WEBVTT

NOTE duration:"00:44:10.4000000"

NOTE language:en-us

NOTE Confidence: 0.83471704

00:00:00.000 --> 00:00:03.010 The hearts go out to his wife.

NOTE Confidence: 0.83471704

00:00:03.010 --> 00:00:05.100 Doctor Kellie Martin is two

NOTE Confidence: 0.83471704

00:00:05.100 --> 00:00:07.655 children tests and Jacob and just

NOTE Confidence: 0.83471704

00:00:07.655 --> 00:00:09.983 take a moment just to silence

NOTE Confidence: 0.83471704

00:00:09.983 --> 00:00:12.269 just to recognize Tony's legacy.

NOTE Confidence: 0.86117405

00:00:21.180 --> 00:00:24.435 Well, thank you, so let's now turn

NOTE Confidence: 0.86117405

00:00:24.435 --> 00:00:28.108 to our first of two great speakers.

NOTE Confidence: 0.86117405

00:00:28.110 --> 00:00:30.894 We were very fortunate this year

NOTE Confidence: 0.86117405

00:00:30.894 --> 00:00:33.560 to recruit Doctor Jeffrey Ishizuka.

NOTE Confidence: 0.86117405

00:00:33.560 --> 00:00:38.026 Jeff is an assistant professor of medicine.

NOTE Confidence: 0.86117405

00:00:38.030 --> 00:00:39.377 And Jeff's work.

NOTE Confidence: 0.86117405

00:00:39.377 --> 00:00:41.622 Previously at Harvard was was

NOTE Confidence: 0.86117405

00:00:41.622 --> 00:00:44.408 focused on the biology of T cells.

NOTE Confidence: 0.86117405

00:00:44.410 --> 00:00:46.162 Discovering knew better understanding

NOTE Confidence: 0.86117405

00:00:46.162 --> 00:00:48.790 of that biology and and and

NOTE Confidence: 0.86117405

00:00:48.857 --> 00:00:50.417 ultimately leveraging that science

NOTE Confidence: 0.86117405

00:00:50.417 --> 00:00:53.708 to what is likely to be the next

NOTE Confidence: 0.86117405

00:00:53.708 --> 00:00:55.460 generation of amino therapies.

NOTE Confidence: 0.86117405

00:00:55.460 --> 00:00:58.001 And we're really very fortunate to have

NOTE Confidence: 0.86117405

00:00:58.001 --> 00:01:01.381 Jeff as one of our physician scientists in

NOTE Confidence: 0.86117405

00:01:01.381 --> 00:01:04.380 the center of molecular Italian Colosseum,

NOTE Confidence: 0.86117405

00:01:04.380 --> 00:01:06.510 member of the Melanoma program,

NOTE Confidence: 0.86117405

00:01:06.510 --> 00:01:09.276 and physician scientists in general at.

NOTE Confidence: 0.86117405

00:01:09.280 --> 00:01:10.920 At Yale and Smile also,

NOTE Confidence: 0.86117405

00:01:10.920 --> 00:01:13.528 Jeff really excited to hear about your work.

NOTE Confidence: 0.86117405

00:01:13.530 --> 00:01:17.040 Turn it over to you.

NOTE Confidence: 0.86117405

00:01:17.040 --> 00:01:17.370 Thank

NOTE Confidence: 0.84582025

00:01:17.370 --> 00:01:19.536 you so much Charlie, really appreciate

NOTE Confidence: 0.84582025

00:01:19.536 --> 00:01:22.659 it and let me just project my slides.

NOTE Confidence: 0.84582025

00:01:22.660 --> 00:01:25.204 How there we go?

NOTE Confidence: 0.84582025

00:01:25.204 --> 00:01:27.954 Yes, thank you so much and thank you

NOTE Confidence: 0.84582025

00:01:27.954 --> 00:01:29.809 for the opportunity to speak today.

NOTE Confidence: 0.84582025

00:01:29.810 --> 00:01:32.234 Today I'm going to be talking to you

NOTE Confidence: 0.84582025

00:01:32.234 --> 00:01:34.398 about some of the work we've done.

NOTE Confidence: 0.84582025

00:01:34.400 --> 00:01:36.515 Targeting double stranded RNA in

NOTE Confidence: 0.84582025

00:01:36.515 --> 00:01:38.207 order to overcome immunotherapy

NOTE Confidence: 0.84582025

00:01:38.207 --> 00:01:39.891 resistance and also update on

NOTE Confidence: 0.84582025

00:01:39.891 --> 00:01:41.685 other ongoing projects in the lab.

NOTE Confidence: 0.84582025

00:01:41.690 --> 00:01:45.270 This is my disclosure slide.

NOTE Confidence: 0.84582025

00:01:45.270 --> 00:01:48.310 I wanted to begin with the overall survival

NOTE Confidence: 0.84582025

00:01:48.310 --> 00:01:50.797 curves from the Checkmate 067 trial,

NOTE Confidence: 0.84582025

00:01:50.800 --> 00:01:54.398 which is likely familiar to this audience.

NOTE Confidence: 0.84582025

00:01:54.400 --> 00:01:56.035 These curves represent survival in

NOTE Confidence: 0.84582025

00:01:56.035 --> 00:01:57.670 advanced Melanoma by patients treated

NOTE Confidence: 0.84582025

00:01:57.716 --> 00:01:59.168 with immune checkpoint blockade.

NOTE Confidence: 0.84582025

00:01:59.170 --> 00:02:00.193 In this case,

NOTE Confidence: 0.84582025

00:02:00.193 --> 00:02:01.898 with antibodies targeting PD 1C,

NOTE Confidence: 0.84582025

00:02:01.900 --> 00:02:04.640 TL A4 or the combination.

NOTE Confidence: 0.84582025

00:02:04.640 --> 00:02:06.482 I wanted to start here because

NOTE Confidence: 0.84582025

00:02:06.482 --> 00:02:08.043 Melanoma has been something of

NOTE Confidence: 0.84582025

00:02:08.043 --> 00:02:09.723 a touchstone for the use of

NOTE Confidence: 0.84582025

00:02:09.723 --> 00:02:11.310 checkpoint blockade in solid tumors.

NOTE Confidence: 0.84582025

00:02:11.310 --> 00:02:12.755 First indication approved and remains

NOTE Confidence: 0.84582025

00:02:12.755 --> 00:02:14.836 one of the indications in which immune

NOTE Confidence: 0.84582025

00:02:14.836 --> 00:02:16.301 checkpoint blockade is most effective

NOTE Confidence: 0.84582025

00:02:16.301 --> 00:02:17.969 in these data are outstanding,

NOTE Confidence: 0.84582025

00:02:17.970 --> 00:02:19.788 particularly when compared with the pre

NOTE Confidence: 0.84582025

00:02:19.788 --> 00:02:21.609 immunotherapy standard of Care Dakar Busine,

NOTE Confidence: 0.84582025

00:02:21.610 --> 00:02:23.125 which had an overall survival

NOTE Confidence: 0.84582025

00:02:23.125 --> 00:02:25.600 of five to 10% at five years.

NOTE Confidence: 0.84582025

00:02:25.600 --> 00:02:26.020 However,

NOTE Confidence: 0.84582025

00:02:26.020 --> 00:02:27.700 even in this disease,

NOTE Confidence: 0.84582025

00:02:27.700 --> 00:02:29.140 large proportion of patients

NOTE Confidence: 0.84582025

00:02:29.140 --> 00:02:30.580 don't experience durable benefit.

NOTE Confidence: 0.84582025

00:02:30.580 --> 00:02:32.992 The situation which is which is

NOTE Confidence: 0.84582025

00:02:32.992 --> 00:02:35.103 actually more challenging in other

NOTE Confidence: 0.84582025

00:02:35.103 --> 00:02:37.689 diseases where responses are less good.

NOTE Confidence: 0.84582025

00:02:37.690 --> 00:02:39.363 And this is really the focus of

NOTE Confidence: 0.84582025

00:02:39.363 --> 00:02:40.811 our work to improve responses

NOTE Confidence: 0.84582025

00:02:40.811 --> 00:02:42.815 in this disease and in others.

NOTE Confidence: 0.8365905

00:02:46.340 --> 00:02:47.840 Certainly, however, if you check,

NOTE Confidence: 0.8365905

00:02:47.840 --> 00:02:49.454 my blockade is rapidly reshaping the

NOTE Confidence: 0.8365905

00:02:49.454 --> 00:02:51.420 landscape of cancer care across indications.

NOTE Confidence: 0.8365905

00:02:51.420 --> 00:02:53.212 I was preparing for this talk and I

NOTE Confidence: 0.8365905

00:02:53.212 --> 00:02:55.762 had to go through and update this slide

NOTE Confidence: 0.8365905

00:02:55.762 --> 00:02:57.506 because indications have nearly doubled

NOTE Confidence: 0.8365905

00:02:57.506 --> 00:02:59.106 since its original publication by

NOTE Confidence: 0.8365905

00:02:59.106 --> 00:03:01.494 Tony Ribas and Jed will Chuck in 2018.

NOTE Confidence: 0.8365905

00:03:01.494 --> 00:03:03.150 Although many of us have followed

NOTE Confidence: 0.8365905

00:03:03.209 --> 00:03:04.879 this emerging data very closely,

NOTE Confidence: 0.8365905

00:03:04.880 --> 00:03:07.850 I have to admit that it gave me pause to

NOTE Confidence: 0.8365905

00:03:07.928 --> 00:03:11.048 consider the pace of change in this field.

NOTE Confidence: 0.8365905

00:03:11.050 --> 00:03:14.249 The advancement of PD one access approvals

NOTE Confidence: 0.8365905

00:03:14.249 --> 00:03:16.529 continues through lymphomas and solid

NOTE Confidence: 0.8365905

00:03:16.529 --> 00:03:18.629 tumors of desperate tissue origins.

NOTE Confidence: 0.8365905

00:03:18.630 --> 00:03:20.414 Combination approaches have also

NOTE Confidence: 0.8365905

00:03:20.414 --> 00:03:21.752 proliferated, including approaches,

NOTE Confidence: 0.8365905

00:03:21.752 --> 00:03:23.694 approvals in music, leoma,

NOTE Confidence: 0.8365905

00:03:23.694 --> 00:03:26.110 breast cancer, and others.

NOTE Confidence: 0.8365905

00:03:26.110 --> 00:03:27.385 Successful combinations include

NOTE Confidence: 0.8365905

00:03:27.385 --> 00:03:29.085 combinations of checkpoint inhibitors

NOTE Confidence: 0.8365905

00:03:29.085 --> 00:03:30.920 with other checkpoint inhibitors,

NOTE Confidence: 0.8365905

00:03:30.920 --> 00:03:32.228 chemotherapies and touristing

NOTE Confidence: 0.8365905

00:03:32.228 --> 00:03:33.100 kinese inhibitors,

NOTE Confidence: 0.8365905

00:03:33.100 --> 00:03:35.716 and notably many here at Yale,

NOTE Confidence: 0.8365905

00:03:35.720 --> 00:03:38.779 have played critical roles in this dance.

NOTE Confidence: 0.84251946

00:03:41.580 --> 00:03:43.230 Still, for all the advances,

NOTE Confidence: 0.84251946

00:03:43.230 --> 00:03:45.726 there have been a lot of failures and

NOTE Confidence: 0.84251946

00:03:45.726 --> 00:03:48.158 there remain a lot of ongoing challenges.

NOTE Confidence: 0.84251946

00:03:48.160 --> 00:03:50.128 For most, many patients don't respond,

NOTE Confidence: 0.84251946

00:03:50.130 --> 00:03:51.780 indeed, considered across all indications,

NOTE Confidence: 0.84251946

00:03:51.780 --> 00:03:53.894 most patients don't respond in a few

NOTE Confidence: 0.84251946

00:03:53.894 --> 00:03:55.885 of the response rates listed are

NOTE Confidence: 0.84251946

00:03:55.885 --> 00:03:57.937 really based on earlier trials that

NOTE Confidence: 0.84251946

00:03:57.937 --> 00:04:00.028 likely overestimated response rates.

NOTE Confidence: 0.84251946

00:04:00.030 --> 00:04:01.920 Many of them also include

NOTE Confidence: 0.84251946

00:04:01.920 --> 00:04:02.676 biomarker cutpoints,

NOTE Confidence: 0.84251946

00:04:02.680 --> 00:04:07.189 PDL 1 positive ITI and this sort of thing.

NOTE Confidence: 0.84251946

00:04:07.190 --> 00:04:09.233 And in my mind there are really a couple

NOTE Confidence: 0.84251946

00:04:09.233 --> 00:04:11.319 of big areas in which we can improve.

NOTE Confidence: 0.84251946

00:04:11.320 --> 00:04:14.365 1st for all of the new indications,

NOTE Confidence: 0.84251946

00:04:14.370 --> 00:04:16.710 few combinations involving novel

NOTE Confidence: 0.84251946

00:04:16.710 --> 00:04:19.050 targets have been approved.

NOTE Confidence: 0.84251946

00:04:19.050 --> 00:04:21.918 2nd, we have a limited mechanistic

NOTE Confidence: 0.84251946

00:04:21.918 --> 00:04:24.849 understanding of how these agents work.

NOTE Confidence: 0.84251946

00:04:24.850 --> 00:04:25.130 Accordingly,

NOTE Confidence: 0.84251946

00:04:25.130 --> 00:04:27.090 the biomarkers that we used to deploy

NOTE Confidence: 0.84251946

00:04:27.090 --> 00:04:29.009 them lack sensitivity and specificity,

NOTE Confidence: 0.84251946

00:04:29.010 --> 00:04:31.810 and there's not a great way to rationally

NOTE Confidence: 0.84251946

00:04:31.810 --> 00:04:33.488 prioritize combinations with anti PD one.

NOTE Confidence: 0.84928113

00:04:35.570 --> 00:04:37.418 So it's worth considering for a moment what

NOTE Confidence: 0.84928113

00:04:37.418 --> 00:04:39.139 we've learned about response and resistance,

NOTE Confidence: 0.84928113

00:04:39.140 --> 00:04:40.876 not so much in the interest of

NOTE Confidence: 0.84928113

00:04:40.876 --> 00:04:42.184 an extensive overview for which

NOTE Confidence: 0.84928113

00:04:42.184 --> 00:04:43.474 we wouldn't have time today,

NOTE Confidence: 0.84928113

00:04:43.480 --> 00:04:45.688 but in terms of the pathways that have

NOTE Confidence: 0.84928113

00:04:45.688 --> 00:04:48.308 given the strongest clinical signals to date.

NOTE Confidence: 0.84928113

00:04:48.310 --> 00:04:50.606 The data shown here are from the study

NOTE Confidence: 0.84928113

00:04:50.606 --> 00:04:53.172 by Merck of over 300 different patients

NOTE Confidence: 0.84928113

00:04:53.172 --> 00:04:55.530 across 22 different tumor tissue types.

NOTE Confidence: 0.84928113

00:04:55.530 --> 00:04:59.130 These figures show responses.

NOTE Confidence: 0.84928113

00:04:59.130 --> 00:05:01.450 Non response defined as CR

NOTE Confidence: 0.84928113

00:05:01.450 --> 00:05:04.190 or PR versus no CR PR.

NOTE Confidence: 0.84928113

00:05:04.190 --> 00:05:05.942 When graphed with tumor mutational burden

NOTE Confidence: 0.84928113

00:05:05.942 --> 00:05:09.354 on the Y axis and a gene expression profile

NOTE Confidence: 0.84928113

00:05:09.354 --> 00:05:10.668 representing tumor microenvironment,

NOTE Confidence: 0.84928113

00:05:10.670 --> 00:05:12.470 inflammation kind of T cell

NOTE Confidence: 0.84928113

00:05:12.470 --> 00:05:14.270 inflammation on the X axis.

NOTE Confidence: 0.84928113

00:05:14.270 --> 00:05:17.258 The genes in this profile are listed in the

NOTE Confidence: 0.84928113

00:05:17.258 --> 00:05:20.028 upper right here and notably include PDL,

NOTE Confidence: 0.84928113

00:05:20.030 --> 00:05:23.333 one among them as well as several MHC related

NOTE Confidence: 0.84928113

00:05:23.333 --> 00:05:26.147 genes and kind of T cell related genes.

NOTE Confidence: 0.82015085

00:05:28.360 --> 00:05:30.226 Tumor mutational burden, as you know,

NOTE Confidence: 0.82015085

00:05:30.230 --> 00:05:32.148 is often used as a surrogate for

NOTE Confidence: 0.82015085

00:05:32.148 --> 00:05:34.071 too many antigens and the gene

NOTE Confidence: 0.82015085

00:05:34.071 --> 00:05:35.455 expression profile really points

NOTE Confidence: 0.82015085

00:05:35.455 --> 00:05:37.100 to information of the tumor,

NOTE Confidence: 0.82015085

00:05:37.100 --> 00:05:38.858 micro environment and the authors make

NOTE Confidence: 0.82015085

00:05:38.858 --> 00:05:40.840 two points that are important here.

