WEBVTT

NOTE duration:"00:31:37.4510000"

NOTE language:en-us

NOTE Confidence: 0.9024154

00:00:00.000 --> 00:00:03.952 You know the areas that we're going to

NOTE Confidence: 0.9024154

00:00:03.952 --> 00:00:07.288 focus on today, or two critical ones,

NOTE Confidence: 0.9024154

00:00:07.288 --> 00:00:08.896 namely mute on Koleji,

NOTE Confidence: 0.9024154

00:00:08.900 --> 00:00:11.553 for which we really committed you centers

NOTE Confidence: 0.9024154

00:00:11.553 --> 00:00:14.530 and resources as well as computational work,

NOTE Confidence: 0.9024154

00:00:14.530 --> 00:00:17.761 which I think is critical in this next phase

NOTE Confidence: 0.9024154

00:00:17.761 --> 00:00:20.958 of Cancer Research in the 21st century.

NOTE Confidence: 0.9024154

00:00:20.960 --> 00:00:23.366 Anile open with our first speaker,

NOTE Confidence: 0.9024154

00:00:23.370 --> 00:00:25.380 as many of you know,

NOTE Confidence: 0.9024154

00:00:25.380 --> 00:00:28.236 doctor Marcus bosenberg is a leader in our

NOTE Confidence: 0.9024154

00:00:28.236 --> 00:00:30.608 Cancer Center professor of dermatology,

NOTE Confidence: 0.9024154

00:00:30.610 --> 00:00:31.948 pathology and Immunobiology.

NOTE Confidence: 0.9024154

00:00:31.948 --> 00:00:34.624 Co leader of the genomics genetics

NOTE Confidence: 0.9024154

00:00:34.624 --> 00:00:37.068 and epigenetics research program.

NOTE Confidence: 0.9024154

00:00:37.070 --> 00:00:40.766 Director of the else boren kins skin cancer,

NOTE Confidence: 0.9024154

00:00:40.770 --> 00:00:43.787 as well as a very active member

NOTE Confidence: 0.9024154

00:00:43.787 --> 00:00:46.309 of the faculty in theology.

NOTE Confidence: 0.9024154

00:00:46.310 --> 00:00:48.194 Enough leading nationally internationally

NOTE Confidence: 0.9024154

00:00:48.194 --> 00:00:50.078 recognized amount of pathologists

NOTE Confidence: 0.9024154

00:00:50.078 --> 00:00:52.320 and most most recently serving,

NOTE Confidence: 0.9024154

00:00:52.320 --> 00:00:55.146 really quite brilliantly as our interim

NOTE Confidence: 0.9024154

00:00:55.146 --> 00:00:58.780 leader and director of the L centerview know.

NOTE Confidence: 0.9024154

00:00:58.780 --> 00:01:02.497 Cology is really part of that launch.

NOTE Confidence: 0.9024154

00:01:02.500 --> 00:01:04.850 Marcus is research has been,

NOTE Confidence: 0.9024154

00:01:04.850 --> 00:01:07.190 as you know, prolific, focused.

NOTE Confidence: 0.9024154

00:01:07.190 --> 00:01:09.696 I pour it on the genetics and

NOTE Confidence: 0.9024154

00:01:09.696 --> 00:01:11.950 cellular changes that result in

NOTE Confidence: 0.9024154

00:01:11.950 --> 00:01:14.166 Melanoma while concurrently building

NOTE Confidence: 0.9024154

00:01:14.166 --> 00:01:16.382 innovative new laboratory models

NOTE Confidence: 0.9024154

00:01:16.462 --> 00:01:18.917 animal models to understand cancer,

NOTE Confidence: 0.9024154

00:01:18.920 --> 00:01:21.260 to define our immune response,

NOTE Confidence: 0.9024154

00:01:21.260 --> 00:01:23.132 responding and also even

NOTE Confidence: 0.9024154

00:01:23.132 --> 00:01:24.536 launching new centers.

NOTE Confidence: 0.9024154

00:01:24.540 --> 00:01:25.650 Precision oncology,

NOTE Confidence: 0.9024154

00:01:25.650 --> 00:01:28.425 precision cancer medison to help

NOTE Confidence: 0.9024154

00:01:28.425 --> 00:01:31.381 us define models to further the

NOTE Confidence: 0.9024154

00:01:31.381 --> 00:01:34.195 research of many of our faculty so.

NOTE Confidence: 0.9024154

00:01:34.200 --> 00:01:34.568 Marcus,

NOTE Confidence: 0.9024154

00:01:34.568 --> 00:01:36.408 thank you for volunteering to

NOTE Confidence: 0.9024154

00:01:36.408 --> 00:01:38.270 speak at our virtual form.

NOTE Confidence: 0.876604

00:01:40.020 --> 00:01:41.830 Great, thanks so much Charlie.

NOTE Confidence: 0.876604

00:01:41.830 --> 00:01:43.630 Thanks for the kind introduction.

NOTE Confidence: 0.876604

00:01:43.630 --> 00:01:46.507 Just someone give me an odd that

NOTE Confidence: 0.876604

00:01:46.507 --> 00:01:49.977 they can hear me and see the alright

NOTE Confidence: 0.876604

00:01:49.977 --> 00:01:52.750 sounds good great so I'll start.

NOTE Confidence: 0.876604

00:01:52.750 --> 00:01:56.320 Today's topic will be targeting innate

NOTE Confidence: 0.876604

00:01:56.320 --> 00:01:59.336 immunity to enhance anti cancer

NOTE Confidence: 0.876604

00:01:59.336 --> 00:02:03.060 immune responses and I think you know.

NOTE Confidence: 0.876604

00:02:03.060 --> 00:02:06.260 What we've seen, even in the last decade,

NOTE Confidence: 0.876604

00:02:06.260 --> 00:02:08.135 has been a remarkable transformation

NOTE Confidence: 0.876604

00:02:08.135 --> 00:02:11.059 about how we think about treating cancer.

NOTE Confidence: 0.876604

00:02:11.060 --> 00:02:12.260 A decade ago.

NOTE Confidence: 0.876604

00:02:12.260 --> 00:02:14.420 You know, aside from area snow,

NOTE Confidence: 0.876604

00:02:14.420 --> 00:02:17.199 if you look around Yale and other

NOTE Confidence: 0.876604

00:02:17.199 --> 00:02:19.460 institutions, and there are a

NOTE Confidence: 0.876604

00:02:19.460 --> 00:02:21.860 number of other people as well.

NOTE Confidence: 0.876604

00:02:21.860 --> 00:02:23.860 But there wasn't that much

NOTE Confidence: 0.876604

00:02:23.860 --> 00:02:25.460 interested in on Koleji.

NOTE Confidence: 0.876604

00:02:25.460 --> 00:02:27.028 There have been longstanding

NOTE Confidence: 0.876604

00:02:27.028 --> 00:02:29.860 efforts in a couple of cancer types,

NOTE Confidence: 0.876604

00:02:29.860 --> 00:02:31.860 including Melanoma, such as IO2,

NOTE Confidence: 0.876604

00:02:31.860 --> 00:02:32.688 systemic therapy,

NOTE Confidence: 0.876604

00:02:32.688 --> 00:02:34.344 and adaptive transferring to

NOTE Confidence: 0.876604

00:02:34.344 --> 00:02:35.586 Myrtle trading lymphocytes.

NOTE Confidence: 0.876604

00:02:35.590 --> 00:02:38.257 On both of those sort of pioneered

NOTE Confidence: 0.876604

00:02:38.257 --> 00:02:40.766 by Steve Rosenberg at NCI and then

NOTE Confidence: 0.876604

00:02:40.766 --> 00:02:43.221 over the early 2000s CLI four and

NOTE Confidence: 0.876604

00:02:43.221 --> 00:02:45.849 PD one PD L1 checkpoint blocking

NOTE Confidence: 0.876604

00:02:45.849 --> 00:02:47.828 therapies were developed and if

NOTE Confidence: 0.876604

00:02:47.828 --> 00:02:50.131 you look at the impact that this

NOTE Confidence: 0.876604

00:02:50.131 --> 00:02:53.171 is had in terms of the number of

NOTE Confidence: 0.876604

00:02:53.171 --> 00:02:55.752 cancer types where these are now

NOTE Confidence: 0.876604

00:02:55.752 --> 00:02:57.584 standard of care therapies,

NOTE Confidence: 0.876604

00:02:57.590 --> 00:03:00.271 you could argue that this is amongst

NOTE Confidence: 0.876604

00:03:00.271 --> 00:03:02.224 the greatest advances ever and

NOTE Confidence: 0.876604

00:03:02.224 --> 00:03:04.069 cancer therapeutics and resulted in

NOTE Confidence: 0.876604

00:03:04.069 --> 00:03:06.569 sort of the first large decline.

NOTE Confidence: 0.876604

00:03:06.570 --> 00:03:09.545 And cancer mortality over the last year,

NOTE Confidence: 0.876604

00:03:09.550 --> 00:03:11.670 especially with the effects in

NOTE Confidence: 0.876604

00:03:11.670 --> 00:03:13.366 lung cancer attributed to,

NOTE Confidence: 0.876604

00:03:13.370 --> 00:03:15.920 for instance, the PD one PD,

NOTE Confidence: 0.876604

00:03:15.920 --> 00:03:18.140 L1 blockade and this breakthrough

NOTE Confidence: 0.876604

00:03:18.140 --> 00:03:21.019 was awarded the Nobel Prize in 2018.

NOTE Confidence: 0.876604

00:03:21.020 --> 00:03:22.608 There's a nice video,

NOTE Confidence: 0.876604

00:03:22.608 --> 00:03:25.700 the PBS that's made about Jim Allison.

NOTE Confidence: 0.876604

00:03:25.700 --> 00:03:26.876 Related to that.

NOTE Confidence: 0.876604

00:03:26.876 --> 00:03:29.228 That's just been out and following

NOTE Confidence: 0.876604

00:03:29.228 --> 00:03:31.219 on that initial success,

NOTE Confidence: 0.876604

00:03:31.220 --> 00:03:34.391 a lot of companies change their portfolios

NOTE Confidence: 0.876604

00:03:34.391 --> 00:03:37.929 to try to do PD one blockade plus.

NOTE Confidence: 0.876604

00:03:37.930 --> 00:03:40.471 Other drugs as the new sort of

NOTE Confidence: 0.876604

00:03:40.471 --> 00:03:42.586 standard clinical trial that was

NOTE Confidence: 0.876604

00:03:42.586 --> 00:03:44.017 instituted in Disappointingly

NOTE Confidence: 0.876604

00:03:44.017 --> 00:03:46.402 the success of these approaches,

NOTE Confidence: 0.876604

00:03:46.410 --> 00:03:49.378 was not really what had been anticipated.

NOTE Confidence: 0.876604

00:03:49.380 --> 00:03:52.348 PD one blockade continued to have low,

NOTE Confidence: 0.876604

00:03:52.350 --> 00:03:54.385 but real levels of effects

NOTE Confidence: 0.876604

00:03:54.385 --> 00:03:57.010 in a variety of cancer types,

NOTE Confidence: 0.876604

00:03:57.010 --> 00:03:59.761 but the addition of 2nd drugs almost

NOTE Confidence: 0.876604

00:03:59.761 --> 00:04:01.930 overwhelmingly did not have significant

NOTE Confidence: 0.876604

00:04:01.930 --> 00:04:04.215 benefit beyond PD one blockade,

NOTE Confidence: 0.876604

00:04:04.220 --> 00:04:07.146 so there's a lot of interest in

NOTE Confidence: 0.876604

00:04:07.146 --> 00:04:09.220 developing combination therapy approaches.

NOTE Confidence: 0.876604

00:04:09.220 --> 00:04:10.084 In which cancer,

NOTE Confidence: 0.876604

00:04:10.084 --> 00:04:12.100 me know therapy is a component of

NOTE Confidence: 0.876604

00:04:12.159 --> 00:04:14.599 that and will focus a little bit more

NOTE Confidence: 0.876604

00:04:14.599 --> 00:04:16.327 about targeting components of the

NOTE Confidence: 0.876604

00:04:16.327 --> 00:04:18.439 innate immune system to enhance that.

NOTE Confidence: 0.876604

00:04:18.440 --> 00:04:20.864 and I would argue here is that the

NOTE Confidence: 0.876604

00:04:20.864 --> 00:04:22.888 mechanism of how these drugs work,

NOTE Confidence: 0.876604

00:04:22.890 --> 00:04:25.212 and in general how anti cancer

NOTE Confidence: 0.876604

00:04:25.212 --> 00:04:27.293 immune responses happen is really

NOTE Confidence: 0.876604

00:04:27.293 --> 00:04:28.670 not well understood.

