WEBVTT

00:00:00.000 --> 00:00:03.128 Sure, there's enough time for both of you,

00:00:03.130 --> 00:00:05.060 so I see folks here.

00:00:05.060 --> 00:00:07.573 The numbers are going up and appreciate

00:00:07.573 --> 00:00:09.951 folks logging on welcome everyone once

00:00:09.951 --> 00:00:12.364 again to Cancer Center, grand rounds,

00:00:12.364 --> 00:00:14.274 and we're really very privileged

00:00:14.274 --> 00:00:17.495 today to have two of our exceptional

00:00:17.495 --> 00:00:18.998 physician scientists presenting.

00:00:19.000 --> 00:00:21.040 You know, really and frankly,

00:00:21.040 --> 00:00:23.055 what's exciting is it it

00:00:23.055 --> 00:00:24.667 once again highlights the

00:00:24.667 --> 00:00:26.338 extraordinary work in immunology.

00:00:26.340 --> 00:00:28.956 Immuno biology at Yale and at

00:00:28.956 --> 00:00:31.790 the impact on this ultimately.

NOTE Confidence: 0.879088

00:00:31.790 --> 00:00:34.198 In our cancer therapy and in our

NOTE Confidence: 0.879088

00:00:34.198 --> 00:00:35.790 understanding of cancer biology,

NOTE Confidence: 0.879088

00:00:35.790 --> 00:00:38.317 so let me turn to our first

NOTE Confidence: 0.879088

00:00:38.317 --> 00:00:40.530 speaker to ensure we have time.

NOTE Confidence: 0.879088

00:00:40.530 --> 00:00:43.064 Our first speaker is Doctor David Hafler,

NOTE Confidence: 0.879088

00:00:43.070 --> 00:00:44.418 who is, you know,

NOTE Confidence: 0.879088

00:00:44.418 --> 00:00:46.853 is the ugly professor and chair of

NOTE Confidence: 0.879088

00:00:46.853 --> 00:00:49.212 the Department of the Rolla G and

NOTE Confidence: 0.879088

00:00:49.212 --> 00:00:51.083 Professor of Immunology, Immunobiology,

NOTE Confidence: 0.879088

00:00:51.083 --> 00:00:52.172 and David's accomplishments

NOTE Confidence: 0.879088

00:00:52.172 --> 00:00:53.987 are are really quite Legion.

NOTE Confidence: 0.879088

00:00:53.990 --> 00:00:55.810 Renee actually prepared a synopsis,

NOTE Confidence: 0.879088

00:00:55.810 --> 00:00:58.744 and I just said that I want to make

NOTE Confidence: 0.879088

00:00:58.744 --> 00:01:01.266 sure David has time to present.

NOTE Confidence: 0.879088

00:01:01.270 --> 00:01:02.106 I won't.

NOTE Confidence: 0.879088

00:01:02.106 --> 00:01:04.196 Go through all of it,

NOTE Confidence: 0.879088

00:01:04.200 --> 00:01:06.368 but his accomplishments in

NOTE Confidence: 0.879088

00:01:06.368 --> 00:01:07.994 terms of understanding.

NOTE Confidence: 0.879088

00:01:08.000 --> 00:01:10.252 Advancing neuroscience and understanding

NOTE Confidence: 0.879088

00:01:10.252 --> 00:01:13.630 that human autoimmunity in an understanding

NOTE Confidence: 0.879088

00:01:13.705 --> 00:01:15.915 how to leverage our understanding

NOTE Confidence: 0.879088

00:01:15.915 --> 00:01:18.125 of immunology to impacting human

NOTE Confidence: 0.879088

00:01:18.201 --> 00:01:20.546 disease is really quite impressive.

NOTE Confidence: 0.879088

00:01:20.550 --> 00:01:23.328 And among his awards include the

NOTE Confidence: 0.879088

00:01:23.328 --> 00:01:26.070 distal Prize for Ms Research,

NOTE Confidence: 0.879088

00:01:26.070 --> 00:01:28.078 the University of Miami

NOTE Confidence: 0.879088

00:01:28.078 --> 00:01:29.584 Distinguished Alumni Award,

NOTE Confidence: 0.879088

00:01:29.590 --> 00:01:32.254 the American Urology Association,

NOTE Confidence: 0.879088

00:01:32.254 --> 00:01:33.586 Adams Lectureship.

NOTE Confidence: 0.879088

00:01:33.590 --> 00:01:34.688 And most recently,

NOTE Confidence: 0.879088

00:01:34.688 --> 00:01:37.680 and I think a year or so ago,

NOTE Confidence: 0.879088

00:01:37.680 --> 00:01:39.822 election to the National Academy of

NOTE Confidence: 0.879088

00:01:39.822 --> 00:01:42.027 Medicine and and David has really

NOTE Confidence: 0.879088

00:01:42.027 --> 00:01:43.812 been an incredibly engaged member

NOTE Confidence: 0.879088

00:01:43.812 --> 00:01:45.870 of our Cancer Center faculty.

NOTE Confidence: 0.879088

00:01:45.870 --> 00:01:47.354 I think David's leadership,

NOTE Confidence: 0.879088

00:01:47.354 --> 00:01:49.588 I think, has advanced the cause

NOTE Confidence: 0.879088

00:01:49.588 --> 00:01:51.448 of our brain tumor program,

NOTE Confidence: 0.879088

00:01:51.450 --> 00:01:52.605 among other things,

NOTE Confidence: 0.879088

00:01:52.605 --> 00:01:55.722 an David thank you for making the time

NOTE Confidence: 0.879088

00:01:55.722 --> 00:01:58.137 to share your work with us today.

NOTE Confidence: 0.9125635

00:01:59.550 --> 00:02:00.846 Thank you Charlie.

NOTE Confidence: 0.9125635

00:02:00.846 --> 00:02:03.870 It's really a pleasure to be here.

NOTE Confidence: 0.9125635

00:02:03.870 --> 00:02:08.049 And let me turn this on and.

NOTE Confidence: 0.9125635

00:02:08.050 --> 00:02:11.786 My cell phone, so I'd like to do today

NOTE Confidence: 0.9125635

00:02:11.786 --> 00:02:14.544 is to present some new unpublished

NOTE Confidence: 0.9125635

00:02:14.544 --> 00:02:18.541 work which really epitomizes to me of

NOTE Confidence: 0.9125635

00:02:18.541 --> 00:02:21.134 physician scientists of learning from

NOTE Confidence: 0.9125635

00:02:21.134 --> 00:02:24.472 the patient and just in a nutshell,

NOTE Confidence: 0.9125635

00:02:24.472 --> 00:02:27.636 what I'm going to show you is

NOTE Confidence: 0.9125635

00:02:27.636 --> 00:02:29.350 very fundamental question,

NOTE Confidence: 0.9125635

00:02:29.350 --> 00:02:32.416 which is what induces the checkpoint

NOTE Confidence: 0.9125635

00:02:32.416 --> 00:02:35.640 inhibitors particular PD one Tim three lag,

NOTE Confidence: 0.9125635

00:02:35.640 --> 00:02:38.916 3 digit on human T cells.

NOTE Confidence: 0.9125635

00:02:38.920 --> 00:02:40.690 And that's gonna be the nature

NOTE Confidence: 0.9125635

00:02:40.690 --> 00:02:43.118 of the talk that the work has

NOTE Confidence: 0.9125635

00:02:43.118 --> 00:02:44.694 been submitted for publication.

NOTE Confidence: 0.9125635

00:02:44.700 --> 00:02:45.960 It was put online,

NOTE Confidence: 0.9125635

00:02:45.960 --> 00:02:48.284 a bio RX being one's interest in

NOTE Confidence: 0.9125635

00:02:48.284 --> 00:02:50.480 seeing the paper itself and upfront.

NOTE Confidence: 0.9125635

00:02:50.480 --> 00:02:52.860 I want to really, now Stamos Amita,

NOTE Confidence: 0.9125635

00:02:52.860 --> 00:02:54.220 who really really performed

NOTE Confidence: 0.9125635

00:02:54.220 --> 00:02:56.260 this work in our laboratory tone

NOTE Confidence: 0.9125635

00:02:56.317 --> 00:02:57.987 was now an assistant professor

NOTE Confidence: 0.9125635

00:02:57.987 --> 00:02:59.657 and then pursuing this work.

NOTE Confidence: 0.9125635

00:02:59.660 --> 00:03:00.680 It wanted knowledge.

NOTE Confidence: 0.9125635

00:03:00.680 --> 00:03:02.720 My long term collaborator, Vijay Kutru.

NOTE Confidence: 0.9125635

00:03:02.720 --> 00:03:04.420 Yes, you see a Yale,

NOTE Confidence: 0.9125635

00:03:04.420 --> 00:03:06.460 a sticker that he was here

NOTE Confidence: 0.9125635

00:03:06.460 --> 00:03:07.820 helping us recruit students.

NOTE Confidence: 0.9125635

00:03:07.820 --> 00:03:10.130 Don't tell the people in Boston.

NOTE Confidence: 0.9125635

00:03:10.130 --> 00:03:12.270 Enjoy dulberg in the Softmod

NOTE Confidence: 0.9125635

00:03:12.270 --> 00:03:14.410 who did the computational work.

NOTE Confidence: 0.9125635

00:03:14.410 --> 00:03:15.902 So the question is,

NOTE Confidence: 0.9125635

00:03:15.902 --> 00:03:17.767 what are the regulatory mechanism

NOTE Confidence: 0.9125635

00:03:17.767 --> 00:03:20.035 for induction of a Co inhibitory

NOTE Confidence: 0.9125635

00:03:20.035 --> 00:03:21.865 receptors on human T cells?

NOTE Confidence: 0.9125635

00:03:21.870 --> 00:03:24.846 But I'll show you is surprisingly type one,

NOTE Confidence: 0.9125635

00:03:24.850 --> 00:03:26.342 interferons induce Cohen Cohen

NOTE Confidence: 0.9125635

00:03:26.342 --> 00:03:28.580 territory receptors on human T cells,

NOTE Confidence: 0.9125635

00:03:28.580 --> 00:03:31.436 so that's the bottom line of what I'm

NOTE Confidence: 0.9125635

00:03:31.436 --> 00:03:34.176 going to show you over 30 minutes.

NOTE Confidence: 0.9125635

00:03:34.180 --> 00:03:36.538 We worked through the in vitro

NOTE Confidence: 0.9125635

00:03:36.538 --> 00:03:37.717 transcriptional regulatory network

NOTE Confidence: 0.9125635

00:03:37.717 --> 00:03:39.831 for this interferon beta response and

NOTE Confidence: 0.9125635

00:03:39.831 --> 00:03:42.341 then we identified an in vivo model

NOTE Confidence: 0.9125635

00:03:42.341 --> 00:03:44.336 where abara load strongly correlate's.

NOTE Confidence: 0.9125635

00:03:44.340 --> 00:03:46.330 With type one interferon signature,

NOTE Confidence: 0.9125635

00:03:46.330 --> 00:03:48.458 which allowed us to perform an in

NOTE Confidence: 0.9125635

00:03:48.458 --> 00:03:50.887 vivo validation of the in vitro

NOTE Confidence: 0.9125635

00:03:50.887 --> 00:03:52.342 interferon transcriptional regulatory

NOTE Confidence: 0.9125635

00:03:52.342 --> 00:03:54.282 network Co inhibitory receptors.

NOTE Confidence: 0.9125635

00:03:54.290 --> 00:03:58.007 So that's what my talk will be.

NOTE Confidence: 0.9125635

00:03:58.010 --> 00:04:00.467 Now it's been known for a number

NOTE Confidence: 0.9125635

00:04:00.467 --> 00:04:02.000 of years to work.

NOTE Confidence: 0.9125635

00:04:02.000 --> 00:04:04.247 Button from Vijay Kutru and be ready

NOTE Confidence: 0.9125635

00:04:04.247 --> 00:04:06.428 given we've had a program Project

NOTE Confidence: 0.9125635

00:04:06.428 --> 00:04:08.726 Grant 2 program project grants looking

NOTE Confidence: 0.9125635

00:04:08.726 --> 00:04:10.290 Cohen inventory molecules valene

NOTE Confidence: 0.9125635

00:04:10.290 --> 00:04:13.979 sharp for well over 25 years that PD one Tim,

NOTE Confidence: 0.9125635

00:04:13.979 --> 00:04:16.157 three lag three and TIGIT ARCO,

NOTE Confidence: 0.9125635

00:04:16.160 --> 00:04:18.338 regulated and expressed as a module.

NOTE Confidence: 0.9125635

00:04:18.340 --> 00:04:19.792 So here we have.

NOTE Confidence: 0.9125635

00:04:19.792 --> 00:04:21.970 Hopefully you will see the pointer.

NOTE Confidence: 0.9125635

00:04:21.970 --> 00:04:23.785 I won't advance the slide

NOTE Confidence: 0.9125635

00:04:23.785 --> 00:04:25.237 while I'm doing this,

NOTE Confidence: 0.9125635

00:04:25.240 --> 00:04:27.910 but you can see that there.

NOTE Confidence: 0.9125635

00:04:27.910 --> 00:04:30.100 Expression of PD one Tim,

NOTE Confidence: 0.9125635

00:04:30.100 --> 00:04:33.907 three lag three and TIGIT on C4 and CD8

NOTE Confidence: 0.9125635

00:04:33.907 --> 00:04:37.258 cells that their modulated together.

NOTE Confidence: 0.9125635

00:04:37.260 --> 00:04:39.976 And that this is a new spot.

NOTE Confidence: 0.9125635

00:04:39.980 --> 00:04:41.147 I'll 27 here.

NOTE Confidence: 0.9125635

00:04:41.147 --> 00:04:43.870 We have the induction of Tim 3

NOTE Confidence: 0.9125635

00:04:43.958 --> 00:04:46.926 not so much PD one but lag three

NOTE Confidence: 0.9125635

00:04:46.926 --> 00:04:49.705 and TIGIT by I'll 27 you knock

NOTE Confidence: 0.9125635

00:04:49.705 --> 00:04:52.430 down aisle 27 the mouse you lose

NOTE Confidence: 0.9125635

00:04:52.430 --> 00:04:54.380 the induction by aisle 27.

NOTE Confidence: 0.9125635

00:04:54.380 --> 00:04:55.932 That's the upregulation and

NOTE Confidence: 0.9125635

00:04:55.932 --> 00:04:57.872 downregulation by the knock down.

NOTE Confidence: 0.9125635

00:04:57.880 --> 00:05:00.984 Now it's been known for a long time.

NOTE Confidence: 0.9125635

00:05:00.990 --> 00:05:02.930 That type one interferon signatures,

NOTE Confidence: 0.9125635

00:05:02.930 --> 00:05:04.880 or enriching chronic viral infection,

NOTE Confidence: 0.9125635

00:05:04.880 --> 00:05:06.820 and both mouse and humans,

NOTE Confidence: 0.9125635

00:05:06.820 --> 00:05:09.655 and that chronic viral infection

NOTE Confidence: 0.9125635

00:05:09.655 --> 00:05:11.923 induces T cell exhaustion.

NOTE Confidence: 0.9125635

00:05:11.930 --> 00:05:13.845 Really first identified by Rafi

NOTE Confidence: 0.9125635

00:05:13.845 --> 00:05:16.257 Ahmed in the HIV system and

NOTE Confidence: 0.9125635

00:05:16.257 --> 00:05:18.807 in El CMV infection and that's

NOTE Confidence: 0.9125635

00:05:18.807 --> 00:05:20.928 associated with expression and Co

NOTE Confidence: 0.9125635

00:05:20.928 --> 00:05:22.868 inhibitory receptors such as PD,

NOTE Confidence: 0.7671486

00:05:22.870 --> 00:05:24.542 One Tim, three lag.

NOTE Confidence: 0.7671486

00:05:24.542 --> 00:05:26.632 Three antigen is interferon signature

NOTE Confidence: 0.7671486

00:05:26.632 --> 00:05:29.024 with the LC MP model suggesting that

NOTE Confidence: 0.7671486

00:05:29.024 --> 00:05:31.757 there may be an Association with type

NOTE Confidence: 0.7671486

00:05:31.757 --> 00:05:34.547 one interferons and these cone hitori

NOTE Confidence: 0.7671486

00:05:34.547 --> 00:05:37.828 molecules so wish to ask do they

NOTE Confidence: 0.7671486

00:05:37.828 --> 00:05:40.222 induce these receptors again here's

NOTE Confidence: 0.7671486

00:05:40.222 --> 00:05:43.646 why I showed you in terms of mouse.

NOTE Confidence: 0.7671486

00:05:43.650 --> 00:05:46.723 An you know first experiments and when

NOTE Confidence: 0.7671486

00:05:46.723 --> 00:05:49.860 I googled in photograph of human,

NOTE Confidence: 0.7671486

00:05:49.860 --> 00:05:53.630 I swear this is what showed up and I know

NOTE Confidence: 0.7671486

00:05:53.731 --> 00:05:57.505 way mean to denigrate mouse immunologist.

NOTE Confidence: 0.7671486

00:05:57.510 --> 00:05:59.434 By showing this picture,

NOTE Confidence: 0.7671486

00:05:59.434 --> 00:06:03.728 but one can see is that in CD4 cells,

NOTE Confidence: 0.7671486

00:06:03.730 --> 00:06:06.120 either with with no cytokine

NOTE Confidence: 0.7671486

00:06:06.120 --> 00:06:08.510 I'll 27 or interferon beta.

NOTE Confidence: 0.7671486

00:06:08.510 --> 00:06:11.898 This market induction of Tim three lag

NOTE Confidence: 0.7671486

00:06:11.898 --> 00:06:14.808 three and PD one. By interference.

NOTE Confidence: 0.7671486

00:06:14.808 --> 00:06:19.850 So now we go into more depth to show this.

NOTE Confidence: 0.7671486

00:06:19.850 --> 00:06:21.746 Here's how the experiments were done.

NOTE Confidence: 0.7671486

00:06:21.750 --> 00:06:23.646 We took CD4 CD 8 cells.

NOTE Confidence: 0.7671486

00:06:23.650 --> 00:06:26.140 That was CD.

NOTE Confidence: 0.7671486

00:06:26.140 --> 00:06:28.570 That were CD 45 negative positive.

NOTE Confidence: 0.7671486

00:06:28.570 --> 00:06:31.412 That is a naive T cells and

NOTE Confidence: 0.7671486

00:06:31.412 --> 00:06:33.429 stimulate them for non use.

NOTE Confidence: 0.7671486

00:06:33.430 --> 00:06:35.050 Different different time points

NOTE Confidence: 0.7671486

00:06:35.050 --> 00:06:36.670 with CD3 plus minus.

NOTE Confidence: 0.7671486

00:06:36.670 --> 00:06:41.008 I'll 27 and interferon beta and one can see.

NOTE Confidence: 0.7671486

00:06:41.010 --> 00:06:43.206 The induction of here's a control.

NOTE Confidence: 0.7671486

00:06:43.210 --> 00:06:45.292 The market induction of lag three

NOTE Confidence: 0.7671486

00:06:45.292 --> 00:06:47.619 and Tim three with interfere on.

NOTE Confidence: 0.7671486

00:06:47.620 --> 00:06:49.852 Here's the control and he is

NOTE Confidence: 0.7671486

00:06:49.852 --> 00:06:51.650 looking at Tim three PD.

NOTE Confidence: 0.7671486

00:06:51.650 --> 00:06:54.163 One here is a summary of data

NOTE Confidence: 0.7671486

00:06:54.163 --> 00:06:56.789 with Tim three lag through in PD,

NOTE Confidence: 0.7671486

00:06:56.790 --> 00:06:58.445 one individually and the summary

NOTE Confidence: 0.7671486

00:06:58.445 --> 00:07:00.596 of Tim three lag 3P1 positive

NOTE Confidence: 0.7671486

00:07:00.596 --> 00:07:02.296 cells within this market.

NOTE Confidence: 0.7671486

00:07:02.300 --> 00:07:04.238 Induction by type one interferons interferon

NOTE Confidence: 0.7671486

00:07:04.238 --> 00:07:06.699 beta of these Co inhibitory molecules.

NOTE Confidence: 0.7671486

00:07:06.700 --> 00:07:09.283 But surprisingly unlike in the mouse with

NOTE Confidence: 0.7671486

00:07:09.283 --> 00:07:12.487 digit is Co regulated part of the module?

NOTE Confidence: 0.7671486

00:07:12.490 --> 00:07:16.599 These other Co inhibitory molecules in human.

NOTE Confidence: 0.7671486

00:07:16.600 --> 00:07:19.505 We saw that TIGIT use digit expression

NOTE Confidence: 0.7671486

00:07:19.505 --> 00:07:22.282 in the presence of interferon is

NOTE Confidence: 0.7671486

00:07:22.282 --> 00:07:25.558 markedly decreased from 25% down to four,

NOTE Confidence: 0.7671486

00:07:25.558 --> 00:07:28.244 12% from 28% when look the

NOTE Confidence: 0.7671486

00:07:28.244 --> 00:07:30.484 RNA expression we saw there.

NOTE Confidence: 0.7671486

00:07:30.490 --> 00:07:32.278 In fact two modules,

NOTE Confidence: 0.7671486

00:07:32.278 --> 00:07:34.513 one with interferon with Lag,

NOTE Confidence: 0.7671486

00:07:34.520 --> 00:07:36.780 3 Tim, three PD,

NOTE Confidence: 0.7671486

00:07:36.780 --> 00:07:39.605 one increase with interferon beta

NOTE Confidence: 0.7671486

00:07:39.605 --> 00:07:43.208 and the other module with digit.

NOTE Confidence: 0.7671486

00:07:43.210 --> 00:07:44.389 The Jennifer subtest.

NOTE Confidence: 0.7671486

00:07:44.389 --> 00:07:45.568 Nine other modules,

NOTE Confidence: 0.7671486

00:07:45.570 --> 00:07:47.928 a CD 160 being decreased by

NOTE Confidence: 0.7671486

00:07:47.928 --> 00:07:49.107 type One interferon.

NOTE Confidence: 0.7671486

00:07:49.110 --> 00:07:51.385 So these data show that in humans

NOTE Confidence: 0.7671486

00:07:51.385 --> 00:07:53.256 there are two modules regulated

NOTE Confidence: 0.7671486

00:07:53.256 --> 00:07:55.301 by interferon that in fact

NOTE Confidence: 0.7671486

00:07:55.301 --> 00:07:57.360 go in opposite directions.

NOTE Confidence: 0.7671486

00:07:57.360 --> 00:07:58.539 Here's a kinetex.

NOTE Confidence: 0.7671486

00:07:58.539 --> 00:08:01.290 Overtime the induction of Tim three lag,

NOTE Confidence: 0.7671486

00:08:01.290 --> 00:08:02.074 three PD,

NOTE Confidence: 0.7671486

00:08:02.074 --> 00:08:04.426 one with the decrease in digit.