NOTE Confidence: 0.82015085

00:05:40.840 --> 00:05:43.003 First, that these are two of the

NOTE Confidence: 0.82015085

00:05:43.003 --> 00:05:44.580 strongest predictors they could find.

NOTE Confidence: 0.82015085

00:05:44.580 --> 00:05:46.230 Reviewing one of the largest

NOTE Confidence: 0.82015085

00:05:46.230 --> 00:05:47.550 and most comprehensive datasets

NOTE Confidence: 0.82015085

00:05:47.550 --> 00:05:48.950 that existed at the time.

NOTE Confidence: 0.82015085

00:05:48.950 --> 00:05:50.534 Really, it's telling us in second

NOTE Confidence: 0.82015085

00:05:50.534 --> 00:05:52.409 that they appear to predict response

NOTE Confidence: 0.82015085

00:05:52.409 --> 00:05:53.937 independently of one another.

NOTE Confidence: 0.82015085

00:05:53.940 --> 00:05:56.271 That is to say that although the

NOTE Confidence: 0.82015085

00:05:56.271 --> 00:05:58.379 best responses are in that kind of.

NOTE Confidence: 0.82015085

00:05:58.380 --> 00:06:01.334 Upper right quadrant that you actually get

NOTE Confidence: 0.82015085

00:06:01.334 --> 00:06:04.567 a good number of responses in a T cell.

NOTE Confidence: 0.82015085

00:06:04.570 --> 00:06:06.074 Inflamed only micro environment,

NOTE Confidence: 0.82015085

00:06:06.074 --> 00:06:09.219 or in TMB only TB high only tumors.

NOTE Confidence: 0.7979447

00:06:11.570 --> 00:06:13.226 For the sake of time today,

NOTE Confidence: 0.7979447

00:06:13.230 --> 00:06:14.910 I won't spend a lot of time

NOTE Confidence: 0.7979447

00:06:14.910 --> 00:06:16.540 on TMB or antigen load,

NOTE Confidence: 0.7979447

00:06:16.540 --> 00:06:18.190 so it's obviously an important consideration.

NOTE Confidence: 0.7979447

00:06:18.190 --> 00:06:20.122 Instead, I'm just going to talk about

NOTE Confidence: 0.7979447

00:06:20.122 --> 00:06:20.950 tumor microenvironment information,

NOTE Confidence: 0.7979447

00:06:20.950 --> 00:06:23.158 which is really the focus of our lab.

NOTE Confidence: 0.7979447

00:06:23.160 --> 00:06:24.532 Aside from the work by the Merck

NOTE Confidence: 0.7979447

00:06:24.532 --> 00:06:26.571 Group A number of lines of evidence

NOTE Confidence: 0.7979447

00:06:26.571 --> 00:06:27.975 have established inadequate tumor

NOTE Confidence: 0.7979447

00:06:27.975 --> 00:06:28.677 microenvironment information.

NOTE Confidence: 0.7979447

00:06:28.680 --> 00:06:30.661 As one of the most prominent mechanisms

NOTE Confidence: 0.7979447

00:06:30.661 --> 00:06:33.410 of resistance to me, no therapy.

NOTE Confidence: 0.7979447

00:06:33.410 --> 00:06:34.200 Most dramatically,

NOTE Confidence: 0.7979447

00:06:34.200 --> 00:06:36.965 this occurs in immune desert type tumors,

NOTE Confidence: 0.7979447

00:06:36.970 --> 00:06:39.346 which entirely lack T cell infiltrate,

NOTE Confidence: 0.7979447

00:06:39.350 --> 00:06:40.602 as depicted here. However,

NOTE Confidence: 0.7979447

00:06:40.602 --> 00:06:43.830 it can also occur in a different phenotype.

NOTE Confidence: 0.7979447

00:06:43.830 --> 00:06:45.146 The so-called immune excluded

NOTE Confidence: 0.7979447

00:06:45.146 --> 00:06:47.120 tumors which have anti tumor immune

NOTE Confidence: 0.7979447

00:06:47.171 --> 00:06:48.739 cells at the site of the tumor,

NOTE Confidence: 0.7979447

00:06:48.740 --> 00:06:49.900 although they are excluded

NOTE Confidence: 0.7979447

00:06:49.900 --> 00:06:51.060 from the tumor core,

NOTE Confidence: 0.7979447

00:06:51.060 --> 00:06:52.840 either by physical barriers

NOTE Confidence: 0.7979447

00:06:52.840 --> 00:06:54.620 or by immune signaling.

NOTE Confidence: 0.7979447

00:06:54.620 --> 00:06:54.932 Finally,

NOTE Confidence: 0.7979447

00:06:54.932 --> 00:06:57.428 we believe that there is the T cell

NOTE Confidence: 0.7979447

00:06:57.428 --> 00:06:59.426 inflamed type of tumor that have

NOTE Confidence: 0.7979447

00:06:59.426 --> 00:07:01.046 diffuse infiltration of T cells

NOTE Confidence: 0.7979447

00:07:01.111 --> 00:07:02.938 that tend to be PD L1 positive,

NOTE Confidence: 0.7979447

00:07:02.940 --> 00:07:05.845 and these are the ones that we

NOTE Confidence: 0.7979447

00:07:05.845 --> 00:07:08.559 believe respond best to immunotherapy.

NOTE Confidence: 0.7979447

00:07:08.560 --> 00:07:09.202 To date,

NOTE Confidence: 0.7979447

00:07:09.202 --> 00:07:10.807 there's been progress in identifying

NOTE Confidence: 0.7979447

00:07:10.807 --> 00:07:12.686 therapeutic strategies to enhance this

NOTE Confidence: 0.7979447

00:07:12.686 --> 00:07:13.988 tumor microenvironment information,

NOTE Confidence: 0.7979447

00:07:13.990 --> 00:07:16.144 many of which involve either real

NOTE Confidence: 0.7979447

00:07:16.144 --> 00:07:18.355 or simulated infection of the tumor

NOTE Confidence: 0.7979447

00:07:18.355 --> 00:07:20.135 to trigger anti tumor immunity,

NOTE Confidence: 0.7979447

00:07:20.140 --> 00:07:22.429 and I think about them in kind

NOTE Confidence: 0.7979447

00:07:22.429 --> 00:07:24.130 of two big buckets.

NOTE Confidence: 0.7979447

00:07:24.130 --> 00:07:26.224 The first is the provision of

NOTE Confidence: 0.7979447

00:07:26.224 --> 00:07:27.620 exogenous sources that mimic

NOTE Confidence: 0.7979447

00:07:27.690 --> 00:07:29.560 nucleic acid ligands to tumors.

NOTE Confidence: 0.7979447

00:07:29.560 --> 00:07:31.008 This includes sting agonist,

NOTE Confidence: 0.7979447

00:07:31.008 --> 00:07:33.180 MDA 5 or rig I agonist,

NOTE Confidence: 0.7979447

00:07:33.180 --> 00:07:34.992 double stranded RNA sensing

NOTE Confidence: 0.7979447

00:07:34.992 --> 00:07:37.257 pathways and uncle lytic viruses.

NOTE Confidence: 0.7979447

00:07:37.260 --> 00:07:40.445 The other is the induction of endogenous

NOTE Confidence: 0.7979447

00:07:40.445 --> 00:07:42.900 sources of nucleic acid ligands,

NOTE Confidence: 0.7979447

00:07:42.900 --> 00:07:44.310 primarily endogenous retroviruses,

NOTE Confidence: 0.7979447

00:07:44.310 --> 00:07:47.130 although others have been published recently,

NOTE Confidence: 0.7979447

00:07:47.130 --> 00:07:50.630 alualu repeats in humans.

NOTE Confidence: 0.7979447

00:07:50.630 --> 00:07:52.952 And examples of this include a

NOTE Confidence: 0.7979447

00:07:52.952 --> 00:07:55.450 deciding in CDK 46 inhibitors.

NOTE Confidence: 0.781458700000001

00:07:57.470 --> 00:08:00.067 So my interest in turning these cold

NOTE Confidence: 0.781458700000001

00:08:00.067 --> 00:08:01.968 microenvironments hot and kind of

NOTE Confidence: 0.781458700000001

00:08:01.968 --> 00:08:04.152 providing these logins to tuners really

NOTE Confidence: 0.781458700000001

00:08:04.152 --> 00:08:06.624 developed out of work in the Canings

NOTE Confidence: 0.781458700000001

00:08:06.624 --> 00:08:08.665 lab was finishing my postdoctoral work

NOTE Confidence: 0.781458700000001

00:08:08.665 --> 00:08:11.220 there and through the type of experiment

NOTE Confidence: 0.781458700000001

00:08:11.220 --> 00:08:13.716 that I'm showing here on the left,

NOTE Confidence: 0.781458700000001

00:08:13.720 --> 00:08:16.240 you have kind of a transplantable tumor

NOTE Confidence: 0.781458700000001

00:08:16.240 --> 00:08:18.770 cell line, something like a B16 Melanoma,

NOTE Confidence: 0.781458700000001

00:08:18.770 --> 00:08:21.658 and the way the experiment works is to,

NOTE Confidence: 0.781458700000001

00:08:21.660 --> 00:08:23.998 in fact, that cell line with a

NOTE Confidence: 0.781458700000001

00:08:23.998 --> 00:08:26.273 library of CRISPR CAS 9 guides

NOTE Confidence: 0.781458700000001

00:08:26.273 --> 00:08:27.865 that knockout thousands of.

NOTE Confidence: 0.781458700000001

00:08:27.870 --> 00:08:29.220 Immunologically relevant genes.

NOTE Confidence: 0.781458700000001

00:08:29.220 --> 00:08:32.789 In the genome and then to kind of

NOTE Confidence: 0.781458700000001

00:08:32.789 --> 00:08:34.835 select those guides until you have

NOTE Confidence: 0.781458700000001

00:08:34.835 --> 00:08:37.620 a pool of knockout tumor cell lines

NOTE Confidence: 0.781458700000001

00:08:37.620 --> 00:08:40.146 that is then implanted into mice

NOTE Confidence: 0.781458700000001

00:08:40.150 --> 00:08:41.994 under increasing immune selective

NOTE Confidence: 0.781458700000001

00:08:41.994 --> 00:08:43.838 pressure from extremely immunodeficient

NOTE Confidence: 0.781458700000001

00:08:43.838 --> 00:08:46.381 mice that lack T cells to mice with

NOTE Confidence: 0.781458700000001

00:08:46.381 --> 00:08:47.870 an intact immune cell system.

NOTE Confidence: 0.781458700000001

00:08:47.870 --> 00:08:49.710 2 mice treated with immunotherapy.

NOTE Confidence: 0.781458700000001

00:08:49.710 --> 00:08:50.802 In this case,

NOTE Confidence: 0.781458700000001

00:08:50.802 --> 00:08:52.622 the irradiated GM CSF secreting

NOTE Confidence: 0.781458700000001

00:08:52.622 --> 00:08:54.500 whole tumor cell vaccine GBX,

NOTE Confidence: 0.781458700000001

00:08:54.500 --> 00:08:57.636 plus anti PD one kind of strong

NOTE Confidence: 0.781458700000001

00:08:57.636 --> 00:08:58.980 immunotherapy treatment regiment.

NOTE Confidence: 0.781458700000001

00:08:58.980 --> 00:09:01.320 Would grow these tumors for about

NOTE Confidence: 0.781458700000001

00:09:01.320 --> 00:09:03.899 2 weeks and then remove them.

NOTE Confidence: 0.781458700000001

00:09:03.900 --> 00:09:06.360 Harvested tumors and sequence the sequence.

NOTE Confidence: 0.781458700000001

00:09:06.360 --> 00:09:08.544 The barcodes sequence the guides using

NOTE Confidence: 0.781458700000001

00:09:08.544 --> 00:09:10.870 them as barcodes and quantitating.

NOTE Confidence: 0.781458700000001

00:09:10.870 --> 00:09:12.595 Enrichment and depletion of each

NOTE Confidence: 0.781458700000001

00:09:12.595 --> 00:09:14.810 guy and the way we interpreted

NOTE Confidence: 0.781458700000001

00:09:14.810 --> 00:09:17.288 this experiment was to compare high

NOTE Confidence: 0.781458700000001

00:09:17.288 --> 00:09:19.889 to lower mean selective pressure.

NOTE Confidence: 0.781458700000001

00:09:19.890 --> 00:09:21.530 So immunotherapy treated to

NOTE Confidence: 0.781458700000001

00:09:21.530 --> 00:09:23.110 immunodeficient mice, for example,

NOTE Confidence: 0.781458700000001

00:09:23.110 --> 00:09:25.390 and to interpret it that guides

NOTE Confidence: 0.781458700000001

00:09:25.390 --> 00:09:26.860 that were depleted.

NOTE Confidence: 0.781458700000001

00:09:26.860 --> 00:09:28.090 Comparing height alone,

NOTE Confidence: 0.781458700000001

00:09:28.090 --> 00:09:30.140 selective pressure represented Jews that,

NOTE Confidence: 0.781458700000001

00:09:30.140 --> 00:09:32.060 when deleted, convert sensitivity.

NOTE Confidence: 0.781458700000001

00:09:32.060 --> 00:09:33.980 To the mean system,

NOTE Confidence: 0.781458700000001

00:09:33.980 --> 00:09:36.208 and therefore potential targets

NOTE Confidence: 0.781458700000001

00:09:36.208 --> 00:09:37.879 for combination therapy.

NOTE Confidence: 0.781458700000001

00:09:37.880 --> 00:09:38.654 In contrast,

NOTE Confidence: 0.781458700000001

00:09:38.654 --> 00:09:40.589 guides that were enriched under

NOTE Confidence: 0.781458700000001

00:09:40.589 --> 00:09:42.120 strongly selective pressure suggested

NOTE Confidence: 0.781458700000001

00:09:42.120 --> 00:09:44.304 to US jeans that were lost made

NOTE Confidence: 0.781458700000001

00:09:44.304 --> 00:09:45.790 tumors resistant to new therapy.

NOTE Confidence: 0.8393771

00:09:48.360 --> 00:09:50.264 And a lot of the targets that we

NOTE Confidence: 0.8393771

00:09:50.264 --> 00:09:52.047 found this way actually ended up in

NOTE Confidence: 0.8393771

00:09:52.047 --> 00:09:54.178 the kind of realm of double stranded

NOTE Confidence: 0.8393771

00:09:54.178 --> 00:09:56.238 RNA sensing or antiviral triggering,

NOTE Confidence: 0.8393771

00:09:56.240 --> 00:09:58.445 and this is really the area that

NOTE Confidence: 0.8393771

00:09:58.445 --> 00:10:00.799 I focused on throughout my time.

NOTE Confidence: 0.8393771

00:10:00.800 --> 00:10:03.329 And this guy is thinking because a lot of

NOTE Confidence: 0.8393771

00:10:03.329 --> 00:10:05.619 what we know about viral infection comes

NOTE Confidence: 0.8393771

00:10:05.619 --> 00:10:08.079 from the study of exonerees viruses.

NOTE Confidence: 0.8393771

00:10:08.080 --> 00:10:11.020 But of course the genome is comprised

NOTE Confidence: 0.8393771

00:10:11.020 --> 00:10:13.656 largely of repetitive elements that have

NOTE Confidence: 0.8393771

00:10:13.656 --> 00:10:16.694 the potential to form double stranded RNA.

NOTE Confidence: 0.8393771

00:10:16.700 --> 00:10:18.855 These could be small interspersed

NOTE Confidence: 0.8393771

00:10:18.855 --> 00:10:21.010 nuclear elements and obvious retrovirus.

NOTE Confidence: 0.8393771

00:10:21.010 --> 00:10:23.158 Endogenous retroviruses are long

NOTE Confidence: 0.8393771

00:10:23.158 --> 00:10:26.380 interspersed nuclear elements or or others.

NOTE Confidence: 0.8393771

00:10:26.380 --> 00:10:28.788 And so we considered that that we've

NOTE Confidence: 0.8393771

00:10:28.788 --> 00:10:30.879 Co evolved with these elements.

NOTE Confidence: 0.8393771

00:10:30.880 --> 00:10:32.656 With these kind of viral remnants

NOTE Confidence: 0.8393771

00:10:32.656 --> 00:10:34.732 in many cases and ourselves have

NOTE Confidence: 0.8393771

00:10:34.732 --> 00:10:36.817 developed systems to regulate double

NOTE Confidence: 0.8393771

00:10:36.817 --> 00:10:38.966 stranded RNA sensing to distinguish

NOTE Confidence: 0.8393771

00:10:38.966 --> 00:10:40.630 between double stranded RNA.

NOTE Confidence: 0.8393771

00:10:40.630 --> 00:10:43.162 That's a result of normal cellular

NOTE Confidence: 0.8393771

00:10:43.162 --> 00:10:45.460 activity and exogenous viral threats.

