WEBVTT

NOTE duration: ”00:10:00.466”

NOTE Confidence: 0.91541576

00:00:00.160 --> 00:00:01.760 To do is just briefly

NOTE Confidence: 0.91541576

00:00:01.760 --> 00:00:02.720 go over kind of our

NOTE Confidence: 0.91541576

00:00:02.720 --> 00:00:03.699 approach towards

NOTE Confidence: 0.94433737

00:00:04.880 --> 00:00:06.879 studying cancer immunology in humans.

NOTE Confidence: 0.94433737

00:00:06.879 --> 00:00:09.119 And my particular interest moving

NOTE Confidence: 0.94433737

00:00:09.119 --> 00:00:10.400 forward is going to be

NOTE Confidence: 0.94433737

00:00:10.400 --> 00:00:12.080 in studying immune and cancer

NOTE Confidence: 0.94433737

00:00:12.080 --> 00:00:13.620 cell interactions and how

NOTE Confidence: 0.81507313

00:00:13.920 --> 00:00:14.660 they shape

NOTE Confidence: 0.87508535

00:00:15.224 --> 00:00:17.005 anti tumor immunity overall.

NOTE Confidence: 0.9120966

00:00:18.185 --> 00:00:19.564 But we do this in

NOTE Confidence: 0.98489964

00:00:20.825 --> 00:00:22.265 by by first taking a

NOTE Confidence: 0.98489964

00:00:22.265 --> 00:00:23.085 look at

NOTE Confidence: 0.9061378

00:00:23.945 --> 00:00:26.505 patient specimens, clinical questions, relevant

NOTE Confidence: 0.9061378

00:00:26.505 --> 00:00:27.325 clinical questions,

NOTE Confidence: 0.99159664

00:00:27.945 --> 00:00:28.925 and then using

NOTE Confidence: 0.96442807

00:00:29.260 --> 00:00:30.960 techniques to try and understand

NOTE Confidence: 0.96442807

00:00:31.020 --> 00:00:33.100 fundamental aspects of human immunology.

NOTE Confidence: 0.96442807

00:00:33.100 --> 00:00:34.060 And so to do this,

NOTE Confidence: 0.96442807

00:00:34.060 --> 00:00:35.920 we first have simple questions

NOTE Confidence: 0.9119408

00:00:36.380 --> 00:00:38.060 using high dimensional techniques such

NOTE Confidence: 0.9119408

00:00:38.060 --> 00:00:39.280 as single cell sequencing.

NOTE Confidence: 0.90612006

00:00:40.540 --> 00:00:42.315 For example, what who are

NOTE Confidence: 0.90612006

00:00:42.315 --> 00:00:43.274 we looking at? What is

NOTE Confidence: 0.90612006

00:00:43.274 --> 00:00:44.015 the transcriptional,

NOTE Confidence: 0.94125295

00:00:44.875 --> 00:00:46.715 heterogeneity that is present within

NOTE Confidence: 0.94125295

00:00:46.715 --> 00:00:48.574 tumors and immune cells?

NOTE Confidence: 0.9697399

00:00:49.274 --> 00:00:50.394 What is the function and

NOTE Confidence: 0.9697399

00:00:50.394 --> 00:00:51.675 what is the interaction that's

NOTE Confidence: 0.9697399

00:00:51.675 --> 00:00:53.274 going? And in the case

NOTE Confidence: 0.9697399

00:00:53.274 --> 00:00:54.300 of t cells, which is

NOTE Confidence: 0.9697399

00:00:54.380 --> 00:00:55.280 where our biases

NOTE Confidence: 0.97790414

00:00:56.059 --> 00:00:57.020 lies, we then ask, you

NOTE Confidence: 0.97790414

00:00:57.020 --> 00:00:58.140 know, where else can we

NOTE Confidence: 0.97790414

00:00:58.140 --> 00:00:59.840 trace these t cells to?

NOTE Confidence: 0.87379074

00:01:00.300 --> 00:01:00.800 And,

NOTE Confidence: 0.8544438

00:01:02.300 --> 00:01:04.300 how are the microenvironment really

NOTE Confidence: 0.8544438

00:01:04.300 --> 00:01:04.800 influencing,

NOTE Confidence: 0.7800491

00:01:05.340 --> 00:01:07.360 Timur and Mindy? And, ultimately,

NOTE Confidence: 0.9994911

00:01:07.819 --> 00:01:08.319 with

NOTE Confidence: 0.96278

00:01:08.725 --> 00:01:10.325 the the phenotypes that we

NOTE Confidence: 0.96278

00:01:10.325 --> 00:01:11.465 identify and

NOTE Confidence: 0.78652436

00:01:11.924 --> 00:01:12.584 these fundamental

NOTE Confidence: 0.967977

00:01:13.125 --> 00:01:14.884 mechanisms that we identify, how

NOTE Confidence: 0.967977

00:01:14.884 --> 00:01:16.325 can we leverage this back

NOTE Confidence: 0.967977

00:01:16.325 --> 00:01:17.685 into the clinic for clinical

NOTE Confidence: 0.967977

00:01:17.685 --> 00:01:18.185 intervention?

