

WEBVTT

NOTE duration:"00:49:49.700000"

NOTE recognizability:0.783

NOTE language:en-us

NOTE Confidence: 0.824819200714286

00:00:00.000 --> 00:00:03.136 Got it. So it's my distinct pleasure

NOTE Confidence: 0.824819200714286

00:00:03.136 --> 00:00:05.898 to introduce Chen Yan to us today.

NOTE Confidence: 0.824819200714286

00:00:05.900 --> 00:00:07.664 He's one of the invited speakers for

NOTE Confidence: 0.824819200714286

00:00:07.664 --> 00:00:09.540 this year for the Melanoma program.

NOTE Confidence: 0.824819200714286

00:00:09.540 --> 00:00:11.358 So for those that don't know,

NOTE Confidence: 0.824819200714286

00:00:11.360 --> 00:00:13.712 Melanoma program is a fairly well

NOTE Confidence: 0.824819200714286

00:00:13.712 --> 00:00:16.013 established 1 going back to the 1980s

NOTE Confidence: 0.824819200714286

00:00:16.013 --> 00:00:18.037 when we started the first what wasn't me,

NOTE Confidence: 0.824819200714286

00:00:18.040 --> 00:00:20.740 other folks started the first

NOTE Confidence: 0.824819200714286

00:00:20.740 --> 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 --> 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,

NOTE Confidence: 0.824819200714286

00:00:28.830 --> 00:00:30.405 wrote the first version of the Yale.
NOTE Confidence: 0.824819200714286

00:00:30.410 --> 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 --> 00:00:39.556 We just submitted the 4th iteration.
NOTE Confidence: 0.824819200714286

00:00:39.560 --> 00:00:41.720 So one of the best things about working
NOTE Confidence: 0.824819200714286

00:00:41.720 --> 00:00:44.004 here is actually our colleagues and I
NOTE Confidence: 0.824819200714286

00:00:44.004 --> 00:00:46.100 think Chin actually exemplifies that.
NOTE Confidence: 0.824819200714286

00:00:46.100 --> 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 --> 00:00:53.200 actually on epigenetics and renal
NOTE Confidence: 0.824819200714286

00:00:53.200 --> 00:00:54.440 cell carcinoma.
NOTE Confidence: 0.824819200714286

00:00:54.440 --> 00:00:56.183 But at some point it became clear
NOTE Confidence: 0.824819200714286

00:00:56.183 --> 00:00:58.477 that some of the things that he was
NOTE Confidence: 0.824819200714286

00:00:58.477 --> 00:00:59.967 studying were very applicable to
NOTE Confidence: 0.824819200714286

00:01:00.023 --> 00:01:02.522 Melanoma as well and he submitted a
NOTE Confidence: 0.824819200714286

00:01:02.522 --> 00:01:03.962 developmental research project to

NOTE Confidence: 0.824819200714286
00:01:03.962 --> 00:01:06.134 the sport in its previous iteration.
NOTE Confidence: 0.824819200714286
00:01:06.140 --> 00:01:07.752 And that subsequently blossomed
NOTE Confidence: 0.824819200714286
00:01:07.752 --> 00:01:09.364 to a full project.
NOTE Confidence: 0.824819200714286
00:01:09.370 --> 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 --> 00:01:16.335 both in terms of his scientific depth
NOTE Confidence: 0.824819200714286
00:01:16.335 --> 00:01:17.988 and in terms of his personality.
NOTE Confidence: 0.824819200714286
00:01:17.990 --> 00:01:19.220 He's definitely one of us.
NOTE Confidence: 0.824819200714286
00:01:19.220 --> 00:01:21.060 And I actually don't care that he's the
NOTE Confidence: 0.824819200714286
00:01:21.060 --> 00:01:22.786 scientific Co director of the breast unit.
NOTE Confidence: 0.824819200714286
00:01:22.790 --> 00:01:24.530 As far as we're concerned, he's ours.
NOTE Confidence: 0.824819200714286
00:01:24.530 --> 00:01:25.810 So without further ado,
NOTE Confidence: 0.824819200714286
00:01:25.810 --> 00:01:27.130 chin, the floor is yours.
NOTE Confidence: 0.824819200714286
00:01:27.130 --> 00:01:27.620 Thank you.
NOTE Confidence: 0.815876828888889

