WEBVTT

NOTE duration:"00:42:16.0400000"

NOTE recognizability:0.841

NOTE language:en-us

NOTE Confidence: 0.763722411428571

00:00:00.000 --> 00:00:01.233 Good morning, everyone.

NOTE Confidence: 0.763722411428571

00:00:01.233 --> 00:00:03.882 As you trickle in, I'm just going

NOTE Confidence: 0.763722411428571

00:00:03.882 --> 00:00:05.552 to start presenting this morning's

NOTE Confidence: 0.763722411428571

00:00:05.552 --> 00:00:07.232 grand round speaker, Ben Liu.

NOTE Confidence: 0.763722411428571

00:00:07.232 --> 00:00:09.664 So Ben Liu is one of our graduates and

NOTE Confidence: 0.763722411428571

00:00:09.664 --> 00:00:11.590 he actually exemplifies what we're trying

NOTE Confidence: 0.763722411428571

00:00:11.590 --> 00:00:14.166 to do in the Cancer Center in terms

NOTE Confidence: 0.763722411428571

00:00:14.166 --> 00:00:16.165 of building a pathway for training.

NOTE Confidence: 0.763722411428571

00:00:16.165 --> 00:00:18.835 So as some of you know,

NOTE Confidence: 0.763722411428571

00:00:18.840 --> 00:00:22.188 we have a whole list of T30 twos and K

NOTE Confidence: 0.763722411428571

00:00:22.188 --> 00:00:24.184 twelves and our goal is that people go

NOTE Confidence: 0.763722411428571

00:00:24.184 --> 00:00:26.200 from one program to another to another.

NOTE Confidence: 0.763722411428571

00:00:26.200 --> 00:00:29.572 And so Ben, who he graduated

NOTE Confidence: 0.763722411428571

00:00:29.572 --> 00:00:30.796 from NYU Medical School,

NOTE Confidence: 0.763722411428571

00:00:30.800 --> 00:00:32.408 came here as a resident and

NOTE Confidence: 0.763722411428571

00:00:32.408 --> 00:00:33.480 then joined our fellowship.

NOTE Confidence: 0.763722411428571

00:00:33.480 --> 00:00:34.860 And as a fellow,

NOTE Confidence: 0.763722411428571

00:00:34.860 --> 00:00:37.732 he joined Doctor Herbst T32 and now he's

NOTE Confidence: 0.763722411428571

00:00:37.732 --> 00:00:41.559 a trainee on the K12 in Immuno Oncology.

NOTE Confidence: 0.763722411428571

00:00:41.560 --> 00:00:43.758 The only problem is that Ben sometimes

NOTE Confidence: 0.763722411428571

00:00:43.758 --> 00:00:46.038 does things a little bit backwards.

NOTE Confidence: 0.763722411428571

00:00:46.040 --> 00:00:48.116 So he's currently finishing his PhD,

NOTE Confidence: 0.763722411428571

00:00:48.120 --> 00:00:50.128 but yet he's a faculty member and this

NOTE Confidence: 0.763722411428571

00:00:50.128 --> 00:00:51.639 makes it extremely complicated when

NOTE Confidence: 0.763722411428571

00:00:51.639 --> 00:00:54.120 it comes to the paperwork of the K12.

NOTE Confidence: 0.763722411428571

00:00:54.120 --> 00:00:55.394 So if there are other trainees in

NOTE Confidence: 0.763722411428571

00:00:55.394 --> 00:00:56.827 the room who are hoping to come

NOTE Confidence: 0.763722411428571

00:00:56.827 --> 00:00:57.675 up through this pathway,

NOTE Confidence: 0.763722411428571

00:00:57.680 --> 00:01:00.039 please do it in the right order.

NOTE Confidence: 0.763722411428571

00:01:00.040 --> 00:01:02.720 But all that aside,

NOTE Confidence: 0.763722411428571

00:01:02.720 --> 00:01:05.636 OK if you that's true too.

NOTE Confidence: 0.763722411428571

00:01:05.640 --> 00:01:07.692 So if you want to go by the chaotic

NOTE Confidence: 0.763722411428571

00:01:07.692 --> 00:01:09.840 method then all I can say is I

NOTE Confidence: 0.763722411428571

00:01:09.840 --> 00:01:11.014 strongly recommend Doctor David

NOTE Confidence: 0.763722411428571

00:01:11.014 --> 00:01:12.599 Heffler as an amazing mentor.

NOTE Confidence: 0.763722411428571

00:01:12.600 --> 00:01:15.560 He's done a great job with Ben who

NOTE Confidence: 0.763722411428571

00:01:15.560 --> 00:01:18.038 is doing amazing work on actually

NOTE Confidence: 0.763722411428571

00:01:18.038 --> 00:01:19.277 three major projects.

NOTE Confidence: 0.763722411428571

00:01:19.280 --> 00:01:21.955 One focuses on brain metastasis

NOTE Confidence: 0.763722411428571

00:01:21.955 --> 00:01:23.560 in lung cancer,

NOTE Confidence: 0.763722411428571

00:01:23.560 --> 00:01:25.204 one on Melanoma and liquid biopsies

NOTE Confidence: 0.763722411428571

00:01:25.204 --> 00:01:26.894 and that's the one he's going

NOTE Confidence: 0.763722411428571

00:01:26.894 --> 00:01:28.234 to be talking about today.

NOTE Confidence: 0.763722411428571

00:01:28.240 --> 00:01:30.448 And the third one is single cell RNA

NOTE Confidence: 0.763722411428571

00:01:30.448 --> 00:01:32.064 sequencing studies of glioma patients

NOTE Confidence: 0.763722411428571

00:01:32.064 --> 00:01:33.754 treated with anti TIGIT antibodies.

NOTE Confidence: 0.763722411428571

00:01:33.760 --> 00:01:35.755 So there are very few people who

NOTE Confidence: 0.763722411428571

00:01:35.755 --> 00:01:37.773 can shoulder all of this while being

NOTE Confidence: 0.763722411428571

00:01:37.773 --> 00:01:39.482 a chief fellow and AT30T trainee

NOTE Confidence: 0.763722411428571

00:01:39.482 --> 00:01:40.987 and AK12 trainee and everything

NOTE Confidence: 0.763722411428571

00:01:40.987 --> 00:01:43.172 else that and a dad I think and

NOTE Confidence: 0.763722411428571

00:01:43.172 --> 00:01:44.397 everything else that Ben does.

NOTE Confidence: 0.763722411428571

00:01:44.400 --> 00:01:45.556 So without further ado,

NOTE Confidence: 0.763722411428571

00:01:45.556 --> 00:01:47.714 I'd like to welcome Ben to give

NOTE Confidence: 0.763722411428571

00:01:47.714 --> 00:01:48.797 us his presentation.

NOTE Confidence: 0.868415086

00:01:53.760 --> 00:01:54.920 Thank you so much, Doctor,

NOTE Confidence: 0.868415086

00:01:54.920 --> 00:01:57.560 for that very kind introduction.

NOTE Confidence: 0.868415086

00:01:57.560 --> 00:01:58.844 Good morning everyone.

NOTE Confidence: 0.868415086

00:01:58.844 --> 00:02:01.840 Hope everyone had a very nice Thanksgiving.

NOTE Confidence: 0.868415086

00:02:01.840 --> 00:02:04.000 I can tell you that I'm very thankful to

NOTE Confidence: 0.868415086

00:02:04.000 --> 00:02:06.320 be standing up here on the podium today

NOTE Confidence: 0.868415086

00:02:06.320 --> 00:02:08.273 and for the opportunity to share some

NOTE Confidence: 0.868415086

00:02:08.273 --> 00:02:10.682 of our work that has been supported by

NOTE Confidence: 0.868415086

00:02:10.682 --> 00:02:12.879 the Skinspur over the past five years.

NOTE Confidence: 0.868415086

00:02:12.880 --> 00:02:14.820 I do have to say that I think it speaks

NOTE Confidence: 0.868415086

00:02:14.872 --> 00:02:16.888 a lot to our cancer centering community

NOTE Confidence: 0.868415086

00:02:16.888 --> 00:02:18.779 that we're willing to amplify even

NOTE Confidence: 0.868415086

00:02:18.779 --> 00:02:20.394 junior investigators such as myself.

NOTE Confidence: 0.868415086

00:02:20.400 --> 00:02:22.514 And I'm incredibly grateful to my mentors,

NOTE Confidence: 0.868415086

00:02:22.520 --> 00:02:24.248 Dr. Haffler and Dr.

NOTE Confidence: 0.868415086

00:02:24.248 --> 00:02:26.348 Kluger for nominating me to

NOTE Confidence: 0.868415086

00:02:26.348 --> 00:02:28.761 represent our team on this project.

NOTE Confidence: 0.868415086

00:02:28.761 --> 00:02:31.083 So I've titled my talk Immune

NOTE Confidence: 0.868415086

00:02:31.083 --> 00:02:32.200 Liquid Biopsies,

NOTE Confidence: 0.868415086

00:02:32.200 --> 00:02:34.560 Remote Learning and Remote Control.

NOTE Confidence: 0.868415086

00:02:34.560 --> 00:02:36.664 And the topic here is a little bit

NOTE Confidence: 0.868415086

00:02:36.664 --> 00:02:38.282 different than the liquid biopsies that

NOTE Confidence: 0.868415086

00:02:38.282 --> 00:02:40.639 I think many of you are familiar with,

NOTE Confidence: 0.868415086

00:02:40.640 --> 00:02:41.880 which are more tumor centric.

NOTE Confidence: 0.868415086

00:02:41.880 --> 00:02:42.690 And yeah,

NOTE Confidence: 0.868415086

00:02:42.690 --> 00:02:44.310 I'm specifically referring to

NOTE Confidence: 0.868415086

00:02:44.310 --> 00:02:46.240 circulating tumor cell free DNA.

NOTE Confidence: 0.919951568214286

00:02:48.640 --> 00:02:50.264 But I think what we're starting to

NOTE Confidence: 0.919951568214286

00:02:50.264 --> 00:02:52.021 realize is that these liquid biopsies

NOTE Confidence: 0.919951568214286

00:02:52.021 --> 00:02:53.361 are really powerful companion

NOTE Confidence: 0.919951568214286

00:02:53.361 --> 00:02:54.951 diagnostics that are really trying

NOTE Confidence: 0.919951568214286

00:02:54.951 --> 00:02:56.553 to become game changers in care.

NOTE Confidence: 0.919951568214286

00:02:56.560 --> 00:02:59.143 And it's my hope that with additional

NOTE Confidence: 0.919951568214286

00:02:59.143 --> 00:03:01.145 work on immune profiling that

NOTE Confidence: 0.919951568214286

00:03:01.145 --> 00:03:04.022 these two will start to emerge as

NOTE Confidence: 0.919951568214286

00:03:04.022 --> 00:03:06.560 important tools to help us improve

NOTE Confidence: 0.919951568214286

00:03:06.560 --> 00:03:10.040 our care for patients with cancer.

NOTE Confidence: 0.919951568214286

00:03:10.040 --> 00:03:11.780 And so I have no personal

NOTE Confidence: 0.919951568214286

00:03:11.780 --> 00:03:12.360 financial disclosures.

NOTE Confidence: 0.919951568214286

00:03:12.360 --> 00:03:14.225 Some data in the presentation

NOTE Confidence: 0.919951568214286

00:03:14.225 --> 00:03:15.717 was generated in collaboration

NOTE Confidence: 0.919951568214286

00:03:15.717 --> 00:03:17.759 with Repertoire immune medicines.

NOTE Confidence: 0.941969954545455

00:03:20.080 --> 00:03:21.394 And just to briefly go over

NOTE Confidence: 0.941969954545455

00:03:21.394 --> 00:03:22.560 the structure of my talk,

NOTE Confidence: 0.941969954545455

00:03:22.560 --> 00:03:24.338 I'm first going to talk a little

NOTE Confidence: 0.941969954545455

00:03:24.338 --> 00:03:26.185 bit about some evidence that we

NOTE Confidence: 0.941969954545455

00:03:26.185 --> 00:03:27.890 have that the broader systemic

NOTE Confidence: 0.941969954545455

00:03:27.890 --> 00:03:29.932 immune response is really a critical

NOTE Confidence: 0.941969954545455

00:03:29.932 --> 00:03:31.557 component to anti tumor immunity.

NOTE Confidence: 0.941969954545455

00:03:31.560 --> 00:03:33.478 And then going to review some rationale

NOTE Confidence: 0.941969954545455

00:03:33.478 --> 00:03:35.697 and prior work that's been done in this

NOTE Confidence: 0.941969954545455

00:03:35.697 --> 00:03:37.600 space of immune profiling in the blood.

NOTE Confidence: 0.941969954545455

00:03:37.600 --> 00:03:39.178 And I'm going to talk through

NOTE Confidence: 0.941969954545455

00:03:39.178 --> 00:03:40.560 two stories that we have,

NOTE Confidence: 0.941969954545455

00:03:40.560 --> 00:03:43.465 one which is published and one which

NOTE Confidence: 0.941969954545455

00:03:43.465 --> 00:03:45.825 is being prepared for submission that

NOTE Confidence: 0.941969954545455

00:03:45.825 --> 00:03:48.456 really focuses on using the T cell

NOTE Confidence: 0.941969954545455

00:03:48.456 --> 00:03:50.304 receptor as a molecular barcode to

NOTE Confidence: 0.941969954545455

00:03:50.304 --> 00:03:53.138 help us understand what what is the

NOTE Confidence: 0.941969954545455

00:03:53.138 --> 00:03:55.388 relationship between T cells in the

NOTE Confidence: 0.941969954545455

00:03:55.388 --> 00:03:58.040 tumor and T cells within the blood.

NOTE Confidence: 0.941969954545455

00:03:58.040 --> 00:04:00.126 I'm going to close by discussing a

NOTE Confidence: 0.941969954545455

00:04:00.126 --> 00:04:03.107 little bit of our early efforts to try

NOTE Confidence: 0.941969954545455

00:04:03.107 --> 00:04:05.127 and translate our biological discoveries

NOTE Confidence: 0.941969954545455

00:04:05.191 --> 00:04:07.198 into clinically relevant biomarkers.

NOTE Confidence: 0.842695048

00:04:11.000 --> 00:04:14.908 And so just to start, as we all know,

NOTE Confidence: 0.842695048

00:04:14.908 --> 00:04:16.576 immune checkpoint inhibitors have

NOTE Confidence: 0.842695048

00:04:16.576 --> 00:04:18.632 really revolutionized the way that

NOTE Confidence: 0.842695048

00:04:18.632 --> 00:04:20.672 we treat patients with cancer.

