WEBVTT

NOTE duration:"00:49:49.7000000"

NOTE recognizability:0.783

NOTE language:en-us

NOTE Confidence: 0.824819200714286

 $00:00:00.000 \rightarrow 00:00:03.136$ Got it. So it's my distinct pleasure

NOTE Confidence: 0.824819200714286

 $00:00:03.136 \rightarrow 00:00:05.898$ to introduce Chen Yan to us today.

NOTE Confidence: 0.824819200714286

 $00{:}00{:}05{.}900 \dashrightarrow 00{:}00{:}07{.}664$ He's one of the invited speakers for

NOTE Confidence: 0.824819200714286

 $00{:}00{:}07{.}664 \dashrightarrow 00{:}00{:}09{.}540$ this year for the Melanoma program.

NOTE Confidence: 0.824819200714286

 $00:00:09.540 \longrightarrow 00:00:11.358$ So for those that don't know,

NOTE Confidence: 0.824819200714286

 $00:00:11.360 \longrightarrow 00:00:13.712$ Melanoma program is a fairly well

NOTE Confidence: 0.824819200714286

 $00{:}00{:}13.712 \dashrightarrow 00{:}00{:}16.013$ established 1 going back to the 1980s

NOTE Confidence: 0.824819200714286

 $00:00:16.013 \rightarrow 00:00:18.037$ when we started the first what wasn't me,

NOTE Confidence: 0.824819200714286

 $00:00:18.040 \longrightarrow 00:00:20.740$ other folks started the first

NOTE Confidence: 0.824819200714286

 $00:00:20.740 \longrightarrow 00:00:22.454$ interdisciplinary disease team,

NOTE Confidence: 0.824819200714286

00:00:22.454 --> 00:00:25.976 John Kirkwood and Steve Arians specifically.

NOTE Confidence: 0.824819200714286

 $00:00:25.980 \longrightarrow 00:00:27.359$ And then as the years went by,

NOTE Confidence: 0.824819200714286

00:00:27.360 --> 00:00:28.830 Ruth Taliban, who's sitting here,

 $00:00:28.830 \rightarrow 00:00:30.405$ wrote the first version of the Yale.

NOTE Confidence: 0.824819200714286

 $00{:}00{:}30{.}410 \dashrightarrow 00{:}00{:}33{.}218$ Or in skin cancer first funded in I

NOTE Confidence: 0.824819200714286

 $00{:}00{:}33{.}218$ --> $00{:}00{:}36{.}489$ think 2006 or 7 or something like that?

NOTE Confidence: 0.824819200714286

 $00:00:36.490 \rightarrow 00:00:39.556$ We just submitted the 4th iteration.

NOTE Confidence: 0.824819200714286

 $00{:}00{:}39{.}560 \dashrightarrow 00{:}00{:}41{.}720$ So one of the best things about working

NOTE Confidence: 0.824819200714286

 $00{:}00{:}41.720 \dashrightarrow 00{:}00{:}44.004$ here is actually our colleagues and I

NOTE Confidence: 0.824819200714286

 $00:00:44.004 \rightarrow 00:00:46.100$ think Chin actually exemplifies that.

NOTE Confidence: 0.824819200714286

 $00:00:46.100 \rightarrow 00:00:50.000$ So you came to us from from Harvard where

NOTE Confidence: 0.824819200714286

00:00:50.000 - > 00:00:51.600 he worked in the lab of Bill Kalen,

NOTE Confidence: 0.824819200714286

 $00:00:51.600 \rightarrow 00:00:53.200$ actually on epigenetics and renal

NOTE Confidence: 0.824819200714286

 $00{:}00{:}53.200 \dashrightarrow 00{:}00{:}54.440$ cell carcinoma.

NOTE Confidence: 0.824819200714286

 $00{:}00{:}54.440 \dashrightarrow 00{:}00{:}56.183$ But at some point it became clear

NOTE Confidence: 0.824819200714286

 $00{:}00{:}56.183 \dashrightarrow 00{:}00{:}58.477$ that some of the things that he was

NOTE Confidence: 0.824819200714286

 $00:00:58.477 \rightarrow 00:00:59.967$ studying were very applicable to

NOTE Confidence: 0.824819200714286

 $00{:}01{:}00{.}023 \dashrightarrow 00{:}01{:}02.522$ Melanoma as well and he submitted a

NOTE Confidence: 0.824819200714286

 $00:01:02.522 \rightarrow 00:01:03.962$ developmental research project to

 $00{:}01{:}03{.}962 \dashrightarrow 00{:}01{:}06{.}134$ the sport in its previous iteration.

NOTE Confidence: 0.824819200714286

 $00:01:06.140 \longrightarrow 00:01:07.752$ And that subsequently blossomed

NOTE Confidence: 0.824819200714286

 $00{:}01{:}07{.}752 \dashrightarrow 00{:}01{:}09{.}364$ to a full project.

NOTE Confidence: 0.824819200714286

 $00:01:09.370 \rightarrow 00:01:11.323$ We are thrilled to have Chen working with us.

NOTE Confidence: 0.824819200714286

00:01:11.330 --> 00:01:12.076 We couldn't,

NOTE Confidence: 0.824819200714286

00:01:12.076 --> 00:01:14.687 we couldn't ask for a better collaborator,

NOTE Confidence: 0.824819200714286

 $00{:}01{:}14.690 \dashrightarrow 00{:}01{:}16.335$ both in terms of his scientific depth

NOTE Confidence: 0.824819200714286

 $00:01:16.335 \rightarrow 00:01:17.988$ and in terms of his personality.

NOTE Confidence: 0.824819200714286

 $00:01:17.990 \longrightarrow 00:01:19.220$ He's definitely one of us.

NOTE Confidence: 0.824819200714286

 $00{:}01{:}19{.}220 \dashrightarrow 00{:}01{:}21{.}060$ And I actually don't care that he's the

NOTE Confidence: 0.824819200714286

 $00:01:21.060 \longrightarrow 00:01:22.786$ scientific Co director of the breast unit.

NOTE Confidence: 0.824819200714286

 $00{:}01{:}22.790 \dashrightarrow 00{:}01{:}24.530$ As far as we're concerned, he's ours.

NOTE Confidence: 0.824819200714286

 $00:01:24.530 \longrightarrow 00:01:25.810$ So without further ado,

NOTE Confidence: 0.824819200714286

 $00{:}01{:}25{.}810 \dashrightarrow 00{:}01{:}27{.}130$ chin, the floor is yours.

NOTE Confidence: 0.824819200714286

 $00:01:27.130 \longrightarrow 00:01:27.620$ Thank you.

00:01:31.230 --> 00:01:33.379 Well, thank you Harry for your kind

NOTE Confidence: 0.815876828888889

00:01:33.379 --> 00:01:35.363 introduction and and I was also

NOTE Confidence: 0.815876828888889

 $00:01:35.363 \rightarrow 00:01:37.237$ like to thank my normal program for NOTE Confidence: 0.815876828888889

 $00:01:37.237 \rightarrow 00:01:39.067$ nominating me here to present here.

NOTE Confidence: 0.815876828888889

00:01:39.070 --> 00:01:41.534 I would say Cancer Center ground is

NOTE Confidence: 0.815876828888889

 $00{:}01{:}41{.}534 \dashrightarrow 00{:}01{:}44{.}204$ one of the event that actually led

NOTE Confidence: 0.815876828888889

 $00{:}01{:}44{.}204$ --> $00{:}01{:}47{.}613$ me to work on Melanoma and on my way

NOTE Confidence: 0.815876828888889

00:01:47.613 --> 00:01:50.021 back from Grandma's talks and I was

NOTE Confidence: 0.815876828888889

 $00{:}01{:}50{.}030 \dashrightarrow 00{:}01{:}52{.}490$ working together with Marcus Bosenberg.

NOTE Confidence: 0.815876828888889

 $00:01:52.490 \longrightarrow 00:01:54.738$ I bought a decade ago and we were

NOTE Confidence: 0.815876828888889

 $00{:}01{:}54.738 \dashrightarrow 00{:}01{:}56.826$ talking about Jerry 1B who might be

NOTE Confidence: 0.815876828888889

 $00:01:56.826 \rightarrow 00:01:58.890$ which might be important in Melanoma.

NOTE Confidence: 0.815876828888889

 $00:01:58.890 \longrightarrow 00:02:01.200$ I was working on Jerry one.

NOTE Confidence: 0.815876828888889

00:02:01.200 --> 00:02:04.357 Because I generally knockout my and well,

NOTE Confidence: 0.815876828888889

 $00:02:04.360 \dashrightarrow 00:02:05.848$ we just started the collaboration and

NOTE Confidence: 0.815876828888889

 $00:02:05.848 \longrightarrow 00:02:07.963$ it's a very fun collaboration and this is

- NOTE Confidence: 0.815876828888889
- 00:02:07.963 --> 00:02:09.900 something I'm going to tell you today.

 $00:02:13.350 \longrightarrow 00:02:16.590$ So let me get this started.

NOTE Confidence: 0.5680343

 $00:02:16.590 \longrightarrow 00:02:17.880$ Fixed the pointer.

NOTE Confidence: 0.837761892

 $00{:}02{:}22{.}450 \dashrightarrow 00{:}02{:}24{.}810$ So this is my disclosure.

NOTE Confidence: 0.837761892

 $00:02:24.810 \dashrightarrow 00:02:26.722$ So what I'm going to do is first

NOTE Confidence: 0.837761892

 $00{:}02{:}26.722 \dashrightarrow 00{:}02{:}28.891$ you give you a very quick overview

NOTE Confidence: 0.837761892

 $00:02:28.891 \rightarrow 00:02:30.938$ of cancer epigenetics and then you

NOTE Confidence: 0.837761892

 $00:02:30.938 \longrightarrow 00:02:33.038$ tell you two stories related to

NOTE Confidence: 0.837761892

00:02:33.038 - > 00:02:35.348 this histone demethylase KDM 5B,

NOTE Confidence: 0.837761892

 $00:02:35.348 \rightarrow 00:02:38.493$ how it recognizes drug resistance

NOTE Confidence: 0.837761892

 $00:02:38.493 \longrightarrow 00:02:40.380$ and immune evasion.

NOTE Confidence: 0.837761892

00:02:40.380 --> 00:02:42.528 So as many of you know,

NOTE Confidence: 0.837761892

 $00:02:42.530 \longrightarrow 00:02:44.620$ the epigenetics is study of

NOTE Confidence: 0.837761892

 $00{:}02{:}44.620 \dashrightarrow 00{:}02{:}46.710$ health heroical traits that does

NOTE Confidence: 0.837761892

 $00{:}02{:}46.785 \dashrightarrow 00{:}02{:}49.125$ not depend on the underlying DNA

 $00:02:49.125 \rightarrow 00:02:51.388$ sequences and the major epigenetic

NOTE Confidence: 0.837761892

 $00:02:51.388 \rightarrow 00:02:53.896$ mechanism include DNA methylation.

NOTE Confidence: 0.837761892

00:02:53.900 --> 00:02:55.624 Put his own structure,

NOTE Confidence: 0.837761892

 $00{:}02{:}55{.}624 \dashrightarrow 00{:}02{:}58{.}490$ histone modifications and non coding on it.

NOTE Confidence: 0.837761892

 $00{:}02{:}58{.}490 \dashrightarrow 00{:}03{:}01{.}124$ There's a number of regulators of

NOTE Confidence: 0.837761892

 $00{:}03{:}01{.}124 \dashrightarrow 00{:}03{:}03{.}380$ IPG netting mechanism including the

NOTE Confidence: 0.837761892

 $00:03:03.380 \rightarrow 00:03:05.540$ coronary modernness which are involved

NOTE Confidence: 0.837761892

 $00:03:05.540 \rightarrow 00:03:08.149$ in moving the nuclear zones around

NOTE Confidence: 0.837761892

 $00{:}03{:}08{.}150 \dashrightarrow 00{:}03{:}11{.}438$ and rider eraser and the readers

NOTE Confidence: 0.837761892

00:03:11.438 --> 00:03:15.280 of histone or DNA modifications.

NOTE Confidence: 0.837761892

 $00:03:15.280 \longrightarrow 00:03:17.394$ So what I'm going to tell you

NOTE Confidence: 0.837761892

 $00{:}03{:}17{.}394 \dashrightarrow 00{:}03{:}19{.}380$ today mainly focus on KDM 5B which

NOTE Confidence: 0.837761892

 $00{:}03{:}19{.}380 \dashrightarrow 00{:}03{:}21{.}678$ is an eraser which is involved in

NOTE Confidence: 0.837761892

 $00{:}03{:}21.678 \dashrightarrow 00{:}03{:}23.158$ removing a certain modification

NOTE Confidence: 0.837761892

 $00:03:23.158 \rightarrow 00:03:25.347$ and sandbag one which I'm touched

NOTE Confidence: 0.837761892

 $00:03:25.347 \rightarrow 00:03:27.375$ upon which is the right approach.

- NOTE Confidence: 0.873892465384615
- 00:03:29.880 --> 00:03:32.484 So many of you are quite familiar
- NOTE Confidence: 0.873892465384615
- $00{:}03{:}32{.}484 \dashrightarrow 00{:}03{:}34{.}267$ with this hallmarks of cancer
- NOTE Confidence: 0.873892465384615
- $00:03:34.267 \rightarrow 00:03:36.627$ and what I'm going to tell you a
- NOTE Confidence: 0.873892465384615
- 00:03:36.700 00:03:38.878 little bit about is the immune,
- NOTE Confidence: 0.873892465384615
- $00:03:38.880 \longrightarrow 00:03:40.844$ the immune invasion that
- NOTE Confidence: 0.873892465384615
- $00:03:40.844 \longrightarrow 00:03:43.299$ cancer cells have to achieve.
- NOTE Confidence: 0.873892465384615
- 00:03:43.300 --> 00:03:46.020 And if you look at it on the right side,
- NOTE Confidence: 0.873892465384615
- $00:03:46.020 \longrightarrow 00:03:47.396$ this is a new,
- NOTE Confidence: 0.873892465384615
- $00{:}03{:}47.396 \dashrightarrow 00{:}03{:}49.460$ those are new hallmarks that have
- NOTE Confidence: 0.873892465384615
- 00:03:49.533 --> 00:03:51.597 been added to the hallmarks of
- NOTE Confidence: 0.873892465384615
- 00:03:51.597 00:03:54.096 cancer and two of which actually
- NOTE Confidence: 0.873892465384615
- $00{:}03{:}54.096 \dashrightarrow 00{:}03{:}56.196$ quite related to epigenetics,
- NOTE Confidence: 0.873892465384615
- $00{:}03{:}56{.}200 \dashrightarrow 00{:}03{:}59{.}116$ including unlocking phenotypic.
- NOTE Confidence: 0.873892465384615
- $00:03:59.116 \dashrightarrow 00:04:03.004$ Plasticity and epigenetic reprogramming.
- NOTE Confidence: 0.873892465384615
- $00:04:03.010 \rightarrow 00:04:07.290$ So that's what I'm going to tell you today.
- NOTE Confidence: 0.873892465384615

00:04:07.290 --> 00:04:11.421 So as many of you know epigenetic can

NOTE Confidence: 0.873892465384615

 $00:04:11.421 \longrightarrow 00:04:14.007$ epigenetics can regulate many of the

NOTE Confidence: 0.873892465384615

 $00:04:14.007 \dashrightarrow 00:04:17.418$ cell fate and also a lot of mechanisms NOTE Confidence: 0.873892465384615

00:04:17.418 --> 00:04:19.970 are involved in anti tumor immunity

NOTE Confidence: 0.873892465384615

 $00:04:19.970 \rightarrow 00:04:23.442$ and just on the tumor cells for example,

NOTE Confidence: 0.873892465384615

 $00:04:23.450 \rightarrow 00:04:25.730$ it has been shown DNA machination,

NOTE Confidence: 0.873892465384615

 $00{:}04{:}25.730 \dashrightarrow 00{:}04{:}27.974$ histone modifications have been

NOTE Confidence: 0.873892465384615

 $00:04:27.974 \rightarrow 00:04:30.779$ involved in regulating tumor antigen

NOTE Confidence: 0.873892465384615

 $00:04:30.779 \rightarrow 00:04:33.050$ expression and cytokine secretion,

NOTE Confidence: 0.873892465384615

00:04:33.050 - 00:04:35.174 PDL one expression and

NOTE Confidence: 0.873892465384615

00:04:35.174 --> 00:04:36.767 also chromatin structure.

NOTE Confidence: 0.873892465384615

 $00{:}04{:}36{.}770 \dashrightarrow 00{:}04{:}39{.}200$ Have been shown to be important

NOTE Confidence: 0.873892465384615

00:04:39.200 --> 00:04:41.400 to response to cytotoxic attack,

NOTE Confidence: 0.873892465384615

 $00{:}04{:}41{.}400 \dashrightarrow 00{:}04{:}43{.}480$ and those modifications are also

NOTE Confidence: 0.873892465384615

 $00:04:43.480 \rightarrow 00:04:45.560$ important on other immune cells,

NOTE Confidence: 0.873892465384615

 $00:04:45.560 \rightarrow 00:04:47.624$ including cytotoxic T cells,

- NOTE Confidence: 0.873892465384615
- 00:04:47.624 --> 00:04:49.688 dendritic cells and macrophages,
- NOTE Confidence: 0.873892465384615
- $00:04:49.690 \longrightarrow 00:04:52.540$ which is not duplicated here.
- NOTE Confidence: 0.873892465384615
- $00:04:52.540 \rightarrow 00:04:54.703$ So just a brief introduction on my
- NOTE Confidence: 0.873892465384615
- $00{:}04{:}54{.}703 \dashrightarrow 00{:}04{:}56{.}499$ laboratory and we are interested
- NOTE Confidence: 0.873892465384615
- $00:04:56.499 \dashrightarrow 00:04:58.499$ in cancer epigenetics of course.
- NOTE Confidence: 0.873892465384615
- $00{:}04{:}58.500 \dashrightarrow 00{:}05{:}00.876$ And one of the area we are interested
- NOTE Confidence: 0.873892465384615
- $00:05:00.876 \dashrightarrow 00:05:03.692$ in is a cancer metastasis shown here.
- NOTE Confidence: 0.873892465384615
- $00:05:03.692 \rightarrow 00:05:07.020$ Just one of the example where we showed
- NOTE Confidence: 0.873892465384615
- $00{:}05{:}07{.}103 \dashrightarrow 00{:}05{:}10{.}334$ one of the target called CCR two is a
- NOTE Confidence: 0.873892465384615
- $00:05:10.334 \rightarrow 00:05:13.059$ driver of breast cancer metastasis.
- NOTE Confidence: 0.873892465384615
- 00:05:13.060 00:05:14.716 And you can look at here,
- NOTE Confidence: 0.873892465384615
- 00:05:14.720 --> 00:05:16.436 if you knock down CCR two,
- NOTE Confidence: 0.873892465384615
- $00:05:16.440 \longrightarrow 00:05:18.337$ you can suppress the ability of those
- NOTE Confidence: 0.873892465384615
- 00:05:18.337 --> 00:05:20.192 breast cancer cells to metastasis to the
- NOTE Confidence: 0.873892465384615
- $00:05:20.192 \rightarrow 00:05:21.920$ lung and if you overexpress CCR two,
- NOTE Confidence: 0.873892465384615

 $00:05:21.920 \longrightarrow 00:05:22.420$ you.

NOTE Confidence: 0.873892465384615

 $00:05:22.420 \longrightarrow 00:05:24.420$ And rescue this phenotype.