NOTE Confidence: 0.8393771

00:10:45.460 --> 00:10:47.780 And so we thought that by targeting some

NOTE Confidence: 0.8393771

00:10:47.780 --> 00:10:50.587 of the genes that control this regulation,

NOTE Confidence: 0.8393771

00:10:50.590 --> 00:10:52.300 we might sensitize tumor cells

NOTE Confidence: 0.8393771

00:10:52.300 --> 00:10:53.326 to tumor therapy.

NOTE Confidence: 0.8393771

00:10:53.330 --> 00:10:55.717 Trigger this kind of anti virus state.

NOTE Confidence: 0.78675884

00:10:57.800 --> 00:11:00.537 And the top hits that we discovered

NOTE Confidence: 0.78675884

00:11:00.537 --> 00:11:02.963 through this process in the antiviral

NOTE Confidence: 0.78675884

00:11:02.963 --> 00:11:04.928 sensing arena was this paid.

NOTE Confidence: 0.78675884

00:11:04.930 --> 00:11:07.162 R18 R is an adenosine deaminase

NOTE Confidence: 0.78675884

00:11:07.162 --> 00:11:09.680 that acts on double stranded RNA.

NOTE Confidence: 0.78675884

00:11:09.680 --> 00:11:12.445 It has a long cytoplasmic P-150 isoform.

NOTE Confidence: 0.78675884

00:11:12.450 --> 00:11:15.408 That's interferon inducible and a short.

NOTE Confidence: 0.78675884

00:11:15.410 --> 00:11:18.590 Constitu Tively Express P110I support him.

NOTE Confidence: 0.78675884

00:11:18.590 --> 00:11:20.758 The main known function of edar is to

NOTE Confidence: 0.78675884

00:11:20.758 --> 00:11:22.284 catalyze the conversion of adenosine

NOTE Confidence: 0.78675884

00:11:22.284 --> 00:11:24.720 to in a scene and double stranded RNA.

NOTE Confidence: 0.78675884

00:11:24.720 --> 00:11:27.264 And it's thought that in so doing it

NOTE Confidence: 0.78675884

00:11:27.264 --> 00:11:29.630 prevents double stranded RNA sensing in

NOTE Confidence: 0.78675884

00:11:29.630 --> 00:11:31.705 the triggering of antiviral immunity.

NOTE Confidence: 0.78675884

00:11:31.710 --> 00:11:33.024 Kind of autoimmunity.

NOTE Confidence: 0.78675884

00:11:33.024 --> 00:11:33.462 Accordingly,

NOTE Confidence: 0.78675884

00:11:33.462 --> 00:11:36.090 there is an autoimmune syndrome called

NOTE Confidence: 0.78675884

00:11:36.150 --> 00:11:38.310 Acardi Goutieres syndrome that is

NOTE Confidence: 0.78675884

00:11:38.310 --> 00:11:40.038 associated with biallelic mutations

NOTE Confidence: 0.78675884

00:11:40.038 --> 00:11:42.510 of a Darwin on the catalytic domain.

NOTE Confidence: 0.78675884

00:11:42.510 --> 00:11:44.586 It can be quite severe effects

NOTE Confidence: 0.78675884

00:11:44.586 --> 00:11:46.660 children and mimics viral infection.

NOTE Confidence: 0.78675884

00:11:46.660 --> 00:11:47.452 However, Interestingly,

NOTE Confidence: 0.78675884

00:11:47.452 --> 00:11:49.432 the parents of affected patients

NOTE Confidence: 0.78675884

00:11:49.432 --> 00:11:51.818 who have monolith mutations in the

NOTE Confidence: 0.78675884

00:11:51.818 --> 00:11:53.718 catalytic domain have evidence of

NOTE Confidence: 0.78675884

00:11:53.718 --> 00:11:55.194 increased signatures of interferon

NOTE Confidence: 0.78675884

00:11:55.194 --> 00:11:56.839 gene expression in the blood,

NOTE Confidence: 0.78675884

00:11:56.840 --> 00:11:59.096 but have no detectable disease phenotype,

NOTE Confidence: 0.78675884

00:11:59.100 --> 00:12:01.739 suggesting that there's a gene dose effect.

NOTE Confidence: 0.8696512

00:12:03.950 --> 00:12:05.654 So to begin to validate our

NOTE Confidence: 0.8696512

00:12:05.654 --> 00:12:07.900 one as a potential drug target

NOTE Confidence: 0.8696512

00:12:07.900 --> 00:12:09.460 for combination immunotherapy.

NOTE Confidence: 0.8696512

00:12:09.460 --> 00:12:11.812 We created dedicated knockout tumor cell

NOTE Confidence: 0.8696512

00:12:11.812 --> 00:12:14.650 lines again using the B16 Melanoma model.

NOTE Confidence: 0.8696512

00:12:14.650 --> 00:12:16.415 This transplantable tumor model and

NOTE Confidence: 0.8696512

00:12:16.415 --> 00:12:18.738 we implanted these into mice under

NOTE Confidence: 0.8696512

00:12:18.738 --> 00:12:20.229 increasing selective pressure.

NOTE Confidence: 0.8696512

00:12:20.230 --> 00:12:22.580 It means selective pressure starting

NOTE Confidence: 0.8696512

00:12:22.580 --> 00:12:24.460 with the extremely immunodeficient

NOTE Confidence: 0.8696512

00:12:24.460 --> 00:12:26.881 nods give gamma mice that entirely

NOTE Confidence: 0.8696512

00:12:26.881 --> 00:12:28.766 lack adaptive immunity and have

NOTE Confidence: 0.8696512

00:12:28.833 --> 00:12:30.689 only impaired innate immunity.

NOTE Confidence: 0.8696512

00:12:30.690 --> 00:12:31.740 In these mice,

NOTE Confidence: 0.8696512

00:12:31.740 --> 00:12:33.840 looking at the 8 Arnold tumors,

NOTE Confidence: 0.8696512

00:12:33.840 --> 00:12:35.590 either P-150 knockouts in Orange,

NOTE Confidence: 0.8696512

00:12:35.590 --> 00:12:37.666 P-150 P, 110 knockouts in red

NOTE Confidence: 0.8696512

00:12:37.666 --> 00:12:39.440 compared to controls and Gray,

NOTE Confidence: 0.8696512

00:12:39.440 --> 00:12:42.240 and looking at tumor volume on the top,

NOTE Confidence: 0.8696512

00:12:42.240 --> 00:12:43.990 or survival in the bottom,

NOTE Confidence: 0.8696512

00:12:43.990 --> 00:12:46.370 you can see a sort of minimal

NOTE Confidence: 0.8696512

00:12:46.370 --> 00:12:48.885 decrease in the growth of the

NOTE Confidence: 0.8696512

00:12:48.885 --> 00:12:51.245 Darnell tumors compared to controls.

NOTE Confidence: 0.8696512

00:12:51.250 --> 00:12:54.526 And a minimal increase in survival.

NOTE Confidence: 0.8696512

00:12:54.530 --> 00:12:55.164 In contrast,

NOTE Confidence: 0.8696512

00:12:55.164 --> 00:12:57.066 when planted these tumors into wild

NOTE Confidence: 0.8696512

00:12:57.066 --> 00:12:59.347 type mice with an intact immune system,

NOTE Confidence: 0.8696512

00:12:59.350 --> 00:13:01.144 you see a significant decrease in

NOTE Confidence: 0.8696512

00:13:01.144 --> 00:13:03.418 the growth of tumors in a significant

NOTE Confidence: 0.8696512

00:13:03.418 --> 00:13:05.113 survival advantage for the mice.

NOTE Confidence: 0.8696512

00:13:05.120 --> 00:13:05.470 Finally,

NOTE Confidence: 0.8696512

00:13:05.470 --> 00:13:07.570 when we implemented these tumors into

NOTE Confidence: 0.8696512

00:13:07.570 --> 00:13:09.620 mice and treated with anti PD one,

NOTE Confidence: 0.8696512

00:13:09.620 --> 00:13:12.315 we saw a near 100% cure rate for

NOTE Confidence: 0.8696512

00:13:12.315 --> 00:13:14.870 mice treated that were a Darnall and

NOTE Confidence: 0.8696512

00:13:14.947 --> 00:13:17.866 almost no cures in the control chambers.

NOTE Confidence: 0.8696512

00:13:17.870 --> 00:13:19.580 So to start to understand

NOTE Confidence: 0.8696512

00:13:19.580 --> 00:13:20.948 the mechanism of this,

NOTE Confidence: 0.8696512

00:13:20.950 --> 00:13:23.099 we looked at the tumor micro environment

NOTE Confidence: 0.8696512

00:13:23.099 --> 00:13:25.212 of untreated a Darnall and control

NOTE Confidence: 0.8696512

00:13:25.212 --> 00:13:27.097 tumors 14 days after implantation,

NOTE Confidence: 0.8696512

00:13:27.100 --> 00:13:29.431 and we did this using immuno histo

NOTE Confidence: 0.8696512

00:13:29.431 --> 00:13:31.973 chemistry and as you can see on the

NOTE Confidence: 0.8696512

00:13:31.973 --> 00:13:33.927 left in control tumors you have

NOTE Confidence: 0.8696512

00:13:33.927 --> 00:13:35.997 the immune desert type phenotype.

NOTE Confidence: 0.8696512

00:13:36.000 --> 00:13:38.450 Almost no CD8T cells infiltrating.

NOTE Confidence: 0.8696512

00:13:38.450 --> 00:13:38.940 In contrast,

NOTE Confidence: 0.8696512

00:13:38.940 --> 00:13:40.655 in a Darnall tumors we saw this

NOTE Confidence: 0.8696512

00:13:40.655 --> 00:13:42.477 T cell inflamed phenotype with

NOTE Confidence: 0.8696512

00:13:42.477 --> 00:13:44.372 diffuse infiltration of CD8T cells.

NOTE Confidence: 0.8696512

00:13:44.380 --> 00:13:45.940 Quantitative here on the right.

NOTE Confidence: 0.78991807

00:13:48.570 --> 00:13:50.050 To understand this more deeply,

NOTE Confidence: 0.78991807

00:13:50.050 --> 00:13:52.200 we next perform flow cytometry.

NOTE Confidence: 0.78991807

00:13:52.200 --> 00:13:54.312 Again with tumors 14 days after

NOTE Confidence: 0.78991807

00:13:54.312 --> 00:13:56.250 implantation in the untreated setting,

NOTE Confidence: 0.78991807

00:13:56.250 --> 00:13:58.090 and as you might predict,

NOTE Confidence: 0.78991807

00:13:58.090 --> 00:14:00.792 we saw an increase in CD 45

NOTE Confidence: 0.78991807

00:14:00.792 --> 00:14:03.516 positive immune cells and a Darnell

NOTE Confidence: 0.78991807

00:14:03.516 --> 00:14:05.496 tumors compared with controls.

NOTE Confidence: 0.78991807

00:14:05.500 --> 00:14:08.380 And then looking within the CD 45 compartment

NOTE Confidence: 0.78991807

00:14:08.380 --> 00:14:11.596 we saw increases in CD 3 positive T cells,

NOTE Confidence: 0.78991807

00:14:11.600 --> 00:14:13.400 CD 4 positive T cells,

NOTE Confidence: 0.78991807

00:14:13.400 --> 00:14:15.190 CD 8 positive T cells,

NOTE Confidence: 0.78991807

00:14:15.190 --> 00:14:19.425 gamma Delta T cells and NK cells.

NOTE Confidence: 0.78991807

00:14:19.430 --> 00:14:22.382 In contrast, when we looked at

NOTE Confidence: 0.78991807

00:14:22.382 --> 00:14:23.366 immunosuppressive populations,

NOTE Confidence: 0.78991807

00:14:23.370 --> 00:14:25.342 including mdse and tumor

NOTE Confidence: 0.78991807

00:14:25.342 --> 00:14:26.328 associated neutrophils,

NOTE Confidence: 0.78991807

00:14:26.330 --> 00:14:29.792 we saw significant increases in control

NOTE Confidence: 0.78991807

00:14:29.792 --> 00:14:33.649 tumors relative to a Darnall tumors.

NOTE Confidence: 0.78991807

00:14:33.650 --> 00:14:35.460 Finally, to probe the micro

NOTE Confidence: 0.78991807

00:14:35.460 --> 00:14:36.908 environment yet more deeply,

NOTE Confidence: 0.78991807

00:14:36.910 --> 00:14:39.076 we perform single cell RNA sequencing.

NOTE Confidence: 0.78991807

00:14:39.080 --> 00:14:41.495 These are the populations we

NOTE Confidence: 0.78991807

00:14:41.495 --> 00:14:43.427 recovered with myeloid populations

NOTE Confidence: 0.78991807

00:14:43.427 --> 00:14:46.264 in the upper right and T cell

NOTE Confidence: 0.78991807

00:14:46.264 --> 00:14:48.230 populations in the bottom left.

NOTE Confidence: 0.78991807

00:14:48.230 --> 00:14:49.542 As you can see,

NOTE Confidence: 0.78991807

00:14:49.542 --> 00:14:51.182 using these density plots that

NOTE Confidence: 0.78991807

00:14:51.182 --> 00:14:53.259 we adapted for this purpose,

NOTE Confidence: 0.78991807

00:14:53.260 --> 00:14:55.843 you get a strong signal from suppressive

NOTE Confidence: 0.78991807

00:14:55.843 --> 00:14:57.685 myeloid populations and to like

NOTE Confidence: 0.78991807

00:14:57.685 --> 00:14:59.713 macrophages and mdse in control tumors.

NOTE Confidence: 0.78991807

00:14:59.720 --> 00:15:01.874 But a weaker signal from inflammatory

NOTE Confidence: 0.78991807

00:15:01.874 --> 00:15:03.310 monocytes and CD8T cells.

NOTE Confidence: 0.78991807

00:15:03.310 --> 00:15:03.894 In contrast,

NOTE Confidence: 0.78991807

00:15:03.894 --> 00:15:05.646 in the 8 Arnold tumors you

NOTE Confidence: 0.78991807

00:15:05.646 --> 00:15:07.880 have hardly any signal from the

NOTE Confidence: 0.78991807

00:15:07.880 --> 00:15:09.068 suppressive minded populations

NOTE Confidence: 0.78991807

00:15:09.068 --> 00:15:11.456 and and enrichment of single from

NOTE Confidence: 0.78991807

00:15:11.456 --> 00:15:13.356 inflammatory monocytes and CD8T cells.

NOTE Confidence: 0.8100181

00:15:15.920 --> 00:15:17.795 To understand what's driving this

NOTE Confidence: 0.8100181

00:15:17.795 --> 00:15:19.670 change in the micro environment,

NOTE Confidence: 0.8100181

00:15:19.670 --> 00:15:21.812 we wanted to study the double

NOTE Confidence: 0.8100181

00:15:21.812 --> 00:15:23.670 stranded RNA sensing pathways that

NOTE Confidence: 0.8100181

00:15:23.670 --> 00:15:25.485 we thought could be associated

NOTE Confidence: 0.8100181

00:15:25.485 --> 00:15:27.550 with the phenotypes we'd observed.

NOTE Confidence: 0.8100181

00:15:27.550 --> 00:15:30.070 Specifically, we wanted to understand the

NOTE Confidence: 0.8100181

00:15:30.070 --> 00:15:32.800 role of protein kinase are an MD5 rig,

NOTE Confidence: 0.8100181

00:15:32.800 --> 00:15:35.299 I and nouns which are both associated

NOTE Confidence: 0.8100181

00:15:35.299 --> 00:15:37.602 with his internal sensors of nucleic

NOTE Confidence: 0.8100181

00:15:37.602 --> 00:15:39.547 acids in double stranded RNA,

NOTE Confidence: 0.8100181

00:15:39.550 --> 00:15:41.186 specifically protein kinase power

NOTE Confidence: 0.8100181

00:15:41.186 --> 00:15:42.822 is associated with translation

NOTE Confidence: 0.8100181

00:15:42.822 --> 00:15:44.418 arrest in a pop ptosis.

NOTE Confidence: 0.8100181

00:15:44.420 --> 00:15:46.810 Upon binding double stranded RNA.

NOTE Confidence: 0.8100181

00:15:46.810 --> 00:15:50.058 Where is MD5 regarding mass induced type

NOTE Confidence: 0.8100181

00:15:50.058 --> 00:15:53.129 one interferon in the antiviral state?

NOTE Confidence: 0.8100181

00:15:53.130 --> 00:15:56.028 To test the role of each of these sensors,

NOTE Confidence: 0.8100181

00:15:56.030 --> 00:15:58.094 we generated a series of double

NOTE Confidence: 0.8100181

00:15:58.094 --> 00:15:59.844 and triple knockout tumor cell

NOTE Confidence: 0.8100181

00:15:59.844 --> 00:16:02.035 lines and probe some of the in

NOTE Confidence: 0.8100181

00:16:02.035 --> 00:16:03.896 vitro phenotypes that we previously

NOTE Confidence: 0.8100181

00:16:03.896 --> 00:16:06.230 previously studied in a Darnell tumors.