NOTE Confidence: 0.9074853

00:01:18.884 --> 00:01:21.159 And so, one vignette I'd

NOTE Confidence: 0.9074853

00:01:21.159 --> 00:01:22.039 like to just bring up

NOTE Confidence: 0.9074853

00:01:22.039 --> 00:01:23.319 that's published that I'll briefly

NOTE Confidence: 0.9074853

00:01:23.319 --> 00:01:24.119 go over, and this is

NOTE Confidence: 0.9074853

00:01:24.119 --> 00:01:25.560 actually, a project I was

NOTE Confidence: 0.9074853

00:01:25.560 --> 00:01:27.020 co mentored with doctor Kluger

NOTE Confidence: 0.9074853

00:01:27.240 --> 00:01:28.539 and funded by the Skinspor,

NOTE Confidence: 0.9106652

00:01:29.959 --> 00:01:30.759 that we did in the

NOTE Confidence: 0.9106652

00:01:30.759 --> 00:01:31.259 extracranial

NOTE Confidence: 0.8836253

00:01:31.560 --> 00:01:33.420 setting with patients with melanoma.

NOTE Confidence: 0.97359735

00:01:34.200 --> 00:01:35.179 We first identified

NOTE Confidence: 0.99784064

00:01:35.479 --> 00:01:35.979 that

NOTE Confidence: 0.97044003

00:01:36.435 --> 00:01:36.935 there's

NOTE Confidence: 0.99970406

00:01:37.634 --> 00:01:38.134 a

NOTE Confidence: 0.7148958

00:01:38.834 --> 00:01:39.334 subpopulation

NOTE Confidence: 0.9074549

00:01:39.635 --> 00:01:40.915 of CD8 T cells that

NOTE Confidence: 0.9074549

00:01:40.915 --> 00:01:42.375 is tumor antigen specific,

NOTE Confidence: 0.9622073

00:01:43.715 --> 00:01:46.375 but is actually highly resembles

NOTE Confidence: 0.9622073

00:01:46.595 --> 00:01:47.555 recently described,

NOTE Confidence: 0.9076605

00:01:47.875 --> 00:01:49.475 CD8 regulatory T cells, and

NOTE Confidence: 0.9076605

00:01:49.475 --> 00:01:51.335 so it dampens antitumor immunity.

NOTE Confidence: 0.98652744

00:01:52.850 --> 00:01:53.970 We were able to trace

NOTE Confidence: 0.98652744

00:01:53.970 --> 00:01:55.350 these out into the blood

NOTE Confidence: 0.9917412

00:01:55.730 --> 00:01:57.250 and found that the levels

NOTE Confidence: 0.9917412

00:01:57.250 --> 00:01:57.970 that we find in the

NOTE Confidence: 0.9917412

00:01:57.970 --> 00:01:59.330 blood correlate with those that

NOTE Confidence: 0.9917412

00:01:59.330 --> 00:02:00.230 are in the tumor.

NOTE Confidence: 0.9727129

00:02:00.930 --> 00:02:02.870 And as mentioned, they impair

NOTE Confidence: 0.9727129

00:02:02.930 --> 00:02:04.935 antitumor immunity, and what we've

NOTE Confidence: 0.9727129

00:02:04.935 --> 00:02:06.055 found was that it does

NOTE Confidence: 0.9727129

00:02:06.055 --> 00:02:08.215 so by targeting other antigen

NOTE Confidence: 0.9727129

00:02:08.215 --> 00:02:09.355 specific t cells

NOTE Confidence: 0.8116644

00:02:09.735 --> 00:02:11.735 and that ultimately this results

NOTE Confidence: 0.8116644

00:02:11.735 --> 00:02:12.235 in

NOTE Confidence: 0.83502054

00:02:13.014 --> 00:02:14.794 poor patient outcomes.