NOTE Confidence: 0.873892465384615

 $00:05:24.420 \longrightarrow 00:05:26.366$ And of course we are very interested

NOTE Confidence: 0.873892465384615

 $00:05:26.366 \rightarrow 00:05:28.353$ in the immune invasion part of the

NOTE Confidence: 0.873892465384615

 $00:05:28.353 \rightarrow 00:05:30.637$ talk I'm going to talk about then and

NOTE Confidence: 0.873892465384615

 $00{:}05{:}30{.}637 \dashrightarrow 00{:}05{:}32{.}997$ this is something that I will mention later.

NOTE Confidence: 0.873892465384615

 $00:05:33.000 \rightarrow 00:05:35.690$ And so I'm not going to go over this figure.

NOTE Confidence: 0.873892465384615

 $00:05:35.690 \dashrightarrow 00:05:38.308$ And we are also interested in drug

NOTE Confidence: 0.873892465384615

 $00:05:38.308 \rightarrow 00:05:41.137$ resistance and I will tell you about our

NOTE Confidence: 0.873892465384615

 $00:05:41.137 \rightarrow 00:05:43.370$ work on the drug resistance in Melanoma,

NOTE Confidence: 0.873892465384615

 $00:05:43.370 \longrightarrow 00:05:46.778$ but this is a diagram actually found a.

NOTE Confidence: 0.873892465384615

 $00:05:46.780 \dashrightarrow 00:05:48.904$ Had breast cancer walk where we

NOTE Confidence: 0.873892465384615

 $00{:}05{:}48{.}904 \dashrightarrow 00{:}05{:}51{.}261$ showed that trastuzumab resistant

NOTE Confidence: 0.873892465384615

 $00{:}05{:}51{.}261 \dashrightarrow 00{:}05{:}53{.}929$ cells have increased oxidative

NOTE Confidence: 0.873892465384615

 $00:05:53.929 \rightarrow 00:05:57.266$ phosphorylation and if you block

NOTE Confidence: 0.873892465384615

 $00:05:57.266 \rightarrow 00:06:00.095$ oxidative phosphorylation with only a,

 $00:06:00.095 \rightarrow 00:06:02.370$ if you combine that with transfusion level,

NOTE Confidence: 0.873892465384615

 $00{:}06{:}02{.}370 \dashrightarrow 00{:}06{:}05{.}328$ you can actually regress the tumor

NOTE Confidence: 0.873892465384615

 $00:06:05.328 \dashrightarrow 00:06:08.799$ formation by the drug resistant cells.

NOTE Confidence: 0.873892465384615

 $00:06:08.800 \longrightarrow 00:06:10.372$ As a matter of because we

NOTE Confidence: 0.873892465384615

 $00:06:10.372 \rightarrow 00:06:11.760$ are interested in the area,

NOTE Confidence: 0.873892465384615

 $00{:}06{:}11.760 \dashrightarrow 00{:}06{:}13.960$ we are also interested in

NOTE Confidence: 0.873892465384615

00:06:13.960 --> 00:06:15.280 developing epigenetic drugs.

NOTE Confidence: 0.873892465384615

 $00:06:15.280 \rightarrow 00:06:17.701$ And I will tell you some of the work

NOTE Confidence: 0.873892465384615

 $00{:}06{:}17.701 \dashrightarrow 00{:}06{:}19.967$ on KDM 5 inhibitor development.

NOTE Confidence: 0.873892465384615

 $00{:}06{:}19{.}970 \dashrightarrow 00{:}06{:}22{.}805$ And this is a some work that we have

NOTE Confidence: 0.873892465384615

00:06:22.805 --> 00:06:26.053 done a couple years ago where we

NOTE Confidence: 0.873892465384615

00:06:26.053 --> 00:06:27.957 characterized I potent bromodomain

NOTE Confidence: 0.873892465384615

 $00{:}06{:}28.037 \dashrightarrow 00{:}06{:}31.055$ inhibitor where we show that this

NOTE Confidence: 0.873892465384615

 $00{:}06{:}31.055 \dashrightarrow 00{:}06{:}33.497$ bromodomain inhibitor and HW 870 can

NOTE Confidence: 0.873892465384615

00:06:33.497 -> 00:06:35.660 not only inhibit the ability of the

 $00:06:35.731 \rightarrow 00:06:38.219$ cell tumor cells to grow but you can.

NOTE Confidence: 0.873892465384615

 $00{:}06{:}38{.}220 \dashrightarrow 00{:}06{:}41{.}298$ Also hit on the macrophages by

NOTE Confidence: 0.873892465384615

 $00:06:41.298 \rightarrow 00:06:44.398$ suppressing the expression of CSF 1A,

NOTE Confidence: 0.873892465384615

00:06:44.398 --> 00:06:46.494 critical regulator of macrophage

NOTE Confidence: 0.873892465384615

 $00{:}06{:}46{.}494 \dashrightarrow 00{:}06{:}48{.}590$ polarization and the macrophage

NOTE Confidence: 0.873892465384615

 $00{:}06{:}48.664 \dashrightarrow 00{:}06{:}50.682$ proliferation and this drug actually

NOTE Confidence: 0.873892465384615

 $00:06:50.682 \rightarrow 00:06:52.290$ have entered the phase one clinical

NOTE Confidence: 0.873892465384615

00:06:52.341 --> 00:06:53.673 trial in in China and moving

NOTE Confidence: 0.873892465384615

 $00:06:53.673 \longrightarrow 00:06:54.561$ into phase two very

NOTE Confidence: 0.8063752266666667

 $00{:}06{:}54{.}609 \dashrightarrow 00{:}06{:}54{.}840$ soon.

NOTE Confidence: 0.612246446875

 $00{:}06{:}57{.}220 \dashrightarrow 00{:}06{:}59{.}530$ So my laboratory had been focusing

NOTE Confidence: 0.612246446875

 $00{:}06{:}59{.}530 \dashrightarrow 00{:}07{:}03{.}287$ on a group of England called KDM 5

NOTE Confidence: 0.612246446875

 $00{:}07{:}03.287 \dashrightarrow 00{:}07{:}06.135$ histone demethylase and and as you can

NOTE Confidence: 0.612246446875

 $00:07:06.135 \rightarrow 00:07:08.868$ see here this group of vendors have

NOTE Confidence: 0.612246446875

 $00:07:08.868 \rightarrow 00:07:12.332$ four of them and they they are called

NOTE Confidence: 0.612246446875

 $00{:}07{:}12.425 \dashrightarrow 00{:}07{:}15.264$ KDM 5 ABC D or Jared 1A1B1C and 1D

- NOTE Confidence: 0.612246446875
- $00{:}07{:}15.264 \dashrightarrow 00{:}07{:}18.335$ and all of those have this team JC
- NOTE Confidence: 0.612246446875
- $00:07:18.335 \dashrightarrow 00:07:21.198$ domain which is the Jumanji C domain,
- NOTE Confidence: 0.612246446875
- $00:07:21.200 \rightarrow 00:07:24.320$ it's hydroxylase domain and the by
- NOTE Confidence: 0.612246446875
- $00:07:24.320 \rightarrow 00:07:26.400$ hydroxylation of the methanation.
- NOTE Confidence: 0.612246446875
- $00:07:26.400 \rightarrow 00:07:28.410$ Group and the removal of formal dehyde.
- NOTE Confidence: 0.612246446875
- $00:07:28.410 \dashrightarrow 00:07:31.968$ They actually can demate the histones.
- NOTE Confidence: 0.612246446875
- $00:07:31.970 \rightarrow 00:07:34.644$ So this group of landline can demonstrate,
- NOTE Confidence: 0.612246446875
- 00:07:34.650 -> 00:07:37.170 try and demonstrate nice thing
- NOTE Confidence: 0.612246446875
- $00:07:37.170 \longrightarrow 00:07:39.186$ four on histone H3.
- NOTE Confidence: 0.612246446875
- $00{:}07{:}39{.}190 \dashrightarrow 00{:}07{:}40{.}910$ And because those machination
- NOTE Confidence: 0.612246446875
- $00:07:40.910 \longrightarrow 00:07:43.060$ marks are critical marks for
- NOTE Confidence: 0.612246446875
- 00:07:43.060 -> 00:07:44.709 actually transcribed genes,
- NOTE Confidence: 0.612246446875
- 00:07:44.710 --> 00:07:47.930 so by doing so this group of
- NOTE Confidence: 0.612246446875
- $00{:}07{:}47.930 \dashrightarrow 00{:}07{:}50.780$ online can silence transcription.
- NOTE Confidence: 0.612246446875
- $00:07:50.780 \longrightarrow 00:07:52.256$ But that's not the whole story.
- NOTE Confidence: 0.612246446875

 $00:07:52.260 \rightarrow 00:07:54.984$ And all those protein actually have

NOTE Confidence: 0.612246446875

 $00:07:54.984 \longrightarrow 00:07:57.320$ other domains including 80 rich

NOTE Confidence: 0.612246446875

 $00:07:57.320 \longrightarrow 00:07:59.520$ interactive domain which is involved

NOTE Confidence: 0.612246446875

 $00{:}07{:}59{.}520$ --> $00{:}08{:}02{.}905$ in DNA binding and some of the PhD

NOTE Confidence: 0.612246446875

 $00:08:02.905 \longrightarrow 00:08:05.233$ fingers which are involved in binding

NOTE Confidence: 0.612246446875

 $00{:}08{:}05{.}240 \dashrightarrow 00{:}08{:}07{.}076$ specific histone modifications.

NOTE Confidence: 0.612246446875

00:08:07.076 --> 00:08:08.300 In addition,

NOTE Confidence: 0.612246446875

 $00:08:08.300 \longrightarrow 00:08:10.778$ they can interact with many other

NOTE Confidence: 0.612246446875

00:08:10.778 --> 00:08:12.948 proteins involved in chromatin remodeling

NOTE Confidence: 0.612246446875

 $00:08:12.948 \dashrightarrow 00:08:14.624$ and transcription recognition.

NOTE Confidence: 0.612246446875

 $00:08:14.624 \rightarrow 00:08:16.460$ So they have.

NOTE Confidence: 0.612246446875

 $00{:}08{:}16.460 \dashrightarrow 00{:}08{:}18.150$ It has been documented that

NOTE Confidence: 0.612246446875

00:08:18.150 --> 00:08:19.840 this group ENDLINE cannot only.

NOTE Confidence: 0.612246446875

 $00:08:19.840 \dashrightarrow 00:08:21.204$ The transcription repressor they

NOTE Confidence: 0.612246446875

 $00:08:21.204 \longrightarrow 00:08:22.568$ can be transcription activated

NOTE Confidence: 0.612246446875

 $00:08:22.568 \rightarrow 00:08:24.030$ in some other settings.

- NOTE Confidence: 0.811010291666667
- 00:08:26.110 --> 00:08:27.826 So today's talk we'll we'll be,
- NOTE Confidence: 0.811010291666667
- 00:08:27.830 --> 00:08:30.518 I'll be focusing on on this protein
- NOTE Confidence: 0.811010291666667
- 00:08:30.518 --> 00:08:33.215 called Kadian 5B or Jerry 1B.
- NOTE Confidence: 0.811010291666667
- 00:08:33.215 --> 00:08:35.275 Also another known name
- NOTE Confidence: 0.811010291666667
- 00:08:35.275 --> 00:08:37.750 is called the PLU One.
- NOTE Confidence: 0.811010291666667
- $00:08:37.750 \longrightarrow 00:08:40.800$ Because there's a number of.
- NOTE Confidence: 0.811010291666667
- $00:08:40.800 \longrightarrow 00:08:42.940$ Evidence showing that uh
- NOTE Confidence: 0.811010291666667
- $00:08:42.940 \longrightarrow 00:08:45.615$ Kadian 5B has oncogenic role.
- NOTE Confidence: 0.811010291666667
- $00:08:45.620 \dashrightarrow 00:08:47.228$ It was shown to be overexpressed
- NOTE Confidence: 0.811010291666667
- $00:08:47.228 \rightarrow 00:08:48.300$ in many cancer types,
- NOTE Confidence: 0.811010291666667
- 00:08:48.300 --> 00:08:50.181 including skin cancer.
- NOTE Confidence: 0.811010291666667
- $00{:}08{:}50{.}181 \dashrightarrow 00{:}08{:}53{.}316$ Initially was identified as a
- NOTE Confidence: 0.811010291666667
- $00{:}08{:}53.316 \dashrightarrow 00{:}08{:}55.774$ downstream gene downstream of her
- NOTE Confidence: 0.811010291666667
- $00{:}08{:}55{.}774 \dashrightarrow 00{:}08{:}58{.}510$ 2IN breast cancer because it was
- NOTE Confidence: 0.811010291666667
- $00:08:58.598 \dashrightarrow 00:09:01.559$ shown to be downregulated by anti to
- NOTE Confidence: 0.811010291666667

 $00:09:01.559 \rightarrow 00:09:04.988$ anybody in her two overexpression cells.

NOTE Confidence: 0.811010291666667

 $00:09:04.990 \longrightarrow 00:09:07.486$ And these have been shown by 90 points

NOTE Confidence: 0.811010291666667

 $00:09:07.486 \rightarrow 00:09:09.660$ group that is amplified in luminal

NOTE Confidence: 0.811010291666667

 $00:09:09.660 \rightarrow 00:09:11.880$ breast cancer and it's a potential

NOTE Confidence: 0.811010291666667

 $00:09:11.945 \longrightarrow 00:09:13.449$ luminal linearity driving oncogene

NOTE Confidence: 0.811010291666667

 $00:09:13.449 \longrightarrow 00:09:18.220$ and we have shown in any in mouse.

NOTE Confidence: 0.811010291666667

 $00:09:18.220 \longrightarrow 00:09:21.894$ Me, I'd be single cells that are

NOTE Confidence: 0.811010291666667

 $00{:}09{:}21.894 \dashrightarrow 00{:}09{:}24.723$ Jerry 1B can recruit Gallant St to

NOTE Confidence: 0.811010291666667

00:09:24.723 --> 00:09:27.357 regulate Fox A1 expression and that

NOTE Confidence: 0.811010291666667

 $00{:}09{:}27.357 \dashrightarrow 00{:}09{:}29.153$ contribute to estrogen receptor

NOTE Confidence: 0.811010291666667

 $00{:}09{:}29{.}153 \dashrightarrow 00{:}09{:}31{.}278$ target gene expression and in

NOTE Confidence: 0.811010291666667

 $00:09:31.278 \longrightarrow 00:09:34.720$ fact if you look at the estrogen.

NOTE Confidence: 0.811010291666667

 $00:09:34.720 \longrightarrow 00:09:36.588$ Except the positive tumors

NOTE Confidence: 0.811010291666667

 $00:09:36.588 \longrightarrow 00:09:38.456$ in for breast cancer,

NOTE Confidence: 0.811010291666667

00:09:38.460 --> 00:09:41.160 higher activity of Jerry won't

NOTE Confidence: 0.811010291666667

 $00:09:41.160 \dashrightarrow 00:09:45.626$ be OK and 5B is correlated with

- NOTE Confidence: 0.811010291666667
- $00:09:45.626 \rightarrow 00:09:49.736$ poor prognosis of those patients.
- NOTE Confidence: 0.811010291666667
- 00:09:49.740 $\operatorname{-->}$ 00:09:52.015 And and then you point out group
- NOTE Confidence: 0.811010291666667
- $00{:}09{:}52.015 \dashrightarrow 00{:}09{:}55.086$ has also shown that Kadian 5B can
- NOTE Confidence: 0.811010291666667
- $00:09:55.086 \rightarrow 00:09:56.601$ promote transcriptomic heterogeneity
- NOTE Confidence: 0.8110102916666667
- $00:09:56.601 \rightarrow 00:09:59.459$ and this actually contribute to the
- NOTE Confidence: 0.811010291666667
- $00:09:59.459 \rightarrow 00:10:01.569$ the rapeutic resistance and this is
- NOTE Confidence: 0.811010291666667
- $00:10:01.569 \rightarrow 00:10:04.930$ just one of the mechanism that this
- NOTE Confidence: 0.811010291666667
- $00:10:04.930 \longrightarrow 00:10:06.840$ could contribute to resistance.
- NOTE Confidence: 0.811010291666667
- 00:10:06.840 --> 00:10:09.990 I will tell you more about our
- NOTE Confidence: 0.811010291666667
- $00:10:09.990 \longrightarrow 00:10:12.429$ work on a different angle.
- NOTE Confidence: 0.811010291666667
- 00:10:12.430 --> 00:10:13.242 In addition,
- NOTE Confidence: 0.811010291666667
- $00{:}10{:}13.242 \dashrightarrow 00{:}10{:}15.678$ when we deplete KDM 5B first
- NOTE Confidence: 0.811010291666667
- $00{:}10{:}15.678 \dashrightarrow 00{:}10{:}18.015$ initially in breast cancer cells
- NOTE Confidence: 0.811010291666667
- 00:10:18.015 --> 00:10:19.947 in syngeneic mouse model,
- NOTE Confidence: 0.811010291666667
- 00:10:19.950 --> 00:10:22.266 you can see down regulation of
- NOTE Confidence: 0.811010291666667

00:10:22.266 --> 00:10:24.629 KADIAN 5B can decrease the ability

NOTE Confidence: 0.811010291666667

 $00{:}10{:}24.629 \dashrightarrow 00{:}10{:}26.867$ of those tumor cells to grow.

NOTE Confidence: 0.811010291666667

00:10:26.870 --> 00:10:31.070 And it was shown by Mihan honing

NOTE Confidence: 0.811010291666667

 $00:10:31.070 \rightarrow 00:10:34.699$ scope that if you suppress.

NOTE Confidence: 0.811010291666667

 $00:10:34.700 \rightarrow 00:10:36.610$ Expression in normal cells initially,

NOTE Confidence: 0.811010291666667

 $00{:}10{:}36{.}610 \dashrightarrow 00{:}10{:}39{.}346$ those tumor cells actually grow faster.

NOTE Confidence: 0.811010291666667

00:10:39.350 --> 00:10:41.530 However, after you serial transplantation,

NOTE Confidence: 0.811010291666667

 $00:10:41.530 \longrightarrow 00:10:43.322$ those cells still crash,

NOTE Confidence: 0.811010291666667

 $00:10:43.322 \rightarrow 00:10:45.562$ so suggesting that it's required

NOTE Confidence: 0.811010291666667

 $00{:}10{:}45.562 \dashrightarrow 00{:}10{:}48.774$ for Melanoma maintenance instead of

NOTE Confidence: 0.811010291666667

 $00:10:48.774 \rightarrow 00:10:51.458$ putting refreshing initial proliferation.