NOTE Confidence: 0.842695048

00:04:20.680 --> 00:04:22.800 And it's in large part due to work

NOTE Confidence: 0.842695048

00:04:22.800 --> 00:04:24.448 such that's been done by Doctor

NOTE Confidence: 0.842695048

00:04:24.448 --> 00:04:26.384 Kruger and many of you out in

NOTE Confidence: 0.842695048

00:04:26.384 --> 00:04:29.844 the audience and the gold mark,

NOTE Confidence: 0.842695048

00:04:29.844 --> 00:04:32.496 the gold standard for the potential

NOTE Confidence: 0.842695048

00:04:32.496 --> 00:04:34.880 that immunotherapies have for treating

NOTE Confidence: 0.842695048

00:04:34.880 --> 00:04:37.780 patients with cancer remains in

NOTE Confidence: 0.842695048

00:04:37.780 --> 00:04:39.688 Melanoma amongst other cancer types.

NOTE Confidence: 0.842695048

00:04:39.688 --> 00:04:42.555 But you can see that these are really

NOTE Confidence: 0.842695048

00:04:42.555 --> 00:04:44.183 practice changing survival curves

NOTE Confidence: 0.842695048

00:04:44.183 --> 00:04:46.552 from the Checkmate 067 trial which

NOTE Confidence: 0.842695048

00:04:46.552 --> 00:04:48.880 was a frontline trial looking at

NOTE Confidence: 0.842695048

00:04:48.880 --> 00:04:52.008 anti PD one and or anti CTLA for

NOTE Confidence: 0.842695048

00:04:52.008 --> 00:04:54.878 for patients with advanced Melanoma.

NOTE Confidence: 0.842695048

00:04:54.880 --> 00:04:56.976 So you can also tell from these curves

NOTE Confidence: 0.842695048

00:04:56.976 --> 00:04:59.176 that about 50% of patients still fail

NOTE Confidence: 0.842695048

00:04:59.176 --> 00:05:02.245 to derive long term benefit and I think

NOTE Confidence: 0.842695048

00:05:02.245 --> 00:05:04.648 it's it caused into question why,

NOTE Confidence: 0.842695048

00:05:04.648 --> 00:05:05.632 why is that?

NOTE Confidence: 0.842695048

00:05:05.632 --> 00:05:08.025 What, what are the mechanisms that

NOTE Confidence: 0.842695048

00:05:08.025 --> 00:05:11.758 are causing them to not be able to

NOTE Confidence: 0.842695048

00:05:11.760 --> 00:05:13.605 amount of systemic immune response

NOTE Confidence: 0.842695048

00:05:13.605 --> 00:05:16.080 that can result in tumor rejection

NOTE Confidence: 0.842695048

00:05:16.080 --> 00:05:18.248 and are there markers that we can use

NOTE Confidence: 0.842695048

00:05:18.248 --> 00:05:20.519 to try and identify these patients

NOTE Confidence: 0.842695048

00:05:20.520 --> 00:05:22.320 and are there therapeutic avenues

NOTE Confidence: 0.842695048

00:05:22.320 --> 00:05:25.780 that we can explore by learning

NOTE Confidence: 0.842695048

00:05:25.780 --> 00:05:27.835 with this information.

NOTE Confidence: 0.842695048

00:05:27.840 --> 00:05:30.536 And so a a better understanding of the

NOTE Confidence: 0.842695048

00:05:30.536 --> 00:05:31.670 fundamental determinants dictating

NOTE Confidence: 0.842695048

00:05:31.670 --> 00:05:33.675 clinical response are really needed

NOTE Confidence: 0.824951098333333

00:05:35.760 --> 00:05:38.329 just to review what our current understanding

NOTE Confidence: 0.824951098333333

00:05:38.329 --> 00:05:40.320 of immune checkpoint inhibitors are.

NOTE Confidence: 0.824951098333333

00:05:40.320 --> 00:05:42.060 When immune checkpoint inhibitors

NOTE Confidence: 0.824951098333333

00:05:42.060 --> 00:05:44.235 were first introduced into a

NOTE Confidence: 0.824951098333333

00:05:44.235 --> 00:05:46.118 clinic now over a decade ago,

NOTE Confidence: 0.824951098333333

00:05:46.120 --> 00:05:48.640 the the thought was really that these

NOTE Confidence: 0.824951098333333

00:05:48.640 --> 00:05:51.172 agents target negative signals within

NOTE Confidence: 0.824951098333333

00:05:51.172 --> 00:05:53.887 the local tumor microenvironment and

NOTE Confidence: 0.824951098333333

00:05:53.887 --> 00:05:56.404 thereby reinvigorate T cells which

NOTE Confidence: 0.824951098333333

00:05:56.404 --> 00:05:59.512 we believe to be the primary factor

NOTE Confidence: 0.824951098333333

00:05:59.512 --> 00:06:02.485 immune cells and resulting in tumor

NOTE Confidence: 0.824951098333333

00:06:02.485 --> 00:06:05.225 rejection reinvigorating these local

NOTE Confidence: 0.824951098333333

00:06:05.225 --> 00:06:09.360 T cells to recognize that tumor.

NOTE Confidence: 0.824951098333333

00:06:09.360 --> 00:06:11.320 Well, we've since come to learn though

NOTE Confidence: 0.824951098333333

00:06:11.320 --> 00:06:14.148 that at least in part the the potential

NOTE Confidence: 0.824951098333333

00:06:14.148 --> 00:06:16.159 for immune checkpoint inhibitors to

NOTE Confidence: 0.824951098333333

00:06:16.160 --> 00:06:21.000 mount successful tumor rejection is

NOTE Confidence: 0.824951098333333

00:06:21.000 --> 00:06:25.284 the the need to induce immune responses

NOTE Confidence: 0.824951098333333

00:06:25.284 --> 00:06:27.156 beyond the local microenvironment.

NOTE Confidence: 0.824951098333333

00:06:27.160 --> 00:06:29.395 And several groups including those

NOTE Confidence: 0.824951098333333

00:06:29.395 --> 00:06:32.346 here at Yale have identified the tumor

NOTE Confidence: 0.824951098333333

00:06:32.346 --> 00:06:35.328 during lymph node for example as one

NOTE Confidence: 0.824951098333333

00:06:35.328 --> 00:06:37.962 reservoir for tumor specific stem like

NOTE Confidence: 0.824951098333333

00:06:37.962 --> 00:06:41.103 T cells that help to regenerate and

NOTE Confidence: 0.824951098333333

00:06:41.103 --> 00:06:43.638 sustain anti tumor immune responses.

NOTE Confidence: 0.824951098333333

00:06:43.640 --> 00:06:46.286 This is nicely illustrated in preclinical

NOTE Confidence: 0.824951098333333

00:06:46.286 --> 00:06:49.426 models whereby we can block lymphocyte

NOTE Confidence: 0.824951098333333

00:06:49.426 --> 00:06:53.164 trafficking and in doing so we see

NOTE Confidence: 0.824951098333333

00:06:53.164 --> 00:06:56.440 that anti tumor immunity is really

NOTE Confidence: 0.824951098333333

00:06:56.440 --> 00:06:58.564 impaired in the efficacy of immune

NOTE Confidence: 0.824951098333333

00:06:58.564 --> 00:07:00.480 checkpoint inhibitors is also limited.

NOTE Confidence: 0.824951098333333

00:07:00.480 --> 00:07:02.237 This has been demonstrated by several groups,

NOTE Confidence: 0.824951098333333

00:07:02.240 --> 00:07:06.030 including two papers out of groups

NOTE Confidence: 0.824951098333333

00:07:06.030 --> 00:07:08.748 from Yale from Nick Joshi's lab and

NOTE Confidence: 0.824951098333333

00:07:08.748 --> 00:07:10.393 then also from Marcus Bosenberg

NOTE Confidence: 0.824951098333333

00:07:10.393 --> 00:07:11.717 and Richard Favell's lab.

NOTE Confidence: 0.89084478

00:07:14.920 --> 00:07:18.256 We also know that immune checkpoint

NOTE Confidence: 0.89084478

00:07:18.256 --> 00:07:21.522 inhibitors not only recruit new T cells

NOTE Confidence: 0.89084478

00:07:21.522 --> 00:07:23.204 to the local tumor microenvironment,

NOTE Confidence: 0.89084478

00:07:23.204 --> 00:07:26.179 but that these T cells may have actual

NOTE Confidence: 0.89084478

00:07:26.179 --> 00:07:28.559 actually be recognizing different antigens.

NOTE Confidence: 0.89084478

00:07:28.560 --> 00:07:30.590 And we're assessing that based off of

NOTE Confidence: 0.89084478

00:07:30.590 --> 00:07:32.718 their T cell receptor sequences termed

NOTE Confidence: 0.89084478

00:07:32.718 --> 00:07:35.112 novel chronotypes here on the right.

NOTE Confidence: 0.902142325

00:07:38.120 --> 00:07:40.325 And perhaps some of the most exciting

NOTE Confidence: 0.902142325

00:07:40.325 --> 00:07:42.630 data that's merging is the potential

NOTE Confidence: 0.902142325

00:07:42.630 --> 00:07:44.620 benefit of immune checkpoint inhibitors

NOTE Confidence: 0.902142325

00:07:44.684 --> 00:07:46.686 to work in early stage disease even

NOTE Confidence: 0.902142325

00:07:46.686 --> 00:07:48.559 after the tumor has been removed,

NOTE Confidence: 0.902142325

00:07:48.560 --> 00:07:51.038 the macroscopic tumor has been removed.

NOTE Confidence: 0.902142325

00:07:51.040 --> 00:07:53.609 And so these are disease free survival

NOTE Confidence: 0.902142325

00:07:53.609 --> 00:07:55.825 curves on recent trials that have

NOTE Confidence: 0.902142325

00:07:55.825 --> 00:07:58.254 explored anti PD one therapy in the

NOTE Confidence: 0.902142325

00:07:58.327 --> 00:08:00.599 adjuvant and neoadjuvant settings.

NOTE Confidence: 0.902142325

00:08:00.600 --> 00:08:03.071 And what these data reinforces is that

NOTE Confidence: 0.902142325

00:08:03.071 --> 00:08:04.691 checkpoint blockade really potentiates

NOTE Confidence: 0.902142325

00:08:04.691 --> 00:08:07.211 immune surveillance beyond the local

NOTE Confidence: 0.902142325

00:08:07.211 --> 00:08:09.772 microenvironment and helps to prevent

NOTE Confidence: 0.902142325

00:08:09.772 --> 00:08:13.280 tumor regrowth and disease recurrence.

NOTE Confidence: 0.902831324

00:08:16.880 --> 00:08:20.205 So in this setting you know we

NOTE Confidence: 0.902831324

00:08:20.205 --> 00:08:23.378 really believe that a systemic immune

NOTE Confidence: 0.902831324

00:08:23.378 --> 00:08:25.845 response is an important contributor

NOTE Confidence: 0.902831324

00:08:25.845 --> 00:08:28.462 to effective anti tumor immunity and

NOTE Confidence: 0.902831324

00:08:28.462 --> 00:08:30.172 our underlying hypothesis for this

NOTE Confidence: 0.902831324

00:08:30.172 --> 00:08:32.363 project was that blood based tumor

NOTE Confidence: 0.902831324

00:08:32.363 --> 00:08:34.649 related T cells really have distinct

NOTE Confidence: 0.902831324

00:08:34.649 --> 00:08:36.434 characteristics and can be informative

NOTE Confidence: 0.902831324

00:08:36.434 --> 00:08:39.840 of local tumor immune microenvironment.

NOTE Confidence: 0.902831324

00:08:39.840 --> 00:08:41.610 Our translational goal is therefore

NOTE Confidence: 0.902831324

00:08:41.610 --> 00:08:43.380 to try and identify clinically

NOTE Confidence: 0.902831324

00:08:43.435 --> 00:08:45.310 relevant biomarkers which can be

NOTE Confidence: 0.902831324

00:08:45.310 --> 00:08:47.020 obtained non invasively through the

NOTE Confidence: 0.902831324

00:08:47.020 --> 00:08:49.050 blood to try and assess inform us

NOTE Confidence: 0.902831324

00:08:49.050 --> 00:08:51.038 on anti tumor immune responses

NOTE Confidence: 0.756713162307692

00:08:53.720 --> 00:08:56.600 and so prior work in this arena have

NOTE Confidence: 0.756713162307692

00:08:56.600 --> 00:08:58.920 nominated several blood based biomarkers.

NOTE Confidence: 0.756713162307692

00:08:58.920 --> 00:09:00.720 However uptake into the clinic

NOTE Confidence: 0.756713162307692

00:09:00.720 --> 00:09:02.300 is likely challenged in part

NOTE Confidence: 0.756713162307692

00:09:02.300 --> 00:09:03.800 due to the lack of specificity.

NOTE Confidence: 0.756713162307692

00:09:03.800 --> 00:09:06.098 So several serum cytokines which we

NOTE Confidence: 0.756713162307692

00:09:06.098 --> 00:09:08.986 know to be context dependence are not

NOTE Confidence: 0.756713162307692

00:09:08.986 --> 00:09:11.956 widely used or due to inavailability

NOTE Confidence: 0.756713162307692

00:09:11.956 --> 00:09:14.601 of certain techniques within our

NOTE Confidence: 0.756713162307692

00:09:14.601 --> 00:09:17.768 clinical labs such as the ability to

NOTE Confidence: 0.756713162307692

00:09:17.768 --> 00:09:20.034 determine T cell receptor diversity

NOTE Confidence: 0.756713162307692

00:09:20.034 --> 00:09:22.440 or clone sizes in clinical labs.

NOTE Confidence: 0.882026240869565

00:09:24.680 --> 00:09:27.144 And so our general approach has been to

NOTE Confidence: 0.882026240869565

00:09:27.144 --> 00:09:30.046 first take a deep dive and deep look into T

NOTE Confidence: 0.882026240869565

00:09:30.046 --> 00:09:32.399 cells within the tumor microenvironments.

NOTE Confidence: 0.882026240869565

00:09:32.400 --> 00:09:34.496 And in order to do that we employed

NOTE Confidence: 0.882026240869565

00:09:34.496 --> 00:09:35.960 using single cell sequencing.

NOTE Confidence: 0.882026240869565

00:09:35.960 --> 00:09:39.544 This is a technique that allows us to

NOTE Confidence: 0.882026240869565

00:09:39.544 --> 00:09:41.320 simultaneously characterize both the

NOTE Confidence: 0.882026240869565

00:09:41.320 --> 00:09:43.350 gene expression profile of individual

NOTE Confidence: 0.882026240869565

00:09:43.350 --> 00:09:46.479 cells and in the case of T cells also

NOTE Confidence: 0.882026240869565

00:09:46.479 --> 00:09:48.744 the full length T cell receptor sequence.

NOTE Confidence: 0.882026240869565

00:09:48.744 --> 00:09:50.760 Now the T cell receptor is

NOTE Confidence: 0.882026240869565

00:09:50.825 --> 00:09:52.760 really an essential component to

NOTE Confidence: 0.882026240869565

00:09:52.760 --> 00:09:54.960 everything that AT cell can do.

NOTE Confidence: 0.882026240869565

00:09:54.960 --> 00:09:57.270 The T cell receptor is what allows

NOTE Confidence: 0.882026240869565

00:09:57.270 --> 00:09:59.872 T cells to become activated when

NOTE Confidence: 0.882026240869565

00:09:59.872 --> 00:10:02.437 it encounters its cognate antigen.