NOTE Confidence: 0.876604

00:04:28.670 --> 00:04:30.782 Just to go back a little bit in

NOTE Confidence: 0.876604

00:04:30.782 --> 00:04:32.854 terms of what's innate immunity

NOTE Confidence: 0.876604

00:04:32.854 --> 00:04:34.818 and what's adaptive immunity.

NOTE Confidence: 0.876604

00:04:34.820 --> 00:04:37.130 Most aspects of immunity have a

NOTE Confidence: 0.876604

00:04:37.130 --> 00:04:39.060 strong basis in haematopoiesis and

NOTE Confidence: 0.876604

00:04:39.060 --> 00:04:40.980 the cell types that are derived,

NOTE Confidence: 0.876604

00:04:40.980 --> 00:04:43.316 at least in part from bone marrow and

NOTE Confidence: 0.876604

00:04:43.316 --> 00:04:45.284 going from pluripotent stem cells

NOTE Confidence: 0.876604

00:04:45.284 --> 00:04:47.489 to mile wooden lymphoid precursors,

NOTE Confidence: 0.876604

00:04:47.490 --> 00:04:50.024 pretty much everything in the myeloid side,

NOTE Confidence: 0.876604

00:04:50.030 --> 00:04:52.894 so the mass cells and all of these

NOTE Confidence: 0.876604

00:04:52.894 --> 00:04:55.605 guys over here on the right are

NOTE Confidence: 0.876604

00:04:55.605 --> 00:04:57.965 part of the innate immune system

NOTE Confidence: 0.876604

00:04:57.965 --> 00:05:00.125 and T cells and B cells.

NOTE Confidence: 0.876604

00:05:00.130 --> 00:05:02.405 Make up the primary component

NOTE Confidence: 0.876604

00:05:02.405 --> 00:05:04.680 of adaptive immune immunity and

NOTE Confidence: 0.889917499999999

00:05:04.763 --> 00:05:07.948 So what are the characteristics of the

NOTE Confidence: 0.889917499999999

00:05:07.948 --> 00:05:10.499 adaptive immune system to sort of to

NOTE Confidence: 0.889917499999999

00:05:10.499 --> 00:05:12.962 get that out of the way while we're

NOTE Confidence: 0.889917499999999

00:05:12.962 --> 00:05:14.970 talking about innate immunity, well,

NOTE Confidence: 0.889917499999999

00:05:14.970 --> 00:05:17.770 somatic hypermutation of the T Cell Receptor,

NOTE Confidence: 0.889917499999999

00:05:17.770 --> 00:05:20.020 an amino globulin loci and recombination

NOTE Confidence: 0.889917499999999

00:05:20.020 --> 00:05:22.738 of those loci allow for billions of

NOTE Confidence: 0.889917499999999

00:05:22.738 --> 00:05:24.648 different clones within every human

NOTE Confidence: 0.889917499999999

00:05:24.648 --> 00:05:26.773 that have distinct reactivity set

NOTE Confidence: 0.889917499999999

00:05:26.773 --> 00:05:29.365 allow for the recognition of almost

NOTE Confidence: 0.889917499999999

00:05:29.365 --> 00:05:31.108 countless and diverse sets of.

NOTE Confidence: 0.889917499999999

00:05:31.108 --> 00:05:33.867 Antigens for which one can have a response

NOTE Confidence: 0.889917499999999

00:05:33.867 --> 00:05:36.057 that's either Pisati Seller B cell

NOTE Confidence: 0.889917499999999

00:05:36.057 --> 00:05:38.338 mediated and these responses typically

NOTE Confidence: 0.889917499999999

00:05:38.338 --> 00:05:40.813 associated with what's called memory,

NOTE Confidence: 0.889917499999999

00:05:40.820 --> 00:05:42.896 which typically means that after an

NOTE Confidence: 0.889917499999999

00:05:42.896 --> 00:05:45.499 initial exposure to a particular antigen,

NOTE Confidence: 0.889917499999999

00:05:45.500 --> 00:05:47.840 something that's recognizable by these cells,

NOTE Confidence: 0.889917499999999

00:05:47.840 --> 00:05:50.295 there's an increased response the

NOTE Confidence: 0.889917499999999

00:05:50.295 --> 00:05:53.850 next time that Amazon is encountered.

NOTE Confidence: 0.889917499999999

00:05:53.850 --> 00:05:56.298 How do you know whether T cells are B?

NOTE Confidence: 0.889917499999999

00:05:56.300 --> 00:05:57.388 Cells are actually important

NOTE Confidence: 0.889917499999999

00:05:57.388 --> 00:05:58.748 in any of these processes.

NOTE Confidence: 0.889917499999999

00:05:58.750 --> 00:06:01.375 What you're looking at here is a

NOTE Confidence: 0.889917499999999

00:06:01.375 --> 00:06:03.927 Kaplan Meier plot of a pre clinical.

NOTE Confidence: 0.889917499999999

00:06:03.930 --> 00:06:04.660 Tumor experiment,

NOTE Confidence: 0.889917499999999

00:06:04.660 --> 00:06:07.580 in which a line that we have developed

NOTE Confidence: 0.889917499999999

00:06:07.654 --> 00:06:09.810 number one point 7 is in Grafton,

NOTE Confidence: 0.889917499999999

00:06:09.810 --> 00:06:11.114 subcutaneously in a mouse,

NOTE Confidence: 0.889917499999999

00:06:11.114 --> 00:06:14.227 and if a mouse succumbs to in a large

NOTE Confidence: 0.889917499999999

00:06:14.227 --> 00:06:16.037 tumor that's resulting survival law.

NOTE Confidence: 0.889917499999999

00:06:16.040 --> 00:06:18.161 So there's no mice alive in mice

NOTE Confidence: 0.889917499999999

00:06:18.161 --> 00:06:20.190 that have had tumor outgrowth.

NOTE Confidence: 0.889917499999999

00:06:20.190 --> 00:06:20.536 However,

NOTE Confidence: 0.889917499999999

00:06:20.536 --> 00:06:23.650 if you have this line extend out the side,

NOTE Confidence: 0.889917499999999

00:06:23.650 --> 00:06:25.050 as it does here,

NOTE Confidence: 0.889917499999999

00:06:25.050 --> 00:06:28.229 that means that the mouse was cured of its

NOTE Confidence: 0.889917499999999

00:06:28.229 --> 00:06:31.259 tumor and lived life span up to 60 days,

NOTE Confidence: 0.889917499999999

00:06:31.260 --> 00:06:32.331 as illustrated here.

NOTE Confidence: 0.889917499999999

00:06:32.331 --> 00:06:34.116 Well, what can be done?

NOTE Confidence: 0.889917499999999

00:06:34.120 --> 00:06:34.808 In mice,

NOTE Confidence: 0.889917499999999

00:06:34.808 --> 00:06:36.528 which is not really typically

NOTE Confidence: 0.889917499999999

00:06:36.528 --> 00:06:37.560 ethical in humans,

NOTE Confidence: 0.889917499999999

00:06:37.560 --> 00:06:39.636 is that you can actually deplete

NOTE Confidence: 0.889917499999999

00:06:39.636 --> 00:06:41.415 certain components of the immune

NOTE Confidence: 0.889917499999999

00:06:41.415 --> 00:06:43.055 system or in graph tumors.

NOTE Confidence: 0.889917499999999

00:06:43.060 --> 00:06:45.321 In mice that are deficient for those

NOTE Confidence: 0.889917499999999

00:06:45.321 --> 00:06:47.190 components of the immune system.

NOTE Confidence: 0.889917499999999

00:06:47.190 --> 00:06:48.171 In this case,

NOTE Confidence: 0.889917499999999

00:06:48.171 --> 00:06:50.133 what you can see is treatment

NOTE Confidence: 0.889917499999999

00:06:50.133 --> 00:06:52.202 with the drug that was developed

NOTE Confidence: 0.889917499999999

00:06:52.202 --> 00:06:54.760 here at Yale by Aaron Rings Group.

NOTE Confidence: 0.889917499999999

00:06:54.760 --> 00:06:57.496 This is a cloud of project that's now in

NOTE Confidence: 0.889917499999999

00:06:57.496 --> 00:06:59.919 press in nature through owners group.

NOTE Confidence: 0.889917499999999

00:06:59.920 --> 00:07:01.296 This drug annihilating derivative

NOTE Confidence: 0.889917499999999

00:07:01.296 --> 00:07:03.423 result in about a 30% cure,

NOTE Confidence: 0.889917499999999

00:07:03.423 --> 00:07:06.244 depleting with CD8 anti CD 8 antibody.

NOTE Confidence: 0.889917499999999

00:07:06.250 --> 00:07:08.427 Prevented that cure rate and CD four

NOTE Confidence: 0.889917499999999

00:07:08.427 --> 00:07:11.170 also did at a little bit longer latency

NOTE Confidence: 0.889917499999999

00:07:11.170 --> 00:07:13.420 while blockade of NK cells didn't

NOTE Confidence: 0.889917499999999

00:07:13.420 --> 00:07:15.580 result in any extended survivals.

NOTE Confidence: 0.889917499999999

00:07:15.580 --> 00:07:17.892 So what I'm kind of bringing up now

NOTE Confidence: 0.889917499999999

00:07:17.892 --> 00:07:20.940 is a concept that if you really want

NOTE Confidence: 0.889917499999999

00:07:20.940 --> 00:07:23.480 to understand how these things work,

NOTE Confidence: 0.889917499999999

00:07:23.480 --> 00:07:25.472 it's typically useful to have a

NOTE Confidence: 0.889917499999999

00:07:25.472 --> 00:07:27.262 system to evaluate what functional

NOTE Confidence: 0.889917499999999

00:07:27.262 --> 00:07:29.227 components are at play here,

NOTE Confidence: 0.889917499999999

00:07:29.230 --> 00:07:31.384 and that's been a difficulty with

NOTE Confidence: 0.889917499999999

00:07:31.384 --> 00:07:32.820 the innate immune system,

NOTE Confidence: 0.889917499999999

00:07:32.820 --> 00:07:34.752 which will talk about second quick

NOTE Confidence: 0.889917499999999

00:07:34.752 --> 00:07:37.359 segue here to B cells and anti

NOTE Confidence: 0.889917499999999

00:07:37.359 --> 00:07:39.019 cancer immune responses which.

NOTE Confidence: 0.889917499999999

00:07:39.020 --> 00:07:41.396 Had a big splash earlier in the year

NOTE Confidence: 0.889917499999999

00:07:41.396 --> 00:07:43.491 where there were three papers in

NOTE Confidence: 0.889917499999999

00:07:43.491 --> 00:07:45.286 nature in January suggesting that

NOTE Confidence: 0.889917499999999

00:07:45.286 --> 00:07:47.746 the cells have a role in anti cancer

NOTE Confidence: 0.889917499999999

00:07:47.746 --> 00:07:49.796 immunity and I would say that this

NOTE Confidence: 0.889917499999999

00:07:49.796 --> 00:07:52.140 issue is still not really fully resolved.

NOTE Confidence: 0.889917499999999

00:07:52.140 --> 00:07:53.844 All of those patient papers tended

NOTE Confidence: 0.889917499999999

00:07:53.844 --> 00:07:55.829 to be a correlative and weren't

NOTE Confidence: 0.889917499999999

00:07:55.829 --> 00:07:56.619 really functional.

NOTE Confidence: 0.889917499999999

00:07:56.620 --> 00:07:59.036 Studies now show example of that in a

NOTE Confidence: 0.889917499999999

00:07:59.036 --> 00:08:01.522 bit what is known and has been known

NOTE Confidence: 0.889917499999999

00:08:01.522 --> 00:08:03.824 for awhile is that when you have

NOTE Confidence: 0.889917499999999

00:08:03.824 --> 00:08:06.211 elevated number of T cells and cancer,

NOTE Confidence: 0.90716255

00:08:06.220 --> 00:08:09.406 you tend to have elevated B cells as well.