NOTE Confidence: 0.8100181

00:16:06.230 --> 00:16:06.644 Specifically,

NOTE Confidence: 0.8100181

00:16:06.644 --> 00:16:09.128 we looked 1st at growth inhibition.

NOTE Confidence: 0.8100181

00:16:09.130 --> 00:16:11.200 So when you stimulate control

NOTE Confidence: 0.8100181

00:16:11.200 --> 00:16:13.270 tumors with interferon in vitro,

NOTE Confidence: 0.8100181

00:16:13.270 --> 00:16:16.959 there's a slight defect in growth that's

NOTE Confidence: 0.8100181

00:16:16.959 --> 00:16:20.240 magnified when you knockout eight R1.

NOTE Confidence: 0.8100181

00:16:20.240 --> 00:16:22.160 Looking at our double knockouts,

NOTE Confidence: 0.8100181

00:16:22.160 --> 00:16:25.216 we saw no effect of knocking out rig.

NOTE Confidence: 0.8100181

00:16:25.220 --> 00:16:27.947 I MDA 5 or Mens but saw that knocking

NOTE Confidence: 0.8100181

00:16:27.947 --> 00:16:30.810 out peak PQR reduced the phenotype to

NOTE Confidence: 0.8100181

00:16:30.810 --> 00:16:33.649 the levels observed in control tumors,

NOTE Confidence: 0.8100181

00:16:33.650 --> 00:16:36.980 suggesting a PQR was alone.

NOTE Confidence: 0.8100181

00:16:36.980 --> 00:16:38.840 Responsible for the in vitro

NOTE Confidence: 0.8100181

00:16:38.840 --> 00:16:40.700 growth defect that we'd observed.

NOTE Confidence: 0.8100181

00:16:40.700 --> 00:16:44.459 We next looked at interferon beta production.

NOTE Confidence: 0.8100181

00:16:44.460 --> 00:16:47.439 And this was again an in vitro Aliza and

NOTE Confidence: 0.8100181

00:16:47.439 --> 00:16:50.230 tumor cells stimulated with interferon.

NOTE Confidence: 0.8100181

00:16:50.230 --> 00:16:51.878 As you can see,

NOTE Confidence: 0.8100181

00:16:51.878 --> 00:16:53.526 control tumors produce no

NOTE Confidence: 0.8100181

00:16:53.526 --> 00:16:54.350 detectable interferon,

NOTE Confidence: 0.8100181

00:16:54.350 --> 00:16:56.530 whereas a Darnall tumors

NOTE Confidence: 0.8100181

00:16:56.530 --> 00:16:58.165 produces significant quantity.

NOTE Confidence: 0.8100181

00:16:58.170 --> 00:17:00.006 This is maintained from the loss

NOTE Confidence: 0.8100181

00:17:00.006 --> 00:17:02.221 of Rig I suggesting that guy is

NOTE Confidence: 0.8100181

00:17:02.221 --> 00:17:03.766 not involved in the phenotype.

NOTE Confidence: 0.8100181

00:17:03.770 --> 00:17:04.080 However,

NOTE Confidence: 0.8100181

00:17:04.080 --> 00:17:05.630 following the loss of MDA,

NOTE Confidence: 0.8100181

00:17:05.630 --> 00:17:07.918 Five Man's or PK are you see a

NOTE Confidence: 0.8100181

00:17:07.918 --> 00:17:08.889 significant reduction suggesting

NOTE Confidence: 0.8100181

00:17:08.889 --> 00:17:10.917 that all three of these sensors,

NOTE Confidence: 0.8100181

00:17:10.920 --> 00:17:13.013 or these two sensors in this adapter

NOTE Confidence: 0.8100181

00:17:13.013 --> 00:17:15.280 have a role to play in phenotype.

NOTE Confidence: 0.767478799999999

00:17:17.480 --> 00:17:19.517 We next wanted to understand which of

NOTE Confidence: 0.767478799999999

00:17:19.517 --> 00:17:21.313 these double stranded RNA sensing pathways

NOTE Confidence: 0.767478799999999

00:17:21.313 --> 00:17:23.770 was required for the in vivo phenotype of

NOTE Confidence: 0.767478799999999

00:17:23.770 --> 00:17:25.620 sensitization to whom checkpoint blockade.

NOTE Confidence: 0.767478799999999

00:17:25.620 --> 00:17:27.988 So we took our double and triple knockout

NOTE Confidence: 0.767478799999999

00:17:27.988 --> 00:17:30.297 tumor cell lines and implanted them into

NOTE Confidence: 0.767478799999999

00:17:30.297 --> 00:17:33.246 mice, treating the mice with PD one.

NOTE Confidence: 0.767478799999999

00:17:33.250 --> 00:17:34.302 Antibodies targeting PD one,

NOTE Confidence: 0.767478799999999

00:17:34.302 --> 00:17:37.150 and as you can see in our control experiment,

NOTE Confidence: 0.767478799999999

00:17:37.150 --> 00:17:39.034 control tumors continue to grow out

NOTE Confidence: 0.767478799999999

00:17:39.034 --> 00:17:41.461 as they did previously for us in the

NOTE Confidence: 0.767478799999999

00:17:41.461 --> 00:17:42.846 eternal summers respond well to,

NOTE Confidence: 0.767478799999999

00:17:42.850 --> 00:17:45.250 you know, therapy.

NOTE Confidence: 0.767478799999999

00:17:45.250 --> 00:17:46.850 This phenotype persisted following

NOTE Confidence: 0.767478799999999

00:17:46.850 --> 00:17:49.898 loss of PQR, suggesting that PQR is

NOTE Confidence: 0.767478799999999

00:17:49.898 --> 00:17:52.670 alone not required for the phenotype.

NOTE Confidence: 0.767478799999999

00:17:52.670 --> 00:17:53.274 Similarly.

NOTE Confidence: 0.767478799999999

00:17:53.274 --> 00:17:56.898 It persisted following loss of MD5,

NOTE Confidence: 0.767478799999999

00:17:56.900 --> 00:17:59.924 suggesting MDA 5 alone does not

NOTE Confidence: 0.767478799999999

00:17:59.924 --> 00:18:01.436 explain the phenotype.

NOTE Confidence: 0.767478799999999

00:18:01.440 --> 00:18:01.767 However.

NOTE Confidence: 0.767478799999999

00:18:01.767 --> 00:18:03.729 Following the deletion of both PK

NOTE Confidence: 0.767478799999999

00:18:03.729 --> 00:18:05.992 are in MDA 5 together with eight

NOTE Confidence: 0.767478799999999

00:18:05.992 --> 00:18:08.262 or one we no longer observe any

NOTE Confidence: 0.767478799999999

00:18:08.262 --> 00:18:10.207 difference between the growth of

NOTE Confidence: 0.767478799999999

00:18:10.207 --> 00:18:12.262 eight R1 knowledge control tumors

NOTE Confidence: 0.767478799999999

00:18:12.262 --> 00:18:13.738 treated with immunotherapy.

NOTE Confidence: 0.767478799999999

00:18:13.738 --> 00:18:14.230 Together,

NOTE Confidence: 0.767478799999999

00:18:14.230 --> 00:18:16.408 these results suggested to us that

NOTE Confidence: 0.767478799999999

00:18:16.408 --> 00:18:18.758 growth inhibition by PQR or antiviral

NOTE Confidence: 0.767478799999999

00:18:18.758 --> 00:18:21.266 sensing by MDA 5 amounts sufficient

NOTE Confidence: 0.767478799999999

00:18:21.266 --> 00:18:23.052 mediate sensitivity to no therapy

NOTE Confidence: 0.767478799999999

00:18:23.052 --> 00:18:25.117 but that at least one is required.

NOTE Confidence: 0.782579

00:18:28.290 --> 00:18:30.270 We next wanted to understand which

NOTE Confidence: 0.782579

00:18:30.270 --> 00:18:32.002 double stranded RNA sensing pathway

NOTE Confidence: 0.782579

00:18:32.002 --> 00:18:34.114 was required for the enhanced community

NOTE Confidence: 0.782579

00:18:34.114 --> 00:18:36.462 filtration for the inflammation in the

NOTE Confidence: 0.782579

00:18:36.462 --> 00:18:38.527 tumor microenvironment that we'd observed.

NOTE Confidence: 0.782579

00:18:38.530 --> 00:18:41.138 And so we again used our double and

NOTE Confidence: 0.782579

00:18:41.138 --> 00:18:42.939 triple knockout tumor cell lines.

NOTE Confidence: 0.782579

00:18:42.940 --> 00:18:45.124 In this time return to our habit of

NOTE Confidence: 0.782579

00:18:45.124 --> 00:18:47.340 looking at the tumor microenvironment,

NOTE Confidence: 0.782579

00:18:47.340 --> 00:18:48.700 dissecting the tumors out,

NOTE Confidence: 0.782579

00:18:48.700 --> 00:18:50.060 separating out the cells,

NOTE Confidence: 0.782579

00:18:50.060 --> 00:18:52.328 and quantitating them.

NOTE Confidence: 0.782579

00:18:52.330 --> 00:18:56.635 To look which sensor was was required.

NOTE Confidence: 0.782579

00:18:56.640 --> 00:18:58.236 In our control tumors,

NOTE Confidence: 0.782579

00:18:58.236 --> 00:19:00.630 you see a relatively low infiltration

NOTE Confidence: 0.782579

00:19:00.699 --> 00:19:02.959 of immune cells that significantly

NOTE Confidence: 0.782579

00:19:02.959 --> 00:19:05.490 increased following loss of eight R1.

NOTE Confidence: 0.782579

00:19:05.490 --> 00:19:06.190 And Interestingly,

NOTE Confidence: 0.782579

00:19:06.190 --> 00:19:07.240 this phenotype is,

NOTE Confidence: 0.782579

00:19:07.240 --> 00:19:08.920 if anything exaggerated following

NOTE Confidence: 0.782579

00:19:08.920 --> 00:19:11.440 loss of protein kinase are however

NOTE Confidence: 0.782579

00:19:11.508 --> 00:19:13.393 it's attenuated following loss of

NOTE Confidence: 0.782579

00:19:13.393 --> 00:19:15.661 MBA 5 and oblated following the

NOTE Confidence: 0.782579

00:19:15.661 --> 00:19:17.569 loss of the two senses together.

NOTE Confidence: 0.782579

00:19:17.570 --> 00:19:19.420 A similar pattern followed when

NOTE Confidence: 0.782579

00:19:19.420 --> 00:19:21.670 we looked at the proportion of

NOTE Confidence: 0.782579

00:19:21.670 --> 00:19:23.662 the 45 positive immune cells that

NOTE Confidence: 0.782579

00:19:23.662 --> 00:19:25.419 was comprised of CD8T cells,

NOTE Confidence: 0.782579

00:19:25.420 --> 00:19:25.848 again,

NOTE Confidence: 0.782579

00:19:25.848 --> 00:19:28.416 increases in eight are null that

NOTE Confidence: 0.782579

00:19:28.416 --> 00:19:30.485 persisted following loss of PQR

NOTE Confidence: 0.782579

00:19:30.485 --> 00:19:31.905 was attenuated following loss

NOTE Confidence: 0.782579

00:19:31.905 --> 00:19:34.234 of MD5 with loss following the

NOTE Confidence: 0.782579

00:19:34.234 --> 00:19:36.339 loss of both sensors together.

NOTE Confidence: 0.782579

00:19:36.340 --> 00:19:39.175 When we look at a immunosuppressive mdse,

NOTE Confidence: 0.782579

00:19:39.180 --> 00:19:41.265 we saw the opposite pattern

NOTE Confidence: 0.782579

00:19:41.265 --> 00:19:43.350 increases in control that persisted

NOTE Confidence: 0.782579

00:19:43.417 --> 00:19:45.267 or work were even increased.

NOTE Confidence: 0.782579

00:19:45.270 --> 00:19:47.825 Further following loss of PQR and no

NOTE Confidence: 0.782579

00:19:47.825 --> 00:19:50.211 loss of the phenotype following loss

NOTE Confidence: 0.782579

00:19:50.211 --> 00:19:53.800 of MDA 5 for the two sensors together.

NOTE Confidence: 0.78578705

00:19:56.900 --> 00:19:58.482 This suggested to us that MBA five

NOTE Confidence: 0.78578705

00:19:58.482 --> 00:20:00.179 may be playing the predominant role.

NOTE Confidence: 0.78578705

00:20:00.180 --> 00:20:02.304 And inducing tumor microenvironment

NOTE Confidence: 0.78578705

00:20:02.304 --> 00:20:04.428 inflammation may darnel tumors.

NOTE Confidence: 0.78578705

00:20:04.430 --> 00:20:05.567 To confirm this,

NOTE Confidence: 0.78578705

00:20:05.567 --> 00:20:08.220 we looked at the production of interferon

NOTE Confidence: 0.78578705

00:20:08.287 --> 00:20:10.873 beta interferon gamma in the tumor

NOTE Confidence: 0.78578705

00:20:10.873 --> 00:20:13.190 microenvironment of the eternal jiggers.

NOTE Confidence: 0.78578705

00:20:13.190 --> 00:20:15.437 And we saw a similar pattern again

NOTE Confidence: 0.78578705

00:20:15.437 --> 00:20:17.651 increases in a terminal tumors that

NOTE Confidence: 0.78578705

00:20:17.651 --> 00:20:20.402 persisted following loss of PQR but was

NOTE Confidence: 0.78578705

00:20:20.477 --> 00:20:23.015 lost after law after loss of MD5 or the

NOTE Confidence: 0.78578705

00:20:23.015 --> 00:20:25.316 two sensors together in the same pattern.

NOTE Confidence: 0.78578705

00:20:25.320 --> 00:20:27.604 Again looking at tumor

NOTE Confidence: 0.78578705

00:20:27.604 --> 00:20:29.317 lysate interferon gamma.

NOTE Confidence: 0.78578705

00:20:29.320 --> 00:20:31.160 So haven't seen having seen

NOTE Confidence: 0.78578705

00:20:31.160 --> 00:20:33.000 this powerful dual mechanism for

NOTE Confidence: 0.78578705

00:20:33.068 --> 00:20:35.280 sensitizing tumors to immunotherapy.

NOTE Confidence: 0.78578705

00:20:35.280 --> 00:20:38.008 We asked whether loss of eight R1 was

NOTE Confidence: 0.78578705

00:20:38.008 --> 00:20:40.300 sufficient to overcome commonly acquired

NOTE Confidence: 0.78578705

00:20:40.300 --> 00:20:43.378 mechanisms of resistance to amino therapy,

NOTE Confidence: 0.78578705

00:20:43.380 --> 00:20:44.553 including genetic aberrations

NOTE Confidence: 0.78578705

00:20:44.553 --> 00:20:46.508 that have been identified as

NOTE Confidence: 0.78578705

00:20:46.508 --> 00:20:48.490 enriched when comparing discordant,

NOTE Confidence: 0.78578705

00:20:48.490 --> 00:20:48.916 responsive,

NOTE Confidence: 0.78578705

00:20:48.916 --> 00:20:49.342 pretreatment,

NOTE Confidence: 0.78578705

00:20:49.342 --> 00:20:51.046 and resistant posttreatment lesions.

NOTE Confidence: 0.78578705

00:20:51.050 --> 00:20:54.280 Matched with the same patient.

NOTE Confidence: 0.78578705

00:20:54.280 --> 00:20:56.505 Known mechanisms that fit this

NOTE Confidence: 0.78578705

00:20:56.505 --> 00:20:59.502 description include the loss of MHC one

NOTE Confidence: 0.78578705

00:20:59.502 --> 00:21:01.952 through mutations of HLA or beta 2M,

NOTE Confidence: 0.78578705

00:21:01.960 --> 00:21:03.166 loss of targeting,

NOTE Confidence: 0.78578705

00:21:03.166 --> 00:21:04.774 children expressing through Mino,

NOTE Confidence: 0.78578705

00:21:04.780 --> 00:21:06.800 editing mutations and interferon sensing

NOTE Confidence: 0.78578705

00:21:06.800 --> 00:21:08.820 pathways including interferon gamma receptor,

NOTE Confidence: 0.78578705

00:21:08.820 --> 00:21:09.630 the Jackson,

NOTE Confidence: 0.78578705

00:21:09.630 --> 00:21:10.440 the stats.

NOTE Confidence: 0.81089616

00:21:12.610 --> 00:21:16.080 And we focused first on the loss of MHC one,

NOTE Confidence: 0.81089616

00:21:16.080 --> 00:21:18.720 as mediated by loss of data to microblogging

NOTE Confidence: 0.81089616

00:21:18.720 --> 00:21:21.252 which has been repeatedly identified as

NOTE Confidence: 0.81089616

00:21:21.252 --> 00:21:23.964 important in challenging form of resistance.