NOTE Confidence: 0.882026240869565

00:10:02.440 --> 00:10:07.426 And the the global diversity of the T

NOTE Confidence: 0.882026240869565

00:10:07.426 --> 00:10:10.680 cell repertoire is really really immense.

NOTE Confidence: 0.882026240869565

00:10:10.680 --> 00:10:13.120 And so having a high resolution view of

NOTE Confidence: 0.882026240869565

00:10:13.120 --> 00:10:15.677 the the sequence is really important.

NOTE Confidence: 0.882026240869565

00:10:15.680 --> 00:10:17.493 And when T cells do encounter their

NOTE Confidence: 0.882026240869565

00:10:17.493 --> 00:10:19.080 cognate peptides or their androgens,

NOTE Confidence: 0.882026240869565

00:10:19.080 --> 00:10:21.348 they become activated and they proliferate

NOTE Confidence: 0.882026240869565

00:10:21.348 --> 00:10:24.037 and all of these sister clones are

NOTE Confidence: 0.882026240869565

00:10:24.037 --> 00:10:26.634 share the same T cell receptor sequence.

NOTE Confidence: 0.882026240869565

00:10:26.640 --> 00:10:28.360 And so in that sense,

NOTE Confidence: 0.882026240869565

00:10:28.360 --> 00:10:30.670 the T cell receptor sequence is

NOTE Confidence: 0.882026240869565

00:10:30.670 --> 00:10:33.266 really a a useful molecular biomarker

NOTE Confidence: 0.882026240869565

00:10:33.266 --> 00:10:35.660 for us to be able to link T cells

NOTE Confidence: 0.882026240869565

00:10:35.722 --> 00:10:37.948 that are clonally related within the

NOTE Confidence: 0.882026240869565

00:10:37.948 --> 00:10:40.480 tumor and the blood.

NOTE Confidence: 0.882026240869565

00:10:40.480 --> 00:10:42.328 And we can then ask the question based

NOTE Confidence: 0.882026240869565

00:10:42.328 --> 00:10:44.278 off of his gene expression profile,

NOTE Confidence: 0.882026240869565

00:10:44.280 --> 00:10:45.760 how are these cells changing?

NOTE Confidence: 0.882026240869565

00:10:45.760 --> 00:10:48.680 What can we learn in these two spaces?

NOTE Confidence: 0.962282331111111

00:10:51.280 --> 00:10:52.612 And so in this first portion

NOTE Confidence: 0.962282331111111

00:10:52.612 --> 00:10:53.799 of the talk, I'm going to

NOTE Confidence: 0.809963740833333

00:10:56.000 --> 00:10:57.494 talk a little bit more about

NOTE Confidence: 0.809963740833333

00:10:57.494 --> 00:10:59.599 using TCR as a molecular barcode.

NOTE Confidence: 0.809963740833333

00:10:59.600 --> 00:11:01.952 And I'd really like to just acknowledge

NOTE Confidence: 0.809963740833333

00:11:01.952 --> 00:11:03.884 Liliana Luca who was a former post

NOTE Confidence: 0.809963740833333

00:11:03.884 --> 00:11:05.858 doc in our lab and junior faculty

NOTE Confidence: 0.809963740833333

00:11:05.858 --> 00:11:08.117 member in our lab who's now an

NOTE Confidence: 0.809963740833333

00:11:08.117 --> 00:11:09.397 independent investigator in France.

NOTE Confidence: 0.809963740833333

00:11:09.400 --> 00:11:11.480 She was really an important

NOTE Confidence: 0.809963740833333

00:11:11.480 --> 00:11:13.560 architect in driving this project

NOTE Confidence: 0.809963740833333

00:11:13.632 --> 00:11:15.677 forward to this initial story.

NOTE Confidence: 0.809963740833333

00:11:15.680 --> 00:11:19.984 And so for this initial or the initial

NOTE Confidence: 0.809963740833333

00:11:19.984 --> 00:11:22.920 look at using TCR as a barcode,

NOTE Confidence: 0.809963740833333

00:11:22.920 --> 00:11:24.936 we performed single cell RNA sequencing

NOTE Confidence: 0.809963740833333

00:11:24.936 --> 00:11:26.772 and T cell receptor sequencing

NOTE Confidence: 0.809963740833333

00:11:26.772 --> 00:11:29.144 from in blood and tumor from 11

NOTE Confidence: 0.809963740833333

00:11:29.144 --> 00:11:31.120 patients with stage 4 Melanoma.

NOTE Confidence: 0.809963740833333

00:11:31.120 --> 00:11:33.862 These patients all had mixed histologies

NOTE Confidence: 0.809963740833333

00:11:33.862 --> 00:11:36.335 and treatment histories and the the

NOTE Confidence: 0.809963740833333

00:11:36.335 --> 00:11:38.525 purpose of this initial look was

NOTE Confidence: 0.809963740833333

00:11:38.525 --> 00:11:41.514 to try and assess a global look at

NOTE Confidence: 0.809963740833333

00:11:41.514 --> 00:11:44.760 what these clonal related T cells,

NOTE Confidence: 0.809963740833333

00:11:44.760 --> 00:11:46.185 global features of these clonal

NOTE Confidence: 0.809963740833333

00:11:46.185 --> 00:11:47.040 related T cells.

NOTE Confidence: 0.914377805714286

00:11:49.600 --> 00:11:52.995 The way that we went about identifying

NOTE Confidence: 0.914377805714286

00:11:53.000 --> 00:11:55.160 tumor T cells which we think are relevant

NOTE Confidence: 0.914377805714286

00:11:55.160 --> 00:11:57.611 to the anti tumor immune response was by

NOTE Confidence: 0.914377805714286

00:11:57.611 --> 00:11:59.918 looking at how clonal extended they are.

NOTE Confidence: 0.914377805714286

00:11:59.920 --> 00:12:01.990 This helps us differentiate T cells

NOTE Confidence: 0.914377805714286

00:12:01.990 --> 00:12:04.120 that we may be located within the

NOTE Confidence: 0.914377805714286

00:12:04.120 --> 00:12:06.057 tumor but that are not actively

NOTE Confidence: 0.914377805714286

00:12:06.057 --> 00:12:08.679 participating in the inter tumor response.

NOTE Confidence: 0.914377805714286

00:12:08.680 --> 00:12:10.993 We then link these over into the blood and

NOTE Confidence: 0.914377805714286

00:12:10.993 --> 00:12:13.716 we termed for this initial story these cells,

NOTE Confidence: 0.914377805714286

00:12:13.720 --> 00:12:15.240 these cloning related but blood

NOTE Confidence: 0.914377805714286

00:12:15.240 --> 00:12:16.760 based cells as circulating tumor

NOTE Confidence: 0.914377805714286

00:12:16.816 --> 00:12:17.863 infiltrating lymphocytes which

NOTE Confidence: 0.914377805714286

00:12:17.863 --> 00:12:19.957 I'll refer to as circulating tills.

NOTE Confidence: 0.852747558461538

00:12:22.760 --> 00:12:25.028 And so these circulating tills are a

NOTE Confidence: 0.852747558461538

00:12:25.028 --> 00:12:26.720 relatively rare population in the blood.

NOTE Confidence: 0.852747558461538

00:12:26.720 --> 00:12:28.799 They are comprised of less than 10%

NOTE Confidence: 0.852747558461538

00:12:28.800 --> 00:12:32.188 of our total T cells and you can see

NOTE Confidence: 0.852747558461538

00:12:32.188 --> 00:12:33.256 that they're predominantly located

NOTE Confidence: 0.852747558461538

00:12:33.256 --> 00:12:34.838 within the CDAT cell compartments.

NOTE Confidence: 0.852747558461538

00:12:34.840 --> 00:12:37.000 So what I'm showing is on the right

NOTE Confidence: 0.852747558461538

00:12:37.000 --> 00:12:39.034 is a dimensionality reduction plot

NOTE Confidence: 0.852747558461538

00:12:39.034 --> 00:12:41.872 of our single cell RNA sequencing

NOTE Confidence: 0.852747558461538

00:12:41.880 --> 00:12:43.745 and the circulating tilts are

NOTE Confidence: 0.852747558461538

00:12:43.745 --> 00:12:45.237 highlighted in dark green.

NOTE Confidence: 0.852747558461538

00:12:45.240 --> 00:12:47.634 You can see that they're predominantly

NOTE Confidence: 0.852747558461538

00:12:47.634 --> 00:12:50.320 distributed within the CDAT cell compartment.

NOTE Confidence: 0.852747558461538

00:12:50.320 --> 00:12:52.756 These cells are clonal expanded not

NOTE Confidence: 0.852747558461538

00:12:52.756 --> 00:12:55.525 only within the tumor but also within

NOTE Confidence: 0.852747558461538

00:12:55.525 --> 00:12:57.338 the blood and that interestingly

NOTE Confidence: 0.852747558461538

00:12:57.338 --> 00:12:59.168 this population seems to accumulate

NOTE Confidence: 0.852747558461538

00:12:59.168 --> 00:13:01.157 over the course of your disease

NOTE Confidence: 0.940896806363636

00:13:03.520 --> 00:13:05.404 and so we can perform differential

NOTE Confidence: 0.940896806363636

00:13:05.404 --> 00:13:07.641 expression analysis to try and take an

NOTE Confidence: 0.940896806363636

00:13:07.641 --> 00:13:09.186 unbiased look at the transcriptional

NOTE Confidence: 0.940896806363636

00:13:09.186 --> 00:13:10.680 features of this population.

NOTE Confidence: 0.940896806363636

00:13:10.680 --> 00:13:12.871 These circulating tills are the ones that

NOTE Confidence: 0.940896806363636

00:13:12.871 --> 00:13:15.121 are located in the right and the all

NOTE Confidence: 0.940896806363636

00:13:15.121 --> 00:13:17.325 other blood T cells are located on the

NOTE Confidence: 0.940896806363636

00:13:17.325 --> 00:13:19.397 left and we're focusing on CDAT cells.

NOTE Confidence: 0.940896806363636

00:13:19.400 --> 00:13:21.824 In this case, what we find is that

NOTE Confidence: 0.940896806363636

00:13:21.824 --> 00:13:24.112 they share features of icytotoxicity,

NOTE Confidence: 0.940896806363636

00:13:24.112 --> 00:13:27.600 tissue residence, cell migration,

NOTE Confidence: 0.940896806363636

00:13:27.600 --> 00:13:32.479 tissue homing and importantly as a A,

NOTE Confidence: 0.940896806363636

00:13:32.480 --> 00:13:35.238 it's kind of a A a check.

NOTE Confidence: 0.940896806363636

00:13:35.240 --> 00:13:37.550 They they lack features of naive

NOTE Confidence: 0.940896806363636

00:13:37.550 --> 00:13:39.799 or memory markers such as CCR 7,

NOTE Confidence: 0.940896806363636

00:13:39.800 --> 00:13:43.460 TCF 7 and these are features that

NOTE Confidence: 0.940896806363636

00:13:43.460 --> 00:13:46.120 was this is important to us because

NOTE Confidence: 0.940896806363636

00:13:46.120 --> 00:13:48.474 it reinforces the fact that these

NOTE Confidence: 0.940896806363636

00:13:48.474 --> 00:13:50.754 are cells that have been activated

NOTE Confidence: 0.940896806363636

00:13:50.829 --> 00:13:52.552 and are actively participating

NOTE Confidence: 0.940896806363636

00:13:52.552 --> 00:13:54.320 in the immune response.

NOTE Confidence: 0.737756353333333

00:13:58.240 --> 00:13:59.440 We can also ask the question,

NOTE Confidence: 0.737756353333333

00:13:59.440 --> 00:14:02.960 how are these circling tills related to the

NOTE Confidence: 0.737756353333333

00:14:02.960 --> 00:14:06.600 features of tumor cells or tumor T cells.

NOTE Confidence: 0.737756353333333

00:14:06.600 --> 00:14:10.030 And so the first analysis that we did was we

NOTE Confidence: 0.737756353333333

00:14:10.117 --> 00:14:13.576 generated a gene set that is characteristic

NOTE Confidence: 0.737756353333333

00:14:13.576 --> 00:14:17.760 of expanded T cells within the tumor.

NOTE Confidence: 0.737756353333333

00:14:17.760 --> 00:14:20.480 We then took a look at the expression

NOTE Confidence: 0.737756353333333

00:14:20.480 --> 00:14:23.560 of these this expanded tilde gene set

NOTE Confidence: 0.737756353333333

00:14:23.560 --> 00:14:25.780 within our circulating till population as

NOTE Confidence: 0.737756353333333

00:14:25.780 --> 00:14:28.023 compared with all other blood cells and

NOTE Confidence: 0.737756353333333

00:14:28.023 --> 00:14:30.404 we do see that there is a enrichment for

NOTE Confidence: 0.737756353333333

00:14:30.404 --> 00:14:32.798 this population or these this gene set.

NOTE Confidence: 0.737756353333333

00:14:32.800 --> 00:14:36.528 We can also ask our circulating

NOTE Confidence: 0.737756353333333

00:14:36.528 --> 00:14:40.346 tills characteristic of gene sets

NOTE Confidence: 0.737756353333333

00:14:40.346 --> 00:14:43.370 of T cells which are specifically

NOTE Confidence: 0.737756353333333

00:14:43.370 --> 00:14:46.704 expanded within the the the tumor and

NOTE Confidence: 0.737756353333333

00:14:46.704 --> 00:14:49.568 thereby removing genes that may be

NOTE Confidence: 0.737756353333333

00:14:49.568 --> 00:14:51.828 just generally associated with clonal

NOTE Confidence: 0.737756353333333

00:14:51.828 --> 00:14:54.140 expansion and we again see that there

NOTE Confidence: 0.737756353333333

00:14:54.140 --> 00:14:56.359 is an enrichment for this gene set.

NOTE Confidence: 0.737756353333333

00:14:56.360 --> 00:14:58.856 One thing that I will point out is

NOTE Confidence: 0.737756353333333

00:14:58.856 --> 00:15:01.212 that there there are several hallmark

NOTE Confidence: 0.737756353333333

00:15:01.212 --> 00:15:04.332 genes which are have been described as

NOTE Confidence: 0.737756353333333

00:15:04.332 --> 00:15:07.014 important features for T cell dysfunction

NOTE Confidence: 0.737756353333333

00:15:07.014 --> 00:15:09.736 or tumor exhaustion such as our Co

NOTE Confidence: 0.737756353333333

00:15:09.736 --> 00:15:11.800 inhibitory checkpoints such as CTLA 4

NOTE Confidence: 0.737756353333333

00:15:11.869 --> 00:15:14.536 Tim 3 which is encoded by the gene HAV

NOTE Confidence: 0.737756353333333

00:15:14.536 --> 00:15:17.032 CR2 and then the transcription factor

NOTE Confidence: 0.737756353333333

00:15:17.032 --> 00:15:19.691 Tox PD one is also found although not

NOTE Confidence: 0.737756353333333

00:15:19.691 --> 00:15:21.233 listed displayed here on this screen.