NOTE Confidence: 0.787109

00:08:06.930 --> 00:08:09.090 So just take a step back.

NOTE Confidence: 0.787109

00:08:09.090 --> 00:08:11.970 Why do we have an interest in Tidjane?

NOTE Confidence: 0.787109

00:08:11.970 --> 00:08:14.202 I mention this because under the

NOTE Confidence: 0.787109

00:08:14.202 --> 00:08:16.093 leadership of Antonio Mora we're

NOTE Confidence: 0.787109

00:08:16.093 --> 00:08:18.431 about to embark upon a phase one

NOTE Confidence: 0.787109

00:08:18.431 --> 00:08:20.250 clinical trial in patients with

NOTE Confidence: 0.787109

00:08:20.250 --> 00:08:22.770 glioblastoma with anti TIGIT or anti PD.

NOTE Confidence: 0.787109

00:08:22.770 --> 00:08:25.650 One or a combination of of the two,

NOTE Confidence: 0.787109

00:08:25.650 --> 00:08:27.090 working with Jemal eternal

NOTE Confidence: 0.787109

00:08:27.090 --> 00:08:28.890 and lead in my lab.

NOTE Confidence: 0.787109

00:08:28.890 --> 00:08:29.943 By Liliana Luca.

NOTE Confidence: 0.787109

00:08:29.943 --> 00:08:32.789 So why an interest in tinge of this

NOTE Confidence: 0.787109

00:08:32.789 --> 00:08:35.293 work goes back to 2012 work done by

NOTE Confidence: 0.787109

00:08:35.293 --> 00:08:38.079 S Duluth Lozano in the laboratory.

NOTE Confidence: 0.787109

00:08:38.080 --> 00:08:40.500 We've always been impressed with

NOTE Confidence: 0.787109

00:08:40.500 --> 00:08:42.920 the biologic effects of blocking

NOTE Confidence: 0.787109

00:08:43.000 --> 00:08:45.460 with anti TIGIT looking at Tibet.

NOTE Confidence: 0.787109

00:08:45.460 --> 00:08:48.220 The gamut of fear on Gata,

NOTE Confidence: 0.787109

00:08:48.220 --> 00:08:50.530 3RF-9 and and RRC expression.

NOTE Confidence: 0.787109

00:08:50.530 --> 00:08:54.306 And one can see that with anti TIGIT

NOTE Confidence: 0.787109

00:08:54.306 --> 00:08:57.132 antibody there's a market loss of

NOTE Confidence: 0.787109

00:08:57.132 --> 00:09:00.345 these cytokines in culture and if you

15

NOTE Confidence: 0.787109

00:09:00.345 --> 00:09:03.467 knock down ticket here within SHR Now

NOTE Confidence: 0.787109

00:09:03.467 --> 00:09:05.848 you have market increases engagement

NOTE Confidence: 0.787109

00:09:05.848 --> 00:09:08.824 affair on and decreases dial 10.

NOTE Confidence: 0.787109

00:09:08.830 --> 00:09:10.750 So comparing PD one antigen,

NOTE Confidence: 0.787109

00:09:10.750 --> 00:09:13.249 our hands in human systems been very

NOTE Confidence: 0.787109

00:09:13.249 --> 00:09:15.993 impressed with the effects of ticket and

NOTE Confidence: 0.787109

00:09:15.993 --> 00:09:18.405 also just comparing Ms two glioblastoma,

NOTE Confidence: 0.787109

00:09:18.410 --> 00:09:21.063 there really isn't a big difference between

NOTE Confidence: 0.787109

00:09:21.063 --> 00:09:24.529 PDL one or PD1 between Ms and brain tumors,

NOTE Confidence: 0.787109

00:09:24.530 --> 00:09:26.828 but there is a virtual absolute

NOTE Confidence: 0.787109

00:09:26.828 --> 00:09:28.360 difference between TIGIT expression,

NOTE Confidence: 0.787109

00:09:28.360 --> 00:09:31.224 typically on the CD 8 cells in patients

NOTE Confidence: 0.787109

00:09:31.224 --> 00:09:33.727 with GBM virtually absent in Ms,

NOTE Confidence: 0.787109

00:09:33.730 --> 00:09:35.944 he was looking at teacher by

NOTE Confidence: 0.787109

00:09:35.944 --> 00:09:37.940 flow and tills versus blood,

NOTE Confidence: 0.787109

00:09:37.940 --> 00:09:40.496 suggesting the potential importance of digit.

NOTE Confidence: 0.787109

00:09:40.500 --> 00:09:42.464 In the central nervous

NOTE Confidence: 0.787109

00:09:42.464 --> 00:09:43.937 system for glioblastoma.

NOTE Confidence: 0.787109

00:09:43.940 --> 00:09:46.220 So first one to work through.

NOTE Confidence: 0.787109

00:09:46.220 --> 00:09:48.445 After that identification of the

NOTE Confidence: 0.787109

00:09:48.445 --> 00:09:50.670 effect of type One interferons

NOTE Confidence: 0.787109

00:09:50.747 --> 00:09:54.261 wanted to work through the in vitro

NOTE Confidence: 0.787109

00:09:54.261 --> 00:09:55.767 transcriptional regulatory network.

NOTE Confidence: 0.787109

00:09:55.770 --> 00:09:58.380 So we use the same model

NOTE Confidence: 0.787109

00:09:58.380 --> 00:10:00.120 that would be regift.

NOTE Confidence: 0.787109

00:10:00.120 --> 00:10:02.856 Near Youssef used in terms of setting up

NOTE Confidence: 0.787109

00:10:02.856 --> 00:10:05.130 identifying the TH17A regulatory network,

NOTE Confidence: 0.787109

00:10:05.130 --> 00:10:09.360 and this is work done by a soft in BJ's lab,

NOTE Confidence: 0.787109

00:10:09.360 --> 00:10:11.436 so we needed to have higher

NOTE Confidence: 0.787109

00:10:11.436 --> 00:10:12.820 resolution transcriptomic data to

NOTE Confidence: 0.787109

00:10:12.878 --> 00:10:14.750 construct the regulatory network.

NOTE Confidence: 0.787109

00:10:14.750 --> 00:10:17.410 For those of you who aren't engaging

NOTE Confidence: 0.787109

00:10:17.410 --> 00:10:20.138 in terms of looking at RNA now,

NOTE Confidence: 0.787109

00:10:20.140 --> 00:10:22.317 what we used to do is to

NOTE Confidence: 0.787109

00:10:22.317 --> 00:10:24.760 take a T cell stimulate,

NOTE Confidence: 0.787109

00:10:24.760 --> 00:10:27.298 measure the RNA 4 hours later

NOTE Confidence: 0.787109

00:10:27.298 --> 00:10:30.129 and say this is what it is.

NOTE Confidence: 0.787109

00:10:30.130 --> 00:10:32.800 We've learned that their complex regulatory

NOTE Confidence: 0.787109

00:10:32.800 --> 00:10:35.870 networks and one needs to really do this.

NOTE Confidence: 0.787109

00:10:35.870 --> 00:10:38.510 The kinetics overtime to construct

NOTE Confidence: 0.787109

00:10:38.510 --> 00:10:40.622 a dynamic regulatory network.

NOTE Confidence: 0.787109

00:10:40.630 --> 00:10:41.728 Such a performance.

NOTE Confidence: 0.787109

00:10:41.728 --> 00:10:44.930 This network we took dive CD4 CD 8 cells,

NOTE Confidence: 0.787109

00:10:44.930 --> 00:10:45.646 stimulate them,

NOTE Confidence: 0.787109

00:10:45.646 --> 00:10:47.436 measure them in different time

NOTE Confidence: 0.787109

00:10:47.436 --> 00:10:49.220 points with control versus type.

NOTE Confidence: 0.787109

00:10:49.220 --> 00:10:51.368 One interferon did bulk RNA sequencing.

NOTE Confidence: 0.787109

00:10:51.370 --> 00:10:53.338 We did 34 samples time three

NOTE Confidence: 0.787109

00:10:53.338 --> 00:10:55.068 replicates with the same healthy

NOTE Confidence: 0.787109

00:10:55.068 --> 00:10:57.150 donor and we decided that rather

NOTE Confidence: 0.787109

00:10:57.150 --> 00:10:59.249 than looking at human variation,

NOTE Confidence: 0.787109

00:10:59.250 --> 00:11:01.212 which is significant mediated by the

NOTE Confidence: 0.787109

00:11:01.212 --> 00:11:03.539 by the genetics of the individuals,

NOTE Confidence: 0.787109

00:11:03.540 --> 00:11:05.688 we do what mouse immunologists do,

NOTE Confidence: 0.787109

00:11:05.690 --> 00:11:08.126 which is pick one strain of

NOTE Confidence: 0.787109

00:11:08.126 --> 00:11:10.750 mice and study it in detail.

NOTE Confidence: 0.787109

00:11:10.750 --> 00:11:13.396 And we measured are we did RNA seek RT

NOTE Confidence: 0.787109

00:11:13.396 --> 00:11:17.008 PCR protein for flow so that this is a

NOTE Confidence: 0.787109

00:11:17.008 --> 00:11:18.916 transcriptomic analysis of interferon

NOTE Confidence: 0.787109

00:11:18.916 --> 00:11:20.968 beta high temporal resolution.

NOTE Confidence: 0.787109

00:11:20.970 --> 00:11:22.765 We so differential expression of

NOTE Confidence: 0.787109

00:11:22.765 --> 00:11:25.064 gene levels for eight different time

19

NOTE Confidence: 0.787109

00:11:25.064 --> 00:11:26.856 points with interferon stimulation.

NOTE Confidence: 0.810376

00:11:26.860 --> 00:11:29.828 Here's a log 2 expression so we have

NOTE Confidence: 0.810376

00:11:29.828 --> 00:11:31.190 differential expression patterns.

NOTE Confidence: 0.810376

00:11:31.190 --> 00:11:33.150 We have an early expression

NOTE Confidence: 0.810376

00:11:33.150 --> 00:11:34.718 pattern here and here.

NOTE Confidence: 0.810376

00:11:34.720 --> 00:11:37.858 We have an intermediate expression pattern.

NOTE Confidence: 0.810376

00:11:37.860 --> 00:11:40.401 A late expression pattern over here and

NOTE Confidence: 0.810376

00:11:40.401 --> 00:11:43.278 finally a bimodal expression pattern goes up,

NOTE Confidence: 0.810376

00:11:43.280 --> 00:11:46.460 down and back up.

NOTE Confidence: 0.810376

00:11:46.460 --> 00:11:48.665 So in performing it just

NOTE Confidence: 0.810376

00:11:48.665 --> 00:11:49.547 transcriptomic analysis,

NOTE Confidence: 0.810376

00:11:49.550 --> 00:11:52.190 we looked divided into transcription factors.

NOTE Confidence: 0.810376

00:11:52.190 --> 00:11:53.995 Here CD four cells with

NOTE Confidence: 0.810376

00:11:53.995 --> 00:11:55.800 different kinetics and these are

NOTE Confidence: 0.810376

00:11:55.866 --> 00:11:57.930 different transcription factors.

NOTE Confidence: 0.810376

00:11:57.930 --> 00:12:00.130 Again, we can see early

NOTE Confidence: 0.810376

00:12:00.130 --> 00:12:01.450 transcription factors immediately,

NOTE Confidence: 0.810376

00:12:01.450 --> 00:12:03.139 transcription factors induced

NOTE Confidence: 0.810376

00:12:03.139 --> 00:12:05.954 and we identified different Co

NOTE Confidence: 0.810376

00:12:05.954 --> 00:12:07.844 inhibitory receptors and different

NOTE Confidence: 0.810376

00:12:07.844 --> 00:12:10.273 T cell related genes for both the

NOTE Confidence: 0.810376

00:12:10.273 --> 00:12:12.916 CD four and for the CDA population.

NOTE Confidence: 0.810376

00:12:12.920 --> 00:12:15.602 Again, in looking at the effect

NOTE Confidence: 0.810376

00:12:15.602 --> 00:12:16.496 of interferon.

NOTE Confidence: 0.810376

00:12:16.500 --> 00:12:19.181 And what it does in terms of

NOTE Confidence: 0.810376

00:12:19.181 --> 00:12:20.769 the transcriptional networks is

NOTE Confidence: 0.810376

00:12:20.769 --> 00:12:22.947 critical to look over time 'cause

NOTE Confidence: 0.810376

00:12:22.947 --> 00:12:25.624 there's a dynamic change in these

NOTE Confidence: 0.810376

00:12:25.624 --> 00:12:27.644 transcription factors and Co

NOTE Confidence: 0.810376

00:12:27.644 --> 00:12:29.159 inhibitory receptors overtime.

NOTE Confidence: 0.810376

00:12:29.160 --> 00:12:32.058 So we identified the most differentially

NOTE Confidence: 0.810376

00:12:32.058 --> 00:12:33.990 expressed transcription factors and

NOTE Confidence: 0.810376

00:12:34.059 --> 00:12:36.593 about 20 of them here and these

NOTE Confidence: 0.810376

00:12:36.593 --> 00:12:38.155 are transcription factors that

NOTE Confidence: 0.810376

00:12:38.155 --> 00:12:39.783 were differentially regulated and

NOTE Confidence: 0.810376

00:12:39.783 --> 00:12:42.652 decreased in both CD4 and CD8T cells,

NOTE Confidence: 0.810376

00:12:42.652 --> 00:12:45.564 and we as a reality check we

NOTE Confidence: 0.810376

00:12:45.564 --> 00:12:47.890 asked of these word known.

NOTE Confidence: 0.810376

00:12:47.890 --> 00:12:49.510 Interferon responsive gene.

NOTE Confidence: 0.810376

00:12:49.510 --> 00:12:52.750 So here's the IFN responsive responsive

NOTE Confidence: 0.810376

00:12:52.750 --> 00:12:55.695 gene score overtime and then the

NOTE Confidence: 0.810376

00:12:55.695 --> 00:12:58.020 green represents regulators for Co

NOTE Confidence: 0.810376

00:12:58.100 --> 00:13:00.990 inhibitory receptors until the yellow

NOTE Confidence: 0.810376

00:13:00.990 --> 00:13:03.880 HIV signatures in progressive patients.

NOTE Confidence: 0.810376

00:13:03.880 --> 00:13:06.550 And then I'll 27 regulators.

NOTE Confidence: 0.810376

00:13:06.550 --> 00:13:10.274 So we we want to examine these

NOTE Confidence: 0.810376

00:13:10.274 --> 00:13:11.870 transcriptional for these

NOTE Confidence: 0.810376

00:13:11.968 --> 00:13:15.200 transcriptional factors in detail.

NOTE Confidence: 0.810376

00:13:15.200 --> 00:13:18.512 So in order to do this and presented dilemma,

NOTE Confidence: 0.810376

00:13:18.520 --> 00:13:20.260 we had to develop new technology

NOTE Confidence: 0.810376

00:13:20.260 --> 00:13:21.997 because I called the Heisenberg

NOTE Confidence: 0.810376

00:13:21.997 --> 00:13:24.057 uncertainty principle of immunology.

NOTE Confidence: 0.810376

00:13:24.060 --> 00:13:26.208 The process of examining the cell

NOTE Confidence: 0.810376

00:13:26.208 --> 00:13:28.120 with activation perturb the system.

NOTE Confidence: 0.810376

00:13:28.120 --> 00:13:30.376 Some of looking for an electron

NOTE Confidence: 0.810376

00:13:30.376 --> 00:13:32.170 after hitting it with HV.

NOTE Confidence: 0.810376

00:13:32.170 --> 00:13:34.550 So we had to develop a gene

NOTE Confidence: 0.810376

00:13:34.550 --> 00:13:36.879 knockdown the early time points and

NOTE Confidence: 0.810376

00:13:36.879 --> 00:13:38.939 primary T cell without activating

NOTE Confidence: 0.810376

00:13:38.939 --> 00:13:41.879 T cells and again this is all work

NOTE Confidence: 0.810376

00:13:41.879 --> 00:13:44.094 developed by Tomo by Thomas Anita.

NOTE Confidence: 0.810376

00:13:44.094 --> 00:13:46.656 We used an efficient lentiviral vectors

NOTE Confidence: 0.810376

00:13:46.656 --> 00:13:48.768 that developed by wearing a green.

NOTE Confidence: 0.810376

00:13:48.770 --> 00:13:50.795 And basically one takes a

NOTE Confidence: 0.810376

00:13:50.795 --> 00:13:52.820 viral like particles V LP's

NOTE Confidence: 0.810376

00:13:52.906 --> 00:13:55.276 which is incorporated with TPX,

NOTE Confidence: 0.810376

00:13:55.280 --> 00:13:57.878 which degrades Sam Sam HD one,

NOTE Confidence: 0.810376

00:13:57.880 --> 00:13:58.824 removes restrictions,

NOTE Confidence: 0.810376

00:13:58.824 --> 00:14:01.184 you can transfect primary human

NOTE Confidence: 0.810376

00:14:01.184 --> 00:14:03.530 T cells with this Sam S1,

NOTE Confidence: 0.810376

00:14:03.530 --> 00:14:06.554 which now allows transfection with SH RNA,

NOTE Confidence: 0.810376

00:14:06.560 --> 00:14:08.730 HIV, HIV, lentivirus and all.

NOTE Confidence: 0.810376

00:14:08.730 --> 00:14:12.636 This can be done in an activated T cells.

NOTE Confidence: 0.810376

00:14:12.640 --> 00:14:14.896 Could knock down the gene and

NOTE Confidence: 0.810376

00:14:14.896 --> 00:14:17.410 then do the the incubation.

NOTE Confidence: 0.810376

00:14:17.410 --> 00:14:20.098 So here we have night CD.

NOTE Confidence: 0.810376

00:14:20.100 --> 00:14:21.664 Or cells incubated without

NOTE Confidence: 0.810376

00:14:21.664 --> 00:14:24.010 CD3 CD 28 with this procedure,

NOTE Confidence: 0.810376

00:14:24.010 --> 00:14:26.170 knocking down the different genes

NOTE Confidence: 0.810376

00:14:26.170 --> 00:14:28.827 and then there is stimulated with

NOTE Confidence: 0.810376

00:14:28.827 --> 00:14:31.335 and without interferon beta and then

NOTE Confidence: 0.810376

00:14:31.335 --> 00:14:33.589 measured five days later and then

NOTE Confidence: 0.810376

00:14:33.589 --> 00:14:36.098 we perform fax GFP of we sort of

NOTE Confidence: 0.810376

00:14:36.098 --> 00:14:38.246 the GFP positive cells were knocked

NOTE Confidence: 0.810376

00:14:38.246 --> 00:14:40.665 down and did bulk RNA sequencing

NOTE Confidence: 0.810376

00:14:40.665 --> 00:14:43.197 and you can see very efficient

NOTE Confidence: 0.810376

00:14:43.197 --> 00:14:45.516 knockdown in the GFP positive cells.

NOTE Confidence: 0.810376

00:14:45.520 --> 00:14:47.470 With these different transcription factors.

NOTE Confidence: 0.810376

00:14:47.470 --> 00:14:51.040 This is a monumental amount to work.

NOTE Confidence: 0.810376

00:14:51.040 --> 00:14:52.168 Performed by tomo.

NOTE Confidence: 0.810376

00:14:52.168 --> 00:14:54.048 So we perform principal component

NOTE Confidence: 0.810376

00:14:54.048 --> 00:14:56.408 analysis to changes in the total

NOTE Confidence: 0.810376

00:14:56.408 --> 00:14:58.343 RNA expression after the interferon

NOTE Confidence: 0.810376

00:14:58.343 --> 00:15:00.618 signature associated with each knockdown.

NOTE Confidence: 0.810376

00:15:00.620 --> 00:15:03.406 So let me just say that again,

NOTE Confidence: 0.79101753

00:15:03.410 --> 00:15:05.400 so these are PCA plots.

NOTE Confidence: 0.79101753

00:15:05.400 --> 00:15:07.405 We knock down each transcription

NOTE Confidence: 0.79101753

00:15:07.405 --> 00:15:09.803 factor and then looked at all

NOTE Confidence: 0.79101753

00:15:09.803 --> 00:15:11.747 the RNA expression and then put

NOTE Confidence: 0.79101753

00:15:11.747 --> 00:15:14.179 that into a principle component.

NOTE Confidence: 0.79101753

00:15:14.180 --> 00:15:15.724 One in principle component,

NOTE Confidence: 0.79101753

00:15:15.724 --> 00:15:19.065 to what that revealed is that the interferon

NOTE Confidence: 0.79101753

00:15:19.065 --> 00:15:21.440 one stimulated genes are positive.

NOTE Confidence: 0.79101753

00:15:21.440 --> 00:15:25.075 Regulated by we call interferon

NOTE Confidence: 0.79101753

00:15:25.075 --> 00:15:28.716 regulated module one, this modulator

NOTE Confidence: 0.79101753

00:15:28.716 --> 00:15:31.628 increased the downstream interferon.

NOTE Confidence: 0.79101753

00:15:31.630 --> 00:15:36.340 Stimulated genes with module 2 represented

NOTE Confidence: 0.79101753

00:15:36.340 --> 00:15:39.480 transcription factors that negatively

NOTE Confidence: 0.79101753

00:15:39.579 --> 00:15:43.699 regulated the interferon interferon genes.

NOTE Confidence: 0.79101753

00:15:43.700 --> 00:15:46.388 So to go into more detail,

NOTE Confidence: 0.79101753

00:15:46.390 --> 00:15:48.625 we first have the interferon

NOTE Confidence: 0.79101753

00:15:48.625 --> 00:15:49.966 regulated module one,

NOTE Confidence: 0.79101753

00:15:49.970 --> 00:15:52.586 so a something that a transcription

NOTE Confidence: 0.79101753

00:15:52.586 --> 00:15:55.317 factor that knocks down the gene

NOTE Confidence: 0.79101753

00:15:55.317 --> 00:15:57.587 will lead to decreased expression,

NOTE Confidence: 0.79101753

00:15:57.590 --> 00:15:59.830 which means as positive regulating.

NOTE Confidence: 0.79101753

00:15:59.830 --> 00:16:02.812 So the interferon regular module one

NOTE Confidence: 0.79101753

00:16:02.812 --> 00:16:04.800 regulates the conical interferon

NOTE Confidence: 0.79101753

00:16:04.874 --> 00:16:06.818 stimulated genes over here.

NOTE Confidence: 0.79101753

00:16:06.820 --> 00:16:10.012 Where is interferon regulated module two over

NOTE Confidence: 0.79101753

00:16:10.012 --> 00:16:12.839 here regulates these non Canonical jeans?

NOTE Confidence: 0.79101753

00:16:12.840 --> 00:16:15.080 Interferon stimulated genes perhaps

NOTE Confidence: 0.79101753

00:16:15.080 --> 00:16:18.975 a greater interest was looking at the

NOTE Confidence: 0.79101753

00:16:18.975 --> 00:16:21.687 Co inhibitory receptors so we have.

