571428

00:53:42.878 --> 00:53:44.480 figure out if they can do that and

NOTE Confidence: 0.754209888571428

00:53:44.480 --> 00:53:46.032 they have already done it on the TCGS.

NOTE Confidence: 0.754209888571428

00:53:46.040 --> 00:53:47.816 So you can kind of replicate it because

NOTE Confidence: 0.754209888571428

00:53:47.816 --> 00:53:49.434 that that might be a way to to say,

NOTE Confidence: 0.754209888571428

00:53:49.440 --> 00:53:49.770 OK,

NOTE Confidence: 0.754209888571428

00:53:49.770 --> 00:53:52.080 now you've put it through an AI

NOTE Confidence: 0.754209888571428

00:53:52.080 --> 00:53:54.111 system and they say this tumor

NOTE Confidence: 0.754209888571428

00:53:54.111 --> 00:53:55.532 is this thing and this patient's

NOTE Confidence: 0.754209888571428

00:53:55.532 --> 00:53:56.987 going to recur much more or this

NOTE Confidence: 0.754209888571428

00:53:56.987 --> 00:53:57.999 patient might respond better.

NOTE Confidence: 0.754209888571428

00:53:58.000 --> 00:54:00.144 So that that's that's a strategy that I

NOTE Confidence: 0.754209888571428

00:54:00.144 --> 00:54:02.399 think a lot of us are thinking about.

NOTE Confidence: 0.754209888571428

00:54:02.400 --> 00:54:04.480 Great question for the

NOTE Confidence: 0.663871534375

00:54:08.000 --> 00:54:09.200 community service and making

NOTE Confidence: 0.663871534375

00:54:09.200 --> 00:54:11.000 these mouse models and thank you

NOTE Confidence: 0.663871534375

00:54:11.059 --> 00:54:12.439 for sharing with us as well.

NOTE Confidence: 0.663871534375

00:54:12.440 --> 00:54:15.090 I'm curious from the immuno

NOTE Confidence: 0.663871534375

00:54:15.090 --> 00:54:16.680 oncology metabolism world,

NOTE Confidence: 0.663871534375

00:54:16.680 --> 00:54:19.092 you know we talked a lot about the obesity

NOTE Confidence: 0.663871534375

00:54:19.092 --> 00:54:20.917 paradox in Melanoma and lung cancer.

NOTE Confidence: 0.663871534375

00:54:20.920 --> 00:54:23.195 Do patients with obesity respond

NOTE Confidence: 0.663871534375

00:54:23.195 --> 00:54:24.560 better to immunotherapy.

NOTE Confidence: 0.663871534375

00:54:24.560 --> 00:54:27.616 So I'm wondering if you know knowing that

NOTE Confidence: 0.663871534375

00:54:27.616 --> 00:54:29.880 RCC actually is associated with obesity.

NOTE Confidence: 0.663871534375

00:54:29.880 --> 00:54:31.896 I'm I'm wondering if you can speak

NOTE Confidence: 0.663871534375

00:54:31.896 --> 00:54:34.125 to your mouse models if if you've

NOTE Confidence: 0.663871534375

00:54:34.125 --> 00:54:35.441 observed any potential difference

NOTE Confidence: 0.663871534375

00:54:35.441 --> 00:54:37.146 in the response to immunotherapy

NOTE Confidence: 0.663871534375

00:54:37.146 --> 00:54:39.212 in in these models because it in

NOTE Confidence: 0.663871534375

00:54:39.212 --> 00:54:40.654 mice with obesity and if not maybe

NOTE Confidence: 0.663871534375

00:54:40.654 --> 00:54:42.297 we can collaborate that. Yeah.

NOTE Confidence: 0.663871534375

00:54:42.297 --> 00:54:44.857 So. So it's a great question and

NOTE Confidence: 0.663871534375

00:54:44.857 --> 00:54:46.639 something that's very near and dear.

NOTE Confidence: 0.663871534375

00:54:46.640 --> 00:54:46.896 So.

NOTE Confidence: 0.663871534375

00:54:46.896 --> 00:54:49.200 So I I do have funding through the DoD

NOTE Confidence: 0.663871534375

00:54:49.263 --> 00:54:51.482 to look at obesity in kidney cancer

NOTE Confidence: 0.663871534375

00:54:51.482 --> 00:54:53.458 and these models and we've we've

NOTE Confidence: 0.663871534375

00:54:53.458 --> 00:54:55.014 been utilizing the transplantation

NOTE Confidence: 0.663871534375

00:54:55.014 --> 00:54:57.865 models we so we do we did the GEM

NOTE Confidence: 0.663871534375

00:54:57.865 --> 00:55:00.150 model first we we did fat feed them

NOTE Confidence: 0.663871534375

00:55:00.150 --> 00:55:02.142 they're they're hard to to feed

NOTE Confidence: 0.663871534375

00:55:02.142 --> 00:55:03.797 because of the mixed background.

