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

 $00{:}00{:}05{.}100 \dashrightarrow 00{:}00{:}07{.}655$  children tests and Jacob and just

NOTE Confidence: 0.83471704

 $00{:}00{:}07{.}655 \dashrightarrow 00{:}00{:}09{.}983$  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

 $00:00:21.180 \longrightarrow 00:00:24.435$  Well, thank you, so let's now turn

NOTE Confidence: 0.86117405

 $00{:}00{:}24.435 \dashrightarrow 00{:}00{:}28.108$  to our first of two great speakers.

NOTE Confidence: 0.86117405

 $00{:}00{:}28.110 \dashrightarrow 00{:}00{:}30.894$  We were very fortunate this year

NOTE Confidence: 0.86117405

 $00{:}00{:}30{.}894 \dashrightarrow 00{:}00{:}33{.}560$  to recruit Doctor Jeffrey Ishizuka.

NOTE Confidence: 0.86117405

 $00:00:33.560 \rightarrow 00:00:38.026$  Jeff is an assistant professor of medicine.

NOTE Confidence: 0.86117405

 $00{:}00{:}38.030 \dashrightarrow 00{:}00{:}39.377$  And Jeff's work.

NOTE Confidence: 0.86117405

 $00{:}00{:}39{.}377 \dashrightarrow 00{:}00{:}41.622$  Previously at Harvard was was

NOTE Confidence: 0.86117405

 $00{:}00{:}41.622 \dashrightarrow 00{:}00{:}44.408$  focused on the biology of T cells.

NOTE Confidence: 0.86117405

 $00:00:44.410 \rightarrow 00:00:46.162$  Discovering knew better understanding

- NOTE Confidence: 0.86117405
- $00{:}00{:}46.162 \dashrightarrow 00{:}00{:}48.790$  of that biology and and and

 $00{:}00{:}48.857 \dashrightarrow 00{:}00{:}50.417$  ultimately leveraging that science

NOTE Confidence: 0.86117405

 $00:00:50.417 \longrightarrow 00:00:53.708$  to what is likely to be the next

NOTE Confidence: 0.86117405

 $00:00:53.708 \rightarrow 00:00:55.460$  generation of amino therapies.

NOTE Confidence: 0.86117405

 $00:00:55.460 \rightarrow 00:00:58.001$  And we're really very fortunate to have

NOTE Confidence: 0.86117405

 $00{:}00{:}58{.}001 \dashrightarrow 00{:}01{:}01{.}381$  Jeff as one of our physician scientists in

NOTE Confidence: 0.86117405

 $00{:}01{:}01{.}381 \dashrightarrow 00{:}01{:}04{.}380$  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

 $00:01:06.510 \dashrightarrow 00:01:09.276$  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

 $00:01:10.920 \rightarrow 00:01:13.528$  Jeff really excited to hear about your work.

NOTE Confidence: 0.86117405

 $00{:}01{:}13.530 \dashrightarrow 00{:}01{:}17.040$  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 $\operatorname{-->}$ 00:01:19.536 you so much Charlie, really appreciate

NOTE Confidence: 0.84582025

 $00:01:19.536 \rightarrow 00:01:22.659$  it and let me just project my slides.

 $00:01:22.660 \rightarrow 00:01:25.204$  How there we go?

NOTE Confidence: 0.84582025

 $00:01:25.204 \dashrightarrow 00:01:27.954$  Yes, thank you so much and thank you

NOTE Confidence: 0.84582025

 $00:01:27.954 \rightarrow 00:01:29.809$  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

 $00{:}01{:}32.234 \dashrightarrow 00{:}01{:}34.398$  about some of the work we've done.

NOTE Confidence: 0.84582025

 $00:01:34.400 \dashrightarrow 00:01:36.515$  Targeting double stranded RNA in NOTE Confidence: 0.84582025

 $00:01:36.515 \rightarrow 00:01:38.207$  order to overcome immunotherapy

NOTE Confidence: 0.84582025

 $00{:}01{:}38{.}207 \dashrightarrow 00{:}01{:}39{.}891$  resistance and also update on

NOTE Confidence: 0.84582025

 $00{:}01{:}39{.}891 \dashrightarrow 00{:}01{:}41{.}685$  other ongoing projects in the lab.

NOTE Confidence: 0.84582025

 $00:01:41.690 \rightarrow 00:01:45.270$  This is my disclosure slide.

NOTE Confidence: 0.84582025

 $00:01:45.270 \rightarrow 00:01:48.310$  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

 $00:01:50.800 \dashrightarrow 00:01:54.398$  which is likely familiar to this audience.

NOTE Confidence: 0.84582025

 $00:01:54.400 \dashrightarrow 00:01:56.035$  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

 $00:01:57.716 \rightarrow 00:01:59.168$  with immune checkpoint blockade.

- NOTE Confidence: 0.84582025
- $00:01:59.170 \longrightarrow 00:02:00.193$  In this case,
- NOTE Confidence: 0.84582025
- $00{:}02{:}00{.}193 \dashrightarrow 00{:}02{:}01{.}898$  with antibodies targeting PD 1C,
- NOTE Confidence: 0.84582025
- $00{:}02{:}01{.}900 \dashrightarrow 00{:}02{:}04{.}640$  TL A4 or the combination.
- NOTE Confidence: 0.84582025
- $00:02:04.640 \longrightarrow 00:02:06.482$  I wanted to start here because
- NOTE Confidence: 0.84582025
- $00{:}02{:}06.482 \dashrightarrow 00{:}02{:}08.043$  Melanoma has been something of
- NOTE Confidence: 0.84582025
- 00:02:08.043 --> 00:02:09.723 a touch<br/>stone for the use of
- NOTE Confidence: 0.84582025
- $00:02:09.723 \longrightarrow 00:02:11.310$  checkpoint blockade in solid tumors.
- NOTE Confidence: 0.84582025
- $00:02:11.310 \longrightarrow 00:02:12.755$  First indication approved and remains
- NOTE Confidence: 0.84582025
- $00{:}02{:}12.755 \dashrightarrow 00{:}02{:}14.836$  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
- $00:02:16.301 \longrightarrow 00:02:17.969$  in these data are outstanding,
- NOTE Confidence: 0.84582025
- $00{:}02{:}17{.}970 \dashrightarrow 00{:}02{:}19{.}788$  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
- $00{:}02{:}21.610 \dashrightarrow 00{:}02{:}23.125$  which had an overall survival
- NOTE Confidence: 0.84582025
- $00:02:23.125 \longrightarrow 00:02:25.600$  of five to 10% at five years.
- NOTE Confidence: 0.84582025

- $00:02:25.600 \rightarrow 00:02:26.020$  However,
- NOTE Confidence: 0.84582025
- $00{:}02{:}26.020 \dashrightarrow 00{:}02{:}27.700$  even in this disease,
- NOTE Confidence: 0.84582025
- 00:02:27.700 --> 00:02:29.140 large proportion of patients
- NOTE Confidence: 0.84582025
- $00:02:29.140 \longrightarrow 00:02:30.580$  don't experience durable benefit.
- NOTE Confidence: 0.84582025
- $00{:}02{:}30{.}580 \dashrightarrow 00{:}02{:}32{.}992$  The situation which is which is
- NOTE Confidence: 0.84582025
- $00:02:32.992 \rightarrow 00:02:35.103$  actually more challenging in other
- NOTE Confidence: 0.84582025
- $00:02:35.103 \rightarrow 00:02:37.689$  diseases where responses are less good.
- NOTE Confidence: 0.84582025
- $00:02:37.690 \longrightarrow 00:02:39.363$  And this is really the focus of
- NOTE Confidence: 0.84582025
- $00{:}02{:}39{.}363 \dashrightarrow 00{:}02{:}40{.}811$  our work to improve responses
- NOTE Confidence: 0.84582025
- $00{:}02{:}40{.}811 \dashrightarrow 00{:}02{:}42{.}815$  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
- $00:02:47.840 \rightarrow 00:02:49.454$  my blockade is rapidly reshaping the
- NOTE Confidence: 0.8365905
- $00:02:49.454 \rightarrow 00:02:51.420$  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
- $00{:}02{:}53{.}212 \dashrightarrow 00{:}02{:}55{.}762$  had to go through and update this slide
- NOTE Confidence: 0.8365905
- $00:02:55.762 \longrightarrow 00:02:57.506$  because indications have nearly doubled

- NOTE Confidence: 0.8365905
- $00:02:57.506 \rightarrow 00:02:59.106$  since its original publication by

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

 $00:03:03.209 \rightarrow 00:03:04.879$  this emerging data very closely,

NOTE Confidence: 0.8365905

 $00{:}03{:}04.880 \dashrightarrow 00{:}03{:}07.850$  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

 $00:03:14.249 \rightarrow 00:03:16.529$  continues through lymphomas and solid

NOTE Confidence: 0.8365905

 $00:03:16.529 \rightarrow 00:03:18.629$  tumors of desperate tissue origins.

NOTE Confidence: 0.8365905

 $00{:}03{:}18.630 \dashrightarrow 00{:}03{:}20.414$  Combination approaches have also

NOTE Confidence: 0.8365905

 $00{:}03{:}20{.}414 \dashrightarrow 00{:}03{:}21{.}752$  proliferated, including approaches,

NOTE Confidence: 0.8365905

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

NOTE Confidence: 0.8365905

 $00:03:23.694 \longrightarrow 00:03:26.110$  breast cancer, and others.

NOTE Confidence: 0.8365905

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

NOTE Confidence: 0.8365905

 $00:03:27.385 \rightarrow 00:03:29.085$  combinations of checkpoint inhibitors

 $00:03:29.085 \rightarrow 00:03:30.920$  with other checkpoint inhibitors,

NOTE Confidence: 0.8365905

 $00{:}03{:}30{.}920 \dashrightarrow 00{:}03{:}32{.}228$  chemotherapies and touristing

NOTE Confidence: 0.8365905

 $00:03:32.228 \longrightarrow 00:03:33.100$  kinese inhibitors,

NOTE Confidence: 0.8365905

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

NOTE Confidence: 0.8365905

 $00:03:35.720 \dashrightarrow 00:03:38.779$  have played critical roles in this dance.

NOTE Confidence: 0.84251946

 $00:03:41.580 \longrightarrow 00:03:43.230$  Still, for all the advances,

NOTE Confidence: 0.84251946

 $00{:}03{:}43{.}230 \dashrightarrow 00{:}03{:}45{.}726$  there have been a lot of failures and

NOTE Confidence: 0.84251946

 $00:03:45.726 \dashrightarrow 00:03:48.158$  there remain a lot of ongoing challenges.

NOTE Confidence: 0.84251946

 $00{:}03{:}48{.}160 \dashrightarrow 00{:}03{:}50{.}128$  For most, many patients don't respond,

NOTE Confidence: 0.84251946

 $00{:}03{:}50{.}130 \dashrightarrow 00{:}03{:}51{.}780$  indeed, considered across all indications,

NOTE Confidence: 0.84251946

 $00{:}03{:}51{.}780 \dashrightarrow 00{:}03{:}53{.}894$  most patients don't respond in a few

NOTE Confidence: 0.84251946

 $00{:}03{:}53{.}894 \dashrightarrow 00{:}03{:}55{.}885$  of the response rates listed are

NOTE Confidence: 0.84251946

 $00{:}03{:}55{.}885 \dashrightarrow 00{:}03{:}57{.}937$  really based on earlier trials that

NOTE Confidence: 0.84251946

 $00:03:57.937 \rightarrow 00:04:00.028$  likely overestimated response rates.

NOTE Confidence: 0.84251946

 $00:04:00.030 \longrightarrow 00:04:01.920$  Many of them also include

NOTE Confidence: 0.84251946

 $00:04:01.920 \longrightarrow 00:04:02.676$  biomarker cutpoints,

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

 $00:04:09.233 \rightarrow 00:04:11.319$  of big areas in which we can improve.

NOTE Confidence: 0.84251946

 $00:04:11.320 \longrightarrow 00:04:14.365$  1st for all of the new indications,

NOTE Confidence: 0.84251946

 $00:04:14.370 \longrightarrow 00:04:16.710$  few combinations involving novel

NOTE Confidence: 0.84251946

 $00:04:16.710 \longrightarrow 00:04:19.050$  targets have been approved.

NOTE Confidence: 0.84251946

 $00:04:19.050 \longrightarrow 00:04:21.918$  2nd, we have a limited mechanistic

NOTE Confidence: 0.84251946

 $00:04:21.918 \longrightarrow 00:04:24.849$  understanding of how these agents work.

NOTE Confidence: 0.84251946

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

NOTE Confidence: 0.84251946

 $00:04:25.130 \longrightarrow 00:04:27.090$  the biomarkers that we used to deploy

NOTE Confidence: 0.84251946

 $00{:}04{:}27.090 \dashrightarrow 00{:}04{:}29.009$  them lack sensitivity and specificity,

NOTE Confidence: 0.84251946

 $00{:}04{:}29{.}010 \dashrightarrow 00{:}04{:}31{.}810$  and there's not a great way to rationally

NOTE Confidence: 0.84251946

 $00{:}04{:}31{.}810 \dashrightarrow 00{:}04{:}33{.}488$  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,

 $00:04:39.140 \longrightarrow 00:04:40.876$  not so much in the interest of

NOTE Confidence: 0.84928113

 $00{:}04{:}40.876 \dashrightarrow 00{:}04{:}42.184$  an extensive overview for which

NOTE Confidence: 0.84928113

 $00:04:42.184 \longrightarrow 00:04:43.474$  we wouldn't have time today,

NOTE Confidence: 0.84928113

 $00{:}04{:}43{.}480 \dashrightarrow 00{:}04{:}45{.}688$  but in terms of the pathways that have

NOTE Confidence: 0.84928113

 $00{:}04{:}45.688 \dashrightarrow 00{:}04{:}48.308$  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

 $00{:}04{:}50{.}606 \dashrightarrow 00{:}04{:}53{.}172$  by Merck of over 300 different patients

NOTE Confidence: 0.84928113

 $00{:}04{:}53.172 \dashrightarrow 00{:}04{:}55.530$  across 22 different tumor tissue types.

NOTE Confidence: 0.84928113

 $00{:}04{:}55{.}530 \dashrightarrow 00{:}04{:}59{.}130$  These figures show responses.

NOTE Confidence: 0.84928113

 $00:04:59.130 \longrightarrow 00:05:01.450$  Non response defined as CR

NOTE Confidence: 0.84928113

 $00{:}05{:}01{.}450 \dashrightarrow 00{:}05{:}04{.}190$  or PR versus no CR PR.

NOTE Confidence: 0.84928113

 $00{:}05{:}04{.}190 \dashrightarrow 00{:}05{:}05{.}942$  When graphed with tumor mutational burden

NOTE Confidence: 0.84928113

 $00{:}05{:}05{.}942 \dashrightarrow 00{:}05{:}09{.}354$  on the Y axis and a gene expression profile

NOTE Confidence: 0.84928113

 $00{:}05{:}09{.}354 \dashrightarrow 00{:}05{:}10.668$  representing tumor microenvironment,

NOTE Confidence: 0.84928113

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

NOTE Confidence: 0.84928113

 $00:05:12.470 \longrightarrow 00:05:14.270$  inflammation on the X axis.

 $00{:}05{:}14.270 \dashrightarrow 00{:}05{:}17.258$  The genes in this profile are listed in the

NOTE Confidence: 0.84928113

 $00{:}05{:}17.258 \dashrightarrow 00{:}05{:}20.028$  upper right here and notably include PDL,

NOTE Confidence: 0.84928113

 $00{:}05{:}20{.}030 \dashrightarrow 00{:}05{:}23{.}333$  one among them as well as several MHC related

NOTE Confidence: 0.84928113

 $00:05:23.333 \rightarrow 00:05:26.147$  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

 $00{:}05{:}30{.}230 \dashrightarrow 00{:}05{:}32{.}148$  is often used as a surrogate for

NOTE Confidence: 0.82015085

 $00{:}05{:}32{.}148 \dashrightarrow 00{:}05{:}34{.}071$  too many antigens and the gene

NOTE Confidence: 0.82015085

 $00:05:34.071 \rightarrow 00:05:35.455$  expression profile really points

NOTE Confidence: 0.82015085

 $00:05:35.455 \rightarrow 00:05:37.100$  to information of the tumor,

NOTE Confidence: 0.82015085

 $00{:}05{:}37{.}100 \dashrightarrow 00{:}05{:}38{.}858$  micro environment and the authors make

NOTE Confidence: 0.82015085

 $00:05:38.858 \dashrightarrow 00:05:40.840$  two points that are important here.