NOTE Confidence: 0.79101753

00:16:21.690 --> 00:16:24.078 Interferon regulated module one

NOTE Confidence: 0.79101753

00:16:24.078 --> 00:16:27.660 over here which is bath map.

NOTE Confidence: 0.79101753

00:16:27.660 --> 00:16:31.570 ETS2 SP 140 which differentially

NOTE Confidence: 0.79101753

00:16:31.570 --> 00:16:33.916 regulate lag 3.

NOTE Confidence: 0.79101753

00:16:33.920 --> 00:16:39.681 PD1 PD L1 slam F6 and other

NOTE Confidence: 0.79101753

00:16:39.681 --> 00:16:41.327 transcription factors.

NOTE Confidence: 0.79101753

00:16:41.330 --> 00:16:44.098 And then we have stat one and stat

NOTE Confidence: 0.79101753

00:16:44.098 --> 00:16:45.701 three which positively regulate

NOTE Confidence: 0.79101753

00:16:45.701 --> 00:16:48.185 Tim three but not lag 3.

NOTE Confidence: 0.79101753

00:16:48.190 --> 00:16:50.374 So we see that these different

NOTE Confidence: 0.79101753

00:16:50.374 --> 00:16:51.466 transcription factors differentially

NOTE Confidence: 0.79101753

00:16:51.466 --> 00:16:53.519 regulate different Co inhibitory receptors.

NOTE Confidence: 0.79101753

00:16:53.520 --> 00:16:55.212 And here's a summary.

NOTE Confidence: 0.79101753

00:16:55.212 --> 00:16:57.327 The data just showed you,

NOTE Confidence: 0.79101753

00:16:57.330 --> 00:17:00.120 which is the effect of these

NOTE Confidence: 0.79101753

00:17:00.120 --> 00:17:01.050 transcription factors.

NOTE Confidence: 0.79101753

00:17:01.050 --> 00:17:02.349 Interferon stimulated stimulation,

NOTE Confidence: 0.79101753

00:17:02.349 --> 00:17:05.380 so again there are two modules of

NOTE Confidence: 0.79101753

00:17:05.448 --> 00:17:07.332 transcription factors based on

NOTE Confidence: 0.79101753

00:17:07.332 --> 00:17:09.687 the global effects on interferon

NOTE Confidence: 0.79101753

00:17:09.687 --> 00:17:10.610 stimulated genes,

NOTE Confidence: 0.79101753

00:17:10.610 --> 00:17:12.430 thereby directly regulated by

NOTE Confidence: 0.79101753

00:17:12.430 --> 00:17:13.340 different modules,

NOTE Confidence: 0.79101753

00:17:13.340 --> 00:17:15.148 transcription factors and then

NOTE Confidence: 0.79101753

00:17:15.148 --> 00:17:17.408 Co inhibitory receptors are also

NOTE Confidence: 0.79101753

00:17:17.408 --> 00:17:19.251 regulated by interferon associate

NOTE Confidence: 0.79101753

00:17:19.251 --> 00:17:21.451 transcription factors and which up

NOTE Confidence: 0.79101753

00:17:21.451 --> 00:17:24.259 regulate and down regulate these receptors.

NOTE Confidence: 0.79101753

00:17:24.260 --> 00:17:26.530 So we have for example,

NOTE Confidence: 0.79101753

00:17:26.530 --> 00:17:31.130 a MoD in module one, the which is a bath.

NOTE Confidence: 0.79101753

00:17:31.130 --> 00:17:33.695 ETS2 math one which positively

NOTE Confidence: 0.79101753

00:17:33.695 --> 00:17:37.868 regulate lag 3 Tim three and PD one

NOTE Confidence: 0.79101753

00:17:37.868 --> 00:17:40.378 but negatively regulate a TIGIT.

NOTE Confidence: 0.79101753

00:17:40.380 --> 00:17:43.355 BTL BTL A and CD 160 again.

NOTE Confidence: 0.79101753

00:17:43.360 --> 00:17:46.335 Going along with the flow cytometry data.

NOTE Confidence: 0.79101753

00:17:46.340 --> 00:17:49.238 And again this I showed you step

NOTE Confidence: 0.79101753

00:17:49.238 --> 00:17:51.030 one and three here.

NOTE Confidence: 0.79101753

00:17:51.030 --> 00:17:53.202 Positively regulate Tim three

NOTE Confidence: 0.79101753

00:17:53.202 --> 00:17:55.917 but negatively regulate PD one.

NOTE Confidence: 0.79101753

00:17:55.920 --> 00:17:58.194 So then we performed a hierarchical

NOTE Confidence: 0.79101753

00:17:58.194 --> 00:17:59.710 backbone network analysis transcription

NOTE Confidence: 0.79101753

00:17:59.765 --> 00:18:00.170 factors.

NOTE Confidence: 0.79101753

00:18:00.170 --> 00:18:02.865 I'll just go over this very briefly,

NOTE Confidence: 0.79101753

00:18:02.870 --> 00:18:05.180 but basically looked at gene expression,

NOTE Confidence: 0.79101753

00:18:05.180 --> 00:18:06.338 overtime, differential expression,

NOTE Confidence: 0.79101753

00:18:06.338 --> 00:18:07.496 protein, DNA bonding,

NOTE Confidence: 0.79101753

00:18:07.500 --> 00:18:09.044 a transcription factor database

NOTE Confidence: 0.79101753

00:18:09.044 --> 00:18:09.816 is integrated.

NOTE Confidence: 0.79101753

00:18:09.820 --> 00:18:12.550 Those data looked at a rank list

NOTE Confidence: 0.79101753

00:18:12.550 --> 00:18:14.492 of transcription factors which we

NOTE Confidence: 0.79101753

00:18:14.492 --> 00:18:16.586 perturbed and knocked down as I

NOTE Confidence: 0.79101753

00:18:16.586 --> 00:18:18.569 showed you integrated those data

NOTE Confidence: 0.79101753

00:18:18.569 --> 00:18:20.993 into refine network model and what

NOTE Confidence: 0.79101753

00:18:20.993 --> 00:18:23.650 we found was at the early and

NOTE Confidence: 0.79101753

00:18:23.650 --> 00:18:25.150 intermediate network contain more

NOTE Confidence: 0.79101753

00:18:25.212 --> 00:18:27.400 up regulated transcription factors.

NOTE Confidence: 0.79101753

00:18:27.400 --> 00:18:29.940 And downregulated in contrast late

NOTE Confidence: 0.79101753

00:18:29.940 --> 00:18:32.780 network had more downregulated in up,

NOTE Confidence: 0.79101753

00:18:32.780 --> 00:18:34.732 regulated transcription factors and

NOTE Confidence: 0.79101753

00:18:34.732 --> 00:18:36.196 interferon induced differentiation.

NOTE Confidence: 0.79101753

00:18:36.200 --> 00:18:38.640 Involves dominance of the up

NOTE Confidence: 0.79101753

00:18:38.640 --> 00:18:40.104 regulated transcription factors.

NOTE Confidence: 0.79101753

00:18:40.110 --> 00:18:43.435 The first 16 hours over here which

NOTE Confidence: 0.79101753

00:18:43.435 --> 00:18:46.869 then the dominance of down regulated

NOTE Confidence: 0.79101753

00:18:46.869 --> 00:18:49.429 transcription factors over here.

NOTE Confidence: 0.79101753

00:18:49.430 --> 00:18:50.998 And just a summary.

NOTE Confidence: 0.79101753

00:18:50.998 --> 00:18:52.958 So there were dominant transcription

NOTE Confidence: 0.79101753

00:18:52.958 --> 00:18:55.494 factors that bridge each wave to the next.

NOTE Confidence: 0.79101753

00:18:55.500 --> 00:18:57.745 So the green circles represent

NOTE Confidence: 0.79101753

00:18:57.745 --> 00:18:59.541 a transcription factors that

NOTE Confidence: 0.79101753

00:18:59.541 --> 00:19:01.958 are differentially expressed in

NOTE Confidence: 0.79101753

00:19:01.958 --> 00:19:03.848 one transcriptional wave.

NOTE Confidence: 0.80999196

00:19:03.850 --> 00:19:07.036 Where is the purple circles represent

NOTE Confidence: 0.80999196

00:19:07.036 --> 00:19:09.160 transcription factors that differential

NOTE Confidence: 0.80999196

00:19:09.230 --> 00:19:11.920 expressed in all transcriptional waves.

NOTE Confidence: 0.80999196

00:19:11.920 --> 00:19:14.560 So Cal offense tattoo are early

NOTE Confidence: 0.80999196

00:19:14.560 --> 00:19:15.880 intermediate transcription factors.

NOTE Confidence: 0.80999196

00:19:15.880 --> 00:19:17.428 Math blimp one?

NOTE Confidence: 0.80999196

00:19:17.428 --> 00:19:20.008 An MIP are intermediate transcription

NOTE Confidence: 0.80999196

00:19:20.008 --> 00:19:24.304 factors and stat one hit 1A and T bet or

NOTE Confidence: 0.80999196

00:19:24.304 --> 00:19:26.351 bimodal transcription factors apart show

NOTE Confidence: 0.80999196

00:19:26.351 --> 00:19:29.444 this it just to get the bigger picture

NOTE Confidence: 0.80999196

00:19:29.444 --> 00:19:32.720 of the what nature does in terms of the

NOTE Confidence: 0.80999196

00:19:32.807 --> 00:19:35.677 biologic complexity of these systems.

NOTE Confidence: 0.80999196

00:19:35.680 --> 00:19:38.320 So a dear friend of mine,

NOTE Confidence: 0.80999196

00:19:38.320 --> 00:19:42.168 somebody may know of one of the great.

NOTE Confidence: 0.80999196

00:19:42.170 --> 00:19:44.198 Textbook authors of immunology.

NOTE Confidence: 0.80999196

00:19:44.198 --> 00:19:47.240 Abul Abbas would say to me,

NOTE Confidence: 0.80999196

00:19:47.240 --> 00:19:51.344 in Vivo Baratas and then in vitro maybe.

NOTE Confidence: 0.80999196

00:19:51.350 --> 00:19:54.102 So the challenge for us was to find

NOTE Confidence: 0.80999196

00:19:54.102 --> 00:19:56.739 an envy both system which replicate

NOTE Confidence: 0.80999196

00:19:56.739 --> 00:19:59.529 all this lovely in vitro data.

NOTE Confidence: 0.80999196

00:19:59.530 --> 00:19:59.895 So.

NOTE Confidence: 0.80999196

00:19:59.895 --> 00:20:02.450 Like to show you it in Beeville.

NOTE Confidence: 0.80999196

00:20:02.450 --> 00:20:05.106 Model that we did not develop a nature

NOTE Confidence: 0.80999196

00:20:05.106 --> 00:20:07.309 developed for us with the viral load.

NOTE Confidence: 0.80999196

00:20:07.310 --> 00:20:09.026 Strongly correlate with interferon

NOTE Confidence: 0.80999196

00:20:09.026 --> 00:20:11.600 T cell signature which is COVID-19.

NOTE Confidence: 0.80999196

00:20:11.600 --> 00:20:14.302 So this is work that is presently

NOTE Confidence: 0.80999196

00:20:14.302 --> 00:20:15.074 under revision.

NOTE Confidence: 0.80999196

00:20:15.080 --> 00:20:16.328 That nature communication,

NOTE Confidence: 0.80999196

00:20:16.328 --> 00:20:20.015 led by a team of individual or for two

NOTE Confidence: 0.80999196

00:20:20.015 --> 00:20:22.815 at the end where we perform single cell.

NOTE Confidence: 0.80999196

00:20:22.820 --> 00:20:25.070 Now sis of patients with healthy

NOTE Confidence: 0.80999196

00:20:25.070 --> 00:20:26.570 controls and various COVID-19

NOTE Confidence: 0.80999196

00:20:26.633 --> 00:20:28.628 samples of individuals with mild,

NOTE Confidence: 0.80999196

00:20:28.630 --> 00:20:31.096 severe or moderate severe disease and

NOTE Confidence: 0.80999196

00:20:31.096 --> 00:20:33.660 basically for the purpose of this talk.

NOTE Confidence: 0.80999196

00:20:33.660 --> 00:20:36.476 But we found this out as a very

NOTE Confidence: 0.80999196

00:20:36.476 --> 00:20:38.095 strong correlation between the

NOTE Confidence: 0.80999196

00:20:38.095 --> 00:20:40.627 interferon score and the viral load,

NOTE Confidence: 0.80999196

00:20:40.630 --> 00:20:42.354 as measured by PCR.

NOTE Confidence: 0.80999196

00:20:42.354 --> 00:20:43.216 Nasal swabs,

NOTE Confidence: 0.80999196

00:20:43.220 --> 00:20:43.970 in fact,

NOTE Confidence: 0.80999196

00:20:43.970 --> 00:20:46.595 if you look at the correlation time

NOTE Confidence: 0.80999196

00:20:46.595 --> 00:20:48.957 difference between here and the

NOTE Confidence: 0.80999196

00:20:48.957 --> 00:20:50.869 respective change interferon score,

NOTE Confidence: 0.80999196

00:20:50.870 --> 00:20:54.270 we had a remarkable R ^{2} .9 seven.

NOTE Confidence: 0.80999196

00:20:54.270 --> 00:20:56.370 So nature had accidentally given

NOTE Confidence: 0.80999196

00:20:56.370 --> 00:20:59.821 us a in vivo model of type one

NOTE Confidence: 0.80999196

00:20:59.821 --> 00:21:02.761 interferons in their effect on T cells.

NOTE Confidence: 0.80999196

00:21:02.770 --> 00:21:06.170 So if you look at the interferon signature,

NOTE Confidence: 0.80999196

00:21:06.170 --> 00:21:08.720 it's higher in progressive Covid patients,

NOTE Confidence: 0.80999196

00:21:08.720 --> 00:21:09.630 his controlled,

NOTE Confidence: 0.80999196

00:21:09.630 --> 00:21:12.360 stable progressive CD4 CD 8 cells.

NOTE Confidence: 0.80999196

00:21:12.360 --> 00:21:15.288 One can see that the type one interferon

NOTE Confidence: 0.80999196

00:21:15.288 --> 00:21:18.468 score went up with more progressive disease,

NOTE Confidence: 0.80999196

00:21:18.470 --> 00:21:20.906 so then we wish to ask.

NOTE Confidence: 0.80999196

00:21:20.910 --> 00:21:22.137 Looking at these,

NOTE Confidence: 0.80999196

00:21:22.137 --> 00:21:24.182 the interferon stimulated T cells

NOTE Confidence: 0.80999196

00:21:24.182 --> 00:21:26.924 in ex vivo with a similar to what

NOTE Confidence: 0.80999196

00:21:26.924 --> 00:21:29.700 we saw in vitro with our interferon

NOTE Confidence: 0.80999196

00:21:29.700 --> 00:21:31.164 transcriptional signature and

NOTE Confidence: 0.80999196

00:21:31.164 --> 00:21:33.116 the answer is yes.

NOTE Confidence: 0.80999196

00:21:33.120 --> 00:21:35.738 So here is CD4 cells CD 8

NOTE Confidence: 0.80999196

00:21:35.738 --> 00:21:37.590 cells this this column.

NOTE Confidence: 0.80999196

00:21:37.590 --> 00:21:39.218 Here are the controls,

NOTE Confidence: 0.80999196

00:21:39.218 --> 00:21:40.846 stable and progressive patients.

NOTE Confidence: 0.80999196

00:21:40.850 --> 00:21:43.430 So we see this module too.

NOTE Confidence: 0.80999196

00:21:43.430 --> 00:21:45.890 Upregulated these are highly upregulated.

NOTE Confidence: 0.80999196

00:21:45.890 --> 00:21:49.826 PD one Tim, three CTO for lag three.

NOTE Confidence: 0.80999196

00:21:49.830 --> 00:21:53.106 Precisely what we saw in vitro in

NOTE Confidence: 0.80999196

00:21:53.106 --> 00:21:58.159 CD4 and CD8 cells, whereas module 1.

NOTE Confidence: 0.80999196

00:21:58.160 --> 00:22:01.470 Which led to downregulation again

NOTE Confidence: 0.80999196

00:22:01.470 --> 00:22:06.010 of TIGIT BTL ACD 160 and such.

NOTE Confidence: 0.80999196

00:22:06.010 --> 00:22:10.850 So we had a extremely.

NOTE Confidence: 0.80999196

00:22:10.850 --> 00:22:12.578 Could the recapitulation what

NOTE Confidence: 0.80999196

00:22:12.578 --> 00:22:14.738 we saw on in vitro.

NOTE Confidence: 0.80999196

00:22:14.740 --> 00:22:17.140 Here's expression of Co inhibitory receptors

NOTE Confidence: 0.80999196

00:22:17.140 --> 00:22:19.920 for the controls and COVID-19 patients.

NOTE Confidence: 0.80999196

00:22:19.920 --> 00:22:21.216 Just to summarize,

NOTE Confidence: 0.80999196

00:22:21.216 --> 00:22:25.109 here's like 3 going up to three going up,

NOTE Confidence: 0.80999196

00:22:25.110 --> 00:22:27.270 whereas TIGIT Slam 6 and

NOTE Confidence: 0.80999196

00:22:27.270 --> 00:22:29.430 layer one all went down.

NOTE Confidence: 0.80999196

00:22:29.430 --> 00:22:33.798 Similar to what we saw in vitro.

NOTE Confidence: 0.80999196

00:22:33.800 --> 00:22:37.580 So we looked at the T cells induced in vitro,

NOTE Confidence: 0.80999196

00:22:37.580 --> 00:22:39.542 which led to with an interferon

NOTE Confidence: 0.80999196

00:22:39.542 --> 00:22:41.372 score and asked that really

NOTE Confidence: 0.80999196

00:22:41.372 --> 00:22:43.184 mirrored the transcriptional wave

NOTE Confidence: 0.80999196

00:22:43.184 --> 00:22:45.449 score aren't dividing covid CD4

NOTE Confidence: 0.807308

00:22:45.518 --> 00:22:48.238 and CD8T cells and basically one can see

NOTE Confidence: 0.807308

00:22:48.238 --> 00:22:50.820 then dividing CD four and eight cells

NOTE Confidence: 0.807308

00:22:50.820 --> 00:22:53.526 that the in vitro interference core very

NOTE Confidence: 0.807308

00:22:53.526 --> 00:22:56.095 much recapitulate if we saw in vitro.

NOTE Confidence: 0.807308

00:22:56.100 --> 00:22:59.026 And finally we looked at the relation

NOTE Confidence: 0.807308

00:22:59.026 --> 00:23:01.995 between regulators that we saw in vivo and

NOTE Confidence: 0.807308

00:23:01.995 --> 00:23:04.599 in vitro in this intermediate wave network.

NOTE Confidence: 0.807308

00:23:04.600 --> 00:23:05.920 The positive regulated

NOTE Confidence: 0.807308

00:23:05.920 --> 00:23:07.680 transcription factors in red,

NOTE Confidence: 0.807308

00:23:07.680 --> 00:23:11.200 negative and blue, and we saw that SP.

NOTE Confidence: 0.807308

00:23:11.200 --> 00:23:13.400 140 is a bidirectional regulator,

NOTE Confidence: 0.807308

00:23:13.400 --> 00:23:16.094 so this is the regulator which

NOTE Confidence: 0.807308

00:23:16.094 --> 00:23:19.338 induces lag three and other Co

NOTE Confidence: 0.807308

00:23:19.338 --> 00:23:22.046 inhibitory molecules while inhibiting.

NOTE Confidence: 0.807308

00:23:22.050 --> 00:23:25.698 Going the opposite direction for ticket.

NOTE Confidence: 0.807308

00:23:25.700 --> 00:23:27.954 And then we looked at the relationship

NOTE Confidence: 0.807308

00:23:27.954 --> 00:23:30.049 between late faith covid for lag free,

NOTE Confidence: 0.807308

00:23:30.050 --> 00:23:32.255 Tim three and PD one and found

NOTE Confidence: 0.807308

00:23:32.255 --> 00:23:34.442 that BSL three instaff 3A positive

NOTE Confidence: 0.807308

00:23:34.442 --> 00:23:36.776 regulated flag 3 and 10 three.

NOTE Confidence: 0.807308

00:23:36.780 --> 00:23:37.652 And finally,

NOTE Confidence: 0.807308

00:23:37.652 --> 00:23:40.268 looking directly in patients to the

NOTE Confidence: 0.807308

00:23:40.268 --> 00:23:42.958 SP140B cell three and stat three

NOTE Confidence: 0.807308

00:23:42.958 --> 00:23:45.138 while elevated in COVID-19 cells,

NOTE Confidence: 0.807308

00:23:45.140 --> 00:23:47.564 so we're able to recapitulate what

NOTE Confidence: 0.807308

00:23:47.564 --> 00:23:50.696 we saw in terms of induction wisco

NOTE Confidence: 0.807308

00:23:50.696 --> 00:23:53.081 inhibitory molecules in vivo in

NOTE Confidence: 0.807308

00:23:53.081 --> 00:23:56.138 terms of what we thought on Pedro.

NOTE Confidence: 0.807308

00:23:56.140 --> 00:23:57.319 So in summary,

NOTE Confidence: 0.807308

00:23:57.319 --> 00:24:00.070 interferon is a major driver of cone

NOTE Confidence: 0.807308

00:24:00.150 --> 00:24:03.615 hitori receptor regulation and human T cells.

NOTE Confidence: 0.807308

00:24:03.620 --> 00:24:05.584 The computational and biologic

NOTE Confidence: 0.807308

00:24:05.584 --> 00:24:06.566 approaches identifies.

NOTE Confidence: 0.807308

00:24:06.570 --> 00:24:08.840 Regulatory networks under interferon one.

NOTE Confidence: 0.807308

00:24:08.840 --> 00:24:11.100 Responses in human T cells.

NOTE Confidence: 0.807308

00:24:11.100 --> 00:24:13.836 There are modules of transcription factors

NOTE Confidence: 0.807308

00:24:13.836 --> 00:24:16.080 that control interferon stimulated genes.

NOTE Confidence: 0.807308

00:24:16.080 --> 00:24:16.526 Colon,

NOTE Confidence: 0.807308

00:24:16.526 --> 00:24:18.756 hip to receptors and interferon

NOTE Confidence: 0.807308

00:24:18.756 --> 00:24:21.176 which really highlights the novel

NOTE Confidence: 0.807308

00:24:21.176 --> 00:24:22.859 noncanonical transcription factors

NOTE Confidence: 0.807308

00:24:22.859 --> 00:24:25.664 beyond the conventional Jack stat

NOTE Confidence: 0.807308

00:24:25.664 --> 00:24:28.330 pathways that we previously knew about.