NOTE Confidence: 0.9894572

00:02:15.575 --> 00:02:16.775 But the second vignette that

NOTE Confidence: 0.9894572

00:02:16.775 --> 00:02:17.735 I'd like to focus on

NOTE Confidence: 0.9894572

00:02:17.735 --> 00:02:19.495 really stems from our ability

NOTE Confidence: 0.9894572

00:02:19.495 --> 00:02:20.794 to leverage kind of

NOTE Confidence: 0.9994828

00:02:21.870 --> 00:02:23.810 fundamental aspects that we've learned

NOTE Confidence: 0.8515382

00:02:24.350 --> 00:02:25.169 through the years

NOTE Confidence: 0.9558573

00:02:25.710 --> 00:02:26.669 and to bring them back

NOTE Confidence: 0.9558573

00:02:26.669 --> 00:02:28.110 into the clinic. And so,

NOTE Confidence: 0.9558573

00:02:28.270 --> 00:02:29.970 this is ongoing work that,

NOTE Confidence: 0.89801127

00:02:30.350 --> 00:02:31.090 is unpublished,

NOTE Confidence: 0.8478495

00:02:31.389 --> 00:02:31.889 but,

NOTE Confidence: 0.96449184

00:02:32.270 --> 00:02:32.770 that

NOTE Confidence: 0.99978423

00:02:33.695 --> 00:02:34.835 we are working

NOTE Confidence: 0.99885356

00:02:35.375 --> 00:02:36.655 on right now in patients

NOTE Confidence: 0.99885356

00:02:36.655 --> 00:02:37.395 with glioblastoma.

NOTE Confidence: 0.9944712

00:02:37.935 --> 00:02:38.435 So

NOTE Confidence: 0.99685466

00:02:38.815 --> 00:02:40.035 in patients with glioblastoma,

NOTE Confidence: 0.98287785

00:02:40.335 --> 00:02:42.014 immune checkpoints really have not

NOTE Confidence: 0.98287785

00:02:42.014 --> 00:02:43.535 worked well. Anti p d

NOTE Confidence: 0.98287785

00:02:43.535 --> 00:02:44.735 one regimens have failed to

NOTE Confidence: 0.98287785

00:02:44.735 --> 00:02:46.355 improve survival for patients,

NOTE Confidence: 0.99969137

00:02:46.735 --> 00:02:47.555 in multiple

NOTE Confidence: 0.9884843

00:02:48.150 --> 00:02:50.730 phase three trials. Hypothesized mechanisms

NOTE Confidence: 0.9884843

00:02:50.790 --> 00:02:51.850 of failure include

NOTE Confidence: 0.91008735

00:02:52.550 --> 00:02:54.389 activation of regulatory t cells,

NOTE Confidence: 0.91008735

00:02:54.389 --> 00:02:56.169 so the suppressive t cells,

NOTE Confidence: 0.91008735

00:02:56.389 --> 00:02:58.230 in addition to changes in

NOTE Confidence: 0.91008735

00:02:58.230 --> 00:02:59.669 the cancer cell plasticity and

NOTE Confidence: 0.91008735

00:02:59.669 --> 00:03:01.290 glioblastoma cancer cells,

NOTE Confidence: 0.87592953

00:03:02.064 --> 00:03:03.905 among many other regimens. But,

NOTE Confidence: 0.9581721

00:03:04.224 --> 00:03:05.745 a couple years back, we

NOTE Confidence: 0.9581721

00:03:05.745 --> 00:03:06.245 leveraged,

NOTE Confidence: 0.90909076

00:03:06.784 --> 00:03:08.644 this kind of institutional expertise

NOTE Confidence: 0.90909076

00:03:08.864 --> 00:03:10.465 in regulatory t cell biology

NOTE Confidence: 0.90909076

00:03:10.465 --> 00:03:11.284 and identified,

NOTE Confidence: 0.6761772

00:03:12.144 --> 00:03:12.644 alternative,

NOTE Confidence: 0.8451135

00:03:13.754 --> 00:03:15.370 coin receptor called TIGIT,

NOTE Confidence: 0.99593276

00:03:15.750 --> 00:03:17.750 which we understand to be,

NOTE Confidence: 0.95851755

00:03:18.310 --> 00:03:20.070 unlike PD one, more important

NOTE Confidence: 0.95851755

00:03:20.070 --> 00:03:22.170 for stabilizing the suppressive function

NOTE Confidence: 0.9378948

00:03:22.550 --> 00:03:24.090 of regulatory T cells.

NOTE Confidence: 0.8849935

00:03:24.470 --> 00:03:25.770 This is work that was

NOTE Confidence: 0.8849935

00:03:25.830 --> 00:03:26.870 done out of the Haffler

NOTE Confidence: 0.8849935

00:03:26.870 --> 00:03:28.170 lab that suggests that,

NOTE Confidence: 0.90975493

00:03:28.724 --> 00:03:30.965 TIGIT expressing regulatory T cells

NOTE Confidence: 0.90975493

00:03:30.965 --> 00:03:33.125 are more suppressive than TIGIT

NOTE Confidence: 0.90975493

00:03:33.125 --> 00:03:34.885 negative, not nonsuppressing T cells,

NOTE Confidence: 0.90975493

00:03:34.885 --> 00:03:36.485 and that when placed into

NOTE Confidence: 0.90975493

00:03:36.485 --> 00:03:37.705 pro inflammatory environments,

NOTE Confidence: 0.97657686

00:03:38.485 --> 00:03:40.345 TIGIT engagement, TIGIT signaling

NOTE Confidence: 0.7935895

00:03:40.940 --> 00:03:42.480 through CD one five five,

NOTE Confidence: 0.98621607

00:03:42.860 --> 00:03:44.959 helps stabilize the suppressive phenotype.