NOTE Confidence: 0.90716255

00:08:09.410 --> 00:08:11.345 Uh, that correlation coefficient from

NOTE Confidence: 0.90716255

00:08:11.345 --> 00:08:14.568 an RNA POV is about a row of about .7,

NOTE Confidence: 0.90716255

00:08:14.570 --> 00:08:17.207 so it's a pretty high correlation in terms of

NOTE Confidence: 0.90716255

00:08:17.207 --> 00:08:20.066 be selling T celko infiltration into tumors,

NOTE Confidence: 0.90716255

00:08:20.070 --> 00:08:22.128 but that doesn't necessarily say that

NOTE Confidence: 0.90716255

00:08:22.128 --> 00:08:23.860 they're actually doing things there,

NOTE Confidence: 0.90716255

00:08:23.860 --> 00:08:25.816 and clinically we typically it's very

NOTE Confidence: 0.90716255

00:08:25.816 --> 00:08:28.670 common to use a drug called Rituxan Mab,

NOTE Confidence: 0.90716255

00:08:28.670 --> 00:08:31.290 which is a CD20 anti CD 20 in a body

NOTE Confidence: 0.90716255

00:08:31.367 --> 00:08:34.511 which results in depletion of B cells and

NOTE Confidence: 0.90716255

00:08:34.511 --> 00:08:37.270 the patients that are treated that way.

NOTE Confidence: 0.90716255

00:08:37.270 --> 00:08:39.020 And typically these patients don't

NOTE Confidence: 0.90716255

00:08:39.020 --> 00:08:41.178 have really much higher rates of

NOTE Confidence: 0.90716255

00:08:41.178 --> 00:08:42.578 cancers you might anticipate.

NOTE Confidence: 0.90716255

00:08:42.580 --> 00:08:44.960 If that were a primary method of

NOTE Confidence: 0.90716255

00:08:44.960 --> 00:08:46.324 restraining that particular arm

NOTE Confidence: 0.90716255

00:08:46.324 --> 00:08:47.816 of the immune system, however,

NOTE Confidence: 0.90716255

00:08:47.816 --> 00:08:50.308 I think there's still more work that

NOTE Confidence: 0.90716255

00:08:50.308 --> 00:08:52.328 hopefully will be done in this area.

NOTE Confidence: 0.90716255

00:08:52.330 --> 00:08:54.493 This is an experiment that I was

NOTE Confidence: 0.90716255

00:08:54.493 --> 00:08:56.803 referring to in which you can actually

NOTE Confidence: 0.90716255

00:08:56.803 --> 00:08:59.167 graph the same kind of tumor into

NOTE Confidence: 0.90716255

00:08:59.167 --> 00:09:00.777 a B cell deficient mouse.

NOTE Confidence: 0.90716255

00:09:00.780 --> 00:09:01.758 Here at LAX,

NOTE Confidence: 0.90716255

00:09:01.758 --> 00:09:03.714 the heavy chain that's needed prior

NOTE Confidence: 0.90716255

00:09:03.714 --> 00:09:05.764 to class switching of these cells

NOTE Confidence: 0.90716255

00:09:05.764 --> 00:09:08.258 and in a normal mouse say with PD,

NOTE Confidence: 0.90716255

00:09:08.260 --> 00:09:09.880 one therapy or spontaneous rejection.

NOTE Confidence: 0.90716255

00:09:09.880 --> 00:09:12.950 This is this curve here, or black sticks in.

NOTE Confidence: 0.90716255

00:09:12.950 --> 00:09:15.925 Black them you empty mice which lack B

NOTE Confidence: 0.90716255

00:09:15.925 --> 00:09:18.508 cells actually reject as well or better,

NOTE Confidence: 0.90716255

00:09:18.510 --> 00:09:21.518 while rag mice that lack both B&T cells.

NOTE Confidence: 0.90716255

00:09:21.520 --> 00:09:24.425 So a second way of evaluating whether

NOTE Confidence: 0.90716255

00:09:24.425 --> 00:09:26.081 lymphocytes more generally are

NOTE Confidence: 0.90716255

00:09:26.081 --> 00:09:28.139 needed results an outgrowth of the

NOTE Confidence: 0.90716255

00:09:28.139 --> 00:09:30.538 tumors so that you don't have that.

NOTE Confidence: 0.90716255

00:09:30.540 --> 00:09:32.760 This is a collaborative project with

NOTE Confidence: 0.90716255

00:09:32.760 --> 00:09:35.049 Harriet clickers lab by Bill Damski,

NOTE Confidence: 0.90716255

00:09:35.050 --> 00:09:38.522 who is going to be a new faculty

NOTE Confidence: 0.90716255

00:09:38.522 --> 00:09:41.570 member in dermatology in July.

NOTE Confidence: 0.90716255

00:09:41.570 --> 00:09:44.000 So what are the characteristics

NOTE Confidence: 0.90716255

00:09:44.000 --> 00:09:46.430 of the innate immune system?

NOTE Confidence: 0.90716255

00:09:46.430 --> 00:09:49.238 So it's typically a rapid response

NOTE Confidence: 0.90716255

00:09:49.238 --> 00:09:52.694 of system in which it's kind of

NOTE Confidence: 0.90716255

00:09:52.694 --> 00:09:55.179 hard wired to wrecking sentries,

NOTE Confidence: 0.90716255

00:09:55.180 --> 00:09:57.650 certain pathogen or pathogen molecular

NOTE Confidence: 0.90716255

00:09:57.650 --> 00:10:00.120 patterns that viruses or bacteria.

NOTE Confidence: 0.90716255

00:10:00.120 --> 00:10:02.135 Might happen or not typically

NOTE Confidence: 0.90716255

00:10:02.135 --> 00:10:03.344 present in eukaryotes,

NOTE Confidence: 0.90716255

00:10:03.350 --> 00:10:05.370 so it allows for almost

NOTE Confidence: 0.90716255

00:10:05.370 --> 00:10:07.390 like a barrier or reflex.

NOTE Confidence: 0.90716255

00:10:07.390 --> 00:10:09.410 If response to these type

NOTE Confidence: 0.90716255

00:10:09.410 --> 00:10:11.026 of molecules one recognize,

NOTE Confidence: 0.90716255

00:10:11.030 --> 00:10:13.490 but also the innate immune system

NOTE Confidence: 0.90716255

00:10:13.490 --> 00:10:15.130 can regulate enhance activation

NOTE Confidence: 0.90716255

00:10:15.196 --> 00:10:17.086 of the adaptive immune system.

NOTE Confidence: 0.90716255

00:10:17.090 --> 00:10:19.708 This has been known in vaccine biology

NOTE Confidence: 0.90716255

00:10:19.708 --> 00:10:22.198 and it's also known or understood

NOTE Confidence: 0.90716255

00:10:22.198 --> 00:10:24.353 the role within dirt excels.

NOTE Confidence: 0.90716255

00:10:24.360 --> 00:10:27.006 Play Witcher view to be part

NOTE Confidence: 0.90716255

00:10:27.006 --> 00:10:29.490 of the innate immune system.

NOTE Confidence: 0.90716255

00:10:29.490 --> 00:10:31.518 And their activation of T cells

NOTE Confidence: 0.90716255

00:10:31.518 --> 00:10:32.870 and T cell responses.

NOTE Confidence: 0.90716255

00:10:32.870 --> 00:10:35.040 So the question really is is what's

NOTE Confidence: 0.90716255

00:10:35.040 --> 00:10:37.389 the role of these various components

NOTE Confidence: 0.90716255

00:10:37.389 --> 00:10:40.077 in anti cancer immune responses and?

NOTE Confidence: 0.90716255

00:10:40.080 --> 00:10:42.104 It's useful to have an idea of what

NOTE Confidence: 0.90716255

00:10:42.104 --> 00:10:43.744 we're talking about here in terms

NOTE Confidence: 0.90716255

00:10:43.744 --> 00:10:45.358 of what the components might be.

NOTE Confidence: 0.90716255

00:10:45.360 --> 00:10:47.292 There's a lot of confusion and

NOTE Confidence: 0.90716255

00:10:47.292 --> 00:10:49.429 a lot of debate as to what.

NOTE Confidence: 0.90716255

00:10:49.430 --> 00:10:51.314 Sort of subsets of things that

NOTE Confidence: 0.90716255

00:10:51.314 --> 00:10:52.570 are related to macrophyllus.

NOTE Confidence: 0.90716255

00:10:52.570 --> 00:10:54.768 I'm not going to get into that.

NOTE Confidence: 0.90716255

00:10:54.770 --> 00:10:56.654 It's not enough time to really

NOTE Confidence: 0.90716255

00:10:56.654 --> 00:10:57.910 fully go into that.

NOTE Confidence: 0.90716255

00:10:57.910 --> 00:10:59.690 In this session there's different

NOTE Confidence: 0.90716255

00:10:59.690 --> 00:11:01.470 subsets of dendritic cells which

NOTE Confidence: 0.90716255

00:11:01.524 --> 00:11:03.246 a few of which are labeled here.

NOTE Confidence: 0.90716255

00:11:03.250 --> 00:11:04.490 Neutrophils are granulocytes down

NOTE Confidence: 0.90716255

00:11:04.490 --> 00:11:06.350 the bottom here and then there

NOTE Confidence: 0.90716255

00:11:06.400 --> 00:11:08.110 are some components of cells that

NOTE Confidence: 0.90716255

00:11:08.110 --> 00:11:09.250 are derived from lymphoid

NOTE Confidence: 0.9131504

00:11:09.307 --> 00:11:11.724 precursors, but kind of have some aspects

NOTE Confidence: 0.9131504

00:11:11.724 --> 00:11:13.963 of innate immunity in that they may

NOTE Confidence: 0.9131504

00:11:13.963 --> 00:11:16.112 or may not have the memory response.

NOTE Confidence: 0.9131504

00:11:16.120 --> 00:11:18.034 It's debated with some of these

NOTE Confidence: 0.9131504

00:11:18.034 --> 00:11:20.338 and also they have the ability to.

NOTE Confidence: 0.9131504

00:11:20.340 --> 00:11:22.090 Rapid respond to certain common

NOTE Confidence: 0.9131504

00:11:22.090 --> 00:11:23.490 molecular signatures which typically

NOTE Confidence: 0.9131504

00:11:23.490 --> 00:11:25.249 B&T cells don't do as regularly,

NOTE Confidence: 0.9131504

00:11:25.250 --> 00:11:27.126 so these are kind of a little

NOTE Confidence: 0.9131504

00:11:27.126 --> 00:11:29.195 bit in between depending on what

NOTE Confidence: 0.9131504

00:11:29.195 --> 00:11:30.795 aspect you're talking about,

NOTE Confidence: 0.9131504

00:11:30.800 --> 00:11:32.768 might fall in between the two.

NOTE Confidence: 0.9131504

00:11:32.770 --> 00:11:34.822 Errands group has also found some

NOTE Confidence: 0.9131504

00:11:34.822 --> 00:11:36.190 really interesting therapies that

NOTE Confidence: 0.9131504

00:11:36.241 --> 00:11:37.666 stimulate NK cells the same.

NOTE Confidence: 0.9131504

00:11:37.670 --> 00:11:39.626 When I was talking about you,

NOTE Confidence: 0.9131504

00:11:39.630 --> 00:11:41.786 wait for his talk to do that

NOTE Confidence: 0.9131504

00:11:41.786 --> 00:11:43.230 more and more depth,

NOTE Confidence: 0.9131504

00:11:43.230 --> 00:11:45.732 and he may have talked a little bit about

NOTE Confidence: 0.9131504

00:11:45.732 --> 00:11:48.139 that during this grand rounds recently.

NOTE Confidence: 0.9131504

00:11:48.140 --> 00:11:50.144 But I think there's a more

NOTE Confidence: 0.9131504

00:11:50.144 --> 00:11:51.950 of a story there that.

NOTE Confidence: 0.9131504

00:11:51.950 --> 00:11:54.266 And certainly can follow up with.

NOTE Confidence: 0.9131504

00:11:54.270 --> 00:11:56.520 So the question with innate immunity

NOTE Confidence: 0.9131504

00:11:56.520 --> 00:11:59.487 has been for awhile as is it actually

NOTE Confidence: 0.9131504

00:11:59.487 --> 00:12:01.575 fighting cancer or is it promoting

NOTE Confidence: 0.9131504

00:12:01.651 --> 00:12:03.527 cancer with certain aspects?

NOTE Confidence: 0.9131504

00:12:03.530 --> 00:12:06.057 and I think most people would view

NOTE Confidence: 0.9131504

00:12:06.057 --> 00:12:08.433 most components of the innate immune

NOTE Confidence: 0.9131504

00:12:08.433 --> 00:12:10.473 system to be promoting cancer,

NOTE Confidence: 0.9131504

00:12:10.480 --> 00:12:12.410 at least in some level.

NOTE Confidence: 0.9131504

00:12:12.410 --> 00:12:14.720 And how might we know that?

NOTE Confidence: 0.9131504

00:12:14.720 --> 00:12:15.056 Well,

NOTE Confidence: 0.9131504

00:12:15.056 --> 00:12:17.408 in certain cancer types where as a

NOTE Confidence: 0.9131504

00:12:17.408 --> 00:12:19.634 pathologist one sees something called

NOTE Confidence: 0.9131504

00:12:19.634 --> 00:12:21.678 metaplasia. So at the junction.