NOTE Confidence: 0.807308

00:24:28.330 --> 00:24:30.652 We then demonstrate the relevance of

NOTE Confidence: 0.807308

00:24:30.652 --> 00:24:34.282 our in vitro T cell type one interferon

NOTE Confidence: 0.807308

00:24:34.282 --> 00:24:37.288 responses by integrating single cell RNA.

NOTE Confidence: 0.807308

00:24:37.290 --> 00:24:39.070 See data from COVID-19.

NOTE Confidence: 0.807308

00:24:39.070 --> 00:24:42.220 Patients were strong T cell into fair.

NOTE Confidence: 0.807308

00:24:42.220 --> 00:24:44.575 One response was observed and

NOTE Confidence: 0.807308

00:24:44.575 --> 00:24:48.556 finally we identify SP 140 as a key

NOTE Confidence: 0.807308

00:24:48.556 --> 00:24:51.121 regulator that differentiates Lag 3

NOTE Confidence: 0.807308

00:24:51.121 --> 00:24:53.723 digit expression during acute viral

NOTE Confidence: 0.807308

00:24:53.723 --> 00:24:57.195 infection as well as Aaron Vivo systems.

NOTE Confidence: 0.807308

00:24:57.200 --> 00:25:00.105 So let me just acknowledge the individuals.

NOTE Confidence: 0.807308

00:25:00.110 --> 00:25:02.190 Again, this truly represents the

NOTE Confidence: 0.807308

00:25:02.190 --> 00:25:03.854 work of Thomas Amita.

NOTE Confidence: 0.807308

00:25:03.860 --> 00:25:05.940 Here, members of the laboratory

NOTE Confidence: 0.807308

00:25:05.940 --> 00:25:08.020 contributed various parts of this.

NOTE Confidence: 0.807308

00:25:08.020 --> 00:25:08.852 My long,

NOTE Confidence: 0.807308

00:25:08.852 --> 00:25:10.100 long term collaborator,

NOTE Confidence: 0.807308

00:25:10.100 --> 00:25:12.284 collaborator PJ Kutru Shadow Bergen is

NOTE Confidence: 0.807308

00:25:12.284 --> 00:25:15.089 off Marty and also wondering knowledge.

NOTE Confidence: 0.807308

00:25:15.090 --> 00:25:17.430 The covered work led by audio

NOTE Confidence: 0.807308

00:25:17.430 --> 00:25:19.514 Untermann with Tomo Jonas Scoop

NOTE Confidence: 0.807308

00:25:19.514 --> 00:25:21.326 and enough Tally Kaminski.

NOTE Confidence: 0.807308

00:25:21.330 --> 00:25:24.658 So I'll stop there and take any questions.

NOTE Confidence: 0.807308

00:25:24.660 --> 00:25:25.490 Thank you.

NOTE Confidence: 0.8629724

00:25:26.100 --> 00:25:27.318 David, thank you.

NOTE Confidence: 0.8629724

00:25:27.318 --> 00:25:30.160 What an incredible body of work and

NOTE Confidence: 0.8629724

00:25:30.240 --> 00:25:32.264 congratulations on sorting through

NOTE Confidence: 0.8629724

00:25:32.264 --> 00:25:35.300 what is clearly a very complex.

NOTE Confidence: 0.8629724

00:25:35.300 --> 00:25:37.420 Regulatory system, let me ask,

NOTE Confidence: 0.8629724

00:25:37.420 --> 00:25:40.796 and this is sort of my concrete question,

NOTE Confidence: 0.8629724

00:25:40.800 --> 00:25:42.508 which is you know.

NOTE Confidence: 0.8629724

00:25:42.508 --> 00:25:44.216 Obviously you're sorting through

NOTE Confidence: 0.8629724

00:25:44.216 --> 00:25:46.299 what's driving expression of Tim.

NOTE Confidence: 0.8629724

00:25:46.300 --> 00:25:48.988 Three lag, three TIGIT an realizing

NOTE Confidence: 0.8629724

00:25:48.988 --> 00:25:51.246 that almost the Holy Grail

NOTE Confidence: 0.8629724

00:25:51.246 --> 00:25:53.906 today is what's the next PD one?

NOTE Confidence: 0.8629724

00:25:53.910 --> 00:25:55.674 So does this work?

NOTE Confidence: 0.8629724

00:25:55.674 --> 00:25:57.879 Help us understand the relative

NOTE Confidence: 0.8629724

00:25:57.879 --> 00:26:00.453 merits of these targets and in

NOTE Confidence: 0.8629724

00:26:00.453 --> 00:26:02.503 the future of immuno oncology

NOTE Confidence: 0.8629724

00:26:02.586 --> 00:26:04.908 or give us some insight there.

NOTE Confidence: 0.83932835

00:26:06.100 --> 00:26:08.164 Great question. I think the short

NOTE Confidence: 0.83932835

00:26:08.164 --> 00:26:10.399 answer is probably not at one level.

NOTE Confidence: 0.83932835

00:26:10.400 --> 00:26:11.776 It gives us insight,

NOTE Confidence: 0.83932835

00:26:11.776 --> 00:26:14.410 so I guess one could ask what

NOTE Confidence: 0.83932835

00:26:14.410 --> 00:26:16.855 what induces type one interferons

NOTE Confidence: 0.83932835

00:26:16.855 --> 00:26:18.811 in different tissues and.

NOTE Confidence: 0.83932835

00:26:18.820 --> 00:26:21.564 And how are tumors so presumably in

NOTE Confidence: 0.83932835

00:26:21.564 --> 00:26:24.280 tumors are secreting type one interferons.

NOTE Confidence: 0.83932835

00:26:24.280 --> 00:26:27.646 We know they are and that that may be

NOTE Confidence: 0.83932835

00:26:27.646 --> 00:26:30.158 influencing the local team environment.

NOTE Confidence: 0.83932835

00:26:30.160 --> 00:26:33.409 But the reason why I say no is my

NOTE Confidence: 0.83932835

00:26:33.409 --> 00:26:35.871 suspicion is that each organ has

NOTE Confidence: 0.83932835

00:26:35.871 --> 00:26:38.490 his own set of regulatory module

NOTE Confidence: 0.83932835

00:26:38.490 --> 00:26:41.080 for controlling LG cells work.

NOTE Confidence: 0.83932835

00:26:41.080 --> 00:26:43.450 We just completed an extensive

NOTE Confidence: 0.83932835

00:26:43.450 --> 00:26:45.820 analysis paper published in Science

NOTE Confidence: 0.83932835

00:26:45.895 --> 00:26:48.765 Immunology doing a single cell RNA seek.

NOTE Confidence: 0.83932835

00:26:48.770 --> 00:26:51.262 In T cells from normal spinal fluid

NOTE Confidence: 0.83932835

00:26:51.262 --> 00:26:53.590 is normal yell graduate students and

NOTE Confidence: 0.83932835

00:26:53.590 --> 00:26:57.000 see that over 50% of the T cells.

NOTE Confidence: 0.83932835

00:26:57.000 --> 00:26:59.275 In this DSL or PD,

NOTE Confidence: 0.83932835

00:26:59.280 --> 00:27:00.868 one positive high expression

NOTE Confidence: 0.83932835

00:27:00.868 --> 00:27:02.853 digit in three with spontaneous

NOTE Confidence: 0.83932835

00:27:02.853 --> 00:27:04.429 production of gamma interferon.

NOTE Confidence: 0.83932835

00:27:04.430 --> 00:27:07.244 So I think each organ and that's

NOTE Confidence: 0.83932835

00:27:07.244 --> 00:27:09.968 why I showed the Ms GBM data.

NOTE Confidence: 0.83932835

00:27:09.970 --> 00:27:12.874 I think looking at what is expressed in

NOTE Confidence: 0.83932835

00:27:12.874 --> 00:27:15.119 tumors compared to autoimmune disease,

NOTE Confidence: 0.83932835

00:27:15.120 --> 00:27:17.454 which goes the opposite direction may

NOTE Confidence: 0.83932835

00:27:17.454 --> 00:27:21.060 give us insight as to what is the next

NOTE Confidence: 0.83932835

00:27:21.060 --> 00:27:23.040 Holy Grail coding inventory molecule.

NOTE Confidence: 0.83932835

00:27:23.040 --> 00:27:25.368 I think that would be perhaps

NOTE Confidence: 0.83932835

00:27:25.368 --> 00:27:28.219 the best way of addressing it.

NOTE Confidence: 0.83932835

00:27:28.220 --> 00:27:29.720 And this is more mechanistic,

NOTE Confidence: 0.83932835

00:27:29.720 --> 00:27:31.550 and it was surprising because it's

NOTE Confidence: 0.83932835

00:27:31.550 --> 00:27:33.618 a Vijay kept saying well Style 27.

NOTE Confidence: 0.83932835

00:27:33.620 --> 00:27:35.420 Can't you find it kept saying?

NOTE Confidence: 0.83932835

00:27:35.420 --> 00:27:37.513 Well we keep looking and kept saying

NOTE Confidence: 0.83932835

00:27:37.513 --> 00:27:39.064 what you're doing the experiment

NOTE Confidence: 0.83932835

00:27:39.064 --> 00:27:40.858 wrong and I didn't show them

NOTE Confidence: 0.83932835

00:27:40.858 --> 00:27:42.620 picture of Donald but you know,

NOTE Confidence: 0.83932835

00:27:42.620 --> 00:27:44.321 we just couldn't get it to work

NOTE Confidence: 0.83932835

00:27:44.321 --> 00:27:45.857 and then we explore different

NOTE Confidence: 0.83932835

00:27:45.857 --> 00:27:47.717 like going hit or molecules.

NOTE Confidence: 0.83932835

00:27:47.720 --> 00:27:49.616 And then it's very simple observation

NOTE Confidence: 0.83932835

00:27:49.616 --> 00:27:51.200 and actually predicted based on

NOTE Confidence: 0.83932835

00:27:51.200 --> 00:27:52.520 all the viral immunology work.

NOTE Confidence: 0.83906287

00:27:53.270 --> 00:27:55.769 Yeah, thank you, Ann Habermann has a

NOTE Confidence: 0.83906287

00:27:55.769 --> 00:27:58.358 question which is how long does the

NOTE Confidence: 0.83906287

00:27:58.358 --> 00:28:00.536 T cell response to interferon persist

NOTE Confidence: 0.83906287

00:28:00.608 --> 00:28:02.967 and why would this be a desirable

NOTE Confidence: 0.83906287

00:28:02.967 --> 00:28:04.690 response during a viral infection?

NOTE Confidence: 0.7784325

00:28:06.290 --> 00:28:09.090 Well, I I think in terms of

NOTE Confidence: 0.7784325

00:28:09.090 --> 00:28:11.320 covid there cleared two phases.

NOTE Confidence: 0.7784325

00:28:11.320 --> 00:28:13.410 The initial phase of the

NOTE Confidence: 0.7784325

00:28:13.410 --> 00:28:14.664 high interferon response.

NOTE Confidence: 0.7784325

00:28:14.670 --> 00:28:16.765 We thought the intermediate phase

NOTE Confidence: 0.7784325

00:28:16.765 --> 00:28:18.860 and then with time disappears.

NOTE Confidence: 0.7784325

00:28:18.860 --> 00:28:21.756 If one can generate so there really are

NOTE Confidence: 0.7784325

00:28:21.756 --> 00:28:23.889 these biphasic interferon response?

NOTE Confidence: 0.7784325

00:28:23.890 --> 00:28:26.898 Is this what nature does to try to

NOTE Confidence: 0.7784325

00:28:26.898 --> 00:28:29.936 clear clear viruses and we suspect that

NOTE Confidence: 0.7784325

00:28:29.936 --> 00:28:33.097 one reason why patients do badly and

NOTE Confidence: 0.7784325

00:28:33.097 --> 00:28:36.142 we're positive that the loss of TIGIT.

NOTE Confidence: 0.7784325

00:28:36.150 --> 00:28:38.230 Which is induced by interference.

NOTE Confidence: 0.7784325

00:28:38.230 --> 00:28:40.325 We have persistent high interference

NOTE Confidence: 0.7784325

00:28:40.325 --> 00:28:42.420 signature leads to a loss

NOTE Confidence: 0.7784325

00:28:42.493 --> 00:28:44.049 of the mean regulation.

NOTE Confidence: 0.7784325

00:28:44.050 --> 00:28:47.030 We actually wrote a grant

NOTE Confidence: 0.7784325

00:28:47.030 --> 00:28:48.818 that supplemental grant.

NOTE Confidence: 0.7784325

00:28:48.820 --> 00:28:50.296 Hypothesising that Tim three

NOTE Confidence: 0.7784325

00:28:50.296 --> 00:28:52.940 PD one go up and teacher will

NOTE Confidence: 0.7784325

00:28:52.940 --> 00:28:54.735 go down in covid patients.

NOTE Confidence: 0.7784325

00:28:54.740 --> 00:28:56.960 I don't like hypothesis driven science.

NOTE Confidence: 0.7784325

00:28:56.960 --> 00:28:59.920 It seemed like a long shot and were

NOTE Confidence: 0.7784325

00:28:59.920 --> 00:29:02.510 shocked to see that was going on.

NOTE Confidence: 0.7784325

00:29:02.510 --> 00:29:05.273 So so in terms of why be desire response

NOTE Confidence: 0.7784325

00:29:05.273 --> 00:29:07.688 because indifference help clear viruses.

NOTE Confidence: 0.7784325

00:29:07.690 --> 00:29:10.259 But then I think it becomes a

NOTE Confidence: 0.7784325

00:29:10.259 --> 00:29:12.130 less desirable response with time.

NOTE Confidence: 0.7784325

00:29:12.130 --> 00:29:14.433 And we suspect that will raise the

NOTE Confidence: 0.7784325

48

00:29:14.433 --> 00:29:17.150 issue that loss of digit which is

NOTE Confidence: 0.7784325

00:29:17.150 --> 00:29:19.640 really quite remarkable in these individuals.

NOTE Confidence: 0.7784325

00:29:19.640 --> 00:29:22.153 May late relate to the hyper mean

NOTE Confidence: 0.7784325

00:29:22.153 --> 00:29:24.458 response that we see in patients.

NOTE Confidence: 0.84229815

00:29:26.060 --> 00:29:28.924 Well, David, thank you for a really a

NOTE Confidence: 0.84229815

00:29:28.924 --> 00:29:31.334 terrific talk and and thank you for

NOTE Confidence: 0.84229815

00:29:31.334 --> 00:29:33.660 sharing that the work in progress.

NOTE Confidence: 0.84229815

00:29:33.660 --> 00:29:34.674 It's really impressive.

NOTE Confidence: 0.84229815

00:29:34.674 --> 00:29:37.640 Let me now turn to our next speaker,

NOTE Confidence: 0.84229815

00:29:37.640 --> 00:29:38.555 Doctor Hairy Cougar,

NOTE Confidence: 0.84229815

00:29:38.555 --> 00:29:41.573 who as you all know is is a professor

NOTE Confidence: 0.84229815

00:29:41.573 --> 00:29:44.003 of medicine and along with Marcus

NOTE Confidence: 0.84229815

00:29:44.003 --> 00:29:45.967 Bosenberg leads or yell Sporen

NOTE Confidence: 0.84229815

00:29:45.967 --> 00:29:48.133 skin cancer which were so pleased,

NOTE Confidence: 0.84229815

00:29:48.140 --> 00:29:50.226 got renewed about a year ago and

NOTE Confidence: 0.84229815

00:29:50.226 --> 00:29:52.489 continues to be extremely productive.

NOTE Confidence: 0.84229815

00:29:52.490 --> 00:29:54.555 Harriet's work in the Cancer

NOTE Confidence: 0.84229815

00:29:54.555 --> 00:29:56.207 Center has been really.

NOTE Confidence: 0.84229815

00:29:56.210 --> 00:29:58.200 Sort of the triple threat.

NOTE Confidence: 0.84229815

00:29:58.200 --> 00:30:00.540 Obviously she is a highly.

NOTE Confidence: 0.84229815

00:30:00.540 --> 00:30:02.676 Respected and highly sought after physician,

NOTE Confidence: 0.84229815

00:30:02.680 --> 00:30:05.326 but at the same time leader in

NOTE Confidence: 0.84229815

00:30:05.326 --> 00:30:07.286 research and immunology in Melanoma

NOTE Confidence: 0.84229815

00:30:07.286 --> 00:30:09.932 and also a leader of our education

NOTE Confidence: 0.84229815

00:30:09.932 --> 00:30:11.885 program and not many people can

NOTE Confidence: 0.84229815

00:30:11.885 --> 00:30:14.530 can do all that and do it so well.

NOTE Confidence: 0.84229815

00:30:14.530 --> 00:30:16.240 Harriet's work I think has really

NOTE Confidence: 0.84229815

00:30:16.307 --> 00:30:18.063 been instrumental in understanding

NOTE Confidence: 0.84229815

00:30:18.063 --> 00:30:19.819 the biology of Melanoma.

NOTE Confidence: 0.84229815

00:30:19.820 --> 00:30:21.600 How do we leverage Immunobiology

NOTE Confidence: 0.84229815

00:30:21.600 --> 00:30:22.668 towards novel therapies?

NOTE Confidence: 0.84229815

00:30:22.670 --> 00:30:24.410 And Anne frankly I suspect

NOTE Confidence: 0.84229815

00:30:24.410 --> 00:30:26.600 willingness to hear about it today,

NOTE Confidence: 0.84229815

00:30:26.600 --> 00:30:28.380 but her work on metastases

NOTE Confidence: 0.84229815

00:30:28.380 --> 00:30:30.628 as well has really, I think.

NOTE Confidence: 0.84229815

00:30:30.628 --> 00:30:31.446 Very insightful,

NOTE Confidence: 0.84229815

00:30:31.446 --> 00:30:34.320 but Harriet thank you for taking the

NOTE Confidence: 0.84229815

00:30:34.320 --> 00:30:36.728 time and sharing your work with us.

NOTE Confidence: 0.8806305

00:30:37.510 --> 00:30:39.490 Thank you Charlie and thanks

NOTE Confidence: 0.8806305

00:30:39.490 --> 00:30:41.074 for that wonderful introduction.

NOTE Confidence: 0.8806305

00:30:41.080 --> 00:30:44.976 I'm just going to share my screen here.

NOTE Confidence: 0.8806305

00:30:44.980 --> 00:30:46.900 So it's always humbling to

NOTE Confidence: 0.8806305

00:30:46.900 --> 00:30:48.436 talk after David Heffler,

NOTE Confidence: 0.8806305

00:30:48.440 --> 00:30:51.114 but that was the assignment I received,

NOTE Confidence: 0.8806305

00:30:51.120 --> 00:30:53.808 so I will do my best here.

NOTE Confidence: 0.8806305

00:30:53.810 --> 00:30:56.771 So I'm going to be talking to you about

NOTE Confidence: 0.8806305

00:30:56.771 --> 00:30:59.808 one of the sport projects which focuses

NOTE Confidence: 0.8806305

00:30:59.808 --> 00:31:03.188 on Co stimulating the the innate immune

NOTE Confidence: 0.8806305

00:31:03.188 --> 00:31:05.773 adaptive immunity to treat Melanoma.

NOTE Confidence: 0.8806305

00:31:05.780 --> 00:31:08.324 So just a few fast facts about Melanoma,

NOTE Confidence: 0.8806305

00:31:08.330 --> 00:31:10.938 so it's a disease of the relatively young

NOTE Confidence: 0.8806305

00:31:10.938 --> 00:31:13.439 most patients present between age 45 and 55.

NOTE Confidence: 0.8806305

00:31:13.440 --> 00:31:15.354 The incidence has been going up

NOTE Confidence: 0.8806305

00:31:15.354 --> 00:31:16.630 actually for decades already,

NOTE Confidence: 0.8806305

00:31:16.630 --> 00:31:18.538 so just by way of example,

NOTE Confidence: 0.8806305

00:31:18.540 --> 00:31:20.298 in 2003 there were around 54,000

NOTE Confidence: 0.8806305

00:31:20.298 --> 00:31:22.370 new cases in the United States,

NOTE Confidence: 0.8806305

00:31:22.370 --> 00:31:24.400 and just a decade and a half

NOTE Confidence: 0.8806305

00:31:24.400 --> 00:31:26.827 later it was already up to 87,000.

NOTE Confidence: 0.8806305

00:31:26.830 --> 00:31:28.979 It's now the fifth most common malignancy

NOTE Confidence: 0.8806305

00:31:28.979 --> 00:31:31.299 among men and the seventh among women,

NOTE Confidence: 0.8806305

00:31:31.300 --> 00:31:33.124 but Fortunately most of our patients

NOTE Confidence: 0.8806305

00:31:33.124 --> 00:31:34.810 present with stage one disease,

NOTE Confidence: 0.8806305

00:31:34.810 --> 00:31:36.874 so stage one refers to diseases

NOTE Confidence: 0.8806305

00:31:36.874 --> 00:31:38.779 confined to the skin and is.

NOTE Confidence: 0.8806305

00:31:38.780 --> 00:31:41.388 Then stage two is confined to the skin

NOTE Confidence: 0.8806305

00:31:41.388 --> 00:31:43.609 and thicker stage three is disease.

NOTE Confidence: 0.8806305

00:31:43.610 --> 00:31:45.563 It's spread to the lymph nodes and

NOTE Confidence: 0.8806305

00:31:45.563 --> 00:31:47.749 stage four is distant dissemination.

NOTE Confidence: 0.8806305

00:31:47.750 --> 00:31:49.820 And that's essentially what kills patients.

NOTE Confidence: 0.8806305

00:31:49.820 --> 00:31:52.809 So we're really going to be talking

NOTE Confidence: 0.8806305

00:31:52.809 --> 00:31:55.329 about stage four disease today.

NOTE Confidence: 0.8806305

00:31:55.330 --> 00:31:57.074 So for mortality, Interestingly,

NOTE Confidence: 0.8806305

00:31:57.074 --> 00:31:59.690 it was going up as well.

NOTE Confidence: 0.8806305

00:31:59.690 --> 00:32:02.306 So for 2000 three 7600 deaths,

NOTE Confidence: 0.8806305

00:32:02.310 --> 00:32:04.106 2017 ninety 700 deaths.

NOTE Confidence: 0.8806305

00:32:04.106 --> 00:32:07.540 But if you start tracking later on 2019,

NOTE Confidence: 0.8806305

00:32:07.540 --> 00:32:10.340 the death rate started to go down

53

NOTE Confidence: 0.8806305

00:32:10.340 --> 00:32:13.640 for the very first time 7230 deaths,

NOTE Confidence: 0.8806305

00:32:13.640 --> 00:32:15.820 and the projected number for

NOTE Confidence: 0.8806305

00:32:15.820 --> 00:32:17.564 this year is 6850.