NOTE Confidence: 0.81089616

00:21:23.970 --> 00:21:25.750 To create this model we

NOTE Confidence: 0.81089616

00:21:25.750 --> 00:21:27.530 again use CRISPR CAS 9.

NOTE Confidence: 0.81089616

00:21:27.530 --> 00:21:29.852 This time deleting beta 2 micro

NOTE Confidence: 0.81089616

00:21:29.852 --> 00:21:32.120 globulin and eight are together.

NOTE Confidence: 0.81089616

00:21:32.120 --> 00:21:34.324 Along with creating match

NOTE Confidence: 0.81089616

00:21:34.324 --> 00:21:36.528 control tumor cell lines.

NOTE Confidence: 0.81089616

00:21:36.530 --> 00:21:38.768 To validate our model of resistance,

NOTE Confidence: 0.81089616

00:21:38.770 --> 00:21:41.442 we compared control in beta two of null

NOTE Confidence: 0.81089616

00:21:41.442 --> 00:21:44.167 tumors in the untreated that is dashed

NOTE Confidence: 0.81089616

00:21:44.167 --> 00:21:46.630 line state versus the treated state.

NOTE Confidence: 0.81089616

00:21:46.630 --> 00:21:48.868 That's the solid lines using again,

NOTE Confidence: 0.81089616

00:21:48.870 --> 00:21:50.922 this strong immunotherapy treatment

NOTE Confidence: 0.81089616

00:21:50.922 --> 00:21:54.000 regimen of GBX and PD one.

NOTE Confidence: 0.81089616

00:21:54.000 --> 00:21:56.485 And we did this because the normal

NOTE Confidence: 0.81089616

00:21:56.485 --> 00:21:58.113 control chambers responded very poorly

NOTE Confidence: 0.81089616

00:21:58.113 --> 00:22:00.475 to PD one and we wanted to make sure

NOTE Confidence: 0.81089616

00:22:00.475 --> 00:22:02.851 that we could see a response in control

NOTE Confidence: 0.81089616

00:22:02.851 --> 00:22:05.124 tumors and then validate that it was

NOTE Confidence: 0.81089616

00:22:05.124 --> 00:22:07.880 lost in the beta two unknown tumors.

NOTE Confidence: 0.81089616

00:22:07.880 --> 00:22:08.621 And sure enough,

NOTE Confidence: 0.81089616

00:22:08.621 --> 00:22:11.179 that's what we did see you can see the

NOTE Confidence: 0.81089616

00:22:11.179 --> 00:22:13.099 control tumors respond albiate transiently.

NOTE Confidence: 0.81089616

00:22:13.100 --> 00:22:13.391 Alternately,

NOTE Confidence: 0.81089616

00:22:13.391 --> 00:22:15.428 do grow out to this strong unit

NOTE Confidence: 0.81089616

00:22:15.428 --> 00:22:16.480 therapy treatment regiment,

NOTE Confidence: 0.81089616

00:22:16.480 --> 00:22:18.010 but made it to heaven.

NOTE Confidence: 0.81089616

00:22:18.010 --> 00:22:19.846 All tumors hardly respond at all.

NOTE Confidence: 0.7943555

00:22:22.400 --> 00:22:24.738 We next looked at a Darnall tumors.

NOTE Confidence: 0.7943555

00:22:24.740 --> 00:22:26.255 This is our positive control

NOTE Confidence: 0.7943555

00:22:26.255 --> 00:22:27.467 experiment using strong again

NOTE Confidence: 0.7943555

00:22:27.467 --> 00:22:29.080 with therapy treatment regimen.

NOTE Confidence: 0.7943555

00:22:29.080 --> 00:22:31.418 We got a great response to treatment.

NOTE Confidence: 0.7943555

00:22:31.420 --> 00:22:33.090 The untreated tumors grow out,

NOTE Confidence: 0.7943555

00:22:33.090 --> 00:22:36.330 albeit more slowly than controls.

NOTE Confidence: 0.7943555

00:22:36.330 --> 00:22:37.058 Strikingly, however,

NOTE Confidence: 0.7943555

00:22:37.058 --> 00:22:38.514 this sensitivity persisted following

NOTE Confidence: 0.7943555

00:22:38.514 --> 00:22:40.710 loss of beta two microglobulin,

NOTE Confidence: 0.7943555

00:22:40.710 --> 00:22:43.164 suggesting that loss of a Darwin

NOTE Confidence: 0.7943555

00:22:43.164 --> 00:22:45.872 in tumors is sufficient to overcome

NOTE Confidence: 0.7943555

00:22:45.872 --> 00:22:47.868 this mechanism of resistance.

NOTE Confidence: 0.7943555

00:22:47.870 --> 00:22:49.879 This result was a bit surprising actually.

NOTE Confidence: 0.7943555

00:22:49.880 --> 00:22:52.288 At first, as it suggests that CD8T

NOTE Confidence: 0.7943555

00:22:52.288 --> 00:22:54.240 cell recognition with MHC one in

NOTE Confidence: 0.7943555

00:22:54.240 --> 00:22:56.221 tumors is not in all cases required

NOTE Confidence: 0.7943555

00:22:56.286 --> 00:22:58.380 for the response to amino therapy.

NOTE Confidence: 0.7943555

00:22:58.380 --> 00:23:00.515 It also raises the question as to

NOTE Confidence: 0.7943555

00:23:00.515 --> 00:23:02.593 whether it could be possible to

NOTE Confidence: 0.7943555

00:23:02.593 --> 00:23:04.423 target tumors that entirely lack

NOTE Confidence: 0.7943555

00:23:04.423 --> 00:23:06.319 high quality CDH cell antigens.

NOTE Confidence: 0.7943555

00:23:06.320 --> 00:23:07.769 A lot of ongoing work in the

NOTE Confidence: 0.7943555

00:23:07.769 --> 00:23:09.354 lab is focused on dissecting the

NOTE Confidence: 0.7943555

00:23:09.354 --> 00:23:10.566 mechanism of this finding,

NOTE Confidence: 0.7943555

00:23:10.570 --> 00:23:12.270 and one of the first

NOTE Confidence: 0.7943555

00:23:12.270 --> 00:23:13.970 things we wanted to know.

NOTE Confidence: 0.7943555

00:23:13.970 --> 00:23:15.920 Is whether antigenic vaccine GBX,

NOTE Confidence: 0.7943555

00:23:15.920 --> 00:23:17.472 which was unsuccessful in

NOTE Confidence: 0.7943555

00:23:17.472 --> 00:23:19.024 translating to human use,

NOTE Confidence: 0.7943555

00:23:19.030 --> 00:23:22.520 was required for this response.

NOTE Confidence: 0.7943555

00:23:22.520 --> 00:23:24.194 This is actually pretty new data

NOTE Confidence: 0.7943555

00:23:24.194 --> 00:23:25.929 or afraid with PD one alone,

NOTE Confidence: 0.7943555

00:23:25.930 --> 00:23:27.925 and found that indeed you still get

NOTE Confidence: 0.7943555

00:23:27.925 --> 00:23:29.897 great responses in a Darwin all tumors.

NOTE Confidence: 0.792159180909091

00:23:31.940 --> 00:23:33.580 Even without the gmax.

NOTE Confidence: 0.792159180909091

00:23:33.580 --> 00:23:35.630 To start to understand this

NOTE Confidence: 0.792159180909091

00:23:35.630 --> 00:23:37.611 mechanism further, we again looked

NOTE Confidence: 0.792159180909091

00:23:37.611 --> 00:23:38.879 in the tumor microenvironment,

NOTE Confidence: 0.792159180909091

00:23:38.880 --> 00:23:41.232 this time focusing on our beta 2M

NOTE Confidence: 0.792159180909091

00:23:41.232 --> 00:23:43.319 null compared to control tumors.

NOTE Confidence: 0.792159180909091

00:23:43.320 --> 00:23:45.846 And so, as you would expect,

NOTE Confidence: 0.792159180909091

00:23:45.850 --> 00:23:47.440 increased immune infiltration

NOTE Confidence: 0.792159180909091

00:23:47.440 --> 00:23:49.560 CD 45 positive cells.

NOTE Confidence: 0.792159180909091

00:23:49.560 --> 00:23:52.038 But now focused on some of these

NOTE Confidence: 0.792159180909091

00:23:52.038 --> 00:23:54.848 MHC one non MHC one restricted

NOTE Confidence: 0.792159180909091

00:23:54.848 --> 00:23:57.068 cytotoxic populations and these

NOTE Confidence: 0.792159180909091

00:23:57.068 --> 00:23:59.604 include granzyme B positive CD

NOTE Confidence: 0.792159180909091

00:23:59.604 --> 00:24:02.355 4 positive T cells and NK cells.

NOTE Confidence: 0.792159180909091

00:24:02.360 --> 00:24:04.435 With the hypothesis that perhaps

NOTE Confidence: 0.792159180909091

00:24:04.435 --> 00:24:06.940 these cells which don't require MHC

NOTE Confidence: 0.792159180909091

00:24:06.940 --> 00:24:09.106 one for recognition of tumor cells.

NOTE Confidence: 0.792159180909091

00:24:09.110 --> 00:24:12.632 May be involved in the phenotype

NOTE Confidence: 0.792159180909091

00:24:12.632 --> 00:24:13.806 we've observed.

NOTE Confidence: 0.792159180909091

00:24:13.810 --> 00:24:15.754 We've also begun to dissect the

NOTE Confidence: 0.792159180909091

00:24:15.754 --> 00:24:17.050 cytokinin kyma kind drivers,

NOTE Confidence: 0.792159180909091

00:24:17.050 --> 00:24:19.350 by which these populations may

NOTE Confidence: 0.792159180909091

00:24:19.350 --> 00:24:21.190 be recruited and activated.

NOTE Confidence: 0.792159180909091

00:24:21.190 --> 00:24:24.462 These graphs are from side to kinda be

NOTE Confidence: 0.792159180909091

00:24:24.462 --> 00:24:27.736 Teresa Beta to null and a Darnall tumors.

NOTE Confidence: 0.792159180909091

00:24:27.740 --> 00:24:29.415 The two prominent chemo kinds

NOTE Confidence: 0.792159180909091

00:24:29.415 --> 00:24:30.755 were identified so far.

NOTE Confidence: 0.792159180909091

00:24:30.760 --> 00:24:33.790 CX CL 10 in CCL 5.

NOTE Confidence: 0.792159180909091

00:24:33.790 --> 00:24:35.170 Which are both significantly

NOTE Confidence: 0.792159180909091

00:24:35.170 --> 00:24:37.240 increased in our beta to emulate

NOTE Confidence: 0.792159180909091

00:24:37.297 --> 00:24:38.989 our one all tumors compared with

NOTE Confidence: 0.792159180909091

00:24:38.989 --> 00:24:41.030 beta to a control control tumors.

NOTE Confidence: 0.76325333

00:24:43.550 --> 00:24:45.614 Notably Ehrenring here at Yale has

NOTE Confidence: 0.76325333

00:24:45.614 --> 00:24:47.284 described a similar phenotype of

NOTE Confidence: 0.76325333

00:24:47.284 --> 00:24:48.730 being able to overcome the loss

NOTE Confidence: 0.76325333

00:24:48.730 --> 00:24:50.631 of MHC one using a modified I'll

NOTE Confidence: 0.76325333

00:24:50.631 --> 00:24:52.305 18 side kind that he designed.

NOTE Confidence: 0.76325333

00:24:52.310 --> 00:24:54.360 So this remains another possibility

NOTE Confidence: 0.76325333

00:24:54.360 --> 00:24:56.410 that we haven't yet explored.

NOTE Confidence: 0.76325333

00:24:56.410 --> 00:24:58.524 However, we think this type of study

NOTE Confidence: 0.76325333

00:24:58.524 --> 00:25:00.136 is important 'cause articulating the

NOTE Confidence: 0.76325333

00:25:00.136 --> 00:25:02.404 general principles by which loss of MHC

NOTE Confidence: 0.76325333

00:25:02.404 --> 00:25:04.931 one can be overcome could lead to new

NOTE Confidence: 0.76325333

00:25:04.931 --> 00:25:06.490 treatment approaches to target tumor

NOTE Confidence: 0.76325333

00:25:06.490 --> 00:25:07.750 specific immune evasion mechanisms.

NOTE Confidence: 0.8231248

00:25:10.820 --> 00:25:13.022 In summary, I hope I've convinced

NOTE Confidence: 0.8231248

00:25:13.022 --> 00:25:14.490 you have several points.

NOTE Confidence: 0.8231248

00:25:14.490 --> 00:25:18.178 First aid are one loss over improves the

NOTE Confidence: 0.8231248

00:25:18.178 --> 00:25:20.787 response to me to therapy. Specifically,

NOTE Confidence: 0.8231248

00:25:20.787 --> 00:25:23.216 it can overcome the lack of evidence.

NOTE Confidence: 0.8231248

00:25:23.220 --> 00:25:26.160 Plain tumor, micro environment and the

NOTE Confidence: 0.8231248

00:25:26.160 --> 00:25:29.080 loss of antigen presentation by image C1.

NOTE Confidence: 0.8231248

00:25:29.080 --> 00:25:30.884 Additionally, this phenotype is

NOTE Confidence: 0.8231248

00:25:30.884 --> 00:25:33.139 driven both by tumor microenvironment,

NOTE Confidence: 0.8231248

00:25:33.140 --> 00:25:34.944 inflammation mediated by MDA

NOTE Confidence: 0.8231248

00:25:34.944 --> 00:25:36.297 5 and sensitization.

NOTE Confidence: 0.8231248

00:25:36.300 --> 00:25:39.990 Interferon driven by PK are.

NOTE Confidence: 0.8231248

00:25:39.990 --> 00:25:42.806 Finally, and I think this may be important.

NOTE Confidence: 0.8231248

00:25:42.810 --> 00:25:44.715 Tumor cells contain sufficient innate

NOTE Confidence: 0.8231248

00:25:44.715 --> 00:25:46.620 lightning into drive therapeutic information.

NOTE Confidence: 0.8231248

00:25:46.620 --> 00:25:48.530 If they are in need.

NOTE Confidence: 0.8231248

00:25:48.530 --> 00:25:50.213 Nucleic acid sensing

NOTE Confidence: 0.8231248

00:25:50.213 --> 00:25:51.896 checkpoints are disabled.

NOTE Confidence: 0.8231248

00:25:51.900 --> 00:25:53.868 And what we think this implies is that

NOTE Confidence: 0.8231248

00:25:53.868 --> 00:25:55.745 there may be other similar innate

NOTE Confidence: 0.8231248

00:25:55.745 --> 00:25:57.410 immune checkpoints that limit the

NOTE Confidence: 0.8231248

00:25:57.410 --> 00:25:59.549 sensing of double stranded RNA or other

NOTE Confidence: 0.8231248

00:25:59.549 --> 00:26:01.308 nucleic acid ligands that we could

NOTE Confidence: 0.8231248

00:26:01.308 --> 00:26:02.778 think about as therapeutic targets.

NOTE Confidence: 0.81072354

00:26:04.830 --> 00:26:06.894 And really, those questions inform the

NOTE Confidence: 0.81072354

00:26:06.894 --> 00:26:09.716 rest of the work that the lab is doing.

NOTE Confidence: 0.81072354

00:26:09.720 --> 00:26:11.712 I've mentioned already a focus on

NOTE Confidence: 0.81072354

00:26:11.712 --> 00:26:13.629 double stranded RNA and eight R1.

NOTE Confidence: 0.81072354

00:26:13.630 --> 00:26:15.210 We're also applying functional genomics

NOTE Confidence: 0.81072354

00:26:15.210 --> 00:26:17.539 to try to identify other novel targets.

NOTE Confidence: 0.81072354

00:26:17.540 --> 00:26:19.370 Really, with the insight that we

NOTE Confidence: 0.81072354

00:26:19.370 --> 00:26:22.047 have to focus on turning on some of

NOTE Confidence: 0.81072354

00:26:22.047 --> 00:26:24.135 these pathways of double stranded RNA

NOTE Confidence: 0.81072354

00:26:24.205 --> 00:26:26.510 sensing or micro violent information.

NOTE Confidence: 0.81072354

00:26:26.510 --> 00:26:29.226 And then we're involved in human translation,

NOTE Confidence: 0.81072354

00:26:29.230 --> 00:26:31.402 doing kind of in depth tumor

NOTE Confidence: 0.81072354

00:26:31.402 --> 00:26:32.488 microenvironment investigation across

NOTE Confidence: 0.81072354

00:26:32.488 --> 00:26:34.268 several different tumor indications.

NOTE Confidence: 0.81072354

00:26:34.270 --> 00:26:36.930 We're always looking for new

NOTE Confidence: 0.81072354

00:26:36.930 --> 00:26:37.994 collaborators there.

NOTE Confidence: 0.81072354

00:26:38.000 --> 00:26:40.888 And all of this comes under the rubric

NOTE Confidence: 0.81072354

00:26:40.888 --> 00:26:42.685 of therapeutically targeting the

NOTE Confidence: 0.81072354

00:26:42.685 --> 00:26:45.215 information in the tumor microenvironment.