NOTE Confidence: 0.9131504

00:12:21.678 --> 00:12:24.000 Of the posterior aspect of the

NOTE Confidence: 0.9131504

00:12:24.084 --> 00:12:25.479 vagina and cervix.

NOTE Confidence: 0.9131504

00:12:25.480 --> 00:12:27.778 There's typically there can be inflammation,

NOTE Confidence: 0.9131504

00:12:27.780 --> 00:12:30.078 depending on the status of HP.

NOTE Confidence: 0.9131504

00:12:30.080 --> 00:12:32.000 The other things like that,

NOTE Confidence: 0.9131504

00:12:32.000 --> 00:12:34.025 which results in inflammation being

NOTE Confidence: 0.9131504

00:12:34.025 --> 00:12:36.050 chronically present at that site

NOTE Confidence: 0.9131504

00:12:36.119 --> 00:12:37.623 and for gastroesophageal reflux

NOTE Confidence: 0.9131504

00:12:37.623 --> 00:12:39.879 once he's also these changes of

NOTE Confidence: 0.9131504

00:12:39.939 --> 00:12:41.729 inflammation and alteration of the

NOTE Confidence: 0.9131504

00:12:41.729 --> 00:12:44.216 cell types that are there that are

NOTE Confidence: 0.9131504

00:12:44.216 --> 00:12:45.956 associated with higher rates of

NOTE Confidence: 0.9131504

00:12:45.956 --> 00:12:48.129 cancer in those particular spots.

NOTE Confidence: 0.9131504

00:12:48.130 --> 00:12:50.433 Also in a variety of models where

NOTE Confidence: 0.9131504

00:12:50.433 --> 00:12:52.360 when you induce inflammation,

NOTE Confidence: 0.9131504

00:12:52.360 --> 00:12:54.748 it tends to be cancer promoting.

NOTE Confidence: 0.9131504

00:12:54.750 --> 00:12:57.000 And the thought process that few

NOTE Confidence: 0.9131504

00:12:57.000 --> 00:13:00.497 people feel is is at at work there is

NOTE Confidence: 0.9131504

00:13:00.497 --> 00:13:02.940 that some of these inflammatory cells,

NOTE Confidence: 0.9131504

00:13:02.940 --> 00:13:05.280 like macrophages, secrete things like veg,

NOTE Confidence: 0.9131504

00:13:05.280 --> 00:13:07.793 F or other factors that are associated

NOTE Confidence: 0.9131504

00:13:07.793 --> 00:13:09.689 with growth or angiogenesis which

NOTE Confidence: 0.9131504

00:13:09.689 --> 00:13:12.300 then allow cancers to Co op that

NOTE Confidence: 0.9131504

00:13:12.300 --> 00:13:14.901 and then grow out and myeloid

NOTE Confidence: 0.9131504

00:13:14.901 --> 00:13:16.197 derived suppressor cells.

NOTE Confidence: 0.9131504

00:13:16.200 --> 00:13:18.540 Or the probably related M2 quote,

NOTE Confidence: 0.9131504

00:13:18.540 --> 00:13:20.692 Unquote subset of Macro

NOTE Confidence: 0.9131504

00:13:20.692 --> 00:13:22.790 Fages and in certain cases,

NOTE Confidence: 0.9131504

00:13:22.790 --> 00:13:23.180 neutrophils,

NOTE Confidence: 0.9131504

00:13:23.180 --> 00:13:25.508 which might also be viewed as

NOTE Confidence: 0.9131504

00:13:25.508 --> 00:13:26.672 the granulocytic MDC's,

NOTE Confidence: 0.9131504

00:13:26.680 --> 00:13:28.232 have been described as

NOTE Confidence: 0.9131504

00:13:28.232 --> 00:13:29.396 being potentially tumor,

NOTE Confidence: 0.9131504

00:13:29.400 --> 00:13:31.012 promoting by growth restriction,

NOTE Confidence: 0.9131504

00:13:31.012 --> 00:13:33.854 but also that they actively suppress the

NOTE Confidence: 0.9131504

00:13:33.854 --> 00:13:36.008 function of the adaptive immune system.

NOTE Confidence: 0.9131504

00:13:36.010 --> 00:13:39.350 And there are ways you can test this ex vivo

NOTE Confidence: 0.9131504

00:13:39.434 --> 00:13:42.626 and looking at T cell proliferation assay,

NOTE Confidence: 0.9131504

00:13:42.630 --> 00:13:44.832 zan secretion of cytokines, things that

NOTE Confidence: 0.9131504

00:13:44.832 --> 00:13:47.290 these cells might do against tumors.

NOTE Confidence: 0.9131504

00:13:47.290 --> 00:13:49.290 It's well established that natural

NOTE Confidence: 0.9131504

00:13:49.290 --> 00:13:51.690 killer cells have a large role.

NOTE Confidence: 0.9131504

00:13:51.690 --> 00:13:52.012 Uh,

NOTE Confidence: 0.9131504

00:13:52.012 --> 00:13:53.944 in eliminate ING cells that don't

NOTE Confidence: 0.9131504

00:13:53.944 --> 00:13:55.925 have MHT class one expressed on

NOTE Confidence: 0.9131504

00:13:55.925 --> 00:13:58.137 their surface and this is a little

NOTE Confidence: 0.9131504

00:13:58.201 --> 00:14:00.756 bit variable in terms of the balance

NOTE Confidence: 0.9131504

00:14:00.756 --> 00:14:02.548 between inhibitory and activating receptors.

NOTE Confidence: 0.9131504

00:14:02.548 --> 00:14:04.956 But there are thought to be the

NOTE Confidence: 0.9131504

00:14:04.956 --> 00:14:06.610 primary way where this occurs,

NOTE Confidence: 0.9131504

00:14:06.610 --> 00:14:07.966 and obviously they're called

NOTE Confidence: 0.9131504

00:14:07.966 --> 00:14:10.000 natural killer cells for a reason.

NOTE Confidence: 0.9131504

00:14:10.000 --> 00:14:12.704 They actually kill in a variety of Contexts,

NOTE Confidence: 0.9131504

00:14:12.710 --> 00:14:14.738 so some of those contexts can

NOTE Confidence: 0.9131504

00:14:14.738 --> 00:14:15.752 be against cancer,

NOTE Confidence: 0.9082676

00:14:15.760 --> 00:14:17.839 and there's also this thought that a

NOTE Confidence: 0.9082676

00:14:17.839 --> 00:14:19.616 certain subtype of macrophages can

NOTE Confidence: 0.9082676

00:14:19.616 --> 00:14:21.696 also participate in killing responses.

NOTE Confidence: 0.9082676

00:14:21.700 --> 00:14:23.996 Either through respiratory burst

NOTE Confidence: 0.9082676

00:14:23.996 --> 00:14:26.866 activity or secretion of cytokines

NOTE Confidence: 0.9082676

00:14:26.866 --> 00:14:29.507 locally in the micro environments.

NOTE Confidence: 0.9082676

00:14:29.510 --> 00:14:31.994 And so it's been attractive hypothesis

NOTE Confidence: 0.9082676

00:14:31.994 --> 00:14:35.772 for a while to try to target cells that

NOTE Confidence: 0.9082676

00:14:35.772 --> 00:14:38.268 seem to be promoting cancer formation

NOTE Confidence: 0.9082676

00:14:38.268 --> 00:14:41.715 and a few ways of doing that have been.

NOTE Confidence: 0.9082676

00:14:41.720 --> 00:14:43.760 It's been known for awhile,

NOTE Confidence: 0.9082676

00:14:43.760 --> 00:14:45.380 but the colonist stimulating

NOTE Confidence: 0.9082676

00:14:45.380 --> 00:14:46.595 factor 1 pathway,

NOTE Confidence: 0.9082676

00:14:46.600 --> 00:14:49.700 so CSF one and its receptor CSF one R are

NOTE Confidence: 0.9082676

00:14:49.784 --> 00:14:53.120 very very important and Macrophiles Biology.

NOTE Confidence: 0.9082676

00:14:53.120 --> 00:14:56.510 One way this was known as there is the so

NOTE Confidence: 0.9082676

00:14:56.602 --> 00:15:00.249 called osteopetrosis model of the opi model.

NOTE Confidence: 0.9082676

00:15:00.250 --> 00:15:03.026 In which CSF one is an inactive illegal

NOTE Confidence: 0.9082676

00:15:03.026 --> 00:15:06.694 in my so my Sutter home was I get for

NOTE Confidence: 0.9082676

00:15:06.694 --> 00:15:09.417 that particular allele oven on fully

NOTE Confidence: 0.9082676

00:15:09.417 --> 00:15:11.812 functional CSF one Lac macrophages?

NOTE Confidence: 0.9082676

00:15:11.820 --> 00:15:13.810 They also lack macrophage related

NOTE Confidence: 0.9082676

00:15:13.810 --> 00:15:15.004 cells like osteoclast,

NOTE Confidence: 0.9082676

00:15:15.010 --> 00:15:17.368 that remodel bone and teeth so

NOTE Confidence: 0.9082676

00:15:17.368 --> 00:15:20.199 these are hard nice to keep around.

NOTE Confidence: 0.9082676

00:15:20.200 --> 00:15:22.671 Then I'll talk about them in just

NOTE Confidence: 0.9082676

00:15:22.671 --> 00:15:25.418 a second a little bit more but

NOTE Confidence: 0.9082676

00:15:25.418 --> 00:15:27.824 that's one idea about how this

NOTE Confidence: 0.9082676

00:15:27.909 --> 00:15:30.795 pathway is relevant for Macro Fages.

NOTE Confidence: 0.9082676

00:15:30.800 --> 00:15:31.176 Um?

NOTE Confidence: 0.9082676

00:15:31.176 --> 00:15:33.432 And so there are small molecule

NOTE Confidence: 0.9082676

00:15:33.432 --> 00:15:35.722 inhibitors that this is a receptor

NOTE Confidence: 0.9082676

00:15:35.722 --> 00:15:37.900 tyrosine kinase that it can be

NOTE Confidence: 0.9082676

00:15:37.900 --> 00:15:39.916 inhibited by small molecules and

NOTE Confidence: 0.9082676

00:15:39.916 --> 00:15:41.896 it's also antibodies that block

NOTE Confidence: 0.9082676

00:15:41.896 --> 00:15:43.696 this receptor tyrosine kinase an.

NOTE Confidence: 0.9082676

00:15:43.696 --> 00:15:46.567 We've used both of these in the context

NOTE Confidence: 0.9082676

00:15:46.567 --> 00:15:48.697 of preclinical modeling and I'll talk

NOTE Confidence: 0.9082676

00:15:48.697 --> 00:15:51.097 about a clinical trial at the end.

NOTE Confidence: 0.9082676

00:15:51.100 --> 00:15:52.888 It's currently underway at Yale and

NOTE Confidence: 0.9082676

00:15:52.888 --> 00:15:55.364 you could have either of these two

NOTE Confidence: 0.9082676

00:15:55.364 --> 00:15:56.996 activities that's actually inhibited

NOTE Confidence: 0.9082676

00:15:56.996 --> 00:15:58.490 and somewhat disappointingly CSF.

NOTE Confidence: 0.9082676

00:15:58.490 --> 00:16:00.569 One R inhibitors as single agents have

NOTE Confidence: 0.9082676

00:16:00.569 --> 00:16:02.790 really not been particularly effective.

NOTE Confidence: 0.9082676

00:16:02.790 --> 00:16:04.610 There's one indication which I

NOTE Confidence: 0.9082676

00:16:04.610 --> 00:16:06.430 believe their FDA approved for

NOTE Confidence: 0.9082676

00:16:06.497 --> 00:16:08.464 it to so called giant cell tumor,

NOTE Confidence: 0.9082676

00:16:08.470 --> 00:16:10.468 which is really composed of macrophages.

NOTE Confidence: 0.9082676

00:16:10.470 --> 00:16:12.798 But I think they've been negative in all

NOTE Confidence: 0.9082676

00:16:12.798 --> 00:16:15.476 or nearly all other single agent indications.

NOTE Confidence: 0.9082676

00:16:15.480 --> 00:16:17.320 There typically also negative in

NOTE Confidence: 0.9082676

00:16:17.320 --> 00:16:19.529 combination with anti PD one blockade

NOTE Confidence: 0.9082676

00:16:19.529 --> 00:16:21.985 and one of the issues with studies of

NOTE Confidence: 0.9082676

00:16:21.985 --> 00:16:24.166 this type is did the drug actually.