NOTE Confidence: 0.9927637

00:03:46.299 --> 00:03:48.060 Now we also know that,

NOTE Confidence: 0.9030644

00:03:48.540 --> 00:03:50.060 TIGIT is highly expressed in

NOTE Confidence: 0.9030644

00:03:50.060 --> 00:03:51.340 addition to its binding partners,

NOTE Confidence: 0.9030644

00:03:51.340 --> 00:03:53.435 highly expressed in glioblastoma,

NOTE Confidence: 0.96212494

00:03:54.535 --> 00:03:56.615 unlike in multiple sclerosis, which

NOTE Confidence: 0.96212494

00:03:56.615 --> 00:03:57.755 is a pro inflammatory

NOTE Confidence: 0.9375063

00:03:58.615 --> 00:04:00.715 condition in the CNS.

NOTE Confidence: 0.94884694

00:04:01.655 --> 00:04:03.815 And that therapeutically targeting both

NOTE Confidence: 0.94884694

00:04:03.815 --> 00:04:04.955 TIGA and PD-one

NOTE Confidence: 0.9684229

00:04:05.255 --> 00:04:07.355 in humans and also

NOTE Confidence: 0.90022874

00:04:07.975 --> 00:04:09.230 in preclinical models,

NOTE Confidence: 0.9093986

00:04:09.690 --> 00:04:11.390 helps improve pro inflammatory

NOTE Confidence: 0.99720836

00:04:11.850 --> 00:04:12.350 conditions.

NOTE Confidence: 0.9720516

00:04:12.810 --> 00:04:13.530 And so,

NOTE Confidence: 0.9763263

00:04:14.010 --> 00:04:16.029 this led to the institutional

NOTE Confidence: 0.9763263

00:04:16.170 --> 00:04:17.150 initiated trial,

NOTE Confidence: 0.8232355

00:04:17.450 --> 00:04:19.290 led by doctor Amearl and

NOTE Confidence: 0.8232355

00:04:19.290 --> 00:04:20.990 close collaboration with doctor Malinturno,

NOTE Confidence: 0.8986596

00:04:22.010 --> 00:04:23.565 and since taken over by

NOTE Confidence: 0.8986596

00:04:23.565 --> 00:04:24.305 doctor Kurz,

NOTE Confidence: 0.9585805

00:04:24.605 --> 00:04:26.445 for this IIT that, is

NOTE Confidence: 0.9585805

00:04:26.445 --> 00:04:28.125 investigating the combination of anti

NOTE Confidence: 0.9585805

00:04:28.125 --> 00:04:29.585 PD one and anti TIGIT

NOTE Confidence: 0.9585805

00:04:29.725 --> 00:04:31.425 in patients with recurrent glioblastoma.

NOTE Confidence: 0.96311116

00:04:32.045 --> 00:04:33.005 And this is a two

NOTE Confidence: 0.96311116

00:04:33.005 --> 00:04:34.125 part trial. The first part

NOTE Confidence: 0.96311116

00:04:34.125 --> 00:04:35.404 was a safety lead in.

NOTE Confidence: 0.96311116

00:04:35.404 --> 00:04:36.930 But the second part, right,

NOTE Confidence: 0.96311116

00:04:37.009 --> 00:04:38.850 is a perioperative condition where

NOTE Confidence: 0.96311116

00:04:38.850 --> 00:04:39.830 patients get

NOTE Confidence: 0.9027175

00:04:40.289 --> 00:04:42.449 one of four treatments prior

NOTE Confidence: 0.9027175

00:04:42.449 --> 00:04:43.650 to going to surgery, so

NOTE Confidence: 0.9027175

00:04:43.650 --> 00:04:45.810 either antitigid alone, anti PD-one

NOTE Confidence: 0.9027175

00:04:45.810 --> 00:04:47.589 alone, the combination, or placebo

NOTE Confidence: 0.948983

00:04:48.050 --> 00:04:50.130 followed by combination afterwards. And

NOTE Confidence: 0.948983

00:04:50.130 --> 00:04:51.650 this really allows for us

NOTE Confidence: 0.948983

00:04:51.650 --> 00:04:52.310 to collect

NOTE Confidence: 0.96511745

00:04:52.995 --> 00:04:53.495 tissue

NOTE Confidence: 0.9294363

00:04:53.875 --> 00:04:55.495 specimens to try and understand

NOTE Confidence: 0.9995372

00:04:55.795 --> 00:04:56.695 aspects of

NOTE Confidence: 0.9817134

00:04:57.315 --> 00:04:58.295 tumor immunity.