NOTE Confidence: 0.811010291666667

 $00:10:51.460 \rightarrow 00:10:54.057$ And they was shown in multiple groups

NOTE Confidence: 0.811010291666667

 $00{:}10{:}54.057 \dashrightarrow 00{:}10{:}56.313$ including ours that KADIAN file be

NOTE Confidence: 0.811010291666667

 $00:10:56.313 \rightarrow 00:10:58.461$ is involved in drug resistance and

NOTE Confidence: 0.811010291666667

00:10:58.461 - 00:11:00.939 shown here just one of the example by

NOTE Confidence: 0.811010291666667

 $00:11:00.939 \rightarrow 00:11:02.526$ actually by a company constellation

- NOTE Confidence: 0.811010291666667
- $00:11:02.526 \rightarrow 00:11:04.644$ where they showed in multiple cancer
- NOTE Confidence: 0.811010291666667
- $00:11:04.644 \dashrightarrow 00:11:06.379$ cell lines including Melanoma.
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}06{.}380 \dashrightarrow 00{:}11{:}10{.}405$ Here if you compare the effect of
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}10{.}405 \dashrightarrow 00{:}11{:}13{.}494$ Canadian five inhibitor on parental
- NOTE Confidence: 0.8110102916666667
- $00:11:13.494 \rightarrow 00:11:16.644$ cells or drug tolerant persister
- NOTE Confidence: 0.811010291666667
- 00:11:16.644 --> 00:11:18.600 cells if you actually in this
- NOTE Confidence: 0.811010291666667
- $00:11:18.600 \rightarrow 00:11:20.780$ case they did a pre treatment of.
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}20.780 \dashrightarrow 00{:}11{:}24.908$ Both S and and they should have shown
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}24{.}908 \dashrightarrow 00{:}11{:}27{.}505$ that the KADIAN 5 inhibitor cannot
- NOTE Confidence: 0.811010291666667
- $00:11:27.505 \rightarrow 00:11:30.790$ inhibit the growth of the parental cells,
- NOTE Confidence: 0.811010291666667
- $00:11:30.790 \rightarrow 00:11:34.630$ but they can prevent the emergence
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}34{.}630 \dashrightarrow 00{:}11{:}37{.}659$ of the drug resistant tolerant.
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}37.659 \dashrightarrow 00{:}11{:}41.157$ Would DP cells or drug tolerant
- NOTE Confidence: 0.811010291666667
- $00:11:41.157 \rightarrow 00:11:44.479$ persister cells or drug resistant cells?
- NOTE Confidence: 0.811010291666667
- $00{:}11{:}44{.}480 \dashrightarrow 00{:}11{:}49{.}072$ In prostate cancer if we cost the
- NOTE Confidence: 0.811010291666667

 $00:11:49.072 \longrightarrow 00:11:52.060$ KADIAN file be knockout model to

NOTE Confidence: 0.811010291666667

 $00:11:52.171 \longrightarrow 00:11:54.932$ the P-10 knockout model in process

NOTE Confidence: 0.811010291666667

 $00{:}11{:}54{.}932 \dashrightarrow 00{:}11{:}57{.}322$ specific deletion and where you

NOTE Confidence: 0.811010291666667

00:11:57.322 --> 00:12:00.101 can see P-10 knockout model can

NOTE Confidence: 0.811010291666667

 $00{:}12{:}00{.}101 \dashrightarrow 00{:}12{:}01{.}877$ form a prostate cancer.

NOTE Confidence: 0.811010291666667

 $00{:}12{:}01{.}880 \dashrightarrow 00{:}12{:}05{.}400$ But if you get relocation 5B you can

NOTE Confidence: 0.811010291666667

 $00{:}12{:}05{.}400 \dashrightarrow 00{:}12{:}08{.}333$ normalize the those those prostate

NOTE Confidence: 0.811010291666667

 $00:12:08.333 \rightarrow 00:12:11.612$ tumors basically you can see the

NOTE Confidence: 0.811010291666667

 $00:12:11.612 \longrightarrow 00:12:14.570$ the the size is much smaller.

NOTE Confidence: 0.811010291666667

 $00{:}12{:}14.570 \dashrightarrow 00{:}12{:}18.338$ Now I want to move back to Melanoma

NOTE Confidence: 0.811010291666667

 $00{:}12{:}18{.}338 \dashrightarrow 00{:}12{:}22{.}224$ because this is a focus on our talk today.

NOTE Confidence: 0.744956012222222

 $00{:}12{:}22{.}230 \dashrightarrow 00{:}12{:}25{.}290$ 1st when we looked at the TCA data set,

NOTE Confidence: 0.744956012222222

 $00{:}12{:}25{.}290 \dashrightarrow 00{:}12{:}27{.}942$ this was done by Goran, a tenant in

NOTE Confidence: 0.744956012222222

 $00:12:27.942 \dashrightarrow 00:12:30.006$ the graduate student at that time.

NOTE Confidence: 0.744956012222222

 $00:12:30.010 \rightarrow 00:12:33.810$ In exposing like who is final right now?

NOTE Confidence: 0.744956012222222

 $00:12:33.810 \longrightarrow 00:12:36.590$ Where he showed that high

00:12:36.590 --> 00:12:40.320 expression is associated with poor

NOTE Confidence: 0.744956012222222

 $00{:}12{:}40{.}320 \dashrightarrow 00{:}12{:}43{.}304$ survival of Melanoma patients.

NOTE Confidence: 0.744956012222222

 $00:12:43.310 \longrightarrow 00:12:47.094$ So now we decided to look at the

NOTE Confidence: 0.744956012222222

 $00{:}12{:}47.094 \dashrightarrow 00{:}12{:}50.326$ Melanoma when we when we followed some

NOTE Confidence: 0.744956012222222

 $00:12:50.326 \rightarrow 00:12:53.442$ of the work from Marcus Bosenberg.

NOTE Confidence: 0.744956012222222

 $00{:}12{:}53{.}442 \dashrightarrow 00{:}12{:}57{.}250$ I have about my normal propagating cells.

NOTE Confidence: 0.744956012222222

 $00{:}12{:}57{.}250 \dashrightarrow 00{:}12{:}59{.}970$ Was published more than a decade ago that

NOTE Confidence: 0.744956012222222

 $00:12:59.970 \rightarrow 00:13:03.068$ if you look at the mouse Melanoma cells,

NOTE Confidence: 0.744956012222222

 $00:13:03.070 \longrightarrow 00:13:06.130$ you can sort them to three

NOTE Confidence: 0.744956012222222

 $00:13:06.130 \rightarrow 00:13:07.150$ different populations,

NOTE Confidence: 0.744956012222222

00:13:07.150 --> 00:13:10.883 the P75P-75 positive cells,

NOTE Confidence: 0.744956012222222

00:13:10.883 --> 00:13:13.589 CD 34 positive cells or the

NOTE Confidence: 0.744956012222222

00:13:13.589 - 00:13:15.290 double negative cells.

NOTE Confidence: 0.744956012222222

00:13:15.290 --> 00:13:17.054 If you look at the ability

NOTE Confidence: 0.744956012222222

 $00{:}13{:}17.054 \dashrightarrow 00{:}13{:}19.150$ of the cells to form tumors,

 $00:13:19.150 \longrightarrow 00:13:22.643$ the CD 34 positive cells can form

NOTE Confidence: 0.744956012222222

 $00{:}13{:}22.643 \dashrightarrow 00{:}13{:}25.110$ tumors very efficiently and the

NOTE Confidence: 0.744956012222222

 $00{:}13{:}25{.}110 \dashrightarrow 00{:}13{:}27{.}738$ double negative cells can do so.

NOTE Confidence: 0.744956012222222

 $00:13:27.740 \rightarrow 00:13:30.932$ With less efficacy but still works

NOTE Confidence: 0.744956012222222

 $00:13:30.932 \longrightarrow 00:13:33.692$ and the PDP 75 positive cells

NOTE Confidence: 0.744956012222222

00:13:33.692 $\operatorname{-->}$ 00:13:36.230 do not actually form tumors if

NOTE Confidence: 0.744956012222222

 $00:13:36.314 \rightarrow 00:13:39.490$ they put them into modern mice.

NOTE Confidence: 0.744956012222222

 $00{:}13{:}39{.}490 \dashrightarrow 00{:}13{:}43{.}242$ So we decided to look at this more

NOTE Confidence: 0.744956012222222

 $00:13:43.242 \rightarrow 00:13:45.240$ systematically and when this is

NOTE Confidence: 0.744956012222222

 $00{:}13{:}45{.}240 \dashrightarrow 00{:}13{:}47{.}375$ just a diagram show a table showing

NOTE Confidence: 0.744956012222222

00:13:47.375 $\operatorname{-->}$ 00:13:49.834 and many of the Yale University

NOTE Confidence: 0.744956012222222

00:13:49.834 --> 00:13:51.914 mouseman normal cell lines generated

NOTE Confidence: 0.744956012222222

00:13:51.985 --> 00:13:54.065 by Marcus Bosenberg Snapstory and

NOTE Confidence: 0.744956012222222

 $00{:}13{:}54.065 \dashrightarrow 00{:}13{:}56.553$ those cell lines are generated was

NOTE Confidence: 0.744956012222222

00:13:56.553 --> 00:13:59.777 fun back six animals and you can do

NOTE Confidence: 0.744956012222222

 $00{:}13{:}59{.}777 \dashrightarrow 00{:}14{:}04{.}523$ use those and use those cells for

- NOTE Confidence: 0.744956012222222
- $00:14:04.523 \rightarrow 00:14:06.647$ syngeneic transplantation experiments.
- NOTE Confidence: 0.744956012222222
- $00:14:06.650 \longrightarrow 00:14:08.785$ And two of the cell lines we.
- NOTE Confidence: 0.744956012222222
- 00:14:08.790 --> 00:14:13.477 Used here uh Young 11.7 which will
- NOTE Confidence: 0.744956012222222
- $00:14:13.477 \longrightarrow 00:14:16.130$ actually I will use it also later
- NOTE Confidence: 0.744956012222222
- $00:14:16.214 \longrightarrow 00:14:18.674$ on on for e-mail invasion studies
- NOTE Confidence: 0.744956012222222
- $00:14:18.674 \rightarrow 00:14:21.096$ and also young ones 3.3 cells.
- NOTE Confidence: 0.744956012222222
- $00:14:21.096 \rightarrow 00:14:23.812$ The reason why we chose those cells
- NOTE Confidence: 0.744956012222222
- $00:14:23.812 \rightarrow 00:14:25.840$ because they only have two populations
- NOTE Confidence: 0.744956012222222
- $00{:}14{:}25{.}840 \dashrightarrow 00{:}14{:}28{.}123$ so these 34 positive and city 34
- NOTE Confidence: 0.744956012222222
- $00{:}14{:}28{.}123 \dashrightarrow 00{:}14{:}30{.}419$ negative both of them can form too much.
- NOTE Confidence: 0.744956012222222
- $00:14:30.420 \longrightarrow 00:14:34.083$ So this provide a nice system to look at
- NOTE Confidence: 0.744956012222222
- $00:14:34.083 \rightarrow 00:14:38.200$ the population changes and when we put.
- NOTE Confidence: 0.744956012222222
- $00{:}14{:}38{.}200 \dashrightarrow 00{:}14{:}41{.}040$ Drugs on onto them.
- NOTE Confidence: 0.744956012222222
- $00{:}14{:}41{.}040 \dashrightarrow 00{:}14{:}44{.}328$ So we used the because those
- NOTE Confidence: 0.744956012222222
- $00{:}14{:}44{.}328 \dashrightarrow 00{:}14{:}47{.}515$ are mutant tumors and we treat
- NOTE Confidence: 0.744956012222222

 $00:14:47.515 \longrightarrow 00:14:50.150$ those cells with rough inhibitor.

NOTE Confidence: 0.744956012222222

 $00{:}14{:}50{.}150 \dashrightarrow 00{:}14{:}52{.}346$ In this case we use actually

NOTE Confidence: 0.744956012222222

 $00:14:52.346 \longrightarrow 00:14:56.560$ use the PX4 or three, two over.

NOTE Confidence: 0.744956012222222

 $00{:}14{:}56{.}560 \dashrightarrow 00{:}14{:}57{.}011$ Stephanie.

NOTE Confidence: 0.744956012222222

00:14:57.011 --> 00:14:57.462 Umm,

NOTE Confidence: 0.744956012222222

 $00{:}14{:}57{.}462 \dashrightarrow 00{:}14{:}59{.}717$ as you can see here,

NOTE Confidence: 0.744956012222222

 $00:14:59.720 \longrightarrow 00:15:01.918$ if you compare the parental cells and

NOTE Confidence: 0.744956012222222

 $00:15:01.918 \rightarrow 00:15:04.217$ you have more CD 34 positive cells.

NOTE Confidence: 0.744956012222222

 $00{:}15{:}04{.}220 \dashrightarrow 00{:}15{:}07{.}219$ If you look at the resistance the

NOTE Confidence: 0.744956012222222

00:15:07.219 --> 00:15:09.764 drug resistant cells you have

NOTE Confidence: 0.744956012222222

 $00{:}15{:}09{.}764 \dashrightarrow 00{:}15{:}13{.}119$ which we delicate as the Yom Young

NOTE Confidence: 0.744956012222222

00:15:13.120 --> 00:15:14.980 1.73 R or resistance,

NOTE Confidence: 0.744956012222222

 $00:15:14.980 \longrightarrow 00:15:18.390$ they have more city 34 negative cells.

NOTE Confidence: 0.744956012222222

 $00:15:18.390 \longrightarrow 00:15:21.552$ When you look at the the effect

NOTE Confidence: 0.744956012222222

 $00{:}15{:}21{.}552 \dashrightarrow 00{:}15{:}23{.}748$ of the Bureau of inhibitor on

NOTE Confidence: 0.744956012222222

 $00:15:23.748 \rightarrow 00:15:25.700$ those soap sub populations,

- NOTE Confidence: 0.744956012222222
- 00:15:25.700 --> 00:15:27.970 you can see 3034 negative.
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}27{.}970 \dashrightarrow 00{:}15{:}31{.}588$ Those are more resistant to be
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}31{.}588 \dashrightarrow 00{:}15{:}34{.}000$ off inhibitor treatment because
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}34{.}102 \dashrightarrow 00{:}15{:}37{.}118$ there's less growth inhibition.
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}37{.}120 \dashrightarrow 00{:}15{:}40{.}540$ And this phenomenon is also reversible.
- NOTE Confidence: 0.744956012222222
- $00:15:40.540 \longrightarrow 00:15:42.120$ If we treat those,
- NOTE Confidence: 0.744956012222222
- $00:15:42.120 \longrightarrow 00:15:44.490$ you can see that they shifted
- NOTE Confidence: 0.744956012222222
- $00:15:44.579 \rightarrow 00:15:45.979$ to the left side,
- NOTE Confidence: 0.744956012222222
- 00:15:45.980 --> 00:15:48.650 meaning CD 34 negative cells.
- NOTE Confidence: 0.744956012222222
- 00:15:48.650 --> 00:15:49.003 However,
- NOTE Confidence: 0.744956012222222
- $00:15:49.003 \rightarrow 00:15:51.827$ if you remove the drug after a couple
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}51{.}827 \dashrightarrow 00{:}15{:}54{.}095$ passages and they will shift it back
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}54.095 \dashrightarrow 00{:}15{:}56.100$ to the parental cell population.
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}56{.}100 \dashrightarrow 00{:}15{:}58{.}158$ So one of the things that was
- NOTE Confidence: 0.744956012222222
- $00{:}15{:}58{.}160 \dashrightarrow 00{:}16{:}01{.}275$ actually who it was a graduate student
- NOTE Confidence: 0.744956012222222

00:16:01.275 --> 00:16:03.686 once Marcus and I basically should

NOTE Confidence: 0.744956012222222

 $00{:}16{:}03.686 \dashrightarrow 00{:}16{:}05.951$ notice that there's an increased

NOTE Confidence: 0.744956012222222

 $00{:}16{:}05{.}951 \dashrightarrow 00{:}16{:}08{.}920$ expression of KDM 5B if we treat

NOTE Confidence: 0.744956012222222

 $00{:}16{:}08{.}920 \dashrightarrow 00{:}16{:}10{.}980$ those cells with BRAF inhibitor.

NOTE Confidence: 0.78673038625

 $00:16:10.980 \longrightarrow 00:16:13.512$ And this is shown in young

NOTE Confidence: 0.78673038625

 $00{:}16{:}13.512 \dashrightarrow 00{:}16{:}15.160$ 1.7 cells, 3.377 cells.

NOTE Confidence: 0.78673038625

 $00:16:15.160 \rightarrow 00:16:17.975$ But also when you compare the parental

NOTE Confidence: 0.78673038625

 $00{:}16{:}17{.}975 \dashrightarrow 00{:}16{:}20{.}880$ with the resistance cells you see the

NOTE Confidence: 0.78673038625

 $00:16:20.880 \rightarrow 00:16:24.940$ similar increase of KADIAN fab expression.

NOTE Confidence: 0.78673038625

 $00:16:24.940 \longrightarrow 00:16:27.768$ And this is reversible if you take

NOTE Confidence: 0.78673038625

 $00{:}16{:}27.768 \dashrightarrow 00{:}16{:}30.901$ out out and be rough inhibitor and

NOTE Confidence: 0.78673038625

 $00:16:30.901 \rightarrow 00:16:34.215$ the expression drops down and it's

NOTE Confidence: 0.78673038625

 $00:16:34.215 \longrightarrow 00:16:39.340$ showing 1.7 cells as well as 3.3 cells.

NOTE Confidence: 0.78673038625

 $00{:}16{:}39{.}340 \dashrightarrow 00{:}16{:}42{.}952$ So when we did the genetic experiment

NOTE Confidence: 0.78673038625

 $00:16:42.952 \rightarrow 00:16:46.237$ when we knocked down kidding 5

NOTE Confidence: 0.78673038625

 $00:16:46.237 \rightarrow 00:16:49.258$ expression by a as shown here.

 $00:16:49.258 \rightarrow 00:16:54.286$ We can see in the one point 11.7 cells,

NOTE Confidence: 0.78673038625

 $00{:}16{:}54{.}286 \dashrightarrow 00{:}16{:}57{.}442$ there's a decrease of CD34 negative

NOTE Confidence: 0.78673038625

 $00{:}16{:}57{.}442 \dashrightarrow 00{:}16{:}59{.}706$ cells after we deplete eighteen 5B.

NOTE Confidence: 0.78673038625

 $00{:}16{:}59{.}706 \dashrightarrow 00{:}17{:}02{.}142$ When we look at the phenotype and

NOTE Confidence: 0.78673038625

 $00{:}17{:}02{.}142 \dashrightarrow 00{:}17{:}04{.}571$ it's consistent to what other people

NOTE Confidence: 0.78673038625

 $00{:}17{:}04{.}571 \dashrightarrow 00{:}17{:}07{.}044$ have seen in other Melanoma setting,

NOTE Confidence: 0.78673038625

00:17:07.044 --> 00:17:09.768 if you knock down killing five,

NOTE Confidence: 0.78673038625

00:17:09.770 --> 00:17:11.535 you actually increase the ability

NOTE Confidence: 0.78673038625

 $00:17:11.535 \longrightarrow 00:17:13.780$ of them to grow in vitro.

NOTE Confidence: 0.739691652727273

 $00:17:16.590 \rightarrow 00:17:21.024$ And then those cells are actually

NOTE Confidence: 0.739691652727273

 $00:17:21.024 \rightarrow 00:17:25.320$ more sensitive to inhibitor treatment?

NOTE Confidence: 0.739691652727273

 $00{:}17{:}25{.}320 \dashrightarrow 00{:}17{:}28{.}430$ So this is not only.

NOTE Confidence: 0.739691652727273

 $00{:}17{:}28{.}430 \dashrightarrow 00{:}17{:}31{.}616$ Two in most cells but also in human cells,

NOTE Confidence: 0.739691652727273

 $00{:}17{:}31.620 \dashrightarrow 00{:}17{:}34.560$ this is you Max cells.

NOTE Confidence: 0.739691652727273

00:17:34.560 --> 00:17:36.786 If you knock down Killian 5B

00:17:36.786 --> 00:17:39.364 and you can see induction HPK

NOTE Confidence: 0.739691652727273

 $00:17:39.364 \longrightarrow 00:17:41.889 4$ trimethylation which is the

NOTE Confidence: 0.739691652727273

 $00{:}17{:}41.889 \dashrightarrow 00{:}17{:}44.817$ substrate of the enzyme and you

NOTE Confidence: 0.739691652727273

 $00:17:44.817 \longrightarrow 00:17:47.457$ can see those cells grow faster.

NOTE Confidence: 0.739691652727273

00:17:47.460 --> 00:17:51.260 However, they are less sensitive,

NOTE Confidence: 0.739691652727273

 $00:17:51.260 \rightarrow 00:17:53.212$ they're they're more sensitive

NOTE Confidence: 0.739691652727273

 $00:17:53.212 \longrightarrow 00:17:55.164$ to BF inhibitor treatment.