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 and I was also
NOTE Confidence: 0.815876828888889

00:01:35.363 --> 00:01:37.237 like to thank my normal program for
NOTE Confidence: 0.815876828888889

00:01:37.237 --> 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 --> 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 --> 00:01:52.490 working together with Marcus Bosenberg.
NOTE Confidence: 0.815876828888889

00:01:52.490 --> 00:01:54.738 I bought a decade ago and we were
NOTE Confidence: 0.815876828888889

00:01:54.738 --> 00:01:56.826 talking about Jerry 1B who might be
NOTE Confidence: 0.815876828888889

00:01:56.826 --> 00:01:58.890 which might be important in Melanoma.
NOTE Confidence: 0.815876828888889

00:01:58.890 --> 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 --> 00:02:05.848 we just started the collaboration and
NOTE Confidence: 0.815876828888889

00:02:05.848 --> 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.
NOTE Confidence: 0.5680343
00:02:13.350 --> 00:02:16.590 So let me get this started.
NOTE Confidence: 0.5680343
00:02:16.590 --> 00:02:17.880 Fixed the pointer.
NOTE Confidence: 0.837761892
00:02:22.450 --> 00:02:24.810 So this is my disclosure.
NOTE Confidence: 0.837761892
00:02:24.810 --> 00:02:26.722 So what I'm going to do is first
NOTE Confidence: 0.837761892
00:02:26.722 --> 00:02:28.891 you give you a very quick overview
NOTE Confidence: 0.837761892
00:02:28.891 --> 00:02:30.938 of cancer epigenetics and then you
NOTE Confidence: 0.837761892
00:02:30.938 --> 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 --> 00:02:38.493 how it recognizes drug resistance
NOTE Confidence: 0.837761892
00:02:38.493 --> 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 --> 00:02:44.620 the epigenetics is study of
NOTE Confidence: 0.837761892
00:02:44.620 --> 00:02:46.710 health heroical traits that does
NOTE Confidence: 0.837761892
00:02:46.785 --> 00:02:49.125 not depend on the underlying DNA
NOTE Confidence: 0.837761892

00:02:49.125 --> 00:02:51.388 sequences and the major epigenetic
NOTE Confidence: 0.837761892

00:02:51.388 --> 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 --> 00:02:58.490 histone modifications and non coding on it.
NOTE Confidence: 0.837761892

00:02:58.490 --> 00:03:01.124 There's a number of regulators of
NOTE Confidence: 0.837761892

00:03:01.124 --> 00:03:03.380 IPG netting mechanism including the
NOTE Confidence: 0.837761892

00:03:03.380 --> 00:03:05.540 coronary modernness which are involved
NOTE Confidence: 0.837761892

00:03:05.540 --> 00:03:08.149 in moving the nuclear zones around
NOTE Confidence: 0.837761892

00:03:08.150 --> 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 --> 00:03:17.394 So what I'm going to tell you
NOTE Confidence: 0.837761892

00:03:17.394 --> 00:03:19.380 today mainly focus on KDM 5B which
NOTE Confidence: 0.837761892

00:03:19.380 --> 00:03:21.678 is an eraser which is involved in
NOTE Confidence: 0.837761892

00:03:21.678 --> 00:03:23.158 removing a certain modification
NOTE Confidence: 0.837761892

00:03:23.158 --> 00:03:25.347 and sandbag one which I'm touched
NOTE Confidence: 0.837761892

00:03:25.347 --> 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 --> 00:03:34.267 with this hallmarks of cancer
NOTE Confidence: 0.873892465384615
00:03:34.267 --> 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 --> 00:03:40.844 the immune invasion that
NOTE Confidence: 0.873892465384615
00:03:40.844 --> 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 --> 00:03:47.396 this is a new,
NOTE Confidence: 0.873892465384615
00:03:47.396 --> 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 --> 00:03:56.196 quite related to epigenetics,
NOTE Confidence: 0.873892465384615
00:03:56.200 --> 00:03:59.116 including unlocking phenotypic.
NOTE Confidence: 0.873892465384615
00:03:59.116 --> 00:04:03.004 Plasticity and epigenetic reprogramming.
NOTE Confidence: 0.873892465384615
00:04:03.010 --> 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 --> 00:04:14.007 epigenetics can regulate many of the