NOTE Confidence: 0.9824515

00:04:59.475 --> 00:05:01.015 And so we've designed

NOTE Confidence: 0.9699995

00:05:01.555 --> 00:05:03.555 translational studies to try and

NOTE Confidence: 0.9699995

00:05:03.555 --> 00:05:04.055 really

NOTE Confidence: 0.89757407

00:05:05.075 --> 00:05:05.575 deeply

NOTE Confidence: 0.98898506

00:05:05.955 --> 00:05:06.960 analyze what

NOTE Confidence: 0.9869744

00:05:07.600 --> 00:05:09.300 are the perturbations that occur

NOTE Confidence: 0.88506603

00:05:09.600 --> 00:05:10.819 following these perioperative

NOTE Confidence: 0.7499312

00:05:11.520 --> 00:05:12.020 treatments.

NOTE Confidence: 0.91017014

00:05:12.560 --> 00:05:14.339 And, the the trial has

NOTE Confidence: 0.91017014

00:05:14.479 --> 00:05:14.979 just

NOTE Confidence: 0.996523

00:05:15.279 --> 00:05:15.779 concluded

NOTE Confidence: 0.84399146

00:05:16.720 --> 00:05:17.919 accrual, so a lot of

NOTE Confidence: 0.84399146

00:05:17.919 --> 00:05:19.475 these studies are ongoing. Has

NOTE Confidence: 0.8660717

00:05:27.615 --> 00:05:29.475 referenced earlier is being run-in

NOTE Confidence: 0.8660717

00:05:29.615 --> 00:05:31.135 close collaboration with Rong Fan

NOTE Confidence: 0.8660717

00:05:31.135 --> 00:05:32.540 and Yang Liu, in addition

NOTE Confidence: 0.8660717

00:05:32.540 --> 00:05:33.980 to Marcello Distasio, who's a

NOTE Confidence: 0.8660717

00:05:33.980 --> 00:05:34.480 neuropathologist.

NOTE Confidence: 0.98360366

00:05:36.300 --> 00:05:37.180 But we do have some

NOTE Confidence: 0.98360366

00:05:37.180 --> 00:05:38.940 preliminary data that does give

NOTE Confidence: 0.98360366

00:05:38.940 --> 00:05:41.339 us, some optimism that, you

NOTE Confidence: 0.98360366

00:05:41.339 --> 00:05:43.100 know, biological activity is occurring

NOTE Confidence: 0.98360366

00:05:43.100 --> 00:05:44.000 in these patients.

NOTE Confidence: 0.96989465

00:05:44.540 --> 00:05:45.980 And these include that at

NOTE Confidence: 0.96989465

00:05:45.980 --> 00:05:47.775 very early time points, we've

NOTE Confidence: 0.96989465

00:05:47.935 --> 00:05:48.675 observed a

NOTE Confidence: 0.9668636

00:05:48.975 --> 00:05:50.675 shift towards effector phenotypes,

NOTE Confidence: 0.9680444

00:05:51.214 --> 00:05:52.735 effector t cell phenotypes in

NOTE Confidence: 0.9680444

00:05:52.735 --> 00:05:54.675 circulating populations in the blood.

NOTE Confidence: 0.9680444

00:05:54.815 --> 00:05:55.854 And so what I'm showing

NOTE Confidence: 0.9680444

00:05:55.854 --> 00:05:57.375 on the bottom are results

NOTE Confidence: 0.9680444

00:05:57.375 --> 00:05:58.815 from flow cytometry data from

NOTE Confidence: 0.9680444

00:05:58.815 --> 00:05:59.794 our safety reading

NOTE Confidence: 0.9606996

00:06:00.175 --> 00:06:01.870 that suggests at day five,

NOTE Confidence: 0.9606996

00:06:01.870 --> 00:06:02.990 as early as day five,

NOTE Confidence: 0.9606996

00:06:02.990 --> 00:06:04.290 we see a shift from,

NOTE Confidence: 0.9187336

00:06:05.630 --> 00:06:06.290 more naive,

NOTE Confidence: 0.9743946

00:06:06.830 --> 00:06:08.830 or memory populations towards effector

NOTE Confidence: 0.9743946

00:06:08.830 --> 00:06:09.330 populations.

NOTE Confidence: 0.9581877

00:06:10.270 --> 00:06:11.630 This is also reflected in

NOTE Confidence: 0.9581877

00:06:11.630 --> 00:06:13.650 their ability to secrete cytotoxic

NOTE Confidence: 0.9581877

00:06:13.870 --> 00:06:14.850 th one cytokines.

NOTE Confidence: 0.89940363

00:06:15.390 --> 00:06:16.485 This occurs from from both

NOTE Confidence: 0.89940363

00:06:16.485 --> 00:06:17.705 CD8s and CD4s.