NOTE Confidence: 0.8019701166666667

 $00:17:57.480 \rightarrow 00:18:00.099$ And if you look at this in animal models,

NOTE Confidence: 0.8019701166666667

 $00{:}18{:}00{.}100 \dashrightarrow 00{:}18{:}03{.}426$ uh, similar things happens when we treat

NOTE Confidence: 0.8019701166666667

 $00{:}18{:}03{.}426 \dashrightarrow 00{:}18{:}06{.}268$ cells with borough inhibitor and you can

NOTE Confidence: 0.8019701166666667

00:18:06.268 --> 00:18:08.577 see KADIAN file being level increase

NOTE Confidence: 0.8019701166666667

00:18:08.577 --> 00:18:11.500 and if you take away the inhibitor,

NOTE Confidence: 0.8019701166666667

 $00{:}18{:}11{.}500 \dashrightarrow 00{:}18{:}14{.}055$ you can see the level drops down.

NOTE Confidence: 0.874118252941176

 $00{:}18{:}17.570 \dashrightarrow 00{:}18{:}20.330$ So Umm, and then we look at the if you

NOTE Confidence: 0.874118252941176

 $00:18:20.404 \rightarrow 00:18:23.015$ look at the population of the cells,

NOTE Confidence: 0.874118252941176

 $00:18:23.020 \rightarrow 00:18:26.048$ you can see increased.

00:18:26.050 --> 00:18:30.470 City City for negative cells.

NOTE Confidence: 0.874118252941176

 $00:18:30.470 \longrightarrow 00:18:32.845$ When we treat the cells

NOTE Confidence: 0.874118252941176

00:18:32.845 --> 00:18:34.270 with Burrough inhibitor,

NOTE Confidence: 0.874118252941176

 $00:18:34.270 \rightarrow 00:18:37.302$ when you take out the inhibit that way

NOTE Confidence: 0.874118252941176

 $00{:}18{:}37{.}302 \dashrightarrow 00{:}18{:}40{.}238$ and then those would not normalize.

NOTE Confidence: 0.874118252941176

 $00:18:40.240 \longrightarrow 00:18:42.886$ So Umm, and this is all consistent

NOTE Confidence: 0.874118252941176

00:18:42.886 --> 00:18:45.837 with our data and others have shown,

NOTE Confidence: 0.874118252941176

00:18:45.840 --> 00:18:46.792 which you're not showing

NOTE Confidence: 0.874118252941176

00:18:46.792 --> 00:18:47.982 here on that KADIAN filing.

NOTE Confidence: 0.874118252941176

 $00:18:47.990 \rightarrow 00:18:50.890$ Hebetor can suppress the emergence

NOTE Confidence: 0.874118252941176

 $00:18:50.890 \rightarrow 00:18:53.210$ of drug resistance cells.

NOTE Confidence: 0.874118252941176

 $00{:}18{:}53{.}210 \dashrightarrow 00{:}18{:}54{.}610$ So to summarize this part,

NOTE Confidence: 0.874118252941176

 $00{:}18{:}54{.}610 \dashrightarrow 00{:}18{:}57{.}203$ we see we have showed that 634

NOTE Confidence: 0.874118252941176

00:18:57.203 --> 00:18:59.468 negative cells are more resistant

NOTE Confidence: 0.874118252941176

 $00{:}18{:}59{.}468 \dashrightarrow 00{:}19{:}02{.}177$ to BRF inhibitor treatment and BF

00:19:02.177 --> 00:19:04.358 inhibitor can increase C30 four

NOTE Confidence: 0.874118252941176

00:19:04.358 --> 00:19:07.202 negative cells and you can induce

NOTE Confidence: 0.874118252941176

00:19:07.202 --> 00:19:10.275 KADIAN file be up recognition and

NOTE Confidence: 0.874118252941176

 $00{:}19{:}10.275 \dashrightarrow 00{:}19{:}13.329$ this is reversible and kadian Fabian

NOTE Confidence: 0.874118252941176

00:19:13.419 $\operatorname{-->}$ 00:19:16.870 N can reduce this population cells and

NOTE Confidence: 0.874118252941176

 $00{:}19{:}16.870 \dashrightarrow 00{:}19{:}20.250$ induce drug resistance sensitivity.

NOTE Confidence: 0.874118252941176

00:19:20.250 --> 00:19:22.586 So now I want to switch switch gear

NOTE Confidence: 0.874118252941176

 $00{:}19{:}22{.}586 \dashrightarrow 00{:}19{:}24{.}635$ to talk about uh immune evasion

NOTE Confidence: 0.874118252941176

 $00{:}19{:}24.635 \dashrightarrow 00{:}19{:}27.142$ and firstly I want to start with

NOTE Confidence: 0.874118252941176

00:19:27.142 --> 00:19:29.266 this cancer immunity cycle on which

NOTE Confidence: 0.874118252941176

00:19:29.266 --> 00:19:32.230 many of you know have seen before.

NOTE Confidence: 0.874118252941176

 $00:19:32.230 \rightarrow 00:19:35.080$ Basically this is a diagram showing

NOTE Confidence: 0.874118252941176

 $00{:}19{:}35{.}166 \dashrightarrow 00{:}19{:}38{.}058$ that the cancer cells interact with

NOTE Confidence: 0.874118252941176

 $00{:}19{:}38.058 \dashrightarrow 00{:}19{:}41.242$ the immune system and and there are

NOTE Confidence: 0.874118252941176

 $00{:}19{:}41{.}242 \dashrightarrow 00{:}19{:}43{.}840$ many ways that cancer cells have

NOTE Confidence: 0.874118252941176

 $00:19:43.932 \longrightarrow 00:19:46.572$ adopted to evade immune evasion

 $00:19:46.572 \dashrightarrow 00:19:49.212$ to evade the immune response.

NOTE Confidence: 0.874118252941176

 $00:19:49.220 \longrightarrow 00:19:50.456$ So as a matter of fact,

NOTE Confidence: 0.874118252941176

 $00:19:50.460 \rightarrow 00:19:53.659$ because of this mechanism and some drugs

NOTE Confidence: 0.874118252941176

 $00:19:53.659 \rightarrow 00:19:56.860$ have been developed including the anti PD1,

NOTE Confidence: 0.874118252941176

 $00{:}19{:}56{.}860 \dashrightarrow 00{:}20{:}01{.}686$ PDL one anti 4 antibodies as well as the

NOTE Confidence: 0.874118252941176

 $00{:}20{:}01.686 \dashrightarrow 00{:}20{:}06.070$ ways to push the effect of on the T cells.

NOTE Confidence: 0.874118252941176

00:20:06.070 --> 00:20:06.418 However,

NOTE Confidence: 0.874118252941176

 $00:20:06.418 \rightarrow 00:20:08.506$ there's not much he's really actually

NOTE Confidence: 0.874118252941176

 $00{:}20{:}08.506 \dashrightarrow 00{:}20{:}10.559$ known about the trafficking of T

NOTE Confidence: 0.874118252941176

 $00:20:10.559 \rightarrow 00:20:12.449$ cells to tumors and the infiltration

NOTE Confidence: 0.874118252941176

 $00:20:12.449 \longrightarrow 00:20:14.950$ of the T cells into the tumor

NOTE Confidence: 0.874118252941176

 $00{:}20{:}14.950 \dashrightarrow 00{:}20{:}17.730$ at that time when we started.

NOTE Confidence: 0.874118252941176

 $00{:}20{:}17.730 \dashrightarrow 00{:}20{:}19.830$ And what's known about epigenetics,

NOTE Confidence: 0.874118252941176

 $00:20:19.830 \longrightarrow 00:20:21.654$ uh, in this setting,

NOTE Confidence: 0.874118252941176

 $00{:}20{:}21.654 \dashrightarrow 00{:}20{:}24.870$ many of you are quite familiar with

 $00:20:24.870 \rightarrow 00:20:27.609$ this concept about code tumor and

NOTE Confidence: 0.874118252941176

 $00{:}20{:}27{.}609 \dashrightarrow 00{:}20{:}30{.}665$ hot tumor code tumor are not really

NOTE Confidence: 0.874118252941176

 $00:20:30.665 \rightarrow 00:20:32.549$ responsive to another treatment,

NOTE Confidence: 0.874118252941176

 $00:20:32.550 \rightarrow 00:20:36.766$ but the hot tumor will enable them to

NOTE Confidence: 0.874118252941176

 $00:20:36.766 \rightarrow 00:20:40.520$ be responsive to even checkpoint block.

NOTE Confidence: 0.874118252941176

 $00{:}20{:}40.520 \dashrightarrow 00{:}20{:}43.046$ And a sub couple for epigenetic.

NOTE Confidence: 0.874118252941176

00:20:43.050 --> 00:20:45.750 Uh regulators have been shown

NOTE Confidence: 0.874118252941176

 $00:20:45.750 \longrightarrow 00:20:48.450$ to be critical for this.

NOTE Confidence: 0.757766613

 $00{:}20{:}50{.}470 \dashrightarrow 00{:}20{:}53{.}578$ Code to how the transition and

NOTE Confidence: 0.757766613

 $00{:}20{:}53{.}578 \dashrightarrow 00{:}20{:}57{.}207$ if we treat this the tumors with

NOTE Confidence: 0.757766613

 $00{:}20{:}57{.}207 \dashrightarrow 00{:}20{:}59{.}802$ a couple of inhibitors against

NOTE Confidence: 0.757766613

 $00:20:59.802 \rightarrow 00:21:02.660$ those targets like DMT inhibitors.

NOTE Confidence: 0.757766613

 $00{:}21{:}02.660 \dashrightarrow 00{:}21{:}05.838$ Two inhibitors. You can ship them to

NOTE Confidence: 0.757766613

 $00:21:05.838 \longrightarrow 00:21:09.870$ be more hard to become more hot hot.

NOTE Confidence: 0.757766613

00:21:09.870 - 00:21:11.790 Um, in some of the settings,

NOTE Confidence: 0.757766613

 $00:21:11.790 \longrightarrow 00:21:14.500$ not in all the settings.

 $00{:}21{:}14.500 \dashrightarrow 00{:}21{:}18.340$ And this is kind of related to what

NOTE Confidence: 0.757766613

 $00{:}21{:}18{.}340 \dashrightarrow 00{:}21{:}21{.}726$ we are trying to do and at that time

NOTE Confidence: 0.757766613

00:21:21.726 --> 00:21:24.839 actually a couple of years ago before

NOTE Confidence: 0.757766613

 $00{:}21{:}24.839 \dashrightarrow 00{:}21{:}28.790$ that and we have looked at the cadian 5B.

NOTE Confidence: 0.757766613

 $00{:}21{:}28{.}790 \dashrightarrow 00{:}21{:}32{.}526$ And how it's related to other genes when NOTE Confidence: 0.757766613

00:21:32.526 --> 00:21:36.378 we look at the TCA Melanoma data set?

NOTE Confidence: 0.757766613

00:21:36.380 --> 00:21:38.184 And to our surprise,

NOTE Confidence: 0.757766613

00:21:38.184 --> 00:21:40.439 actually KADIAN 5 expression was

NOTE Confidence: 0.757766613

 $00{:}21{:}40{.}439 \dashrightarrow 00{:}21{:}43{.}225$ shown to be negatively correlated with

NOTE Confidence: 0.757766613

 $00:21:43.225 \rightarrow 00:21:46.020$ many of the immune related genes.

NOTE Confidence: 0.757766613

 $00{:}21{:}46{.}020 \dashrightarrow 00{:}21{:}47{.}826$ And if you look at those top

NOTE Confidence: 0.757766613

 $00:21:47.826 \longrightarrow 00:21:48.342$ signaling pathway,

NOTE Confidence: 0.757766613

 $00:21:48.350 \longrightarrow 00:21:50.264$ those are all immune system related

NOTE Confidence: 0.757766613

 $00{:}21{:}50{.}264 \dashrightarrow 00{:}21{:}52{.}062$ genes and those are negative

NOTE Confidence: 0.757766613

 $00{:}21{:}52.062 \dashrightarrow 00{:}21{:}53.372$ coordinate with expression.

- $00:21:53.372 \longrightarrow 00:21:56.046$ If you look at the the identity
- NOTE Confidence: 0.757766613
- $00:21:56.046 \longrightarrow 00:21:57.330$ of those genes,
- NOTE Confidence: 0.757766613
- $00:21:57.330 \longrightarrow 00:21:58.950$ those shown here are the gene
- NOTE Confidence: 0.757766613
- $00:21:58.950 \longrightarrow 00:22:01.030$ names and on the right side of
- NOTE Confidence: 0.757766613
- $00{:}22{:}01{.}030 \dashrightarrow 00{:}22{:}03{.}158$ the Spielman score and you can see
- NOTE Confidence: 0.757766613
- $00:22:03.158 \longrightarrow 00:22:04.643$ many of the silo kinds,
- NOTE Confidence: 0.757766613
- 00:22:04.650 --> 00:22:07.240 for example interferon gamma and
- NOTE Confidence: 0.751778822631579
- $00{:}22{:}09{.}890 \dashrightarrow 00{:}22{:}11{.}914$ TNF A6796 O 10 which are involved in
- NOTE Confidence: 0.751778822631579
- 00:22:11.914 --> 00:22:14.267 T cell recruitment are all negative
- NOTE Confidence: 0.751778822631579
- $00:22:14.267 \longrightarrow 00:22:16.492$ coordinate with cadian fair expression.
- NOTE Confidence: 0.751778822631579
- $00{:}22{:}16.500 \dashrightarrow 00{:}22{:}19.055$ And some of the targets for immune
- NOTE Confidence: 0.751778822631579
- $00{:}22{:}19.055 \dashrightarrow 00{:}22{:}21.062$ checkpoint blockade PDL one CPT
- NOTE Confidence: 0.751778822631579
- $00{:}22{:}21.062 \dashrightarrow 00{:}22{:}22.750$ for also negative coordinate
- NOTE Confidence: 0.751778822631579
- $00:22:22.750 \longrightarrow 00:22:24.438$ with KADIAN fabric expression.
- NOTE Confidence: 0.751778822631579
- $00:22:24.440 \longrightarrow 00:22:26.282$ This will be important when we
- NOTE Confidence: 0.751778822631579
- $00:22:26.282 \rightarrow 00:22:28.388$ are trying to look at the e-mail

00:22:28.390 --> 00:22:32.230 checkpoint blockade resistant tumors.

NOTE Confidence: 0.751778822631579

 $00:22:32.230 \longrightarrow 00:22:35.236$ So when we looked at the KDM 5 be

NOTE Confidence: 0.751778822631579

 $00:22:35.236 \rightarrow 00:22:37.320$ expression protein expression in

NOTE Confidence: 0.751778822631579

 $00{:}22{:}37{.}320 \dashrightarrow 00{:}22{:}40{.}650$ melanomas and if you compare nonresponse

NOTE Confidence: 0.751778822631579

 $00{:}22{:}40.650 \dashrightarrow 00{:}22{:}42.809$ boundaries with and responders,

NOTE Confidence: 0.751778822631579

 $00{:}22{:}42.810 \dashrightarrow 00{:}22{:}45.324$ we can see increased expression location

NOTE Confidence: 0.751778822631579

 $00:22:45.324 \longrightarrow 00:22:48.848$ 5B which is shown in red in those non

NOTE Confidence: 0.751778822631579

 $00:22:48.848 \rightarrow 00:22:51.078$ responders compared to the responders

NOTE Confidence: 0.751778822631579

 $00{:}22{:}51.078 \dashrightarrow 00{:}22{:}54.590$ and and the quantification is shown here.

NOTE Confidence: 0.751778822631579

 $00{:}22{:}54{.}590 \dashrightarrow 00{:}22{:}57{.}281$ So this motivates us to look at the role

NOTE Confidence: 0.751778822631579

 $00:22:57.281 \rightarrow 00:23:00.228$ of Canadian file be using animal models.

NOTE Confidence: 0.751778822631579

 $00{:}23{:}00{.}230 \dashrightarrow 00{:}23{:}02{.}440$ So as I mentioned earlier.

NOTE Confidence: 0.751778822631579

00:23:02.440 --> 00:23:04.268 Um, Marcus Bosenberg snapped,

NOTE Confidence: 0.751778822631579

 $00{:}23{:}04{.}268 \dashrightarrow 00{:}23{:}06{.}553$ had generated a series of

NOTE Confidence: 0.751778822631579

 $00:23:06.553 \rightarrow 00:23:08.560$ why UM or young models.

00:23:08.560 - 00:23:11.232 Uh, one of the models that we started

NOTE Confidence: 0.751778822631579

 $00:23:11.232 \longrightarrow 00:23:13.982$ to use is this Yamaha 1.7 models.

NOTE Confidence: 0.751778822631579

00:23:13.982 -> 00:23:16.808 Yeah, this stand for ER stands

NOTE Confidence: 0.751778822631579

 $00:23:16.808 \rightarrow 00:23:18.980$ for exposed to radiation,

NOTE Confidence: 0.751778822631579

 $00:23:18.980 \longrightarrow 00:23:22.155$ meaning those cells will radiate

NOTE Confidence: 0.751778822631579

 $00{:}23{:}22.155 \dashrightarrow 00{:}23{:}25.287$ so that they have more mutations,

NOTE Confidence: 0.751778822631579

 $00:23:25.287 \rightarrow 00:23:27.741$ they can generate more antigens that

NOTE Confidence: 0.751778822631579

 $00:23:27.741 \rightarrow 00:23:30.567$ can be recognized by the immune system.

NOTE Confidence: 0.751778822631579

 $00{:}23{:}30{.}570 \dashrightarrow 00{:}23{:}33{.}138$ So when we knocked out Kadian 5B in

NOTE Confidence: 0.751778822631579

 $00:23:33.138 \longrightarrow 00:23:35.290$ those cells, as you can see here,

NOTE Confidence: 0.751778822631579

 $00{:}23{:}35{.}290 \dashrightarrow 00{:}23{:}37{.}840$ those cells can initially can grow,

NOTE Confidence: 0.751778822631579

 $00:23:37.840 \rightarrow 00:23:41.040$ then they got fully rejected after a while.

NOTE Confidence: 0.751778822631579

 $00:23:41.040 \rightarrow 00:23:45.450$ And the more importantly when we challenge

NOTE Confidence: 0.751778822631579

 $00:23:45.450 \longrightarrow 00:23:48.190$ those animals with the cells control

NOTE Confidence: 0.751778822631579

 $00:23:48.190 \rightarrow 00:23:51.080$ cells which normally can grow very well,

NOTE Confidence: 0.751778822631579

 $00:23:51.080 \rightarrow 00:23:52.632$ they never grow up.
$00{:}23{:}52{.}632 \dashrightarrow 00{:}23{:}55{.}686$ So this is very important imagine that if

NOTE Confidence: 0.751778822631579

 $00{:}23{:}55{.}686 \dashrightarrow 00{:}23{:}58{.}725$ we have to treat patient with a drug and

NOTE Confidence: 0.751778822631579

 $00{:}23{:}58.725 \dashrightarrow 00{:}24{:}01.773$ case for example in this case KADIAN 5

NOTE Confidence: 0.751778822631579

 $00:24:01.773 \rightarrow 00:24:06.258$ targeting drug and those patient will not,

NOTE Confidence: 0.751778822631579

 $00{:}24{:}06{.}260 \dashrightarrow 00{:}24{:}08{.}425$ will not have recurrence because

NOTE Confidence: 0.751778822631579

 $00{:}24{:}08{.}425 \dashrightarrow 00{:}24{:}11{.}559$ they they will should never grow up

NOTE Confidence: 0.751778822631579

 $00:24:11.559 \rightarrow 00:24:13.779$ because the immune memory response.