NOTE Confidence: 0.8806305

00:32:17.570 --> 00:32:20.545 And this is because of

NOTE Confidence: 0.8806305

00:32:20.545 --> 00:32:22.925 our improved meta static.

NOTE Confidence: 0.8806305

00:32:22.930 --> 00:32:24.760 Approved therapies for metastatic disease,

NOTE Confidence: 0.8806305

00:32:24.760 --> 00:32:25.688 particularly immunotherapy.

NOTE Confidence: 0.8806305

00:32:25.688 --> 00:32:28.008 And that's what I'm going

NOTE Confidence: 0.8806305

00:32:28.008 --> 00:32:30.310 to be talking about today.

NOTE Confidence: 0.8806305

00:32:30.310 --> 00:32:32.710 So we've known for years that some Melanoma

NOTE Confidence: 0.8806305

00:32:32.710 --> 00:32:35.027 patients are cured by old-fashioned therapy.

NOTE Confidence: 0.8806305

00:32:35.030 --> 00:32:37.046 If you do a medister tech,

NOTE Confidence: 0.8806305

00:32:37.050 --> 00:32:37.724 to me,

NOTE Confidence: 0.8806305

00:32:37.724 --> 00:32:40.420 this is an old series published in 2011.

NOTE Confidence: 0.8806305

00:32:40.420 --> 00:32:43.073 You can see that eight or ten

NOTE Confidence: 0.8806305

00:32:43.073 --> 00:32:44.799 years at approximately 5 or 7%

NOTE Confidence: 0.8806305

00:32:44.800 --> 00:32:47.050 of patients are still alive.

NOTE Confidence: 0.8806305

00:32:47.050 --> 00:32:48.150 Chemotherapy you actually see

NOTE Confidence: 0.8806305

00:32:48.150 --> 00:32:49.800 a similar kind of a figure,

NOTE Confidence: 0.8806305

00:32:49.800 --> 00:32:51.175 and we don't think chemotherapy

NOTE Confidence: 0.8806305

00:32:51.175 --> 00:32:52.000 really prolongs survival.

NOTE Confidence: 0.8806305

00:32:52.000 --> 00:32:53.710 Maybe it's just Natural History

NOTE Confidence: 0.8806305

00:32:53.710 --> 00:32:55.724 of disease that some people live

NOTE Confidence: 0.8806305

00:32:55.724 --> 00:32:56.696 for a long time.

NOTE Confidence: 0.8806305

00:32:56.700 --> 00:32:58.956 Now over here on the right you see

NOTE Confidence: 0.8806305

00:32:58.956 --> 00:33:01.578 the the five year survival data from

NOTE Confidence: 0.8806305

00:33:01.578 --> 00:33:04.101 our flagship phase three study of

NOTE Confidence: 0.8806305

00:33:04.101 --> 00:33:06.456 epilim abalon versus nivolumab alone

NOTE Confidence: 0.8806305

00:33:06.456 --> 00:33:08.727 versus the combination thereof at

NOTE Confidence: 0.8806305

00:33:08.727 --> 00:33:11.828 where at five years you see 26% of

NOTE Confidence: 0.8806305

00:33:11.828 --> 00:33:14.156 patients are alive with EPI alone

NOTE Confidence: 0.8806305

00:33:14.156 --> 00:33:17.259 44% with anti PD one alone and 52%

NOTE Confidence: 0.8806305

00:33:17.260 --> 00:33:19.588 or maybe even higher than that.

NOTE Confidence: 0.8806305

00:33:19.590 --> 00:33:22.929 With the combination of the two drugs.

NOTE Confidence: 0.8806305

00:33:22.930 --> 00:33:24.610 So what we're really trying to

NOTE Confidence: 0.8806305

00:33:24.610 --> 00:33:26.140 do in the Melanoma field,

NOTE Confidence: 0.8806305

00:33:26.140 --> 00:33:27.600 especially the drug development field,

NOTE Confidence: 0.8806305

00:33:27.600 --> 00:33:29.256 is to raise the tennis tail

NOTE Confidence: 0.8806305

00:33:29.256 --> 00:33:31.109 at the end of the curve.

NOTE Confidence: 0.8806305

00:33:31.110 --> 00:33:33.094 So this is a figure that I borrowed

NOTE Confidence: 0.8806305

00:33:33.094 --> 00:33:35.192 from one in Microsoft students, Irina,

NOTE Confidence: 0.8806305

00:33:35.192 --> 00:33:37.236 who I'll mention as we go along,

NOTE Confidence: 0.8806305

00:33:37.240 --> 00:33:38.404 just showing that targeted

NOTE Confidence: 0.8806305

00:33:38.404 --> 00:33:39.277 therapy and chemotherapy.

NOTE Confidence: 0.8806305

00:33:39.280 --> 00:33:41.152 You're very low down here with

NOTE Confidence: 0.8806305

00:33:41.152 --> 00:33:42.400 people in Malibu starting

NOTE Confidence: 0.83978784

00:33:42.465 --> 00:33:43.887 to push up. We're pushing up

NOTE Confidence: 0.83978784

00:33:43.887 --> 00:33:45.501 further with Anti PD one even

NOTE Confidence: 0.83978784

00:33:45.501 --> 00:33:46.870 further with the combination.

NOTE Confidence: 0.83978784

00:33:46.870 --> 00:33:49.030 But really, what we need to do is to

NOTE Confidence: 0.83978784

00:33:49.030 --> 00:33:51.250 get new drugs and drug combinations,

NOTE Confidence: 0.83978784

00:33:51.250 --> 00:33:53.259 so hopefully in the next five years

NOTE Confidence: 0.83978784

00:33:53.259 --> 00:33:55.778 will have a five year survival of 80%.

NOTE Confidence: 0.83978784

00:33:55.780 --> 00:33:57.680 And eventually we'll reach 100%,

NOTE Confidence: 0.83978784

00:33:57.680 --> 00:34:01.656 and until then we still have employment.

NOTE Confidence: 0.83978784

00:34:01.660 --> 00:34:03.785 So what are the limitations

NOTE Confidence: 0.83978784

00:34:03.785 --> 00:34:04.635 of immunotherapy's,

NOTE Confidence: 0.83978784

00:34:04.640 --> 00:34:07.196 the Society of Immunotherapy or City?

NOTE Confidence: 0.83978784

00:34:07.200 --> 00:34:10.574 Which is the big society that Mario

NOTE Confidence: 0.83978784

00:34:10.574 --> 00:34:12.999 presides over recently formed a

NOTE Confidence: 0.83978784

00:34:12.999 --> 00:34:15.687 task force to define to provide

NOTE Confidence: 0.83978784

00:34:15.687 --> 00:34:17.919 some clinical definitions of.

NOTE Confidence: 0.83978784

00:34:17.920 --> 00:34:18.874 Limitations so firstly,

NOTE Confidence: 0.83978784

00:34:18.874 --> 00:34:20.464 not all patients respond upfront.

NOTE Confidence: 0.83978784

00:34:20.470 --> 00:34:22.070 We call that primary resistance.

NOTE Confidence: 0.83978784

00:34:22.070 --> 00:34:23.984 Then there's some patients that will

NOTE Confidence: 0.83978784

00:34:23.984 --> 00:34:25.260 respond and subsequently progress.

NOTE Confidence: 0.83978784

00:34:25.260 --> 00:34:26.850 So we call that secondary

NOTE Confidence: 0.83978784

00:34:26.850 --> 00:34:28.122 resistance or required resistance.

NOTE Confidence: 0.83978784

00:34:28.130 --> 00:34:30.083 The third problem that we have is

NOTE Confidence: 0.83978784

00:34:30.083 --> 00:34:31.959 that we sometimes give combinations.

NOTE Confidence: 0.83978784

00:34:31.960 --> 00:34:32.827 So for example,

NOTE Confidence: 0.83978784

00:34:32.827 --> 00:34:36.100 when we give a pill and an urban Nevada map,

NOTE Confidence: 0.83978784

00:34:36.100 --> 00:34:38.074 we give the two together for

NOTE Confidence: 0.83978784

00:34:38.074 --> 00:34:40.363 four cycles and then we continue

NOTE Confidence: 0.83978784

00:34:40.363 --> 00:34:42.155 with Nevada map monotherapy.

NOTE Confidence: 0.83978784

00:34:42.160 --> 00:34:44.464 So if somebody has a nice response in

NOTE Confidence: 0.83978784

00:34:44.464 --> 00:34:46.937 the beginning and then 18 months later

NOTE Confidence: 0.83978784

00:34:46.937 --> 00:34:48.772 when they're on monotherapy maintenance,

NOTE Confidence: 0.83978784

00:34:48.780 --> 00:34:50.046 they then progress.

NOTE Confidence: 0.83978784

00:34:50.046 --> 00:34:53.000 Is that resistance to the combination or

NOTE Confidence: 0.83978784

00:34:53.076 --> 00:34:55.736 is that resistance to the monotherapy and

NOTE Confidence: 0.83978784

00:34:55.736 --> 00:34:58.779 all of these things need to be defined?

NOTE Confidence: 0.83978784

00:34:58.780 --> 00:35:00.880 And then how do we define regrowth

NOTE Confidence: 0.83978784

00:35:00.880 --> 00:35:02.290 after patient stops therapy?

NOTE Confidence: 0.83978784

00:35:02.290 --> 00:35:04.246 So we normally treat for a

NOTE Confidence: 0.83978784

00:35:04.246 --> 00:35:06.226 limited period of time being at

NOTE Confidence: 0.83978784

00:35:06.226 --> 00:35:08.347 one years one year or two years.

NOTE Confidence: 0.83978784

00:35:08.350 --> 00:35:10.576 However long we treat for specific disease,

NOTE Confidence: 0.83978784

00:35:10.580 --> 00:35:12.568 if a patient is in off therapy

NOTE Confidence: 0.83978784

00:35:12.568 --> 00:35:14.090 and then has regrowth,

NOTE Confidence: 0.83978784

00:35:14.090 --> 00:35:15.685 does that mean they're actually

NOTE Confidence: 0.83978784

00:35:15.685 --> 00:35:17.280 resistant to the original code?

NOTE Confidence: 0.83978784

00:35:17.280 --> 00:35:18.870 Because in theory the tumor

NOTE Confidence: 0.83978784

00:35:18.870 --> 00:35:20.142 should have been gone.

NOTE Confidence: 0.83978784

00:35:20.150 --> 00:35:22.369 Or are they just dependent on it

NOTE Confidence: 0.83978784

00:35:22.369 --> 00:35:25.228 and we need to continue so the task

NOTE Confidence: 0.83978784

00:35:25.228 --> 00:35:27.844 force is starting to define all of

NOTE Confidence: 0.83978784

00:35:27.844 --> 00:35:30.308 these categories and to come up with?

NOTE Confidence: 0.83978784

00:35:30.310 --> 00:35:31.990 Specific definitions that can be

NOTE Confidence: 0.83978784

00:35:31.990 --> 00:35:34.046 used for clinical track for drug

NOTE Confidence: 0.83978784

00:35:34.046 --> 00:35:35.641 development so that all trials

NOTE Confidence: 0.83978784

00:35:35.641 --> 00:35:37.200 are designed the same way.

NOTE Confidence: 0.83978784

00:35:37.200 --> 00:35:38.436 We've started on that,

NOTE Confidence: 0.83978784

00:35:38.436 --> 00:35:39.981 but we're chipping away at

NOTE Confidence: 0.83978784

00:35:39.981 --> 00:35:41.458 all of these questions,

NOTE Confidence: 0.83978784

00:35:41.460 --> 00:35:43.242 and I think many valuable faculty

NOTE Confidence: 0.83978784

00:35:43.242 --> 00:35:44.430 are actually participating in

NOTE Confidence: 0.83978784

00:35:44.486 --> 00:35:45.926 this endeavour with concurrent

NOTE Confidence: 0.83978784

00:35:45.926 --> 00:35:47.366 with the clinical definitions,

NOTE Confidence: 0.83978784

00:35:47.370 --> 00:35:49.986 we really need to work on the science.

NOTE Confidence: 0.83978784

00:35:49.990 --> 00:35:50.620 So really,

NOTE Confidence: 0.83978784

00:35:50.620 --> 00:35:53.140 what I'm going to talk about mostly today

NOTE Confidence: 0.83978784

00:35:53.205 --> 00:35:55.564 is is translation going back and forth.

NOTE Confidence: 0.83978784

00:35:55.570 --> 00:35:56.224 So what?

NOTE Confidence: 0.83978784

00:35:56.224 --> 00:35:57.859 Why do patients develop resistance?

NOTE Confidence: 0.83978784

00:35:57.860 --> 00:35:59.500 Or many many potential mechanisms

NOTE Confidence: 0.83978784

00:35:59.500 --> 00:36:01.140 of resistance have been described,

NOTE Confidence: 0.83978784

00:36:01.140 --> 00:36:02.019 and I think.

NOTE Confidence: 0.83978784

00:36:02.019 --> 00:36:04.397 You know half of the cancer immunology world

NOTE Confidence: 0.83978784

00:36:04.397 --> 00:36:06.773 is now working on one or other of these.

NOTE Confidence: 0.83978784

00:36:06.780 --> 00:36:08.810 So some of the some of these

NOTE Confidence: 0.83978784

00:36:08.810 --> 00:36:10.679 tumors are just desert rumors,

NOTE Confidence: 0.83978784

00:36:10.680 --> 00:36:12.762 lack of till of tumor infiltrating

00:36:12.762 --> 00:36:14.910 lymphocytes within the tumors you can have,

00:36:14.910 --> 00:36:17.510 in effect of priming of your T cells.

00:36:17.510 --> 00:36:19.460 We know that defective antigen presentation,

00:36:19.460 --> 00:36:20.756 such as bile acid,

00:36:20.756 --> 00:36:21.080 beta,

00:36:21.080 --> 00:36:22.705 two microglobulin in the tumor

00:36:22.705 --> 00:36:24.005 cells will cause resistance.

00:36:24.010 --> 00:36:25.630 Sometimes T cells get exhausted

00:36:25.630 --> 00:36:26.926 as David just mentioned.

00:36:26.930 --> 00:36:29.279 Of course lack of PDL one in the tumor

00:36:29.279 --> 00:36:31.143 or in the tumor microenvironment

00:36:31.143 --> 00:36:33.441 suggests that we don't live PD

00:36:33.505 --> 00:36:34.852 one. Inhibition isn't going

00:36:34.852 --> 00:36:37.036 to do very much over there.

00:36:37.040 --> 00:36:38.710 And then the other costimulatory

00:36:38.710 --> 00:36:40.046 or Co inhibitory molecules

NOTE Confidence: 0.8146802

00:36:40.046 --> 00:36:41.539 that David just mentioned,

NOTE Confidence: 0.8146802

00:36:41.540 --> 00:36:42.575 particularly teachers and

NOTE Confidence: 0.8146802

00:36:42.575 --> 00:36:44.645 Lag 3 might also be present,

NOTE Confidence: 0.8146802

00:36:44.650 --> 00:36:47.611 and maybe it's just not sufficient in

NOTE Confidence: 0.8146802

00:36:47.611 --> 00:36:50.996 all cases to inhibit PD one or PDL 1.

NOTE Confidence: 0.8146802

00:36:51.000 --> 00:36:53.730 And finally there there are many other

NOTE Confidence: 0.8146802

00:36:53.730 --> 00:36:56.356 immune inhibitory cells that we need to

NOTE Confidence: 0.8146802

00:36:56.356 --> 00:36:58.432 focus on in the tumor microenvironment,

NOTE Confidence: 0.8146802

00:36:58.440 --> 00:37:00.810 and sometimes those might just be

NOTE Confidence: 0.8146802

00:37:00.810 --> 00:37:03.278 overpowering the role of the T cells.

NOTE Confidence: 0.8146802

00:37:03.280 --> 00:37:06.311 So examples are MD's season T regs

NOTE Confidence: 0.8146802

00:37:06.311 --> 00:37:09.310 which might need inhibition as well.

NOTE Confidence: 0.8146802

00:37:09.310 --> 00:37:10.890 So when we started putting

NOTE Confidence: 0.8146802

00:37:10.890 --> 00:37:12.890 together the renewal of the spore,

NOTE Confidence: 0.8146802

00:37:12.890 --> 00:37:14.726 one of the projects that we

NOTE Confidence: 0.8146802

00:37:14.726 --> 00:37:16.356 worked on is specifically looking

NOTE Confidence: 0.8146802

00:37:16.356 --> 00:37:18.086 at the innate immune system.

NOTE Confidence: 0.8146802

00:37:18.090 --> 00:37:20.040 So Sucic, when she was here,

NOTE Confidence: 0.8146802

00:37:20.040 --> 00:37:21.680 provided all of the preliminary

NOTE Confidence: 0.8146802

00:37:21.680 --> 00:37:23.689 data which I'll be reviewing very

NOTE Confidence: 0.8146802

00:37:23.689 --> 00:37:25.239 quickly and some sewers left,

NOTE Confidence: 0.8146802

00:37:25.240 --> 00:37:27.190 Marcus has become a key collaborator,

NOTE Confidence: 0.8146802

00:37:27.190 --> 00:37:29.283 and actually it's now become a whole

NOTE Confidence: 0.8146802

00:37:29.283 --> 00:37:31.369 village in the whole party because

NOTE Confidence: 0.8146802

00:37:31.369 --> 00:37:33.619 all of the investigators and trainees

NOTE Confidence: 0.8146802

00:37:33.619 --> 00:37:35.784 listed over here on the right are

NOTE Confidence: 0.8146802

00:37:35.784 --> 00:37:37.302 quite involved in this project,

NOTE Confidence: 0.8146802

00:37:37.302 --> 00:37:39.474 and I'll mention some of their.

NOTE Confidence: 0.8146802

00:37:39.480 --> 00:37:42.140 Contribuciones as we go along.

NOTE Confidence: 0.8146802

00:37:42.140 --> 00:37:44.270 So Sue started off looking at

NOTE Confidence: 0.8146802

00:37:44.270 --> 00:37:46.270 Marcus is young 1.7 models,

NOTE Confidence: 0.8146802

00:37:46.270 --> 00:37:48.424 so I'm sure everybody knows that

NOTE Confidence: 0.8146802

00:37:48.424 --> 00:37:51.089 this is a cell line that was

NOTE Confidence: 0.8146802

00:37:51.089 --> 00:37:53.763 generated from the from a gym model.

NOTE Confidence: 0.8146802

00:37:53.770 --> 00:37:56.020 It's byref mutant and P tenancy.

NOTE Confidence: 0.8146802

00:37:56.020 --> 00:37:58.540 DK into a null and when you take

NOTE Confidence: 0.8146802

00:37:58.540 --> 00:38:00.857 this young 1.7 and you treated with

NOTE Confidence: 0.8146802

00:38:00.857 --> 00:38:04.086 anti PD one you see over here there's

NOTE Confidence: 0.8146802

00:38:04.086 --> 00:38:06.138 absolutely no tumor regression.

NOTE Confidence: 0.8146802

00:38:06.140 --> 00:38:08.015 If you irradiate the cells

NOTE Confidence: 0.8146802

00:38:08.015 --> 00:38:09.515 and generated the second.

NOTE Confidence: 0.8146802

00:38:09.520 --> 00:38:12.268 This tortoise airline called Yammer 1.7.

NOTE Confidence: 0.8146802

00:38:12.270 --> 00:38:14.268 ER stands for exposed to radiation.

NOTE Confidence: 0.8146802

00:38:14.270 --> 00:38:16.926 You get some sensitivity to anti PD one,

NOTE Confidence: 0.8146802

00:38:16.930 --> 00:38:19.145 but ultimately with time these

NOTE Confidence: 0.8146802

00:38:19.145 --> 00:38:21.880 tumors to grow out as well.

NOTE Confidence: 0.8146802

00:38:21.880 --> 00:38:24.112 So the first question next to asked was

NOTE Confidence: 0.8146802

00:38:24.112 --> 00:38:26.705 what was actually in these in these tumors.

NOTE Confidence: 0.8146802

00:38:26.710 --> 00:38:29.730 So all of this work was done by Kurt Perry,

NOTE Confidence: 0.8146802

00:38:29.730 --> 00:38:31.536 who's over here on the right.

NOTE Confidence: 0.8146802

00:38:31.540 --> 00:38:33.868 We can see his picture and he's actually

NOTE Confidence: 0.8146802

00:38:33.868 --> 00:38:36.378 one of the new fellows that match to.

NOTE Confidence: 0.8146802

00:38:36.380 --> 00:38:38.372 Our program will be very thrilled

NOTE Confidence: 0.8146802

00:38:38.372 --> 00:38:41.163 to have him as part of our

NOTE Confidence: 0.8146802

00:38:41.163 --> 00:38:42.549 medical oncology fellowship.

NOTE Confidence: 0.8146802

00:38:42.550 --> 00:38:44.590 So first question that they asked

NOTE Confidence: 0.8146802

00:38:44.590 --> 00:38:46.491 was what was the infiltrating

NOTE Confidence: 0.8146802

00:38:46.491 --> 00:38:48.816 tumor content in these mass?

NOTE Confidence: 0.8146802

00:38:48.820 --> 00:38:50.084 In these mass melanomas?

NOTE Confidence: 0.8146802

00:38:50.084 --> 00:38:52.506 And it turns out that the predominant

NOTE Confidence: 0.8146802

00:38:52.506 --> 00:38:55.272 cell type was actually terms or

NOTE Confidence: 0.8146802

00:38:55.272 --> 00:38:56.655 tumor associated macrophages.

NOTE Confidence: 0.8146802

00:38:56.660 --> 00:38:59.103 The next question that they asked was

NOTE Confidence: 0.8146802

00:38:59.103 --> 00:39:01.759 what kind of macrophages are these?

NOTE Confidence: 0.8146802

00:39:01.760 --> 00:39:05.420 Are there more inflammatory or inhibitory?

NOTE Confidence: 0.8146802

00:39:05.420 --> 00:39:07.232 Classic definition of M1 and M2

NOTE Confidence: 0.8146802

00:39:07.232 --> 00:39:09.353 and over here on the right you

NOTE Confidence: 0.8146802

00:39:09.353 --> 00:39:11.334 see a contour plot where on the

NOTE Confidence: 0.8146802

00:39:11.399 --> 00:39:13.311 X axis you've got F 480 and the

NOTE Confidence: 0.8146802

00:39:13.311 --> 00:39:16.400 Y axis you've got like 6 E.