NOTE Confidence: 0.82015085

 $00{:}05{:}40{.}840 \dashrightarrow 00{:}05{:}43{.}003$  First, that these are two of the

NOTE Confidence: 0.82015085

 $00:05:43.003 \dashrightarrow 00:05:44.580$  strongest predictors they could find.

NOTE Confidence: 0.82015085

 $00{:}05{:}44.580 \dashrightarrow 00{:}05{:}46.230$  Reviewing one of the largest

NOTE Confidence: 0.82015085

 $00:05:46.230 \dashrightarrow 00:05:47.550$  and most comprehensive datasets

 $00{:}05{:}47.550 \dashrightarrow 00{:}05{:}48.950$  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

 $00:05:50.534 \rightarrow 00:05:52.409$  that they appear to predict response

NOTE Confidence: 0.82015085

 $00:05:52.409 \rightarrow 00:05:53.937$  independently of one another.

NOTE Confidence: 0.82015085

 $00{:}05{:}53{.}940 \dashrightarrow 00{:}05{:}56{.}271$  That is to say that although the

NOTE Confidence: 0.82015085

 $00{:}05{:}56{.}271 \dashrightarrow 00{:}05{:}58{.}379$  best responses are in that kind of.

NOTE Confidence: 0.82015085

 $00:05:58.380 \longrightarrow 00:06:01.334$  Upper right quadrant that you actually get

NOTE Confidence: 0.82015085

 $00:06:01.334 \rightarrow 00:06:04.567$  a good number of responses in a T cell.

NOTE Confidence: 0.82015085

 $00{:}06{:}04.570 \dashrightarrow 00{:}06{:}06{.}074$  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

 $00:06:14.910 \longrightarrow 00:06:16.540$  on TMB or antigen load,

NOTE Confidence: 0.7979447

 $00:06:16.540 \longrightarrow 00:06:18.190$  so it's obviously an important consideration.

NOTE Confidence: 0.7979447

 $00:06:18.190 \dashrightarrow 00:06:20.122$  Instead, I'm just going to talk about

NOTE Confidence: 0.7979447

 $00:06:20.122 \rightarrow 00:06:20.950$  tumor microenvironment information,

- NOTE Confidence: 0.7979447
- $00:06:20.950 \longrightarrow 00:06:23.158$  which is really the focus of our lab.

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

 $00:06:26.571 \rightarrow 00:06:27.975$  have established inadequate tumor

NOTE Confidence: 0.7979447

 $00:06:27.975 \dashrightarrow 00:06:28.677$  microenvironment information.

NOTE Confidence: 0.7979447

 $00{:}06{:}28.680 \dashrightarrow 00{:}06{:}30.661$  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

 $00{:}06{:}34.200 \dashrightarrow 00{:}06{:}36.965$  this occurs in immune desert type tumors,

NOTE Confidence: 0.7979447

 $00:06:36.970 \dashrightarrow 00:06:39.346$  which entirely lack T cell infiltrate,

NOTE Confidence: 0.7979447

 $00{:}06{:}39{.}350 \dashrightarrow 00{:}06{:}40{.}602$  as depicted here. However,

NOTE Confidence: 0.7979447

 $00:06:40.602 \rightarrow 00:06:43.830$  it can also occur in a different phenotype.

NOTE Confidence: 0.7979447

 $00{:}06{:}43.830 \dashrightarrow 00{:}06{:}45.146$  The so-called immune excluded

NOTE Confidence: 0.7979447

 $00{:}06{:}45{.}146 \dashrightarrow 00{:}06{:}47{.}120$  tumors which have anti tumor immune

NOTE Confidence: 0.7979447

 $00{:}06{:}47.171 \dashrightarrow 00{:}06{:}48.739$  cells at the site of the tumor,

 $00:06:48.740 \longrightarrow 00:06:49.900$  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

 $00:06:52.840 \longrightarrow 00:06:54.620$  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

 $00{:}06{:}57{.}428 \dashrightarrow 00{:}06{:}59{.}426$  inflamed type of tumor that have

NOTE Confidence: 0.7979447

 $00{:}06{:}59{.}426 \dashrightarrow 00{:}07{:}01{.}046$  diffuse infiltration of T cells

NOTE Confidence: 0.7979447

00:07:01.111 $\operatorname{-->}$ 00:07:02.938 that tend to be PD L1 positive,

NOTE Confidence: 0.7979447

 $00{:}07{:}02{.}940 \dashrightarrow 00{:}07{:}05{.}845$  and these are the ones that we

NOTE Confidence: 0.7979447

 $00{:}07{:}05.845 \dashrightarrow 00{:}07{:}08.559$  believe respond best to immunother apy.

NOTE Confidence: 0.7979447

 $00{:}07{:}08.560 \dashrightarrow 00{:}07{:}09.202$  To date,

NOTE Confidence: 0.7979447

 $00{:}07{:}09{.}202 \dashrightarrow 00{:}07{:}10{.}807$  there's been progress in identifying

NOTE Confidence: 0.7979447

00:07:10.807 --> 00:07:12.686 the<br/>rapeutic strategies to enhance this

NOTE Confidence: 0.7979447

 $00:07:12.686 \rightarrow 00:07:13.988$  tumor microenvironment information,

NOTE Confidence: 0.7979447

 $00:07:13.990 \longrightarrow 00:07:16.144$  many of which involve either real

- NOTE Confidence: 0.7979447
- $00:07:16.144 \rightarrow 00:07:18.355$  or simulated infection of the tumor

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

NOTE Confidence: 0.7979447

 $00{:}07{:}20{.}140 \dashrightarrow 00{:}07{:}22{.}429$  and I think about them in kind

NOTE Confidence: 0.7979447

 $00:07:22.429 \longrightarrow 00:07:24.130$  of two big buckets.

NOTE Confidence: 0.7979447

 $00:07:24.130 \longrightarrow 00:07:26.224$  The first is the provision of

NOTE Confidence: 0.7979447

 $00:07:26.224 \longrightarrow 00:07:27.620$  exogenous sources that mimic

NOTE Confidence: 0.7979447

 $00:07:27.690 \longrightarrow 00:07:29.560$  nucleic acid ligands to tumors.

NOTE Confidence: 0.7979447

 $00:07:29.560 \longrightarrow 00:07:31.008$  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

 $00:07:33.180 \dashrightarrow 00:07:34.992$  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

 $00{:}07{:}37{.}260 \dashrightarrow 00{:}07{:}40{.}445$  The other is the induction of endogenous

NOTE Confidence: 0.7979447

 $00{:}07{:}40.445 \dashrightarrow 00{:}07{:}42.900$  sources of nucleic acid ligands,

NOTE Confidence: 0.7979447

 $00{:}07{:}42.900 \dashrightarrow 00{:}07{:}44.310$  primarily endogenous retroviruses,

NOTE Confidence: 0.7979447

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

 $00:07:47.130 \longrightarrow 00:07:50.630$  alualu repeats in humans.

NOTE Confidence: 0.7979447

 $00{:}07{:}50{.}630 \dashrightarrow 00{:}07{:}52{.}952$  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

 $00:07:57.470 \rightarrow 00:08:00.067$  So my interest in turning these cold

NOTE Confidence: 0.781458700000001

 $00{:}08{:}00{.}067 \dashrightarrow 00{:}08{:}01{.}968$  microenvironments hot and kind of

NOTE Confidence: 0.781458700000001

 $00:08:01.968 \dashrightarrow 00:08:04.152$  providing these logins to tuners really NOTE Confidence: 0.781458700000001

 $00:08:04.152 \rightarrow 00:08:06.624$  developed out of work in the Canings

NOTE Confidence: 0.781458700000001

 $00:08:06.624 \rightarrow 00:08:08.665$  lab was finishing my postdoctoral work

NOTE Confidence: 0.781458700000001

 $00{:}08{:}08{.}665 \dashrightarrow 00{:}08{:}11{.}220$  there and through the type of experiment

NOTE Confidence: 0.781458700000001

 $00{:}08{:}11.220 \dashrightarrow 00{:}08{:}13.716$  that I'm showing here on the left,

NOTE Confidence: 0.781458700000001

 $00{:}08{:}13.720 \dashrightarrow 00{:}08{:}16.240$  you have kind of a transplantable tumor

NOTE Confidence: 0.781458700000001

 $00{:}08{:}16.240 \dashrightarrow 00{:}08{:}18.770$  cell line, something like a B16 Melanoma,

NOTE Confidence: 0.781458700000001

 $00:08:18.770 \dashrightarrow 00:08:21.658$  and the way the experiment works is to,

NOTE Confidence: 0.781458700000001

 $00{:}08{:}21.660 \dashrightarrow 00{:}08{:}23.998$  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

 $00:08:26.273 \longrightarrow 00:08:27.865$  that knockout thousands of.

- NOTE Confidence: 0.781458700000001
- 00:08:27.870 --> 00:08:29.220 Immunologically relevant genes.
- NOTE Confidence: 0.781458700000001
- $00:08:29.220 \longrightarrow 00:08:32.789$  In the genome and then to kind of
- NOTE Confidence: 0.781458700000001
- $00:08:32.789 \longrightarrow 00:08:34.835$  select those guides until you have
- NOTE Confidence: 0.781458700000001
- $00:08:34.835 \dashrightarrow 00:08:37.620$  a pool of knockout tumor cell lines
- NOTE Confidence: 0.781458700000001
- $00{:}08{:}37{.}620 \dashrightarrow 00{:}08{:}40{.}146$  that is then implanted into mice
- NOTE Confidence: 0.781458700000001
- $00:08:40.150 \rightarrow 00:08:41.994$  under increasing immune selective
- NOTE Confidence: 0.781458700000001
- 00:08:41.994 --> 00:08:43.838 pressure from extremely immunodeficient
- NOTE Confidence: 0.781458700000001
- $00:08:43.838 \dashrightarrow 00:08:46.381$  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
- $00:08:47.870 \rightarrow 00:08:49.710$  2 mice treated with immunotherapy.
- NOTE Confidence: 0.781458700000001
- $00:08:49.710 \longrightarrow 00:08:50.802$  In this case,
- NOTE Confidence: 0.781458700000001
- $00:08:50.802 \dashrightarrow 00:08:52.622$  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
- $00:08:57.636 \rightarrow 00:08:58.980$  immunotherapy treatment regiment.
- NOTE Confidence: 0.781458700000001

 $00:08:58.980 \dashrightarrow 00:09:01.320$  Would grow these tumors for about

NOTE Confidence: 0.781458700000001

 $00:09:01.320 \longrightarrow 00:09:03.899$  2 weeks and then remove them.

NOTE Confidence: 0.781458700000001

 $00:09:03.900 \rightarrow 00:09:06.360$  Harvested tumors and sequence the sequence.

NOTE Confidence: 0.781458700000001

 $00:09:06.360 \rightarrow 00:09:08.544$  The barcodes sequence the guides using

NOTE Confidence: 0.781458700000001

 $00{:}09{:}08.544 \dashrightarrow 00{:}09{:}10.870$  them as barcodes and quantitating.

NOTE Confidence: 0.781458700000001

 $00{:}09{:}10.870 \dashrightarrow 00{:}09{:}12.595$  Enrichment and depletion of each

NOTE Confidence: 0.781458700000001

 $00:09:12.595 \rightarrow 00:09:14.810$  guy and the way we interpreted

NOTE Confidence: 0.781458700000001

 $00:09:14.810 \rightarrow 00:09:17.288$  this experiment was to compare high

NOTE Confidence: 0.781458700000001

 $00:09:17.288 \dashrightarrow 00:09:19.889$  to lower mean selective pressure.

NOTE Confidence: 0.781458700000001

 $00:09:19.890 \longrightarrow 00:09:21.530$  So immunotherapy treated to

NOTE Confidence: 0.781458700000001

 $00:09:21.530 \dashrightarrow 00:09:23.110$  immunodeficient mice, for example,

NOTE Confidence: 0.781458700000001

 $00{:}09{:}23.110 \dashrightarrow 00{:}09{:}25.390$  and to interpret it that guides

NOTE Confidence: 0.781458700000001

 $00{:}09{:}25{.}390 \dashrightarrow 00{:}09{:}26{.}860$  that were depleted.

NOTE Confidence: 0.781458700000001

 $00:09:26.860 \rightarrow 00:09:28.090$  Comparing height alone,

NOTE Confidence: 0.781458700000001

 $00:09:28.090 \rightarrow 00:09:30.140$  selective pressure represented Jews that,

NOTE Confidence: 0.781458700000001

 $00:09:30.140 \longrightarrow 00:09:32.060$  when deleted, convert sensitivity.

- NOTE Confidence: 0.781458700000001
- $00:09:32.060 \longrightarrow 00:09:33.980$  To the mean system,
- NOTE Confidence: 0.781458700000001
- $00:09:33.980 \rightarrow 00:09:36.208$  and therefore potential targets
- NOTE Confidence: 0.781458700000001
- $00:09:36.208 \longrightarrow 00:09:37.879$  for combination therapy.
- NOTE Confidence: 0.781458700000001
- $00:09:37.880 \longrightarrow 00:09:38.654$  In contrast,
- NOTE Confidence: 0.781458700000001
- $00:09:38.654 \dashrightarrow 00:09:40.589$  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
- $00:09:42.120 \longrightarrow 00:09:44.304$  to US jeans that were lost made
- NOTE Confidence: 0.781458700000001
- $00:09:44.304 \rightarrow 00:09:45.790$  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
- $00{:}09{:}50{.}264 \dashrightarrow 00{:}09{:}52{.}047$  found this way actually ended up in
- NOTE Confidence: 0.8393771
- $00{:}09{:}52{.}047 \dashrightarrow 00{:}09{:}54{.}178$  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
- $00:09:56.240 \longrightarrow 00:09:58.445$  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
- $00{:}10{:}00{.}800 \dashrightarrow 00{:}10{:}03{.}329$  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

 $00{:}10{:}05{.}619 \dashrightarrow 00{:}10{:}08{.}079$  from the study of exone rees 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

 $00{:}10{:}13.656 \dashrightarrow 00{:}10{:}16.694$  the potential to form double stranded RNA.

NOTE Confidence: 0.8393771

 $00{:}10{:}16{.}700 \dashrightarrow 00{:}10{:}18{.}855$  These could be small interspersed

NOTE Confidence: 0.8393771

 $00{:}10{:}18.855 \dashrightarrow 00{:}10{:}21.010$  nuclear elements and obvious retrovirus.

NOTE Confidence: 0.8393771

 $00:10:21.010 \rightarrow 00:10:23.158$  Endogenous retroviruses are long

NOTE Confidence: 0.8393771

 $00{:}10{:}23.158 \dashrightarrow 00{:}10{:}26.380$  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

 $00{:}10{:}28.788 \dashrightarrow 00{:}10{:}30.879$  Co evolved with these elements.

NOTE Confidence: 0.8393771

 $00{:}10{:}30{.}880 \dashrightarrow 00{:}10{:}32{.}656$  With these kind of viral remnants

NOTE Confidence: 0.8393771

 $00{:}10{:}32.656 \dashrightarrow 00{:}10{:}34.732$  in many cases and ourselves have

NOTE Confidence: 0.8393771

 $00{:}10{:}34.732 \dashrightarrow 00{:}10{:}36.817$  developed systems to regulate double

NOTE Confidence: 0.8393771

 $00:10:36.817 \longrightarrow 00:10:38.966$  stranded RNA sensing to distinguish

NOTE Confidence: 0.8393771

 $00{:}10{:}38.966 \dashrightarrow 00{:}10{:}40.630$  between double stranded RNA.