NOTE Confidence: 0.751778822631579

 $00:24:13.780 \longrightarrow 00:24:15.365$ So this is actually translated

NOTE Confidence: 0.751778822631579

 $00:24:15.365 \longrightarrow 00:24:16.615$ to 100% survival,

NOTE Confidence: 0.751778822631579

 $00:24:16.615 \rightarrow 00:24:20.305$ which is uh, this is great.

NOTE Confidence: 0.751778822631579

 $00:24:20.310 \longrightarrow 00:24:22.893$ And then we look at the UM uh T

NOTE Confidence: 0.751778822631579

 $00{:}24{:}22{.}893 \dashrightarrow 00{:}24{:}25{.}239$ cell infiltration when we compare

NOTE Confidence: 0.751778822631579

 $00{:}24{:}25{.}239 \dashrightarrow 00{:}24{:}28{.}691$ the control cells and KADIAN file B

NOTE Confidence: 0.751778822631579

 $00:24:28.691 \rightarrow 00:24:31.550$ knockout tumors at the very early stage,

NOTE Confidence: 0.751778822631579

 $00{:}24{:}31{.}550 \dashrightarrow 00{:}24{:}34{.}196$ you can see the T cell infiltration

 $00:24:34.196 \longrightarrow 00:24:35.330$ either by e-mail,

NOTE Confidence: 0.751778822631579

 $00{:}24{:}35{.}330 \dashrightarrow 00{:}24{:}38{.}828$ histochemistry as well as fax analysis.

NOTE Confidence: 0.751778822631579

 $00{:}24{:}38{.}830 \dashrightarrow 00{:}24{:}41{.}392$ And there's another way to say that

NOTE Confidence: 0.751778822631579

 $00:24:41.392 \rightarrow 00:24:44.355$ this is immune system dependent on we

NOTE Confidence: 0.751778822631579

 $00:24:44.355 \rightarrow 00:24:47.308$ compared the ability of cells to grow

NOTE Confidence: 0.751778822631579

 $00{:}24{:}47{.}308 \dashrightarrow 00{:}24{:}50{.}360$ in wild type cell wild type mice or rats.

NOTE Confidence: 0.751778822631579

 $00{:}24{:}50{.}360 \dashrightarrow 00{:}24{:}54{.}008$ Deficient mice and as you can see here

NOTE Confidence: 0.751778822631579

 $00:24:54.008 \longrightarrow 00:24:57.808$ the the the B6 is the wild type.

NOTE Confidence: 0.751778822631579

 $00{:}24{:}57{.}810 \dashrightarrow 00{:}25{:}00{.}029$ Those two curves are what I have

NOTE Confidence: 0.751778822631579

 $00:25:00.029 \rightarrow 00:25:02.417$ showed you before and if you look at

NOTE Confidence: 0.751778822631579

 $00{:}25{:}02{.}417 \dashrightarrow 00{:}25{:}04{.}918$ the the ability of cells you grow in

NOTE Confidence: 0.751778822631579

 $00{:}25{:}04{.}918 \dashrightarrow 00{:}25{:}06{.}698$ rectification mice the control goes

NOTE Confidence: 0.751778822631579

 $00{:}25{:}06.698 \dashrightarrow 00{:}25{:}10.662$ here and then can be deficient once grow

NOTE Confidence: 0.751778822631579

 $00{:}25{:}10.662 \dashrightarrow 00{:}25{:}14.430$ kind of similarly although slightly slower.

NOTE Confidence: 0.751778822631579

 $00:25:14.430 \longrightarrow 00:25:17.280$ So this basically set up the

NOTE Confidence: 0.751778822631579

 $00:25:17.280 \longrightarrow 00:25:20.477$ stage that Kadian 5B which is

- NOTE Confidence: 0.751778822631579
- $00{:}25{:}20.477 \dashrightarrow 00{:}25{:}22.869$ critical for immune evasion.
- NOTE Confidence: 0.751778822631579
- $00:25:22.870 \longrightarrow 00:25:26.110$ So the next question is what's the mechanism,
- NOTE Confidence: 0.751778822631579
- $00:25:26.110 \longrightarrow 00:25:26.742$ right?
- NOTE Confidence: 0.751778822631579
- $00:25:26.742 \longrightarrow 00:25:28.638$ So how to?
- NOTE Confidence: 0.751778822631579
- $00:25:28.640 \longrightarrow 00:25:29.933$ To understand this,
- NOTE Confidence: 0.751778822631579
- $00{:}25{:}29{.}933 \dashrightarrow 00{:}25{:}32{.}950$ we are look dead on a sequencing
- NOTE Confidence: 0.751778822631579
- 00:25:33.034 --> 00:25:35.380 comparing Yammer 1.7 cells,
- NOTE Confidence: 0.751778822631579
- $00:25:35.380 \rightarrow 00:25:37.930$ probably knockout versus wild type.
- NOTE Confidence: 0.751778822631579
- $00{:}25{:}37{.}930 \dashrightarrow 00{:}25{:}40{.}303$ And we can see there's an induction
- NOTE Confidence: 0.751778822631579
- 00:25:40.303 --> 00:25:42.717 of a lot of signaling pathway
- NOTE Confidence: 0.751778822631579
- 00:25:42.717 --> 00:25:45.790 involved in DNA on a sensing pathway
- NOTE Confidence: 0.769697436730769
- $00:25:45.872 \rightarrow 00:25:49.106$ and showing here that generation analysis,
- NOTE Confidence: 0.769697436730769
- 00:25:49.110 00:25:51.735 the instrument parts where you
- NOTE Confidence: 0.769697436730769
- $00{:}25{:}51{.}735 \dashrightarrow 00{:}25{:}53{.}972$ can see there's an enrichment
- NOTE Confidence: 0.769697436730769
- $00{:}25{:}53{.}972 \dashrightarrow 00{:}25{:}55{.}548$ regarding like research pathways
- NOTE Confidence: 0.769697436730769

00:25:55.548 --> 00:25:57.729 at Sonic DNA sensing pathway,

NOTE Confidence: 0.769697436730769

 $00{:}25{:}57{.}730 \dashrightarrow 00{:}25{:}59{.}530$ those are all induced after

NOTE Confidence: 0.769697436730769

00:25:59.530 --> 00:26:01.910 you get rid of Canning Vale B.

NOTE Confidence: 0.769697436730769

 $00:26:01.910 \rightarrow 00:26:05.430$ So now how does this actually work?

NOTE Confidence: 0.769697436730769

 $00{:}26{:}05{.}430 \dashrightarrow 00{:}26{:}07{.}430$ And are those sensing pathway

NOTE Confidence: 0.769697436730769

 $00{:}26{:}07{.}430 \dashrightarrow 00{:}26{:}09{.}990$ critical for the function of KDM 5B?

NOTE Confidence: 0.769697436730769

 $00:26:09.990 \longrightarrow 00:26:12.366$ As as many of you know that the

NOTE Confidence: 0.769697436730769

 $00{:}26{:}12.366 \dashrightarrow 00{:}26{:}14.716$ double strand DNA double strand on

NOTE Confidence: 0.769697436730769

00:26:14.716 --> 00:26:16.826 the Ascension sensed through those

NOTE Confidence: 0.769697436730769

00:26:16.826 --> 00:26:19.235 pathways and double strand DNA is

NOTE Confidence: 0.769697436730769

 $00:26:19.235 \rightarrow 00:26:21.150$ sensed through cgas sting pathway

NOTE Confidence: 0.769697436730769

 $00{:}26{:}21.150 \dashrightarrow 00{:}26{:}25.030$ to big TV K1F3F7 and the interferon

NOTE Confidence: 0.769697436730769

 $00:26:25.030 \longrightarrow 00:26:27.622$ response and this need to induction

NOTE Confidence: 0.769697436730769

 $00:26:27.622 \rightarrow 00:26:29.587$ interferon stimulated genes.

NOTE Confidence: 0.769697436730769

 $00{:}26{:}29{.}590 \dashrightarrow 00{:}26{:}31{.}977$ And the double stranded on a could

NOTE Confidence: 0.769697436730769

 $00{:}26{:}31{.}977 \dashrightarrow 00{:}26{:}34{.}169$ be sensed through regard MDA 5

 $00:26:34.169 \longrightarrow 00:26:36.004$ maps Altos three and basically

NOTE Confidence: 0.769697436730769

 $00:26:36.004 \rightarrow 00:26:38.269$ also signals through and activate

NOTE Confidence: 0.769697436730769

 $00:26:38.269 \rightarrow 00:26:40.217$ interference and steam engines.

NOTE Confidence: 0.769697436730769

 $00{:}26{:}40{.}220 \dashrightarrow 00{:}26{:}42{.}964$ So what we did is we knock cloud

NOTE Confidence: 0.769697436730769

 $00:26:42.964 \rightarrow 00:26:44.732$ each single component through

NOTE Confidence: 0.769697436730769

 $00:26:44.732 \rightarrow 00:26:47.720$ this pathway and see what happens

NOTE Confidence: 0.769697436730769

 $00:26:47.720 \longrightarrow 00:26:49.456$ when we knock out the Canadian 5B.

NOTE Confidence: 0.769697436730769

 $00:26:49.460 \longrightarrow 00:26:52.322$ As you see it does not grow in the

NOTE Confidence: 0.769697436730769

 $00{:}26{:}52{.}322 \dashrightarrow 00{:}26{:}55{.}395$ wild type cells do grow if we combine

NOTE Confidence: 0.769697436730769

 $00{:}26{:}55{.}395 \dashrightarrow 00{:}26{:}57{.}830$ that with knock out of the mouse or

NOTE Confidence: 0.769697436730769

 $00:26:57.830 \longrightarrow 00:26:59.740$ steam and the important mediator of.

NOTE Confidence: 0.769697436730769

00:26:59.740 --> 00:27:01.680 Christian Arnie or double Strand

NOTE Confidence: 0.769697436730769

00:27:01.680 --> 00:27:02.844 DNA sensing pathway,

NOTE Confidence: 0.769697436730769

 $00{:}27{:}02.850 \dashrightarrow 00{:}27{:}06.154$ you can see partial rescue right here.

NOTE Confidence: 0.769697436730769

 $00{:}27{:}06.160 \dashrightarrow 00{:}27{:}08.552$ If you get rid of both of them

 $00:27:08.552 \rightarrow 00:27:10.730$ you see much better rescue.

NOTE Confidence: 0.769697436730769

 $00{:}27{:}10.730 \dashrightarrow 00{:}27{:}14.410$ So we went on and when the upstream

NOTE Confidence: 0.769697436730769

 $00:27:14.410 \longrightarrow 00:27:17.236$ when we get rid of the sea gas or

NOTE Confidence: 0.769697436730769

00:27:17.236 --> 00:27:20.260 MDA 5 and you can also see partial

NOTE Confidence: 0.769697436730769

00:27:20.260 --> 00:27:23.509 rescue if you get rid of both of them.

NOTE Confidence: 0.769697436730769

00:27:23.510 --> 00:27:26.905 You can see pretty good rescue response

NOTE Confidence: 0.769697436730769

 $00{:}27{:}26{.}905 \dashrightarrow 00{:}27{:}31{.}308$ in this case when in two independent.

NOTE Confidence: 0.769697436730769

 $00:27:31.310 \longrightarrow 00:27:33.650$ So how many established that?

NOTE Confidence: 0.769697436730769

 $00{:}27{:}33.650 \dashrightarrow 00{:}27{:}36.494$ Now we want to understand why

NOTE Confidence: 0.769697436730769

 $00:27:36.494 \rightarrow 00:27:38.390$ those pathways are activated.

NOTE Confidence: 0.769697436730769

 $00{:}27{:}38{.}390 \dashrightarrow 00{:}27{:}40{.}606$ So why would the sense that we notice

NOTE Confidence: 0.769697436730769

 $00{:}27{:}40.610 \dashrightarrow 00{:}27{:}43.872$ is that when we compare the control

NOTE Confidence: 0.769697436730769

 $00:27:43.872 \longrightarrow 00:27:46.308$ cells with the knockout cells,

NOTE Confidence: 0.769697436730769

 $00{:}27{:}46.308 \dashrightarrow 00{:}27{:}49.941$ we can see the induction of double

NOTE Confidence: 0.769697436730769

 $00{:}27{:}49{.}941 \dashrightarrow 00{:}27{:}53{.}086$ stranded on a in Kadian 5B knock out

NOTE Confidence: 0.769697436730769

 $00:27:53.086 \longrightarrow 00:27:55.412$ cells and then we have seen this

- NOTE Confidence: 0.769697436730769
- $00:27:55.412 \longrightarrow 00:27:57.199$ also in two months as well.
- NOTE Confidence: 0.769697436730769
- 00:27:57.200 --> 00:28:00.520 And this motivated us to go back and
- NOTE Confidence: 0.769697436730769
- $00:28:00.520 \longrightarrow 00:28:03.660$ to realize our only sequencing data.
- NOTE Confidence: 0.769697436730769
- $00:28:03.660 \rightarrow 00:28:07.660$ For expressing those retro elements
- NOTE Confidence: 0.769697436730769
- $00{:}28{:}07.660$ --> $00{:}28{:}10.849$ and those retirement are part of junk
- NOTE Confidence: 0.769697436730769
- $00:28:10.849 \rightarrow 00:28:13.303$ genome and then people are totally
- NOTE Confidence: 0.769697436730769
- $00:28:13.303 \rightarrow 00:28:15.606$ normally ignore and it turned out
- NOTE Confidence: 0.769697436730769
- 00:28:15.606 00:28:17.937 to be very important in this case.
- NOTE Confidence: 0.769697436730769
- $00:28:17.940 \longrightarrow 00:28:19.655$ And what we have seen is that
- NOTE Confidence: 0.769697436730769
- 00:28:19.655 --> 00:28:21.039 we knock out Kadian 5B,
- NOTE Confidence: 0.769697436730769
- $00:28:21.040 \longrightarrow 00:28:24.034$ we can see induction of those
- NOTE Confidence: 0.769697436730769
- $00:28:24.034 \rightarrow 00:28:26.030$ retro elements and especially
- NOTE Confidence: 0.769697436730769
- $00:28:26.121 \rightarrow 00:28:28.996$ some of the endogenous retrovirus.
- NOTE Confidence: 0.769697436730769
- $00{:}28{:}29{.}000 \dashrightarrow 00{:}28{:}29{.}420$ Animals.
- NOTE Confidence: 0.769697436730769
- $00{:}28{:}29{.}420 \dashrightarrow 00{:}28{:}33{.}702$ And the one with which is called MOV 30 and
- NOTE Confidence: 0.769697436730769

 $00:28:33.702 \rightarrow 00:28:37.068$ you can see multiple of those showing up.

NOTE Confidence: 0.769697436730769

 $00{:}28{:}37.068 \dashrightarrow 00{:}28{:}39.732$ And then we study is actually

NOTE Confidence: 0.769697436730769

 $00{:}28{:}39{.}732 \dashrightarrow 00{:}28{:}42{.}190$ critical for the interferon response

NOTE Confidence: 0.769697436730769

 $00:28:42.190 \longrightarrow 00:28:45.260$ because if we knock down M30 with

NOTE Confidence: 0.769697436730769

00:28:45.260 --> 00:28:47.060 SRAM as you can see here,

NOTE Confidence: 0.769697436730769

 $00{:}28{:}47.060 \dashrightarrow 00{:}28{:}50.938$ you can see the down recognition or

NOTE Confidence: 0.769697436730769

 $00:28:50.938 \rightarrow 00:28:53.176$ interference imagines suggesting that

NOTE Confidence: 0.769697436730769

 $00:28:53.176 \rightarrow 00:28:56.110$ this is at least partially contribute

NOTE Confidence: 0.769697436730769

 $00:28:56.110 \longrightarrow 00:28:59.218$ to the interferon induction and maybe

NOTE Confidence: 0.769697436730769

 $00:28:59.218 \rightarrow 00:29:01.813$ the response to e-mail evasion.

NOTE Confidence: 0.769697436730769

 $00:29:01.820 \longrightarrow 00:29:03.899$ And the one thing that we were

NOTE Confidence: 0.769697436730769

 $00{:}29{:}03{.}899 \dashrightarrow 00{:}29{:}05{.}734$ puzzled about is that since I

NOTE Confidence: 0.769697436730769

 $00:29:05.734 \longrightarrow 00:29:07.771$ showed you that both DNA and only

NOTE Confidence: 0.769697436730769

 $00:29:07.839 \rightarrow 00:29:09.739$ sensing password are required,

NOTE Confidence: 0.769697436730769

 $00:29:09.740 \rightarrow 00:29:12.260$ where are those DNA coming from?

NOTE Confidence: 0.769697436730769

 $00:29:12.260 \longrightarrow 00:29:14.220$ And we postulated that those

 $00:29:14.220 \longrightarrow 00:29:16.180$ DNA will be coming from

NOTE Confidence: 0.762787830714286

 $00:29:16.257 \rightarrow 00:29:19.373$ reverse transcription of those only

NOTE Confidence: 0.762787830714286

 $00{:}29{:}19{.}373 \dashrightarrow 00{:}29{:}22{.}844$ species that that would generate

NOTE Confidence: 0.762787830714286

 $00:29:22.844 \rightarrow 00:29:27.400$ through after we get rid of Kadian 5B.

NOTE Confidence: 0.762787830714286

 $00{:}29{:}27{.}400 \dashrightarrow 00{:}29{:}30{.}536$ And one experiment we did is use

NOTE Confidence: 0.762787830714286

 $00:29:30.536 \longrightarrow 00:29:31.880$ reverse transcriptase inhibitor.

NOTE Confidence: 0.762787830714286

 $00{:}29{:}31.880 \dashrightarrow 00{:}29{:}34.778$ This is a cocktail of reverse transcript ase

NOTE Confidence: 0.762787830714286

 $00{:}29{:}34.778 \dashrightarrow 00{:}29{:}37.010$ inhibitors used for HIV treatment and

NOTE Confidence: 0.762787830714286

 $00{:}29{:}37.010 \dashrightarrow 00{:}29{:}40.312$ where we see if you treat the cells with

NOTE Confidence: 0.762787830714286

 $00:29:40.312 \longrightarrow 00:29:42.456$ those reverse transcriptase inhibitor.

NOTE Confidence: 0.762787830714286

 $00:29:42.460 \longrightarrow 00:29:46.289$ You can see suppression of the interference

NOTE Confidence: 0.762787830714286

 $00:29:46.289 \rightarrow 00:29:48.876$ imaging expression suggesting that this

NOTE Confidence: 0.762787830714286

 $00:29:48.876 \rightarrow 00:29:51.907$ DNA might be created through this pathway.

NOTE Confidence: 0.762787830714286

 $00{:}29{:}51{.}910 \dashrightarrow 00{:}29{:}54{.}268$ So now with all those mechanisms,

NOTE Confidence: 0.762787830714286

 $00{:}29{:}54{.}270 \dashrightarrow 00{:}29{:}56{.}532$ now the question is can we

 $00:29:56.532 \rightarrow 00:29:58.480$ translate it to targeting this?

NOTE Confidence: 0.762787830714286

 $00:29:58.480 \longrightarrow 00:30:00.712$ The quick question is that can

NOTE Confidence: 0.762787830714286

 $00:30:00.712 \longrightarrow 00:30:02.725$ we induce under tumor immune

NOTE Confidence: 0.762787830714286

00:30:02.725 --> 00:30:04.990 response with KDM 5 inhibitors?

NOTE Confidence: 0.762787830714286

00:30:04.990 --> 00:30:08.894 So as I mentioned because there's a lot

NOTE Confidence: 0.762787830714286

 $00:30:08.894 \rightarrow 00:30:13.280$ of evidence showing that KDM five are NOTE Confidence: 0.762787830714286

 $00:30:13.280 \longrightarrow 00:30:16.585$ critical for cancer initiation progression.