NOTE Confidence: 0.81072354

00:26:45.220 --> 00:26:46.940 In just the last couple of minutes here,

NOTE Confidence: 0.81072354

00:26:46.940 --> 00:26:48.886 I want to quickly mention some of

NOTE Confidence: 0.81072354

00:26:48.886 --> 00:26:50.763 the ongoing projects in the lab that

NOTE Confidence: 0.81072354

00:26:50.763 --> 00:26:52.245 I haven't talked about this far.

NOTE Confidence: 0.81072354

00:26:52.250 --> 00:26:56.876 First, I mentioned just the project.

NOTE Confidence: 0.81072354

00:26:56.880 --> 00:26:59.210 Describing how to Riker environment

NOTE Confidence: 0.81072354

00:26:59.210 --> 00:27:01.074 inflammation can overcome the

NOTE Confidence: 0.81072354

00:27:01.074 --> 00:27:02.340 loss of MHC one.

NOTE Confidence: 0.81072354

00:27:02.340 --> 00:27:05.280 This is being led by Jessica Way,

NOTE Confidence: 0.81072354

00:27:05.280 --> 00:27:08.556 but she's Additionally leading a project.

NOTE Confidence: 0.81072354

00:27:08.560 --> 00:27:10.480 Looking at human tumors and trying

NOTE Confidence: 0.81072354

00:27:10.480 --> 00:27:12.544 to turn these pathways on in ex

NOTE Confidence: 0.81072354

00:27:12.544 --> 00:27:14.231 vivo samples as well as doing deep

NOTE Confidence: 0.81072354

00:27:14.296 --> 00:27:16.316 dissection of the micro environment.

NOTE Confidence: 0.81072354

00:27:16.320 --> 00:27:18.623 Where we go is working on novel

NOTE Confidence: 0.81072354

00:27:18.623 --> 00:27:20.361 strategies to detect double stranded

NOTE Confidence: 0.81072354

00:27:20.361 --> 00:27:23.097 RNA and to mimic the sensors of double

NOTE Confidence: 0.81072354

00:27:23.160 --> 00:27:25.953 stranded RNA that we believe will be

NOTE Confidence: 0.81072354

00:27:25.953 --> 00:27:27.588 compatible with functional genomic

NOTE Confidence: 0.81072354

00:27:27.588 --> 00:27:29.778 screening in the identification of

NOTE Confidence: 0.81072354

00:27:29.778 --> 00:27:31.530 novel cancer immunotherapy targets.

NOTE Confidence: 0.81072354

00:27:31.530 --> 00:27:32.234 And finally,

NOTE Confidence: 0.81072354

00:27:32.234 --> 00:27:36.182 even Kim who is in the lab focused on the

NOTE Confidence: 0.81072354

00:27:36.182 --> 00:27:38.807 comparison of discordant response lesions.

NOTE Confidence: 0.81072354

00:27:38.810 --> 00:27:41.700 So responsive and resistant lesions.

NOTE Confidence: 0.81072354

00:27:41.700 --> 00:27:44.112 From the same patient trying to

NOTE Confidence: 0.81072354

00:27:44.112 --> 00:27:45.720 understand novel mechanisms of

NOTE Confidence: 0.81072354

00:27:45.785 --> 00:27:47.435 resistance to new therapies so

NOTE Confidence: 0.81072354

00:27:47.435 --> 00:27:49.870 that we can focus on overcoming.

NOTE Confidence: 0.81072354

00:27:49.870 --> 00:27:52.246 With that I want to thank everybody in

NOTE Confidence: 0.81072354

00:27:52.246 --> 00:27:54.670 our lab as well as our collaborators

NOTE Confidence: 0.81072354

00:27:54.670 --> 00:27:56.736 and mentors here at, you know,

NOTE Confidence: 0.81072354

00:27:56.736 --> 00:27:57.720 have been fantastic.

NOTE Confidence: 0.81072354

00:27:57.720 --> 00:27:59.676 I also wanted knowledge at Nikki

NOTE Confidence: 0.81072354

00:27:59.676 --> 00:28:01.268 Ning my form. Enter drumming.

NOTE Confidence: 0.81072354

00:28:01.268 --> 00:28:04.113 So much of the work that I presented early

NOTE Confidence: 0.81072354

00:28:04.113 --> 00:28:06.219 derives from from studies with them,

NOTE Confidence: 0.81072354

00:28:06.220 --> 00:28:07.852 and of course our funding here

NOTE Confidence: 0.81072354

00:28:07.852 --> 00:28:09.849 at the Cancer Center and the

NOTE Confidence: 0.81072354

00:28:09.849 --> 00:28:11.130 International Research Alliance.

NOTE Confidence: 0.81072354

00:28:11.130 --> 00:28:13.086 With that, I will wrap up.

NOTE Confidence: 0.81072354

00:28:13.090 --> 00:28:16.024 Thank you so much for the chance to present,

NOTE Confidence: 0.81072354

00:28:16.030 --> 00:28:17.986 and I'm happy to take questions.

NOTE Confidence: 0.825338

00:28:19.150 --> 00:28:21.250 Jeff, thank you. That's just

NOTE Confidence: 0.825338

00:28:21.250 --> 00:28:23.350 terrific work and really exciting.

NOTE Confidence: 0.825338

00:28:23.350 --> 00:28:26.710 And we we have folks can submit questions.

NOTE Confidence: 0.825338

00:28:26.710 --> 00:28:28.390 We have one question.

NOTE Confidence: 0.825338

00:28:28.390 --> 00:28:29.650 Mike Hurwitz asked.

NOTE Confidence: 0.825338

00:28:29.650 --> 00:28:32.548 So given the response in eight R1

NOTE Confidence: 0.825338

00:28:32.548 --> 00:28:35.948 knockouts in the absence of MHC class one,

NOTE Confidence: 0.825338

00:28:35.950 --> 00:28:38.368 do you think that's function of

NOTE Confidence: 0.825338

00:28:38.368 --> 00:28:41.626 CD4T cells or NK cells, or both?

NOTE Confidence: 0.825338

00:28:41.626 --> 00:28:44.020 Or some other mechanism? Yeah,

NOTE Confidence: 0.87834716

00:28:44.020 --> 00:28:46.324 I think that's a great question and we

NOTE Confidence: 0.87834716

00:28:46.324 --> 00:28:49.810 definitely would love to know that answer.

NOTE Confidence: 0.87834716

00:28:49.810 --> 00:28:52.216 Best hypothesis Now is that partially

NOTE Confidence: 0.87834716

00:28:52.216 --> 00:28:55.755 based on some of the work that Ehrenring

NOTE Confidence: 0.87834716

00:28:55.755 --> 00:28:58.090 is presented in Marcus Bosenberg.

NOTE Confidence: 0.87834716

00:28:58.090 --> 00:29:00.506 NK cells could be an important player there.

NOTE Confidence: 0.87834716

00:29:00.510 --> 00:29:02.050 Certainly there increased and we

NOTE Confidence: 0.87834716

00:29:02.050 --> 00:29:04.220 started to see some cytokines in Kemah

NOTE Confidence: 0.87834716

00:29:04.220 --> 00:29:05.936 kinds that may activate them further,

NOTE Confidence: 0.87834716

00:29:05.940 --> 00:29:08.012 but you know, we don't even know for

NOTE Confidence: 0.87834716

00:29:08.012 --> 00:29:10.167 sure that CD8T cells aren't important.

NOTE Confidence: 0.87834716

00:29:10.170 --> 00:29:11.976 That's an experiment we're doing now.

NOTE Confidence: 0.87834716

00:29:11.980 --> 00:29:14.099 We just know they're not recognizing the

NOTE Confidence: 0.87834716

00:29:14.100 --> 00:29:16.060 tumor, but could they be activated through

NOTE Confidence: 0.87834716

00:29:16.060 --> 00:29:17.915 cross presentation or another means is

NOTE Confidence: 0.87834716

00:29:17.915 --> 00:29:19.530 another question that we're investigating.

NOTE Confidence: 0.7803051

00:29:20.700 --> 00:29:23.570 And then you know, in related work.

NOTE Confidence: 0.7803051

00:29:23.570 --> 00:29:24.941 Obviously Akiko, Saki,

NOTE Confidence: 0.7803051

00:29:24.941 --> 00:29:28.140 and Anna Pile of working independently on

NOTE Confidence: 0.7803051

00:29:28.218 --> 00:29:31.344 Rig Rig I are iguana, which which it is.

NOTE Confidence: 0.7803051

00:29:31.344 --> 00:29:33.780 But which obviously is not necessarily

NOTE Confidence: 0.7803051

00:29:33.856 --> 00:29:36.280 related to the function vadar one,

NOTE Confidence: 0.7803051

00:29:36.280 --> 00:29:37.732 and you know how?

NOTE Confidence: 0.7803051

00:29:37.732 --> 00:29:40.906 How do you see those two with those

NOTE Confidence: 0.7803051

00:29:40.906 --> 00:29:44.070 two sort of bodies of work relating?

NOTE Confidence: 0.7803051

00:29:44.070 --> 00:29:45.710 Yeah, so this is

NOTE Confidence: 0.7803051

00:29:45.710 --> 00:29:48.374 a great question Charlie and actually

NOTE Confidence: 0.7803051

00:29:48.374 --> 00:29:51.910 Akiko is one of my mentors here and.

NOTE Confidence: 0.7803051

00:29:51.910 --> 00:29:54.826 Collaborators and we've talked about this.

NOTE Confidence: 0.7803051

00:29:54.830 --> 00:29:58.225 We're actually in the process of testing.

NOTE Confidence: 0.7803051

00:29:58.230 --> 00:30:02.736 Are a guy at. Egotist with the innate

NOTE Confidence: 0.7803051

00:30:02.736 --> 00:30:04.548 arnolin control tumor cell lines and

NOTE Confidence: 0.7803051

00:30:04.548 --> 00:30:06.885 you know the colloquial way we we

NOTE Confidence: 0.7803051

00:30:06.885 --> 00:30:09.202 thought about this is kind of as a

NOTE Confidence: 0.7803051

00:30:09.202 --> 00:30:10.841 maximum inflammation bomb because what

NOTE Confidence: 0.7803051

00:30:10.841 --> 00:30:13.019 we've shown is that any interferon

NOTE Confidence: 0.7803051

00:30:13.019 --> 00:30:14.541 producing stimulus can trigger this

NOTE Confidence: 0.7803051

00:30:14.541 --> 00:30:16.050 8 Arnold amplification of sensing,

NOTE Confidence: 0.7803051

00:30:16.050 --> 00:30:18.418 and so our hypothesis would be that if

NOTE Confidence: 0.7803051

00:30:18.418 --> 00:30:20.470 you initiate signaling through a guy,

NOTE Confidence: 0.7803051

00:30:20.470 --> 00:30:22.502 even if there a guy is not involved

NOTE Confidence: 0.7803051

00:30:22.502 --> 00:30:24.899 in the pathways we've described here,

NOTE Confidence: 0.7803051

00:30:24.900 --> 00:30:26.475 you basically create a massive

NOTE Confidence: 0.7803051

00:30:26.475 --> 00:30:27.424 amplification of interferon,

NOTE Confidence: 0.7803051

00:30:27.424 --> 00:30:29.320 buy by further knocking out eight

NOTE Confidence: 0.7803051

00:30:29.320 --> 00:30:31.534 R1 so that remains to be seen,

NOTE Confidence: 0.7803051

00:30:31.534 --> 00:30:33.430 but that's what I would hypothesize.

NOTE Confidence: 0.8670604

00:30:33.830 --> 00:30:34.892 Yeah, that's interesting.

NOTE Confidence: 0.8670604

00:30:34.892 --> 00:30:36.662 It sounds like a great

NOTE Confidence: 0.8670604

00:30:36.662 --> 00:30:38.158 opportunity to look at that.

NOTE Confidence: 0.8670604

00:30:38.160 --> 00:30:41.157 Well, I I want to keep us on time,

NOTE Confidence: 0.8670604

00:30:41.160 --> 00:30:42.400 so Jeff, thank you.

NOTE Confidence: 0.8670604

00:30:42.400 --> 00:30:44.260 I know there are other questions

NOTE Confidence: 0.8670604

00:30:44.326 --> 00:30:46.258 coming in and people should certainly

NOTE Confidence: 0.8670604

00:30:46.258 --> 00:30:48.490 reach out to you directly, Jeff.

NOTE Confidence: 0.8670604

00:30:48.490 --> 00:30:50.870 But thank you for a superb presentation

NOTE Confidence: 0.8670604

00:30:50.870 --> 00:30:53.807 and let me now turn to our second speaker,

NOTE Confidence: 0.8670604

00:30:53.810 --> 00:30:56.130 doctor Robert Bone and Bob Bone is a

NOTE Confidence: 0.8670604

00:30:56.130 --> 00:30:58.138 professor of medicine in hematology,

NOTE Confidence: 0.8670604

00:30:58.140 --> 00:31:00.831 and recently the past year joins us as the

NOTE Confidence: 0.8670604

00:31:00.831 --> 00:31:03.128 director of the Benign Hematology program,

NOTE Confidence: 0.8670604

00:31:03.130 --> 00:31:05.846 as well as the medical director of

NOTE Confidence: 0.8670604

00:31:05.846 --> 00:31:07.540 the Hemophilia Treatment Center.

NOTE Confidence: 0.8670604

00:31:07.540 --> 00:31:09.156 Prior to joining Yale,

NOTE Confidence: 0.8670604

00:31:09.156 --> 00:31:11.176 Bob was founding faculty member

NOTE Confidence: 0.8670604

00:31:11.176 --> 00:31:13.745 and leader at the Frank Netter

NOTE Confidence: 0.8670604

00:31:13.745 --> 00:31:15.835 School of Medicine at Quinnipiac,

NOTE Confidence: 0.8670604

00:31:15.840 --> 00:31:18.784 as well as a professor of medicine at

NOTE Confidence: 0.8670604

00:31:18.784 --> 00:31:21.416 the University of Connecticut School of

NOTE Confidence: 0.8670604

00:31:21.416 --> 00:31:24.140 Medicine and Bob throughout his career,

NOTE Confidence: 0.8670604

00:31:24.140 --> 00:31:27.101 really has been a leader in in in the

NOTE Confidence: 0.8670604

00:31:27.101 --> 00:31:29.615 clinical care and sort of advancing

NOTE Confidence: 0.8670604

00:31:29.615 --> 00:31:32.344 work in hemostasis thrombosis as well

NOTE Confidence: 0.8670604

00:31:32.344 --> 00:31:34.520 as benign hematologic conditions.

NOTE Confidence: 0.8670604

00:31:34.520 --> 00:31:35.816 And we're really,

NOTE Confidence: 0.8670604

00:31:35.816 --> 00:31:37.544 very fortunate Bob to.

NOTE Confidence: 0.8670604

00:31:37.550 --> 00:31:38.218 That Bob,

NOTE Confidence: 0.8670604

00:31:38.218 --> 00:31:40.222 now leading this section and sharing

NOTE Confidence: 0.8670604

00:31:40.222 --> 00:31:41.740 with his work with us.

NOTE Confidence: 0.8670604

00:31:41.740 --> 00:31:43.020 So Bob thank you.

NOTE Confidence: 0.9011822

00:31:44.410 --> 00:31:47.134 Thank you, Charlie for that introduction

NOTE Confidence: 0.9011822

00:31:47.134 --> 00:31:50.090 and for the opportunity to speak today.

NOTE Confidence: 0.9011822

00:31:50.090 --> 00:31:52.890 Let me just share my screen here.

NOTE Confidence: 0.9011822

00:31:52.890 --> 00:31:55.760 So good afternoon everybody.

NOTE Confidence: 0.9011822

00:31:55.760 --> 00:31:58.358 And what I would like to do in the

NOTE Confidence: 0.9011822

00:31:58.358 --> 00:32:00.996 next 25 minutes or so is discuss with

NOTE Confidence: 0.9011822

00:32:00.996 --> 00:32:04.060 you some of the advances that have a

NOTE Confidence: 0.9011822

00:32:04.060 --> 00:32:06.544 curd in the treatment of hemophilia

NOTE Confidence: 0.9011822

00:32:06.550 --> 00:32:08.800 and what I hope to show you is that

NOTE Confidence: 0.9011822

00:32:08.800 --> 00:32:11.285 over the past five years there have

NOTE Confidence: 0.9011822

00:32:11.285 --> 00:32:13.219 really been significant and substantial

NOTE Confidence: 0.9011822

00:32:13.219 --> 00:32:15.727 advances which came in the background

NOTE Confidence: 0.9011822

00:32:15.727 --> 00:32:18.421 of really several decades of really

NOTE Confidence: 0.9011822

00:32:18.421 --> 00:32:20.806 only modest advances in therapy.