- NOTE Confidence: 0.8393771
- $00{:}10{:}40.630 \dashrightarrow 00{:}10{:}43.162$  That's a result of normal cellular

 $00:10:43.162 \rightarrow 00:10:45.460$  activity and exogenous viral threats.

NOTE Confidence: 0.8393771

 $00:10:45.460 \longrightarrow 00:10:47.780$  And so we thought that by targeting some

NOTE Confidence: 0.8393771

 $00:10:47.780 \rightarrow 00:10:50.587$  of the genes that control this regulation,

NOTE Confidence: 0.8393771

 $00{:}10{:}50{.}590 \dashrightarrow 00{:}10{:}52{.}300$  we might sensitize tumor cells

NOTE Confidence: 0.8393771

 $00:10:52.300 \longrightarrow 00:10:53.326$  to tumor therapy.

NOTE Confidence: 0.8393771

 $00:10:53.330 \rightarrow 00:10:55.717$  Trigger this kind of anti virus state.

NOTE Confidence: 0.78675884

 $00:10:57.800 \longrightarrow 00:11:00.537$  And the top hits that we discovered

NOTE Confidence: 0.78675884

 $00{:}11{:}00{.}537 \dashrightarrow 00{:}11{:}02{.}963$  through this process in the antiviral

NOTE Confidence: 0.78675884

 $00:11:02.963 \longrightarrow 00:11:04.928$  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

 $00{:}11{:}07{.}162 \dashrightarrow 00{:}11{:}09{.}680$  that acts on double stranded RNA.

NOTE Confidence: 0.78675884

 $00{:}11{:}09{.}680 \dashrightarrow 00{:}11{:}12{.}445$  It has a long cytoplasmic P-150 isoform.

NOTE Confidence: 0.78675884

 $00{:}11{:}12{.}450 \dashrightarrow 00{:}11{:}15{.}408$  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.

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

NOTE Confidence: 0.78675884

 $00:11:20.758 \rightarrow 00:11:22.284$  catalyze the conversion of a denosine

NOTE Confidence: 0.78675884

 $00{:}11{:}22{.}284 \dashrightarrow 00{:}11{:}24{.}720$  to in a scene and double stranded RNA.

NOTE Confidence: 0.78675884

 $00:11:24.720 \longrightarrow 00:11:27.264$  And it's thought that in so doing it

NOTE Confidence: 0.78675884

 $00{:}11{:}27.264 \dashrightarrow 00{:}11{:}29.630$  prevents double stranded RNA sensing in

NOTE Confidence: 0.78675884

 $00:11:29.630 \longrightarrow 00:11:31.705$  the triggering of antiviral immunity.

NOTE Confidence: 0.78675884

 $00:11:31.710 \longrightarrow 00:11:33.024$  Kind of autoimmunity.

NOTE Confidence: 0.78675884

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

NOTE Confidence: 0.78675884

 $00{:}11{:}33.462 \dashrightarrow 00{:}11{:}36.090$  there is an autoimmune syndrome called

NOTE Confidence: 0.78675884

 $00{:}11{:}36{.}150 \dashrightarrow 00{:}11{:}38{.}310$  Acardi Goutieres syndrome that is

NOTE Confidence: 0.78675884

 $00{:}11{:}38{.}310 \dashrightarrow 00{:}11{:}40{.}038$  associated with biallelic mutations

NOTE Confidence: 0.78675884

 $00:11:40.038 \dashrightarrow 00:11:42.510$  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

 $00{:}11{:}47{.}452 \dashrightarrow 00{:}11{:}49{.}432$  the parents of affected patients

- NOTE Confidence: 0.78675884
- $00{:}11{:}49{.}432 \dashrightarrow 00{:}11{:}51{.}818$  who have monolith mutations in the

 $00:11:51.818 \rightarrow 00:11:53.718$  catalytic domain have evidence of

NOTE Confidence: 0.78675884

 $00:11:53.718 \rightarrow 00:11:55.194$  increased signatures of interferon

NOTE Confidence: 0.78675884

 $00:11:55.194 \rightarrow 00:11:56.839$  gene expression in the blood,

NOTE Confidence: 0.78675884

 $00:11:56.840 \rightarrow 00:11:59.096$  but have no detectable disease phenotype,

NOTE Confidence: 0.78675884

 $00{:}11{:}59{.}100 \dashrightarrow 00{:}12{:}01{.}739$  suggesting that there's a gene dose effect.

NOTE Confidence: 0.8696512

 $00:12:03.950 \longrightarrow 00:12:05.654$  So to begin to validate our

NOTE Confidence: 0.8696512

 $00:12:05.654 \longrightarrow 00:12:07.900$  one as a potential drug target

NOTE Confidence: 0.8696512

 $00{:}12{:}07{.}900 \dashrightarrow 00{:}12{:}09{.}460$  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

 $00{:}12{:}11.812 \dashrightarrow 00{:}12{:}14.650$  lines again using the B16 Melanoma model.

NOTE Confidence: 0.8696512

 $00{:}12{:}14.650 \dashrightarrow 00{:}12{:}16.415$  This transplantable tumor model and

NOTE Confidence: 0.8696512

 $00{:}12{:}16.415 \dashrightarrow 00{:}12{:}18.738$  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

 $00:12:20.230 \rightarrow 00:12:22.580$  It means selective pressure starting

 $00:12:22.580 \rightarrow 00:12:24.460$  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

 $00{:}12{:}30.690 \dashrightarrow 00{:}12{:}31.740$  In these mice,

NOTE Confidence: 0.8696512

 $00:12:31.740 \longrightarrow 00:12:33.840$  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

 $00{:}12{:}37.666 \dashrightarrow 00{:}12{:}39.440$  compared to controls and Gray,

NOTE Confidence: 0.8696512

 $00{:}12{:}39{.}440 \dashrightarrow 00{:}12{:}42{.}240$  and looking at tumor volume on the top,

NOTE Confidence: 0.8696512

 $00:12:42.240 \longrightarrow 00:12:43.990$  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

 $00:12:46.370 \longrightarrow 00:12:48.885$  decrease in the growth of the

NOTE Confidence: 0.8696512

 $00{:}12{:}48.885 \dashrightarrow 00{:}12{:}51.245$  Darnell tumors compared to controls.

NOTE Confidence: 0.8696512

 $00{:}12{:}51{.}250 \dashrightarrow 00{:}12{:}54{.}526$  And a minimal increase in survival.

NOTE Confidence: 0.8696512

 $00:12:54.530 \longrightarrow 00:12:55.164$  In contrast,

- NOTE Confidence: 0.8696512
- $00:12:55.164 \rightarrow 00:12:57.066$  when planted these tumors into wild

 $00{:}12{:}57.066 \dashrightarrow 00{:}12{:}59.347$  type mice with an intact immune system,

NOTE Confidence: 0.8696512

 $00:12:59.350 \longrightarrow 00:13:01.144$  you see a significant decrease in

NOTE Confidence: 0.8696512

 $00:13:01.144 \rightarrow 00:13:03.418$  the growth of tumors in a significant

NOTE Confidence: 0.8696512

 $00:13:03.418 \longrightarrow 00:13:05.113$  survival advantage for the mice.

NOTE Confidence: 0.8696512

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

NOTE Confidence: 0.8696512

 $00{:}13{:}05{.}470 \dashrightarrow 00{:}13{:}07{.}570$  when we implemented these tumors into

NOTE Confidence: 0.8696512

 $00:13:07.570 \rightarrow 00:13:09.620$  mice and treated with anti PD one,

NOTE Confidence: 0.8696512

 $00{:}13{:}09{.}620 \dashrightarrow 00{:}13{:}12{.}315$  we saw a near 100% cure rate for

NOTE Confidence: 0.8696512

 $00:13:12.315 \rightarrow 00:13:14.870$  mice treated that were a Darnall and

NOTE Confidence: 0.8696512

 $00{:}13{:}14.947 \dashrightarrow 00{:}13{:}17.866$  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

 $00{:}13{:}19{.}580 \dashrightarrow 00{:}13{:}20{.}948$  the mechanism of this,

NOTE Confidence: 0.8696512

 $00{:}13{:}20{.}950 \dashrightarrow 00{:}13{:}23{.}099$  we looked at the tumor micro environment

NOTE Confidence: 0.8696512

 $00{:}13{:}23.099 \dashrightarrow 00{:}13{:}25.212$  of untreated a Darnall and control

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

 $00{:}13{:}29{.}431 \dashrightarrow 00{:}13{:}31{.}973$  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

 $00:13:33.927 \rightarrow 00:13:35.997$  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

 $00{:}13{:}38{.}940 \dashrightarrow 00{:}13{:}40{.}655$  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

 $00{:}13{:}44{.}380 \dashrightarrow 00{:}13{:}45{.}940$  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

 $00{:}13{:}50.050 \dashrightarrow 00{:}13{:}52.200$  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

 $00:13:54.312 \rightarrow 00:13:56.250$  implantation in the untreated setting,

NOTE Confidence: 0.78991807

 $00:13:56.250 \rightarrow 00:13:58.090$  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
- $00{:}14{:}00{.}792 \dashrightarrow 00{:}14{:}03{.}516$  positive immune cells and a Darnell
- NOTE Confidence: 0.78991807
- $00{:}14{:}03.516 \dashrightarrow 00{:}14{:}05.496$  tumors compared with controls.
- NOTE Confidence: 0.78991807
- $00:14:05.500 \rightarrow 00:14:08.380$  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
- $00{:}14{:}15{.}190 \dashrightarrow 00{:}14{:}19{.}425$  gamma Delta T cells and NK cells.
- NOTE Confidence: 0.78991807
- $00:14:19.430 \longrightarrow 00:14:22.382$  In contrast, when we looked at
- NOTE Confidence: 0.78991807
- 00:14:22.382 --> 00:14:23.366 immunosuppressive populations,
- NOTE Confidence: 0.78991807
- $00:14:23.370 \rightarrow 00:14:25.342$  including mdse and tumor
- NOTE Confidence: 0.78991807
- $00{:}14{:}25{.}342 \dashrightarrow 00{:}14{:}26{.}328$  associated neutrophils,
- NOTE Confidence: 0.78991807
- $00:14:26.330 \rightarrow 00:14:29.792$  we saw significant increases in control
- NOTE Confidence: 0.78991807
- $00{:}14{:}29.792 \dashrightarrow 00{:}14{:}33.649$  tumors relative to a Darnall tumors.
- NOTE Confidence: 0.78991807
- $00:14:33.650 \rightarrow 00:14:35.460$  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

 $00:14:36.910 \rightarrow 00:14:39.076$  we perform single cell RNA sequencing.

NOTE Confidence: 0.78991807

 $00:14:39.080 \longrightarrow 00:14:41.495$  These are the populations we

NOTE Confidence: 0.78991807

 $00:14:41.495 \longrightarrow 00:14:43.427$  recovered with myeloid populations

NOTE Confidence: 0.78991807

 $00{:}14{:}43{.}427 \dashrightarrow 00{:}14{:}46{.}264$  in the upper right and T cell

NOTE Confidence: 0.78991807

 $00:14:46.264 \rightarrow 00:14:48.230$  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

 $00:14:49.542 \longrightarrow 00:14:51.182$  using these density plots that

NOTE Confidence: 0.78991807

 $00{:}14{:}51{.}182 \dashrightarrow 00{:}14{:}53{.}259$  we adapted for this purpose,

NOTE Confidence: 0.78991807

 $00{:}14{:}53.260 \dashrightarrow 00{:}14{:}55.843$  you get a strong signal from suppressive

NOTE Confidence: 0.78991807

 $00{:}14{:}55{.}843 \dashrightarrow 00{:}14{:}57{.}685$  myeloid populations and to like

NOTE Confidence: 0.78991807

 $00:14:57.685 \rightarrow 00:14:59.713$  macrophages and mdse in control tumors.

NOTE Confidence: 0.78991807

 $00{:}14{:}59{.}720 \dashrightarrow 00{:}15{:}01{.}874$  But a weaker signal from inflammatory

NOTE Confidence: 0.78991807

 $00:15:01.874 \longrightarrow 00:15:03.310$  monocytes and CD8T cells.

NOTE Confidence: 0.78991807

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

NOTE Confidence: 0.78991807

 $00:15:03.894 \rightarrow 00:15:05.646$  in the 8 Arnold tumors you

 $00:15:05.646 \rightarrow 00:15:07.880$  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

 $00{:}15{:}09{.}068 \dashrightarrow 00{:}15{:}11{.}456$  and and enrichment of single from

NOTE Confidence: 0.78991807

 $00:15:11.456 \rightarrow 00:15:13.356$  inflammatory monocytes and CD8T cells.

NOTE Confidence: 0.8100181

 $00{:}15{:}15{.}920 \dashrightarrow 00{:}15{:}17{.}795$  To understand what's driving this

NOTE Confidence: 0.8100181

 $00{:}15{:}17.795 \dashrightarrow 00{:}15{:}19.670$  change in the micro environment,

NOTE Confidence: 0.8100181

 $00:15:19.670 \longrightarrow 00:15:21.812$  we wanted to study the double

NOTE Confidence: 0.8100181

 $00{:}15{:}21.812 \dashrightarrow 00{:}15{:}23.670$  stranded RNA sensing pathways that

NOTE Confidence: 0.8100181

 $00{:}15{:}23.670 \dashrightarrow 00{:}15{:}25.485$  we thought could be associated

NOTE Confidence: 0.8100181

 $00:15:25.485 \rightarrow 00:15:27.550$  with the phenotypes we'd observed.

NOTE Confidence: 0.8100181

 $00{:}15{:}27{.}550 \dashrightarrow 00{:}15{:}30{.}070$  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

 $00{:}15{:}32{.}800 \dashrightarrow 00{:}15{:}35{.}299$  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

 $00:15:37.602 \rightarrow 00:15:39.547$  acids in double stranded RNA,

 $00:15:39.550 \rightarrow 00:15:41.186$  specifically protein kinase power

NOTE Confidence: 0.8100181

 $00{:}15{:}41{.}186 \dashrightarrow 00{:}15{:}42{.}822$  is associated with translation

NOTE Confidence: 0.8100181

 $00:15:42.822 \longrightarrow 00:15:44.418$  arrest in a pop ptosis.

NOTE Confidence: 0.8100181

 $00:15:44.420 \longrightarrow 00:15:46.810$  Upon binding double stranded RNA.

NOTE Confidence: 0.8100181

 $00{:}15{:}46.810 \dashrightarrow 00{:}15{:}50.058$  Where is MD5 regarding mass induced type

NOTE Confidence: 0.8100181

 $00{:}15{:}50.058 \dashrightarrow 00{:}15{:}53.129$  one interferon in the antiviral state?

NOTE Confidence: 0.8100181

 $00:15:53.130 \longrightarrow 00:15:56.028$  To test the role of each of these sensors,

NOTE Confidence: 0.8100181

 $00:15:56.030 \rightarrow 00:15:58.094$  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

 $00:15:59.844 \rightarrow 00:16:02.035$  lines and probe some of the in

NOTE Confidence: 0.8100181

 $00{:}16{:}02.035 \dashrightarrow 00{:}16{:}03.896$  vitro phenotypes that we previously

NOTE Confidence: 0.8100181

 $00:16:03.896 \rightarrow 00:16:06.230$  previously studied in a Darnell tumors.

NOTE Confidence: 0.8100181

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

NOTE Confidence: 0.8100181

 $00:16:06.644 \dashrightarrow 00:16:09.128$  we looked 1st at growth inhibition.

NOTE Confidence: 0.8100181

 $00{:}16{:}09{.}130 \dashrightarrow 00{:}16{:}11{.}200$  So when you stimulate control

NOTE Confidence: 0.8100181

 $00:16:11.200 \rightarrow 00:16:13.270$  tumors with interferon in vitro,

 $00:16:13.270 \rightarrow 00:16:16.959$  there's a slight defect in growth that's

NOTE Confidence: 0.8100181

 $00:16:16.959 \rightarrow 00:16:20.240$  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

 $00:16:22.160 \rightarrow 00:16:25.216$  we saw no effect of knocking out rig.