NOTE Confidence: 0.762787830714286

 $00{:}30{:}16{.}590 \dashrightarrow 00{:}30{:}19{.}362$ So we have started working on

NOTE Confidence: 0.762787830714286

 $00{:}30{:}19{.}362 \dashrightarrow 00{:}30{:}23{.}375$ this on to by multiple methods to

NOTE Confidence: 0.762787830714286

 $00:30:23.375 \rightarrow 00:30:25.843$ develop locating file inhibitors.

NOTE Confidence: 0.762787830714286

 $00{:}30{:}25.850 \dashrightarrow 00{:}30{:}29.287$ So initially with that panel ground from

NOTE Confidence: 0.762787830714286

00:30:29.287 --> 00:30:31.719 Yale Small Molecule Screening Center

NOTE Confidence: 0.762787830714286

 $00{:}30{:}31{.}719 \dashrightarrow 00{:}30{:}34{.}617$ now called Yale Center for Monica.

NOTE Confidence: 0.762787830714286

 $00:30:34.620 \rightarrow 00:30:35.071$ Discovery,

NOTE Confidence: 0.762787830714286

00:30:35.071 -> 00:30:37.326 we have done some screening,

NOTE Confidence: 0.762787830714286

 $00:30:37.330 \rightarrow 00:30:39.630$ biochemical screening for KADIAN

 $00:30:39.630 \longrightarrow 00:30:41.355$ 5D methods inhibitor.

NOTE Confidence: 0.762787830714286

00:30:41.360 --> 00:30:43.520 And initially we did 100,000 compounds

NOTE Confidence: 0.762787830714286

 $00:30:43.520 \rightarrow 00:30:46.136$ with those as a preliminary data we

NOTE Confidence: 0.762787830714286

 $00:30:46.136 \rightarrow 00:30:48.705$ were able to obtain support for NCI

NOTE Confidence: 0.762787830714286

00:30:48.777 --> 00:30:50.847 experimental security program where we

NOTE Confidence: 0.762787830714286

 $00{:}30{:}50{.}847 \dashrightarrow 00{:}30{:}54{.}579$ were able to assemble a team about 30

NOTE Confidence: 0.762787830714286

 $00:30:54.579 \rightarrow 00:30:57.897$ scientists to to develop those inhibitors.

NOTE Confidence: 0.762787830714286

 $00{:}30{:}57{.}900 \dashrightarrow 00{:}31{:}01{.}060$ So we have done a high school screening

NOTE Confidence: 0.762787830714286

 $00:31:01.060 \longrightarrow 00:31:03.405$ about 200,000 compounds those are high

NOTE Confidence: 0.762787830714286

 $00{:}31{:}03{.}405 \dashrightarrow 00{:}31{:}05{.}872$ quality compounds and have done extensive

NOTE Confidence: 0.762787830714286

 $00:31:05.872 \rightarrow 00:31:08.137$ medicinal chemistry optimization of some

NOTE Confidence: 0.762787830714286

 $00:31:08.137 \dashrightarrow 00:31:11.664$ of the compounds and we have solved.

NOTE Confidence: 0.762787830714286

00:31:11.664 --> 00:31:13.828 25 uh crystal structures,

NOTE Confidence: 0.762787830714286

 $00{:}31{:}13.830 \dashrightarrow 00{:}31{:}16.490$ can you find a way with different inhibitors

NOTE Confidence: 0.762787830714286

 $00{:}31{:}16{.}490 \dashrightarrow 00{:}31{:}18{.}890$ and shown here just the two of them,

 $00:31:18.890 \rightarrow 00:31:21.725$ basically showing that they combined

NOTE Confidence: 0.762787830714286

 $00{:}31{:}21.725 \dashrightarrow 00{:}31{:}25.100$ very tightly to the active site.

NOTE Confidence: 0.762787830714286

 $00{:}31{:}25{.}100 \dashrightarrow 00{:}31{:}27{.}485$ One thing that I want to mention that those

NOTE Confidence: 0.762787830714286

 $00:31:27.485 \rightarrow 00:31:29.477$ inhibitors are all pancaking from inhibitors.

NOTE Confidence: 0.762787830714286

 $00:31:29.480 \longrightarrow 00:31:32.330$ They hit both all Canadian five

NOTE Confidence: 0.762787830714286

 $00{:}31{:}32{.}330 \dashrightarrow 00{:}31{:}34{.}230$ family members because the

NOTE Confidence: 0.762787830714286

00:31:34.315 --> 00:31:37.138 Catholic side is very similar,

NOTE Confidence: 0.762787830714286

 $00:31:37.138 \longrightarrow 00:31:40.068$ very similar for all those

NOTE Confidence: 0.762787830714286

00:31:40.068 --> 00:31:43.738 Canadian 5A family members.

NOTE Confidence: 0.762787830714286

 $00{:}31{:}43.740 \dashrightarrow 00{:}31{:}47.547$ So even with with those and we decided to

NOTE Confidence: 0.762787830714286

 $00{:}31{:}47{.}547{\:}-{:}>00{:}31{:}51{.}839$ ask what the Canadian five inhibitor can do.

NOTE Confidence: 0.762787830714286

 $00:31:51.840 \dashrightarrow 00:31:55.670$ And the one thing that we decided to do is

NOTE Confidence: 0.762787830714286

 $00{:}31{:}55.766 \dashrightarrow 00{:}31{:}59.598$ we selected four KDM 5 and inhibitor here.

NOTE Confidence: 0.762787830714286

 $00:31:59.600 \rightarrow 00:32:01.750$ Those are high quality specific

NOTE Confidence: 0.762787830714286

 $00:32:01.750 \longrightarrow 00:32:03.040$ calling from inhibitor.

NOTE Confidence: 0.762787830714286

 $00:32:03.040 \rightarrow 00:32:05.152$ As you can see here they all induce

 $00{:}32{:}05{.}152 \dashrightarrow 00{:}32{:}07{.}233$ HK for translation which is the

NOTE Confidence: 0.762787830714286

 $00{:}32{:}07{.}233 \dashrightarrow 00{:}32{:}09{.}459$ substrate of the reaction and then

NOTE Confidence: 0.762787830714286

 $00:32:09.529 \rightarrow 00:32:11.601$ did not do anything to the other

NOTE Confidence: 0.762787830714286

 $00:32:11.601 \rightarrow 00:32:14.430$ of the histone modifications.

NOTE Confidence: 0.762787830714286

 $00{:}32{:}14.430 \dashrightarrow 00{:}32{:}17.294$ And we did those actually in I'm 6-7

NOTE Confidence: 0.762787830714286

 $00{:}32{:}17{.}294 \dashrightarrow 00{:}32{:}19{.}579$ and multiple human breast cancer cells

NOTE Confidence: 0.762787830714286

 $00{:}32{:}19{.}579 \dashrightarrow 00{:}32{:}22{.}680$ and and when we looked at the gene

NOTE Confidence: 0.762787830714286

00:32:22.680 --> 00:32:25.050 expression changes to our surprise we

NOTE Confidence: 0.762787830714286

 $00{:}32{:}25{.}050 \dashrightarrow 00{:}32{:}27{.}852$ see the top pathway that's upregulate

NOTE Confidence: 0.762787830714286

 $00:32:27.852 \rightarrow 00:32:29.864$ are those interference signaling

NOTE Confidence: 0.762787830714286

 $00:32:29.864 \rightarrow 00:32:32.122$ pathway at that time I was like

NOTE Confidence: 0.762787830714286

 $00:32:32.122 \rightarrow 00:32:33.615$ interfering pathway is not something

NOTE Confidence: 0.762787830714286

00:32:33.615 --> 00:32:37.770 I want to work on not so much now.

NOTE Confidence: 0.762787830714286

00:32:37.770 --> 00:32:38.805 So, so anyway,

NOTE Confidence: 0.762787830714286

 $00{:}32{:}38{.}805 \dashrightarrow 00{:}32{:}41{.}220$ so when we see there's an induction

00:32:41.296 - > 00:32:43.301 interfering pathway and we have

NOTE Confidence: 0.762787830714286

 $00:32:43.301 \longrightarrow 00:32:45.790$ seen this in multiple cell lines,

NOTE Confidence: 0.762787830714286

 $00:32:45.790 \rightarrow 00:32:47.110$ multiple drugs.

NOTE Confidence: 0.762787830714286

 $00{:}32{:}47{.}110 \dashrightarrow 00{:}32{:}50{.}410$ And we were able to.

NOTE Confidence: 0.762787830714286

 $00:32:50.410 \longrightarrow 00:32:52.410$ Understand how this actually worked.

NOTE Confidence: 0.762787830714286

 $00{:}32{:}52{.}410 \dashrightarrow 00{:}32{:}55{.}162$ And at the end we were able to

NOTE Confidence: 0.762787830714286

 $00{:}32{:}55{.}162 \dashrightarrow 00{:}32{:}57{.}840$ show that KADIAN 5 inhibitor can

NOTE Confidence: 0.762787830714286

 $00{:}32{:}57{.}840 \dashrightarrow 00{:}32{:}59{.}920$ induce H3K4 termination at the

NOTE Confidence: 0.762787830714286

00:32:59.920 --> 00:33:02.000 steam promoter and by doing

NOTE Confidence: 0.693358643272727

 $00:33:02.075 \rightarrow 00:33:06.360$ so, it actually induce Stein expression.

NOTE Confidence: 0.693358643272727

 $00{:}33{:}06{.}360 \dashrightarrow 00{:}33{:}08{.}916$ And this need to the interferon

NOTE Confidence: 0.693358643272727

 $00:33:08.920 \longrightarrow 00:33:10.520$ stimulated gene expression and

NOTE Confidence: 0.693358643272727

 $00{:}33{:}10{.}520 \dashrightarrow 00{:}33{:}12{.}920$ listening to the T cell infiltration.

NOTE Confidence: 0.876932511333333

 $00{:}33{:}15{.}070 \dashrightarrow 00{:}33{:}18{.}390$ So this is a little bit different from

NOTE Confidence: 0.876932511333333

 $00:33:18.390 \rightarrow 00:33:21.600$ what other people have been trying to.

NOTE Confidence: 0.876932511333333

00:33:21.600 - 00:33:23.700 Uh, to activate this pathway

 $00:33:23.700 \rightarrow 00:33:25.800$ through either using Steam agonist,

NOTE Confidence: 0.876932511333333

 $00:33:25.800 \longrightarrow 00:33:31.209$ which the limitation of those drugs and is.

NOTE Confidence: 0.876932511333333

 $00:33:31.210 \longrightarrow 00:33:33.208$ Many of the cancer cells you

NOTE Confidence: 0.876932511333333

 $00:33:33.208 \rightarrow 00:33:34.540$ actually have Stein silence.

NOTE Confidence: 0.876932511333333

 $00:33:34.540 \longrightarrow 00:33:37.144$ So by inducing Stein and this

NOTE Confidence: 0.876932511333333

 $00{:}33{:}37{.}144 \dashrightarrow 00{:}33{:}39{.}436$ provide another mechanism how we

NOTE Confidence: 0.876932511333333

 $00:33:39.436 \dashrightarrow 00:33:41.826$ can activate this signaling pathway.

NOTE Confidence: 0.876932511333333

 $00:33:41.830 \rightarrow 00:33:45.286$ So now and we actually tested KADIAN 5

NOTE Confidence: 0.876932511333333

00:33:45.286 --> 00:33:47.688 inhibitor in multiple human Melanoma

NOTE Confidence: 0.876932511333333

 $00{:}33{:}47.688 \dashrightarrow 00{:}33{:}51.069$ cells and we can see induction of

NOTE Confidence: 0.876932511333333

 $00{:}33{:}51{.}156 \dashrightarrow 00{:}33{:}54{.}061$ sting and in this case in Western

NOTE Confidence: 0.876932511333333

 $00{:}33{:}54.061 \dashrightarrow 00{:}33{:}56.466$ border here and the induction

NOTE Confidence: 0.876932511333333

 $00{:}33{:}56{.}466 \dashrightarrow 00{:}33{:}58{.}778$ of interference steam engines.

NOTE Confidence: 0.876932511333333

 $00{:}33{:}58.780 \dashrightarrow 00{:}34{:}00.724$ And so we thought this is the shoe

NOTE Confidence: 0.876932511333333

 $00{:}34{:}00{.}724 \dashrightarrow 00{:}34{:}02{.}576$ bat and the Canadian five inhibitor

 $00:34:02.576 \longrightarrow 00:34:03.880$ is going to work.

NOTE Confidence: 0.876932511333333

 $00:34:03.880 \rightarrow 00:34:07.360$ And to our surprise, nothing happened.

NOTE Confidence: 0.876932511333333

 $00:34:07.360 \longrightarrow 00:34:09.089$ And when we took put this in

NOTE Confidence: 0.876932511333333

 $00:34:09.089 \rightarrow 00:34:10.200$ the mouseman normal cells,

NOTE Confidence: 0.876932511333333

 $00{:}34{:}10{.}200 \dashrightarrow 00{:}34{:}11{.}584$ the Yammer 1.7 cells,

NOTE Confidence: 0.876932511333333

 $00{:}34{:}11{.}584 \dashrightarrow 00{:}34{:}14{.}210$ the model system that we have tested.

NOTE Confidence: 0.876932511333333

 $00{:}34{:}14{.}210 \dashrightarrow 00{:}34{:}18{.}690$ 2 into 2 Canadian farm inhibitor and

NOTE Confidence: 0.876932511333333

 $00:34:18.690 \rightarrow 00:34:22.806$ the retro element was were not induced,

NOTE Confidence: 0.876932511333333

 $00:34:22.810 \rightarrow 00:34:25.888$ the interference images were not induced,

NOTE Confidence: 0.876932511333333

 $00:34:25.890 \rightarrow 00:34:26.654$ nothing happened.

NOTE Confidence: 0.876932511333333

 $00{:}34{:}26{.}654 \dashrightarrow 00{:}34{:}29{.}710$ So we did not want to give up

NOTE Confidence: 0.876932511333333

 $00:34:29.710 \longrightarrow 00:34:31.840$ because we thought maybe there's

NOTE Confidence: 0.876932511333333

 $00{:}34{:}31{.}840 \dashrightarrow 00{:}34{:}34{.}782$ some limitation of the drugs and so

NOTE Confidence: 0.876932511333333

 $00{:}34{:}34{.}782 \dashrightarrow 00{:}34{:}37{.}006$ we did those rescue experiment to

NOTE Confidence: 0.876932511333333

 $00{:}34{:}37.006 \dashrightarrow 00{:}34{:}38.886$ understand whether the critical the

NOTE Confidence: 0.876932511333333

 $00:34:38.886 \rightarrow 00:34:40.830$ community activity is required or not.

- NOTE Confidence: 0.876932511333333
- $00:34:40.830 \longrightarrow 00:34:44.064$ So what we did is that for.
- NOTE Confidence: 0.876932511333333
- $00:34:44.070 \longrightarrow 00:34:45.420$ I'll call it Yama cells.
- NOTE Confidence: 0.876932511333333
- $00:34:45.420 \longrightarrow 00:34:48.312$ We reintroduced either wild type or
- NOTE Confidence: 0.876932511333333
- 00:34:48.312 --> 00:34:51.339 mutant KADIAN 5B into those cells.
- NOTE Confidence: 0.876932511333333
- $00:34:51.340 \rightarrow 00:34:54.820$ Those mutant are dead Canadian 5B.
- NOTE Confidence: 0.876932511333333
- $00{:}34{:}54{.}820 \dashrightarrow 00{:}34{:}56{.}848$ And as you can see here,
- NOTE Confidence: 0.876932511333333
- $00{:}34{:}56{.}850 \dashrightarrow 00{:}34{:}59{.}338$ in both cases you can see wild type
- NOTE Confidence: 0.876932511333333
- $00{:}34{:}59{.}338 \dashrightarrow 00{:}35{:}01{.}778$ or mutant Canadian 5B can suppress
- NOTE Confidence: 0.876932511333333
- $00:35:01.778 \dashrightarrow 00:35:04.450$ the expression of retro elements and
- NOTE Confidence: 0.876932511333333
- $00:35:04.450 \longrightarrow 00:35:06.370$ those interference stimulate genes.
- NOTE Confidence: 0.876932511333333
- 00:35:06.370 --> 00:35:06.864 Moreover,
- NOTE Confidence: 0.876932511333333
- $00{:}35{:}06{.}864 \dashrightarrow 00{:}35{:}09{.}828$ both of those can induce the
- NOTE Confidence: 0.876932511333333
- $00{:}35{:}09{.}828 \dashrightarrow 00{:}35{:}12{.}050$ growth of those tumors.
- NOTE Confidence: 0.876932511333333
- $00:35:12.050 \longrightarrow 00:35:13.136$ So now what?
- NOTE Confidence: 0.876932511333333
- $00{:}35{:}13.136 \dashrightarrow 00{:}35{:}16.096$ Now we are back to the starting point
- NOTE Confidence: 0.876932511333333

 $00:35:16.096 \dashrightarrow 00:35:18.847$ and kind of depressed right at time.

NOTE Confidence: 0.876932511333333

 $00{:}35{:}18.850 \dashrightarrow 00{:}35{:}21.722$ So we went on and decided to look

NOTE Confidence: 0.876932511333333

 $00:35:21.722 \rightarrow 00:35:24.160$ at all the repressive mechanisms

NOTE Confidence: 0.876932511333333

 $00:35:24.160 \longrightarrow 00:35:26.750$ and to see which one might work.

NOTE Confidence: 0.876932511333333

 $00:35:26.750 \longrightarrow 00:35:27.962$ And one of the things that

NOTE Confidence: 0.876932511333333

 $00:35:27.962 \longrightarrow 00:35:29.090$ we decided to look at is,

NOTE Confidence: 0.876932511333333

 $00:35:29.090 \longrightarrow 00:35:30.254$ is actually inhibitor for

NOTE Confidence: 0.876932511333333

 $00:35:30.254 \rightarrow 00:35:32.000$ example and those are two higher

NOTE Confidence: 0.876932511333333

 $00{:}35{:}32.053 \dashrightarrow 00{:}35{:}33.609$ quantities that true inhibitor,

NOTE Confidence: 0.876932511333333

 $00:35:33.610 \longrightarrow 00:35:35.680$ it did not do much either.

NOTE Confidence: 0.876932511333333

 $00:35:35.680 \rightarrow 00:35:38.504$ Umm, and then uh,

NOTE Confidence: 0.876932511333333

 $00{:}35{:}38{.}504 \dashrightarrow 00{:}35{:}39{.}210$ it.

NOTE Confidence: 0.876932511333333

 $00{:}35{:}39{.}210 \dashrightarrow 00{:}35{:}41{.}120$ There's some clue that HK9

NOTE Confidence: 0.876932511333333

00:35:41.120 - > 00:35:42.648 message transfers would work,

NOTE Confidence: 0.876932511333333

 $00:35:42.650 \longrightarrow 00:35:44.612$ and we use a pretty dirty

NOTE Confidence: 0.876932511333333

 $00:35:44.612 \rightarrow 00:35:45.920$ actually actually canine method.

 $00:35:45.920 \rightarrow 00:35:48.350$ Transfers inhibit the code channel thing

NOTE Confidence: 0.876932511333333

 $00:35:48.350 \dashrightarrow 00:35:51.688$ and it can inhibit actually K9 translation.

NOTE Confidence: 0.876932511333333

 $00{:}35{:}51.690 \dashrightarrow 00{:}35{:}55.020$ You can see induction of MOV 30 and some

NOTE Confidence: 0.876932511333333

 $00:35:55.020 \rightarrow 00:35:58.228$ of the interferon stimulated genes.