NOTE Confidence: 0.819520096842105

00:15:24.400 --> 00:15:26.913 And so we can see that circulating

NOTE Confidence: 0.819520096842105

00:15:26.913 --> 00:15:29.592 tills are are not representative of

NOTE Confidence: 0.819520096842105

00:15:29.592 --> 00:15:32.634 features of exhaustion within the tumor

NOTE Confidence: 0.819520096842105

00:15:32.640 --> 00:15:35.496 but that there is a good concordance

NOTE Confidence: 0.819520096842105

00:15:35.496 --> 00:15:37.744 between a cytotoxicity signature between

NOTE Confidence: 0.819520096842105

00:15:37.744 --> 00:15:40.324 this population and the the degree

NOTE Confidence: 0.819520096842105

00:15:40.324 --> 00:15:42.034 of cytotoxicity within the tumor.

NOTE Confidence: 0.89447998

00:15:45.600 --> 00:15:47.077 And we can also ask the question,

NOTE Confidence: 0.89447998

00:15:47.080 --> 00:15:49.887 are T cells that have been described

NOTE Confidence: 0.89447998

00:15:49.887 --> 00:15:51.720 to be predictive of response

NOTE Confidence: 0.89447998

00:15:51.720 --> 00:15:53.320 to immune checkpoint blockade,

NOTE Confidence: 0.89447998

00:15:53.320 --> 00:15:55.636 are those T cells also found

NOTE Confidence: 0.89447998

00:15:55.636 --> 00:15:56.794 within the circulation?

NOTE Confidence: 0.89447998

00:15:56.800 --> 00:15:59.187 So this is work out of Nirha

NOTE Confidence: 0.89447998

00:15:59.187 --> 00:16:01.053 Cohen's group whereby he generated

NOTE Confidence: 0.89447998

00:16:01.053 --> 00:16:03.357 2 gene signatures of CDAT cells,

NOTE Confidence: 0.89447998

00:16:03.360 --> 00:16:05.446 one that was enriched in patients who

NOTE Confidence: 0.89447998

00:16:05.446 --> 00:16:07.440 responded to immune checkpoint blockade,

NOTE Confidence: 0.89447998

00:16:07.440 --> 00:16:08.860 another which was enriched

NOTE Confidence: 0.89447998

00:16:08.860 --> 00:16:10.635 in those who were resistance.

NOTE Confidence: 0.89447998

00:16:10.640 --> 00:16:12.863 And then we took a look to see whether

NOTE Confidence: 0.89447998

00:16:12.863 --> 00:16:15.540 or not these gene signatures what what

NOTE Confidence: 0.89447998

00:16:15.540 --> 00:16:18.639 are the global distribution of these cells.

NOTE Confidence: 0.89447998

00:16:18.640 --> 00:16:20.768 What we find is that the resistance

NOTE Confidence: 0.89447998

00:16:20.768 --> 00:16:22.433 signature is really only enriched

NOTE Confidence: 0.89447998

00:16:22.433 --> 00:16:24.521 within T cells which are exclusively

NOTE Confidence: 0.89447998

00:16:24.521 --> 00:16:26.932 found within the tumor and not found

NOTE Confidence: 0.89447998

00:16:26.932 --> 00:16:29.592 within circulation whereby the response

NOTE Confidence: 0.89447998

00:16:29.592 --> 00:16:32.520 signature is found in T cells that

NOTE Confidence: 0.89447998

00:16:32.520 --> 00:16:34.120 are shared in both compartments.

NOTE Confidence: 0.89447998

00:16:34.120 --> 00:16:37.074 And I think what this point illustrates

NOTE Confidence: 0.89447998

00:16:37.074 --> 00:16:41.580 is that the a key component to a

NOTE Confidence: 0.89447998

00:16:41.580 --> 00:16:43.680 good response to immune checkpoint

NOTE Confidence: 0.89447998

00:16:43.680 --> 00:16:47.760 blockade is prior systemic priming

NOTE Confidence: 0.89447998

00:16:47.760 --> 00:16:50.556 of the anti tumor immune response.

NOTE Confidence: 0.861911983333333

00:16:52.680 --> 00:16:54.437 And so just to summarize from this

NOTE Confidence: 0.861911983333333

00:16:54.437 --> 00:16:56.330 first portion of the talk we've we've

NOTE Confidence: 0.861911983333333

00:16:56.330 --> 00:16:58.055 described that circling tills are

NOTE Confidence: 0.861911983333333

00:16:58.055 --> 00:17:00.259 enriched with genes and are associated

NOTE Confidence: 0.861911983333333

00:17:00.259 --> 00:17:01.743 with clonal expansion specifically

NOTE Confidence: 0.861911983333333

00:17:01.743 --> 00:17:04.151 within the tumor and that the degree

NOTE Confidence: 0.861911983333333

00:17:04.151 --> 00:17:05.691 of cytotoxicity but not exhaustion

NOTE Confidence: 0.861911983333333

00:17:05.691 --> 00:17:07.428 are reflected in circulating tills.

NOTE Confidence: 0.861911983333333

00:17:07.428 --> 00:17:10.051 You find that tumor T cells that

NOTE Confidence: 0.861911983333333

00:17:10.051 --> 00:17:11.699 are predictive of immunotherapy

NOTE Confidence: 0.861911983333333

00:17:11.699 --> 00:17:14.168 response are also shared within the

NOTE Confidence: 0.861911983333333

00:17:14.168 --> 00:17:15.893 blood and that hallmark features

NOTE Confidence: 0.861911983333333

00:17:15.893 --> 00:17:17.760 of a productive anti tumor immune

NOTE Confidence: 0.861911983333333

00:17:17.760 --> 00:17:19.440 response may be reflected in the blood.

NOTE Confidence: 0.878912314615385

00:17:22.800 --> 00:17:25.520 So one of the assumptions from this early

NOTE Confidence: 0.878912314615385

00:17:25.520 --> 00:17:28.079 work was that the most tumor relevant

NOTE Confidence: 0.878912314615385

00:17:28.079 --> 00:17:31.074 or most relevant T cells to the anti

NOTE Confidence: 0.878912314615385

00:17:31.074 --> 00:17:33.610 tumor immune response are those that

NOTE Confidence: 0.878912314615385

00:17:33.610 --> 00:17:35.960 are most largely clonally expanded.

NOTE Confidence: 0.878912314615385

00:17:35.960 --> 00:17:37.395 And around the time that we were

NOTE Confidence: 0.878912314615385

00:17:37.395 --> 00:17:38.240 performing this initial work,

NOTE Confidence: 0.878912314615385

00:17:38.240 --> 00:17:40.652 there were also groups that had

NOTE Confidence: 0.878912314615385

00:17:40.652 --> 00:17:43.735 described that you can use strictly the

NOTE Confidence: 0.878912314615385

00:17:43.735 --> 00:17:46.055 transcriptional signature of T cells

NOTE Confidence: 0.878912314615385

00:17:46.055 --> 00:17:48.615 to accurately predict whether or not

NOTE Confidence: 0.878912314615385

00:17:48.615 --> 00:17:51.893 these T cells were neo oxygen specific,

NOTE Confidence: 0.878912314615385

00:17:51.893 --> 00:17:55.158 whether they're truly tumor specific.

NOTE Confidence: 0.878912314615385

00:17:55.160 --> 00:17:57.600 One such paper was out of Steve Rosenberg's

NOTE Confidence: 0.878912314615385

00:17:57.600 --> 00:18:00.000 group at the National Cancer Institute

NOTE Confidence: 0.878912314615385

00:18:00.000 --> 00:18:02.316 whereby he described 2 gene signatures,

NOTE Confidence: 0.878912314615385

00:18:02.320 --> 00:18:05.526 one for CD4T cells and one for CD8T

NOTE Confidence: 0.878912314615385

00:18:05.526 --> 00:18:08.600 cells that can with high accuracy,

NOTE Confidence: 0.878912314615385

00:18:08.600 --> 00:18:12.120 predicts whether or not a given T cell

NOTE Confidence: 0.878912314615385

00:18:12.120 --> 00:18:15.438 was likely to be neo Entergen specific.

NOTE Confidence: 0.878912314615385

00:18:15.440 --> 00:18:17.239 And so we simply ask the question,

NOTE Confidence: 0.878912314615385

00:18:17.240 --> 00:18:18.980 can the transcriptional identification

NOTE Confidence: 0.878912314615385

00:18:18.980 --> 00:18:21.590 of tumor specific T cells improve

NOTE Confidence: 0.878912314615385

00:18:21.652 --> 00:18:23.952 our understanding of the blood

NOTE Confidence: 0.878912314615385

00:18:23.952 --> 00:18:25.480 and tumor relationship.

NOTE Confidence: 0.715701025833333

00:18:29.200 --> 00:18:31.510 And so we then apply this transcription

NOTE Confidence: 0.715701025833333

00:18:31.510 --> 00:18:33.079 prediction to our own data.

NOTE Confidence: 0.715701025833333

00:18:33.080 --> 00:18:36.312 And so these are the CDAT cells that

NOTE Confidence: 0.715701025833333

00:18:36.312 --> 00:18:39.440 I had shown in the previous section

NOTE Confidence: 0.715701025833333

00:18:39.440 --> 00:18:41.786 and this is all from the tumor and

NOTE Confidence: 0.715701025833333

00:18:41.786 --> 00:18:44.102 we've identified those that we think

NOTE Confidence: 0.715701025833333

00:18:44.102 --> 00:18:46.436 are likely tumor neo antigen specific.

NOTE Confidence: 0.715701025833333

00:18:46.436 --> 00:18:48.770 I apologize about the colouring of

NOTE Confidence: 0.715701025833333

00:18:48.840 --> 00:18:51.440 the the graph on the right over here.

NOTE Confidence: 0.715701025833333

00:18:51.440 --> 00:18:53.688 But what we can see is that using

NOTE Confidence: 0.715701025833333

00:18:53.688 --> 00:18:55.464 our previous definition of expanded

NOTE Confidence: 0.715701025833333

00:18:55.464 --> 00:18:57.400 or unexpanded T cells that you

NOTE Confidence: 0.715701025833333

00:18:57.400 --> 00:18:58.800 have to trust me on the coloring,

NOTE Confidence: 0.715701025833333

00:18:58.800 --> 00:19:01.464 but the vast majority of them are also

NOTE Confidence: 0.715701025833333

00:19:01.464 --> 00:19:03.956 predicted to be in the antigen specific.

NOTE Confidence: 0.715701025833333

00:19:03.960 --> 00:19:05.580 But I think an important point

NOTE Confidence: 0.715701025833333

00:19:05.580 --> 00:19:07.062 is that of the unexpended,

NOTE Confidence: 0.715701025833333

00:19:07.062 --> 00:19:09.260 there's also a portion that we were

NOTE Confidence: 0.715701025833333

00:19:09.320 --> 00:19:11.240 not capturing before and that are

NOTE Confidence: 0.715701025833333

00:19:11.240 --> 00:19:14.095 actually unexpended within the tumor

NOTE Confidence: 0.715701025833333

00:19:14.095 --> 00:19:16.392 migraine environment to functionally

NOTE Confidence: 0.715701025833333

00:19:16.392 --> 00:19:19.704 confirm that these predicted T cells

NOTE Confidence: 0.715701025833333

00:19:19.704 --> 00:19:22.872 do in fact recognize new antigens.

NOTE Confidence: 0.715701025833333

00:19:22.880 --> 00:19:24.805 We collaborated with rapid farming

NOTE Confidence: 0.715701025833333

00:19:24.805 --> 00:19:27.116 medicines and with data that was

NOTE Confidence: 0.715701025833333

00:19:27.116 --> 00:19:29.820 generated by Ruth Haliband's lab as

NOTE Confidence: 0.715701025833333

00:19:29.820 --> 00:19:33.544 well to analyze wholexom sequencing

NOTE Confidence: 0.715701025833333

00:19:33.544 --> 00:19:37.118 and bulk RNA sequencing to be able to

NOTE Confidence: 0.715701025833333

00:19:37.118 --> 00:19:40.300 predict for each individual patients neo

NOTE Confidence: 0.715701025833333

00:19:40.300 --> 00:19:43.120 antigens and tumor associated antigens.

NOTE Confidence: 0.715701025833333

00:19:43.120 --> 00:19:45.654 We then ran these peptides that were

NOTE Confidence: 0.715701025833333

00:19:45.654 --> 00:19:47.828 synthesized in a relatively high

NOTE Confidence: 0.715701025833333

00:19:47.828 --> 00:19:50.864 throughput manner against select T cell

NOTE Confidence: 0.715701025833333

00:19:50.864 --> 00:19:53.520 receptor sequences and tested for reactivity.

NOTE Confidence: 0.79086559125

00:19:56.200 --> 00:19:59.328 What we find in this data is that the

NOTE Confidence: 0.79086559125

00:19:59.328 --> 00:20:03.024 vast majority of those NEO TCR predicted

NOTE Confidence: 0.79086559125

00:20:03.024 --> 00:20:05.890 T cells account for basically all of

NOTE Confidence: 0.79086559125

00:20:05.890 --> 00:20:08.952 the the T cell receptor sequences that

NOTE Confidence: 0.79086559125

00:20:08.952 --> 00:20:11.316 elicited react functional reactivity

NOTE Confidence: 0.79086559125

00:20:11.320 --> 00:20:14.420 and that the only clonotype that

NOTE Confidence: 0.79086559125

00:20:14.420 --> 00:20:17.430 wasn't that was reactive but was not

NOTE Confidence: 0.79086559125

00:20:17.430 --> 00:20:19.840 predicted to be neo antigen specific.

NOTE Confidence: 0.79086559125

00:20:19.840 --> 00:20:22.600 It was in fact reactive to CMV and

NOTE Confidence: 0.79086559125

00:20:22.600 --> 00:20:25.362 this peptide was included as a negative

NOTE Confidence: 0.79086559125

00:20:25.362 --> 00:20:27.240 control for by the repertoire team.

NOTE Confidence: 0.95779278

00:20:29.680 --> 00:20:31.120 And so using this approach,

NOTE Confidence: 0.95779278

00:20:31.120 --> 00:20:37.640 we then analyzed cutaneous 17 patients

NOTE Confidence: 0.95779278

00:20:37.640 --> 00:20:39.620 with cutaneous Melanoma who are

NOTE Confidence: 0.95779278

00:20:39.620 --> 00:20:41.600 immunotherapy naive and we chose

NOTE Confidence: 0.95779278

00:20:41.664 --> 00:20:43.776 to focus on a more biologically

NOTE Confidence: 0.95779278

00:20:43.776 --> 00:20:46.200 homogeneous cohort to try and really

NOTE Confidence: 0.95779278

00:20:46.200 --> 00:20:50.000 eliminate any treatment related effects.