NOTE Confidence: 0.9872911

00:06:18.404 --> 00:06:19.285 And based off of our

NOTE Confidence: 0.9872911

00:06:19.285 --> 00:06:19.785 preclinical,

NOTE Confidence: 0.5552113

00:06:20.565 --> 00:06:21.065 hypotheses,

NOTE Confidence: 0.90469366

00:06:21.445 --> 00:06:22.265 TIGIT would,

NOTE Confidence: 0.89661145

00:06:23.205 --> 00:06:24.345 differentially impact,

NOTE Confidence: 0.94933075

00:06:24.725 --> 00:06:26.565 regulatory T cell phenotype. We

NOTE Confidence: 0.94933075

00:06:26.565 --> 00:06:28.425 also do see shifts in

NOTE Confidence: 0.94933075

00:06:28.645 --> 00:06:29.385 the phenotype,

NOTE Confidence: 0.79268634

00:06:29.845 --> 00:06:31.685 down regulation of FOXP3 and

NOTE Confidence: 0.79268634

00:06:31.685 --> 00:06:32.460 up regulation of regulation of

NOTE Confidence: 0.79268634

00:06:32.460 --> 00:06:34.620 CD226 in circling Tregs as

NOTE Confidence: 0.79268634

00:06:34.620 --> 00:06:35.120 well.

NOTE Confidence: 0.971529

00:06:36.140 --> 00:06:37.980 And, I guess, not shown

NOTE Confidence: 0.971529

00:06:37.980 --> 00:06:39.600 here is, we also see

NOTE Confidence: 0.971529

00:06:39.820 --> 00:06:40.320 a

NOTE Confidence: 0.9290389

00:06:40.779 --> 00:06:43.040 relative trend towards decreased suppressive

NOTE Confidence: 0.9290389

00:06:43.180 --> 00:06:44.960 function in circling Tregs.

NOTE Confidence: 0.9189107

00:06:46.435 --> 00:06:47.714 In one patient who we

NOTE Confidence: 0.9189107

00:06:47.714 --> 00:06:48.755 were able to collect both

NOTE Confidence: 0.9189107

00:06:48.755 --> 00:06:50.055 pre and post treatment,

NOTE Confidence: 0.85459507

00:06:51.714 --> 00:06:52.535 tumor samples,

NOTE Confidence: 0.9784115

00:06:52.995 --> 00:06:54.275 we ran single cell RNA

NOTE Confidence: 0.9784115

00:06:54.275 --> 00:06:55.654 and T cell receptor sequencing.

NOTE Confidence: 0.9335051

00:06:56.195 --> 00:06:57.475 And what we observed was

NOTE Confidence: 0.9335051

00:06:57.475 --> 00:06:59.414 that, at the post combination

NOTE Confidence: 0.9335051

00:06:59.555 --> 00:07:00.055 treatments

NOTE Confidence: 0.9670418

00:07:00.595 --> 00:07:01.720 sample, we do see an

NOTE Confidence: 0.9670418

00:07:01.720 --> 00:07:02.339 infiltration of,

NOTE Confidence: 0.9661165

00:07:03.360 --> 00:07:05.140 the absolute quantity of,

NOTE Confidence: 0.7969273

00:07:06.160 --> 00:07:08.000 infiltrating T cells as represented

NOTE Confidence: 0.7969273

00:07:08.000 --> 00:07:09.300 by CD three staining,

NOTE Confidence: 0.9558606

00:07:10.000 --> 00:07:11.200 but also a shift in

NOTE Confidence: 0.9558606

00:07:11.200 --> 00:07:12.720 the the amino phenotype. So

NOTE Confidence: 0.9558606

00:07:12.720 --> 00:07:14.260 we see a much larger

NOTE Confidence: 0.9558606

00:07:14.320 --> 00:07:15.460 expansion of

NOTE Confidence: 0.94613427

00:07:16.044 --> 00:07:16.544 effector

NOTE Confidence: 0.8071551

00:07:16.925 --> 00:07:18.065 CDT cells,

NOTE Confidence: 0.99010676

00:07:18.764 --> 00:07:20.365 in addition to actual clonal

NOTE Confidence: 0.99010676

00:07:20.365 --> 00:07:20.865 expansion.