NOTE Confidence: 0.873892465384615

00:04:14.007 --> 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 --> 00:04:23.442 and just on the tumor cells for example,

NOTE Confidence: 0.873892465384615

00:04:23.450 --> 00:04:25.730 it has been shown DNA machination,

NOTE Confidence: 0.873892465384615

00:04:25.730 --> 00:04:27.974 histone modifications have been

NOTE Confidence: 0.873892465384615

00:04:27.974 --> 00:04:30.779 involved in regulating tumor antigen

NOTE Confidence: 0.873892465384615

00:04:30.779 --> 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 --> 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 --> 00:04:43.480 and those modifications are also

NOTE Confidence: 0.873892465384615

00:04:43.480 --> 00:04:45.560 important on other immune cells,

NOTE Confidence: 0.873892465384615

00:04:45.560 --> 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 --> 00:04:52.540 which is not duplicated here.
NOTE Confidence: 0.873892465384615
00:04:52.540 --> 00:04:54.703 So just a brief introduction on my
NOTE Confidence: 0.873892465384615
00:04:54.703 --> 00:04:56.499 laboratory and we are interested
NOTE Confidence: 0.873892465384615
00:04:56.499 --> 00:04:58.499 in cancer epigenetics of course.
NOTE Confidence: 0.873892465384615
00:04:58.500 --> 00:05:00.876 And one of the area we are interested
NOTE Confidence: 0.873892465384615
00:05:00.876 --> 00:05:03.692 in is a cancer metastasis shown here.
NOTE Confidence: 0.873892465384615
00:05:03.692 --> 00:05:07.020 Just one of the example where we showed
NOTE Confidence: 0.873892465384615
00:05:07.103 --> 00:05:10.334 one of the target called CCR two is a
NOTE Confidence: 0.873892465384615
00:05:10.334 --> 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 --> 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 --> 00:05:21.920 lung and if you overexpress CCR two,
NOTE Confidence: 0.873892465384615

00:05:21.920 --> 00:05:22.420 you.
NOTE Confidence: 0.873892465384615

00:05:22.420 --> 00:05:24.420 And rescue this phenotype.
NOTE Confidence: 0.873892465384615

00:05:24.420 --> 00:05:26.366 And of course we are very interested
NOTE Confidence: 0.873892465384615

00:05:26.366 --> 00:05:28.353 in the immune invasion part of the
NOTE Confidence: 0.873892465384615

00:05:28.353 --> 00:05:30.637 talk I'm going to talk about then and
NOTE Confidence: 0.873892465384615

00:05:30.637 --> 00:05:32.997 this is something that I will mention later.
NOTE Confidence: 0.873892465384615

00:05:33.000 --> 00:05:35.690 And so I'm not going to go over this figure.
NOTE Confidence: 0.873892465384615

00:05:35.690 --> 00:05:38.308 And we are also interested in drug
NOTE Confidence: 0.873892465384615

00:05:38.308 --> 00:05:41.137 resistance and I will tell you about our
NOTE Confidence: 0.873892465384615

00:05:41.137 --> 00:05:43.370 work on the drug resistance in Melanoma,
NOTE Confidence: 0.873892465384615

00:05:43.370 --> 00:05:46.778 but this is a diagram actually found a.
NOTE Confidence: 0.873892465384615

00:05:46.780 --> 00:05:48.904 Had breast cancer walk where we
NOTE Confidence: 0.873892465384615

00:05:48.904 --> 00:05:51.261 showed that trastuzumab resistant
NOTE Confidence: 0.873892465384615

00:05:51.261 --> 00:05:53.929 cells have increased oxidative
NOTE Confidence: 0.873892465384615

00:05:53.929 --> 00:05:57.266 phosphorylation and if you block
NOTE Confidence: 0.873892465384615