NOTE Confidence: 0.8768581

00:16:26.180 --> 00:16:28.555 Affectively inhibit macrophages or even

NOTE Confidence: 0.8768581

00:16:28.555 --> 00:16:30.455 deplete macrofossils were typically

NOTE Confidence: 0.8768581

00:16:30.455 --> 00:16:33.442 very hard to deplete and so this is

NOTE Confidence: 0.8768581

00:16:33.442 --> 00:16:35.136 also called pharmacodynamics to see

NOTE Confidence: 0.8768581

00:16:35.136 --> 00:16:37.166 if your drug had the intended effect,

NOTE Confidence: 0.8768581

00:16:37.170 --> 00:16:39.858 and I think sometimes it's been a

NOTE Confidence: 0.8768581

00:16:39.858 --> 00:16:42.171 little less clearer that it's been

NOTE Confidence: 0.8768581

00:16:42.171 --> 00:16:44.705 full effect as opposed to a partial

NOTE Confidence: 0.8768581

00:16:44.782 --> 00:16:47.026 effect for some of these drugs.

NOTE Confidence: 0.8768581

00:16:47.030 --> 00:16:49.846 So can we use preclinical models to help

NOTE Confidence: 0.8768581

00:16:49.846 --> 00:16:52.710 define a role for makefiles in cancer?

NOTE Confidence: 0.8768581

00:16:52.710 --> 00:16:55.531 I had described an approach before with

NOTE Confidence: 0.8768581

00:16:55.531 --> 00:16:58.130 those Kaplan Meier plots where we use.

NOTE Confidence: 0.8768581

00:16:58.130 --> 00:16:59.093 Antibodies to deplete,

NOTE Confidence: 0.8768581

00:16:59.093 --> 00:17:01.020 for instance CDA, positive T cell,

NOTE Confidence: 0.8768581

00:17:01.020 --> 00:17:03.571 CD 4 positive T cells, or NK cells.

NOTE Confidence: 0.8768581

00:17:03.571 --> 00:17:05.156 Well, those approaches don't tend

NOTE Confidence: 0.8768581

00:17:05.156 --> 00:17:07.438 to work very well for macro fibers,

NOTE Confidence: 0.8768581

00:17:07.440 --> 00:17:10.248 and even using the anti CSF one R and

NOTE Confidence: 0.8768581

00:17:10.248 --> 00:17:12.899 nobody even with the right type of IgG,

NOTE Confidence: 0.8768581

00:17:12.900 --> 00:17:14.820 that would be typically more depleting,

NOTE Confidence: 0.8768581

00:17:14.820 --> 00:17:17.388 doesn't really tend to work in this subset.

NOTE Confidence: 0.8768581

00:17:17.390 --> 00:17:18.985 The genetic models which are

NOTE Confidence: 0.8768581

00:17:18.985 --> 00:17:20.920 actually probably not bad for this,

NOTE Confidence: 0.8768581

00:17:20.920 --> 00:17:23.304 and the Mets it off lab and others

NOTE Confidence: 0.8768581

00:17:23.304 --> 00:17:25.740 have used these in a cancer context.

NOTE Confidence: 0.8768581

00:17:25.740 --> 00:17:27.595 These are very hard models to work

NOTE Confidence: 0.8768581

00:17:27.595 --> 00:17:29.959 with as I mentioned before because.

NOTE Confidence: 0.8768581

00:17:29.960 --> 00:17:31.658 Even the teeth don't form properly,

NOTE Confidence: 0.8768581

00:17:31.660 --> 00:17:33.075 they don't breed particularly well

NOTE Confidence: 0.8768581

00:17:33.075 --> 00:17:34.490 suited to feed themselves Chow.

NOTE Confidence: 0.8768581

00:17:34.490 --> 00:17:36.464 You have to really, really baby them,

NOTE Confidence: 0.8768581

00:17:36.470 --> 00:17:37.964 like a watch them very closely

NOTE Confidence: 0.8768581

00:17:37.964 --> 00:17:39.651 to actually do a full experiment

NOTE Confidence: 0.8768581

00:17:39.651 --> 00:17:41.559 and then doing cohort type work.

NOTE Confidence: 0.8768581

00:17:41.560 --> 00:17:43.258 It is difficult 'cause they don't

NOTE Confidence: 0.8768581

00:17:43.258 --> 00:17:44.680 tend to live particularly long,

NOTE Confidence: 0.8768581

00:17:44.680 --> 00:17:46.680 even postnatally.

NOTE Confidence: 0.8768581

00:17:46.680 --> 00:17:48.468 And you can deplete in macrophages

NOTE Confidence: 0.8768581

00:17:48.468 --> 00:17:50.010 from spleen and peripheral blood,

NOTE Confidence: 0.8768581

00:17:50.010 --> 00:17:51.094 but within the tumor,

NOTE Confidence: 0.8768581

00:17:51.094 --> 00:17:53.350 if you look at them pretty carefully,

NOTE Confidence: 0.8768581

00:17:53.350 --> 00:17:55.168 they tend not to have been

NOTE Confidence: 0.8768581

00:17:55.168 --> 00:17:56.380 depleted in those areas,

NOTE Confidence: 0.8768581

00:17:56.380 --> 00:17:58.198 so this is an area obviously

NOTE Confidence: 0.8768581

00:17:58.198 --> 00:17:59.410 of interest in growth,

NOTE Confidence: 0.8768581

00:17:59.410 --> 00:18:01.335 so it's hard to know what the

NOTE Confidence: 0.8768581

00:18:01.335 --> 00:18:03.350 real role of these things are,

NOTE Confidence: 0.8768581

00:18:03.350 --> 00:18:06.068 but we have done some work looking at CSF.

NOTE Confidence: 0.8768581

00:18:06.070 --> 00:18:08.310 One R Inhibitors and we published a few

NOTE Confidence: 0.8768581

00:18:08.310 --> 00:18:10.620 years back with Mark Smith from Brisbane,

NOTE Confidence: 0.8768581

00:18:10.620 --> 00:18:12.490 Australia.

NOTE Confidence: 0.8768581

00:18:12.490 --> 00:18:15.185 A drug that Plexxikon had developed that

NOTE Confidence: 0.8768581

00:18:15.185 --> 00:18:17.290 wasn't specific just for CSF one R,

NOTE Confidence: 0.8768581

00:18:17.290 --> 00:18:19.348 but that was its highest potency

NOTE Confidence: 0.8768581

00:18:19.348 --> 00:18:20.720 towards that particular receptor.

NOTE Confidence: 0.8768581

00:18:20.720 --> 00:18:23.256 And one thing I'd like to bring your

NOTE Confidence: 0.8768581

00:18:23.256 --> 00:18:25.506 attention to is that wouldn't it be

NOTE Confidence: 0.8768581

00:18:25.506 --> 00:18:27.903 great if there were human models where

NOTE Confidence: 0.8768581

00:18:27.903 --> 00:18:30.231 you could actually see an effective

NOTE Confidence: 0.8768581

00:18:30.231 --> 00:18:32.714 anti cancer immune response and you

NOTE Confidence: 0.8768581

00:18:32.714 --> 00:18:34.418 could actually deplete macrophages?

NOTE Confidence: 0.8768581

00:18:34.420 --> 00:18:35.218 And we think,

NOTE Confidence: 0.8768581

00:18:35.218 --> 00:18:37.080 and we hope that we may have

NOTE Confidence: 0.8768581

00:18:37.147 --> 00:18:39.047 developed something like that.

NOTE Confidence: 0.8768581

00:18:39.050 --> 00:18:41.129 And this is with my colleague vision

NOTE Confidence: 0.8768581

00:18:41.129 --> 00:18:43.167 with zombie who directs the Center

NOTE Confidence: 0.8768581

00:18:43.167 --> 00:18:45.339 for precision cancer modeling at Yale,

NOTE Confidence: 0.8768581

00:18:45.340 --> 00:18:47.657 sort of preclinical testing core at Yale,

NOTE Confidence: 0.8768581

00:18:47.660 --> 00:18:49.646 in which we've taken tumor fragments.

NOTE Confidence: 0.8768581

00:18:49.650 --> 00:18:51.300 And we were seeing full

NOTE Confidence: 0.8768581

00:18:51.300 --> 00:18:52.290 checkpoint inhibitor response,

NOTE Confidence: 0.8768581

00:18:52.290 --> 00:18:53.666 including elimination of tumor

NOTE Confidence: 0.8768581

00:18:53.666 --> 00:18:55.730 cells within four or five days

NOTE Confidence: 0.8768581

00:18:55.792 --> 00:18:57.257 in a fully indietro model,

NOTE Confidence: 0.8768581

00:18:57.260 --> 00:18:58.910 this has been mouse first,

NOTE Confidence: 0.8768581

00:18:58.910 --> 00:19:01.136 but we're trying to build this up

NOTE Confidence: 0.8768581

00:19:01.136 --> 00:19:03.513 and towards a human setting an the

NOTE Confidence: 0.8768581

00:19:03.513 --> 00:19:05.518 overall goal is to, for instance.

NOTE Confidence: 0.8768581

00:19:05.518 --> 00:19:08.110 Flow sort the cells that make up these

NOTE Confidence: 0.8768581

00:19:08.181 --> 00:19:10.677 tumors and deplete macrophages that way,

NOTE Confidence: 0.8768581

00:19:10.680 --> 00:19:12.710 which will work in terms of getting

NOTE Confidence: 0.8768581

00:19:12.710 --> 00:19:14.950 rid of those and putting back the

NOTE Confidence: 0.8768581

00:19:14.950 --> 00:19:16.906 components that you think will be

NOTE Confidence: 0.8683355

00:19:16.974 --> 00:19:18.666 important for these anti

NOTE Confidence: 0.8683355

00:19:18.666 --> 00:19:19.935 cancer immune responses.

NOTE Confidence: 0.8683355

00:19:19.940 --> 00:19:21.655 So stupid too and hopefully

NOTE Confidence: 0.8683355

00:19:21.655 --> 00:19:23.370 that will be something else.

NOTE Confidence: 0.8683355

00:19:23.370 --> 00:19:25.090 Hear more about with overtime.

NOTE Confidence: 0.8683355

00:19:25.090 --> 00:19:27.407 So one thing I talk about briefly

NOTE Confidence: 0.8683355

00:19:27.407 --> 00:19:30.212 now too is CD 40 as a target

NOTE Confidence: 0.8683355

00:19:30.212 --> 00:19:31.942 which is on dendritic cells,

NOTE Confidence: 0.8683355

00:19:31.950 --> 00:19:34.344 macrophages and to some extent other cells,

NOTE Confidence: 0.8683355

00:19:34.350 --> 00:19:36.610 including in the filial cells.

NOTE Confidence: 0.8683355

00:19:36.610 --> 00:19:38.978 And CD 40 Los results in a B

NOTE Confidence: 0.8683355

00:19:38.978 --> 00:19:40.939 cell class switching defect.

NOTE Confidence: 0.8683355

00:19:40.940 --> 00:19:43.467 But it's been developed as an agonist

NOTE Confidence: 0.8683355

00:19:43.467 --> 00:19:45.633 CD 40 antibody, not a blocking.

NOTE Confidence: 0.8683355

00:19:45.633 --> 00:19:46.716 Anybody want it?

NOTE Confidence: 0.8683355

00:19:46.720 --> 00:19:47.803 Stimulates this particular

NOTE Confidence: 0.8683355

00:19:47.803 --> 00:19:49.247 receptor and Bob Vonderheide?

NOTE Confidence: 0.8683355

00:19:49.250 --> 00:19:52.130 Who is the Cancer Center director at Penn,

NOTE Confidence: 0.8683355

00:19:52.130 --> 00:19:55.018 has been developing this for over 10 years.

NOTE Confidence: 0.8683355

00:19:55.020 --> 00:19:56.795 For pancreatic cancer and with

NOTE Confidence: 0.8683355

00:19:56.795 --> 00:19:58.215 the former colleague Sukach

NOTE Confidence: 0.8683355

00:19:58.215 --> 00:20:00.180 and also with Catherine Miller.

NOTE Confidence: 0.8683355

00:20:00.180 --> 00:20:01.158 And more recently,

NOTE Confidence: 0.8683355

00:20:01.158 --> 00:20:02.462 we've published preclinical models

NOTE Confidence: 0.8683355

00:20:02.462 --> 00:20:04.150 looking at Agona CD 40 therapy,

NOTE Confidence: 0.8683355

00:20:04.150 --> 00:20:06.590 and I'd say at this point in time,

NOTE Confidence: 0.8683355

00:20:06.590 --> 00:20:08.110 the mechanism isn't entirely clear.