NOTE Confidence: 0.95779278

00:20:50.000 --> 00:20:51.952 We then applied the NEO TCR 8 and

NOTE Confidence: 0.95779278

00:20:51.952 --> 00:20:54.198 neo TCR 4 signatures to predict and

NOTE Confidence: 0.95779278

00:20:54.198 --> 00:20:56.568 identify reactive T cells and then in

NOTE Confidence: 0.95779278

00:20:56.568 --> 00:20:58.392 similar fashion link them back into

NOTE Confidence: 0.95779278

00:20:58.392 --> 00:21:00.875 T cells within the blood based off

NOTE Confidence: 0.95779278

00:21:00.875 --> 00:21:03.560 of their T cell receptor sequences.

NOTE Confidence: 0.95779278

00:21:03.560 --> 00:21:05.960 In total, we identified about 7000

NOTE Confidence: 0.95779278

00:21:05.960 --> 00:21:08.064 reactive CDAT cells which again

NOTE Confidence: 0.95779278

00:21:08.064 --> 00:21:10.686 reinforces that this is a relatively

NOTE Confidence: 0.95779278

00:21:10.686 --> 00:21:11.560 rare population.

NOTE Confidence: 0.875864301428571

00:21:14.880 --> 00:21:17.964 We again find that they're predominantly

NOTE Confidence: 0.875864301428571

00:21:17.964 --> 00:21:20.415 CD8 that they're highly expanded and

NOTE Confidence: 0.875864301428571

00:21:20.415 --> 00:21:23.040 also have a restricted clonal diversity.

NOTE Confidence: 0.875864301428571

00:21:23.040 --> 00:21:24.853 So what I'm showing here on the

NOTE Confidence: 0.875864301428571

00:21:24.853 --> 00:21:27.136 right is a linearized metric for

NOTE Confidence: 0.875864301428571

00:21:27.136 --> 00:21:29.176 the degree of clonal expansion

NOTE Confidence: 0.875864301428571

00:21:29.176 --> 00:21:31.420 within the blood and the tumor.

NOTE Confidence: 0.875864301428571

00:21:31.420 --> 00:21:33.800 Matched reactive are the ones that are

NOTE Confidence: 0.875864301428571

00:21:33.873 --> 00:21:36.799 predicted to be reactive based off of

NOTE Confidence: 0.875864301428571

00:21:36.799 --> 00:21:38.760 their tumor transcriptional signature.

NOTE Confidence: 0.875864301428571

00:21:38.760 --> 00:21:40.960 Unreactive are ones that were

NOTE Confidence: 0.875864301428571

00:21:40.960 --> 00:21:43.160 unreactive but also found within

NOTE Confidence: 0.875864301428571

00:21:43.236 --> 00:21:46.264 the tumor and then also the ones

NOTE Confidence: 0.875864301428571

00:21:46.264 --> 00:21:48.280 that were only found in the blood.

NOTE Confidence: 0.912079513

00:21:51.200 --> 00:21:54.140 We also find that there's a higher

NOTE Confidence: 0.912079513

00:21:54.140 --> 00:21:56.001 frequency of previously reported

NOTE Confidence: 0.912079513

00:21:56.001 --> 00:21:58.641 tumor antigen specific TCR sequences

NOTE Confidence: 0.912079513

00:21:58.641 --> 00:22:00.753 in our reactive population,

NOTE Confidence: 0.912079513

00:22:00.760 --> 00:22:03.952 and to do this analysis we use

NOTE Confidence: 0.912079513

00:22:03.952 --> 00:22:06.361 publicly available databases of TCR

NOTE Confidence: 0.912079513

00:22:06.361 --> 00:22:08.756 sequences that had been annotated

NOTE Confidence: 0.912079513

00:22:08.756 --> 00:22:10.840 with their functional epitopes

NOTE Confidence: 0.888838393888889

00:22:13.520 --> 00:22:15.960 to try and understand in a more specific

NOTE Confidence: 0.888838393888889

00:22:15.960 --> 00:22:17.543 manner the transcriptional features

NOTE Confidence: 0.888838393888889

00:22:17.543 --> 00:22:20.279 of these reactive T cell population.

NOTE Confidence: 0.888838393888889

00:22:20.280 --> 00:22:22.475 We collaborated with Doctor Yuval

NOTE Confidence: 0.888838393888889

00:22:22.475 --> 00:22:25.400 Kluger's group and they had developed

NOTE Confidence: 0.888838393888889

00:22:25.400 --> 00:22:28.465 a novel computational method for

NOTE Confidence: 0.888838393888889

00:22:28.465 --> 00:22:30.492 identifying the differential

NOTE Confidence: 0.888838393888889

00:22:30.492 --> 00:22:33.316 abundance of certain populations.

NOTE Confidence: 0.888838393888889

00:22:33.320 --> 00:22:35.234 Wes Lewis was a graduate student

NOTE Confidence: 0.888838393888889

00:22:35.234 --> 00:22:37.843 in his lab who applied this to our

NOTE Confidence: 0.888838393888889

00:22:37.843 --> 00:22:40.028 data set and what we find is that

NOTE Confidence: 0.888838393888889

00:22:40.028 --> 00:22:41.512 we can identify a subpopulation

NOTE Confidence: 0.888838393888889

00:22:41.512 --> 00:22:43.531 of cells that are differentially

NOTE Confidence: 0.888838393888889

00:22:43.531 --> 00:22:46.477 enriched for tumor reactive T cells.

NOTE Confidence: 0.861705938125

00:22:48.880 --> 00:22:51.424 A look at the differential expression

NOTE Confidence: 0.861705938125

00:22:51.424 --> 00:22:54.051 gene signature shows that in the

NOTE Confidence: 0.861705938125

00:22:54.051 --> 00:22:55.759 unmatched and unreactive cells,

NOTE Confidence: 0.861705938125

00:22:55.760 --> 00:22:57.056 there's again an enrichment

NOTE Confidence: 0.861705938125

00:22:57.056 --> 00:22:58.676 for naive and memory markers.

NOTE Confidence: 0.861705938125

00:22:58.680 --> 00:23:00.876 In line with our previous work,

NOTE Confidence: 0.861705938125

00:23:00.880 --> 00:23:03.364 there's a high degree of cytotoxicity

NOTE Confidence: 0.861705938125

00:23:03.364 --> 00:23:06.076 that's both found within our reactive

NOTE Confidence: 0.861705938125

00:23:06.076 --> 00:23:08.036 and our unreactive populations.

NOTE Confidence: 0.861705938125

00:23:08.040 --> 00:23:10.440 There's signs of cell trafficking,

NOTE Confidence: 0.861705938125

00:23:10.440 --> 00:23:14.316 tissue resonance and MK associated markers

NOTE Confidence: 0.861705938125

00:23:14.320 --> 00:23:16.330 and there's one marker in particular

NOTE Confidence: 0.861705938125

00:23:16.330 --> 00:23:18.957 that really stood out to us and this

NOTE Confidence: 0.861705938125

00:23:18.957 --> 00:23:20.487 is the killer cell immunoglobulin

NOTE Confidence: 0.861705938125

00:23:20.487 --> 00:23:22.730 like receptor family which occurred

NOTE Confidence: 0.861705938125

00:23:22.730 --> 00:23:26.560 to DL3 is one of those subtypes here.

NOTE Confidence: 0.861705938125

00:23:26.560 --> 00:23:28.590 And the reason why this is interesting

NOTE Confidence: 0.861705938125

00:23:28.590 --> 00:23:31.592 to us is because this work current

NOTE Confidence: 0.861705938125

00:23:31.592 --> 00:23:34.312 expressing CDAT cells was recently

NOTE Confidence: 0.861705938125

00:23:34.312 --> 00:23:37.299 described in autoimmunity and in

NOTE Confidence: 0.861705938125

00:23:37.299 --> 00:23:40.106 infection as being important mechanism

NOTE Confidence: 0.861705938125

00:23:40.106 --> 00:23:41.918 for restoring peripheral tolerance.

NOTE Confidence: 0.861705938125

00:23:41.920 --> 00:23:44.359 So just a little bit about the CUR receptor.

NOTE Confidence: 0.861705938125

00:23:44.360 --> 00:23:46.640 So they're best understood for

NOTE Confidence: 0.861705938125

00:23:46.640 --> 00:23:49.345 their function and role within NK

NOTE Confidence: 0.861705938125

00:23:49.345 --> 00:23:52.320 cells and they in part a negative

NOTE Confidence: 0.7928755

00:23:55.280 --> 00:23:59.259 suppression signal upon encounter

NOTE Confidence: 0.7928755

00:23:59.259 --> 00:24:02.519 with class one Class 2 MHC.

NOTE Confidence: 0.628647091818182

00:24:04.600 --> 00:24:07.757 So they're in in fact Co inhibitory

NOTE Confidence: 0.628647091818182

00:24:07.757 --> 00:24:10.996 signaling within NK cell within CDAT cells.

NOTE Confidence: 0.628647091818182

00:24:10.996 --> 00:24:13.948 So they denote this regulatory like

NOTE Confidence: 0.628647091818182

00:24:13.948 --> 00:24:17.124 T cell which is analogous to the live

NOTE Confidence: 0.628647091818182

00:24:17.124 --> 00:24:19.508 49 expressing CDAT cells that Harvey

NOTE Confidence: 0.628647091818182

00:24:19.508 --> 00:24:21.956 cancers group had described in mice.

NOTE Confidence: 0.628647091818182

00:24:21.960 --> 00:24:24.438 But these cells have a high expression

NOTE Confidence: 0.628647091818182

00:24:24.438 --> 00:24:26.400 of the transcription factor HELIOS,

NOTE Confidence: 0.628647091818182

00:24:26.400 --> 00:24:28.660 and although the mechanism

NOTE Confidence: 0.628647091818182

00:24:28.660 --> 00:24:30.355 isn't fully understood,

NOTE Confidence: 0.628647091818182

00:24:30.360 --> 00:24:32.934 they can target pathogenic T cells

NOTE Confidence: 0.628647091818182

00:24:32.934 --> 00:24:35.515 in autoimmune D infection and kill

NOTE Confidence: 0.628647091818182

00:24:35.515 --> 00:24:37.873 them in a contact dependent manner.

NOTE Confidence: 0.628647091818182

00:24:37.880 --> 00:24:41.064 And so in essence this is a alternative

NOTE Confidence: 0.628647091818182

00:24:41.064 --> 00:24:43.240 mechanism to try and eliminate

NOTE Confidence: 0.628647091818182

00:24:43.240 --> 00:24:47.440 hyperinflamed or hyperactive T cells.

NOTE Confidence: 0.628647091818182

00:24:47.440 --> 00:24:49.904 The role in tumor immunity is not really

NOTE Confidence: 0.628647091818182

00:24:49.904 --> 00:24:51.638 well described or well understood.

NOTE Confidence: 0.879434508333333

00:24:53.920 --> 00:24:55.240 So turning back to our data,

NOTE Confidence: 0.879434508333333

00:24:55.240 --> 00:24:57.600 we can take a look at gene signatures

NOTE Confidence: 0.879434508333333

00:24:57.600 --> 00:25:00.118 that are characteristic of these auto,

NOTE Confidence: 0.879434508333333

00:25:00.120 --> 00:25:02.860 these Kerr CD8 regulatory cells

NOTE Confidence: 0.879434508333333

00:25:02.860 --> 00:25:04.542 in autoimmunity and compared

NOTE Confidence: 0.879434508333333

00:25:04.542 --> 00:25:05.997 to them with our population,

NOTE Confidence: 0.879434508333333

00:25:06.000 --> 00:25:09.920 our reactive population in Melanoma.

NOTE Confidence: 0.879434508333333

00:25:09.920 --> 00:25:12.080 What we find is that there's a broad

NOTE Confidence: 0.879434508333333

00:25:12.080 --> 00:25:14.239 expression of the Kerr family of receptors.

NOTE Confidence: 0.879434508333333

00:25:14.240 --> 00:25:16.720 There's also high expression of

NOTE Confidence: 0.879434508333333

00:25:16.720 --> 00:25:19.200 cytotoxicity and NK associated genes

NOTE Confidence: 0.879434508333333

00:25:19.200 --> 00:25:20.894 in addition to many of the other

NOTE Confidence: 0.879434508333333

00:25:20.894 --> 00:25:22.639 features that I pointed out before.

NOTE Confidence: 0.879434508333333

00:25:22.640 --> 00:25:23.012 Importantly,

NOTE Confidence: 0.879434508333333

00:25:23.012 --> 00:25:25.244 there's a high expression of the

NOTE Confidence: 0.879434508333333

00:25:25.244 --> 00:25:26.360 transcription factor HELIOS,

NOTE Confidence: 0.879434508333333

00:25:26.360 --> 00:25:28.322 which is thought to be essential

NOTE Confidence: 0.879434508333333

00:25:28.322 --> 00:25:30.073 to their regulatory function or

NOTE Confidence: 0.879434508333333

00:25:30.073 --> 00:25:31.902 their suppressive function and a

NOTE Confidence: 0.879434508333333

00:25:31.902 --> 00:25:33.557 notable absence of Co stimulatory

NOTE Confidence: 0.878902685555556

00:25:35.920 --> 00:25:38.266 molecules. You can also see from

NOTE Confidence: 0.878902685555556

00:25:38.266 --> 00:25:40.784 the slide that this gene signature

NOTE Confidence: 0.878902685555556

00:25:40.784 --> 00:25:43.863 seems to be fairly specific for this

NOTE Confidence: 0.878902685555556

00:25:43.863 --> 00:25:45.395 reactive subpop subpopulation reactive

NOTE Confidence: 0.878902685555556

00:25:45.395 --> 00:25:47.682 cells as compared with all other

NOTE Confidence: 0.878902685555556

00:25:47.682 --> 00:25:49.560 CDAT cells found within the blood.

NOTE Confidence: 0.814018251785714

00:25:52.280 --> 00:25:54.400 We can also perform GENESAT

NOTE Confidence: 0.814018251785714

00:25:54.400 --> 00:25:57.560 enrichment analysis and we do find a

NOTE Confidence: 0.814018251785714

00:25:57.560 --> 00:25:59.009 statistically significant enrichment

NOTE Confidence: 0.814018251785714

00:25:59.009 --> 00:26:02.815 for the top 200 genes of human cure

NOTE Confidence: 0.814018251785714

00:26:02.815 --> 00:26:05.000 CDAT cells found in autoimmunity.

NOTE Confidence: 0.814018251785714

00:26:05.000 --> 00:26:07.037 And we can also ask the question,

NOTE Confidence: 0.814018251785714

00:26:07.040 --> 00:26:09.605 does this population or does

NOTE Confidence: 0.814018251785714

00:26:09.605 --> 00:26:12.212 this cure CDAT cell population?

NOTE Confidence: 0.814018251785714

00:26:12.212 --> 00:26:14.827 Does it represent distinct differentiation

NOTE Confidence: 0.814018251785714

00:26:14.827 --> 00:26:17.957 state or is it part of a continuum

NOTE Confidence: 0.814018251785714

00:26:17.957 --> 00:26:19.680 within clonally related T cells?