NOTE Confidence: 0.8100181

 $00{:}16{:}25{.}220 \dashrightarrow 00{:}16{:}27{.}947$  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

 $00{:}16{:}30{.}810 \dashrightarrow 00{:}16{:}33{.}649$  the levels observed in control tumors,

NOTE Confidence: 0.8100181

 $00:16:33.650 \longrightarrow 00:16:36.980$  suggesting a PQR was alone.

NOTE Confidence: 0.8100181

 $00{:}16{:}36{.}980 \dashrightarrow 00{:}16{:}38{.}840$  Responsible for the in vitro

NOTE Confidence: 0.8100181

 $00{:}16{:}38{.}840 \dashrightarrow 00{:}16{:}40{.}700$  growth defect that we'd observed.

NOTE Confidence: 0.8100181

 $00{:}16{:}40.700 \dashrightarrow 00{:}16{:}44.459$  We next looked at interferon beta production.

NOTE Confidence: 0.8100181

 $00{:}16{:}44{.}460 \dashrightarrow 00{:}16{:}47{.}439$  And this was again an in vitro Aliza and

NOTE Confidence: 0.8100181

 $00{:}16{:}47{.}439 \dashrightarrow 00{:}16{:}50{.}230$  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

- $00:16:53.526 \longrightarrow 00:16:54.350$  detectable interferon,
- NOTE Confidence: 0.8100181
- $00{:}16{:}54{.}350 \dashrightarrow 00{:}16{:}56{.}530$  whereas a Darnall tumors
- NOTE Confidence: 0.8100181
- $00{:}16{:}56{.}530 \dashrightarrow 00{:}16{:}58{.}165$  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
- $00{:}17{:}00{.}006 \dashrightarrow 00{:}17{:}02{.}221$  of Rig I suggesting that guy is
- NOTE Confidence: 0.8100181
- $00{:}17{:}02{.}221 \dashrightarrow 00{:}17{:}03{.}766$  not involved in the phenotype.
- NOTE Confidence: 0.8100181
- $00:17:03.770 \longrightarrow 00:17:04.080$  However,
- NOTE Confidence: 0.8100181
- $00:17:04.080 \rightarrow 00:17:05.630$  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
- $00{:}17{:}08.889 \dashrightarrow 00{:}17{:}10.917$  that all three of these sensors,
- NOTE Confidence: 0.8100181
- $00{:}17{:}10.920 \dashrightarrow 00{:}17{:}13.013$  or these two sensors in this adapter
- NOTE Confidence: 0.8100181
- $00:17:13.013 \rightarrow 00:17:15.280$  have a role to play in phenotype.
- NOTE Confidence: 0.767478799999999
- $00{:}17{:}17{.}480 \dashrightarrow 00{:}17{:}19{.}517$  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
- $00:17:21.313 \rightarrow 00:17:23.770$  was required for the in vivo phenotype of

 $00:17:23.770 \rightarrow 00:17:25.620$  sensitization to whom checkpoint blockade.

NOTE Confidence: 0.767478799999999

 $00{:}17{:}25.620 \dashrightarrow 00{:}17{:}27.988$  So we took our double and triple knock out

NOTE Confidence: 0.767478799999999

 $00{:}17{:}27{.}988 \dashrightarrow 00{:}17{:}30{.}297$  tumor cell lines and implanted them into

NOTE Confidence: 0.767478799999999

 $00:17:30.297 \rightarrow 00:17:33.246$  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

 $00{:}17{:}34{.}302 \dashrightarrow 00{:}17{:}37{.}150$  and as you can see in our control experiment,

NOTE Confidence: 0.767478799999999

 $00{:}17{:}37{.}150 \dashrightarrow 00{:}17{:}39{.}034$  control tumors continue to grow out

NOTE Confidence: 0.767478799999999

 $00:17:39.034 \rightarrow 00:17:41.461$  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

 $00:17:42.850 \longrightarrow 00:17:45.250$  you know, therapy.

NOTE Confidence: 0.767478799999999

 $00{:}17{:}45.250 \dashrightarrow 00{:}17{:}46.850$  This phenotype persisted following

NOTE Confidence: 0.767478799999999

 $00{:}17{:}46.850 \dashrightarrow 00{:}17{:}49.898$  loss of PQR, suggesting that PQR is

NOTE Confidence: 0.767478799999999

 $00{:}17{:}49.898 \dashrightarrow 00{:}17{:}52.670$  alone not required for the phenotype.

NOTE Confidence: 0.767478799999999

 $00:17:52.670 \longrightarrow 00:17:53.274$  Similarly.

NOTE Confidence: 0.767478799999999

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

 $00:17:56.900 \rightarrow 00:17:59.924$  suggesting MDA 5 alone does not

NOTE Confidence: 0.767478799999999

 $00:17:59.924 \rightarrow 00:18:01.436$  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

 $00:18:03.729 \longrightarrow 00:18:05.992$  are in MDA 5 together with eight

NOTE Confidence: 0.767478799999999

 $00:18:05.992 \longrightarrow 00:18:08.262$  or one we no longer observe any

NOTE Confidence: 0.767478799999999

 $00{:}18{:}08{.}262 \dashrightarrow 00{:}18{:}10{.}207$  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

 $00{:}18{:}12.262 \dashrightarrow 00{:}18{:}13.738$  treated with immunotherapy.

NOTE Confidence: 0.767478799999999

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

NOTE Confidence: 0.767478799999999

 $00{:}18{:}14.230 \dashrightarrow 00{:}18{:}16.408$  these results suggested to us that

NOTE Confidence: 0.767478799999999

 $00:18:16.408 \longrightarrow 00:18:18.758$  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

 $00:18:21.266 \rightarrow 00:18:23.052$  mediate sensitivity to no therapy

NOTE Confidence: 0.767478799999999

 $00:18:23.052 \rightarrow 00:18:25.117$  but that at least one is required.

NOTE Confidence: 0.782579

 $00{:}18{:}28{.}290 \dashrightarrow 00{:}18{:}30{.}270$  We next wanted to understand which

- NOTE Confidence: 0.782579
- $00:18:30.270 \rightarrow 00:18:32.002$  double stranded RNA sensing pathway

 $00{:}18{:}32{.}002 \dashrightarrow 00{:}18{:}34{.}114$  was required for the enhanced community

NOTE Confidence: 0.782579

 $00{:}18{:}34{.}114 \dashrightarrow 00{:}18{:}36{.}462$  filtration for the inflammation in the

NOTE Confidence: 0.782579

 $00:18:36.462 \rightarrow 00:18:38.527$  tumor microenvironment that we'd observed.

NOTE Confidence: 0.782579

 $00{:}18{:}38{.}530 \dashrightarrow 00{:}18{:}41{.}138$  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

 $00{:}18{:}42{.}940 \dashrightarrow 00{:}18{:}45{.}124$  In this time return to our habit of

NOTE Confidence: 0.782579

 $00:18:45.124 \rightarrow 00:18:47.340$  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

 $00:18:48.700 \longrightarrow 00:18:50.060$  separating out the cells,

NOTE Confidence: 0.782579

 $00:18:50.060 \longrightarrow 00:18:52.328$  and quantitating them.

NOTE Confidence: 0.782579

 $00{:}18{:}52{.}330 \dashrightarrow 00{:}18{:}56{.}635$  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

 $00{:}19{:}00{.}699 \dashrightarrow 00{:}19{:}02{.}959$  of immune cells that significantly

 $00:19:02.959 \rightarrow 00:19:05.490$  increased following loss of eight R1. NOTE Confidence: 0.782579  $00:19:05.490 \longrightarrow 00:19:06.190$  And Interestingly, NOTE Confidence: 0.782579  $00:19:06.190 \rightarrow 00:19:07.240$  this phenotype is, NOTE Confidence: 0.782579  $00:19:07.240 \rightarrow 00:19:08.920$  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  $00{:}19{:}13{.}393 \dashrightarrow 00{:}19{:}15{.}661$  MBA 5 and oblated following the NOTE Confidence: 0.782579  $00:19:15.661 \rightarrow 00:19:17.569$  loss of the two senses together. NOTE Confidence: 0.782579  $00{:}19{:}17{.}570 \dashrightarrow 00{:}19{:}19{.}420$  A similar pattern followed when NOTE Confidence: 0.782579  $00:19:19.420 \longrightarrow 00:19:21.670$  we looked at the proportion of NOTE Confidence: 0.782579  $00:19:21.670 \longrightarrow 00:19:23.662$  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  $00:19:25.848 \rightarrow 00:19:28.416$  increases in eight are null that NOTE Confidence: 0.782579  $00:19:28.416 \rightarrow 00:19:30.485$  persisted following loss of PQR NOTE Confidence: 0.782579  $00:19:30.485 \rightarrow 00:19:31.905$  was attenuated following loss

- NOTE Confidence: 0.782579
- $00:19:31.905 \rightarrow 00:19:34.234$  of MD5 with loss following the

 $00:19:34.234 \rightarrow 00:19:36.339$  loss of both sensors together.

NOTE Confidence: 0.782579

 $00:19:36.340 \rightarrow 00:19:39.175$  When we look at a immunosuppressive mdse,

NOTE Confidence: 0.782579

 $00{:}19{:}39{.}180 \dashrightarrow 00{:}19{:}41{.}265$  we saw the opposite pattern

NOTE Confidence: 0.782579

 $00{:}19{:}41{.}265 \dashrightarrow 00{:}19{:}43{.}350$  increases in control that persisted

NOTE Confidence: 0.782579

 $00{:}19{:}43.417 \dashrightarrow 00{:}19{:}45.267$  or work were even increased.

NOTE Confidence: 0.782579

 $00{:}19{:}45{.}270 \dashrightarrow 00{:}19{:}47{.}825$  Further following loss of PQR and no

NOTE Confidence: 0.782579

 $00:19:47.825 \rightarrow 00:19:50.211$  loss of the phenotype following loss

NOTE Confidence: 0.782579

 $00{:}19{:}50{.}211 \dashrightarrow 00{:}19{:}53{.}800$  of MDA 5 for the two sensors together.

NOTE Confidence: 0.78578705

 $00{:}19{:}56{.}900 \dashrightarrow 00{:}19{:}58{.}482$  This suggested to us that MBA five

NOTE Confidence: 0.78578705

 $00{:}19{:}58{.}482 \dashrightarrow 00{:}20{:}00{.}179$  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

 $00{:}20{:}02{.}304 \dashrightarrow 00{:}20{:}04{.}428$  inflammation may darnel tumors.

NOTE Confidence: 0.78578705

 $00:20:04.430 \longrightarrow 00:20:05.567$  To confirm this,

NOTE Confidence: 0.78578705

 $00{:}20{:}05{.}567 \dashrightarrow 00{:}20{:}08{.}220$  we looked at the production of interferon
$00{:}20{:}08{.}287 \dashrightarrow 00{:}20{:}10.873$  beta interferon gamma in the tumor

NOTE Confidence: 0.78578705

 $00{:}20{:}10.873 \dashrightarrow 00{:}20{:}13.190$  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

 $00{:}20{:}15{.}437 \dashrightarrow 00{:}20{:}17{.}651$  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

 $00{:}20{:}20{.}477 \dashrightarrow 00{:}20{:}23.015$  lost after law after loss of MD5 or the

NOTE Confidence: 0.78578705

 $00:20:23.015 \rightarrow 00:20:25.316$  two sensors together in the same pattern.

NOTE Confidence: 0.78578705

 $00:20:25.320 \longrightarrow 00:20:27.604$  Again looking at tumor

NOTE Confidence: 0.78578705

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

NOTE Confidence: 0.78578705

 $00:20:29.320 \longrightarrow 00:20:31.160$  So haven't seen having seen

NOTE Confidence: 0.78578705

 $00{:}20{:}31.160 \dashrightarrow 00{:}20{:}33.000$  this powerful dual mechanism for

NOTE Confidence: 0.78578705

 $00{:}20{:}33.068 \dashrightarrow 00{:}20{:}35.280$  sensitizing tumors to immunotherapy.

NOTE Confidence: 0.78578705

 $00{:}20{:}35{.}280 \dashrightarrow 00{:}20{:}38{.}008$  We asked whether loss of eight R1 was

NOTE Confidence: 0.78578705

 $00{:}20{:}38.008 \dashrightarrow 00{:}20{:}40.300$  sufficient to overcome commonly acquired

NOTE Confidence: 0.78578705

 $00:20:40.300 \rightarrow 00:20:43.378$  mechanisms of resistance to amino therapy,

NOTE Confidence: 0.78578705

 $00:20:43.380 \longrightarrow 00:20:44.553$  including genetic aberrations

- NOTE Confidence: 0.78578705
- $00{:}20{:}44.553 \dashrightarrow 00{:}20{:}46.508$  that have been identified as

 $00:20:46.508 \rightarrow 00:20:48.490$  enriched when comparing discordant,

NOTE Confidence: 0.78578705

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

NOTE Confidence: 0.78578705

 $00:20:48.916 \longrightarrow 00:20:49.342$  pretreatment,

NOTE Confidence: 0.78578705

 $00:20:49.342 \rightarrow 00:20:51.046$  and resistant posttreatment lesions.

NOTE Confidence: 0.78578705

 $00{:}20{:}51.050 \dashrightarrow 00{:}20{:}54.280$  Matched with the same patient.

NOTE Confidence: 0.78578705

 $00{:}20{:}54.280 \dashrightarrow 00{:}20{:}56.505$  Known mechanisms that fit this

NOTE Confidence: 0.78578705

 $00{:}20{:}56.505 \dashrightarrow 00{:}20{:}59.502$  description include the loss of MHC one

NOTE Confidence: 0.78578705

 $00{:}20{:}59{.}502 \dashrightarrow 00{:}21{:}01{.}952$  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

 $00{:}21{:}03.166 \dashrightarrow 00{:}21{:}04.774$  children expressing through Mino,

NOTE Confidence: 0.78578705

 $00{:}21{:}04.780 \dashrightarrow 00{:}21{:}06.800$  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

 $00{:}21{:}09{.}630 \dashrightarrow 00{:}21{:}10{.}440$  the stats.

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

NOTE Confidence: 0.81089616

 $00:21:16.080 \rightarrow 00:21:18.720$  as mediated by loss of data to microblogging

NOTE Confidence: 0.81089616

 $00:21:18.720 \longrightarrow 00:21:21.252$  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

 $00{:}21{:}23{.}970 \dashrightarrow 00{:}21{:}25{.}750$  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

 $00:21:27.530 \longrightarrow 00:21:29.852$  This time deleting beta 2 micro

NOTE Confidence: 0.81089616

 $00:21:29.852 \rightarrow 00:21:32.120$  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

 $00{:}21{:}34{.}324 \dashrightarrow 00{:}21{:}36{.}528$  control tumor cell lines.

NOTE Confidence: 0.81089616

 $00{:}21{:}36{.}530 \dashrightarrow 00{:}21{:}38{.}768$  To validate our model of resistance,

NOTE Confidence: 0.81089616

 $00{:}21{:}38{.}770 \dashrightarrow 00{:}21{:}41{.}442$  we compared control in beta two of null

NOTE Confidence: 0.81089616

 $00{:}21{:}41{.}442 \dashrightarrow 00{:}21{:}44{.}167$  tumors in the untreated that is dashed

NOTE Confidence: 0.81089616

 $00{:}21{:}44.167 \dashrightarrow 00{:}21{:}46.630$  line state versus the treated state.

NOTE Confidence: 0.81089616

 $00:21:46.630 \rightarrow 00:21:48.868$  That's the solid lines using again,

NOTE Confidence: 0.81089616

 $00:21:48.870 \rightarrow 00:21:50.922$  this strong immunotherapy treatment

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

NOTE Confidence: 0.81089616

 $00{:}21{:}54.000 \dashrightarrow 00{:}21{:}56.485$  And we did this because the normal

NOTE Confidence: 0.81089616

 $00{:}21{:}56{.}485 \dashrightarrow 00{:}21{:}58{.}113$  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

 $00{:}22{:}00{.}475 \dashrightarrow 00{:}22{:}02{.}851$  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

 $00{:}22{:}05{.}124 \dashrightarrow 00{:}22{:}07{.}880$  lost in the beta two unknown tumors.