NOTE Confidence: 0.8146802

00:39:16.400 --> 00:39:18.122 It turns out that there at

NOTE Confidence: 0.8146802

00:39:18.122 --> 00:39:18.983 least three populations,

NOTE Confidence: 0.8146802

00:39:18.990 --> 00:39:20.718 and they're probably more than that,

NOTE Confidence: 0.8146802

00:39:20.720 --> 00:39:22.160 and just in a nutshell,

NOTE Confidence: 0.8146802

00:39:22.160 --> 00:39:23.888 the terms that have highlights 6,

NOTE Confidence: 0.8146802

00:39:23.890 --> 00:39:26.186 three like 6 E and low EF 480,

NOTE Confidence: 0.8146802

00:39:26.190 --> 00:39:27.834 or those that are more inflammatory

NOTE Confidence: 0.8146802

00:39:27.834 --> 00:39:30.080 in the ones on the right over here

NOTE Confidence: 0.8146802

00:39:30.080 --> 00:39:31.724 are those that are presumed to

NOTE Confidence: 0.8405346

00:39:31.779 --> 00:39:32.820 be more inhibitory.

NOTE Confidence: 0.83383965

00:39:35.970 --> 00:39:38.500 So at that point they said, OK, we've got.

NOTE Confidence: 0.83383965

00:39:38.500 --> 00:39:39.620 We've got these terms.

NOTE Confidence: 0.83383965

00:39:39.620 --> 00:39:41.587 We need to try to modulate them,

NOTE Confidence: 0.83383965

00:39:41.590 --> 00:39:43.246 and there are many, many mechanisms

NOTE Confidence: 0.83383965

00:39:43.246 --> 00:39:44.680 out there for modulating terms.

NOTE Confidence: 0.83383965

00:39:44.680 --> 00:39:46.661 But the ones that they chose to

NOTE Confidence: 0.83383965

00:39:46.661 --> 00:39:48.332 work on with CD, 40, agonism,

NOTE Confidence: 0.83383965

00:39:48.332 --> 00:39:49.737 and CSF, one R inhibition,

NOTE Confidence: 0.83383965

00:39:49.740 --> 00:39:51.786 and in the beginning they used

NOTE Confidence: 0.83383965

00:39:51.786 --> 00:39:53.150 a small molecule inhibitor.

NOTE Confidence: 0.83383965

00:39:53.150 --> 00:39:55.316 So if you take these memory

NOTE Confidence: 0.83383965

00:39:55.316 --> 00:39:57.410 cells and implant them in mice,

NOTE Confidence: 0.83383965

00:39:57.410 --> 00:40:00.370 and you treat either with control vehicle or.

NOTE Confidence: 0.83383965

00:40:00.370 --> 00:40:01.554 The CD 40 agonist.

NOTE Confidence: 0.83383965

00:40:01.554 --> 00:40:03.330 You'll see some some decrease in

NOTE Confidence: 0.83383965

00:40:03.395 --> 00:40:05.222 the size of the tumors with the

NOTE Confidence: 0.83383965

00:40:05.222 --> 00:40:07.521 CD 40 agonist if you give the CSF

NOTE Confidence: 0.83383965

00:40:07.521 --> 00:40:09.266 one receptor inhibitor you get a

NOTE Confidence: 0.83383965

00:40:09.266 --> 00:40:10.696 similar amount of tumor reduction.

NOTE Confidence: 0.83383965

00:40:10.700 --> 00:40:12.416 If you give the two together,

NOTE Confidence: 0.83383965

00:40:12.420 --> 00:40:13.458 you get synergism.

NOTE Confidence: 0.83383965

00:40:13.458 --> 00:40:17.150 As you can see by the red line over here.

NOTE Confidence: 0.83383965

00:40:17.150 --> 00:40:19.341 So to look back into the similar

NOTE Confidence: 0.83383965

00:40:19.341 --> 00:40:19.967 contour plots,

NOTE Confidence: 0.83383965

00:40:19.970 --> 00:40:22.308 what is the content of these different

NOTE Confidence: 0.83383965

00:40:22.308 --> 00:40:24.491 tumors within the mice treated in the

NOTE Confidence: 0.83383965

00:40:24.491 --> 00:40:26.857 graph over here on the left you can

NOTE Confidence: 0.83383965

00:40:26.857 --> 00:40:29.034 see that when you give doublet therapy,

69

NOTE Confidence: 0.83383965

00:40:29.040 --> 00:40:31.231 the CD 40 agonist in the CSF

NOTE Confidence: 0.83383965

00:40:31.231 --> 00:40:32.170 one receptor inhibitory,

NOTE Confidence: 0.83383965

00:40:32.170 --> 00:40:34.319 the main difference is that you get

NOTE Confidence: 0.83383965

00:40:34.319 --> 00:40:36.463 an increase in this little group over

NOTE Confidence: 0.83383965

00:40:36.463 --> 00:40:39.060 here on the right in the upper corner,

NOTE Confidence: 0.83383965

00:40:39.060 --> 00:40:41.924 which are like 60 high and in 480 low and are

NOTE Confidence: 0.83383965

00:40:41.924 --> 00:40:44.378 presumed to be more inflammatory macrophages,

NOTE Confidence: 0.83383965

00:40:44.380 --> 00:40:45.319 and that's essentially

NOTE Confidence: 0.83383965

00:40:45.319 --> 00:40:46.884 verified on the bar graph.

NOTE Confidence: 0.83383965

00:40:46.890 --> 00:40:48.560 Over here on the left.

NOTE Confidence: 0.83383965

00:40:48.560 --> 00:40:49.430 On the right,

NOTE Confidence: 0.83383965

00:40:49.430 --> 00:40:51.460 at the bottom over here you can

NOTE Confidence: 0.83383965

00:40:51.525 --> 00:40:53.789 see this to the changes in the in

NOTE Confidence: 0.83383965

00:40:53.789 --> 00:40:55.780 the immune infiltrating content,

NOTE Confidence: 0.83383965

00:40:55.780 --> 00:40:57.730 and I think what's most interesting

NOTE Confidence: 0.83383965

00:40:57.730 --> 00:40:59.946 over here is that when you give

NOTE Confidence: 0.83383965

00:40:59.946 --> 00:41:01.638 the CD 40 agonist along with

NOTE Confidence: 0.83383965

00:41:01.638 --> 00:41:03.650 the CSF one receptor inhibitor,

NOTE Confidence: 0.83383965

00:41:03.650 --> 00:41:05.618 you do get an increase of

NOTE Confidence: 0.83383965

00:41:05.618 --> 00:41:06.930 infiltration of T cells.

NOTE Confidence: 0.83383965

00:41:06.930 --> 00:41:09.378 So possibly we might be able to make

NOTE Confidence: 0.83383965

00:41:09.378 --> 00:41:11.076 desert those desert tumors more

NOTE Confidence: 0.83383965

00:41:11.076 --> 00:41:13.820 inflamed by using a regimen such as this.

NOTE Confidence: 0.83383965

00:41:13.820 --> 00:41:15.668 And in addition you get more

NOTE Confidence: 0.83383965

00:41:15.668 --> 00:41:17.420 PD one high T cells.

NOTE Confidence: 0.8104826

00:41:19.820 --> 00:41:22.214 So Catherine Miller Jensen on the main

NOTE Confidence: 0.8104826

00:41:22.214 --> 00:41:24.475 campus is developed a technology for

NOTE Confidence: 0.8104826

00:41:24.475 --> 00:41:26.430 single cell site eccentric creation,

NOTE Confidence: 0.8104826

00:41:26.430 --> 00:41:29.038 and she looked at what the difference of

NOTE Confidence: 0.8104826

00:41:29.038 --> 00:41:30.812 was between these different treatment

NOTE Confidence: 0.8104826

00:41:30.812 --> 00:41:33.791 arms and what you can see here on

NOTE Confidence: 0.8104826

00:41:33.791 --> 00:41:35.599 the principle component analysis.

NOTE Confidence: 0.8104826

00:41:35.600 --> 00:41:38.330 On the left is that if you only treat with

NOTE Confidence: 0.8104826

00:41:38.402 --> 00:41:40.487 assistive one receptor inhibitor versus

NOTE Confidence: 0.8104826

00:41:40.487 --> 00:41:43.679 the city for The Agonist inhibitor alone,

NOTE Confidence: 0.8104826

00:41:43.680 --> 00:41:44.766 versus the combination,

NOTE Confidence: 0.8104826

00:41:44.766 --> 00:41:46.938 you get quite a different pattern

NOTE Confidence: 0.8104826

00:41:46.938 --> 00:41:49.296 of cytokine secretion on the right.

NOTE Confidence: 0.8104826

00:41:49.300 --> 00:41:51.836 Oh, I'm sorry in the middle over here,

NOTE Confidence: 0.8104826

00:41:51.840 --> 00:41:53.800 you've got a heat map which we

NOTE Confidence: 0.8104826

00:41:53.800 --> 00:41:55.320 essentially depicts the differences,

NOTE Confidence: 0.8104826

00:41:55.320 --> 00:41:57.632 and some of them are highlighted over here

NOTE Confidence: 0.8104826

00:41:57.632 --> 00:42:00.397 on the right for cytokines and chemo kinds.

NOTE Confidence: 0.8104826

00:42:00.400 --> 00:42:02.290 Pretty much as as one would expect

NOTE Confidence: 0.8104826

00:42:02.290 --> 00:42:04.518 when you give the combination therapy,

NOTE Confidence: 0.8104826

00:42:04.520 --> 00:42:06.739 you get an increase in TNF Alpha.

NOTE Confidence: 0.8104826

00:42:06.740 --> 00:42:08.972 I'll 12 BIL 6 etc and the same

NOTE Confidence: 0.8104826

00:42:08.972 --> 00:42:11.598 for the panel of the side of kinds

NOTE Confidence: 0.8104826

00:42:11.598 --> 00:42:14.028 of the chemo kinds at the bottom.

NOTE Confidence: 0.8104826

00:42:14.030 --> 00:42:15.715 So essentially the doublet therapy

NOTE Confidence: 0.8104826

00:42:15.715 --> 00:42:17.767 over here is inducing quite quite

NOTE Confidence: 0.8104826

00:42:17.767 --> 00:42:19.307 vast changes in the animals.

NOTE Confidence: 0.8104826

00:42:19.310 --> 00:42:21.846 What does it do to the T cells?

NOTE Confidence: 0.8104826

00:42:21.850 --> 00:42:23.758 What else is important over here?

NOTE Confidence: 0.8104826

00:42:23.760 --> 00:42:26.048 What you see on this figure here is

NOTE Confidence: 0.8104826

00:42:26.048 --> 00:42:28.526 that when you give the doublet therapy,

NOTE Confidence: 0.8104826

00:42:28.530 --> 00:42:30.045 you can actually abrogate the

NOTE Confidence: 0.8104826

00:42:30.045 --> 00:42:32.284 effect if you give anti TNF Alpha

NOTE Confidence: 0.8104826

00:42:32.284 --> 00:42:33.616 or anti interferon gamma,

NOTE Confidence: 0.8104826

00:42:33.620 --> 00:42:35.205 again highlighting the the importance

NOTE Confidence: 0.8104826

00:42:35.205 --> 00:42:38.068 of the T cells in this process as well.

NOTE Confidence: 0.8104826

00:42:38.070 --> 00:42:40.198 So with that at the time we concluded

NOTE Confidence: 0.8104826

00:42:40.198 --> 00:42:42.547 that CSF one receptor inhibitors in city

NOTE Confidence: 0.8104826

00:42:42.547 --> 00:42:44.695 for The Agonist treatment can induce

NOTE Confidence: 0.8104826

00:42:44.695 --> 00:42:46.310 an inflammatory term population in

NOTE Confidence: 0.8104826

00:42:46.310 --> 00:42:48.396 the two in the tumor microenvironment.

NOTE Confidence: 0.8104826

00:42:48.396 --> 00:42:51.540 It also induces a functional T cell response.

NOTE Confidence: 0.8104826

00:42:51.540 --> 00:42:53.759 And this is dependent on TNF Alpha

NOTE Confidence: 0.8104826

00:42:53.759 --> 00:42:54.710 and interferon gamma,

NOTE Confidence: 0.8104826

00:42:54.710 --> 00:42:56.498 and these were the preliminary data

NOTE Confidence: 0.8104826

00:42:56.498 --> 00:42:58.829 that we had to start our project.

NOTE Confidence: 0.8104826

00:42:58.830 --> 00:43:00.420 So when we received funding,

NOTE Confidence: 0.8104826

00:43:00.420 --> 00:43:02.639 we by then Curtis Perry had gone

NOTE Confidence: 0.8104826

00:43:02.639 --> 00:43:03.590 off for residency.

NOTE Confidence: 0.8104826

00:43:03.590 --> 00:43:05.704 So Bill Dembski came in to help

NOTE Confidence: 0.8104826

00:43:05.704 --> 00:43:08.255 us and you'll see a whole cast of

NOTE Confidence: 0.8104826

00:43:08.255 --> 00:43:10.240 trainees along the way over here.

NOTE Confidence: 0.8104826

00:43:10.240 --> 00:43:12.814 So Bill Bill did a heroic job over here

00:43:12.814 --> 00:43:15.319 with bringing us closer to the clinic.

00:43:15.320 --> 00:43:17.424 So we decided at that point not to

00:43:17.424 --> 00:43:20.070 use a series of 1 receptor inhibitor,

00:43:20.070 --> 00:43:21.390 the small molecule inhibitor,

00:43:21.390 --> 00:43:23.370 but rather to move towards and.

00:43:23.370 --> 00:43:24.654 Antibody because of precision

00:43:24.654 --> 00:43:25.938 of drugging our target.

00:43:25.940 --> 00:43:27.540 Also in the clinical arena,

00:43:27.540 --> 00:43:29.605 it would be very difficult to take

00:43:29.605 --> 00:43:32.157 a patient who progressed on a PD one

00:43:32.157 --> 00:43:34.497 inhibitor and not to continue the PD

00:43:34.497 --> 00:43:36.525 one inhibitor with the next regiment.

00:43:36.530 --> 00:43:38.225 That's essentially how most regimens

00:43:38.225 --> 00:43:40.256 are now being developed for Melanoma

00:43:40.256 --> 00:43:41.666 and renal cell as well.

NOTE Confidence: 0.8104826

00:43:41.670 --> 00:43:45.200 So the question is what can we add onto a PD?

NOTE Confidence: 0.8104826

00:43:45.200 --> 00:43:47.062 One inhibitor to get us there so

NOTE Confidence: 0.8104826

00:43:47.062 --> 00:43:49.424 he these are large groups of mice

NOTE Confidence: 0.8104826

00:43:49.424 --> 00:43:51.299 treated either with control vehicle,

NOTE Confidence: 0.8104826

00:43:51.300 --> 00:43:53.603 either one of the three drugs alone

NOTE Confidence: 0.8104826

00:43:53.603 --> 00:43:54.950 so anti PD one.

NOTE Confidence: 0.8104826

00:43:54.950 --> 00:43:56.846 CD40 agonist or CSF one receptor.

NOTE Confidence: 0.8104826

00:43:56.850 --> 00:43:58.608 Any doublet of the from among

NOTE Confidence: 0.8104826

00:43:58.608 --> 00:44:00.320 those three and the triplet,

NOTE Confidence: 0.8104826

00:44:00.320 --> 00:44:02.616 and you can see by the Brown line

NOTE Confidence: 0.8104826

00:44:02.616 --> 00:44:04.957 over here that by far the triplet

NOTE Confidence: 0.8104826

00:44:04.957 --> 00:44:06.657 therapy was superior on the

NOTE Confidence: 0.8090304

00:44:06.729 --> 00:44:08.571 right you see the spider plots

NOTE Confidence: 0.8090304

00:44:08.571 --> 00:44:10.730 for the size of these tumors,

NOTE Confidence: 0.8090304

00:44:10.730 --> 00:44:12.590 which in the beginning

NOTE Confidence: 0.8090304

00:44:12.590 --> 00:44:15.100 they'll grow and then shrink.

NOTE Confidence: 0.8090304

00:44:15.100 --> 00:44:16.033 Irina clickbait ever.

NOTE Confidence: 0.8090304

00:44:16.033 --> 00:44:18.575 Who's MD PhD student who is in Marcus's

NOTE Confidence: 0.8090304

00:44:18.575 --> 00:44:21.015 lab at the time or selection Marcus is

NOTE Confidence: 0.8090304

00:44:21.015 --> 00:44:23.171 lab did similar experiments on aranka

NOTE Confidence: 0.8090304

00:44:23.171 --> 00:44:25.626 model because we wanted to go into

NOTE Confidence: 0.8090304

00:44:25.626 --> 00:44:27.922 the clinic in kidney cancer as well.

NOTE Confidence: 0.8090304

00:44:27.930 --> 00:44:29.575 Again, showing their triple therapy

NOTE Confidence: 0.8090304

00:44:29.575 --> 00:44:31.220 was superior to double therapy.

NOTE Confidence: 0.8090304

00:44:31.220 --> 00:44:32.860 Not quite as pretty as

NOTE Confidence: 0.8090304

00:44:32.860 --> 00:44:34.172 in the Melanoma models,

NOTE Confidence: 0.8090304

00:44:34.180 --> 00:44:35.790 but that's then that's consistent

NOTE Confidence: 0.8090304

00:44:35.790 --> 00:44:38.130 with what we see in the clinic,

NOTE Confidence: 0.8090304

00:44:38.130 --> 00:44:40.692 whereby renal cell patients respond less well

NOTE Confidence: 0.8090304

00:44:40.692 --> 00:44:43.170 to these therapies then Melanoma patients.

NOTE Confidence: 0.8090304

00:44:43.170 --> 00:44:44.646 So because it's a sport project,

NOTE Confidence: 0.8090304

00:44:44.650 --> 00:44:46.410 you have to have a clinical Pi and

NOTE Confidence: 0.8090304

00:44:46.410 --> 00:44:48.040 a basic science Pi and everything

NOTE Confidence: 0.8090304

00:44:48.040 --> 00:44:50.014 has to have a clinical trial so

NOTE Confidence: 0.8090304

00:44:50.014 --> 00:44:51.316 to go back to the bedside.

NOTE Confidence: 0.8090304

00:44:51.320 --> 00:44:53.534 What are we going to do with these data?

NOTE Confidence: 0.8090304

00:44:53.540 --> 00:44:55.262 So we formed collaborations with Bristol

NOTE Confidence: 0.8090304

00:44:55.262 --> 00:44:57.381 Myers Squibb and a company called a passage

NOTE Confidence: 0.8090304

00:44:57.381 --> 00:44:59.447 and that makes a CD 40 agonist and we

NOTE Confidence: 0.8090304

00:44:59.447 --> 00:45:02.590 were able to get them to work together.

NOTE Confidence: 0.8090304

00:45:02.590 --> 00:45:04.550 The problem was that there was no

NOTE Confidence: 0.8090304

00:45:04.550 --> 00:45:06.388 phase one data for the triplet.

NOTE Confidence: 0.8090304

00:45:06.390 --> 00:45:08.366 Now could be oralism AB which is the

NOTE Confidence: 0.8090304

00:45:08.366 --> 00:45:10.329 CSF one receptor antibody and the

NOTE Confidence: 0.8090304

00:45:10.329 --> 00:45:12.447 volume Abbott being given to hundreds

NOTE Confidence: 0.8090304

00:45:12.511 --> 00:45:14.615 of patients in BM S LED studies in

NOTE Confidence: 0.8090304

00:45:14.615 --> 00:45:16.286 the activity in Melanoma was modest,

NOTE Confidence: 0.8090304

00:45:16.286 --> 00:45:18.346 but there was a little bit of

NOTE Confidence: 0.8090304

00:45:18.346 --> 00:45:19.526 activity at that point.

NOTE Confidence: 0.8090304

00:45:19.530 --> 00:45:22.338 We knew that a CD 40 agonist can have

NOTE Confidence: 0.8090304

00:45:22.338 --> 00:45:23.708 significant activity in Melanoma

NOTE Confidence: 0.8090304

00:45:23.708 --> 00:45:26.025 based on studies by done by the

NOTE Confidence: 0.8090304

00:45:26.091 --> 00:45:28.125 group at Penn already years ago.

NOTE Confidence: 0.8090304

00:45:28.130 --> 00:45:30.062 But we didn't know very much

NOTE Confidence: 0.8090304

00:45:30.062 --> 00:45:31.350 about the other combinations,

NOTE Confidence: 0.8090304

00:45:31.350 --> 00:45:32.960 so at the time sterilize,

NOTE Confidence: 0.8090304

00:45:32.960 --> 00:45:35.858 brought in a Phase 1 two study of APX.

NOTE Confidence: 0.8090304

00:45:35.860 --> 00:45:36.504 005 AM.

NOTE Confidence: 0.8090304

00:45:36.504 --> 00:45:37.470 In other words,

NOTE Confidence: 0.8090304

00:45:37.470 --> 00:45:39.402 the CD 40 agonist plus nivo in

NOTE Confidence: 0.8090304

00:45:39.402 --> 00:45:41.148 Melanoma and lung cancer started at

NOTE Confidence: 0.8090304

00:45:41.148 --> 00:45:43.157 around that time and we rolled a

NOTE Confidence: 0.8090304

00:45:43.220 --> 00:45:45.566 good number of patients there and

NOTE Confidence: 0.8090304

00:45:45.566 --> 00:45:47.130 actually saw phenomenal responses.

NOTE Confidence: 0.8090304

00:45:47.130 --> 00:45:49.418 So this is an example of a patient

NOTE Confidence: 0.8090304

00:45:49.418 --> 00:45:51.508 treated by doctors know who had

NOTE Confidence: 0.8090304

00:45:51.508 --> 00:45:52.597 a mucosal Melanoma,

NOTE Confidence: 0.8090304

00:45:52.600 --> 00:45:54.484 which tends to be very resistant

NOTE Confidence: 0.8090304

00:45:54.484 --> 00:45:56.469 to implement map in the volume.

NOTE Confidence: 0.8090304

00:45:56.470 --> 00:45:58.645 Evan the patient indeed had

NOTE Confidence: 0.8090304

00:45:58.645 --> 00:45:59.950 progressed on there.

NOTE Confidence: 0.8090304

00:45:59.950 --> 00:46:02.030 So we put the patient on the CD

NOTE Confidence: 0.8090304

00:46:02.030 --> 00:46:03.858 40 agonist plus nevala mehrban.

NOTE Confidence: 0.8090304

00:46:03.860 --> 00:46:05.612 The patients had a complete response

NOTE Confidence: 0.8090304

00:46:05.612 --> 00:46:07.604 and remains of therapy couple of years

NOTE Confidence: 0.8090304

00:46:07.604 --> 00:46:09.403 later we have four of these patients

NOTE Confidence: 0.8090304

00:46:09.460 --> 00:46:11.686 and others and implement Melbourne Nivolumab.

NOTE Confidence: 0.8090304

00:46:11.690 --> 00:46:13.190 We don't actually see this,

NOTE Confidence: 0.8090304

00:46:13.190 --> 00:46:15.630 so maybe this is the answer to Charlie's

NOTE Confidence: 0.8090304

00:46:15.630 --> 00:46:17.706 question is what's the next anti PD?

NOTE Confidence: 0.8090304

00:46:17.710 --> 00:46:19.950 Why?