00:05:57.266 --> 00:06:00.095 oxidative phosphorylation with only a,

NOTE Confidence: 0.873892465384615
00:06:00.095 --> 00:06:02.370 if you combine that with transfusion level,
NOTE Confidence: 0.873892465384615
00:06:02.370 --> 00:06:05.328 you can actually regress the tumor
NOTE Confidence: 0.873892465384615
00:06:05.328 --> 00:06:08.799 formation by the drug resistant cells.
NOTE Confidence: 0.873892465384615
00:06:08.800 --> 00:06:10.372 As a matter of because we
NOTE Confidence: 0.873892465384615
00:06:10.372 --> 00:06:11.760 are interested in the area,
NOTE Confidence: 0.873892465384615
00:06:11.760 --> 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 --> 00:06:17.701 And I will tell you some of the work
NOTE Confidence: 0.873892465384615
00:06:17.701 --> 00:06:19.967 on KDM 5 inhibitor development.
NOTE Confidence: 0.873892465384615
00:06:19.970 --> 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 --> 00:06:31.055 inhibitor where we show that this
NOTE Confidence: 0.873892465384615
00:06:31.055 --> 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
NOTE Confidence: 0.873892465384615

00:06:35.731 --> 00:06:38.219 cell tumor cells to grow but you can.
NOTE Confidence: 0.873892465384615

00:06:38.220 --> 00:06:41.298 Also hit on the macrophages by
NOTE Confidence: 0.873892465384615

00:06:41.298 --> 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 --> 00:06:48.590 polarization and the macrophage
NOTE Confidence: 0.873892465384615

00:06:48.664 --> 00:06:50.682 proliferation and this drug actually
NOTE Confidence: 0.873892465384615

00:06:50.682 --> 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 --> 00:06:54.561 into phase two very
NOTE Confidence: 0.806375226666667

00:06:54.609 --> 00:06:54.840 soon.
NOTE Confidence: 0.612246446875

00:06:57.220 --> 00:06:59.530 So my laboratory had been focusing
NOTE Confidence: 0.612246446875

00:06:59.530 --> 00:07:03.287 on a group of England called KDM 5
NOTE Confidence: 0.612246446875

00:07:03.287 --> 00:07:06.135 histone demethylase and and as you can
NOTE Confidence: 0.612246446875

00:07:06.135 --> 00:07:08.868 see here this group of vendors have
NOTE Confidence: 0.612246446875

00:07:08.868 --> 00:07:12.332 four of them and they they are called
NOTE Confidence: 0.612246446875

00:07:12.425 --> 00:07:15.264 KDM 5 ABC D or Jared 1A1B1C and 1D

NOTE Confidence: 0.612246446875

00:07:15.264 --> 00:07:18.335 and all of those have this team JC

NOTE Confidence: 0.612246446875

00:07:18.335 --> 00:07:21.198 domain which is the Jumanji C domain,

NOTE Confidence: 0.612246446875

00:07:21.200 --> 00:07:24.320 it's hydroxylase domain and the by

NOTE Confidence: 0.612246446875

00:07:24.320 --> 00:07:26.400 hydroxylation of the methanation.

NOTE Confidence: 0.612246446875

00:07:26.400 --> 00:07:28.410 Group and the removal of formaldehyde.

NOTE Confidence: 0.612246446875

00:07:28.410 --> 00:07:31.968 They actually can demate the histones.

NOTE Confidence: 0.612246446875

00:07:31.970 --> 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 --> 00:07:39.186 four on histone H3.

NOTE Confidence: 0.612246446875

00:07:39.190 --> 00:07:40.910 And because those machination

NOTE Confidence: 0.612246446875

00:07:40.910 --> 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 --> 00:07:50.780 online can silence transcription.

NOTE Confidence: 0.612246446875

00:07:50.780 --> 00:07:52.256 But that's not the whole story.