NOTE Confidence: 0.94853616

00:07:21.805 --> 00:07:23.645 But maybe most interesting to

NOTE Confidence: 0.94853616

00:07:23.645 --> 00:07:24.764 us based off of our

NOTE Confidence: 0.94853616

00:07:24.764 --> 00:07:26.925 preclinical observations was that if

NOTE Confidence: 0.94853616

00:07:26.925 --> 00:07:27.645 we were to take the

NOTE Confidence: 0.94853616

00:07:27.645 --> 00:07:28.845 t cell receptor sequence and

NOTE Confidence: 0.94853616

00:07:28.845 --> 00:07:29.824 use it as a molecular

NOTE Confidence: 0.94853616

00:07:29.884 --> 00:07:30.384 barcode

NOTE Confidence: 0.9921563

00:07:30.710 --> 00:07:32.070 and track what is the

NOTE Confidence: 0.9921563

00:07:32.070 --> 00:07:34.630 phenotype of regulatory t cells,

NOTE Confidence: 0.9921563

00:07:34.630 --> 00:07:36.010 what we observe is that

NOTE Confidence: 0.95768815

00:07:36.310 --> 00:07:38.310 prior to treatments, regulatory t

NOTE Confidence: 0.95768815

00:07:38.310 --> 00:07:39.770 cells have a very distinct

NOTE Confidence: 0.95768815

00:07:39.830 --> 00:07:41.050 suppressive phenotype.

NOTE Confidence: 0.98891103

00:07:41.750 --> 00:07:43.290 And what's shown here are

NOTE Confidence: 0.96433395

00:07:43.824 --> 00:07:45.504 all of the regulatory T

NOTE Confidence: 0.96433395

00:07:45.504 --> 00:07:47.264 cell clonotypes, which are confined

NOTE Confidence: 0.96433395

00:07:47.264 --> 00:07:49.205 to one phenotypic cluster.

NOTE Confidence: 0.93458074

00:07:49.664 --> 00:07:51.185 But following treatment, we actually

NOTE Confidence: 0.93458074

00:07:51.185 --> 00:07:52.865 see increase in the clonal

NOTE Confidence: 0.93458074

00:07:52.865 --> 00:07:54.164 overlap across different

NOTE Confidence: 0.9784724

00:07:54.465 --> 00:07:55.845 c four effector populations.

NOTE Confidence: 0.93576515

00:07:56.865 --> 00:07:57.905 And this is interesting to

NOTE Confidence: 0.93576515

00:07:57.905 --> 00:07:59.210 us because we would hypothesize

NOTE Confidence: 0.93576515

00:07:59.430 --> 00:08:02.010 that disabling reg TIGIT signaling

NOTE Confidence: 0.93576515

00:08:02.150 --> 00:08:04.310 would destabilize regulatory t cell

NOTE Confidence: 0.93576515

00:08:04.310 --> 00:08:04.810 phenotypes.

NOTE Confidence: 0.9645293

00:08:06.230 --> 00:08:08.090 And so, this is,

NOTE Confidence: 0.7568227

00:08:08.390 --> 00:08:09.530 obviously in

NOTE Confidence: 0.9098175

00:08:09.830 --> 00:08:11.750 preliminary data and data that

NOTE Confidence: 0.9098175

00:08:11.750 --> 00:08:13.005 we're still working on generating,

NOTE Confidence: 0.9098175

00:08:13.005 --> 00:08:13.505 but,

NOTE Confidence: 0.98552006

00:08:13.885 --> 00:08:15.485 it does play in line

NOTE Confidence: 0.98552006

00:08:15.485 --> 00:08:16.305 with the preclinical,

NOTE Confidence: 0.5406381

00:08:16.845 --> 00:08:17.345 hypothesis

NOTE Confidence: 0.9756475

00:08:17.885 --> 00:08:18.625 going in,

NOTE Confidence: 0.9864424

00:08:19.085 --> 00:08:20.865 in a regulatory t cell

NOTE Confidence: 0.85439897

00:08:25.030 --> 00:08:25.530 manner.