NOTE Confidence: 0.9011822

00:32:20.810 --> 00:32:23.960 So just as a brief review here,

NOTE Confidence: 0.9011822

00:32:23.960 --> 00:32:25.760 these are excellent disorders,

NOTE Confidence: 0.9011822

00:32:25.760 --> 00:32:27.110 mostly affecting men,

NOTE Confidence: 0.9011822

00:32:27.110 --> 00:32:29.840 but can also affect women who might

NOTE Confidence: 0.9011822

00:32:29.840 --> 00:32:32.660 have low factor levels due to

NOTE Confidence: 0.9011822

00:32:32.660 --> 00:32:34.756 unequal X chromosome inactivation,

NOTE Confidence: 0.9011822

00:32:34.760 --> 00:32:36.560 hemophilia A&B or deficiencies

NOTE Confidence: 0.9011822

00:32:36.560 --> 00:32:39.260 in factor 8 or 9 respectively.

NOTE Confidence: 0.9011822

00:32:39.260 --> 00:32:41.685 They are clinically identical disorders

NOTE Confidence: 0.9011822

00:32:41.685 --> 00:32:44.664 and the severity of the disease

NOTE Confidence: 0.9011822

00:32:44.664 --> 00:32:47.526 is really relies primarily on the

NOTE Confidence: 0.9011822

00:32:47.526 --> 00:32:49.876 residual factor that is remaining

NOTE Confidence: 0.9011822

00:32:49.876 --> 00:32:52.809 in the blood with those with severe.

NOTE Confidence: 0.9011822

00:32:52.810 --> 00:32:54.800 And moderate disease having less

NOTE Confidence: 0.9011822

00:32:54.800 --> 00:32:57.430 than 5% of factor 8 or factor 9

NOTE Confidence: 0.9011822

00:32:57.430 --> 00:32:59.571 and those with mild disease having

NOTE Confidence: 0.9011822

00:32:59.571 --> 00:33:02.121 a higher value and morbidity and

NOTE Confidence: 0.9011822

00:33:02.121 --> 00:33:04.475 mortality is due to spontaneous

NOTE Confidence: 0.9011822

00:33:04.475 --> 00:33:06.379 and trauma induced bleeding,

NOTE Confidence: 0.9011822

00:33:06.380 --> 00:33:09.010 including bleeding into joints which

NOTE Confidence: 0.9011822

00:33:09.010 --> 00:33:11.640 can cause a hemophilic arthropathy

NOTE Confidence: 0.9011822

00:33:11.721 --> 00:33:14.535 which we can be quite quite disabling.

NOTE Confidence: 0.9011822

00:33:14.540 --> 00:33:16.892 And just the history of hemophilia

NOTE Confidence: 0.9011822

00:33:16.892 --> 00:33:18.916 treatment in the last century

NOTE Confidence: 0.9011822

00:33:18.916 --> 00:33:21.196 is seen briefly on this slide,

NOTE Confidence: 0.9011822

00:33:21.200 --> 00:33:23.592 and at the end of World War Two

NOTE Confidence: 0.9011822

00:33:23.592 --> 00:33:25.812 blood or plasma transfusions were

NOTE Confidence: 0.9011822

00:33:25.812 --> 00:33:27.864 used to treat patients.

NOTE Confidence: 0.9011822

00:33:27.870 --> 00:33:29.830 This these were largely ineffective,

NOTE Confidence: 0.9011822

00:33:29.830 --> 00:33:32.686 is only small amounts of factor 8 or

NOTE Confidence: 0.9011822

00:33:32.686 --> 00:33:36.097 factor 9 could be transfused in the 1960s.

NOTE Confidence: 0.9011822

00:33:36.100 --> 00:33:37.276 Cryoprecipitate was discovered

NOTE Confidence: 0.9011822

00:33:37.276 --> 00:33:39.628 as a source of Factor 8,

NOTE Confidence: 0.9011822

00:33:39.630 --> 00:33:42.087 and that quickly gave way to the

NOTE Confidence: 0.9011822

00:33:42.087 --> 00:33:44.120 use of factor concentrates either

NOTE Confidence: 0.9011822

00:33:44.120 --> 00:33:46.360 factor 8 or factor 9.

NOTE Confidence: 0.9011822

00:33:46.360 --> 00:33:48.535 Purified from the plasma of

NOTE Confidence: 0.9011822

00:33:48.535 --> 00:33:50.710 10s of thousands of donors.

NOTE Confidence: 0.9011822

00:33:50.710 --> 00:33:52.015 And of course,

NOTE Confidence: 0.9011822

00:33:52.015 --> 00:33:53.755 while this advanced care,

NOTE Confidence: 0.9011822

00:33:53.760 --> 00:33:56.142 it also exposed individuals to a

NOTE Confidence: 0.9011822

00:33:56.142 --> 00:33:58.670 number of viral viral particles and

NOTE Confidence: 0.9011822

00:33:58.670 --> 00:34:01.701 hepatitis C and HIV became a very

NOTE Confidence: 0.9011822

00:34:01.701 --> 00:34:04.199 significant problem in this population.

NOTE Confidence: 0.9011822

00:34:04.200 --> 00:34:06.780 And then in the early 90s

NOTE Confidence: 0.9011822

00:34:06.780 --> 00:34:08.980 recombinant factors 8:00 and 9:00,

NOTE Confidence: 0.9011822

00:34:08.980 --> 00:34:12.025 or produced and for the developed world,

NOTE Confidence: 0.9011822

00:34:12.030 --> 00:34:14.495 where economically this was allowable

NOTE Confidence: 0.9011822

00:34:14.495 --> 00:34:16.960 of the treatment of hemophilia

NOTE Confidence: 0.9011822

00:34:17.036 --> 00:34:19.430 with recombinant factors 8 and 9.

NOTE Confidence: 0.9011822

00:34:19.430 --> 00:34:22.735 Became really the standard of

NOTE Confidence: 0.9011822

00:34:22.735 --> 00:34:26.040 care up until very recently.

NOTE Confidence: 0.9011822

00:34:26.040 --> 00:34:29.196 There are now about 145 federally

NOTE Confidence: 0.9011822

00:34:29.196 --> 00:34:31.300 funded hemophilia treatment centers

NOTE Confidence: 0.9011822

00:34:31.376 --> 00:34:34.120 in this country and of course jeliz is

NOTE Confidence: 0.9011822

00:34:34.120 --> 00:34:37.169 one of those is one of those centers.

NOTE Confidence: 0.9011822

00:34:37.170 --> 00:34:38.400 And the therapeutic.

NOTE Confidence: 0.9011822

00:34:38.400 --> 00:34:40.450 The approach in clinical issues

NOTE Confidence: 0.9011822

00:34:40.450 --> 00:34:41.650 are outlined here.

NOTE Confidence: 0.9011822

00:34:41.650 --> 00:34:43.912 Patients with hemophilia can either be

NOTE Confidence: 0.9011822

00:34:43.912 --> 00:34:46.375 treated in what's known as on-demand

NOTE Confidence: 0.9011822

00:34:46.375 --> 00:34:48.159 or episodic factor replacement,

NOTE Confidence: 0.9011822

00:34:48.160 --> 00:34:50.692 which is the treatment with Ivy

NOTE Confidence: 0.9011822

00:34:50.692 --> 00:34:54.284 Factor 8 or factor 9 to treat a

NOTE Confidence: 0.9011822

00:34:54.284 --> 00:34:56.100 bleed or prophylactic therapy.

NOTE Confidence: 0.9011822

00:34:56.100 --> 00:34:57.393 An inhibitor development,

NOTE Confidence: 0.9011822

00:34:57.393 --> 00:34:59.979 that is an Allo antibody directed

NOTE Confidence: 0.9011822

00:34:59.979 --> 00:35:02.159 against Factor 8 or less commonly,

NOTE Confidence: 0.9011822

00:35:02.160 --> 00:35:04.848 factor 9 is a significant problem

NOTE Confidence: 0.9011822

00:35:04.848 --> 00:35:07.918 for patients and may occur in 30 or

NOTE Confidence: 0.9011822

00:35:07.918 --> 00:35:10.455 40% of individuals with hemophilia A

NOTE Confidence: 0.9011822

00:35:10.455 --> 00:35:12.690 and makes treatment very difficult

NOTE Confidence: 0.9011822

00:35:12.765 --> 00:35:15.145 and the goals of therapy are really

NOTE Confidence: 0.9011822

00:35:15.145 --> 00:35:16.165 here to prevent

NOTE Confidence: 0.85170436

00:35:16.241 --> 00:35:17.984 any bleeding. If possible,

NOTE Confidence: 0.85170436

00:35:17.984 --> 00:35:20.606 prevent joint disease and optimize a

NOTE Confidence: 0.85170436

00:35:20.606 --> 00:35:23.528 quality of life for these individuals.

NOTE Confidence: 0.85170436

00:35:23.530 --> 00:35:25.224 And the infusion of factor 8 or

NOTE Confidence: 0.85170436

00:35:25.224 --> 00:35:27.318 factor 9 by patients is traditionally

NOTE Confidence: 0.85170436

00:35:27.318 --> 00:35:29.058 given at home intravenously.

NOTE Confidence: 0.85170436

00:35:29.060 --> 00:35:32.030 Patients from a very young age learn to start

NOTE Confidence: 0.85170436

00:35:32.030 --> 00:35:34.904 an Ivy and infuse factor 8 or factor 9,

NOTE Confidence: 0.85170436

00:35:34.910 --> 00:35:36.530 but because of the short

NOTE Confidence: 0.85170436

00:35:36.530 --> 00:35:37.826 half-life of these drugs,

NOTE Confidence: 0.85170436

00:35:37.830 --> 00:35:39.951 about 12 hours for factor 8 and

NOTE Confidence: 0.85170436

00:35:39.951 --> 00:35:42.379 18 to 24 hours for factor 9,

NOTE Confidence: 0.85170436

00:35:42.380 --> 00:35:44.676 they need to be administered two to

NOTE Confidence: 0.85170436

00:35:44.676 --> 00:35:46.597 three to sometimes four times per

NOTE Confidence: 0.85170436

00:35:46.597 --> 00:35:49.056 week to keep the factor levels in a

NOTE Confidence: 0.85170436

00:35:49.056 --> 00:35:50.826 range that will prevent bleeding.

NOTE Confidence: 0.85170436

00:35:50.830 --> 00:35:52.978 So this is an onerous thing

NOTE Confidence: 0.85170436

00:35:52.978 --> 00:35:54.410 for patients to do.

NOTE Confidence: 0.85170436

00:35:54.410 --> 00:35:57.662 And any advances here would be

NOTE Confidence: 0.85170436

00:35:57.662 --> 00:35:59.830 greatly appreciated by them.

NOTE Confidence: 0.85170436

00:35:59.830 --> 00:36:02.268 So here's the obligatory coagulations

NOTE Confidence: 0.85170436

00:36:02.268 --> 00:36:05.656 slide that I would like to show

NOTE Confidence: 0.85170436

00:36:05.656 --> 00:36:07.997 to to reinforce and emphasize

NOTE Confidence: 0.85170436

00:36:07.997 --> 00:36:11.308 the role that Factor 8 and factor

NOTE Confidence: 0.85170436

00:36:11.308 --> 00:36:13.580 9 having blood coagulation.

NOTE Confidence: 0.85170436

00:36:13.580 --> 00:36:17.304 So what we're seeing here is the

NOTE Confidence: 0.85170436

00:36:17.304 --> 00:36:20.041 tissue factor initiated pathway and

NOTE Confidence: 0.85170436

00:36:20.041 --> 00:36:23.173 activation of factor 10 by tissue

NOTE Confidence: 0.85170436

00:36:23.173 --> 00:36:25.915 factor 7A or activation by factor

NOTE Confidence: 0.85170436

00:36:25.915 --> 00:36:29.160 9 to 9 A by tissue factor 7A.

NOTE Confidence: 0.85170436

00:36:29.160 --> 00:36:32.560 And 9A is also able to activate 9:50

NOTE Confidence: 0.85170436

00:36:32.655 --> 00:36:36.055 A O2 pathways to get down to this

NOTE Confidence: 0.85170436

00:36:36.055 --> 00:36:38.630 all important enzyme factor 10A,

NOTE Confidence: 0.85170436

00:36:38.630 --> 00:36:40.922 and in this latter reaction factor

NOTE Confidence: 0.85170436

00:36:40.922 --> 00:36:43.885 8 serves as a cofactor for the

NOTE Confidence: 0.85170436

00:36:43.885 --> 00:36:45.238 enzyme factor 9A.

NOTE Confidence: 0.85170436

00:36:45.240 --> 00:36:48.166 To act on its substrate factor 10

NOTE Confidence: 0.85170436

00:36:48.166 --> 00:36:50.785 and increases the rate of reaction

NOTE Confidence: 0.85170436

00:36:50.785 --> 00:36:53.767 hundreds of 1000 fold when factor 8

NOTE Confidence: 0.85170436

00:36:53.856 --> 00:36:56.495 is able to align the substrate and

NOTE Confidence: 0.85170436

00:36:56.495 --> 00:36:58.899 enzyme on a phospholipid surface in

NOTE Confidence: 0.85170436

00:36:58.899 --> 00:37:02.978 the correct in. In the correct fashion.

NOTE Confidence: 0.85170436

00:37:02.980 --> 00:37:05.212 One other thing to mention about

NOTE Confidence: 0.85170436

00:37:05.212 --> 00:37:08.141 Factor 8 before we get into some of

NOTE Confidence: 0.85170436

00:37:08.141 --> 00:37:10.610 the details of the advances is that

NOTE Confidence: 0.85170436

00:37:10.610 --> 00:37:13.290 factor 8 travels if you will in the

NOTE Confidence: 0.85170436

00:37:13.290 --> 00:37:15.410 blood bound to von Willebrand factor.

NOTE Confidence: 0.85170436

00:37:15.410 --> 00:37:17.979 Von Willebrand factor is seen here in

NOTE Confidence: 0.85170436

00:37:17.979 --> 00:37:20.018 this linear structure at the bottom,

NOTE Confidence: 0.85170436

00:37:20.020 --> 00:37:22.505 factor 8 is the yellow diagram above,

NOTE Confidence: 0.85170436

00:37:22.510 --> 00:37:25.345 and the binding of factor 8 von

NOTE Confidence: 0.85170436

00:37:25.345 --> 00:37:26.937 Willibrand factor enhances the

NOTE Confidence: 0.85170436

00:37:26.937 --> 00:37:29.086 half life of factor 8 from about

NOTE Confidence: 0.85170436

00:37:29.086 --> 00:37:31.029 2 hours to about 12 hours.

NOTE Confidence: 0.85170436

00:37:31.030 --> 00:37:34.117 So this is a very important interaction.

NOTE Confidence: 0.85170436

00:37:34.120 --> 00:37:36.220 And just to point out here,

NOTE Confidence: 0.85170436

00:37:36.220 --> 00:37:37.955 'cause this will become important

NOTE Confidence: 0.85170436

00:37:37.955 --> 00:37:40.096 later is that the binding site

NOTE Confidence: 0.85170436

00:37:40.096 --> 00:37:42.178 on von Willebrand factor is these

NOTE Confidence: 0.85170436

00:37:42.178 --> 00:37:43.219 two protein domains,

NOTE Confidence: 0.85170436

00:37:43.220 --> 00:37:44.970 designated D prime and D3,

NOTE Confidence: 0.85170436

00:37:44.970 --> 00:37:46.998 and another important point is there

NOTE Confidence: 0.85170436

00:37:46.998 --> 00:37:49.769 appears to be a large portion of the

NOTE Confidence: 0.85170436

00:37:49.769 --> 00:37:52.320 factor 8 molecules termed the B domain,

NOTE Confidence: 0.85170436

00:37:52.320 --> 00:37:55.120 which is not required for factor 8 function,

NOTE Confidence: 0.85170436

00:37:55.120 --> 00:37:57.706 so you could remove that domain

NOTE Confidence: 0.85170436

00:37:57.706 --> 00:38:01.138 and in fact factor 8 has a similar

NOTE Confidence: 0.85170436

00:38:01.138 --> 00:38:04.260 activity than it does with that domain.

NOTE Confidence: 0.85170436

00:38:04.260 --> 00:38:06.885 So the advances in care of hemophilia

NOTE Confidence: 0.85170436

00:38:06.885 --> 00:38:09.641 really over the past five to six

NOTE Confidence: 0.85170436

00:38:09.641 --> 00:38:11.975 years come into three different areas.

NOTE Confidence: 0.85170436

00:38:11.980 --> 00:38:13.138 One is extended,

NOTE Confidence: 0.85170436

00:38:13.138 --> 00:38:14.296 half-life factor concentrates,

NOTE Confidence: 0.85170436

00:38:14.300 --> 00:38:16.225 allowing for patients to infuse

NOTE Confidence: 0.85170436

00:38:16.225 --> 00:38:16.995 less frequently.