NOTE Confidence: 0.8090304

00:46:19.950 --> 00:46:21.990 So we're very excited about this

NOTE Confidence: 0.8090304

00:46:21.990 --> 00:46:24.159 molecule and with that Sarah Weiss.

NOTE Confidence: 0.8090304

00:46:24.160 --> 00:46:26.728 This picture over his over here and I

NOTE Confidence: 0.8090304

00:46:26.728 --> 00:46:29.633 wrote a Phase one slash 1B or phase

NOTE Confidence: 0.8090304

00:46:29.633 --> 00:46:32.238 two for the combination of the triplet.

NOTE Confidence: 0.8090304

00:46:32.240 --> 00:46:34.448 We partnered with the yellow Spore

NOTE Confidence: 0.8090304

00:46:34.448 --> 00:46:37.324 in lung cancer and we were able to

NOTE Confidence: 0.8090304

00:46:37.324 --> 00:46:39.322 get support both from the Cancer

NOTE Confidence: 0.8090304

00:46:39.397 --> 00:46:41.757 Center Bristol Myers and Apixaban.

NOTE Confidence: 0.8090304

00:46:41.760 --> 00:46:43.594 So the phase one trial design is

NOTE Confidence: 0.8090304

00:46:43.594 --> 00:46:45.399 depicted on this picture over here.

NOTE Confidence: 0.8090304

00:46:45.400 --> 00:46:47.020 In the beginning we were very

NOTE Confidence: 0.8090304

00:46:47.020 --> 00:46:48.100 anxious because nobody had

NOTE Confidence: 0.8301139

00:46:48.152 --> 00:46:49.692 ever given two macrophage modulating

NOTE Confidence: 0.8301139

00:46:49.692 --> 00:46:51.541 agents together and we were worried

NOTE Confidence: 0.8301139

00:46:51.541 --> 00:46:53.298 that we were going to get like

NOTE Confidence: 0.8301139

00:46:53.298 --> 00:46:54.360 diffuse macro activate macrophage

NOTE Confidence: 0.8301139

00:46:54.360 --> 00:46:55.760 activating syndrome and kill patients.

NOTE Confidence: 0.8301139

00:46:55.760 --> 00:46:58.000 So we had to go very very gingerly.

NOTE Confidence: 0.8301139

00:46:58.000 --> 00:46:59.400 We will also working with

NOTE Confidence: 0.8301139

00:46:59.400 --> 00:47:00.240 two pharmaceutical companies,

NOTE Confidence: 0.8301139

00:47:00.240 --> 00:47:01.920 each with its own opinion so it

NOTE Confidence: 0.8301139

00:47:01.920 --> 00:47:03.830 could be oralism AB which was being

NOTE Confidence: 0.8301139

00:47:03.830 --> 00:47:05.255 developed by Bristol Myers Squibb

NOTE Confidence: 0.8301139

00:47:05.255 --> 00:47:07.115 dead already did it already defined

NOTE Confidence: 0.8301139

00:47:07.115 --> 00:47:08.924 the recommended phase two dose and

NOTE Confidence: 0.8301139

00:47:08.924 --> 00:47:11.196 we had to stick with the dose that

NOTE Confidence: 0.8301139

00:47:11.196 --> 00:47:13.198 they gave us which was for me.

NOTE Confidence: 0.8301139

00:47:13.200 --> 00:47:13.962 Ramza, kilogram.

NOTE Confidence: 0.8301139

00:47:13.962 --> 00:47:17.010 We escalated the CD 40 agonist very gently,

NOTE Confidence: 0.8301139

00:47:17.010 --> 00:47:19.730 so cohort one only had the doublet therapy

NOTE Confidence: 0.8301139

00:47:19.730 --> 00:47:22.730 at a tenth of the recommended phase.

NOTE Confidence: 0.8301139

00:47:22.730 --> 00:47:25.818 Two dose for the CD 40 agonist within

NOTE Confidence: 0.8301139

00:47:25.818 --> 00:47:28.613 escalated by a half a log into cohort

NOTE Confidence: 0.8301139

00:47:28.613 --> 00:47:30.824 three in Cohort 5 and concurrently

NOTE Confidence: 0.8301139

00:47:30.824 --> 00:47:34.160 added the nevala map on with the goal

NOTE Confidence: 0.8301139

00:47:34.160 --> 00:47:36.060 of ultimately reaching cohort six,

NOTE Confidence: 0.8301139

00:47:36.060 --> 00:47:38.482 which would be 4 doses at the

NOTE Confidence: 0.8301139

00:47:38.482 --> 00:47:40.250 record for of Cabrera.

NOTE Confidence: 0.8301139

00:47:40.250 --> 00:47:40.640 Lismer,

NOTE Confidence: 0.8301139

00:47:40.640 --> 00:47:43.760 the pic surgeon drug and nivolumab at the.

NOTE Confidence: 0.8301139

00:47:43.760 --> 00:47:44.963 Same recommended phase.

NOTE Confidence: 0.8301139

00:47:44.963 --> 00:47:48.830 Two dose of each one of these individually.

NOTE Confidence: 0.8301139

00:47:48.830 --> 00:47:50.954 Once we get to the Cohort 6 or to

NOTE Confidence: 0.8301139

00:47:50.954 --> 00:47:53.167 the recommended phase two regimen,

NOTE Confidence: 0.8301139

00:47:53.170 --> 00:47:56.500 the plan is to go into.

NOTE Confidence: 0.8301139

00:47:56.500 --> 00:47:57.916 The Phase 1B component,

NOTE Confidence: 0.8301139

00:47:57.916 --> 00:47:59.686 which is which is essentially

NOTE Confidence: 0.8301139

00:47:59.686 --> 00:48:01.180 three phase two studies,

NOTE Confidence: 0.8301139

00:48:01.180 --> 00:48:03.340 each one with its Simon phase.

NOTE Confidence: 0.8301139

00:48:03.340 --> 00:48:06.050 Two design, one per disease.

NOTE Confidence: 0.8301139

00:48:06.050 --> 00:48:06.830 At this,

NOTE Confidence: 0.8301139

00:48:06.830 --> 00:48:09.560 this trial has lots of embedded correlates,

NOTE Confidence: 0.8301139

00:48:09.560 --> 00:48:11.510 both blood based and tumor,

NOTE Confidence: 0.8301139

00:48:11.510 --> 00:48:13.070 based with pretreatment biopsies

NOTE Confidence: 0.8301139

00:48:13.070 --> 00:48:14.240 mandatory on treatment,

NOTE Confidence: 0.8301139

00:48:14.240 --> 00:48:14.990 biopsies etc.

NOTE Confidence: 0.8301139

00:48:14.990 --> 00:48:17.990 So to update you on what's going on

NOTE Confidence: 0.8301139

00:48:18.076 --> 00:48:21.140 with the Phase one trial which is an

NOTE Confidence: 0.8301139

00:48:21.140 --> 00:48:23.597 integral part of the sport project.

NOTE Confidence: 0.8301139

00:48:23.600 --> 00:48:25.790 We have completed the Phase 126

NOTE Confidence: 0.8301139

00:48:25.790 --> 00:48:27.758 patients in total have been

NOTE Confidence: 0.8301139

00:48:27.758 --> 00:48:29.923 enrolled sarahs busy preparing the

NOTE Confidence: 0.8301139

00:48:29.923 --> 00:48:32.433 publication for this and that should

NOTE Confidence: 0.8301139

00:48:32.433 --> 00:48:34.904 be going out over the coming weeks.

NOTE Confidence: 0.8301139

00:48:34.910 --> 00:48:37.790 Overall it was reasonably well tolerated.

NOTE Confidence: 0.8301139

00:48:37.790 --> 00:48:38.982 It certainly wasn't candy,

NOTE Confidence: 0.8301139

00:48:38.982 --> 00:48:41.194 though we saw a lot of periorbital

NOTE Confidence: 0.8301139

00:48:41.194 --> 00:48:43.378 edema as well as diffuse edema

NOTE Confidence: 0.8301139

00:48:43.378 --> 00:48:45.328 elevations in CPK AST and a Lt,

NOTE Confidence: 0.8301139

00:48:45.330 --> 00:48:47.208 but those didn't appear to be

NOTE Confidence: 0.8301139

00:48:47.208 --> 00:48:48.147 particularly clinically significant.

NOTE Confidence: 0.8301139

00:48:48.150 --> 00:48:49.406 Fevers Insider Kind release,

NOTE Confidence: 0.8301139

00:48:49.406 --> 00:48:50.976 but a lot of fatigue.

NOTE Confidence: 0.8301139

00:48:50.980 --> 00:48:53.178 I think that was the biggest problem.

NOTE Confidence: 0.8301139

00:48:53.180 --> 00:48:54.745 The other big problem that

NOTE Confidence: 0.8301139

00:48:54.745 --> 00:48:55.997 we saw was skipped.

NOTE Confidence: 0.8301139

00:48:56.000 --> 00:48:57.570 While there was some activity

NOTE Confidence: 0.8301139

00:48:57.570 --> 00:48:59.140 in some of the patients,

NOTE Confidence: 0.8301139

00:48:59.140 --> 00:49:01.162 it was mostly stable disease in

NOTE Confidence: 0.8301139

00:49:01.162 --> 00:49:02.853 progression of disease and not

NOTE Confidence: 0.8301139

00:49:02.853 --> 00:49:04.785 quiet what we've seen in the mice.

NOTE Confidence: 0.8301139

00:49:04.790 --> 00:49:07.222 The trial has preceded to the Phase 1B

NOTE Confidence: 0.8301139

00:49:07.222 --> 00:49:09.388 component in Melanoma and lung cancer.

NOTE Confidence: 0.8301139

00:49:09.390 --> 00:49:11.316 Both are in the first stage,

NOTE Confidence: 0.8301139

00:49:11.320 --> 00:49:13.574 but we've we've completed the phase one.

NOTE Confidence: 0.8301139

00:49:13.580 --> 00:49:16.170 I'm going to show you some examples

NOTE Confidence: 0.8301139

00:49:16.170 --> 00:49:17.880 of correlative studies that we've

NOTE Confidence: 0.8301139

00:49:17.880 --> 00:49:19.756 done and this is still a bit

NOTE Confidence: 0.8301139

00:49:19.756 --> 00:49:21.300 of a work in progress,

NOTE Confidence: 0.8301139

00:49:21.300 --> 00:49:23.652 so we looked at cytokine panels before

NOTE Confidence: 0.8301139

00:49:23.652 --> 00:49:25.808 and on treatments at 24 hours later,

NOTE Confidence: 0.8301139

00:49:25.810 --> 00:49:28.295 and you can see nice increasing interferon

NOTE Confidence: 0.8301139

00:49:28.295 --> 00:49:30.638 gamma as well as in in TNF Alpha.

NOTE Confidence: 0.8301139

00:49:30.640 --> 00:49:32.894 The different cohorts are listed over here,

NOTE Confidence: 0.8301139

00:49:32.900 --> 00:49:35.330 but Code 5 and six are when we hit

NOTE Confidence: 0.8301139

00:49:35.330 --> 00:49:37.397 them at the recommended phase,

NOTE Confidence: 0.8301139

00:49:37.400 --> 00:49:39.338 two dose of deep excision drugs,

NOTE Confidence: 0.8301139

00:49:39.340 --> 00:49:43.570 so that's where you see most of the activity.

NOTE Confidence: 0.8269034

00:49:43.570 --> 00:49:45.316 There are other changes in circulating

NOTE Confidence: 0.8269034

00:49:45.316 --> 00:49:47.060 cytokines and I could spend an

NOTE Confidence: 0.8269034

00:49:47.060 --> 00:49:48.375 hour just talking about this,

NOTE Confidence: 0.8269034

00:49:48.380 --> 00:49:50.151 but I selected a few just just

NOTE Confidence: 0.8269034

00:49:50.151 --> 00:49:52.060 to show you what we're seeing,

NOTE Confidence: 0.8269034

00:49:52.060 --> 00:49:53.758 so we've got the CL 2,

NOTE Confidence: 0.8269034

00:49:53.760 --> 00:49:55.608 which is a side kind that's primarily

NOTE Confidence: 0.8269034

00:49:55.608 --> 00:49:57.440 secreted by dendritic cells and macrophages.

NOTE Confidence: 0.8269034

00:49:57.440 --> 00:49:59.696 Very high levels of the higher dose levels,

NOTE Confidence: 0.8269034

00:49:59.700 --> 00:50:00.894 same with. P.

NOTE Confidence: 0.8269034

00:50:00.894 --> 00:50:02.884 10 and then the macrophage

NOTE Confidence: 0.8269034

00:50:02.884 --> 00:50:04.220 colony stimulating factor,

NOTE Confidence: 0.8269034

00:50:04.220 --> 00:50:06.705 also highest levels in Cohort

NOTE Confidence: 0.8269034

00:50:06.705 --> 00:50:08.693 6 but clear increases.

NOTE Confidence: 0.8269034

00:50:08.700 --> 00:50:09.573 Across the board,

NOTE Confidence: 0.8269034

00:50:09.573 --> 00:50:11.610 we do have the pretreatment and on

NOTE Confidence: 0.8269034

00:50:11.674 --> 00:50:13.299 treatment specimens show me jessel

NOTE Confidence: 0.8269034

00:50:13.299 --> 00:50:15.544 who supposed dark in my lab is

NOTE Confidence: 0.8269034

00:50:15.544 --> 00:50:17.224 busy analyzing these what you see

NOTE Confidence: 0.8269034

00:50:17.224 --> 00:50:18.950 over here is the basic analysis,

NOTE Confidence: 0.8269034

00:50:18.950 --> 00:50:21.449 so these are just this is just a

NOTE Confidence: 0.8269034

00:50:21.449 --> 00:50:23.519 munificent staining a CD4 and CD8

NOTE Confidence: 0.8269034

00:50:23.519 --> 00:50:25.054 before treatment and on treatments

NOTE Confidence: 0.8269034

00:50:25.054 --> 00:50:27.444 on the left is pre and on the right

NOTE Confidence: 0.8269034

00:50:27.444 --> 00:50:29.700 is post and you can see an increase

NOTE Confidence: 0.8269034

00:50:29.768 --> 00:50:31.833 in the infiltration of the CD 8

NOTE Confidence: 0.8269034

00:50:31.833 --> 00:50:33.848 cells which are colored in green.

NOTE Confidence: 0.8269034

00:50:33.850 --> 00:50:35.415 There's also an increase of

NOTE Confidence: 0.8269034

00:50:35.415 --> 00:50:37.489 the CD Force which are in red.

NOTE Confidence: 0.8269034

00:50:37.490 --> 00:50:38.686 CD 68 also actually.

NOTE Confidence: 0.8269034

00:50:38.686 --> 00:50:40.480 Increase in the amount of CD

NOTE Confidence: 0.8269034

00:50:40.546 --> 00:50:42.376 68 on this particular patient,

NOTE Confidence: 0.8269034

00:50:42.380 --> 00:50:44.324 but in some patients we actually

NOTE Confidence: 0.8269034

00:50:44.324 --> 00:50:45.296 see the opposite,

NOTE Confidence: 0.8269034

00:50:45.300 --> 00:50:47.324 so over here you can see that the

NOTE Confidence: 0.8269034

00:50:47.324 --> 00:50:49.114 C8 cells pretreatment were much

NOTE Confidence: 0.8269034

00:50:49.114 --> 00:50:51.149 more dense than post treatment.

00:50:51.150 --> 00:50:53.425 Although you do see some post treatment,

00:50:53.430 --> 00:50:55.698 I don't know how well this projects.

00:50:55.700 --> 00:50:59.924 There's an increase in the CD 68 though.

00:50:59.930 --> 00:51:01.939 Just to highlight one of the challenges

00:51:01.939 --> 00:51:03.749 that we have with doing this.

00:51:03.750 --> 00:51:05.230 Pre Anon treatments studies in

00:51:05.230 --> 00:51:07.337 that it may not come from this

00:51:07.337 --> 00:51:08.747 come from the same site,

00:51:08.750 --> 00:51:10.759 so the pretreatment was a a containers

00:51:10.759 --> 00:51:12.517 tissue metastasis on the back and

00:51:12.517 --> 00:51:14.209 the post treatment in this particular

00:51:14.209 --> 00:51:15.808 patient came from the Gallbladder,

00:51:15.810 --> 00:51:17.550 so it's possible that the tumor

00:51:17.550 --> 00:51:19.057 micro environment in the different

00:51:19.057 --> 00:51:21.094 organs is playing a part over here.

00:51:21.100 --> 00:51:22.846 But because we didn't see much

NOTE Confidence: 0.8269034

00:51:22.846 --> 00:51:24.630 activity in the Phase one trial,

NOTE Confidence: 0.8269034

00:51:24.630 --> 00:51:26.646 we're going back to the bench

NOTE Confidence: 0.8269034

00:51:26.646 --> 00:51:28.984 to try to determine what can we

NOTE Confidence: 0.8269034

00:51:28.984 --> 00:51:30.524 do to improve our trial.

NOTE Confidence: 0.8269034

00:51:30.530 --> 00:51:31.870 So Irina clickbait ever,

NOTE Confidence: 0.8269034

00:51:31.870 --> 00:51:33.545 who was the postdoc working?

NOTE Confidence: 0.8269034

00:51:33.550 --> 00:51:35.220 I'm sorry there's the doctoral

NOTE Confidence: 0.8269034

00:51:35.220 --> 00:51:36.556 student in Marcus's lab,

NOTE Confidence: 0.8269034

00:51:36.560 --> 00:51:37.472 partnered with Deanna,

NOTE Confidence: 0.8269034

00:51:37.472 --> 00:51:39.999 who's working in my lab to ask the

NOTE Confidence: 0.8269034

00:51:39.999 --> 00:51:42.027 question of whether we're actually just

NOTE Confidence: 0.8269034

00:51:42.027 --> 00:51:44.599 giving too much CSF one receptor antibody.

NOTE Confidence: 0.8269034

00:51:44.600 --> 00:51:46.280 So more isn't always better,

NOTE Confidence: 0.8269034

00:51:46.280 --> 00:51:47.932 particularly when we're trying

NOTE Confidence: 0.8269034

00:51:47.932 --> 00:51:49.997 to polarize macrophages and not

NOTE Confidence: 0.8269034

00:51:49.997 --> 00:51:51.920 necessarily knock them off completely.

NOTE Confidence: 0.8269034

00:51:51.920 --> 00:51:54.539 So when we do these experiments in the mice,

NOTE Confidence: 0.8269034

00:51:54.540 --> 00:51:55.995 we were seeing much better

NOTE Confidence: 0.8269034

00:51:55.995 --> 00:51:57.159 activity than the humans,

NOTE Confidence: 0.8269034

00:51:57.160 --> 00:51:58.610 and the question is why?

NOTE Confidence: 0.8269034

00:51:58.610 --> 00:52:00.914 So the dose is selected for the Marin

NOTE Confidence: 0.8269034

00:52:00.914 --> 00:52:02.528 experiments with somewhat random we go

NOTE Confidence: 0.8269034

00:52:02.528 --> 00:52:05.020 based on what is done by other researchers,

NOTE Confidence: 0.8269034

00:52:05.020 --> 00:52:07.124 what's done by format and the amount that

NOTE Confidence: 0.8269034

00:52:07.124 --> 00:52:09.376 we were giving them was 200MG kilogram.

NOTE Confidence: 0.8269034

00:52:09.380 --> 00:52:10.840 So we asked the question.

NOTE Confidence: 0.8269034

00:52:10.840 --> 00:52:11.130 Well,

NOTE Confidence: 0.8269034

00:52:11.130 --> 00:52:13.450 what happens if we give them more CSF?

NOTE Confidence: 0.8269034

00:52:13.450 --> 00:52:14.905 One receptor antibody and keep

NOTE Confidence: 0.8269034

00:52:14.905 --> 00:52:16.360 the other two drug steady?

NOTE Confidence: 0.8269034

00:52:16.360 --> 00:52:19.270 And as you can see in this figure over here,

NOTE Confidence: 0.8269034

00:52:19.270 --> 00:52:20.730 if you give more CSF,

NOTE Confidence: 0.8269034

00:52:20.730 --> 00:52:21.958 one receptor antibody basically

NOTE Confidence: 0.8269034

00:52:21.958 --> 00:52:22.879 doubling the dose.

NOTE Confidence: 0.8289687

00:52:22.880 --> 00:52:24.818 The mice actually do less well

NOTE Confidence: 0.8289687

00:52:24.818 --> 00:52:26.590 die sooner or sacrificed sooner,

NOTE Confidence: 0.8289687

00:52:26.590 --> 00:52:29.614 and as you can see here on the left,

NOTE Confidence: 0.8289687

00:52:29.620 --> 00:52:31.570 the tumor volume is actually bigger

NOTE Confidence: 0.8289687

00:52:31.570 --> 00:52:33.963 when you give the higher dose of

NOTE Confidence: 0.8289687

00:52:33.963 --> 00:52:35.683 the CSF one receptor antibody.

NOTE Confidence: 0.8289687

00:52:35.690 --> 00:52:38.077 So we're still debating what to do

NOTE Confidence: 0.8289687

00:52:38.077 --> 00:52:40.740 about that as we go into the clinic.

NOTE Confidence: 0.8289687

00:52:40.740 --> 00:52:42.084 But then the Meanwhile,

NOTE Confidence: 0.8289687

00:52:42.084 --> 00:52:43.764 because it's a small project,

NOTE Confidence: 0.8289687

00:52:43.770 --> 00:52:46.129 we still need to have an ongoing

NOTE Confidence: 0.8289687

00:52:46.129 --> 00:52:48.154 clinical trial, and the question was,

NOTE Confidence: 0.8289687

00:52:48.154 --> 00:52:50.175 well, is the CSF one receptor

NOTE Confidence: 0.8289687

00:52:50.175 --> 00:52:51.523 the optimal second target,

NOTE Confidence: 0.8289687

00:52:51.530 --> 00:52:54.020 in addition to CD 40 agonist

NOTE Confidence: 0.8289687

00:52:54.020 --> 00:52:55.680 and PD one inhibitors?

NOTE Confidence: 0.8289687

00:52:55.680 --> 00:52:56.778 So it's possible,

NOTE Confidence: 0.8289687

00:52:56.778 --> 00:52:57.876 at least theoretically,

NOTE Confidence: 0.8289687

00:52:57.880 --> 00:53:00.456 that CTA for is a better target because

NOTE Confidence: 0.8289687

00:53:00.456 --> 00:53:03.193 CTA for new mission is is really

NOTE Confidence: 0.8289687

00:53:03.193 --> 00:53:05.213 key for dendritic cell activation.