NOTE Confidence: 0.8683355

00:20:08.110 --> 00:20:10.028 Although we went into that a little

NOTE Confidence: 0.8683355

00:20:10.028 --> 00:20:12.079 bit with both of these manuscripts.

NOTE Confidence: 0.8683355

00:20:12.080 --> 00:20:13.730 But one thing that we can

NOTE Confidence: 0.8683355

00:20:13.730 --> 00:20:15.430 see here is that agonist,

NOTE Confidence: 0.8683355

00:20:15.430 --> 00:20:17.630 CD 40 plus anti PD one blockade in

NOTE Confidence: 0.8683355

00:20:17.630 --> 00:20:20.021 CSF one R blockade works a lot better

NOTE Confidence: 0.8683355

00:20:20.021 --> 00:20:22.448 than any of the other drugs alone,

NOTE Confidence: 0.8683355

00:20:22.450 --> 00:20:24.885 so it has almost 80% cure rates and

NOTE Confidence: 0.8683355

00:20:24.885 --> 00:20:27.020 this is the younger model as well.

NOTE Confidence: 0.8683355

00:20:27.020 --> 00:20:28.976 And then the doublet therapies were

NOTE Confidence: 0.8683355

00:20:28.976 --> 00:20:31.398 PD one plus CD 40 and so forth.

NOTE Confidence: 0.8683355

00:20:31.400 --> 00:20:34.040 Also, don't work as well as the triple,

NOTE Confidence: 0.8683355

00:20:34.040 --> 00:20:36.070 although in humans will see in a

NOTE Confidence: 0.8683355

00:20:36.070 --> 00:20:38.330 second that may be slightly different,

NOTE Confidence: 0.8683355

00:20:38.330 --> 00:20:40.640 but we're seeing this is pretty promising.

NOTE Confidence: 0.8683355

00:20:40.640 --> 00:20:42.650 Prickly on clinical evidence to support

NOTE Confidence: 0.8683355

00:20:42.650 --> 00:20:44.270 using combination therapies with CD40.

NOTE Confidence: 0.8683355

00:20:44.270 --> 00:20:46.268 One of the things that striking

NOTE Confidence: 0.8683355

00:20:46.268 --> 00:20:47.600 with this particular therapy

NOTE Confidence: 0.8683355

00:20:47.663 --> 00:20:49.218 relative to PD one blockade,

NOTE Confidence: 0.8683355

00:20:49.220 --> 00:20:51.200 or PD1 plus ETA four blockade.

NOTE Confidence: 0.8683355

00:20:51.200 --> 00:20:53.970 Here's the T sne plot of a single cell RNA

NOTE Confidence: 0.8683355

00:20:54.038 --> 00:20:56.810 seq experiment where you have two samples,

NOTE Confidence: 0.8683355

00:20:56.810 --> 00:20:59.555 one of which is a mouse which had an

NOTE Confidence: 0.8683355

00:20:59.555 --> 00:21:02.047 injection subcutaneously of a tumor model.

NOTE Confidence: 0.8683355

00:21:02.050 --> 00:21:04.521 Seven day or eight days before and

NOTE Confidence: 0.8683355

00:21:04.521 --> 00:21:07.309 then one day prior to this harvest,

NOTE Confidence: 0.8683355

00:21:07.310 --> 00:21:09.566 mice for either treated with the

NOTE Confidence: 0.8683355

00:21:09.566 --> 00:21:11.070 three drug therapeutic protocol.

NOTE Confidence: 0.8683355

00:21:11.070 --> 00:21:12.950 This-is Agassi, 40 anti PD,

NOTE Confidence: 0.8683355

00:21:12.950 --> 00:21:16.118 one anti CSF 1R versus not treated and

NOTE Confidence: 0.8683355

00:21:16.118 --> 00:21:19.715 for those of you who look at TI sneak lots.

NOTE Confidence: 0.8683355

00:21:19.720 --> 00:21:21.600 What's striking here is that

NOTE Confidence: 0.8683355

00:21:21.600 --> 00:21:23.104 there's almost no overlap.

NOTE Confidence: 0.8683355

00:21:23.110 --> 00:21:25.735 the T cell areas are down here.

NOTE Confidence: 0.8683355

00:21:25.740 --> 00:21:27.956 You can see by the Vijay areas over

NOTE Confidence: 0.8683355

00:21:27.956 --> 00:21:31.065 here and here that there's really huge

NOTE Confidence: 0.8683355

00:21:31.065 --> 00:21:33.053 expression profiling differences between.

NOTE Confidence: 0.8683355

00:21:33.060 --> 00:21:34.925 The various components of these

NOTE Confidence: 0.8683355

00:21:34.925 --> 00:21:36.417 tumor micro environments and

NOTE Confidence: 0.8683355

00:21:36.417 --> 00:21:38.438 we're currently chasing that down.

NOTE Confidence: 0.8683355

00:21:38.440 --> 00:21:39.968 There's also differences in

NOTE Confidence: 0.8683355

00:21:39.968 --> 00:21:41.114 clona type representation,

NOTE Confidence: 0.8683355

00:21:41.120 --> 00:21:45.359 which I won't have time to go into here.

NOTE Confidence: 0.8683355

00:21:45.360 --> 00:21:47.978 And so just to show a little

NOTE Confidence: 0.8683355

00:21:47.978 --> 00:21:49.849 bit of pathology as well.

NOTE Confidence: 0.8683355

00:21:49.850 --> 00:21:51.720 PD one treat tumors don't

NOTE Confidence: 0.8683355

00:21:51.720 --> 00:21:53.590 look that different from this,

NOTE Confidence: 0.8683355

00:21:53.590 --> 00:21:55.718 which is one day after initiation of

NOTE Confidence: 0.8683355

00:21:55.718 --> 00:21:58.025 there might be some slightly increased

NOTE Confidence: 0.8683355

00:21:58.025 --> 00:22:00.689 lymphocytes but not really extensive death,

NOTE Confidence: 0.8683355

00:22:00.690 --> 00:22:02.940 but with the CD 40 agonist

NOTE Confidence: 0.8683355

00:22:02.940 --> 00:22:03.690 containing therapies,

NOTE Confidence: 0.8683355

00:22:03.690 --> 00:22:04.851 we see Thromboses.

NOTE Confidence: 0.8683355

00:22:04.851 --> 00:22:06.786 We see extensive cell death

NOTE Confidence: 0.8683355

00:22:06.786 --> 00:22:08.169 even within one day,

NOTE Confidence: 0.8683355

00:22:08.170 --> 00:22:10.534 and the regression profile is you

NOTE Confidence: 0.8683355

00:22:10.534 --> 00:22:13.679 can see over here on the right is

NOTE Confidence: 0.8683355

00:22:13.679 --> 00:22:15.905 different from what we see with.

NOTE Confidence: 0.89505094

00:22:15.910 --> 00:22:17.821 Uh Anti CTF War anti PD one

NOTE Confidence: 0.89505094

00:22:17.821 --> 00:22:19.280 sort of combination therapies?

NOTE Confidence: 0.89505094

00:22:19.280 --> 00:22:21.260 So there's something that's unique here

NOTE Confidence: 0.89505094

00:22:21.260 --> 00:22:23.610 which also seems to have a vascular

NOTE Confidence: 0.89505094

00:22:23.610 --> 00:22:25.554 component which we don't see the

NOTE Confidence: 0.89505094

00:22:25.554 --> 00:22:27.447 typically with those other therapies.

NOTE Confidence: 0.89505094

00:22:27.450 --> 00:22:29.898 So an interesting thing too is that we tend

NOTE Confidence: 0.89505094

00:22:29.898 --> 00:22:32.596 to think about effects of immune therapies.

NOTE Confidence: 0.89505094

00:22:32.600 --> 00:22:34.532 We tend to think mostly on

NOTE Confidence: 0.89505094

00:22:34.532 --> 00:22:35.498 adaptive immune therapies.

NOTE Confidence: 0.89505094

00:22:35.500 --> 00:22:37.747 This is an image and a rag.

NOTE Confidence: 0.89505094

00:22:37.750 --> 00:22:39.682 My switch when we gave CD

NOTE Confidence: 0.89505094

00:22:39.682 --> 00:22:40.970 40 agonist therapy issues,

NOTE Confidence: 0.89505094

00:22:40.970 --> 00:22:43.175 we actually saw more toxicity in rag

NOTE Confidence: 0.89505094

00:22:43.175 --> 00:22:45.479 mice then we saw on while typing.

NOTE Confidence: 0.89505094

00:22:45.480 --> 00:22:48.378 I'm trying to figure out why that might be,

NOTE Confidence: 0.89505094

00:22:48.380 --> 00:22:50.306 including in Forks in the liver,

NOTE Confidence: 0.89505094

00:22:50.310 --> 00:22:52.445 and so he's her F 480 positive

NOTE Confidence: 0.89505094

00:22:52.445 --> 00:22:54.498 kupfer cells in the control rag,

NOTE Confidence: 0.89505094

00:22:54.500 --> 00:22:56.852 mouse liver and one day after treatment

NOTE Confidence: 0.89505094

00:22:56.852 --> 00:22:59.835 with Agnes CD 40 you can see that extensive.

NOTE Confidence: 0.89505094

00:22:59.840 --> 00:23:02.036 A mini granuloma formation of discover

NOTE Confidence: 0.89505094

00:23:02.036 --> 00:23:04.648 cells was slightly larger granulomas as well.

NOTE Confidence: 0.89505094

00:23:04.650 --> 00:23:06.206 Interesting high dose steroid

NOTE Confidence: 0.89505094

00:23:06.206 --> 00:23:08.151 treatment prevents this from happening

NOTE Confidence: 0.89505094

00:23:08.151 --> 00:23:10.199 even in the absence of lymphocytes,

NOTE Confidence: 0.89505094

00:23:10.200 --> 00:23:12.420 so there's a innate immune dependent

NOTE Confidence: 0.89505094

00:23:12.420 --> 00:23:13.530 aggregation of histiocytes.

NOTE Confidence: 0.89505094

00:23:13.530 --> 00:23:15.465 Also seeing large differences in

NOTE Confidence: 0.89505094

00:23:15.465 --> 00:23:17.013 the histiocyte expression profiles

NOTE Confidence: 0.89505094

00:23:17.013 --> 00:23:18.340 on a single seller,

NOTE Confidence: 0.89505094

00:23:18.340 --> 00:23:19.309 and I see,

NOTE Confidence: 0.89505094

00:23:19.309 --> 00:23:22.410 but I'd say that's a work in progress.

NOTE Confidence: 0.89505094

00:23:22.410 --> 00:23:25.021 One of the things we do see

NOTE Confidence: 0.89505094

00:23:25.021 --> 00:23:27.339 systemically is you can see here's

NOTE Confidence: 0.89505094

00:23:27.339 --> 00:23:29.950 cry about a 1000 to 10,000 fold.

NOTE Confidence: 0.89505094

00:23:29.950 --> 00:23:32.897 Increase in the chemo kind CX CL-10,

NOTE Confidence: 0.89505094

00:23:32.900 --> 00:23:35.483 which is a factor that recruits lymphocytes

NOTE Confidence: 0.89505094

00:23:35.483 --> 00:23:37.611 to the tumor microenvironment and

NOTE Confidence: 0.89505094

00:23:37.611 --> 00:23:40.473 you're seeing a large extension that,

NOTE Confidence: 0.89505094

00:23:40.480 --> 00:23:43.350 with the triple therapy and so some

NOTE Confidence: 0.89505094

00:23:43.350 --> 00:23:46.369 mechanism for the CD 40 agonist therapy,

NOTE Confidence: 0.89505094

00:23:46.370 --> 00:23:48.475 it's more rapid than what

NOTE Confidence: 0.89505094

00:23:48.475 --> 00:23:49.738 we're seeing elsewhere.

NOTE Confidence: 0.89505094

00:23:49.740 --> 00:23:52.631 We see a real big up regulation

NOTE Confidence: 0.89505094

00:23:52.631 --> 00:23:54.790 and systemic cytokines from Serum.

NOTE Confidence: 0.89505094

00:23:54.790 --> 00:23:58.158 We're not sure exactly which cell type yet,

NOTE Confidence: 0.89505094

00:23:58.160 --> 00:23:59.480 although macrophages and

NOTE Confidence: 0.89505094

00:23:59.480 --> 00:24:00.800 Dicesar certainly candidates.

NOTE Confidence: 0.89505094

00:24:00.800 --> 00:24:02.576 We're interested in the vascular effects

NOTE Confidence: 0.89505094

00:24:02.576 --> 00:24:04.699 were seeing next to endothelial cells,

NOTE Confidence: 0.89505094

00:24:04.700 --> 00:24:07.193 and I would say that this sort of suggests

NOTE Confidence: 0.89505094

00:24:07.193 --> 00:24:09.248 that cytokine cycling is obsolete.