NOTE Confidence: 0.876932511333333

 $00:35:58.230 \longrightarrow 00:36:00.919$ So now there are multiple HK9

NOTE Confidence: 0.876932511333333

 $00{:}36{:}00{.}919 \dashrightarrow 00{:}36{:}03{.}013$ methyltransferase and so we knocked out

NOTE Confidence: 0.876932511333333

 $00:36:03.013 \rightarrow 00:36:05.597$ each single one of them to see which one.

NOTE Confidence: 0.876932511333333

 $00{:}36{:}05{.}600 \dashrightarrow 00{:}36{:}10{.}235$ Is critical when we knock out the G9A or

NOTE Confidence: 0.876932511333333

 $00:36:10.240 \rightarrow 00:36:12.336$ SO39H1 and it did not really do anything.

NOTE Confidence: 0.876932511333333

 $00:36:12.340 \longrightarrow 00:36:14.220$ But when we knockout set

NOTE Confidence: 0.876932511333333

 $00:36:14.220 \longrightarrow 00:36:16.100$ B1 which is shown here,

NOTE Confidence: 0.876932511333333

 $00:36:16.100 \rightarrow 00:36:19.956$ you can see robust induction on mobile 30.

NOTE Confidence: 0.876932511333333

 $00{:}36{:}19{.}960 \dashrightarrow 00{:}36{:}22{.}480$ So this is what was a great news.

NOTE Confidence: 0.876932511333333

 $00{:}36{:}22{.}480 \dashrightarrow 00{:}36{:}25{.}056$ So at that time we're quite excited.

NOTE Confidence: 0.876932511333333

 $00:36:25.060 \longrightarrow 00:36:28.196$ And then when we did call e-mail

00:36:28.196 --> 00:36:29.092 precipitation experiment,

NOTE Confidence: 0.876932511333333

 $00:36:29.100 \dashrightarrow 00:36:31.422$ we actually can see that KADIAN

NOTE Confidence: 0.876932511333333

 $00:36:31.422 \rightarrow 00:36:34.039$ file B can interact with set DB1.

NOTE Confidence: 0.876932511333333

 $00:36:34.040 \rightarrow 00:36:35.900$ When we did set DB1 IP,

NOTE Confidence: 0.876932511333333

 $00:36:35.900 \longrightarrow 00:36:42.490$ that's the pull down of Kadian 5B by Sade 1.

NOTE Confidence: 0.779074838571429

 $00:36:42.490 \rightarrow 00:36:45.626$ And then uh, this is quite exciting.

NOTE Confidence: 0.779074838571429

 $00{:}36{:}45{.}630 \dashrightarrow 00{:}36{:}49{.}510$ Then we decided to map the binding of

NOTE Confidence: 0.779074838571429

 $00{:}36{:}49{.}510$ --> $00{:}36{:}53{.}915$ KDM 5B and set DB1 and shown here just

NOTE Confidence: 0.779074838571429

 $00{:}36{:}53{.}915 \dashrightarrow 00{:}36{:}57{.}675$ the the heat map where we ranked

NOTE Confidence: 0.779074838571429

 $00{:}36{:}57{.}675 \dashrightarrow 00{:}37{:}00{.}090$ those KADIAN file B target genes where

NOTE Confidence: 0.779074838571429

 $00{:}37{:}00{.}090 \dashrightarrow 00{:}37{:}02{.}447$ you can see KADIAN file B combined

NOTE Confidence: 0.779074838571429

 $00:37:02.447 \rightarrow 00:37:04.829$ them very well in wild type cells,

NOTE Confidence: 0.779074838571429

 $00:37:04.830 \longrightarrow 00:37:07.380$ not so much in knockout cells.

NOTE Confidence: 0.779074838571429

00:37:07.380 --> 00:37:09.795 When we look at set DB1 binding,

NOTE Confidence: 0.779074838571429

 $00:37:09.800 \rightarrow 00:37:12.460$ you can see a mazingly overlapping

NOTE Confidence: 0.779074838571429

 $00:37:12.460 \longrightarrow 00:37:16.963$ binding of the set DB1 and the HTK 9

 $00:37:16.963 \longrightarrow 00:37:20.160$ formation which is the product of set

NOTE Confidence: 0.722333791

 $00{:}37{:}22{.}320 \dashrightarrow 00{:}37{:}25{.}194$ DB1H3K9 formation is a repressible mark

NOTE Confidence: 0.722333791

 $00{:}37{:}25.194 \dashrightarrow 00{:}37{:}28.040$ that can suppress gene expression.

NOTE Confidence: 0.722333791

 $00{:}37{:}28.040 \dashrightarrow 00{:}37{:}30.848$ And to our surprise, when we look at

NOTE Confidence: 0.722333791

 $00:37:30.848 \rightarrow 00:37:33.148$ the HK4 translation and imagination,

NOTE Confidence: 0.722333791

 $00:37:33.148 \dashrightarrow 00:37:36.919$ which are the substrate of the Kadian 5B,

NOTE Confidence: 0.722333791

 $00:37:36.920 \rightarrow 00:37:39.728$ you can actually do not see much effect.

NOTE Confidence: 0.722333791

 $00{:}37{:}39{.}730 \dashrightarrow 00{:}37{:}42.610$ Suppress a suggestion that KDM 5B

NOTE Confidence: 0.722333791

 $00{:}37{:}42.610 \dashrightarrow 00{:}37{:}45.086$ function add message function is

NOTE Confidence: 0.722333791

 $00:37:45.086 \dashrightarrow 00:37:47.436$ probably silenced in this setting.

NOTE Confidence: 0.722333791

 $00:37:47.440 \longrightarrow 00:37:50.820$ So now those are all.

NOTE Confidence: 0.806272241

 $00{:}37{:}53{.}360 \dashrightarrow 00{:}37{:}58{.}320$ Important and now we want to look at this in.

NOTE Confidence: 0.806272241

 $00{:}37{:}58{.}320 \dashrightarrow 00{:}38{:}00{.}060$ Drug resistance setting and

NOTE Confidence: 0.806272241

 $00{:}38{:}00{.}060 \dashrightarrow 00{:}38{:}02{.}235$ in this case e-mail checkpoint

NOTE Confidence: 0.806272241

 $00{:}38{:}02{.}235 \dashrightarrow 00{:}38{:}03{.}980$ blockade resistance setting.

 $00:38:03.980 \rightarrow 00:38:06.338$ When you look at the KTM 5 be expression,

NOTE Confidence: 0.806272241

 $00{:}38{:}06{.}340 \dashrightarrow 00{:}38{:}08{.}914$ it's actually lower in the patient

NOTE Confidence: 0.806272241

 $00{:}38{:}08{.}914 \dashrightarrow 00{:}38{:}11{.}131$ with computer response to anti

NOTE Confidence: 0.806272241

00:38:11.131 --> 00:38:13.663 PD1 blockade compared to the ones

NOTE Confidence: 0.806272241

 $00{:}38{:}13.663 \dashrightarrow 00{:}38{:}15.580$ with the progressive disease.

NOTE Confidence: 0.806272241

 $00:38:15.580 \longrightarrow 00:38:17.620$ So this is suggesting that if

NOTE Confidence: 0.806272241

 $00:38:17.620 \dashrightarrow 00:38:20.155$ we can lower expression you can

NOTE Confidence: 0.806272241

 $00{:}38{:}20.155 \dashrightarrow 00{:}38{:}22.724$ make the reason tumor sensitive.

NOTE Confidence: 0.806272241

 $00{:}38{:}22.724 \dashrightarrow 00{:}38{:}25.444$ Indeed that's actually true and

NOTE Confidence: 0.806272241

 $00:38:25.444 \rightarrow 00:38:28.498$ we use this young 1.7 model.

NOTE Confidence: 0.806272241

 $00{:}38{:}28{.}498 \dashrightarrow 00{:}38{:}31{.}571$ Which is the parental model for the

NOTE Confidence: 0.806272241

00:38:31.571 --> 00:38:33.996 Yammer 1.7 I have showed you before. NOTE Confidence: 0.806272241

 $00:38:34.000 \dashrightarrow 00:38:39.159$ This model is resistant to all immune

NOTE Confidence: 0.806272241

00:38:39.159 --> 00:38:41.204 checkpoint blockade, PD1 blockade.

NOTE Confidence: 0.806272241

 $00{:}38{:}41{.}204 \dashrightarrow 00{:}38{:}43{.}346$ If you look at this, nothing happens.

NOTE Confidence: 0.806272241

00:38:43.346 --> 00:38:45.524 If you throw CTO four anybody

- NOTE Confidence: 0.806272241
- $00:38:45.524 \longrightarrow 00:38:47.399$ on then nothing happens.
- NOTE Confidence: 0.806272241
- $00{:}38{:}47{.}400 \dashrightarrow 00{:}38{:}50{.}249$ If you combine them still nothing happens.
- NOTE Confidence: 0.806272241
- 00:38:50.250 --> 00:38:52.870 In this very refractory model,
- NOTE Confidence: 0.806272241
- $00:38:52.870 \rightarrow 00:38:54.838$ you can see if you get relocating 5
- NOTE Confidence: 0.806272241
- $00:38:54.838 \dashrightarrow 00:38:56.889$ you can already see some response.
- NOTE Confidence: 0.806272241
- $00:38:56.890 \dashrightarrow 00:38:59.710$ If you combine with PD1 blockade
- NOTE Confidence: 0.806272241
- $00:38:59.710 \longrightarrow 00:39:01.590$ you see synergistic response.
- NOTE Confidence: 0.806272241
- $00:39:01.590 \longrightarrow 00:39:05.510$ It can extend the survival of those animals.
- NOTE Confidence: 0.806272241
- 00:39:05.510 --> 00:39:07.550 You can basically double the
- NOTE Confidence: 0.806272241
- $00:39:07.550 \longrightarrow 00:39:09.182$ survival of those animals.
- NOTE Confidence: 0.806272241
- $00:39:09.190 \longrightarrow 00:39:11.214$ And this is just one of the PD1
- NOTE Confidence: 0.806272241
- $00{:}39{:}11{.}214 \dashrightarrow 00{:}39{:}13{.}022$ resistant model and when we look at
- NOTE Confidence: 0.806272241
- $00{:}39{:}13.022 \dashrightarrow 00{:}39{:}15.130$ the another model which is the Yammer
- NOTE Confidence: 0.806272241
- 00:39:15.130 --> 00:39:16.750 interfering gamma resistant model,
- NOTE Confidence: 0.806272241
- 00:39:16.750 00:39:20.540 you can see similar phenotype.
- NOTE Confidence: 0.806272241

 $00:39:20.540 \longrightarrow 00:39:26.236$ So lastly, is this also true in humans?

NOTE Confidence: 0.806272241

 $00{:}39{:}26{.}240 \dashrightarrow 00{:}39{:}29{.}138$ When we compare the the KADIAN 5

NOTE Confidence: 0.806272241

 $00:39:29.138 \rightarrow 00:39:31.130$ expression with the indulgence

NOTE Confidence: 0.806272241

 $00:39:31.130 \rightarrow 00:39:33.888$ retro elements part of the category

NOTE Confidence: 0.806272241

 $00:39:33.888 \longrightarrow 00:39:35.316$ of the retro elements,

NOTE Confidence: 0.806272241

 $00{:}39{:}35{.}320 \dashrightarrow 00{:}39{:}37{.}480$ you can see the the ones with high

NOTE Confidence: 0.806272241

 $00:39:37.480 \dashrightarrow 00:39:39.557$ Acadian 5 be expression was shown.

NOTE Confidence: 0.806272241

00:39:39.560 - 00:39:40.994 On this you have no expression

NOTE Confidence: 0.806272241

 $00:39:40.994 \longrightarrow 00:39:41.950$ of some of the.

NOTE Confidence: 0.712199291428571

 $00:39:44.420 \rightarrow 00:39:47.878$ You always showing here just one example

NOTE Confidence: 0.712199291428571

00:39:47.880 --> 00:39:50.520 RV 2637 and it's anti correlated

NOTE Confidence: 0.712199291428571

 $00{:}39{:}50{.}520 \dashrightarrow 00{:}39{:}53{.}193$ with Kaden 5 expression and the

NOTE Confidence: 0.712199291428571

 $00{:}39{:}53{.}193 \dashrightarrow 00{:}39{:}55{.}259$ expression is correlated with the

NOTE Confidence: 0.712199291428571

 $00:39:55.259 \dashrightarrow 00:39:57.737$ better response to PD1 blockade is

NOTE Confidence: 0.712199291428571

 $00:39:57.737 \rightarrow 00:40:00.256$ opposite to what we see with PKD and 5B.

NOTE Confidence: 0.712199291428571

 $00:40:00.260 \longrightarrow 00:40:03.522$ So to basically to summarize this part

 $00{:}40{:}03.522 \dashrightarrow 00{:}40{:}06.791$ of my talk which I showed you that Kadian

NOTE Confidence: 0.712199291428571

 $00{:}40{:}06.791 \dashrightarrow 00{:}40{:}09.791$ 5B can interact with set DB1 and and

NOTE Confidence: 0.712199291428571

 $00:40:09.791 \longrightarrow 00:40:13.046$ you can recruit set DB1 to the targets.

NOTE Confidence: 0.712199291428571

00:40:13.050 --> 00:40:15.640 To deposit actually K9 traumatization

NOTE Confidence: 0.712199291428571

 $00:40:15.640 \longrightarrow 00:40:17.194$ to silence retroelements,

NOTE Confidence: 0.712199291428571

 $00:40:17.200 \rightarrow 00:40:19.419$ if you gather with locating 5B you

NOTE Confidence: 0.712199291428571

 $00:40:19.419 \longrightarrow 00:40:21.200$ can activate endogenous retroelements.

NOTE Confidence: 0.712199291428571

 $00{:}40{:}21.200 \dashrightarrow 00{:}40{:}23.020$ You can activate double stranded

NOTE Confidence: 0.712199291428571

 $00{:}40{:}23.020 \dashrightarrow 00{:}40{:}24.840$ on Ascension pathway and double

NOTE Confidence: 0.712199291428571

 $00{:}40{:}24.903 \dashrightarrow 00{:}40{:}27.118$ strand DNA sensing pathways through

NOTE Confidence: 0.712199291428571

 $00{:}40{:}27.118 \dashrightarrow 00{:}40{:}28.890$ the reverse transcription process.

NOTE Confidence: 0.712199291428571

 $00{:}40{:}28.890 \dashrightarrow 00{:}40{:}31.459$ It I need to the better representation

NOTE Confidence: 0.712199291428571

 $00{:}40{:}31{.}459 \dashrightarrow 00{:}40{:}35{.}030$ of the MHC one and the cytokine secretion

NOTE Confidence: 0.712199291428571

 $00{:}40{:}35{.}030 \dashrightarrow 00{:}40{:}38{.}078$ lead to higher immunogenicity and better

NOTE Confidence: 0.712199291428571

 $00{:}40{:}38.078 \dashrightarrow 00{:}40{:}40.948$ response to e-mail checkpoint blockade.

 $00:40:40.950 \longrightarrow 00:40:43.476$ So although with the first group

NOTE Confidence: 0.712199291428571

 $00{:}40{:}43.476 \dashrightarrow 00{:}40{:}46.562$ that show that Kadian 5B is critical

NOTE Confidence: 0.712199291428571

 $00:40:46.562 \longrightarrow 00:40:47.885$ for immune evasion,

NOTE Confidence: 0.712199291428571

 $00{:}40{:}47.890 \dashrightarrow 00{:}40{:}50.026$ we are not the first group to so

NOTE Confidence: 0.712199291428571

 $00{:}40{:}50.026 \dashrightarrow 00{:}40{:}52.429$ shows that B1 has this function and

NOTE Confidence: 0.712199291428571

 $00{:}40{:}52.429 \dashrightarrow 00{:}40{:}54.229$ multiple groups about the similar

NOTE Confidence: 0.712199291428571

 $00{:}40{:}54{.}301 \dashrightarrow 00{:}40{:}58{.}928$ time show that said B1 is involved in.

NOTE Confidence: 0.712199291428571

00:40:58.930 --> 00:41:02.618 Suppressing tumor immunogenicity and

NOTE Confidence: 0.712199291428571

 $00{:}41{:}02.618 \dashrightarrow 00{:}41{:}05.826$ and and this is just multiple papers

NOTE Confidence: 0.712199291428571

 $00:41:05.826 \rightarrow 00:41:08.358$ basically by multiple groups and this

NOTE Confidence: 0.712199291428571

 $00{:}41{:}08{.}358 \dashrightarrow 00{:}41{:}11{.}886$ add to basically add to the what.

NOTE Confidence: 0.712199291428571

00:41:11.890 --> 00:41:12.710 Uh, what?

NOTE Confidence: 0.712199291428571

 $00:41:12.710 \longrightarrow 00:41:15.170$ What do we know about epigenetic

NOTE Confidence: 0.712199291428571

 $00{:}41{:}15{.}170 \dashrightarrow 00{:}41{:}17{.}980$ regulation of the viral mimicry pathway?

NOTE Confidence: 0.7203285616666667

 $00{:}41{:}20.000 \dashrightarrow 00{:}41{:}22.520$ Basically I've showed before that double

NOTE Confidence: 0.7203285616666667

 $00{:}41{:}22.520 \dashrightarrow 00{:}41{:}25.690$ DMT and SD one can do this and here we

- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}25.780 \dashrightarrow 00{:}41{:}29.326$ just showed up and said one can do this
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}29{.}326 \dashrightarrow 00{:}41{:}32{.}276$ and all those inhibitors will be able
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}32.276 \dashrightarrow 00{:}41{:}34.910$ to induce those biometric response and
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}34{.}982 \dashrightarrow 00{:}41{:}37{.}574$ the firm response and better response
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}37{.}574 \dashrightarrow 00{:}41{:}40{.}010$ to e-mail checkable and blockade.
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}40.010 \dashrightarrow 00{:}41{:}42.242$ So now I would like to thank all
- NOTE Confidence: 0.7203285616666667
- $00:41:42.242 \longrightarrow 00:41:44.537$ the people involved in this and
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}44{.}537 \dashrightarrow 00{:}41{:}46{.}617$ especially Marcus Bosenberg group and
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}46.617 \dashrightarrow 00{:}41{:}48.988$ where we had the fun collaboration.
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}48{.}990 \dashrightarrow 00{:}41{:}52{.}721$ A decade on collaboration and and the
- NOTE Confidence: 0.7203285616666667
- $00{:}41{:}52.721 \dashrightarrow 00{:}41{:}56.104$ drug resistant work is led by Shawnee
- NOTE Confidence: 0.7203285616666667
- $00:41:56.104 \rightarrow 00:41:59.338$ anew and Sami Zang and the immune NOTE Confidence: 0.7203285616666667
- $00:41:59.338 \longrightarrow 00:42:02.950$ evasion they walked the net by Samin NOTE Confidence: 0.7203285616666667
- 00:42:03.056 --> 00:42:06.596 Jan and Samin has actually started.
- NOTE Confidence: 0.720328561666667
- $00:42:06.600 \longrightarrow 00:42:08.980$ Isn't Professor Ship at
- NOTE Confidence: 0.7203285616666667

00:42:08.980 --> 00:42:10.765 Shanghai Tech University?

NOTE Confidence: 0.7203285616666667

 $00:42:10.770 \longrightarrow 00:42:13.146$ And on the some of the bad formatting works

NOTE Confidence: 0.7203285616666667

 $00:42:13.146 \rightarrow 00:42:15.723$ are done by Western East High and the glory,

NOTE Confidence: 0.7203285616666667

 $00:42:15.730 \longrightarrow 00:42:19.125$ and also like to thank all the

NOTE Confidence: 0.7203285616666667

 $00{:}42{:}19.130 \dashrightarrow 00{:}42{:}23.225$ youthful members for the kind of help

NOTE Confidence: 0.7203285616666667

 $00:42:23.225 \rightarrow 00:42:26.790$ through the course of this project.