NOTE Confidence: 0.814018251785714

00:26:19.680 --> 00:26:22.128 And I performed pseudo time trajectory

NOTE Confidence: 0.814018251785714

00:26:22.128 --> 00:26:23.760 analysis here which attempts

NOTE Confidence: 0.814018251785714

00:26:23.825 --> 00:26:27.080 to try and order biologically

NOTE Confidence: 0.814018251785714

00:26:27.080 --> 00:26:30.603 related cells along a continuum.

NOTE Confidence: 0.814018251785714

00:26:30.603 --> 00:26:33.256 And what we find is that there seems

NOTE Confidence: 0.814018251785714

00:26:33.256 --> 00:26:36.300 to be a branch trajectory here and

NOTE Confidence: 0.814018251785714

00:26:36.300 --> 00:26:41.450 that in unsupervised analysis we also

NOTE Confidence: 0.814018251785714

00:26:41.450 --> 00:26:44.460 find that Helios which is encoded by

NOTE Confidence: 0.814018251785714

00:26:44.550 --> 00:26:48.288 the gene IKC F2 also came up as one of

NOTE Confidence: 0.814018251785714

00:26:48.288 --> 00:26:50.564 the most differentially expressed an

NOTE Confidence: 0.814018251785714

00:26:50.564 --> 00:26:52.919 associated genes along the trajectory.

NOTE Confidence: 0.792839808333333

00:26:55.920 --> 00:26:57.438 We can also ask the question,

NOTE Confidence: 0.792839808333333

00:26:57.440 --> 00:26:59.617 so if we think that these are

NOTE Confidence: 0.792839808333333

00:26:59.617 --> 00:27:01.200 regulatory cells within the blood,

NOTE Confidence: 0.792839808333333

00:27:01.200 --> 00:27:02.755 do they maintain their transcriptional

NOTE Confidence: 0.792839808333333

00:27:02.755 --> 00:27:03.999 state within the tumor?

NOTE Confidence: 0.792839808333333

00:27:04.000 --> 00:27:05.770 And in essence we're trying to

NOTE Confidence: 0.792839808333333

00:27:05.770 --> 00:27:07.160 understand what might there be,

NOTE Confidence: 0.792839808333333

00:27:07.160 --> 00:27:09.692 what might be their role within

NOTE Confidence: 0.792839808333333

00:27:09.692 --> 00:27:10.958 the tumor microenvironment.

NOTE Confidence: 0.792839808333333

00:27:10.960 --> 00:27:12.589 And So what we can do is we can

NOTE Confidence: 0.792839808333333

00:27:12.589 --> 00:27:14.193 trace these cells based off of

NOTE Confidence: 0.792839808333333

00:27:14.193 --> 00:27:15.563 their T cell receptor sequences

NOTE Confidence: 0.792839808333333

00:27:15.618 --> 00:27:17.676 back into the tumor and look at

NOTE Confidence: 0.792839808333333

00:27:17.676 --> 00:27:18.558 the transcriptional profile.

NOTE Confidence: 0.792839808333333

00:27:18.560 --> 00:27:20.730 And what we see is that this

NOTE Confidence: 0.792839808333333

00:27:20.730 --> 00:27:22.291 Kerr CD8T cell transcriptional

NOTE Confidence: 0.792839808333333

00:27:22.291 --> 00:27:23.959 profile is largely maintained

NOTE Confidence: 0.792839808333333

00:27:23.959 --> 00:27:26.189 within these sister clones within

NOTE Confidence: 0.792839808333333

00:27:26.189 --> 00:27:27.560 the tumor microenvironment.

NOTE Confidence: 0.801193888888889

00:27:29.600 --> 00:27:32.432 We have ongoing work in collaboration

NOTE Confidence: 0.801193888888889

00:27:32.432 --> 00:27:35.137 with Doctor Marcello Distasio and the

NOTE Confidence: 0.801193888888889

00:27:35.137 --> 00:27:37.357 Department of Pathology to try and

NOTE Confidence: 0.801193888888889

00:27:37.360 --> 00:27:39.712 better characterize these histologically

NOTE Confidence: 0.801193888888889

00:27:39.712 --> 00:27:42.064 using spatial multiomic analysis

NOTE Confidence: 0.801193888888889

00:27:42.064 --> 00:27:45.079 in the tumor micro environment.

NOTE Confidence: 0.885015861666667

00:27:47.680 --> 00:27:49.342 And so just to conclude from

NOTE Confidence: 0.885015861666667

00:27:49.342 --> 00:27:51.039 the 2nd portion of the talk,

NOTE Confidence: 0.885015861666667

00:27:51.040 --> 00:27:52.872 we've demonstrated that transcriptional

NOTE Confidence: 0.885015861666667

00:27:52.872 --> 00:27:55.162 signatures can identify a subset

NOTE Confidence: 0.885015861666667

00:27:55.162 --> 00:27:57.546 of tumor reactive T cells which

NOTE Confidence: 0.885015861666667

00:27:57.546 --> 00:27:59.038 are not clonally expanded.

NOTE Confidence: 0.885015861666667

00:27:59.040 --> 00:28:00.705 Differential abundance techniques

NOTE Confidence: 0.885015861666667

00:28:00.705 --> 00:28:03.480 can help us identify subpopulation

NOTE Confidence: 0.885015861666667

00:28:03.480 --> 00:28:06.539 of these reactive T cells which

NOTE Confidence: 0.885015861666667

00:28:06.539 --> 00:28:09.016 largely resemble Kerr CD8 regulatory

NOTE Confidence: 0.885015861666667

00:28:09.016 --> 00:28:11.485 T cells and that these Kerr CD8T

NOTE Confidence: 0.885015861666667

00:28:11.485 --> 00:28:13.385 cells seem to represent a distinct

NOTE Confidence: 0.885015861666667

00:28:13.385 --> 00:28:15.350 differentiation state which is preserved

NOTE Confidence: 0.885015861666667

00:28:15.350 --> 00:28:17.680 in the tumor micro environment.

NOTE Confidence: 0.913466303333333

00:28:21.040 --> 00:28:23.329 And so an important question for us

NOTE Confidence: 0.913466303333333

00:28:23.329 --> 00:28:25.665 is what is the clinical relevance

NOTE Confidence: 0.913466303333333

00:28:25.665 --> 00:28:28.067 of this T cell population And

NOTE Confidence: 0.913466303333333

00:28:28.067 --> 00:28:29.669 because we can't perform single cell

NOTE Confidence: 0.913466303333333

00:28:29.669 --> 00:28:31.438 sequencing on all of our our patients,

NOTE Confidence: 0.913466303333333

00:28:31.440 --> 00:28:33.876 we really wanted to move towards

NOTE Confidence: 0.913466303333333

00:28:33.880 --> 00:28:36.035 markers that could be assessed

NOTE Confidence: 0.913466303333333

00:28:36.035 --> 00:28:37.759 within the chemical laboratory.

NOTE Confidence: 0.913466303333333

00:28:37.760 --> 00:28:38.960 I'm specifically referring

NOTE Confidence: 0.913466303333333

00:28:38.960 --> 00:28:40.560 to using flow cytometry.

NOTE Confidence: 0.913466303333333

00:28:40.560 --> 00:28:42.912 And So what we wanted to do is

NOTE Confidence: 0.913466303333333

00:28:42.912 --> 00:28:44.721 to move from transcriptional

NOTE Confidence: 0.913466303333333

00:28:44.721 --> 00:28:47.468 features over to protein level

NOTE Confidence: 0.913466303333333

00:28:47.468 --> 00:28:50.552 cell surface features which are pre

NOTE Confidence: 0.913466303333333

00:28:50.552 --> 00:28:52.999 conventionally used in flow cytometry.

NOTE Confidence: 0.913466303333333

00:28:53.000 --> 00:28:54.596 And in order to do so,

NOTE Confidence: 0.913466303333333

00:28:54.600 --> 00:28:57.300 we collaborated with Doctor Steve

NOTE Confidence: 0.913466303333333

00:28:57.300 --> 00:28:59.776 Moss Group and Yuan Shin Chan and

NOTE Confidence: 0.913466303333333

00:28:59.776 --> 00:29:01.375 Ji Ping Wang are post docs and

NOTE Confidence: 0.913466303333333

00:29:01.375 --> 00:29:02.971 graduate students in his lab who

NOTE Confidence: 0.913466303333333

00:29:02.971 --> 00:29:04.439 primarily worked on this project.

NOTE Confidence: 0.913466303333333

00:29:04.440 --> 00:29:08.064 And we asked them to see whether or

NOTE Confidence: 0.913466303333333

00:29:08.064 --> 00:29:10.752 not they can construct A classifier

NOTE Confidence: 0.913466303333333

00:29:10.752 --> 00:29:13.118 that is limited to clinical

NOTE Confidence: 0.913466303333333

00:29:13.118 --> 00:29:15.860 variables and also genes that are

NOTE Confidence: 0.913466303333333

00:29:15.942 --> 00:29:18.878 specifically associated with protein

NOTE Confidence: 0.913466303333333

00:29:18.880 --> 00:29:21.079 cell surface proteins.

NOTE Confidence: 0.913466303333333

00:29:21.080 --> 00:29:23.840 We also restrict ourselves to

NOTE Confidence: 0.913466303333333

00:29:23.840 --> 00:29:26.408 genes which are known to correlate

NOTE Confidence: 0.913466303333333

00:29:26.408 --> 00:29:28.577 both at the transcriptional level

NOTE Confidence: 0.913466303333333

00:29:28.577 --> 00:29:30.477 and also the protein level,

NOTE Confidence: 0.913466303333333

00:29:30.480 --> 00:29:32.321 and so they use a they construct

NOTE Confidence: 0.913466303333333

00:29:32.321 --> 00:29:33.877 A LASSO logistic regression model

NOTE Confidence: 0.913466303333333

00:29:33.877 --> 00:29:35.647 which can accurately predict or

NOTE Confidence: 0.913466303333333

00:29:35.647 --> 00:29:37.673 classify cells as being likely

NOTE Confidence: 0.913466303333333

00:29:37.673 --> 00:29:40.838 within our subpopulation or not.

NOTE Confidence: 0.913466303333333

00:29:40.840 --> 00:29:43.185 And when we then apply this back

NOTE Confidence: 0.913466303333333

00:29:43.185 --> 00:29:45.240 into our single cell data set,

NOTE Confidence: 0.913466303333333

00:29:45.240 --> 00:29:48.999 what we find is that this tumor reactive

NOTE Confidence: 0.913466303333333

00:29:48.999 --> 00:29:52.197 or CDAT cell population seems to

NOTE Confidence: 0.913466303333333

00:29:52.200 --> 00:29:54.000 be associated with the poor survival.

NOTE Confidence: 0.913466303333333

00:29:54.000 --> 00:29:56.480 And what we did here was we simply

NOTE Confidence: 0.913466303333333

00:29:56.480 --> 00:29:58.634 split our cohort into a high

NOTE Confidence: 0.913466303333333

00:29:58.634 --> 00:30:01.089 expressing group and a low expressing

NOTE Confidence: 0.913466303333333

00:30:01.089 --> 00:30:03.840 group using a median cut point.

NOTE Confidence: 0.913466303333333

00:30:03.840 --> 00:30:06.008 And what I can tell you is that

NOTE Confidence: 0.913466303333333

00:30:06.008 --> 00:30:08.272 it doesn't matter whether or not

NOTE Confidence: 0.913466303333333

00:30:08.272 --> 00:30:09.924 these patients were immunotherapy

NOTE Confidence: 0.913466303333333

00:30:09.924 --> 00:30:12.439 naive or immunotherapy resistance.

NOTE Confidence: 0.913466303333333

00:30:12.440 --> 00:30:15.120 The mere presence of these cells seem to

NOTE Confidence: 0.913466303333333

00:30:15.120 --> 00:30:17.599 be associated with worst overall survival.

NOTE Confidence: 0.933140132

00:30:22.080 --> 00:30:25.040 Moving towards applying our classifier,

NOTE Confidence: 0.933140132

00:30:25.040 --> 00:30:28.238 applying these features to flow cytometry,

NOTE Confidence: 0.933140132

00:30:28.240 --> 00:30:31.159 we then asked them whether they can

NOTE Confidence: 0.933140132

00:30:31.160 --> 00:30:34.812 construct a hierarchy of these the

NOTE Confidence: 0.933140132

00:30:34.812 --> 00:30:36.804 these genes and protein markers in

NOTE Confidence: 0.933140132

00:30:36.804 --> 00:30:39.589 order for us to be able to develop

NOTE Confidence: 0.933140132

00:30:39.589 --> 00:30:41.240 combinations of markers that we

NOTE Confidence: 0.933140132

00:30:41.240 --> 00:30:42.840 can assess on flow cytometry.

NOTE Confidence: 0.70706884

00:30:44.880 --> 00:30:47.440 And so the first use single

NOTE Confidence: 0.70706884

00:30:47.440 --> 00:30:50.091 cell data that we had generated,

NOTE Confidence: 0.70706884

00:30:50.091 --> 00:30:52.346 but this includes protein level

NOTE Confidence: 0.70706884

00:30:52.346 --> 00:30:54.879 expression that from site seek data.

NOTE Confidence: 0.70706884

00:30:54.880 --> 00:30:57.260 And what I'm showing you here is

NOTE Confidence: 0.70706884

00:30:57.260 --> 00:31:00.644 that the the expression of KRD one

NOTE Confidence: 0.70706884

00:31:00.644 --> 00:31:04.992 as an example that the the site seek

NOTE Confidence: 0.70706884

00:31:04.992 --> 00:31:07.312 expression is relatively similar to

NOTE Confidence: 0.70706884

00:31:07.312 --> 00:31:10.596 what we would see on flow cytometry.

NOTE Confidence: 0.70706884

00:31:10.600 --> 00:31:12.630 We then constructed a decision

NOTE Confidence: 0.70706884

00:31:12.630 --> 00:31:15.093 tree model which allows us to

NOTE Confidence: 0.70706884

00:31:15.093 --> 00:31:17.216 assign a hierarchy and summarizes

NOTE Confidence: 0.70706884

00:31:17.216 --> 00:31:20.000 a combination of markers.

NOTE Confidence: 0.70706884

00:31:20.000 --> 00:31:21.560 And using this model and this,

NOTE Confidence: 0.70706884

00:31:21.560 --> 00:31:24.040 these, this combination of markers,

NOTE Confidence: 0.70706884

00:31:24.040 --> 00:31:26.984 we can accurately classify

NOTE Confidence: 0.70706884

00:31:26.984 --> 00:31:28.560 cells 91% of the time.

NOTE Confidence: 0.843501225789474

00:31:30.680 --> 00:31:33.384 And with the caveat that this is still

NOTE Confidence: 0.843501225789474

00:31:33.384 --> 00:31:35.792 ongoing work and that we have short

NOTE Confidence: 0.843501225789474

00:31:35.792 --> 00:31:37.836 interval fall for this exploratory cohort,

NOTE Confidence: 0.843501225789474

00:31:37.836 --> 00:31:40.342 we do see an early trend in

NOTE Confidence: 0.843501225789474

00:31:40.342 --> 00:31:42.214 separation curves that is in line

NOTE Confidence: 0.843501225789474

00:31:42.214 --> 00:31:44.160 with what we were seeing before.