NOTE Confidence: 0.8289687

00:53:05.220 --> 00:53:06.210 So Kelly Alina,

NOTE Confidence: 0.8289687

00:53:06.210 --> 00:53:07.860 who's one of our wonderful

NOTE Confidence: 0.8289687

00:53:07.860 --> 00:53:09.815 surgeons in the Melanoma group

NOTE Confidence: 0.8289687

00:53:09.815 --> 00:53:11.455 and also surgeon scientists,

NOTE Confidence: 0.8289687

00:53:11.460 --> 00:53:13.656 is doing work in the lab.

NOTE Confidence: 0.8289687

00:53:13.660 --> 00:53:15.802 It, primarily Marcus is lab where she

NOTE Confidence: 0.8289687

00:53:15.802 --> 00:53:18.020 is taking a very aggressive model

NOTE Confidence: 0.8289687

00:53:18.020 --> 00:53:20.080 marine model whereby she injects

NOTE Confidence: 0.8289687

00:53:20.080 --> 00:53:22.470 these cells into the left ventricle.

NOTE Confidence: 0.8289687

00:53:22.470 --> 00:53:24.305 So they developed vast mistake

NOTE Confidence: 0.8289687

00:53:24.305 --> 00:53:25.406 metastases all over,

NOTE Confidence: 0.8289687

00:53:25.410 --> 00:53:26.974 including in the brain.

NOTE Confidence: 0.8289687

00:53:26.974 --> 00:53:29.320 And this model is particularly resistant

NOTE Confidence: 0.8289687

00:53:29.384 --> 00:53:31.280 to anti PD one in Antici TLA 4.

NOTE Confidence: 0.8289687

00:53:31.280 --> 00:53:33.100 So the question is whether the addition

NOTE Confidence: 0.8289687

00:53:33.100 --> 00:53:35.318 of the CD 40 agonist adds something.

NOTE Confidence: 0.8289687

00:53:35.320 --> 00:53:37.018 And as you can see over

NOTE Confidence: 0.8289687

00:53:37.018 --> 00:53:38.500 here with the red bar,

NOTE Confidence: 0.8289687

00:53:38.500 --> 00:53:40.565 the addition of the CD 40 agonist

NOTE Confidence: 0.8289687

00:53:40.565 --> 00:53:42.574 does appear to improve the survival

NOTE Confidence: 0.8289687

00:53:42.574 --> 00:53:44.329 of these nice that typically

NOTE Confidence: 0.8289687

00:53:44.329 --> 00:53:46.329 will be dead within 20 days.

NOTE Confidence: 0.8289687

00:53:46.330 --> 00:53:47.845 This is some subq injection

NOTE Confidence: 0.8289687

00:53:47.845 --> 00:53:49.740 data over here on the left,

NOTE Confidence: 0.8289687

00:53:49.740 --> 00:53:52.220 which we don't have time to go through,

NOTE Confidence: 0.8289687

00:53:52.220 --> 00:53:54.134 but with those data we again

NOTE Confidence: 0.8289687

00:53:54.134 --> 00:53:55.939 approached the passage and we said,

NOTE Confidence: 0.8289687

00:53:55.940 --> 00:53:57.638 well, maybe we should do a

NOTE Confidence: 0.8289687

00:53:57.638 --> 00:53:59.350 different trial now in parallel,

NOTE Confidence: 0.8289687

00:53:59.350 --> 00:54:01.886 and this is our second trial which Kelly

NOTE Confidence: 0.8289687

00:54:01.886 --> 00:54:04.309 and Sarah worked with me to to write.

NOTE Confidence: 0.8289687

00:54:04.310 --> 00:54:06.660 So it's a phase one study of the CD 40

NOTE Confidence: 0.8289687

00:54:06.728 --> 00:54:09.266 agonist in combination with epilim urban,

NOTE Confidence: 0.8289687

00:54:09.270 --> 00:54:10.820 the volume app in Melanoma.

NOTE Confidence: 0.8289687

00:54:10.820 --> 00:54:12.899 So just to highlight some of the

NOTE Confidence: 0.8289687

00:54:12.899 --> 00:54:14.848 challenges of a study like this,

NOTE Confidence: 0.8289687

00:54:14.850 --> 00:54:17.391 we know that a polymer mabona volume

NOTE Confidence: 0.8289687

96

00:54:17.391 --> 00:54:19.746 app toxicity rate of at least 6570%.

NOTE Confidence: 0.8289687

00:54:19.750 --> 00:54:21.965 We're talking about these immune

NOTE Confidence: 0.8289687

00:54:21.965 --> 00:54:24.610 related adverse events all the time.

NOTE Confidence: 0.8289687

00:54:24.610 --> 00:54:26.326 And we also know that sometimes

NOTE Confidence: 0.8289687

00:54:26.326 --> 00:54:27.470 these events occur late,

NOTE Confidence: 0.8289687

00:54:27.470 --> 00:54:29.339 so you can have a patient who

NOTE Confidence: 0.8289687

00:54:29.339 --> 00:54:30.900 is treated comes off therapy,

NOTE Confidence: 0.8289687

00:54:30.900 --> 00:54:32.930 and six months later develops

NOTE Confidence: 0.8289687

00:54:32.930 --> 00:54:34.148 a horrendous toxicity.

NOTE Confidence: 0.8289687

00:54:34.150 --> 00:54:34.930 So how long?

NOTE Confidence: 0.8289687

00:54:34.930 --> 00:54:37.130 How do we design a study like that?

NOTE Confidence: 0.8289687

00:54:37.130 --> 00:54:39.027 How long can we follow the patients?

NOTE Confidence: 0.8289687

00:54:39.030 --> 00:54:41.062 For how long do we go from one

NOTE Confidence: 0.8289687

00:54:41.062 --> 00:54:42.279 cohort to the other?

NOTE Confidence: 0.8289687

00:54:42.280 --> 00:54:44.163 So it took a lot of negotiation

NOTE Confidence: 0.8289687

00:54:44.163 --> 00:54:45.799 back and forth with the FDA,

NOTE Confidence: 0.8289687

00:54:45.800 --> 00:54:47.906 but we put a lot of thought into this

NOTE Confidence: 0.8289687

00:54:47.906 --> 00:54:49.628 really slow trial design where we

NOTE Confidence: 0.8289687

00:54:49.628 --> 00:54:51.490 actually have only two dose levels,

NOTE Confidence: 0.8289687

00:54:51.490 --> 00:54:54.436 so dose level one is a.

NOTE Confidence: 0.8289687

00:54:54.440 --> 00:54:55.940 Third of the recommended phase.

NOTE Confidence: 0.8289687

00:54:55.940 --> 00:54:58.343 Two dose of the seat of the CD 40

NOTE Confidence: 0.8289687

00:54:58.343 --> 00:55:01.020 agonist which is the drug that we're adding,

NOTE Confidence: 0.8289687

00:55:01.020 --> 00:55:04.010 and we give people a map in the volume AB.

NOTE Confidence: 0.8289687

00:55:04.010 --> 00:55:05.500 We only treat three patients.

NOTE Confidence: 0.8289687

00:55:05.500 --> 00:55:07.288 Monitor them for 28 days and

NOTE Confidence: 0.8289687

00:55:07.288 --> 00:55:08.480 then and then enroll

NOTE Confidence: 0.84019953

00:55:08.549 --> 00:55:10.121 another 46 and at that and

NOTE Confidence: 0.84019953

00:55:10.121 --> 00:55:11.780 all of these six patients.

NOTE Confidence: 0.84019953

00:55:11.780 --> 00:55:13.950 They need to be monitored for six

NOTE Confidence: 0.84019953

00:55:13.950 --> 00:55:15.957 weeks so this is going to take

NOTE Confidence: 0.84019953

00:55:15.957 --> 00:55:18.060 us a long time to get through.

NOTE Confidence: 0.84019953

00:55:18.060 --> 00:55:20.516 But what we're hoping is that we'll have

NOTE Confidence: 0.84019953

00:55:20.516 --> 00:55:22.848 a regimen that may not be more toxic,

NOTE Confidence: 0.84019953

00:55:22.850 --> 00:55:24.605 but that will be significantly

NOTE Confidence: 0.84019953

00:55:24.605 --> 00:55:25.307 more effective.

NOTE Confidence: 0.84019953

00:55:25.310 --> 00:55:28.163 Then the PD one and see TLA for that.

NOTE Confidence: 0.84019953

00:55:28.170 --> 00:55:30.473 We have right now to finally bring

NOTE Confidence: 0.84019953

00:55:30.473 --> 00:55:32.937 that tail of the curve up to 80%.

NOTE Confidence: 0.84019953

00:55:32.940 --> 00:55:33.996 We have started.

NOTE Confidence: 0.84019953

00:55:33.996 --> 00:55:35.756 We've enrolled three Melanoma patients

NOTE Confidence: 0.84019953

00:55:35.756 --> 00:55:37.894 or have completed their 28 day DLT

NOTE Confidence: 0.84019953

00:55:37.894 --> 00:55:39.940 period and they did OK with there,

NOTE Confidence: 0.84019953

00:55:39.940 --> 00:55:41.848 but they have not all completed

NOTE Confidence: 0.84019953

00:55:41.848 --> 00:55:43.120 their nine week observation.

NOTE Confidence: 0.84019953

00:55:43.120 --> 00:55:45.028 Before Christmas, we going to enroll.

NOTE Confidence: 0.84019953

00:55:45.030 --> 00:55:46.896 Two more patients have consented and

NOTE Confidence: 0.84019953

00:55:46.896 --> 00:55:48.840 we're looking for the six patient,

NOTE Confidence: 0.84019953

00:55:48.840 --> 00:55:51.374 but they all have to be monitored

NOTE Confidence: 0.84019953

00:55:51.374 --> 00:55:54.308 for 9 weeks before we can proceed.

NOTE Confidence: 0.84019953

00:55:54.310 --> 00:55:56.494 So I'm going to conclude there that

NOTE Confidence: 0.84019953

00:55:56.494 --> 00:55:58.552 Co targeting the innate and adaptive

NOTE Confidence: 0.84019953

00:55:58.552 --> 00:56:00.676 immune system with the CSF one

NOTE Confidence: 0.84019953

00:56:00.676 --> 00:56:02.482 receptor inhibitor or antibody plus

NOTE Confidence: 0.84019953

00:56:02.482 --> 00:56:04.911 CD 40 agonist results in better anti

NOTE Confidence: 0.84019953

00:56:04.911 --> 00:56:06.616 tumor activity than either alone.

NOTE Confidence: 0.84019953

00:56:06.620 --> 00:56:08.923 It also increases the CD 8 tumor

NOTE Confidence: 0.84019953

00:56:08.923 --> 00:56:11.001 content in animals if we treat

NOTE Confidence: 0.84019953

00:56:11.001 --> 00:56:12.711 mice bearing PD one resistant

NOTE Confidence: 0.84019953

00:56:12.711 --> 00:56:14.828 tumors with all with these drugs

NOTE Confidence: 0.84019953

00:56:14.828 --> 00:56:16.880 in combination with anti PD one,

NOTE Confidence: 0.84019953

00:56:16.880 --> 00:56:19.274 it does look better than the doublet.

NOTE Confidence: 0.84019953

00:56:19.280 --> 00:56:21.758 The findings were confirmed in a renal

NOTE Confidence: 0.84019953

00:56:21.758 --> 00:56:23.846 cell carcinoma model where we are

NOTE Confidence: 0.84019953

00:56:23.846 --> 00:56:25.766 in the clinic already testing this.

NOTE Confidence: 0.84019953

00:56:25.770 --> 00:56:28.780 We're having some difficulty with.

NOTE Confidence: 0.84019953

00:56:28.780 --> 00:56:29.653 With insufficient activities,

NOTE Confidence: 0.84019953

00:56:29.653 --> 00:56:31.690 so we're back in the lab right

NOTE Confidence: 0.84019953

00:56:31.739 --> 00:56:33.251 now trying to modify the doses

NOTE Confidence: 0.84019953

00:56:33.251 --> 00:56:34.993 in the regimen before we go back

NOTE Confidence: 0.84019953

00:56:34.993 --> 00:56:35.905 again into the clinic,

NOTE Confidence: 0.84019953

00:56:35.910 --> 00:56:38.286 and this kind of back and forth between

NOTE Confidence: 0.84019953

00:56:38.286 --> 00:56:40.777 the lab in the clinic is something that

NOTE Confidence: 0.84019953

00:56:40.777 --> 00:56:43.389 can only be done at a place like this.

NOTE Confidence: 0.84019953

00:56:43.390 --> 00:56:45.790 We are also at the same time evaluating

NOTE Confidence: 0.84019953

00:56:45.790 --> 00:56:47.860 the combination with the CTL A4 inhibitor

NOTE Confidence: 0.84019953

00:56:47.860 --> 00:56:49.989 and hopefully this will be as exciting,

NOTE Confidence: 0.84019953

00:56:49.990 --> 00:56:51.490 more exciting and just to

NOTE Confidence: 0.84019953

00:56:51.490 --> 00:56:52.690 say the final conclusion,

NOTE Confidence: 0.84019953

00:56:52.690 --> 00:56:54.937 that is that it really takes a

NOTE Confidence: 0.84019953

00:56:54.937 --> 00:56:57.438 village to do a project like this.

NOTE Confidence: 0.84019953

00:56:57.440 --> 00:57:00.568 So all of the the folks have been

NOTE Confidence: 0.84019953

00:57:00.568 --> 00:57:02.420 involved acknowledged on this slide.

NOTE Confidence: 0.84019953

00:57:02.420 --> 00:57:04.330 The scientific collaborators at Yale,

NOTE Confidence: 0.84019953

00:57:04.330 --> 00:57:06.140 colleagues in other labs have

NOTE Confidence: 0.84019953

00:57:06.140 --> 00:57:08.550 helped a lot through this process.

NOTE Confidence: 0.84019953

00:57:08.550 --> 00:57:10.460 Members of my lab members

NOTE Confidence: 0.84019953

00:57:10.460 --> 00:57:11.988 of the Collaborating lab,

NOTE Confidence: 0.84019953

00:57:11.990 --> 00:57:12.756 clinical collaborators,

NOTE Confidence: 0.84019953

00:57:12.756 --> 00:57:13.522 pharmaceutical collaborators,

NOTE Confidence: 0.84019953

00:57:13.522 --> 00:57:15.054 patients and their family,

NOTE Confidence: 0.84019953

00:57:15.060 --> 00:57:16.970 and then finally the funding.

NOTE Confidence: 0.84019953

00:57:16.970 --> 00:57:20.402 So I did mention the sporting skin cancer

NOTE Confidence: 0.84019953

00:57:20.402 --> 00:57:23.528 which which is funded the core project.

NOTE Confidence: 0.84019953

00:57:23.530 --> 00:57:25.910 But the K12 is funded a couple

NOTE Confidence: 0.84019953

00:57:25.910 --> 00:57:27.330 of the investigators here,

NOTE Confidence: 0.84019953

00:57:27.330 --> 00:57:29.050 Kelly Alina and Sarah Weiss,

NOTE Confidence: 0.84019953

00:57:29.050 --> 00:57:31.120 and Cancer Center has supported it,

NOTE Confidence: 0.84019953

00:57:31.120 --> 00:57:33.549 and some of our folks of which

NOTE Confidence: 0.84019953

00:57:33.549 --> 00:57:35.086 have received career development

NOTE Confidence: 0.84019953

00:57:35.086 --> 00:57:37.600 awards as well related to this.

NOTE Confidence: 0.84019953

00:57:37.600 --> 00:57:39.120 So with that I'll stop.

NOTE Confidence: 0.84019953

00:57:39.120 --> 00:57:40.926 I'm happy to take any questions.

NOTE Confidence: 0.84019953

00:57:40.930 --> 00:57:42.150 Thank you for listening.

NOTE Confidence: 0.8341199

00:57:43.150 --> 00:57:44.263 Hurry, thank you.

NOTE Confidence: 0.8341199

00:57:44.263 --> 00:57:46.489 What a great example of translating

NOTE Confidence: 0.8341199

00:57:46.489 --> 00:57:49.269 science into the clinic and folks can

NOTE Confidence: 0.8341199

00:57:49.269 --> 00:57:50.829 certainly submit questions online.

NOTE Confidence: 0.8341199

00:57:50.830 --> 00:57:53.446 So let me I have a question watching

NOTE Confidence: 0.8341199

00:57:53.446 --> 00:57:56.111 'cause I you sort of anticipated my

NOTE Confidence: 0.8341199

00:57:56.111 --> 00:57:59.280 question by adding the CTA four antagonist.

NOTE Confidence: 0.8341199

00:57:59.280 --> 00:58:02.120 But to what extent do you think that

NOTE Confidence: 0.8341199

00:58:02.120 --> 00:58:05.101 triplet might have had greater benefit if

NOTE Confidence: 0.8341199

00:58:05.101 --> 00:58:07.729 they weren't previously exposed to a PD?

NOTE Confidence: 0.8341199

00:58:07.730 --> 00:58:08.498 One antibody?

NOTE Confidence: 0.8341199

00:58:08.498 --> 00:58:10.030 And that's really good

NOTE Confidence: 0.8341199

00:58:10.030 --> 00:58:11.780 question. So the masks were

NOTE Confidence: 0.8341199

00:58:11.780 --> 00:58:14.250 not exposed to PD one antibody,

NOTE Confidence: 0.8341199

00:58:14.250 --> 00:58:15.770 whereas the humans would.

NOTE Confidence: 0.8341199

00:58:15.770 --> 00:58:18.050 And it's possible that you know,

NOTE Confidence: 0.8341199

00:58:18.050 --> 00:58:19.475 we've we've just used that

NOTE Confidence: 0.8341199

00:58:19.475 --> 00:58:20.900 app and developed it yet,

NOTE Confidence: 0.8341199

00:58:20.900 --> 00:58:22.610 and you're of mechanism of resistance,

NOTE Confidence: 0.8341199

00:58:22.610 --> 00:58:24.035 so we haven't done that

NOTE Confidence: 0.8341199

00:58:24.035 --> 00:58:25.175 experiment in the mouse.

NOTE Confidence: 0.8341199

00:58:25.180 --> 00:58:26.320 But that's actually a

NOTE Confidence: 0.8341199

00:58:26.320 --> 00:58:28.030 really good next step to do.

NOTE Confidence: 0.8341199

00:58:28.030 --> 00:58:29.150 It's a great thought.

NOTE Confidence: 0.8341199

00:58:29.150 --> 00:58:30.830 We should expose the mice to

NOTE Confidence: 0.8341199

00:58:30.893 --> 00:58:32.238 PD one inhibitors and then

NOTE Confidence: 0.8341199

00:58:32.238 --> 00:58:33.939 add on the other ones instead

NOTE Confidence: 0.8341199

00:58:33.939 --> 00:58:35.715 of giving all three up front.

NOTE Confidence: 0.81057096

00:58:36.410 --> 00:58:38.270 And this may be impossible,

NOTE Confidence: 0.81057096

00:58:38.270 --> 00:58:40.400 but is there any consideration of

NOTE Confidence: 0.81057096

00:58:40.400 --> 00:58:42.730 combining all four agents in previously?

NOTE Confidence: 0.81057096

00:58:42.730 --> 00:58:47.200 I mean that is a CSF one R CD40 anti CD L4,

NOTE Confidence: 0.81057096

00:58:47.200 --> 00:58:49.648 GTA 4 and PD one and I realized

NOTE Confidence: 0.81057096

00:58:49.648 --> 00:58:52.029 that's a smorgasbord of agents,

NOTE Confidence: 0.81057096

00:58:52.030 --> 00:58:54.268 but is that a conceivable approach?

NOTE Confidence: 0.81057096

00:58:54.270 --> 00:58:56.496 We could, we just got it.

NOTE Confidence: 0.81057096

00:58:56.500 --> 00:58:59.468 We can get through the 1st 3 first,

NOTE Confidence: 0.81057096

00:58:59.470 --> 00:59:02.818 so the CTA for CD for D and P1.

NOTE Confidence: 0.81057096

00:59:02.820 --> 00:59:06.670 So far we're doing OK with toxicity.

NOTE Confidence: 0.81057096

00:59:06.670 --> 00:59:08.983 But we are only on the 1st dose level.

NOTE Confidence: 0.81057096

00:59:08.990 --> 00:59:10.022 It's it's very intimidating

NOTE Confidence: 0.81057096

00:59:10.022 --> 00:59:11.570 to do all of this sure,

NOTE Confidence: 0.81057096

00:59:11.570 --> 00:59:12.862 and then the other question

NOTE Confidence: 0.81057096

00:59:12.862 --> 00:59:14.926 is in what line do you do it?

NOTE Confidence: 0.81057096

00:59:14.930 --> 00:59:17.144 So what we're trying to do now is to

NOTE Confidence: 0.81057096

00:59:17.144 --> 00:59:19.310 actually move it forward to the first line,

NOTE Confidence: 0.81057096

00:59:19.310 --> 00:59:21.018 that that very last trial that I

NOTE Confidence: 0.81057096

00:59:21.018 --> 00:59:22.669 showed with the CTA for antibody.

NOTE Confidence: 0.81057096

00:59:22.670 --> 00:59:26.016 We decided to go in first line.

NOTE Confidence: 0.81057096

00:59:26.020 --> 00:59:27.790 Mostly because of of memory.

NOTE Confidence: 0.81057096

00:59:27.790 --> 00:59:30.079 So if you if you take patients

NOTE Confidence: 0.81057096

00:59:30.079 --> 00:59:32.019 with her previous settling for,

NOTE Confidence: 0.81057096

00:59:32.020 --> 00:59:34.484 you can get additive toxicity over there.

NOTE Confidence: 0.8556669

00:59:36.850 --> 00:59:39.940 But that's a really good idea to do that in

NOTE Confidence: 0.8556669

00:59:39.940 --> 00:59:41.180 the mouse. Thank you.

NOTE Confidence: 0.8556669

00:59:41.180 --> 00:59:43.045 Yeah, well, I know where I

NOTE Confidence: 0.8556669

00:59:43.045 --> 00:59:44.880 know we're just we're out of.

NOTE Confidence: 0.8556669

00:59:44.880 --> 00:59:47.211 We're a little past the hour and I want

NOTE Confidence: 0.8556669

00:59:47.211 --> 00:59:49.520 to be sensitive to everyone's time.

NOTE Confidence: 0.8556669

00:59:49.520 --> 00:59:50.732 So Harriet and David.

NOTE Confidence: 0.8556669

00:59:50.732 --> 00:59:52.920 Thank you both for really exceptional talks.

NOTE Confidence: 0.8556669

00:59:52.920 --> 00:59:54.152 Congratulations on all your

NOTE Confidence: 0.8556669

00:59:54.152 --> 00:59:55.692 work and everyone in attendance.

NOTE Confidence: 0.8556669

00:59:55.700 --> 00:59:59.507 Thank you for joining us and enjoy your day.

NOTE Confidence: 0.8556669

00:59:59.510 --> 01:00:00.900 Thanks. Bye bye.