NOTE Confidence: 0.81089616

 $00{:}22{:}07{.}880 \dashrightarrow 00{:}22{:}08{.}621$  And sure enough,

NOTE Confidence: 0.81089616

 $00{:}22{:}08.621 \dashrightarrow 00{:}22{:}11.179$  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

 $00:22:13.100 \longrightarrow 00:22:13.391$  Alternately,

NOTE Confidence: 0.81089616

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

NOTE Confidence: 0.81089616

 $00:22:15.428 \longrightarrow 00:22:16.480$  therapy treatment regiment,

NOTE Confidence: 0.81089616

 $00{:}22{:}16.480 \dashrightarrow 00{:}22{:}18.010$  but made it to heaven.

NOTE Confidence: 0.81089616

 $00{:}22{:}18.010 \dashrightarrow 00{:}22{:}19.846$  All tumors hardly respond at all.

 $00{:}22{:}22{.}400 \dashrightarrow 00{:}22{:}24.738$  We next looked at a Darnall tumors.

NOTE Confidence: 0.7943555

 $00{:}22{:}24.740 \dashrightarrow 00{:}22{:}26.255$  This is our positive control

NOTE Confidence: 0.7943555

 $00{:}22{:}26.255 \dashrightarrow 00{:}22{:}27.467$  experiment using strong again

NOTE Confidence: 0.7943555

 $00:22:27.467 \rightarrow 00:22:29.080$  with the rapy treatment regimen.

NOTE Confidence: 0.7943555

 $00:22:29.080 \rightarrow 00:22:31.418$  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

 $00:22:33.090 \rightarrow 00:22:36.330$  albeit more slowly than controls.

NOTE Confidence: 0.7943555

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

NOTE Confidence: 0.7943555

 $00{:}22{:}37.058 \dashrightarrow 00{:}22{:}38.514$  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

 $00{:}22{:}40{.}710 \dashrightarrow 00{:}22{:}43{.}164$  suggesting that loss of a Darwin

NOTE Confidence: 0.7943555

 $00{:}22{:}43.164 \dashrightarrow 00{:}22{:}45.872$  in tumors is sufficient to overcome

NOTE Confidence: 0.7943555

 $00{:}22{:}45.872 \dashrightarrow 00{:}22{:}47.868$  this mechanism of resistance.

NOTE Confidence: 0.7943555

 $00:22:47.870 \rightarrow 00:22:49.879$  This result was a bit surprising actually.

NOTE Confidence: 0.7943555

 $00{:}22{:}49{.}880 \dashrightarrow 00{:}22{:}52{.}288$  At first, as it suggests that CD8T

NOTE Confidence: 0.7943555

 $00:22:52.288 \rightarrow 00:22:54.240$  cell recognition with MHC one in

- NOTE Confidence: 0.7943555
- $00{:}22{:}54{.}240 \dashrightarrow 00{:}22{:}56{.}221$  tumors is not in all cases required
- NOTE Confidence: 0.7943555
- $00{:}22{:}56{.}286 \dashrightarrow 00{:}22{:}58{.}380$  for the response to a mino therapy.
- NOTE Confidence: 0.7943555
- $00{:}22{:}58{.}380 \dashrightarrow 00{:}23{:}00{.}515$  It also raises the question as to
- NOTE Confidence: 0.7943555
- $00{:}23{:}00{.}515 \dashrightarrow 00{:}23{:}02{.}593$  whether it could be possible to
- NOTE Confidence: 0.7943555
- $00{:}23{:}02{.}593 \dashrightarrow 00{:}23{:}04{.}423$  target tumors that entirely lack
- NOTE Confidence: 0.7943555
- $00{:}23{:}04{.}423 \dashrightarrow 00{:}23{:}06{.}319$  high quality CDH cell antigens.
- NOTE Confidence: 0.7943555
- $00{:}23{:}06{.}320 \dashrightarrow 00{:}23{:}07{.}769$  A lot of ongoing work in the
- NOTE Confidence: 0.7943555
- $00:23:07.769 \longrightarrow 00:23:09.354$  lab is focused on dissecting the
- NOTE Confidence: 0.7943555
- $00:23:09.354 \longrightarrow 00:23:10.566$  mechanism of this finding,
- NOTE Confidence: 0.7943555
- $00{:}23{:}10.570 \dashrightarrow 00{:}23{:}12.270$  and one of the first
- NOTE Confidence: 0.7943555
- $00:23:12.270 \longrightarrow 00:23:13.970$  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
- $00{:}23{:}19{.}030 \dashrightarrow 00{:}23{:}22{.}520$  was required for this response.
- NOTE Confidence: 0.7943555

 $00:23:22.520 \rightarrow 00:23:24.194$  This is actually pretty new data

NOTE Confidence: 0.7943555

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

NOTE Confidence: 0.7943555

 $00:23:25.930 \rightarrow 00:23:27.925$  and found that indeed you still get

NOTE Confidence: 0.7943555

 $00:23:27.925 \rightarrow 00:23:29.897$  great responses in a Darwin all tumors.

NOTE Confidence: 0.792159180909091

 $00:23:31.940 \longrightarrow 00:23:33.580$  Even without the gmax.

NOTE Confidence: 0.792159180909091

 $00{:}23{:}33{.}580 \dashrightarrow 00{:}23{:}35{.}630$  To start to understand this

NOTE Confidence: 0.792159180909091

 $00:23:35.630 \rightarrow 00:23:37.611$  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

 $00{:}23{:}38{.}880 \dashrightarrow 00{:}23{:}41{.}232$  this time focusing on our beta 2M

NOTE Confidence: 0.792159180909091

 $00:23:41.232 \rightarrow 00:23:43.319$  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

 $00{:}23{:}45.850 \dashrightarrow 00{:}23{:}47.440$  increased immune infiltration

NOTE Confidence: 0.792159180909091

 $00{:}23{:}47{.}440 \dashrightarrow 00{:}23{:}49{.}560$  CD 45 positive cells.

NOTE Confidence: 0.792159180909091

 $00{:}23{:}49{.}560 \dashrightarrow 00{:}23{:}52{.}038$  But now focused on some of these

NOTE Confidence: 0.792159180909091

 $00{:}23{:}52{.}038 \dashrightarrow 00{:}23{:}54{.}848$  MHC one non MHC one restricted

NOTE Confidence: 0.792159180909091

 $00:23:54.848 \rightarrow 00:23:57.068$  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
- $00:23:59.604 \rightarrow 00:24:02.355 4$  positive T cells and NK cells.
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}02{.}360 \dashrightarrow 00{:}24{:}04{.}435$  With the hypothesis that perhaps
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}04{.}435 \dashrightarrow 00{:}24{:}06{.}940$  these cells which don't require MHC
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}06{.}940 \dashrightarrow 00{:}24{:}09{.}106$  one for recognition of tumor cells.
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}09{.}110 \dashrightarrow 00{:}24{:}12.632$  May be involved in the phenotype
- NOTE Confidence: 0.792159180909091
- $00:24:12.632 \longrightarrow 00:24:13.806$  we've observed.
- NOTE Confidence: 0.792159180909091
- $00:24:13.810 \longrightarrow 00:24:15.754$  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
- $00:24:17.050 \longrightarrow 00:24:19.350$  by which these populations may
- NOTE Confidence: 0.792159180909091
- $00:24:19.350 \longrightarrow 00:24:21.190$  be recruited and activated.
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}21{.}190 \dashrightarrow 00{:}24{:}24{.}462$  These graphs are from side to kinda be
- NOTE Confidence: 0.792159180909091
- $00{:}24{:}24{.}462 \dashrightarrow 00{:}24{:}27{.}736$  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
- $00:24:29.415 \longrightarrow 00:24:30.755$  were identified so far.
- NOTE Confidence: 0.792159180909091

 $00:24:30.760 \longrightarrow 00:24:33.790$  CX CL 10 in CCL 5.

NOTE Confidence: 0.792159180909091

 $00{:}24{:}33.790 \dashrightarrow 00{:}24{:}35.170$  Which are both significantly

NOTE Confidence: 0.792159180909091

 $00{:}24{:}35{.}170 \dashrightarrow 00{:}24{:}37{.}240$  increased in our beta to emulate

NOTE Confidence: 0.792159180909091

 $00:24:37.297 \rightarrow 00:24:38.989$  our one all tumors compared with

NOTE Confidence: 0.792159180909091

 $00{:}24{:}38{.}989 \dashrightarrow 00{:}24{:}41{.}030$  beta to a control control tumors.

NOTE Confidence: 0.76325333

 $00{:}24{:}43{.}550 \dashrightarrow 00{:}24{:}45{.}614$  Notably Ehrenring here at Yale has NOTE Confidence: 0.76325333

 $00:24:45.614 \rightarrow 00:24:47.284$  described a similar phenotype of

NOTE Confidence: 0.76325333

 $00:24:47.284 \longrightarrow 00:24:48.730$  being able to overcome the loss

NOTE Confidence: 0.76325333

 $00{:}24{:}48.730 \dashrightarrow 00{:}24{:}50.631$  of MHC one using a modified I'll

NOTE Confidence: 0.76325333

 $00:24:50.631 \longrightarrow 00:24:52.305$  18 side kind that he designed.

NOTE Confidence: 0.76325333

 $00{:}24{:}52{.}310 \dashrightarrow 00{:}24{:}54{.}360$  So this remains another possibility

NOTE Confidence: 0.76325333

 $00{:}24{:}54{.}360 \dashrightarrow 00{:}24{:}56{.}410$  that we haven't yet explored.

NOTE Confidence: 0.76325333

 $00{:}24{:}56{.}410 \dashrightarrow 00{:}24{:}58{.}524$  However, we think this type of study

NOTE Confidence: 0.76325333

 $00{:}24{:}58{.}524 \dashrightarrow 00{:}25{:}00{.}136$  is important 'cause articulating the

NOTE Confidence: 0.76325333

 $00:25:00.136 \rightarrow 00:25:02.404$  general principles by which loss of MHC NOTE Confidence: 0.76325333

 $00:25:02.404 \rightarrow 00:25:04.931$  one can be overcome could lead to new

- NOTE Confidence: 0.76325333
- $00:25:04.931 \rightarrow 00:25:06.490$  treatment approaches to target tumor

 $00:25:06.490 \rightarrow 00:25:07.750$  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

 $00:25:13.022 \rightarrow 00:25:14.490$  you have several points.

NOTE Confidence: 0.8231248

 $00{:}25{:}14{.}490 \dashrightarrow 00{:}25{:}18{.}178$  First aid are one loss over improves the

NOTE Confidence: 0.8231248

 $00{:}25{:}18.178 \dashrightarrow 00{:}25{:}20.787$  response to me to the rapy. Specifically,

NOTE Confidence: 0.8231248

 $00{:}25{:}20.787 \dashrightarrow 00{:}25{:}23.216$  it can overcome the lack of evidence.

NOTE Confidence: 0.8231248

 $00{:}25{:}23{.}220 \dashrightarrow 00{:}25{:}26{.}160$  Plain tumor, micro environment and the

NOTE Confidence: 0.8231248

 $00:25:26.160 \longrightarrow 00:25:29.080$  loss of antigen presentation by image C1.

NOTE Confidence: 0.8231248

 $00:25:29.080 \rightarrow 00:25:30.884$  Additionally, this phenotype is

NOTE Confidence: 0.8231248

 $00:25:30.884 \rightarrow 00:25:33.139$  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

 $00{:}25{:}34{.}944 \dashrightarrow 00{:}25{:}36{.}297$  5 and sensitization.

NOTE Confidence: 0.8231248

 $00{:}25{:}36{.}300 \dashrightarrow 00{:}25{:}39{.}990$  Interferon driven by PK are.

NOTE Confidence: 0.8231248

 $00{:}25{:}39{.}990 \dashrightarrow 00{:}25{:}42{.}806$  Finally, and I think this may be important.

 $00{:}25{:}42.810 \dashrightarrow 00{:}25{:}44.715$  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

 $00{:}25{:}46.620 \dashrightarrow 00{:}25{:}48.530$  If they are in need.

NOTE Confidence: 0.8231248

 $00:25:48.530 \longrightarrow 00:25:50.213$  Nucleic acid sensing

NOTE Confidence: 0.8231248

 $00{:}25{:}50{.}213 \dashrightarrow 00{:}25{:}51{.}896$  checkpoints are disabled.

NOTE Confidence: 0.8231248

 $00{:}25{:}51{.}900 \dashrightarrow 00{:}25{:}53{.}868$  And what we think this implies is that

NOTE Confidence: 0.8231248

 $00{:}25{:}53.868 \dashrightarrow 00{:}25{:}55.745$  there may be other similar innate

NOTE Confidence: 0.8231248

 $00{:}25{:}55{.}745 \dashrightarrow 00{:}25{:}57{.}410$  immune checkpoints that limit the

NOTE Confidence: 0.8231248

 $00{:}25{:}57{.}410 \dashrightarrow 00{:}25{:}59{.}549$  sensing of double stranded RNA or other

NOTE Confidence: 0.8231248

 $00:25:59.549 \rightarrow 00:26:01.308$  nucleic acid ligands that we could

NOTE Confidence: 0.8231248

 $00{:}26{:}01{.}308 \dashrightarrow 00{:}26{:}02{.}778$  think about as the rapeutic targets.

NOTE Confidence: 0.81072354

 $00{:}26{:}04.830 \dashrightarrow 00{:}26{:}06.894$  And really, those questions inform the NOTE Confidence: 0.81072354

NOTE Confidence: 0.81072554

 $00{:}26{:}06{.}894 \dashrightarrow 00{:}26{:}09{.}716$  rest of the work that the lab is doing.

NOTE Confidence: 0.81072354

 $00{:}26{:}09{.}720 \dashrightarrow 00{:}26{:}11{.}712$  I've mentioned already a focus on

NOTE Confidence: 0.81072354

 $00:26:11.712 \dashrightarrow 00:26:13.629$  double stranded RNA and eight R1.

NOTE Confidence: 0.81072354

 $00:26:13.630 \rightarrow 00:26:15.210$  We're also applying functional genomics

 $00:26:15.210 \rightarrow 00:26:17.539$  to try to identify other novel targets.

NOTE Confidence: 0.81072354

 $00:26:17.540 \longrightarrow 00:26:19.370$  Really, with the insight that we

NOTE Confidence: 0.81072354

 $00{:}26{:}19.370 \dashrightarrow 00{:}26{:}22.047$  have to focus on turning on some of

NOTE Confidence: 0.81072354

 $00{:}26{:}22.047 \dashrightarrow 00{:}26{:}24.135$  these pathways of double stranded RNA

NOTE Confidence: 0.81072354

 $00:26:24.205 \longrightarrow 00:26:26.510$  sensing or micro violent information.

NOTE Confidence: 0.81072354

 $00:26:26.510 \longrightarrow 00:26:29.226$  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

 $00:26:31.402 \rightarrow 00:26:32.488$  microenvironment investigation across

NOTE Confidence: 0.81072354

 $00{:}26{:}32.488 \dashrightarrow 00{:}26{:}34.268$  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

 $00:26:36.930 \longrightarrow 00:26:37.994$  collaborators there.

NOTE Confidence: 0.81072354

 $00{:}26{:}38.000 \dashrightarrow 00{:}26{:}40.888$  And all of this comes under the rubric

NOTE Confidence: 0.81072354

 $00{:}26{:}40.888 \dashrightarrow 00{:}26{:}42.685$  of the rapeutically targeting the

NOTE Confidence: 0.81072354

 $00{:}26{:}42.685 \dashrightarrow 00{:}26{:}45.215$  information in the tumor microenvironment.