NOTE Confidence: 0.843501225789474

00:31:44.160 --> 00:31:46.841 That is those who have a higher

NOTE Confidence: 0.843501225789474

00:31:46.841 --> 00:31:48.558 proportion of this subpopulation

NOTE Confidence: 0.843501225789474

00:31:48.558 --> 00:31:53.240 seem to have worse clinical outcome.

NOTE Confidence: 0.843501225789474

00:31:53.240 --> 00:31:55.952 And to validate both our transcriptional

NOTE Confidence: 0.843501225789474

00:31:55.952 --> 00:31:59.318 data and also our protein level data,

NOTE Confidence: 0.843501225789474

00:31:59.320 --> 00:32:00.490 we are collaborating.

NOTE Confidence: 0.843501225789474

00:32:00.490 --> 00:32:02.050 We established A collaboration

NOTE Confidence: 0.843501225789474

00:32:02.050 --> 00:32:03.596 with Doctor Benjamin Fairfax

NOTE Confidence: 0.843501225789474

00:32:03.596 --> 00:32:05.196 at the University of Oxford.

NOTE Confidence: 0.843501225789474

00:32:05.200 --> 00:32:08.386 He's a Melanoma oncologist who has

NOTE Confidence: 0.843501225789474

00:32:08.386 --> 00:32:11.057 generated bulk RNA sequencing data

NOTE Confidence: 0.843501225789474

00:32:11.057 --> 00:32:13.841 and also flow cytometry data from

NOTE Confidence: 0.843501225789474

00:32:13.841 --> 00:32:16.120 over 200 patients with Melanoma

NOTE Confidence: 0.843501225789474

00:32:16.120 --> 00:32:18.760 prior to treatment also on treatment.

NOTE Confidence: 0.843501225789474

00:32:18.760 --> 00:32:21.660 And so we're looking forward

NOTE Confidence: 0.843501225789474

00:32:21.660 --> 00:32:23.239 to seeing those results.

NOTE Confidence: 0.8908728

00:32:26.160 --> 00:32:28.800 And so just to summarize,

NOTE Confidence: 0.8908728

00:32:28.800 --> 00:32:30.738 we believe that the induction of

NOTE Confidence: 0.8908728

00:32:30.738 --> 00:32:32.463 systemic immunity is really a

NOTE Confidence: 0.8908728

00:32:32.463 --> 00:32:33.971 critical component to successful

NOTE Confidence: 0.8908728

00:32:33.971 --> 00:32:35.479 anti tumor immune responses,

NOTE Confidence: 0.8908728

00:32:35.480 --> 00:32:37.260 but that clinical biomarkers

NOTE Confidence: 0.8908728

00:32:37.260 --> 00:32:41.110 which allow us to profile on this

NOTE Confidence: 0.8908728

00:32:41.110 --> 00:32:44.560 population remains an unmet need.

NOTE Confidence: 0.8908728

00:32:44.560 --> 00:32:46.390 We use single cell technologies

NOTE Confidence: 0.8908728

00:32:46.390 --> 00:32:48.648 to try and provide insights into

NOTE Confidence: 0.8908728

00:32:48.648 --> 00:32:50.448 the relationship between T cells

NOTE Confidence: 0.8908728

00:32:50.448 --> 00:32:52.635 within the tumor and those within

NOTE Confidence: 0.8908728

00:32:52.635 --> 00:32:54.892 the blood and that we've identified

NOTE Confidence: 0.8908728

00:32:54.892 --> 00:32:56.857 a subpopulation of tumor reactive

NOTE Confidence: 0.8908728

00:32:56.857 --> 00:32:59.215 Cur CD8 regulatory T cells which

NOTE Confidence: 0.8908728

00:32:59.215 --> 00:33:01.115 may actually suppress anti tumor

NOTE Confidence: 0.8908728

00:33:01.185 --> 00:33:03.181 immunity and negatively correlate

NOTE Confidence: 0.8908728

00:33:03.181 --> 00:33:04.678 with clinical outcome.

NOTE Confidence: 0.8908728

00:33:04.680 --> 00:33:06.720 I think this is largely exploratory,

NOTE Confidence: 0.8908728

00:33:06.720 --> 00:33:09.120 but you know potentially if we

NOTE Confidence: 0.8908728

00:33:09.120 --> 00:33:11.344 can identify this cell population

NOTE Confidence: 0.8908728

00:33:11.344 --> 00:33:13.520 within a clinical cohort,

NOTE Confidence: 0.8908728

00:33:13.520 --> 00:33:14.360 we may be able to

NOTE Confidence: 0.935832312

00:33:16.720 --> 00:33:18.560 explore a new therapeutic Ave.

NOTE Confidence: 0.935832312

00:33:18.560 --> 00:33:20.040 for targeting these cells.

NOTE Confidence: 0.947023780952381

00:33:22.560 --> 00:33:24.080 And so with that I'd like to just

NOTE Confidence: 0.947023780952381

00:33:24.080 --> 00:33:25.896 take a moment to acknowledge all the

NOTE Confidence: 0.947023780952381

00:33:25.896 --> 00:33:27.760 people who've made this work possible.

NOTE Confidence: 0.947023780952381

00:33:27.760 --> 00:33:29.461 I think first and foremost we need

NOTE Confidence: 0.947023780952381

00:33:29.461 --> 00:33:30.879 to acknowledge the patients and

NOTE Confidence: 0.947023780952381

00:33:30.879 --> 00:33:32.880 families who are very generous in

NOTE Confidence: 0.947023780952381

00:33:32.880 --> 00:33:34.560 donating their tissue and blood.

NOTE Confidence: 0.947023780952381

00:33:34.560 --> 00:33:36.560 But also I'd like to thank them and

NOTE Confidence: 0.947023780952381

00:33:36.560 --> 00:33:38.090 acknowledge them just for the motivation

NOTE Confidence: 0.947023780952381

00:33:38.090 --> 00:33:40.221 that they provide all of us for the work

NOTE Confidence: 0.947023780952381

00:33:40.221 --> 00:33:43.360 that we do in the clinic, in the lab.

NOTE Confidence: 0.947023780952381

00:33:43.360 --> 00:33:45.280 And also like to thank my mentors Dr.

NOTE Confidence: 0.947023780952381

00:33:45.280 --> 00:33:46.495 Hathor and Dr.

NOTE Confidence: 0.947023780952381

00:33:46.495 --> 00:33:48.520 Kruger for their unending support

NOTE Confidence: 0.947023780952381

00:33:48.520 --> 00:33:50.639 and really the opportunity to

NOTE Confidence: 0.947023780952381

00:33:50.640 --> 00:33:53.360 perform this research in addition

NOTE Confidence: 0.947023780952381

00:33:53.360 --> 00:33:55.160 to members of the halfway lab.

NOTE Confidence: 0.947023780952381

00:33:55.160 --> 00:33:58.632 So Liliana Luca had mentioned before is

NOTE Confidence: 0.947023780952381

00:33:58.632 --> 00:34:00.962 a independent investigator in France.

NOTE Confidence: 0.947023780952381

00:34:00.962 --> 00:34:04.330 Pierre, Paul and Nick were also essential and

NOTE Confidence: 0.947023780952381

00:34:04.412 --> 00:34:07.800 instrumental in generating data on the study.

NOTE Confidence: 0.947023780952381

00:34:07.800 --> 00:34:09.288 Our collaborators both internally

NOTE Confidence: 0.947023780952381

00:34:09.288 --> 00:34:11.520 here at Yale and also externally.

NOTE Confidence: 0.947023780952381

00:34:11.520 --> 00:34:13.530 So I'm Doctor Yuval Kluger's group

NOTE Confidence: 0.947023780952381

00:34:13.530 --> 00:34:16.157 and Wes Lewis's Wes Lewis for their

NOTE Confidence: 0.947023780952381

00:34:16.157 --> 00:34:18.192 work on the Differential Abundance

NOTE Confidence: 0.947023780952381

00:34:18.192 --> 00:34:20.514 analysis and Steve Ma Yuan Shin Chen

NOTE Confidence: 0.947023780952381

00:34:20.514 --> 00:34:24.040 G Ping Wang for their work on our

NOTE Confidence: 0.947023780952381

00:34:24.040 --> 00:34:25.840 constructing biomarker classifiers.

NOTE Confidence: 0.947023780952381

00:34:25.840 --> 00:34:28.080 As I mentioned before,

NOTE Confidence: 0.947023780952381

00:34:28.080 --> 00:34:29.200 Martello Distasio,

NOTE Confidence: 0.947023780952381

00:34:29.200 --> 00:34:31.060 we have an ongoing collaboration

NOTE Confidence: 0.947023780952381

00:34:31.060 --> 00:34:32.920 to explore the spatial orientation

NOTE Confidence: 0.947023780952381

00:34:32.983 --> 00:34:34.981 of the cell population and Doctor

NOTE Confidence: 0.947023780952381

00:34:34.981 --> 00:34:39.399 Benjamin Fairfax is a collaborator

NOTE Confidence: 0.947023780952381

00:34:39.399 --> 00:34:43.012 who's going to help us explore this

NOTE Confidence: 0.947023780952381

00:34:43.012 --> 00:34:45.077 population in a larger cohort.

NOTE Confidence: 0.947023780952381

00:34:45.080 --> 00:34:47.120 I'd also like to acknowledge our

NOTE Confidence: 0.947023780952381

00:34:47.120 --> 00:34:49.120 collaborators at Repertoire Immune Medicines,

NOTE Confidence: 0.947023780952381

00:34:49.120 --> 00:34:52.836 in addition to the Yale Skins Board whose

NOTE Confidence: 0.947023780952381

00:34:52.836 --> 00:34:57.120 support has really made this effort feasible,

NOTE Confidence: 0.947023780952381

00:34:57.120 --> 00:34:59.919 and also to the core facilities here at Yale.

NOTE Confidence: 0.947023780952381

00:34:59.920 --> 00:35:01.404 And a personal thank you to both

NOTE Confidence: 0.947023780952381

00:35:01.404 --> 00:35:02.840 David Braun and David Schoenfeld,

NOTE Confidence: 0.947023780952381

00:35:02.840 --> 00:35:03.935 who unfortunately couldn't

NOTE Confidence: 0.947023780952381

00:35:03.935 --> 00:35:05.760 be here in person today.

NOTE Confidence: 0.947023780952381

00:35:05.760 --> 00:35:07.674 But they were incredibly generous and

NOTE Confidence: 0.947023780952381

00:35:07.674 --> 00:35:09.812 help with their thoughts and also with

NOTE Confidence: 0.947023780952381

00:35:09.812 --> 00:35:11.688 their time in helping prepare for this

NOTE Confidence: 0.947023780952381

00:35:11.741 --> 00:35:13.836 presentation and also for my funding sources,

NOTE Confidence: 0.947023780952381

00:35:13.840 --> 00:35:15.160 the T32 and the K12,

NOTE Confidence: 0.947023780952381

00:35:15.160 --> 00:35:17.840 as Harry had mentioned before.

NOTE Confidence: 0.947023780952381

00:35:17.840 --> 00:35:18.080 OK.

NOTE Confidence: 0.947023780952381

00:35:18.080 --> 00:35:19.760 I'd be happy to take any questions.

NOTE Confidence: 0.733990485

00:35:26.280 --> 00:35:27.780 Thank you, Ben, for a

NOTE Confidence: 0.733990485

00:35:27.780 --> 00:35:30.520 terrific talk. Any questions?

NOTE Confidence: 0.7409618

00:35:32.920 --> 00:35:35.680 So while people, so we have a few online.

NOTE Confidence: 0.7409618

00:35:35.680 --> 00:35:40.480 Oh yeah, let's do that. Yeah. So

NOTE Confidence: 0.89712026125

00:35:40.480 --> 00:35:41.880 I don't know if people want to unmute,

NOTE Confidence: 0.89712026125

00:35:41.880 --> 00:35:45.960 but I see that SRIVATAM,

NOTE Confidence: 0.89712026125

00:35:45.960 --> 00:35:47.892 has there been an effort to isolate

NOTE Confidence: 0.89712026125

00:35:47.892 --> 00:35:48.720 and phenotypically characterize

NOTE Confidence: 0.89712026125

00:35:48.768 --> 00:35:49.800 these current CDAT cells?

NOTE Confidence: 0.89712026125

00:35:49.800 --> 00:35:51.800 I'm curious to understand the

NOTE Confidence: 0.89712026125

00:35:51.800 --> 00:35:53.800 uncommon state of CDAT cells.

NOTE Confidence: 0.89712026125

00:35:53.800 --> 00:35:55.557 So yes, there has been work in

NOTE Confidence: 0.89712026125

00:35:55.557 --> 00:35:57.084 other contexts to do that and

NOTE Confidence: 0.89712026125

00:35:57.084 --> 00:35:58.512 I didn't show the data today,

NOTE Confidence: 0.89712026125

00:35:58.520 --> 00:36:01.040 but we have also done that

NOTE Confidence: 0.89712026125

00:36:01.040 --> 00:36:03.329 in Melanoma and have largely

NOTE Confidence: 0.89712026125

00:36:03.329 --> 00:36:05.744 validated the the protein level

NOTE Confidence: 0.89712026125

00:36:05.744 --> 00:36:07.639 immunophenotypes of these cells.

NOTE Confidence: 0.869647367142857

00:36:10.040 --> 00:36:13.596 The next question is from Marcus Bosenberg.

NOTE Confidence: 0.869647367142857

00:36:13.600 --> 00:36:16.144 He has do you have a hypothesis as

NOTE Confidence: 0.869647367142857

00:36:16.144 --> 00:36:18.876 to how Cur CDA regulatory T cells

NOTE Confidence: 0.869647367142857

00:36:18.880 --> 00:36:21.320 negatively affect anti cancer

NOTE Confidence: 0.869647367142857

00:36:21.320 --> 00:36:23.760 immune responses and outcome.

NOTE Confidence: 0.869647367142857

00:36:23.760 --> 00:36:26.226 You know I think the mechanism

NOTE Confidence: 0.869647367142857

00:36:26.226 --> 00:36:28.999 for these Cur CDA T cells is still

NOTE Confidence: 0.869647367142857

00:36:28.999 --> 00:36:30.880 really not fully understood.

NOTE Confidence: 0.869647367142857

00:36:30.880 --> 00:36:33.700 The hypothesis has kind of demonstrated

NOTE Confidence: 0.869647367142857

00:36:33.700 --> 00:36:37.247 here on this side or our hypothesis

NOTE Confidence: 0.869647367142857

00:36:37.247 --> 00:36:39.877 is that they're somehow impacting

NOTE Confidence: 0.869647367142857

00:36:39.880 --> 00:36:42.220 tumor antigen specific CDAT cells

NOTE Confidence: 0.869647367142857

00:36:42.220 --> 00:36:44.560 in the tumor micro environment.