NOTE Confidence: 0.89505094

00:24:09.250 --> 00:24:09.575 Very,

NOTE Confidence: 0.89505094

00:24:09.575 --> 00:24:11.200 very important in these responses,

NOTE Confidence: 0.89505094

00:24:11.200 --> 00:24:13.264 and that we will be getting a new

NOTE Confidence: 0.89505094

00:24:13.264 --> 00:24:15.267 you 01 grant with Catherine Miller

NOTE Confidence: 0.89505094

00:24:15.267 --> 00:24:17.811 Jensen as the contact P and me

NOTE Confidence: 0.89505094

00:24:17.811 --> 00:24:19.899 as a secondary API to evaluate

NOTE Confidence: 0.89505094

00:24:19.899 --> 00:24:21.273 single cell cytokine secretion.

NOTE Confidence: 0.89505094

00:24:21.273 --> 00:24:22.888 So RNA levels don't typically

NOTE Confidence: 0.89505094

00:24:22.888 --> 00:24:24.530 aren't very accurate for these.

NOTE Confidence: 0.89505094

00:24:24.530 --> 00:24:26.896 An actual looking at each cell and

NOTE Confidence: 0.89505094

00:24:26.896 --> 00:24:28.890 what cytokines it makes will be

NOTE Confidence: 0.89505094

00:24:28.890 --> 00:24:31.025 helpful in the last minute or so.

NOTE Confidence: 0.89505094

00:24:31.030 --> 00:24:32.486 I will briefly discuss.

NOTE Confidence: 0.89505094

00:24:32.486 --> 00:24:35.336 This is part of spore project for in

NOTE Confidence: 0.89505094

00:24:35.336 --> 00:24:37.696 our skin support and this is a trial

NOTE Confidence: 0.89505094

00:24:37.773 --> 00:24:40.869 that as led by Harriet cougar and Sarah Wise,

NOTE Confidence: 0.89505094

00:24:40.870 --> 00:24:43.574 in which an agonist CD 40 therapy is

NOTE Confidence: 0.89505094

00:24:43.574 --> 00:24:45.605 combined with anti PD one and then

NOTE Confidence: 0.89505094

00:24:45.605 --> 00:24:48.075 an anti CSF one R therapy and this

NOTE Confidence: 0.89505094

00:24:48.075 --> 00:24:50.307 is in patients that have progressed

NOTE Confidence: 0.89505094

00:24:50.307 --> 00:24:52.720 on PD one blockade in Melanoma and

NOTE Confidence: 0.89505094

00:24:52.720 --> 00:24:55.191 also non small cell lung cancer and

NOTE Confidence: 0.89505094

00:24:55.191 --> 00:24:57.620 renal cell carcinoma and I will kind

NOTE Confidence: 0.89505094

00:24:57.687 --> 00:25:00.207 of go through this so we make sure we

NOTE Confidence: 0.89505094

00:25:00.207 --> 00:25:03.458 have enough time for the second talk as well.

NOTE Confidence: 0.89505094

00:25:03.460 --> 00:25:04.832 Here's a brief description

NOTE Confidence: 0.89505094

00:25:04.832 --> 00:25:06.890 of the cohorts that are here,

NOTE Confidence: 0.89505094

00:25:06.890 --> 00:25:09.417 and we're going to move through this

NOTE Confidence: 0.89505094

00:25:09.417 --> 00:25:11.791 relatively rapidly and get to some of

NOTE Confidence: 0.89505094

00:25:11.791 --> 00:25:13.627 the neat stuff and mucosal Melanoma

NOTE Confidence: 0.8776111

00:25:13.693 --> 00:25:15.468 is notoriously hard to treat,

NOTE Confidence: 0.8776111

00:25:15.470 --> 00:25:17.522 tends not to have really high

NOTE Confidence: 0.8776111

00:25:17.522 --> 00:25:19.582 mutation burdens, and here is a

NOTE Confidence: 0.8776111

00:25:19.582 --> 00:25:21.640 patient who had progressed on C5,

NOTE Confidence: 0.8776111

00:25:21.640 --> 00:25:23.350 four plus PD one blockade,

NOTE Confidence: 0.8776111

00:25:23.350 --> 00:25:25.606 and you can see multiple liver

NOTE Confidence: 0.8776111

00:25:25.606 --> 00:25:27.772 lesions that actually cleared by the

NOTE Confidence: 0.8776111

00:25:27.772 --> 00:25:29.865 addition of giving an agonist CD 40,

NOTE Confidence: 0.8776111

00:25:29.870 --> 00:25:32.670 so the two patients I'm showing here

NOTE Confidence: 0.8776111

00:25:32.670 --> 00:25:35.079 didn't necessarily have the anti CSF 1 R.

NOTE Confidence: 0.8776111

00:25:35.080 --> 00:25:37.624 It had very clear responses after a PD,

NOTE Confidence: 0.8776111

00:25:37.630 --> 00:25:40.174 one failure or PD1 Pussy clip for further.

NOTE Confidence: 0.8776111

00:25:40.180 --> 00:25:42.679 So here's a couple more cases where

NOTE Confidence: 0.8776111

00:25:42.679 --> 00:25:45.046 there's a lesion here that's disappeared

NOTE Confidence: 0.8776111

00:25:45.046 --> 00:25:47.888 in a couple other lesions here that

NOTE Confidence: 0.8776111

00:25:47.958 --> 00:25:50.156 are not present at a later time.

NOTE Confidence: 0.8776111

00:25:50.160 --> 00:25:52.631 So this is a trial again by

NOTE Confidence: 0.8776111

00:25:52.631 --> 00:25:54.620 Harriet cougar and Sara Weiss.

NOTE Confidence: 0.8776111

00:25:54.620 --> 00:25:56.480 Part export project for the

NOTE Confidence: 0.8776111

00:25:56.480 --> 00:25:58.340 phase one is moving forward.

NOTE Confidence: 0.8776111

00:25:58.340 --> 00:26:00.818 I think the decisions now or whether

NOTE Confidence: 0.8776111

00:26:00.818 --> 00:26:04.172 or not to have the CSF one R inhibitor

NOTE Confidence: 0.8776111

00:26:04.172 --> 00:26:07.270 around for the next phases of the trial.

NOTE Confidence: 0.8776111

00:26:07.270 --> 00:26:09.615 But one thing that was interesting is

NOTE Confidence: 0.8776111

00:26:09.615 --> 00:26:12.478 that we are seeing a similar cytokine.

NOTE Confidence: 0.8776111

00:26:12.480 --> 00:26:14.783 Profiling is what we see in the

NOTE Confidence: 0.8776111

00:26:14.783 --> 00:26:16.570 mice with dramatic elevations.

NOTE Confidence: 0.8776111

00:26:16.570 --> 00:26:18.958 Avxl 10 in the triple therapy

NOTE Confidence: 0.8776111

00:26:18.958 --> 00:26:20.550 group with some elevations.

NOTE Confidence: 0.8776111

00:26:20.550 --> 00:26:22.811 In Co works that happened to have

NOTE Confidence: 0.8776111

00:26:22.811 --> 00:26:24.759 higher levels of agonist CD 40,

NOTE Confidence: 0.8776111

00:26:24.760 --> 00:26:27.384 and so these are the conclusions that I've

NOTE Confidence: 0.8776111

00:26:27.384 --> 00:26:29.949 I've already mentioned to you along the way,

NOTE Confidence: 0.8776111

00:26:29.950 --> 00:26:31.924 and one thing I'd really briefly

NOTE Confidence: 0.8776111

00:26:31.924 --> 00:26:34.463 like to say is that as part of

NOTE Confidence: 0.8776111

00:26:34.463 --> 00:26:36.750 the Yale Center for me on Koleji,

NOTE Confidence: 0.8776111

00:26:36.750 --> 00:26:38.862 we're starting a list of a set of

NOTE Confidence: 0.8776111

00:26:38.862 --> 00:26:40.653 working groups which are smaller

NOTE Confidence: 0.8776111

00:26:40.653 --> 00:26:42.257 groups around particular complex,

NOTE Confidence: 0.8776111

00:26:42.260 --> 00:26:44.204 and we're trying to be inclusive

NOTE Confidence: 0.8776111

00:26:44.204 --> 00:26:45.500 in these working groups,

NOTE Confidence: 0.8776111

00:26:45.500 --> 00:26:48.182 and I would suggest that you go to the

NOTE Confidence: 0.8776111

00:26:48.182 --> 00:26:50.559 website through Yale Cancer Center and.

NOTE Confidence: 0.8776111

00:26:50.560 --> 00:26:51.272 Elisa Matthews,

NOTE Confidence: 0.8776111

00:26:51.272 --> 00:26:52.340 which was ALLYSIA,

NOTE Confidence: 0.8776111

00:26:52.340 --> 00:26:54.818 is the person who is a scientific

NOTE Confidence: 0.8776111

00:26:54.818 --> 00:26:55.526 program director.

NOTE Confidence: 0.8776111

00:26:55.530 --> 00:26:58.864 She can get you set up so you can join some

NOTE Confidence: 0.8776111

00:26:58.864 --> 00:27:01.916 of these groups should you be interesting.

NOTE Confidence: 0.8776111

00:27:01.920 --> 00:27:04.086 And with that I'll just acknowledge

NOTE Confidence: 0.8776111

00:27:04.086 --> 00:27:05.830 especially arena quick by Eva,

NOTE Confidence: 0.8776111

00:27:05.830 --> 00:27:07.066 who's in my lab,

NOTE Confidence: 0.8776111

00:27:07.066 --> 00:27:10.800 who has done a lot of the pre clinical work.

NOTE Confidence: 0.8776111

00:27:10.800 --> 00:27:12.924 All of the trial work and

NOTE Confidence: 0.8776111

00:27:12.924 --> 00:27:13.986 writing and managing.

NOTE Confidence: 0.8776111

00:27:13.990 --> 00:27:16.120 That's all Harriet Kluber Inserra wise.

NOTE Confidence: 0.8776111

00:27:16.120 --> 00:27:18.542 Earlier work with Sue Kevin I mentioned

NOTE Confidence: 0.8776111

00:27:18.542 --> 00:27:21.100 vision with Asami as part of the

NOTE Confidence: 0.8776111

00:27:21.100 --> 00:27:22.556 center precision cancer modeling.

NOTE Confidence: 0.8776111

00:27:22.560 --> 00:27:24.345 And I'll stop there and just for,

NOTE Confidence: 0.8776111

00:27:24.350 --> 00:27:25.048 I guess,

NOTE Confidence: 0.8776111

00:27:25.048 --> 00:27:26.793 brief minute we can potentially

NOTE Confidence: 0.8776111

00:27:26.793 --> 00:27:28.340 take a question or two.

NOTE Confidence: 0.8776111

00:27:28.340 --> 00:27:28.740 Work

NOTE Confidence: 0.88490915

00:27:28.740 --> 00:27:29.925 is thank you.

NOTE Confidence: 0.88490915

00:27:29.925 --> 00:27:32.295 That's a terrific body of work.

NOTE Confidence: 0.88490915

00:27:32.300 --> 00:27:34.676 Yet let me ask a somewhat

NOTE Confidence: 0.88490915

00:27:34.676 --> 00:27:35.468 complicated question.

NOTE Confidence: 0.88490915

00:27:35.470 --> 00:27:37.050 Instead of multiple parts,

NOTE Confidence: 0.88490915

00:27:37.050 --> 00:27:38.684 which is, you know,

NOTE Confidence: 0.88490915

00:27:38.684 --> 00:27:40.794 you've clearly shown that targeting

NOTE Confidence: 0.88490915

00:27:40.794 --> 00:27:43.078 an innate immunity for this sort

NOTE Confidence: 0.88490915

00:27:43.078 --> 00:27:45.290 of PD one PD L1 responsive cancers

NOTE Confidence: 0.88490915

00:27:45.364 --> 00:27:47.739 potentially moves the needle higher,

NOTE Confidence: 0.88490915

00:27:47.740 --> 00:27:49.910 realizing that within that cohort

NOTE Confidence: 0.88490915

00:27:49.910 --> 00:27:52.502 there are patients who may respond

NOTE Confidence: 0.88490915

00:27:52.502 --> 00:27:55.262 to just PD one alone or PT1 hippie,

NOTE Confidence: 0.88490915

00:27:55.270 --> 00:27:56.966 or things like that.

NOTE Confidence: 0.88490915

00:27:56.966 --> 00:27:59.086 And so how do you?