NOTE Confidence: 0.612246446875

00:07:52.260 --> 00:07:54.984 And all those protein actually have
NOTE Confidence: 0.612246446875

00:07:54.984 --> 00:07:57.320 other domains including 80 rich
NOTE Confidence: 0.612246446875

00:07:57.320 --> 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 --> 00:08:05.233 fingers which are involved in binding
NOTE Confidence: 0.612246446875

00:08:05.240 --> 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 --> 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 --> 00:08:14.624 and transcription recognition.
NOTE Confidence: 0.612246446875

00:08:14.624 --> 00:08:16.460 So they have.
NOTE Confidence: 0.612246446875

00:08:16.460 --> 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 --> 00:08:21.204 The transcription repressor they
NOTE Confidence: 0.612246446875

00:08:21.204 --> 00:08:22.568 can be transcription activated
NOTE Confidence: 0.612246446875

00:08:22.568 --> 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 --> 00:08:40.800 Because there's a number of.
NOTE Confidence: 0.811010291666667
00:08:40.800 --> 00:08:42.940 Evidence showing that uh
NOTE Confidence: 0.811010291666667
00:08:42.940 --> 00:08:45.615 Kadian 5B has oncogenic role.
NOTE Confidence: 0.811010291666667
00:08:45.620 --> 00:08:47.228 It was shown to be overexpressed
NOTE Confidence: 0.811010291666667
00:08:47.228 --> 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 --> 00:08:53.316 Initially was identified as a
NOTE Confidence: 0.811010291666667
00:08:53.316 --> 00:08:55.774 downstream gene downstream of her
NOTE Confidence: 0.811010291666667
00:08:55.774 --> 00:08:58.510 2IN breast cancer because it was
NOTE Confidence: 0.811010291666667
00:08:58.598 --> 00:09:01.559 shown to be downregulated by anti to
NOTE Confidence: 0.811010291666667

00:09:01.559 --> 00:09:04.988 anybody in her two overexpression cells.
NOTE Confidence: 0.811010291666667

00:09:04.990 --> 00:09:07.486 And these have been shown by 90 points
NOTE Confidence: 0.811010291666667

00:09:07.486 --> 00:09:09.660 group that is amplified in luminal
NOTE Confidence: 0.811010291666667

00:09:09.660 --> 00:09:11.880 breast cancer and it's a potential
NOTE Confidence: 0.811010291666667

00:09:11.945 --> 00:09:13.449 luminal linearity driving oncogene
NOTE Confidence: 0.811010291666667

00:09:13.449 --> 00:09:18.220 and we have shown in any in mouse.
NOTE Confidence: 0.811010291666667

00:09:18.220 --> 00:09:21.894 Me, I'd be single cells that are
NOTE Confidence: 0.811010291666667

00:09:21.894 --> 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 --> 00:09:29.153 contribute to estrogen receptor
NOTE Confidence: 0.811010291666667

00:09:29.153 --> 00:09:31.278 target gene expression and in
NOTE Confidence: 0.811010291666667

00:09:31.278 --> 00:09:34.720 fact if you look at the estrogen.
NOTE Confidence: 0.811010291666667

00:09:34.720 --> 00:09:36.588 Except the positive tumors
NOTE Confidence: 0.811010291666667

00:09:36.588 --> 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 --> 00:09:45.626 be OK and 5B is correlated with

NOTE Confidence: 0.811010291666667

00:09:45.626 --> 00:09:49.736 poor prognosis of those patients.

NOTE Confidence: 0.811010291666667

00:09:49.740 --> 00:09:52.015 And and then you point out group

NOTE Confidence: 0.811010291666667

00:09:52.015 --> 00:09:55.086 has also shown that Kadian 5B can

NOTE Confidence: 0.811010291666667

00:09:55.086 --> 00:09:56.601 promote transcriptomic heterogeneity

NOTE Confidence: 0.811010291666667

00:09:56.601 --> 00:09:59.459 and this actually contribute to the

NOTE Confidence: 0.811010291666667

00:09:59.459 --> 00:10:01.569 therapeutic resistance and this is

NOTE Confidence: 0.811010291666667

00:10:01.569 --> 00:10:04.930 just one of the mechanism that this

NOTE Confidence: 0.811010291666667

00:10:04.930 --> 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 --> 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 --> 00:10:15.678 when we deplete KDM 5B first

NOTE Confidence: 0.811010291666667

00:10:15.678 --> 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 --> 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 --> 00:10:34.699 scope that if you suppress.
NOTE Confidence: 0.811010291666667