NOTE Confidence: 0.81072354

 $00{:}26{:}45{.}220 \dashrightarrow 00{:}26{:}46{.}940$  In just the last couple of minutes here,

 $00:26:46.940 \longrightarrow 00:26:48.886$  I want to quickly mention some of

NOTE Confidence: 0.81072354

 $00{:}26{:}48.886 \dashrightarrow 00{:}26{:}50.763$  the ongoing projects in the lab that

NOTE Confidence: 0.81072354

 $00{:}26{:}50.763 \dashrightarrow 00{:}26{:}52.245$  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

 $00{:}26{:}56{.}880 \dashrightarrow 00{:}26{:}59{.}210$  Describing how to Riker environment

NOTE Confidence: 0.81072354

 $00{:}26{:}59{.}210 \dashrightarrow 00{:}27{:}01{.}074$  inflammation can overcome the

NOTE Confidence: 0.81072354

 $00{:}27{:}01.074 \dashrightarrow 00{:}27{:}02.340$  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

 $00{:}27{:}05{.}280 \dashrightarrow 00{:}27{:}08{.}556$  but she's Additionally leading a project.

NOTE Confidence: 0.81072354

 $00{:}27{:}08.560 \dashrightarrow 00{:}27{:}10.480$  Looking at human tumors and trying

NOTE Confidence: 0.81072354

 $00{:}27{:}10{.}480 \dashrightarrow 00{:}27{:}12{.}544$  to turn these pathways on in ex

NOTE Confidence: 0.81072354

 $00{:}27{:}12.544 \dashrightarrow 00{:}27{:}14.231$  vivo samples as well as doing deep

NOTE Confidence: 0.81072354

 $00{:}27{:}14.296 \dashrightarrow 00{:}27{:}16.316$  dissection of the micro environment.

NOTE Confidence: 0.81072354

 $00:27:16.320 \longrightarrow 00:27:18.623$  Where we go is working on novel

NOTE Confidence: 0.81072354

 $00:27:18.623 \longrightarrow 00:27:20.361$  strategies to detect double stranded

NOTE Confidence: 0.81072354

 $00:27:20.361 \longrightarrow 00:27:23.097$  RNA and to mimic the sensors of double

- NOTE Confidence: 0.81072354
- $00{:}27{:}23.160 \dashrightarrow 00{:}27{:}25.953$  stranded RNA that we believe will be

 $00{:}27{:}25{.}953 \dashrightarrow 00{:}27{:}27{.}588$  compatible with functional genomic

NOTE Confidence: 0.81072354

 $00:27:27.588 \rightarrow 00:27:29.778$  screening in the identification of

NOTE Confidence: 0.81072354

 $00:27:29.778 \rightarrow 00:27:31.530$  novel cancer immunotherapy targets.

NOTE Confidence: 0.81072354

 $00:27:31.530 \longrightarrow 00:27:32.234$  And finally,

NOTE Confidence: 0.81072354

 $00{:}27{:}32{.}234 \dashrightarrow 00{:}27{:}36{.}182$  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

 $00:27:38.810 \longrightarrow 00:27:41.700$  So responsive and resistant lesions.

NOTE Confidence: 0.81072354

 $00{:}27{:}41.700 \dashrightarrow 00{:}27{:}44.112$  From the same patient trying to

NOTE Confidence: 0.81072354

 $00{:}27{:}44.112 \dashrightarrow 00{:}27{:}45.720$  understand novel mechanisms of

NOTE Confidence: 0.81072354

 $00{:}27{:}45.785 \dashrightarrow 00{:}27{:}47.435$  resistance to new the rapies so

NOTE Confidence: 0.81072354

 $00{:}27{:}47{.}435 \dashrightarrow 00{:}27{:}49{.}870$  that we can focus on overcoming.

NOTE Confidence: 0.81072354

 $00{:}27{:}49{.}870 \dashrightarrow 00{:}27{:}52{.}246$  With that I want to thank every body in

NOTE Confidence: 0.81072354

 $00{:}27{:}52{.}246 \dashrightarrow 00{:}27{:}54{.}670$  our lab as well as our collaborators

NOTE Confidence: 0.81072354

 $00{:}27{:}54.670 \dashrightarrow 00{:}27{:}56.736$  and mentors here at, you know,

 $00:27:56.736 \longrightarrow 00:27:57.720$  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

 $00:28:01.268 \rightarrow 00:28:04.113$  So much of the work that I presented early

NOTE Confidence: 0.81072354

 $00:28:04.113 \longrightarrow 00:28:06.219$  derives from from studies with them,

NOTE Confidence: 0.81072354

 $00{:}28{:}06{.}220 \dashrightarrow 00{:}28{:}07{.}852$  and of course our funding here

NOTE Confidence: 0.81072354

 $00{:}28{:}07{.}852 \dashrightarrow 00{:}28{:}09{.}849$  at the Cancer Center and the

NOTE Confidence: 0.81072354

 $00{:}28{:}09{.}849 \dashrightarrow 00{:}28{:}11{.}130$  International Research Alliance.

NOTE Confidence: 0.81072354

 $00{:}28{:}11{.}130 \dashrightarrow 00{:}28{:}13{.}086$  With that, I will wrap up.

NOTE Confidence: 0.81072354

 $00:28:13.090 \rightarrow 00:28:16.024$  Thank you so much for the chance to present,

NOTE Confidence: 0.81072354

 $00{:}28{:}16.030 \dashrightarrow 00{:}28{:}17.986$  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

 $00:28:23.350 \rightarrow 00:28:26.710$  And we we have folks can submit questions.

NOTE Confidence: 0.825338

 $00{:}28{:}26{.}710 \dashrightarrow 00{:}28{:}28{.}390$  We have one question.

NOTE Confidence: 0.825338

 $00:28:28.390 \longrightarrow 00:28:29.650$  Mike Hurwitz asked.

- NOTE Confidence: 0.825338
- $00:28:29.650 \rightarrow 00:28:32.548$  So given the response in eight R1

 $00{:}28{:}32{.}548 \dashrightarrow 00{:}28{:}35{.}948$  knockouts in the absence of MHC class one,

NOTE Confidence: 0.825338

 $00:28:35.950 \longrightarrow 00:28:38.368$  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

 $00{:}28{:}44.020 \dashrightarrow 00{:}28{:}46.324$  I think that's a great question and we

NOTE Confidence: 0.87834716

 $00:28:46.324 \rightarrow 00:28:49.810$  definitely would love to know that answer.

NOTE Confidence: 0.87834716

 $00{:}28{:}49{.}810 \dashrightarrow 00{:}28{:}52{.}216$  Best hypothesis Now is that partially

NOTE Confidence: 0.87834716

 $00:28:52.216 \rightarrow 00:28:55.755$  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

 $00{:}28{:}58{.}090 \dashrightarrow 00{:}29{:}00{.}506$  NK cells could be an important player there.

NOTE Confidence: 0.87834716

 $00{:}29{:}00{.}510 \dashrightarrow 00{:}29{:}02{.}050$  Certainly there increased and we

NOTE Confidence: 0.87834716

 $00{:}29{:}02{.}050 \dashrightarrow 00{:}29{:}04{.}220$  started to see some cytokines in Kemah

NOTE Confidence: 0.87834716

 $00:29:04.220 \rightarrow 00:29:05.936$  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

 $00:29:08.012 \rightarrow 00:29:10.167$  sure that CD8T cells aren't important.

NOTE Confidence: 0.87834716

 $00{:}29{:}10.170 \dashrightarrow 00{:}29{:}11.976$  That's an experiment we're doing now.

NOTE Confidence: 0.87834716

 $00{:}29{:}11{.}980 \dashrightarrow 00{:}29{:}14{.}099$  We just know they're not recognizing the NOTE Confidence: 0.87834716

 $00:29:14.100 \rightarrow 00:29:16.060$  tumor, but could they be activated through NOTE Confidence: 0.87834716

 $00:29:16.060 \longrightarrow 00:29:17.915$  cross presentation or another means is

NOTE Confidence: 0.87834716

 $00{:}29{:}17{.}915 \dashrightarrow 00{:}29{:}19{.}530$  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

 $00:29:31.344 \rightarrow 00:29:33.780$  But which obviously is not necessarily

NOTE Confidence: 0.7803051

 $00{:}29{:}33.856 \dashrightarrow 00{:}29{:}36.280$  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

 $00:29:37.732 \longrightarrow 00:29:40.906$  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

 $00:29:44.070 \longrightarrow 00:29:45.710$  Yeah, so this is

- NOTE Confidence: 0.7803051
- $00:29:45.710 \rightarrow 00:29:48.374$  a great question Charlie and actually
- NOTE Confidence: 0.7803051
- $00{:}29{:}48.374 \dashrightarrow 00{:}29{:}51.910$  Akiko is one of my mentors here and.
- NOTE Confidence: 0.7803051
- $00{:}29{:}51{.}910 \dashrightarrow 00{:}29{:}54{.}826$  Collaborators and we've talked about this.
- NOTE Confidence: 0.7803051
- $00:29:54.830 \rightarrow 00:29:58.225$  We're actually in the process of testing.
- NOTE Confidence: 0.7803051
- $00{:}29{:}58{.}230 \dashrightarrow 00{:}30{:}02{.}736$  Are a guy at. Egotist with the innate
- NOTE Confidence: 0.7803051
- $00{:}30{:}02{.}736 \dashrightarrow 00{:}30{:}04{.}548$  arnolin control tumor cell lines and
- NOTE Confidence: 0.7803051
- $00:30:04.548 \dashrightarrow 00:30:06.885$  you know the colloquial way we we
- NOTE Confidence: 0.7803051
- $00{:}30{:}06.885 \dashrightarrow 00{:}30{:}09.202$  thought about this is kind of as a
- NOTE Confidence: 0.7803051
- $00{:}30{:}09{.}202 \dashrightarrow 00{:}30{:}10.841$  maximum inflammation bomb because what
- NOTE Confidence: 0.7803051
- $00:30:10.841 \longrightarrow 00:30:13.019$  we've shown is that any interferon
- NOTE Confidence: 0.7803051
- $00{:}30{:}13.019 \dashrightarrow 00{:}30{:}14.541$  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
- $00:30:18.418 \dashrightarrow 00:30:20.470$  you initiate signaling through a guy,
- NOTE Confidence: 0.7803051
- $00:30:20.470 \longrightarrow 00:30:22.502$  even if there a guy is not involved
- NOTE Confidence: 0.7803051

- $00:30:22.502 \rightarrow 00:30:24.899$  in the pathways we've described here,
- NOTE Confidence: 0.7803051
- $00{:}30{:}24{.}900 \dashrightarrow 00{:}30{:}26{.}475$  you basically create a massive
- NOTE Confidence: 0.7803051
- $00:30:26.475 \longrightarrow 00:30:27.424$  amplification of interferon,
- NOTE Confidence: 0.7803051
- $00{:}30{:}27{.}424 \dashrightarrow 00{:}30{:}29{.}320$  buy by further knocking out eight
- NOTE Confidence: 0.7803051
- $00{:}30{:}29{.}320 \dashrightarrow 00{:}30{:}31{.}534$  R1 so that remains to be seen,
- NOTE Confidence: 0.7803051
- $00:30:31.534 \rightarrow 00:30:33.430$  but that's what I would hypothesize.
- NOTE Confidence: 0.8670604
- $00{:}30{:}33{.}830 \dashrightarrow 00{:}30{:}34{.}892$  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
- $00{:}30{:}36{.}662 \dashrightarrow 00{:}30{:}38{.}158$  opportunity to look at that.
- NOTE Confidence: 0.8670604
- $00{:}30{:}38{.}160 \dashrightarrow 00{:}30{:}41{.}157$  Well, I I want to keep us on time,
- NOTE Confidence: 0.8670604
- $00:30:41.160 \longrightarrow 00:30:42.400$  so Jeff, thank you.
- NOTE Confidence: 0.8670604
- $00{:}30{:}42{.}400 \dashrightarrow 00{:}30{:}44{.}260$  I know there are other questions
- NOTE Confidence: 0.8670604
- $00:30:44.326 \rightarrow 00:30:46.258$  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
- $00{:}30{:}48{.}490 \dashrightarrow 00{:}30{:}50{.}870$  But thank you for a superb presentation
- NOTE Confidence: 0.8670604
- $00:30:50.870 \rightarrow 00:30:53.807$  and let me now turn to our second speaker,

- NOTE Confidence: 0.8670604
- $00:30:53.810 \rightarrow 00:30:56.130$  doctor Robert Bone and Bob Bone is a

 $00{:}30{:}56{.}130 \dashrightarrow 00{:}30{:}58{.}138$  professor of medicine in hematology,

NOTE Confidence: 0.8670604

 $00:30:58.140 \longrightarrow 00:31:00.831$  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

 $00{:}31{:}03{.}130 \dashrightarrow 00{:}31{:}05{.}846$  as well as the medical director of

NOTE Confidence: 0.8670604

 $00{:}31{:}05{.}846 \dashrightarrow 00{:}31{:}07{.}540$  the Hemophilia Treatment Center.

NOTE Confidence: 0.8670604

00:31:07.540 --> 00:31:09.156 Prior to joining Yale,

NOTE Confidence: 0.8670604

 $00{:}31{:}09{.}156 \dashrightarrow 00{:}31{:}11{.}176$  Bob was founding faculty member

NOTE Confidence: 0.8670604

 $00{:}31{:}11{.}176 \dashrightarrow 00{:}31{:}13{.}745$  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

 $00{:}31{:}15.840 \dashrightarrow 00{:}31{:}18.784$  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

 $00{:}31{:}21{.}416 \dashrightarrow 00{:}31{:}24{.}140$  Medicine and Bob throughout his career,

NOTE Confidence: 0.8670604

 $00{:}31{:}24{.}140 \dashrightarrow 00{:}31{:}27{.}101$  really has been a leader in in the

NOTE Confidence: 0.8670604

 $00{:}31{:}27.101 \dashrightarrow 00{:}31{:}29.615$  clinical care and sort of advancing

- $00:31:29.615 \longrightarrow 00:31:32.344$  work in hemostasis thrombosis as well
- NOTE Confidence: 0.8670604
- $00{:}31{:}32{.}344 \dashrightarrow 00{:}31{:}34{.}520$  as benign hematologic conditions.
- NOTE Confidence: 0.8670604
- 00:31:34.520 --> 00:31:35.816 And we're really,
- NOTE Confidence: 0.8670604
- $00:31:35.816 \longrightarrow 00:31:37.544$  very fortunate Bob to.
- NOTE Confidence: 0.8670604
- $00:31:37.550 \longrightarrow 00:31:38.218$  That Bob,
- NOTE Confidence: 0.8670604
- $00{:}31{:}38{.}218$  -->  $00{:}31{:}40{.}222$  now leading this section and sharing
- NOTE Confidence: 0.8670604
- $00:31:40.222 \longrightarrow 00:31:41.740$  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
- $00{:}31{:}44{.}410 \dashrightarrow 00{:}31{:}47{.}134$  Thank you, Charlie for that introduction
- NOTE Confidence: 0.9011822
- $00:31:47.134 \rightarrow 00:31:50.090$  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
- $00{:}31{:}55{.}760 \dashrightarrow 00{:}31{:}58{.}358$  And what I would like to do in the
- NOTE Confidence: 0.9011822
- $00:31:58.358 \longrightarrow 00:32:00.996$  next 25 minutes or so is discuss with
- NOTE Confidence: 0.9011822
- $00{:}32{:}00{.}996 \dashrightarrow 00{:}32{:}04{.}060$  you some of the advances that have a
- NOTE Confidence: 0.9011822
- $00:32:04.060 \rightarrow 00:32:06.544$  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

 $00{:}32{:}08{.}800 \dashrightarrow 00{:}32{:}11{.}285$  over the past five years there have

NOTE Confidence: 0.9011822

 $00:32:11.285 \longrightarrow 00:32:13.219$  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

 $00:32:15.727 \longrightarrow 00:32:18.421$  of really several decades of really

NOTE Confidence: 0.9011822

 $00{:}32{:}18{.}421 \dashrightarrow 00{:}32{:}20{.}806$  only modest advances in the rapy.