NOTE Confidence: 0.97393256

00:08:25.910 --> 00:08:27.830 But what we're also interested

NOTE Confidence: 0.97393256

00:08:27.830 --> 00:08:29.110 in trying to understand is

NOTE Confidence: 0.97393256

00:08:29.110 --> 00:08:31.050 whether there are bidirectional interactions

NOTE Confidence: 0.97393256

00:08:31.190 --> 00:08:33.110 that are occurring. And so

NOTE Confidence: 0.97393256

00:08:33.110 --> 00:08:34.470 a very talented graduate student

NOTE Confidence: 0.97393256

00:08:34.470 --> 00:08:35.610 in our group is currently

NOTE Confidence: 0.98799753

00:08:35.990 --> 00:08:37.350 working on what is the

NOTE Confidence: 0.98799753

00:08:37.350 --> 00:08:38.570 bidirectional signaling

NOTE Confidence: 0.8942912

00:08:39.295 --> 00:08:40.815 that is occurring and has

NOTE Confidence: 0.8942912

00:08:40.815 --> 00:08:42.495 generated some very interesting data

NOTE Confidence: 0.8942912

00:08:42.495 --> 00:08:44.335 to suggest that regulatory T

NOTE Confidence: 0.8942912

00:08:44.335 --> 00:08:45.155 cell interactions

NOTE Confidence: 0.89538205

00:08:45.934 --> 00:08:48.115 with glioblastoma cancer cells actually

NOTE Confidence: 0.89538205

00:08:48.175 --> 00:08:50.115 causes shift towards more mesenchymal

NOTE Confidence: 0.89538205

00:08:50.255 --> 00:08:51.554 like aggressive phenotypes

NOTE Confidence: 0.97389287

00:08:52.569 --> 00:08:53.389 and that this

NOTE Confidence: 0.8862116

00:08:54.170 --> 00:08:55.709 interaction is regulatory

NOTE Confidence: 0.9101808

00:08:56.329 --> 00:08:57.230 Treg specific

NOTE Confidence: 0.8423149

00:08:57.769 --> 00:08:59.389 and can be reversed with

NOTE Confidence: 0.8423149

00:08:59.529 --> 00:09:00.429 t shirt blockade.

NOTE Confidence: 0.85953605

00:09:01.529 --> 00:09:03.690 But that environmental context matters.

NOTE Confidence: 0.85953605

00:09:03.690 --> 00:09:04.350 And so

NOTE Confidence: 0.93856543

00:09:04.730 --> 00:09:06.269 when thinking about the heterogeneity

NOTE Confidence: 0.9605247

00:09:07.085 --> 00:09:07.585 within

NOTE Confidence: 0.9825712

00:09:08.045 --> 00:09:09.505 the solid tumor microenvironments,

NOTE Confidence: 0.9525116

00:09:09.885 --> 00:09:11.745 we also take into consideration

NOTE Confidence: 0.96733356

00:09:12.445 --> 00:09:13.505 metabolic and,

NOTE Confidence: 0.99926966

00:09:14.605 --> 00:09:15.105 other

NOTE Confidence: 0.8388398

00:09:15.565 --> 00:09:17.425 other conditions such as hypoxia.

NOTE Confidence: 0.96279866

00:09:18.125 --> 00:09:19.485 And that potentially, this may

NOTE Confidence: 0.96279866

00:09:19.485 --> 00:09:21.579 lead to avenues for additional

NOTE Confidence: 0.96279866

00:09:21.579 --> 00:09:22.559 therapeutic targeting.

NOTE Confidence: 0.9743539

00:09:23.579 --> 00:09:24.620 And so with that, I'd

NOTE Confidence: 0.9743539

00:09:24.620 --> 00:09:25.660 just like to thank,

NOTE Confidence: 0.9861365

00:09:26.300 --> 00:09:27.740 the patients and families who

NOTE Confidence: 0.9861365

00:09:27.740 --> 00:09:29.179 have made this work possible

NOTE Confidence: 0.9861365

00:09:29.179 --> 00:09:30.860 and all of our, human

NOTE Confidence: 0.9861365

00:09:30.860 --> 00:09:31.600 work possible

NOTE Confidence: 0.9011498

00:09:31.980 --> 00:09:33.899 in addition to, doctor David

NOTE Confidence: 0.9011498

00:09:33.899 --> 00:09:35.605 Haffler, who has been my

NOTE Confidence: 0.9011498

00:09:35.605 --> 00:09:37.045 mentor during my time here

NOTE Confidence: 0.9011498

00:09:37.045 --> 00:09:37.705 at Yale.

NOTE Confidence: 0.9785641

00:09:38.485 --> 00:09:39.545 In addition to,

NOTE Confidence: 0.8970758

00:09:40.005 --> 00:09:41.045 the folks in our group,

NOTE Confidence: 0.8970758

00:09:41.045 --> 00:09:42.245 the greater Hafler lab group,

NOTE Confidence: 0.8970758

00:09:42.245 --> 00:09:43.285 and all of our collaborators

NOTE Confidence: 0.8970758

00:09:43.285 --> 00:09:43.785 around

NOTE Confidence: 0.8796211

00:09:44.165 --> 00:09:45.625 the medical school, including,

NOTE Confidence: 0.9511256

00:09:46.085 --> 00:09:47.684 the support of leadership within

NOTE Confidence: 0.9511256

00:09:47.684 --> 00:09:48.665 the cancer center.

NOTE Confidence: 0.8354142

00:09:49.445 --> 00:09:49.945 And,

NOTE Confidence: 0.889278

00:09:51.640 --> 00:09:53.820 well represented here is also

NOTE Confidence: 0.889278

00:09:53.880 --> 00:09:55.500 leadership within the core facilities

NOTE Confidence: 0.889278

00:09:55.559 --> 00:09:56.920 who have also helped us

NOTE Confidence: 0.889278

00:09:56.920 --> 00:09:58.840 make, this possible, including Waelin

NOTE Confidence: 0.889278

00:09:58.840 --> 00:09:59.900 and Leslie.