NOTE Confidence: 0.88490915

00:27:59.090 --> 00:28:01.568 How do you see the work you're

NOTE Confidence: 0.88490915

00:28:01.568 --> 00:28:03.020 doing help differentiate that?

NOTE Confidence: 0.88490915

00:28:03.020 --> 00:28:05.162 Or do we just give everyone

NOTE Confidence: 0.88490915

00:28:05.162 --> 00:28:06.590 sort of the combination?

NOTE Confidence: 0.88490915

00:28:06.590 --> 00:28:07.172 Then Secondly,

NOTE Confidence: 0.88490915

00:28:07.172 --> 00:28:09.500 is a related note for the tumors that

NOTE Confidence: 0.88490915

00:28:09.559 --> 00:28:11.459 are not actually really benefiting

NOTE Confidence: 0.88490915

00:28:11.459 --> 00:28:13.359 and meaningfully from the current

NOTE Confidence: 0.88490915

00:28:13.424 --> 00:28:15.160 checkpoint inhibitors you know?

NOTE Confidence: 0.88490915

00:28:15.160 --> 00:28:17.729 Where do you see this approach working

NOTE Confidence: 0.88490915

00:28:17.729 --> 00:28:20.150 in that subset of tumors as well?

NOTE Confidence: 0.9162716

00:28:21.290 --> 00:28:23.467 But I I think right now the

NOTE Confidence: 0.9162716

00:28:23.467 --> 00:28:24.789 difficulty in evaluating new

NOTE Confidence: 0.9162716

00:28:24.789 --> 00:28:26.404 combinations of immune therapies is

NOTE Confidence: 0.9162716

00:28:26.404 --> 00:28:28.897 that if you do a standard of care,

NOTE Confidence: 0.9162716

00:28:28.900 --> 00:28:30.881 so your drug plus PD one blockade

NOTE Confidence: 0.9162716

00:28:30.881 --> 00:28:32.699 versus PD one blockade alone,

NOTE Confidence: 0.9162716

00:28:32.700 --> 00:28:35.087 those trials 10, and that's the reference

NOTE Confidence: 0.9162716

00:28:35.087 --> 00:28:37.458 trial that one might use at the end,

NOTE Confidence: 0.9162716

00:28:37.460 --> 00:28:39.532 take a very long time to complete

NOTE Confidence: 0.9162716

00:28:39.532 --> 00:28:41.259 and it takes awhile with.

NOTE Confidence: 0.9162716

00:28:41.260 --> 00:28:43.796 Follow up to know what those results are.

NOTE Confidence: 0.9162716

00:28:43.800 --> 00:28:45.949 Sort of the scenarios that I've just

NOTE Confidence: 0.9162716

00:28:45.949 --> 00:28:47.895 sort of illustrated at these anecdotal

NOTE Confidence: 0.9162716

00:28:47.895 --> 00:28:50.156 cases give one much better indication of

NOTE Confidence: 0.9162716

00:28:50.217 --> 00:28:52.520 whether there's some activity of an agent.

NOTE Confidence: 0.9162716

00:28:52.520 --> 00:28:54.711 And that's basically in the setting of

NOTE Confidence: 0.9162716

00:28:54.711 --> 00:28:56.898 failure of response to existing therapies.

NOTE Confidence: 0.9162716

00:28:56.900 --> 00:28:59.301 So in these cases it was PD

NOTE Confidence: 0.9162716

00:28:59.301 --> 00:29:01.619 one plus ETA 4 in one case,

NOTE Confidence: 0.9162716

00:29:01.620 --> 00:29:04.574 which we use more commonly in Melanoma.

NOTE Confidence: 0.9162716

00:29:04.580 --> 00:29:06.060 But also just with PD,

NOTE Confidence: 0.9162716

00:29:06.060 --> 00:29:07.836 one failure in and of itself.

NOTE Confidence: 0.9162716

00:29:07.840 --> 00:29:09.320 So in those clinical context,

NOTE Confidence: 0.9162716

00:29:09.320 --> 00:29:10.800 which regrettably are still pretty

NOTE Confidence: 0.9162716

00:29:10.800 --> 00:29:12.280 common in many cancer types,

NOTE Confidence: 0.9162716

00:29:12.280 --> 00:29:14.450 you have the opportunity to add on

NOTE Confidence: 0.9162716

00:29:14.450 --> 00:29:16.419 something like agonist CD 40 to evaluate.

NOTE Confidence: 0.9162716

00:29:16.420 --> 00:29:18.540 Weather is what would really be nice to

NOTE Confidence: 0.9162716

00:29:18.540 --> 00:29:20.794 have a biomarker to know when it would

NOTE Confidence: 0.9162716

00:29:20.794 --> 00:29:23.229 be useful to use these other therapies,

NOTE Confidence: 0.9162716

00:29:23.230 --> 00:29:25.281 and that's sort of lacking at the

NOTE Confidence: 0.9162716

00:29:25.281 --> 00:29:27.368 at this time point I would say,

NOTE Confidence: 0.9162716

00:29:27.370 --> 00:29:28.965 but having a better understanding

NOTE Confidence: 0.9162716

00:29:28.965 --> 00:29:31.117 of how these things work would be

NOTE Confidence: 0.9162716

00:29:31.117 --> 00:29:32.853 one step in the second step might

NOTE Confidence: 0.9162716

00:29:32.853 --> 00:29:34.916 be doing a more careful evaluation.

NOTE Confidence: 0.9162716

00:29:34.920 --> 00:29:35.980 Immediately after you started

NOTE Confidence: 0.9162716

00:29:35.980 --> 00:29:36.775 this new therapy,

NOTE Confidence: 0.9162716

00:29:36.780 --> 00:29:39.084 do you see the site of kind of response

NOTE Confidence: 0.9162716

00:29:39.084 --> 00:29:41.550 that you would expect to see in a patient?

NOTE Confidence: 0.9162716

00:29:41.550 --> 00:29:43.116 That's going to benefit and have

NOTE Confidence: 0.9162716

00:29:43.116 --> 00:29:44.737 him earlier cut off if they're

NOTE Confidence: 0.9162716

00:29:44.737 --> 00:29:46.315 not going to along those lines,

NOTE Confidence: 0.9162716

00:29:46.320 --> 00:29:47.910 but I think those are some

NOTE Confidence: 0.9162716

00:29:47.910 --> 00:29:48.970 of the thoughts that

NOTE Confidence: 0.9064048

00:29:48.970 --> 00:29:51.090 people are having at this one time and

NOTE Confidence: 0.9064048

00:29:51.090 --> 00:29:52.983 one other question that you sort of

NOTE Confidence: 0.9064048

00:29:52.983 --> 00:29:55.060 alluded to at the end of your talk.

NOTE Confidence: 0.9064048

00:29:55.060 --> 00:29:57.412 I know you had a recent publication

NOTE Confidence: 0.9064048

00:29:57.412 --> 00:29:59.794 sort of characterizing the sort of non

NOTE Confidence: 0.9064048

00:29:59.794 --> 00:30:01.434 traditionally son exposed class of.

NOTE Confidence: 0.9064048

00:30:01.440 --> 00:30:03.270 With respect to the biology and

NOTE Confidence: 0.9064048

00:30:03.270 --> 00:30:05.159 also their potential benefit or lack

NOTE Confidence: 0.9064048

00:30:05.159 --> 00:30:06.684 of benefit for checkpoint editors,

NOTE Confidence: 0.9064048

00:30:06.690 --> 00:30:08.762 can you just to share a little

NOTE Confidence: 0.9064048

00:30:08.762 --> 00:30:10.708 bit of insight from that work?

NOTE Confidence: 0.88166106

00:30:10.710 --> 00:30:13.110 Yeah, I mean this was kind of nice

NOTE Confidence: 0.88166106

00:30:13.110 --> 00:30:14.795 here 'cause the mucosal Melanoma

NOTE Confidence: 0.88166106

00:30:14.795 --> 00:30:17.512 that was the first case that we had

NOTE Confidence: 0.88166106

00:30:17.512 --> 00:30:19.430 shown in this would be an example

NOTE Confidence: 0.88166106

00:30:19.430 --> 00:30:21.192 of a relatively low mutation burden

NOTE Confidence: 0.88166106

00:30:21.192 --> 00:30:23.380 form of Melanoma is a pretty clear,

NOTE Confidence: 0.88166106

00:30:23.380 --> 00:30:24.965 at least correlation with tumors

NOTE Confidence: 0.88166106

00:30:24.965 --> 00:30:26.550 with higher mutation version being

NOTE Confidence: 0.88166106

00:30:26.599 --> 00:30:28.069 a little bit more responsive

NOTE Confidence: 0.88166106

00:30:28.069 --> 00:30:29.245 to mean checkpoint hitters,

NOTE Confidence: 0.88166106

00:30:29.250 --> 00:30:31.300 but it turns out that.

NOTE Confidence: 0.88166106

00:30:31.300 --> 00:30:33.463 There's a number of people in different

NOTE Confidence: 0.88166106

00:30:33.463 --> 00:30:35.614 venues that are looking for tumors

NOTE Confidence: 0.88166106

00:30:35.614 --> 00:30:37.549 that might have chromosomal changes,

NOTE Confidence: 0.88166106

00:30:37.550 --> 00:30:39.240 which are typically more common

NOTE Confidence: 0.88166106

00:30:39.240 --> 00:30:41.307 in low sun damage melanomas that

NOTE Confidence: 0.88166106

00:30:41.307 --> 00:30:42.882 those might induce trans locations

NOTE Confidence: 0.88166106

00:30:42.882 --> 00:30:45.179 and sort of not like transcripts.

NOTE Confidence: 0.88166106

00:30:45.180 --> 00:30:47.082 That sort of have random proteins

NOTE Confidence: 0.88166106

00:30:47.082 --> 00:30:48.752 that are expressed at reasonably

NOTE Confidence: 0.88166106

00:30:48.752 --> 00:30:50.762 high levels that might be very

NOTE Confidence: 0.88166106

00:30:50.762 --> 00:30:52.809 good targets for immune therapies,

NOTE Confidence: 0.88166106

00:30:52.810 --> 00:30:54.892 so it's not just whether you

NOTE Confidence: 0.88166106

00:30:54.892 --> 00:30:56.630 have mutation burn or not,

NOTE Confidence: 0.88166106

00:30:56.630 --> 00:30:59.094 it just whether you have antigens that

NOTE Confidence: 0.88166106

00:30:59.094 --> 00:31:01.668 your T cells can recognize or not.

NOTE Confidence: 0.88166106

00:31:01.670 --> 00:31:03.056 And right now we're not that

NOTE Confidence: 0.88166106

00:31:03.056 --> 00:31:04.659 great in any level of recognizing

NOTE Confidence: 0.88166106

00:31:04.659 --> 00:31:06.209 which cancers those might be,

NOTE Confidence: 0.88166106

00:31:06.210 --> 00:31:07.545 and it'll probably be different

NOTE Confidence: 0.88166106

00:31:07.545 --> 00:31:08.346 for every patient,

NOTE Confidence: 0.88166106

00:31:08.350 --> 00:31:09.946 so you can't just say well,

NOTE Confidence: 0.88166106

00:31:09.950 --> 00:31:11.285 this person has this particular

NOTE Confidence: 0.88166106

00:31:11.285 --> 00:31:12.620 peptide expressed or so forth.

NOTE Confidence: 0.88166106

00:31:12.620 --> 00:31:14.440 It's also their HLA haplotype and there's

NOTE Confidence: 0.88166106

00:31:14.440 --> 00:31:16.890 a lot of things along that that go into.

NOTE Confidence: 0.88166106

00:31:16.890 --> 00:31:18.360 Whether or not they'll be able

NOTE Confidence: 0.88166106

00:31:18.360 --> 00:31:19.830 to form a productive response.

NOTE Confidence: 0.9102248

00:31:21.790 --> 00:31:24.490 Well, thank you and thank you for that talk.

NOTE Confidence: 0.9102248

00:31:24.490 --> 00:31:26.296 Why don't we will turn it over

NOTE Confidence: 0.9102248

00:31:26.296 --> 00:31:28.089 now to our second speaker?

NOTE Confidence: 0.9102248

00:31:28.090 --> 00:31:29.590 As I mentioned, you know,

NOTE Confidence: 0.9102248

00:31:29.590 --> 00:31:31.494 clear area of priority for the Cancer

NOTE Confidence: 0.9102248

00:31:31.494 --> 00:31:33.333 Center has been in computational biology

NOTE Confidence: 0.9102248

00:31:33.333 --> 00:31:35.594 and were really very fortunate to have

NOTE Confidence: 0.9102248

00:31:35.653 --> 00:31:37.447 doctor more convene speaking to us.