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

 $00:32:25.760 \longrightarrow 00:32:27.110$  mostly affecting men,

NOTE Confidence: 0.9011822

 $00{:}32{:}27{.}110 \dashrightarrow 00{:}32{:}29{.}840$  but can also affect women who might

NOTE Confidence: 0.9011822

 $00:32:29.840 \longrightarrow 00:32:32.660$  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

 $00:32:36.560 \longrightarrow 00:32:39.260$  in factor 8 or 9 respectively.

NOTE Confidence: 0.9011822

 $00{:}32{:}39{.}260 \dashrightarrow 00{:}32{:}41{.}685$  They are clinically identical disorders

 $00:32:41.685 \rightarrow 00:32:44.664$  and the severity of the disease

NOTE Confidence: 0.9011822

 $00:32:44.664 \rightarrow 00:32:47.526$  is really relies primarily on the

NOTE Confidence: 0.9011822

 $00{:}32{:}47{.}526 \dashrightarrow 00{:}32{:}49{.}876$  residual factor that is remaining

NOTE Confidence: 0.9011822

 $00{:}32{:}49{.}876 \dashrightarrow 00{:}32{:}52{.}809$  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

 $00{:}32{:}57{.}430 \dashrightarrow 00{:}32{:}59{.}571$  and those with mild disease having

NOTE Confidence: 0.9011822

 $00{:}32{:}59{.}571 \dashrightarrow 00{:}33{:}02{.}121$  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

 $00{:}33{:}04{.}475 \dashrightarrow 00{:}33{:}06{.}379$  and trauma induced bleeding,

NOTE Confidence: 0.9011822

 $00:33:06.380 \longrightarrow 00:33:09.010$  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

 $00{:}33{:}11.721 \dashrightarrow 00{:}33{:}14.535$  which we can be quite disabling.

NOTE Confidence: 0.9011822

 $00{:}33{:}14.540 \dashrightarrow 00{:}33{:}16.892$  And just the history of hemophilia

NOTE Confidence: 0.9011822

 $00:33:16.892 \rightarrow 00:33:18.916$  treatment in the last century

NOTE Confidence: 0.9011822

 $00:33:18.916 \longrightarrow 00:33:21.196$  is seen briefly on this slide,

- NOTE Confidence: 0.9011822
- $00{:}33{:}21{.}200 \dashrightarrow 00{:}33{:}23{.}592$  and at the end of World War Two

 $00{:}33{:}23{.}592 \dashrightarrow 00{:}33{:}25{.}812$  blood or plasma transfusions were

NOTE Confidence: 0.9011822

 $00:33:25.812 \longrightarrow 00:33:27.864$  used to treat patients.

NOTE Confidence: 0.9011822

 $00:33:27.870 \rightarrow 00:33:29.830$  This these were largely ineffective,

NOTE Confidence: 0.9011822

 $00:33:29.830 \longrightarrow 00:33:32.686$  is only small amounts of factor 8 or

NOTE Confidence: 0.9011822

 $00:33:32.686 \longrightarrow 00:33:36.097$  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

 $00:33:37.276 \longrightarrow 00:33:39.628$  as a source of Factor 8,

NOTE Confidence: 0.9011822

 $00{:}33{:}39{.}630 \dashrightarrow 00{:}33{:}42{.}087$  and that quickly gave way to the

NOTE Confidence: 0.9011822

 $00:33:42.087 \rightarrow 00:33:44.120$  use of factor concentrates either

NOTE Confidence: 0.9011822

 $00:33:44.120 \longrightarrow 00:33:46.360$  factor 8 or factor 9.

NOTE Confidence: 0.9011822

 $00{:}33{:}46{.}360 \dashrightarrow 00{:}33{:}48{.}535$  Purified from the plasma of

NOTE Confidence: 0.9011822

 $00{:}33{:}48{.}535 \dashrightarrow 00{:}33{:}50{.}710$  10s of thousands of donors.

NOTE Confidence: 0.9011822

 $00{:}33{:}50{.}710 \dashrightarrow 00{:}33{:}52{.}015$  And of course,

NOTE Confidence: 0.9011822

 $00{:}33{:}52.015 \dashrightarrow 00{:}33{:}53.755$  while this advanced care,

 $00:33:53.760 \longrightarrow 00:33:56.142$  it also exposed individuals to a

NOTE Confidence: 0.9011822

 $00{:}33{:}56.142 \dashrightarrow 00{:}33{:}58.670$  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

 $00:34:01.701 \rightarrow 00:34:04.199$  significant problem in this population.

NOTE Confidence: 0.9011822

 $00{:}34{:}04{.}200 \dashrightarrow 00{:}34{:}06{.}780$  And then in the early  $90\mathrm{s}$ 

NOTE Confidence: 0.9011822

 $00:34:06.780 \longrightarrow 00:34:08.980$  recombinant factors 8:00 and 9:00,

NOTE Confidence: 0.9011822

 $00:34:08.980 \rightarrow 00:34:12.025$  or produced and for the developed world,

NOTE Confidence: 0.9011822

 $00:34:12.030 \rightarrow 00:34:14.495$  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

 $00{:}34{:}19{.}430 \dashrightarrow 00{:}34{:}22{.}735$  Became really the standard of

NOTE Confidence: 0.9011822

 $00:34:22.735 \rightarrow 00:34:26.040$  care up until very recently.

NOTE Confidence: 0.9011822

 $00:34:26.040 \rightarrow 00:34:29.196$  There are now about 145 federally

NOTE Confidence: 0.9011822

 $00{:}34{:}29{.}196 \dashrightarrow 00{:}34{:}31{.}300$  funded hemophilia treatment centers

NOTE Confidence: 0.9011822

 $00{:}34{:}31{.}376 \dashrightarrow 00{:}34{:}34{.}120$  in this country and of course jeliz is

NOTE Confidence: 0.9011822

 $00:34:34.120 \rightarrow 00:34:37.169$  one of those is one of those centers.

- NOTE Confidence: 0.9011822
- $00{:}34{:}37{.}170 \dashrightarrow 00{:}34{:}38{.}400$  And the the rapeutic.

 $00{:}34{:}38{.}400 \dashrightarrow 00{:}34{:}40{.}450$  The approach in clinical issues

NOTE Confidence: 0.9011822

 $00:34:40.450 \longrightarrow 00:34:41.650$  are outlined here.

NOTE Confidence: 0.9011822

 $00{:}34{:}41{.}650 \dashrightarrow 00{:}34{:}43{.}912$  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

 $00{:}34{:}50{.}692 \dashrightarrow 00{:}34{:}54{.}284$  Factor 8 or factor 9 to treat a

NOTE Confidence: 0.9011822

 $00{:}34{:}54{.}284 \dashrightarrow 00{:}34{:}56{.}100$  bleed or prophylactic the rapy.

NOTE Confidence: 0.9011822

00:34:56.100 --> 00:34:57.393 An inhibitor development,

NOTE Confidence: 0.9011822

 $00{:}34{:}57{.}393 \dashrightarrow 00{:}34{:}59{.}979$  that is an Allo antibody directed

NOTE Confidence: 0.9011822

 $00{:}34{:}59{.}979 \dashrightarrow 00{:}35{:}02{.}159$  against Factor 8 or less commonly,

NOTE Confidence: 0.9011822

 $00{:}35{:}02{.}160 \dashrightarrow 00{:}35{:}04{.}848$  factor 9 is a significant problem

NOTE Confidence: 0.9011822

 $00{:}35{:}04.848 \dashrightarrow 00{:}35{:}07{.}918$  for patients and may occur in 30 or

NOTE Confidence: 0.9011822

 $00{:}35{:}07{.}918 \dashrightarrow 00{:}35{:}10{.}455$  40% of individuals with hemophilia A

 $00:35:10.455 \rightarrow 00:35:12.690$  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

 $00{:}35{:}15{.}145 \dashrightarrow 00{:}35{:}16{.}165$  here to prevent

NOTE Confidence: 0.85170436

00:35:16.241 --> 00:35:17.984 any bleeding. If possible,

NOTE Confidence: 0.85170436

 $00{:}35{:}17{.}984 \dashrightarrow 00{:}35{:}20{.}606$  prevent joint disease and optimize a

NOTE Confidence: 0.85170436

 $00{:}35{:}20.606 \dashrightarrow 00{:}35{:}23.528$  quality of life for these individuals.

NOTE Confidence: 0.85170436

 $00{:}35{:}23{.}530 \dashrightarrow 00{:}35{:}25{.}224$  And the infusion of factor 8 or

NOTE Confidence: 0.85170436

 $00:35:25.224 \rightarrow 00:35:27.318$  factor 9 by patients is traditionally

NOTE Confidence: 0.85170436

 $00{:}35{:}27{.}318 \dashrightarrow 00{:}35{:}29{.}058$  given at home intravenously.

NOTE Confidence: 0.85170436

 $00:35:29.060 \rightarrow 00:35:32.030$  Patients from a very young age learn to start

NOTE Confidence: 0.85170436

 $00:35:32.030 \dashrightarrow 00:35:34.904$  an Ivy and infuse factor 8 or factor 9,

NOTE Confidence: 0.85170436

 $00{:}35{:}34{.}910 \dashrightarrow 00{:}35{:}36{.}530$  but because of the short

NOTE Confidence: 0.85170436

 $00:35:36.530 \longrightarrow 00:35:37.826$  half-life of these drugs,

NOTE Confidence: 0.85170436

 $00{:}35{:}37{.}830 \dashrightarrow 00{:}35{:}39{.}951$  about 12 hours for factor 8 and

NOTE Confidence: 0.85170436

 $00:35:39.951 \longrightarrow 00:35:42.379$  18 to 24 hours for factor 9,

NOTE Confidence: 0.85170436

 $00{:}35{:}42{.}380 \dashrightarrow 00{:}35{:}44{.}676$  they need to be administered two to

- NOTE Confidence: 0.85170436
- $00:35:44.676 \rightarrow 00:35:46.597$  three to sometimes four times per

 $00{:}35{:}46{.}597 \dashrightarrow 00{:}35{:}49{.}056$  week to keep the factor levels in a

NOTE Confidence: 0.85170436

 $00:35:49.056 \rightarrow 00:35:50.826$  range that will prevent bleeding.

NOTE Confidence: 0.85170436

 $00:35:50.830 \rightarrow 00:35:52.978$  So this is an onerous thing

NOTE Confidence: 0.85170436

 $00{:}35{:}52{.}978 \dashrightarrow 00{:}35{:}54{.}410$  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

 $00:35:57.662 \rightarrow 00:35:59.830$  greatly appreciated by them.

NOTE Confidence: 0.85170436

 $00:35:59.830 \rightarrow 00:36:02.268$  So here's the obligatory coagulations

NOTE Confidence: 0.85170436

 $00:36:02.268 \longrightarrow 00:36:05.656$  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

 $00{:}36{:}07{.}997 \dashrightarrow 00{:}36{:}11{.}308$  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

 $00:36:13.580 \longrightarrow 00:36:17.304$  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

 $00:36:20.041 \longrightarrow 00:36:23.173$  activation of factor 10 by tissue

00:36:23.173 --> 00:36:25.915 factor 7A or activation by factor

NOTE Confidence: 0.85170436

 $00{:}36{:}25{.}915 \dashrightarrow 00{:}36{:}29{.}160$ 9 to 9 A by tissue factor 7<br/>A.

NOTE Confidence: 0.85170436

 $00:36:29.160 \longrightarrow 00:36:32.560$  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

 $00{:}36{:}40{.}922 \dashrightarrow 00{:}36{:}43{.}885$ 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

 $00{:}36{:}48.166 \dashrightarrow 00{:}36{:}50.785$  and increases the rate of reaction

NOTE Confidence: 0.85170436

 $00:36:50.785 \longrightarrow 00:36:53.767$  hundreds of 1000 fold when factor 8 NOTE Confidence: 0.85170436

 $00:36:53.856 \rightarrow 00:36:56.495$  is able to align the substrate and

NOTE Confidence: 0.85170436

 $00{:}36{:}56{.}495 \dashrightarrow 00{:}36{:}58{.}899$  enzyme on a phospholipid surface in

NOTE Confidence: 0.85170436

 $00{:}36{:}58.899 \dashrightarrow 00{:}37{:}02.978$  the correct in. In the correct fashion.

NOTE Confidence: 0.85170436

 $00:37:02.980 \rightarrow 00:37:05.212$  One other thing to mention about

NOTE Confidence: 0.85170436

 $00:37:05.212 \longrightarrow 00:37:08.141$  Factor 8 before we get into some of

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

 $00{:}37{:}13.290 \dashrightarrow 00{:}37{:}15.410$  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

 $00:37:20.020 \dashrightarrow 00:37:22.505$  factor 8 is the yellow diagram above,

NOTE Confidence: 0.85170436

 $00:37:22.510 \longrightarrow 00:37:25.345$  and the binding of factor 8 von

NOTE Confidence: 0.85170436

 $00{:}37{:}25{.}345 \dashrightarrow 00{:}37{:}26{.}937$  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

 $00{:}37{:}29.086 \dashrightarrow 00{:}37{:}31.029$  2 hours to about 12 hours.

NOTE Confidence: 0.85170436

 $00{:}37{:}31{.}030 \dashrightarrow 00{:}37{:}34{.}117$  So this is a very important interaction.

NOTE Confidence: 0.85170436

 $00{:}37{:}34{.}120 \dashrightarrow 00{:}37{:}36{.}220$  And just to point out here,

NOTE Confidence: 0.85170436

 $00{:}37{:}36{.}220 \dashrightarrow 00{:}37{:}37{.}955$  '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

 $00{:}37{:}40.096 \dashrightarrow 00{:}37{:}42.178$  on von Willebrand factor is these

 $00:37:42.178 \longrightarrow 00:37:43.219$  two protein domains,

NOTE Confidence: 0.85170436

00:37:43.220 --> 00:37:44.970 designated D prime and D3,

NOTE Confidence: 0.85170436

 $00{:}37{:}44.970 \dashrightarrow 00{:}37{:}46.998$  and another important point is there

NOTE Confidence: 0.85170436

 $00:37:46.998 \rightarrow 00:37:49.769$  appears to be a large portion of the

NOTE Confidence: 0.85170436

 $00{:}37{:}49.769 \dashrightarrow 00{:}37{:}52.320$  factor 8 molecules termed the B domain,

NOTE Confidence: 0.85170436

 $00{:}37{:}52{.}320 \dashrightarrow 00{:}37{:}55{.}120$  which is not required for factor 8 function,

NOTE Confidence: 0.85170436

 $00:37:55.120 \longrightarrow 00:37:57.706$  so you could remove that domain

NOTE Confidence: 0.85170436

 $00{:}37{:}57{.}706 \dashrightarrow 00{:}38{:}01{.}138$  and in fact factor 8 has a similar

NOTE Confidence: 0.85170436

 $00{:}38{:}01{.}138 \dashrightarrow 00{:}38{:}04{.}260$  activity than it does with that domain.

NOTE Confidence: 0.85170436

 $00{:}38{:}04{.}260 \dashrightarrow 00{:}38{:}06{.}885$  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

 $00:38:09.641 \longrightarrow 00:38:11.975$  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

 $00:38:14.300 \dashrightarrow 00:38:16.225$  allowing for patients to infuse

NOTE Confidence: 0.85170436

 $00:38:16.225 \rightarrow 00:38:16.995$  less frequently.

- NOTE Confidence: 0.85170436
- 00:38:17.000 00:38:19.310 The development of non factor 8

 $00:38:19.310 \longrightarrow 00:38:20.465$  or 9 therapeutics,

NOTE Confidence: 0.85170436

 $00:38:20.470 \longrightarrow 00:38:23.530$  and then gene therapy and we'll

NOTE Confidence: 0.85170436

 $00:38:23.530 \longrightarrow 00:38:25.570$  go through these individually

NOTE Confidence: 0.85170436

 $00:38:25.662 \longrightarrow 00:38:28.084$  in the next 15 minutes or so.