00:10:34.700 --> 00:10:36.610 Expression in normal cells initially,
NOTE Confidence: 0.811010291666667

00:10:36.610 --> 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 --> 00:10:43.322 those cells still crash,
NOTE Confidence: 0.811010291666667

00:10:43.322 --> 00:10:45.562 so suggesting that it's required
NOTE Confidence: 0.811010291666667

00:10:45.562 --> 00:10:48.774 for Melanoma maintenance instead of
NOTE Confidence: 0.811010291666667

00:10:48.774 --> 00:10:51.458 putting refreshing initial proliferation.
NOTE Confidence: 0.811010291666667

00:10:51.460 --> 00:10:54.057 And they was shown in multiple groups
NOTE Confidence: 0.811010291666667

00:10:54.057 --> 00:10:56.313 including ours that KADIAN file be
NOTE Confidence: 0.811010291666667

00:10:56.313 --> 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 --> 00:11:02.526 actually by a company constellation

NOTE Confidence: 0.811010291666667
00:11:02.526 --> 00:11:04.644 where they showed in multiple cancer
NOTE Confidence: 0.811010291666667
00:11:04.644 --> 00:11:06.379 cell lines including Melanoma.
NOTE Confidence: 0.811010291666667
00:11:06.380 --> 00:11:10.405 Here if you compare the effect of
NOTE Confidence: 0.811010291666667
00:11:10.405 --> 00:11:13.494 Canadian five inhibitor on parental
NOTE Confidence: 0.811010291666667
00:11:13.494 --> 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 --> 00:11:20.780 case they did a pre treatment of.
NOTE Confidence: 0.811010291666667
00:11:20.780 --> 00:11:24.908 Both S and and they should have shown
NOTE Confidence: 0.811010291666667
00:11:24.908 --> 00:11:27.505 that the KADIAN 5 inhibitor cannot
NOTE Confidence: 0.811010291666667
00:11:27.505 --> 00:11:30.790 inhibit the growth of the parental cells,
NOTE Confidence: 0.811010291666667
00:11:30.790 --> 00:11:34.630 but they can prevent the emergence
NOTE Confidence: 0.811010291666667
00:11:34.630 --> 00:11:37.659 of the drug resistant tolerant.
NOTE Confidence: 0.811010291666667
00:11:37.659 --> 00:11:41.157 Would DP cells or drug tolerant
NOTE Confidence: 0.811010291666667
00:11:41.157 --> 00:11:44.479 persister cells or drug resistant cells?
NOTE Confidence: 0.811010291666667
00:11:44.480 --> 00:11:49.072 In prostate cancer if we cost the
NOTE Confidence: 0.811010291666667

00:11:49.072 --> 00:11:52.060 KADIAN file be knockout model to
NOTE Confidence: 0.811010291666667

00:11:52.171 --> 00:11:54.932 the P-10 knockout model in process
NOTE Confidence: 0.811010291666667

00:11:54.932 --> 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 --> 00:12:01.877 form a prostate cancer.
NOTE Confidence: 0.811010291666667

00:12:01.880 --> 00:12:05.400 But if you get relocation 5B you can
NOTE Confidence: 0.811010291666667

00:12:05.400 --> 00:12:08.333 normalize the those those prostate
NOTE Confidence: 0.811010291666667

00:12:08.333 --> 00:12:11.612 tumors basically you can see the
NOTE Confidence: 0.811010291666667

00:12:11.612 --> 00:12:14.570 the the size is much smaller.
NOTE Confidence: 0.811010291666667

00:12:14.570 --> 00:12:18.338 Now I want to move back to Melanoma
NOTE Confidence: 0.811010291666667

00:12:18.338 --> 00:12:22.224 because this is a focus on our talk today.
NOTE Confidence: 0.744956012222222

00:12:22.230 --> 00:12:25.290 1st when we looked at the TCA data set,
NOTE Confidence: 0.744956012222222

00:12:25.290 --> 00:12:27.942 this was done by Goran, a tenant in
NOTE Confidence: 0.744956012222222

00:12:27.942 --> 00:12:30.006 the graduate student at that time.
NOTE Confidence: 0.744956012222222