NOTE Confidence: 0.7203285616666667

00:42:26.790 - 00:42:30.310 And when I try to start on Melanoma,

NOTE Confidence: 0.7203285616666667

 $00{:}42{:}30{.}310 \dashrightarrow 00{:}42{:}33{.}115$ the SPORE members welcomed me

NOTE Confidence: 0.7203285616666667

00:42:33.115 --> 00:42:36.337 with open arms and that's how

NOTE Confidence: 0.7203285616666667

 $00:42:36.337 \rightarrow 00:42:38.890$ I can get where we are here.

NOTE Confidence: 0.7203285616666667

 $00{:}42{:}38{.}890 \dashrightarrow 00{:}42{:}41{.}077$ And I'd also like to thank all the other.

NOTE Confidence: 0.7203285616666667

 $00:42:41.080 \rightarrow 00:42:42.675$ Funding agencies for their support

NOTE Confidence: 0.7203285616666667

 $00:42:42.675 \longrightarrow 00:42:45.599$ as you can see in a couple of

NOTE Confidence: 0.7203285616666667

00:42:45.599 --> 00:42:46.859 Melanoma Research Foundation,

NOTE Confidence: 0.720328561666667

 $00{:}42{:}46.860 \dashrightarrow 00{:}42{:}48.452$ Melanoma research alliance have

NOTE Confidence: 0.7203285616666667

 $00:42:48.452 \rightarrow 00:42:50.840$ been very helpful in supporting our

- NOTE Confidence: 0.7203285616666667
- $00{:}42{:}50{.}900 \dashrightarrow 00{:}42{:}52{.}682$ research in Melanoma and I would
- NOTE Confidence: 0.7203285616666667
- $00:42:52.682 \longrightarrow 00:42:54.938$ like to thank you all for your
- NOTE Confidence: 0.7203285616666667
- $00{:}42{:}54{.}938 \dashrightarrow 00{:}42{:}56{.}954$ attention and I welcome any questions.
- NOTE Confidence: 0.71509299
- $00:43:09.220 \longrightarrow 00:43:10.360$ Or maybe 1 back.
- NOTE Confidence: 0.7468024765
- 00:43:35.000 00:43:36.468 Yeah. That's a great.
- NOTE Confidence: 0.7468024765
- $00{:}43{:}36{.}468 \dashrightarrow 00{:}43{:}38{.}670$ So the question is whether we
- NOTE Confidence: 0.7468024765
- $00{:}43{:}38.745 \dashrightarrow 00{:}43{:}41.205$ have tried to combine KDM 5
- NOTE Confidence: 0.7468024765
- $00:43:41.205 \longrightarrow 00:43:42.845$ inhibitor with sting agonist,
- NOTE Confidence: 0.7468024765
- $00:43:42.850 \longrightarrow 00:43:43.732$ that's great suggestion.
- NOTE Confidence: 0.7468024765
- 00:43:43.732 --> 00:43:45.496 And we have thought about this,
- NOTE Confidence: 0.7468024765
- $00:43:45.500 \longrightarrow 00:43:47.642$ but we have not had the
- NOTE Confidence: 0.7468024765
- $00{:}43{:}47{.}642 \dashrightarrow 00{:}43{:}50{.}180$ time to do this experiment.
- NOTE Confidence: 0.7468024765
- $00{:}43{:}50{.}180 \dashrightarrow 00{:}43{:}51{.}710$ Yeah, which we should have done, yeah.
- NOTE Confidence: 0.81533074
- $00{:}43{:}54{.}440 \dashrightarrow 00{:}43{:}54{.}930$ OK.
- NOTE Confidence: 0.811770852
- $00{:}43{:}56{.}040 \dashrightarrow 00{:}43{:}58{.}288$ That was a great job. Thank you so much.
- NOTE Confidence: 0.811770852

 $00{:}43{:}58{.}290 \dashrightarrow 00{:}44{:}01{.}020$ And went back and forth a little bit

NOTE Confidence: 0.811770852

 $00{:}44{:}01{.}020 \dashrightarrow 00{:}44{:}03{.}182$ between 10:20 and five inhibition

NOTE Confidence: 0.811770852

 $00:44:03.182 \longrightarrow 00:44:05.578$ and 25 B specific inhibition.

NOTE Confidence: 0.811770852

 $00{:}44{:}05{.}578$ --> $00{:}44{:}08{.}990$ And I know that you think the KDM 5B

NOTE Confidence: 0.811770852

00:44:08.990 --> 00:44:10.860 is the most important one. What about?

NOTE Confidence: 0.52550698

 $00{:}44{:}12.720 \dashrightarrow 00{:}44{:}17.650$ And so we have, we actually have

NOTE Confidence: 0.52550698

00:44:17.650 --> 00:44:20.160 been working on breast cancer and

NOTE Confidence: 0.52550698

 $00{:}44{:}20{.}160 \dashrightarrow 00{:}44{:}22{.}780$ also some other cancer types where

NOTE Confidence: 0.52550698

 $00{:}44{:}22.780 \dashrightarrow 00{:}44{:}26.588$ we have seen is that in actually

NOTE Confidence: 0.52550698

 $00:44:26.588 \rightarrow 00:44:28.716$ maybe I'll show you one slide here.

NOTE Confidence: 0.52550698

00:44:28.720 --> 00:44:31.700 This was just published basically

NOTE Confidence: 0.52550698

 $00{:}44{:}31.700 \dashrightarrow 00{:}44{:}34.946$ this is MC38 with the colorectal

NOTE Confidence: 0.52550698

 $00{:}44{:}34{.}946 \dashrightarrow 00{:}44{:}38{.}649$ cancer where when we treated those.

NOTE Confidence: 0.52550698

 $00{:}44{:}38.650 \dashrightarrow 00{:}44{:}40.642$ So those animals, uh tumor bearing

NOTE Confidence: 0.52550698

 $00{:}44{:}40{.}642 \dashrightarrow 00{:}44{:}42{.}670$ animals with KDM 5 inhibitor,

NOTE Confidence: 0.52550698

 $00{:}44{:}42.670 \dashrightarrow 00{:}44{:}44.210$ you can suppress the ability to grow.

- NOTE Confidence: 0.52550698
- $00:44:44.210 \longrightarrow 00:44:46.710$ So it works incorrect cancer.
- NOTE Confidence: 0.52550698
- $00{:}44{:}46{.}710 \dashrightarrow 00{:}44{:}48{.}974$ Also when we look at the breast cancer
- NOTE Confidence: 0.52550698
- $00{:}44{:}48{.}974 \dashrightarrow 00{:}44{:}51{.}575$ you can see they have some new efficacy.
- NOTE Confidence: 0.52550698
- $00:44:51.580 \longrightarrow 00:44:53.554$ You can also combine that with
- NOTE Confidence: 0.52550698
- 00:44:53.554 --> 00:44:55.637 PD1 blockade and we can have
- NOTE Confidence: 0.52550698
- $00:44:55.637 \rightarrow 00:44:57.377$ I would say additive effect.
- NOTE Confidence: 0.52550698
- $00:44:57.380 \longrightarrow 00:45:02.098$ So it works in multiple cancer types.
- NOTE Confidence: 0.52550698
- $00:45:02.100 \longrightarrow 00:45:04.648$ It's just where we need to find
- NOTE Confidence: 0.52550698
- $00{:}45{:}04{.}648 \dashrightarrow 00{:}45{:}06{.}503$ the correct cancer types and
- NOTE Confidence: 0.52550698
- 00:45:06.503 00:45:08.897 subtypes even to so that we were
- NOTE Confidence: 0.52550698
- $00:45:08.897 \longrightarrow 00:45:11.068$ able to use those inhibitors.
- NOTE Confidence: 0.86637986
- 00:45:13.340 --> 00:45:15.286 Yeah, yeah. So, yeah,
- NOTE Confidence: 0.86637986
- $00{:}45{:}15{.}286 \dashrightarrow 00{:}45{:}16{.}894$ those are all planning.
- NOTE Confidence: 0.86637986
- $00:45:16.900 \longrightarrow 00:45:17.936$ Can you invite me here with us?
- NOTE Confidence: 0.86637986
- $00:45:17.940 \longrightarrow 00:45:21.028$ So, so one of the things that we
- NOTE Confidence: 0.86637986

 $00:45:21.028 \rightarrow 00:45:23.598$ are trying to do is to develop

NOTE Confidence: 0.86637986

00:45:23.600 --> 00:45:26.532 KADIAN file family members,

NOTE Confidence: 0.86637986

 $00:45:26.532 \rightarrow 00:45:27.998$ specific degraders.

NOTE Confidence: 0.86637986

 $00:45:28.000 \longrightarrow 00:45:31.750$ And with the.

NOTE Confidence: 0.86637986

 $00{:}45{:}31.750 \dashrightarrow 00{:}45{:}33.742$ Because with the protect or some

NOTE Confidence: 0.86637986

 $00{:}45{:}33{.}742 \dashrightarrow 00{:}45{:}35{.}882$ other similar kind of mechanism or NOTE Confidence: 0.86637986

00:45:35.882 --> 00:45:37.757 molecular glue type of mechanism

NOTE Confidence: 0.86637986

00:45:37.757 - 00:45:39.559 you can develop a specific

NOTE Confidence: 0.86637986

 $00{:}45{:}39{.}560 \dashrightarrow 00{:}45{:}42{.}206$ degraders against KDM 5 and we

NOTE Confidence: 0.86637986

 $00:45:42.206 \rightarrow 00:45:44.460$ are actually working on that.

NOTE Confidence: 0.86637986

 $00:45:44.460 \rightarrow 00:45:48.928$ We have some potential degraders that NOTE Confidence: 0.86637986

 $00{:}45{:}48{.}928 \dashrightarrow 00{:}45{:}51{.}544$ work specifically on Canadian 5B and NOTE Confidence: 0.86637986

NOTE Confidence: 0.80057980

 $00{:}45{:}51{.}544 \dashrightarrow 00{:}45{:}54{.}108$ some of them work on multiple all

NOTE Confidence: 0.86637986

 $00{:}45{:}54{.}108 \dashrightarrow 00{:}45{:}56{.}150$ kidding 5A in different settings.

NOTE Confidence: 0.555586011666667

 $00{:}45{:}58{.}370 \dashrightarrow 00{:}46{:}00{.}210$ Online question from City Chin.

NOTE Confidence: 0.804168843333333

00:46:02.690 --> 00:46:04.730 Yeah, I can. I can read. I can read it.

- NOTE Confidence: 0.804168843333333
- 00:46:04.730 --> 00:46:08.613 So the question is, do I anticipate?
- NOTE Confidence: 0.804168843333333
- $00:46:08.613 \rightarrow 00:46:12.612$ Other epigenetic reader and writer
- NOTE Confidence: 0.804168843333333
- $00:46:12.612 \longrightarrow 00:46:15.002$ to have similar effect, yes,
- NOTE Confidence: 0.804168843333333
- 00:46:15.002 --> 00:46:17.612 because actually I have showed
- NOTE Confidence: 0.804168843333333
- $00:46:17.612 \longrightarrow 00:46:21.378$ you one in one of the diagram.
- NOTE Confidence: 0.804168843333333
- $00{:}46{:}21.380 \dashrightarrow 00{:}46{:}25.846$ There are multiple other ones on this.
- NOTE Confidence: 0.804168843333333
- 00:46:25.850 --> 00:46:30.176 OK. Yeah. Once which have been shown
- NOTE Confidence: 0.804168843333333
- $00{:}46{:}30{.}176 \dashrightarrow 00{:}46{:}33{.}784$ have similar effect and although I
- NOTE Confidence: 0.804168843333333
- $00{:}46{:}33.784 \dashrightarrow 00{:}46{:}35.982$ have to say in different cancer types
- NOTE Confidence: 0.804168843333333
- $00:46:35.982 \rightarrow 00:46:37.984$ and they have different effect and
- NOTE Confidence: 0.804168843333333
- $00{:}46{:}37{.}984 \dashrightarrow 00{:}46{:}40{.}600$ we just need to find the right one
- NOTE Confidence: 0.804168843333333
- $00:46:40.600 \rightarrow 00:46:42.966$ and that work in the in our setting.
- NOTE Confidence: 0.92254168
- $00:46:46.570 \longrightarrow 00:46:47.780$ OK, that's.
- NOTE Confidence: 0.787420133333333
- 00:46:50.970 --> 00:46:51.720 Question for you.
- NOTE Confidence: 0.620666981666667
- $00{:}46{:}54{.}980 \dashrightarrow 00{:}46{:}57{.}326$ So you showed that Kenny M5
- NOTE Confidence: 0.56578101625

 $00{:}46{:}57{.}340 \dashrightarrow 00{:}47{:}00{.}460$ views anticorrelated with all sorts of

NOTE Confidence: 0.56578101625

 $00{:}47{:}00{.}460 \dashrightarrow 00{:}47{:}03{.}060$ new vectors, both positive and negative.

NOTE Confidence: 0.837579152

 $00:47:05.700 \longrightarrow 00:47:07.060$ What about the cell types?

NOTE Confidence: 0.40944326

00:47:10.790 --> 00:47:11.200 DC.

NOTE Confidence: 0.789690956

 $00:47:13.590 \longrightarrow 00:47:14.650$ Well, that's a great question.

NOTE Confidence: 0.789690956

 $00{:}47{:}14.650 \dashrightarrow 00{:}47{:}17.710$ We have not looked. Yeah.

NOTE Confidence: 0.789690956

 $00{:}47{:}17.710 \dashrightarrow 00{:}47{:}20.610$ So you just need to do something

NOTE Confidence: 0.789690956

 $00{:}47{:}20.610 \dashrightarrow 00{:}47{:}22.827$ also analysis too or just analyze

NOTE Confidence: 0.789690956

 $00{:}47{:}22.827 \dashrightarrow 00{:}47{:}24.820$ single cell data to see to see that.

NOTE Confidence: 0.789690956

 $00{:}47{:}24.820 \dashrightarrow 00{:}47{:}26.410$ Yeah, it's great, great suggestion.

NOTE Confidence: 0.789690956

 $00:47:26.410 \longrightarrow 00:47:27.438$ Yeah, should do that.

NOTE Confidence: 0.82373015

00:47:30.200 --> 00:47:30.770 I don't know.

NOTE Confidence: 0.36768749

 $00:47:32.910 \longrightarrow 00:47:35.720$ Wonderful mechanistic. Right.

NOTE Confidence: 0.736882002

 $00{:}47{:}40.140 \dashrightarrow 00{:}47{:}42.905$ My question is regarding Katie M5B.

NOTE Confidence: 0.736882002

 $00{:}47{:}42.905 \dashrightarrow 00{:}47{:}46.550$ And it's a deck that seemed to be asymmetric.

NOTE Confidence: 0.69929990333333

 $00:47:48.720 \rightarrow 00:47:51.149$ You showed us. I was wondering whether

 $00:47:51.149 \longrightarrow 00:47:53.495$ they would be animators that could

NOTE Confidence: 0.69929990333333

 $00:47:53.495 \rightarrow 00:47:55.973$ maybe the scaffolding effect of paying

NOTE Confidence: 0.69929990333333

 $00{:}47{:}55{.}973$ --> $00{:}47{:}58{.}662$ 5D its interaction with 71 and whether

NOTE Confidence: 0.69929990333333

 $00{:}47{:}58.662 \dashrightarrow 00{:}48{:}01.442$ those could be more appropriate for

NOTE Confidence: 0.699299990333333

 $00:48:01.442 \rightarrow 00:48:05.060$ who gets PDL 1 increased response.

NOTE Confidence: 0.7466141296875

 $00{:}48{:}06{.}990 \dashrightarrow 00{:}48{:}10{.}308$ Yeah, that so answer the question is

NOTE Confidence: 0.7466141296875

 $00{:}48{:}10{.}308 \dashrightarrow 00{:}48{:}13{.}663$ whether we should inhibit the scaffold

NOTE Confidence: 0.7466141296875

 $00:48:13.663 \rightarrow 00:48:16.608$ function location 5B, which is great.

NOTE Confidence: 0.7466141296875

 $00{:}48{:}16.608 \dashrightarrow 00{:}48{:}19.170$ So that's something that we are thinking

NOTE Confidence: 0.7466141296875

 $00:48:19.243 \rightarrow 00:48:21.595$ along the way because we have to first

NOTE Confidence: 0.7466141296875

 $00:48:21.595 \rightarrow 00:48:24.080$ of all we need to identify the domains

NOTE Confidence: 0.7466141296875

 $00{:}48{:}24.080 \dashrightarrow 00{:}48{:}26.420$ that are critical for those interaction.

NOTE Confidence: 0.7466141296875

 $00{:}48{:}26{.}420 \dashrightarrow 00{:}48{:}28{.}760$ And then one of the things that we're trying

NOTE Confidence: 0.7466141296875

 $00{:}48{:}28.760 \dashrightarrow 00{:}48{:}31.020$ to do is you to look for those domains

NOTE Confidence: 0.7466141296875

 $00{:}48{:}31{.}020 \dashrightarrow 00{:}48{:}33{.}894$ that are involved in interacting with

 $00:48:33.894 \rightarrow 00:48:37.268$ said said B1 and then those inhibitors.

NOTE Confidence: 0.7466141296875

 $00{:}48{:}37{.}270 \dashrightarrow 00{:}48{:}40{.}819$ To have more specificity as you as

NOTE Confidence: 0.7466141296875

 $00:48:40.819 \rightarrow 00:48:43.768$ you suggested to target this pathway NOTE Confidence: 0.7466141296875

 $00:48:43.768 \rightarrow 00:48:46.565$ and it's probably better than getting

NOTE Confidence: 0.7466141296875

 $00{:}48{:}46{.}565 \dashrightarrow 00{:}48{:}48{.}875$ 5 inhibitor or 71 inhibitor which

NOTE Confidence: 0.7466141296875

00:48:48.875 --> 00:48:51.120 might have some other off target

NOTE Confidence: 0.7466141296875

 $00:48:51.120 \longrightarrow 00:48:53.486$ effect that we don't want to see.

NOTE Confidence: 0.76170298375

 $00:48:54.870 \longrightarrow 00:48:55.536$ That's what interesting,

NOTE Confidence: 0.76170298375

 $00:48:55.536 \rightarrow 00:48:56.646$ because when you think of,

NOTE Confidence: 0.76170298375

 $00:48:56.650 \rightarrow 00:48:58.318$ for example, LC-1, there are requests

NOTE Confidence: 0.76170298375

 $00:48:58.318 \longrightarrow 00:49:00.219$ that seem to be targeting the.

NOTE Confidence: 0.777380149

 $00:49:03.860 \longrightarrow 00:49:06.476$ But we know that they actually

NOTE Confidence: 0.777380149

00:49:06.476 --> 00:49:08.220 impact step folding effects,

NOTE Confidence: 0.777380149

 $00:49:08.220 \longrightarrow 00:49:12.540$ other proteins that play a role in one.

NOTE Confidence: 0.820704649

 $00{:}49{:}14.840 \dashrightarrow 00{:}49{:}16.508$ I wonder if those types of

NOTE Confidence: 0.820704649

 $00:49:16.508 \longrightarrow 00:49:17.620$ indicators are out there.
NOTE Confidence: 0.88700327

00:49:19.130 --> 00:49:20.974 Yeah, you could be made, but uh,

NOTE Confidence: 0.88700327

 $00{:}49{:}20{.}974 \dashrightarrow 00{:}49{:}23{.}206$ we we don't have those yet.

NOTE Confidence: 0.88700327

 $00:49:23.210 \longrightarrow 00:49:24.419$ Work in progress.

NOTE Confidence: 0.9599048

 $00{:}49{:}30{.}210 \dashrightarrow 00{:}49{:}33{.}618$ OK. If no more questions. Thank you.