NOTE Confidence: 0.869647367142857

00:36:44.560 --> 00:36:47.632 I'm currently in the process of setting up

NOTE Confidence: 0.869647367142857

00:36:47.632 --> 00:36:52.840 assays to try and assess this functionally,

NOTE Confidence: 0.869647367142857

00:36:52.840 --> 00:36:55.234 but my guess would be and it's

NOTE Confidence: 0.869647367142857

00:36:55.234 --> 00:36:56.915 also possible that they're

NOTE Confidence: 0.869647367142857

00:36:56.915 --> 00:36:58.800 they're impacting CD4T cells,

NOTE Confidence: 0.869647367142857

00:36:58.800 --> 00:37:01.200 which is a more direct link from

NOTE Confidence: 0.869647367142857

00:37:01.200 --> 00:37:02.160 the autoimmunity literature.

NOTE Confidence: 0.869647367142857

00:37:02.160 --> 00:37:06.342 But we're first going to explore the

NOTE Confidence: 0.869647367142857

00:37:06.342 --> 00:37:08.714 CDA component because of this negative

NOTE Confidence: 0.869647367142857

00:37:08.714 --> 00:37:11.554 in fact impact that we see in tumors.

NOTE Confidence: 0.869647367142857

00:37:11.560 --> 00:37:13.198 And then the last question was are

NOTE Confidence: 0.869647367142857

00:37:13.198 --> 00:37:14.696 these cells called regulatory based

NOTE Confidence: 0.869647367142857

00:37:14.696 --> 00:37:16.196 on their transcriptional features.

NOTE Confidence: 0.869647367142857

00:37:16.200 --> 00:37:21.028 So this cell population was as I

NOTE Confidence: 0.869647367142857

00:37:21.028 --> 00:37:24.359 mentioned described both in mice and

NOTE Confidence: 0.869647367142857

00:37:24.359 --> 00:37:27.279 also in human autoimmunity infection

NOTE Confidence: 0.869647367142857

00:37:27.280 --> 00:37:30.040 because they are able to actually

NOTE Confidence: 0.869647367142857

00:37:30.040 --> 00:37:34.720 functionally kill autoreactive T cells.

NOTE Confidence: 0.869647367142857

00:37:34.720 --> 00:37:36.519 And so it's not simply just based

NOTE Confidence: 0.869647367142857

00:37:36.519 --> 00:37:37.760 off of transcriptional features,

NOTE Confidence: 0.869647367142857

00:37:37.760 --> 00:37:40.392 although our data is certainly inferring

NOTE Confidence: 0.869647367142857

00:37:40.392 --> 00:37:42.120 from the transcriptional expression.

NOTE Confidence: 0.930382

00:37:45.080 --> 00:37:46.240 I actually have a follow

NOTE Confidence: 0.930382

00:37:46.240 --> 00:37:47.240 up question to Marcus's.

NOTE Confidence: 0.930479644

00:37:47.240 --> 00:37:50.264 Do you think that these are positive

NOTE Confidence: 0.930479644

00:37:50.264 --> 00:37:52.580 CDAT cells might stick and you can

NOTE Confidence: 0.930479644

00:37:52.580 --> 00:37:54.200 revert them to the per negative

NOTE Confidence: 0.367189963333333

00:37:55.800 --> 00:37:57.360 being A tag even because there

NOTE Confidence: 0.72058736

00:37:57.360 --> 00:37:59.568 are antibodies that have been actually

NOTE Confidence: 0.72058736

00:37:59.568 --> 00:38:01.559 given to humans that do that.

NOTE Confidence: 0.893781492

00:38:02.000 --> 00:38:06.400 Yeah. So I think the NKG 2DA

NOTE Confidence: 0.893781492

00:38:06.400 --> 00:38:10.084 antibodies which impact the the kind

NOTE Confidence: 0.893781492

00:38:10.084 --> 00:38:12.039 of analogous Co stimulatory molecule,

NOTE Confidence: 0.893781492

00:38:12.040 --> 00:38:14.253 not the Co inhibitory molecule have

NOTE Confidence: 0.893781492

00:38:14.253 --> 00:38:16.304 been tried and I don't think the

NOTE Confidence: 0.893781492

00:38:16.304 --> 00:38:18.680 data has been all that great for it.

NOTE Confidence: 0.893781492

00:38:18.680 --> 00:38:20.900 But in terms of the plasticity

NOTE Confidence: 0.893781492

00:38:20.900 --> 00:38:22.456 of this cell type,

NOTE Confidence: 0.893781492

00:38:22.456 --> 00:38:24.904 I think especially based off of

NOTE Confidence: 0.893781492

00:38:24.904 --> 00:38:26.538 our the trajectory analysis,

NOTE Confidence: 0.893781492

00:38:26.538 --> 00:38:29.302 I think that it is interesting to try and

NOTE Confidence: 0.893781492

00:38:29.302 --> 00:38:31.320 explore how plastic the cell population is.

NOTE Confidence: 0.893781492

00:38:31.320 --> 00:38:33.308 It does seem like there's a branch

NOTE Confidence: 0.893781492

00:38:33.308 --> 00:38:33.876 differentiation trajectory,

NOTE Confidence: 0.893781492

00:38:33.880 --> 00:38:37.773 but we just don't understand quite yet how

NOTE Confidence: 0.893781492

00:38:37.773 --> 00:38:39.639 these cells are really being generated,

NOTE Confidence: 0.893781492

00:38:39.640 --> 00:38:44.100 what it under what context and to

NOTE Confidence: 0.893781492

00:38:44.100 --> 00:38:45.960 really truly demonstrate their function, just

NOTE Confidence: 0.536440836666667

00:38:52.160 --> 00:38:53.558 speak up. Yeah.

NOTE Confidence: 0.536440836666667

00:38:53.560 --> 00:38:56.560 So with this model in mind, when you

NOTE Confidence: 0.536440836666667

00:38:56.560 --> 00:38:59.400 look at cohorts that are receiving IO,

NOTE Confidence: 0.536440836666667

00:38:59.400 --> 00:39:01.930 there's a relationship between force

NOTE Confidence: 0.536440836666667

00:39:01.930 --> 00:39:04.712 survival and curve positive cell

NOTE Confidence: 0.536440836666667

00:39:04.712 --> 00:39:06.798 strength compared to if you look at

NOTE Confidence: 0.536440836666667

00:39:06.800 --> 00:39:09.120 cohorts that aren't receiving IO.

NOTE Confidence: 0.536440836666667

00:39:09.120 --> 00:39:12.080 Yeah. So the the P value remains about

NOTE Confidence: 0.536440836666667

00:39:12.080 --> 00:39:14.879 the same actually in both cohorts.

NOTE Confidence: 0.536440836666667

00:39:14.880 --> 00:39:18.370 And I think that that that's

NOTE Confidence: 0.536440836666667

00:39:18.370 --> 00:39:19.914 a really interesting point.

NOTE Confidence: 0.536440836666667

00:39:19.920 --> 00:39:23.090 But whether there's a subpopation of

NOTE Confidence: 0.536440836666667

00:39:23.090 --> 00:39:25.160 patients where this is a primary,

NOTE Confidence: 0.536440836666667

00:39:25.160 --> 00:39:26.792 I mean secondary resistance

NOTE Confidence: 0.536440836666667

00:39:26.792 --> 00:39:29.240 mechanism I think is worth exploring

NOTE Confidence: 0.6939328

00:39:31.360 --> 00:39:33.440 wonderful talk. The these care

NOTE Confidence: 0.76237798

00:39:34.080 --> 00:39:35.604 suppressor cells that Mark

NOTE Confidence: 0.76237798

00:39:35.604 --> 00:39:37.509 Davis identified a really hot

NOTE Confidence: 0.76237798

00:39:37.509 --> 00:39:39.100 issue in human immunology now.

NOTE Confidence: 0.76237798

00:39:39.100 --> 00:39:41.480 But just looking at the slide again,

NOTE Confidence: 0.76237798

00:39:41.480 --> 00:39:42.915 do you think the tumor reactive T

NOTE Confidence: 0.76237798

00:39:42.920 --> 00:39:44.474 cells may express the log in for

NOTE Confidence: 0.76237798

00:39:44.480 --> 00:39:47.040 digit CD155 and we looked at that,

NOTE Confidence: 0.925939972

00:39:48.480 --> 00:39:50.368 are you talking about the, the regulatory,

NOTE Confidence: 0.925939972

00:39:50.368 --> 00:39:52.640 so the cures in cells or the no,

NOTE Confidence: 0.925939972

00:39:52.640 --> 00:39:53.720 well, the ones on the left,

NOTE Confidence: 0.925939972

00:39:53.720 --> 00:39:56.330 well the the regulatory cells that

NOTE Confidence: 0.925939972

00:39:56.330 --> 00:39:58.400 care positive expressed digit,

NOTE Confidence: 0.925939972

00:39:58.400 --> 00:39:59.720 yes, they do. The ligand is

NOTE Confidence: 0.877962686666667

00:40:00.560 --> 00:40:02.125 CD155 and what we're learning

NOTE Confidence: 0.877962686666667

00:40:02.125 --> 00:40:04.279 about what CD155 engagement

NOTE Confidence: 0.877962686666667

00:40:04.280 --> 00:40:08.080 does to cancer cells as per PPG.

NOTE Confidence: 0.877962686666667

00:40:08.080 --> 00:40:10.616 I'm just wondering if CD155IS

NOTE Confidence: 0.877962686666667

00:40:10.616 --> 00:40:12.253 expressed on the tumor reactive

NOTE Confidence: 0.877962686666667

00:40:12.253 --> 00:40:14.000 T cells, we looked at that.

NOTE Confidence: 0.888810855384615

00:40:14.640 --> 00:40:16.488 I don't, I mean I'm I'm inferring

NOTE Confidence: 0.888810855384615

00:40:16.488 --> 00:40:18.079 we haven't directly looked at that,

NOTE Confidence: 0.888810855384615

00:40:18.080 --> 00:40:21.568 but I'm inferring and I'd be guessing that

NOTE Confidence: 0.888810855384615

00:40:21.568 --> 00:40:24.280 the expression if present is very low,

NOTE Confidence: 0.888810855384615

00:40:24.280 --> 00:40:26.800 but I think it's definitely worth exploring.

NOTE Confidence: 0.888810855384615

00:40:26.800 --> 00:40:28.417 I, I think the effects of anti

NOTE Confidence: 0.888810855384615

00:40:28.417 --> 00:40:30.234 tiggering anti PD one on the cell

NOTE Confidence: 0.888810855384615

00:40:30.234 --> 00:40:31.579 population for example is something

NOTE Confidence: 0.888810855384615

00:40:31.579 --> 00:40:33.560 that we can take a look at. Absolutely.

NOTE Confidence: 0.753736813636364

00:40:35.640 --> 00:40:37.025 Another question, have you done

NOTE Confidence: 0.753736813636364

00:40:37.025 --> 00:40:38.720 some of the analysis in other

NOTE Confidence: 0.753736813636364

00:40:38.720 --> 00:40:42.360 tumor types in the Lumpsor study?

NOTE Confidence: 0.753736813636364

00:40:42.360 --> 00:40:45.568 Do you see the same new cell

NOTE Confidence: 0.753736813636364

00:40:45.568 --> 00:40:47.280 population of CEA tumor?

NOTE Confidence: 0.792758676153846

00:40:48.200 --> 00:40:50.335 So I haven't so So for those

NOTE Confidence: 0.792758676153846

00:40:50.335 --> 00:40:52.358 who aren't able to hear online,

NOTE Confidence: 0.792758676153846

00:40:52.360 --> 00:40:53.788 Doctor Cleaver asks whether

NOTE Confidence: 0.792758676153846

00:40:53.788 --> 00:40:55.573 I've also found this cell

NOTE Confidence: 0.792758676153846

00:40:55.573 --> 00:40:57.160 population in other tumor types.

NOTE Confidence: 0.792758676153846

00:40:57.160 --> 00:40:58.360 I haven't specifically

NOTE Confidence: 0.792758676153846

00:40:58.360 --> 00:40:59.960 looked under this lens.

NOTE Confidence: 0.792758676153846

00:40:59.960 --> 00:41:04.308 You know, one of the the reasons why I

NOTE Confidence: 0.792758676153846

00:41:04.308 --> 00:41:06.520 think maybe if this population is real,

NOTE Confidence: 0.792758676153846

00:41:06.520 --> 00:41:09.508 it may not be as well described is because

NOTE Confidence: 0.792758676153846

00:41:09.508 --> 00:41:12.387 it has a large transcriptional overlap

NOTE Confidence: 0.792758676153846

00:41:12.387 --> 00:41:15.040 with other cytotoxic CDAT cell populations.

NOTE Confidence: 0.792758676153846

00:41:15.040 --> 00:41:18.190 And so we really need to look

NOTE Confidence: 0.792758676153846

00:41:18.190 --> 00:41:20.152 carefully The enrichment cures,

NOTE Confidence: 0.792758676153846

00:41:20.152 --> 00:41:23.360 for example, can be expressed

NOTE Confidence: 0.792758676153846

00:41:23.360 --> 00:41:26.360 on just activated CDAT cells.

NOTE Confidence: 0.792758676153846

00:41:26.360 --> 00:41:28.412 And so we really need to look a little

NOTE Confidence: 0.792758676153846

00:41:28.412 --> 00:41:30.360 bit more carefully at some of the

NOTE Confidence: 0.792758676153846

00:41:30.360 --> 00:41:32.520 other markers like it Grows or HELIOS.

NOTE Confidence: 0.454049656666667

00:41:36.960 --> 00:41:38.480 There is some more question online.

NOTE Confidence: 0.454049656666667

00:41:38.480 --> 00:41:40.280 So from the inside why

NOTE Confidence: 0.454049656666667

00:41:40.280 --> 00:41:41.999 cure CDAT cell products,

NOTE Confidence: 0.454049656666667

00:41:42.000 --> 00:41:45.293 can you prevent cure CDT cell product?

NOTE Confidence: 0.454049656666667

00:41:45.293 --> 00:41:48.280 I mean, I I apologize, I'm not,

NOTE Confidence: 0.454049656666667

00:41:48.280 --> 00:41:50.638 I'm not sure I fully understand.

NOTE Confidence: 0.454049656666667

00:41:50.640 --> 00:41:54.366 I'm not sure if you mean AT cell product

NOTE Confidence: 0.454049656666667

00:41:54.366 --> 00:41:57.157 that's targeting cure CDAT cells,

NOTE Confidence: 0.454049656666667

00:41:57.160 --> 00:41:59.245 not sure if you're available

NOTE Confidence: 0.454049656666667

00:41:59.245 --> 00:42:00.913 to unmute and discuss.

NOTE Confidence: 0.454049656666667

00:42:00.920 --> 00:42:05.257 But I I I do think that exploring a

NOTE Confidence: 0.454049656666667

00:42:05.257 --> 00:42:08.479 therapy that would target or impact

NOTE Confidence: 0.454049656666667

00:42:08.479 --> 00:42:10.760 these cells would be of interest. OK.

NOTE Confidence: 0.687682612

00:42:14.480 --> 00:42:16.040 Thank you everyone. Thank you.