NOTE Confidence: 0.85170436

00:38:17.000 --> 00:38:19.310 The development of non factor 8

NOTE Confidence: 0.85170436

00:38:19.310 --> 00:38:20.465 or 9 therapeutics,

NOTE Confidence: 0.85170436

00:38:20.470 --> 00:38:23.530 and then gene therapy and we'll

NOTE Confidence: 0.85170436

00:38:23.530 --> 00:38:25.570 go through these individually

NOTE Confidence: 0.85170436

00:38:25.662 --> 00:38:28.084 in the next 15 minutes or so.

NOTE Confidence: 0.85170436

00:38:28.090 --> 00:38:30.155 So the extended Half-life products

NOTE Confidence: 0.85170436

00:38:30.155 --> 00:38:32.220 have been produced by manipulating

NOTE Confidence: 0.85170436

00:38:32.285 --> 00:38:33.505 the recombinant factor eight

NOTE Confidence: 0.85170436

00:38:33.505 --> 00:38:35.335 or nine in a number of

NOTE Confidence: 0.85449994

00:38:35.401 --> 00:38:37.850 different ways, many of which are familiar

NOTE Confidence: 0.85449994

00:38:37.850 --> 00:38:39.861 to you by either adding polyethylene

NOTE Confidence: 0.85449994

00:38:39.861 --> 00:38:42.598 glycol or conjugating the factor to the

NOTE Confidence: 0.85449994

00:38:42.598 --> 00:38:45.248 FC portion of immunoglobulin or albumen,

NOTE Confidence: 0.85449994

00:38:45.250 --> 00:38:46.742 to improve half-life, or,

NOTE Confidence: 0.85449994

00:38:46.742 --> 00:38:48.980 in the case of factor 8,

NOTE Confidence: 0.85449994

00:38:48.980 --> 00:38:51.774 to remove that B domain, which causes

NOTE Confidence: 0.85449994

00:38:51.774 --> 00:38:55.043 a slight increase in the half life.

NOTE Confidence: 0.85449994

00:38:55.050 --> 00:38:57.626 And there are now a number of products

NOTE Confidence: 0.85449994

00:38:57.626 --> 00:39:00.476 that have been approved for use at

NOTE Confidence: 0.85449994

00:39:00.476 --> 00:39:02.180 our extended Half-life products,

NOTE Confidence: 0.85449994

00:39:02.180 --> 00:39:04.015 and I'll draw your attention

NOTE Confidence: 0.85449994

00:39:04.015 --> 00:39:06.680 to the last three on this list.

NOTE Confidence: 0.85449994

00:39:06.680 --> 00:39:09.179 These are factor 9 products which have

NOTE Confidence: 0.85449994

00:39:09.179 --> 00:39:11.179 been manipulated by these methods,

NOTE Confidence: 0.85449994

00:39:11.180 --> 00:39:14.268 seen here and the half life of these

NOTE Confidence: 0.85449994

00:39:14.268 --> 00:39:16.982 products has been extended from 18 to

NOTE Confidence: 0.85449994

00:39:16.982 --> 00:39:20.177 24 hours to upwards of 90 or 100 hours.

NOTE Confidence: 0.85449994

00:39:20.180 --> 00:39:23.444 So this is allowed patients with factor 9

NOTE Confidence: 0.85449994

00:39:23.444 --> 00:39:26.336 deficiency or hemophilia B to be treated.

NOTE Confidence: 0.85449994

00:39:26.340 --> 00:39:27.267 Once a week,

NOTE Confidence: 0.85449994

00:39:27.267 --> 00:39:30.510 once every 10 days and in some circumstances,

NOTE Confidence: 0.85449994

00:39:30.510 --> 00:39:32.400 even once every two weeks.

NOTE Confidence: 0.85449994

00:39:32.400 --> 00:39:34.235 So a significant advance for

NOTE Confidence: 0.85449994

00:39:34.235 --> 00:39:36.070 people needing to give intravenous

NOTE Confidence: 0.85449994

00:39:36.135 --> 00:39:37.707 therapy themselves at home.

NOTE Confidence: 0.85449994

00:39:37.710 --> 00:39:40.734 The advances in hemophilia A with factor 8.

NOTE Confidence: 0.85449994

00:39:40.740 --> 00:39:41.119 However,

NOTE Confidence: 0.85449994

00:39:41.119 --> 00:39:43.393 a much more modest with this

NOTE Confidence: 0.85449994

00:39:43.393 --> 00:39:44.530 type of manipulation,

NOTE Confidence: 0.85449994

00:39:44.530 --> 00:39:46.784 and it turns out that the the

NOTE Confidence: 0.85449994

00:39:46.784 --> 00:39:48.633 degradation in the catabolism and

NOTE Confidence: 0.85449994

00:39:48.633 --> 00:39:50.648 clearance from the circulation of

NOTE Confidence: 0.85449994

00:39:50.648 --> 00:39:53.911 factor 8 is much more linked to the

NOTE Confidence: 0.85449994

00:39:53.911 --> 00:39:55.891 clearance of von Willebrand factor,

NOTE Confidence: 0.85449994

00:39:55.900 --> 00:39:58.570 the protein that it's bound to.

NOTE Confidence: 0.85449994

00:39:58.570 --> 00:40:00.328 So making modifications in the FAQ.

NOTE Confidence: 0.85449994

00:40:00.330 --> 00:40:03.246 After 8 molecule has really had

NOTE Confidence: 0.85449994

00:40:03.246 --> 00:40:05.828 minimal effect up until recently

NOTE Confidence: 0.85449994

00:40:05.828 --> 00:40:08.020 on Factor 8 Half-life.

NOTE Confidence: 0.85449994

00:40:08.020 --> 00:40:10.778 So an interesting construct has been devised,

NOTE Confidence: 0.85449994

00:40:10.780 --> 00:40:13.460 and it's shown on the top panel here

NOTE Confidence: 0.85449994

00:40:13.460 --> 00:40:16.461 and in this construct the D prime and

NOTE Confidence: 0.85449994

00:40:16.461 --> 00:40:19.450 D3 regions of von Willebrand factor,

NOTE Confidence: 0.85449994

00:40:19.450 --> 00:40:21.808 the binding region to factor 8,

NOTE Confidence: 0.85449994

00:40:21.810 --> 00:40:24.922 is linked to an FC portion of an

NOTE Confidence: 0.85449994

00:40:24.922 --> 00:40:26.954 immunoglobulin and linked to the

NOTE Confidence: 0.85449994

00:40:26.954 --> 00:40:29.294 B domain less factor 8 molecule,

NOTE Confidence: 0.85449994

00:40:29.300 --> 00:40:31.658 which also has linked on at

NOTE Confidence: 0.85449994

00:40:31.658 --> 00:40:32.837 this hydrophilic polypeptide,

NOTE Confidence: 0.85449994

00:40:32.840 --> 00:40:35.598 which also can extend the half life.

NOTE Confidence: 0.85449994

00:40:35.600 --> 00:40:39.216 So this product has been called bib 001.

NOTE Confidence: 0.85449994

00:40:39.220 --> 00:40:40.680 And was treated with.

NOTE Confidence: 0.85449994

00:40:40.680 --> 00:40:43.324 Was used to treat a handful of

NOTE Confidence: 0.85449994

00:40:43.324 --> 00:40:45.189 patients in a safety study,

NOTE Confidence: 0.85449994

00:40:45.190 --> 00:40:46.935 and those results were were

NOTE Confidence: 0.85449994

00:40:46.935 --> 00:40:49.149 reported in the New England Journal

NOTE Confidence: 0.85449994

00:40:49.149 --> 00:40:51.159 of Medicine earlier this year,

NOTE Confidence: 0.85449994

00:40:51.160 --> 00:40:53.010 and patients were either treated

NOTE Confidence: 0.85449994

00:40:53.010 --> 00:40:55.597 at two different doses of this new

NOTE Confidence: 0.85449994

00:40:55.597 --> 00:40:57.589 product and the factor a clearance

NOTE Confidence: 0.85449994

00:40:57.589 --> 00:40:59.528 from the circulation was compared

NOTE Confidence: 0.85449994

00:40:59.528 --> 00:41:01.940 to the typical factor 8 clearance

NOTE Confidence: 0.85449994

00:41:01.940 --> 00:41:04.618 seen in the lighter blue bars here

NOTE Confidence: 0.85449994

00:41:04.618 --> 00:41:07.198 and what you can see I think,

NOTE Confidence: 0.85449994

00:41:07.200 --> 00:41:10.863 is that the half life of this newer product.

NOTE Confidence: 0.85449994

00:41:10.870 --> 00:41:12.868 Is now about two days increased,

NOTE Confidence: 0.85449994

00:41:12.870 --> 00:41:15.166 about five or six fold the half life

NOTE Confidence: 0.85449994

00:41:15.166 --> 00:41:17.548 of the standard factor 8 product.

NOTE Confidence: 0.85449994

00:41:17.550 --> 00:41:19.895 So this this product is now in

NOTE Confidence: 0.85449994

00:41:19.895 --> 00:41:21.797 large scale clinical trials and I

NOTE Confidence: 0.85449994

00:41:21.797 --> 00:41:24.202 think in the next year or two we

NOTE Confidence: 0.85449994

00:41:24.202 --> 00:41:26.227 should have some more information,

NOTE Confidence: 0.85449994

00:41:26.230 --> 00:41:28.774 and this may be an advanced

NOTE Confidence: 0.85449994

00:41:28.774 --> 00:41:31.860 for for some of our patients.

NOTE Confidence: 0.85449994

00:41:31.860 --> 00:41:33.636 So let me shift for a minute for

NOTE Confidence: 0.85449994

00:41:33.636 --> 00:41:35.799 the to the non factor product for

NOTE Confidence: 0.85449994

00:41:35.799 --> 00:41:37.832 the treatment of hemophilia and I

NOTE Confidence: 0.85449994

00:41:37.832 --> 00:41:39.108 think their significant advance

NOTE Confidence: 0.85449994

00:41:39.108 --> 00:41:41.370 has been made here and there are

NOTE Confidence: 0.85449994

00:41:41.370 --> 00:41:43.350 three drugs that will talk about

NOTE Confidence: 0.85449994

00:41:43.350 --> 00:41:45.428 will really focus primarily on this

NOTE Confidence: 0.85449994

00:41:45.428 --> 00:41:47.450 first drug which is called EMAS

NOTE Confidence: 0.84887415

00:41:47.511 --> 00:41:50.895 ISM AB. A nemesis Omab is a

NOTE Confidence: 0.84887415

00:41:50.895 --> 00:41:52.668 bispecific monoclonal antibody.

NOTE Confidence: 0.84887415

00:41:52.670 --> 00:41:56.086 That binds the factor 9 and factor 10,

NOTE Confidence: 0.84887415

00:41:56.090 --> 00:41:59.514 so it simulates the activity of Factor 8.

NOTE Confidence: 0.84887415

00:41:59.520 --> 00:42:01.974 Remember that factor 8 is able

NOTE Confidence: 0.84887415

00:42:01.974 --> 00:42:04.580 to colocalize factor 9 and factor

NOTE Confidence: 0.84887415

00:42:04.580 --> 00:42:06.790 10 on a phospholipid surface.

NOTE Confidence: 0.84887415

00:42:06.790 --> 00:42:10.024 This antibody is able to bind factor

NOTE Confidence: 0.84887415

00:42:10.024 --> 00:42:14.057 9A and factor 10 in the circulation an

NOTE Confidence: 0.84887415

00:42:14.057 --> 00:42:17.529 again simulate the activity of Factor 8.

NOTE Confidence: 0.84887415

00:42:17.530 --> 00:42:21.148 So this drug is not exactly like Factor 8.

NOTE Confidence: 0.84887415

00:42:21.150 --> 00:42:21.952 There are.

NOTE Confidence: 0.84887415

00:42:21.952 --> 00:42:23.957 There are certain differences here.

NOTE Confidence: 0.84887415

00:42:23.960 --> 00:42:26.774 It binds to factor 8 and nine

NOTE Confidence: 0.84887415

00:42:26.774 --> 00:42:27.980 in the circulation,

NOTE Confidence: 0.84887415

00:42:27.980 --> 00:42:30.386 not just on the phospholipid membrane.

NOTE Confidence: 0.84887415

00:42:30.390 --> 00:42:31.998 It has different infinities

NOTE Confidence: 0.84887415

00:42:31.998 --> 00:42:34.008 for the substrate and enzyme,

NOTE Confidence: 0.84887415

00:42:34.010 --> 00:42:36.782 and whether or not that becomes an

NOTE Confidence: 0.84887415

00:42:36.782 --> 00:42:39.892 issue for this drug will only know

NOTE Confidence: 0.84887415

00:42:39.892 --> 00:42:42.652 as more experience is is accumulated.

NOTE Confidence: 0.84887415

00:42:42.660 --> 00:42:43.426 But nonetheless,

NOTE Confidence: 0.84887415

00:42:43.426 --> 00:42:46.107 this drug is really shown dramatic activity,

NOTE Confidence: 0.84887415

00:42:46.110 --> 00:42:48.854 so this this is a study that was

NOTE Confidence: 0.84887415

00:42:48.854 --> 00:42:51.697 published a few years ago in the

NOTE Confidence: 0.84887415

00:42:51.697 --> 00:42:53.767 New England Journal of Medicine.

NOTE Confidence: 0.84887415

00:42:53.770 --> 00:42:56.612 Here we had patients who have hemophilia

NOTE Confidence: 0.84887415

00:42:56.612 --> 00:42:58.748 A with inhibitors to factor 8,

NOTE Confidence: 0.84887415

00:42:58.750 --> 00:43:01.326 so a challenging group of patients to

NOTE Confidence: 0.84887415

00:43:01.326 --> 00:43:03.703 treat were treated either with their

NOTE Confidence: 0.84887415

00:43:03.703 --> 00:43:05.708 typical regimen of recombinant factor

NOTE Confidence: 0.84887415

00:43:05.708 --> 00:43:07.982 7A or factor 8, bypassing activity,

NOTE Confidence: 0.84887415

00:43:07.982 --> 00:43:10.824 or with Emma system AB given by

NOTE Confidence: 0.84887415

00:43:10.824 --> 00:43:12.730 subcutaneous injection once a week

NOTE Confidence: 0.84887415

00:43:12.730 --> 00:43:14.525 and the annual bleeding rate.

NOTE Confidence: 0.84887415

00:43:14.530 --> 00:43:17.099 Is been been described on this slide

NOTE Confidence: 0.84887415

00:43:17.099 --> 00:43:20.532 here and you could see if we just look

NOTE Confidence: 0.84887415

00:43:20.532 --> 00:43:23.457 at these blue histograms for a minute here.

NOTE Confidence: 0.84887415

00:43:23.460 --> 00:43:26.496 The annualized bleeding rate in the

NOTE Confidence: 0.84887415

00:43:26.496 --> 00:43:28.969 EMA system app Prophylaxis Group

NOTE Confidence: 0.84887415

00:43:28.969 --> 00:43:31.905 was about five or six and it was

NOTE Confidence: 0.84887415

00:43:31.905 --> 00:43:34.558 almost 30 in the standard of care.

NOTE Confidence: 0.84887415

00:43:34.560 --> 00:43:36.532 Treatment of patients with

NOTE Confidence: 0.84887415

00:43:36.532 --> 00:43:38.504 hemophilia A and inhibitors.

NOTE Confidence: 0.84887415

00:43:38.510 --> 00:43:40.834 So a really significant

NOTE Confidence: 0.84887415

00:43:40.834 --> 00:43:43.158 advantage for these individuals.

NOTE Confidence: 0.84887415

00:43:43.160 --> 00:43:45.421 And then a second study was published

NOTE Confidence: 0.84887415

00:43:45.421 --> 00:43:47.770 with looked at patients with hemophilia

NOTE Confidence: 0.84887415

00:43:47.770 --> 00:43:49.950 A without inhibitors and these.

NOTE Confidence: 0.84887415

00:43:49.950 --> 00:43:51.830 This was a randomized trial.

NOTE Confidence: 0.84887415

00:43:51.830 --> 00:43:53.610 Patients were treated with one

NOTE Confidence: 0.84887415

00:43:53.610 --> 00:43:56.425 of two doses of Emma's is a map

NOTE Confidence: 0.84887415

00:43:56.425 --> 00:43:58.357 either given weekly or every other

NOTE Confidence: 0.84887415

00:43:58.357 --> 00:44:00.499 week by subcutaneous injection,

NOTE Confidence: 0.84887415

00:44:00.500 --> 00:44:02.008 compared with no prophylaxis.

NOTE Confidence: 0.84887415

00:44:02.008 --> 00:44:04.270 About 100 patients in the trial,

NOTE Confidence: 0.84887415

00:44:04.270 --> 00:44:06.465 and again the annual annualized

NOTE Confidence: 0.84887415

00:44:06.465 --> 00:44:08.660 bleeding rate went from about

NOTE Confidence: 0.84887415

00:44:08.741 --> 00:44:10.397 40 to about one or two.