NOTE Confidence: 0.85170436

 $00:38:28.090 \dashrightarrow 00:38:30.155$  So the extended Half-life products

NOTE Confidence: 0.85170436

 $00:38:30.155 \rightarrow 00:38:32.220$  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

 $00{:}38{:}35{.}401 \dashrightarrow 00{:}38{:}37{.}850$  different ways, many of which are familiar

NOTE Confidence: 0.85449994

 $00{:}38{:}37{.}850 \dashrightarrow 00{:}38{:}39{.}861$  to you by either adding polyethylene

NOTE Confidence: 0.85449994

 $00{:}38{:}39{.}861 \dashrightarrow 00{:}38{:}42{.}598$  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

 $00{:}38{:}45{.}250 \dashrightarrow 00{:}38{:}46{.}742$  to improve half-life, or,

NOTE Confidence: 0.85449994

 $00:38:46.742 \longrightarrow 00:38:48.980$  in the case of factor 8,

 $00{:}38{:}48{.}980 \dashrightarrow 00{:}38{:}51{.}774$  to remove that B domain, which causes

NOTE Confidence: 0.85449994

 $00:38:51.774 \longrightarrow 00:38:55.043$  a slight increase in the half life.

NOTE Confidence: 0.85449994

 $00{:}38{:}55{.}050 \dashrightarrow 00{:}38{:}57{.}626$  And there are now a number of products NOTE Confidence: 0.85449994

 $00:38:57.626 \rightarrow 00:39:00.476$  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

 $00:39:02.180 \longrightarrow 00:39:04.015$  and I'll draw your attention

NOTE Confidence: 0.85449994

 $00{:}39{:}04.015 \dashrightarrow 00{:}39{:}06.680$  to the last three on this list.

NOTE Confidence: 0.85449994

 $00:39:06.680 \rightarrow 00:39:09.179$  These are factor 9 products which have

NOTE Confidence: 0.85449994

 $00:39:09.179 \dashrightarrow 00:39:11.179$  been manipulated by these methods,

NOTE Confidence: 0.85449994

 $00{:}39{:}11{.}180 \dashrightarrow 00{:}39{:}14{.}268$  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

 $00{:}39{:}16{.}982 \dashrightarrow 00{:}39{:}20{.}177$  24 hours to upwards of 90 or 100 hours.

NOTE Confidence: 0.85449994

 $00{:}39{:}20{.}180 \dashrightarrow 00{:}39{:}23{.}444$  So this is allowed patients with factor 9

NOTE Confidence: 0.85449994

 $00:39:23.444 \dashrightarrow 00:39:26.336$  deficiency or hemophilia B to be treated.

NOTE Confidence: 0.85449994

 $00{:}39{:}26{.}340 \dashrightarrow 00{:}39{:}27{.}267$  Once a week,

NOTE Confidence: 0.85449994

 $00:39:27.267 \rightarrow 00:39:30.510$  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.

 $00{:}39{:}32{.}400 \dashrightarrow 00{:}39{:}34{.}235$  So a significant advance for

NOTE Confidence: 0.85449994

 $00:39:34.235 \rightarrow 00:39:36.070$  people needing to give intravenous

NOTE Confidence: 0.85449994

 $00:39:36.135 \rightarrow 00:39:37.707$  therapy themselves at home.

NOTE Confidence: 0.85449994

 $00:39:37.710 \longrightarrow 00:39:40.734$  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

 $00:39:41.119 \longrightarrow 00:39:43.393$  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

 $00:39:44.530 \longrightarrow 00:39:46.784$  and it turns out that the the

NOTE Confidence: 0.85449994

 $00{:}39{:}46{.}784 \dashrightarrow 00{:}39{:}48{.}633$  degradation in the catabolism and

NOTE Confidence: 0.85449994

 $00{:}39{:}48.633 \dashrightarrow 00{:}39{:}50.648$  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

 $00{:}39{:}55{.}900 \dashrightarrow 00{:}39{:}58{.}570$  the protein that it's bound to.

NOTE Confidence: 0.85449994

 $00:39:58.570 \rightarrow 00:40:00.328$  So making modifications in the FAQ.

00:40:00.330 --> 00:40:03.246 After 8 molecule has really had

NOTE Confidence: 0.85449994

 $00:40:03.246 \longrightarrow 00:40:05.828$  minimal effect up until recently

NOTE Confidence: 0.85449994

 $00:40:05.828 \longrightarrow 00:40:08.020$  on Factor 8 Half-life.

NOTE Confidence: 0.85449994

 $00:40:08.020 \rightarrow 00:40:10.778$  So an interesting construct has been devised,

NOTE Confidence: 0.85449994

 $00{:}40{:}10.780 \dashrightarrow 00{:}40{:}13.460$  and it's shown on the top panel here

NOTE Confidence: 0.85449994

 $00{:}40{:}13.460 \dashrightarrow 00{:}40{:}16.461$  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

 $00:40:19.450 \longrightarrow 00:40:21.808$  the binding region to factor 8,

NOTE Confidence: 0.85449994

 $00{:}40{:}21.810 \dashrightarrow 00{:}40{:}24.922$  is linked to an FC portion of an

NOTE Confidence: 0.85449994

 $00{:}40{:}24{.}922 \dashrightarrow 00{:}40{:}26{.}954$  immunoglobulin and linked to the

NOTE Confidence: 0.85449994

 $00:40:26.954 \rightarrow 00:40:29.294$  B domain less factor 8 molecule,

NOTE Confidence: 0.85449994

 $00{:}40{:}29{.}300 \dashrightarrow 00{:}40{:}31{.}658$  which also has linked on at

NOTE Confidence: 0.85449994

 $00:40:31.658 \longrightarrow 00:40:32.837$  this hydrophilic polypeptide,

NOTE Confidence: 0.85449994

 $00:40:32.840 \longrightarrow 00:40:35.598$  which also can extend the half life.

NOTE Confidence: 0.85449994

 $00:40:35.600 \longrightarrow 00:40:39.216$  So this product has been called bib 001.

NOTE Confidence: 0.85449994

 $00:40:39.220 \longrightarrow 00:40:40.680$  And was treated with.

- NOTE Confidence: 0.85449994
- $00:40:40.680 \longrightarrow 00:40:43.324$  Was used to treat a handful of

 $00{:}40{:}43{.}324 \dashrightarrow 00{:}40{:}45{.}189$  patients in a safety study,

NOTE Confidence: 0.85449994

 $00{:}40{:}45{.}190 \dashrightarrow 00{:}40{:}46{.}935$  and those results were were

NOTE Confidence: 0.85449994

 $00{:}40{:}46{.}935 \dashrightarrow 00{:}40{:}49{.}149$  reported in the New England Journal

NOTE Confidence: 0.85449994

 $00:40:49.149 \longrightarrow 00:40:51.159$  of Medicine earlier this year,

NOTE Confidence: 0.85449994

 $00{:}40{:}51.160 \dashrightarrow 00{:}40{:}53.010$  and patients were either treated

NOTE Confidence: 0.85449994

 $00{:}40{:}53.010 \dashrightarrow 00{:}40{:}55.597$  at two different doses of this new

NOTE Confidence: 0.85449994

 $00{:}40{:}55{.}597 \dashrightarrow 00{:}40{:}57{.}589$  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

 $00:40:59.528 \rightarrow 00:41:01.940$  to the typical factor 8 clearance

NOTE Confidence: 0.85449994

 $00:41:01.940 \longrightarrow 00:41:04.618$  seen in the lighter blue bars here

NOTE Confidence: 0.85449994

 $00{:}41{:}04.618 \dashrightarrow 00{:}41{:}07.198$  and what you can see I think,

NOTE Confidence: 0.85449994

 $00:41:07.200 \rightarrow 00:41:10.863$  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

 $00{:}41{:}12.870 \dashrightarrow 00{:}41{:}15.166$  about five or six fold the half life
$00:41:15.166 \longrightarrow 00:41:17.548$  of the standard factor 8 product.

NOTE Confidence: 0.85449994

 $00:41:17.550 \longrightarrow 00:41:19.895$  So this this product is now in

NOTE Confidence: 0.85449994

 $00{:}41{:}19.895 \dashrightarrow 00{:}41{:}21.797$  large scale clinical trials and I

NOTE Confidence: 0.85449994

 $00:41:21.797 \rightarrow 00:41:24.202$  think in the next year or two we

NOTE Confidence: 0.85449994

 $00:41:24.202 \rightarrow 00:41:26.227$  should have some more information,

NOTE Confidence: 0.85449994

 $00:41:26.230 \longrightarrow 00:41:28.774$  and this may be an advanced

NOTE Confidence: 0.85449994

 $00:41:28.774 \longrightarrow 00:41:31.860$  for for some of our patients.

NOTE Confidence: 0.85449994

 $00:41:31.860 \longrightarrow 00:41:33.636$  So let me shift for a minute for

NOTE Confidence: 0.85449994

 $00:41:33.636 \longrightarrow 00:41:35.799$  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

 $00:41:41.370 \longrightarrow 00:41:43.350$  three drugs that will talk about

NOTE Confidence: 0.85449994

 $00{:}41{:}43{.}350 \dashrightarrow 00{:}41{:}45{.}428$  will really focus primarily on this

NOTE Confidence: 0.85449994

 $00{:}41{:}45{.}428 \dashrightarrow 00{:}41{:}47{.}450$  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
- $00:41:50.895 \rightarrow 00:41:52.668$  bispecific monoclonal antibody.

NOTE Confidence: 0.84887415

 $00:41:52.670 \longrightarrow 00:41:56.086$  That binds the factor 9 and factor 10,

NOTE Confidence: 0.84887415

 $00:41:56.090 \rightarrow 00:41:59.514$  so it simulates the activity of Factor 8.

NOTE Confidence: 0.84887415

 $00:41:59.520 \longrightarrow 00:42:01.974$  Remember that factor 8 is able

NOTE Confidence: 0.84887415

 $00{:}42{:}01{.}974 \dashrightarrow 00{:}42{:}04{.}580$  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

 $00{:}42{:}06.790 \dashrightarrow 00{:}42{:}10.024$  This antibody is able to bind factor

NOTE Confidence: 0.84887415

 $00{:}42{:}10{.}024 \dashrightarrow 00{:}42{:}14{.}057$  9A and factor 10 in the circulation an

NOTE Confidence: 0.84887415

 $00{:}42{:}14.057 \dashrightarrow 00{:}42{:}17.529$  again simulate the activity of Factor 8.

NOTE Confidence: 0.84887415

 $00{:}42{:}17.530 \dashrightarrow 00{:}42{:}21.148$  So this drug is not exactly like Factor 8.

NOTE Confidence: 0.84887415

 $00{:}42{:}21{.}150 \dashrightarrow 00{:}42{:}21{.}952$  There are.

NOTE Confidence: 0.84887415

 $00{:}42{:}21.952 \dashrightarrow 00{:}42{:}23.957$  There are certain differences here.

NOTE Confidence: 0.84887415

 $00:42:23.960 \longrightarrow 00:42:26.774$  It binds to factor 8 and nine

NOTE Confidence: 0.84887415

 $00{:}42{:}26.774 \dashrightarrow 00{:}42{:}27.980$  in the circulation,

NOTE Confidence: 0.84887415

 $00{:}42{:}27{.}980 \dashrightarrow 00{:}42{:}30{.}386$  not just on the phospholipid membrane.

NOTE Confidence: 0.84887415

- $00:42:30.390 \longrightarrow 00:42:31.998$  It has different infinities
- NOTE Confidence: 0.84887415
- $00{:}42{:}31{.}998 \dashrightarrow 00{:}42{:}34{.}008$  for the substrate and enzyme,
- NOTE Confidence: 0.84887415
- $00{:}42{:}34.010 \dashrightarrow 00{:}42{:}36.782$  and whether or not that becomes an
- NOTE Confidence: 0.84887415
- $00:42:36.782 \rightarrow 00:42:39.892$  issue for this drug will only know
- NOTE Confidence: 0.84887415
- $00:42:39.892 \rightarrow 00:42:42.652$  as more experience is is accumulated.
- NOTE Confidence: 0.84887415
- $00:42:42.660 \longrightarrow 00:42:43.426$  But nonetheless,
- NOTE Confidence: 0.84887415
- $00:42:43.426 \rightarrow 00:42:46.107$  this drug is really shown dramatic activity,
- NOTE Confidence: 0.84887415
- $00:42:46.110 \longrightarrow 00:42:48.854$  so this this is a study that was
- NOTE Confidence: 0.84887415
- 00:42:48.854 $\operatorname{-->}$ 00:42:51.697 published a few years ago in the
- NOTE Confidence: 0.84887415
- $00{:}42{:}51{.}697 \dashrightarrow 00{:}42{:}53{.}767$  New England Journal of Medicine.
- NOTE Confidence: 0.84887415
- $00:42:53.770 \rightarrow 00:42:56.612$  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
- $00:42:58.750 \rightarrow 00:43:01.326$  so a challenging group of patients to
- NOTE Confidence: 0.84887415
- $00:43:01.326 \rightarrow 00:43:03.703$  treat were treated either with their
- NOTE Confidence: 0.84887415
- $00:43:03.703 \rightarrow 00:43:05.708$  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

 $00:43:07.982 \rightarrow 00:43:10.824$  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

 $00:43:12.730 \longrightarrow 00:43:14.525$  and the annual bleeding rate.

NOTE Confidence: 0.84887415

 $00{:}43{:}14.530 \dashrightarrow 00{:}43{:}17.099$  Is been been described on this slide

NOTE Confidence: 0.84887415

 $00:43:17.099 \rightarrow 00:43:20.532$  here and you could see if we just look

NOTE Confidence: 0.84887415

 $00{:}43{:}20{.}532 \dashrightarrow 00{:}43{:}23{.}457$  at these blue histograms for a minute here.

NOTE Confidence: 0.84887415

 $00{:}43{:}23.460 \dashrightarrow 00{:}43{:}26.496$  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

 $00{:}43{:}28{.}969 \dashrightarrow 00{:}43{:}31{.}905$  was about five or six and it was

NOTE Confidence: 0.84887415

 $00:43:31.905 \longrightarrow 00:43:34.558$  almost 30 in the standard of care.

NOTE Confidence: 0.84887415

 $00:43:34.560 \longrightarrow 00:43:36.532$  Treatment of patients with

NOTE Confidence: 0.84887415

 $00{:}43{:}36{.}532 \dashrightarrow 00{:}43{:}38{.}504$  hemophilia A and inhibitors.

NOTE Confidence: 0.84887415

 $00:43:38.510 \longrightarrow 00:43:40.834$  So a really significant

NOTE Confidence: 0.84887415

 $00{:}43{:}40{.}834 \dashrightarrow 00{:}43{:}43{.}158$  advantage for these individuals.

NOTE Confidence: 0.84887415

 $00{:}43{:}43{.}160 \dashrightarrow 00{:}43{:}45{.}421$  And then a second study was published

NOTE Confidence: 0.84887415

 $00{:}43{:}45{.}421 \dashrightarrow 00{:}43{:}47{.}770$  with looked at patients with hemophilia

NOTE Confidence: 0.84887415

 $00{:}43{:}47.770 \dashrightarrow 00{:}43{:}49.950$  A without inhibitors and these.

NOTE Confidence: 0.84887415

 $00{:}43{:}49{.}950 \dashrightarrow 00{:}43{:}51{.}830$  This was a randomized trial.

NOTE Confidence: 0.84887415

 $00{:}43{:}51{.}830 \dashrightarrow 00{:}43{:}53{.}610$  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

 $00{:}43{:}56{.}425 \dashrightarrow 00{:}43{:}58{.}357$  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

 $00:44:02.008 \longrightarrow 00:44:04.270$  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

 $00:44:06.465 \rightarrow 00:44:08.660$  bleeding rate went from about

NOTE Confidence: 0.84887415

 $00{:}44{:}08{.}741 \dashrightarrow 00{:}44{:}10{.}397$  40 to about one or two.