NOTE Confidence: 0.663871534375

00:55:03.800 --> 00:55:05.872 So they they gain weight not as nicely

NOTE Confidence: 0.663871534375

00:55:05.872 --> 00:55:08.293 as if they were a clean genotype but

NOTE Confidence: 0.663871534375

00:55:08.293 --> 00:55:10.139 we do observe earlier onset tumors

NOTE Confidence: 0.663871534375

00:55:10.139 --> 00:55:12.355 in those in those mice but then so

NOTE Confidence: 0.663871534375

00:55:12.360 --> 00:55:14.202 genetically when we implant them and

NOTE Confidence: 0.663871534375

00:55:14.202 --> 00:55:16.212 that's not trivial by the way if

NOTE Confidence: 0.663871534375

00:55:16.212 --> 00:55:17.913 you're going to do us an orthotopic

NOTE Confidence: 0.663871534375

00:55:17.971 --> 00:55:19.581 transplantation model in a fat

NOTE Confidence: 0.663871534375

00:55:19.581 --> 00:55:21.417 mouse because just like humans they

NOTE Confidence: 0.663871534375

00:55:21.417 --> 00:55:22.719 develop a lot of perinephric fat.

NOTE Confidence: 0.663871534375

00:55:22.720 --> 00:55:25.120 So if you try to open up the mouse and

NOTE Confidence: 0.663871534375

00:55:25.192 --> 00:55:27.478 inject it it's like a **** show part

NOTE Confidence: 0.663871534375

00:55:27.478 --> 00:55:29.711 of my French but but but essentially

NOTE Confidence: 0.663871534375

00:55:29.711 --> 00:55:31.622 it's very challenging so so we've

NOTE Confidence: 0.663871534375

00:55:31.622 --> 00:55:34.119 been doing but we do see that the

NOTE Confidence: 0.663871534375

00:55:34.119 --> 00:55:36.136 tumors grow faster in obese which

NOTE Confidence: 0.663871534375

00:55:36.136 --> 00:55:38.790 sort of makes sense because we know

NOTE Confidence: 0.663871534375

00:55:38.790 --> 00:55:41.070 that obesity associated with with

NOTE Confidence: 0.663871534375

00:55:41.070 --> 00:55:43.345 better development of kidney cancers

NOTE Confidence: 0.663871534375

00:55:43.345 --> 00:55:45.547 but in it does suggest in human at

NOTE Confidence: 0.663871534375

00:55:45.547 --> 00:55:47.638 least they seem to be less aggressive.

NOTE Confidence: 0.663871534375

00:55:47.640 --> 00:55:50.160 So we're we're now trying to understand

NOTE Confidence: 0.663871534375

00:55:50.160 --> 00:55:51.763 immunologically what's going on but

NOTE Confidence: 0.663871534375

00:55:51.763 --> 00:55:53.394 I would I think we're talking soon

NOTE Confidence: 0.663871534375

00:55:53.394 --> 00:55:55.383 so I'm happy to talk more about that

NOTE Confidence: 0.663871534375

00:55:55.383 --> 00:55:57.280 Rachel but I think it would be a

NOTE Confidence: 0.663871534375

00:55:57.280 --> 00:55:58.982 really it's a really cool area and

NOTE Confidence: 0.663871534375

00:55:58.982 --> 00:56:00.676 we're we're we're focused on on Trem

NOTE Confidence: 0.663871534375

00:56:00.676 --> 00:56:02.839 2 macrophages which has been shown to

NOTE Confidence: 0.663871534375

00:56:02.839 --> 00:56:04.716 be associated with lipid their the

NOTE Confidence: 0.663871534375

00:56:04.716 --> 00:56:06.306 lipid associated macrophages and and

NOTE Confidence: 0.663871534375

00:56:06.306 --> 00:56:08.400 it's associated with more aggressive tumors.

NOTE Confidence: 0.663871534375

00:56:08.400 --> 00:56:09.597 So we can talk more about that,

NOTE Confidence: 0.663871534375

00:56:09.600 --> 00:56:10.720 but definitely something that we're,

NOTE Confidence: 0.663871534375

00:56:10.720 --> 00:56:11.520 we're thinking a lot about.

NOTE Confidence: 0.20446036

00:56:17.400 --> 00:56:17.640 All right.