00:12:30.010 --> 00:12:33.810 In exposing like who is final right now?
NOTE Confidence: 0.744956012222222

00:12:33.810 --> 00:12:36.590 Where he showed that high

NOTE Confidence: 0.744956012222222
00:12:36.590 --> 00:12:40.320 expression is associated with poor
NOTE Confidence: 0.744956012222222
00:12:40.320 --> 00:12:43.304 survival of Melanoma patients.
NOTE Confidence: 0.744956012222222
00:12:43.310 --> 00:12:47.094 So now we decided to look at the
NOTE Confidence: 0.744956012222222
00:12:47.094 --> 00:12:50.326 Melanoma when we when we followed some
NOTE Confidence: 0.744956012222222
00:12:50.326 --> 00:12:53.442 of the work from Marcus Bosenberg.
NOTE Confidence: 0.744956012222222
00:12:53.442 --> 00:12:57.250 I have about my normal propagating cells.
NOTE Confidence: 0.744956012222222
00:12:57.250 --> 00:12:59.970 Was published more than a decade ago that
NOTE Confidence: 0.744956012222222
00:12:59.970 --> 00:13:03.068 if you look at the mouse Melanoma cells,
NOTE Confidence: 0.744956012222222
00:13:03.070 --> 00:13:06.130 you can sort them to three
NOTE Confidence: 0.744956012222222
00:13:06.130 --> 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 --> 00:13:19.150 of the cells to form tumors,
NOTE Confidence: 0.744956012222222

00:13:19.150 --> 00:13:22.643 the CD 34 positive cells can form
NOTE Confidence: 0.744956012222222

00:13:22.643 --> 00:13:25.110 tumors very efficiently and the
NOTE Confidence: 0.744956012222222

00:13:25.110 --> 00:13:27.738 double negative cells can do so.
NOTE Confidence: 0.744956012222222

00:13:27.740 --> 00:13:30.932 With less efficacy but still works
NOTE Confidence: 0.744956012222222

00:13:30.932 --> 00:13:33.692 and the PDP 75 positive cells
NOTE Confidence: 0.744956012222222

00:13:33.692 --> 00:13:36.230 do not actually form tumors if
NOTE Confidence: 0.744956012222222

00:13:36.314 --> 00:13:39.490 they put them into modern mice.
NOTE Confidence: 0.744956012222222

00:13:39.490 --> 00:13:43.242 So we decided to look at this more
NOTE Confidence: 0.744956012222222

00:13:43.242 --> 00:13:45.240 systematically and when this is
NOTE Confidence: 0.744956012222222

00:13:45.240 --> 00:13:47.375 just a diagram show a table showing
NOTE Confidence: 0.744956012222222

00:13:47.375 --> 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 --> 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 --> 00:14:04.523 use those and use those cells for

NOTE Confidence: 0.744956012222222
00:14:04.523 --> 00:14:06.647 syngeneic transplantation experiments.
NOTE Confidence: 0.744956012222222
00:14:06.650 --> 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 --> 00:14:16.130 actually I will use it also later
NOTE Confidence: 0.744956012222222
00:14:16.214 --> 00:14:18.674 on on for e-mail invasion studies
NOTE Confidence: 0.744956012222222
00:14:18.674 --> 00:14:21.096 and also young ones 3.3 cells.
NOTE Confidence: 0.744956012222222
00:14:21.096 --> 00:14:23.812 The reason why we chose those cells
NOTE Confidence: 0.744956012222222
00:14:23.812 --> 00:14:25.840 because they only have two populations
NOTE Confidence: 0.744956012222222
00:14:25.840 --> 00:14:28.123 so these 34 positive and city 34
NOTE Confidence: 0.744956012222222
00:14:28.123 --> 00:14:30.419 negative both of them can form too much.
NOTE Confidence: 0.744956012222222
00:14:30.420 --> 00:14:34.083 So this provide a nice system to look at
NOTE Confidence: 0.744956012222222
00:14:34.083 --> 00:14:38.200 the the population changes and when we put.
NOTE Confidence: 0.744956012222222
00:14:38.200 --> 00:14:41.040 Drugs on onto them.
NOTE Confidence: 0.744956012222222
00:14:41.040 --> 00:14:44.328 So we used the because those
NOTE Confidence: 0.744956012222222
00:14:44.328 --> 00:14:47.515 are mutant tumors and we treat
NOTE Confidence: 0.744956012222222

00:14:47.515 --> 00:14:50.150 those cells with rough inhibitor.

NOTE Confidence: 0.744956012222222

00:14:50.150 --> 00:14:52.346 In this case we use actually

NOTE Confidence: 0.744956012222222

00:14:52.346 --> 00:14:56.560 use the PX4 or three, two over.

NOTE Confidence: 0.744956012222222

00:14:56.560 --> 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 --> 00:14:59.717 as you can see here,

NOTE Confidence: 0.744956012222222

00:14:59.720 --> 00:15:01.918 if you compare the parental cells and

NOTE Confidence: 0.744956012222222

00:15:01.918 --> 00:15:04.217 you have more CD 34 positive cells.

NOTE Confidence: 0.744956012222222

00:15:04.220 --> 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 --> 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 --> 00:15:18.390 they have more city 34 negative cells.

NOTE Confidence: 0.744956012222222

00:15:18.390 --> 00:15:21.552 When you look at the the effect

NOTE Confidence: 0.744956012222222

00:15:21.552 --> 00:15:23.748 of the Bureau of inhibitor on

NOTE Confidence: 0.744956012222222

00:15:23.748 --> 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 --> 00:15:31.588 Those are more resistant to be

NOTE Confidence: 0.744956012222222

00:15:31.588 --> 00:15:34.000 off inhibitor treatment because

NOTE Confidence: 0.744956012222222

00:15:34.102 --> 00:15:37.118 there's less growth inhibition.

NOTE Confidence: 0.744956012222222

00:15:37.120 --> 00:15:40.540 And this phenomenon is also reversible.

NOTE Confidence: 0.744956012222222

00:15:40.540 --> 00:15:42.120 If we treat those,

NOTE Confidence: 0.744956012222222

00:15:42.120 --> 00:15:44.490 you can see that they shifted

NOTE Confidence: 0.744956012222222

00:15:44.579 --> 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 --> 00:15:51.827 if you remove the drug after a couple

NOTE Confidence: 0.744956012222222

00:15:51.827 --> 00:15:54.095 passages and they will shift it back

NOTE Confidence: 0.744956012222222

00:15:54.095 --> 00:15:56.100 to the parental cell population.

NOTE Confidence: 0.744956012222222

00:15:56.100 --> 00:15:58.158 So one of the things that was

NOTE Confidence: 0.744956012222222

00:15:58.160 --> 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 --> 00:16:05.951 notice that there's an increased
NOTE Confidence: 0.744956012222222

00:16:05.951 --> 00:16:08.920 expression of KDM 5B if we treat
NOTE Confidence: 0.744956012222222

00:16:08.920 --> 00:16:10.980 those cells with BRAF inhibitor.
NOTE Confidence: 0.78673038625

00:16:10.980 --> 00:16:13.512 And this is shown in young
NOTE Confidence: 0.78673038625

00:16:13.512 --> 00:16:15.160 1.7 cells, 3.377 cells.
NOTE Confidence: 0.78673038625

00:16:15.160 --> 00:16:17.975 But also when you compare the parental
NOTE Confidence: 0.78673038625

00:16:17.975 --> 00:16:20.880 with the resistance cells you see the
NOTE Confidence: 0.78673038625

00:16:20.880 --> 00:16:24.940 similar increase of KADIAN fab expression.
NOTE Confidence: 0.78673038625

00:16:24.940 --> 00:16:27.768 And this is reversible if you take
NOTE Confidence: 0.78673038625

00:16:27.768 --> 00:16:30.901 out out and be rough inhibitor and
NOTE Confidence: 0.78673038625

00:16:30.901 --> 00:16:34.215 the expression drops down and it's
NOTE Confidence: 0.78673038625

00:16:34.215 --> 00:16:39.340 showing 1.7 cells as well as 3.3 cells.
NOTE Confidence: 0.78673038625

00:16:39.340 --> 00:16:42.952 So when we did the genetic experiment
NOTE Confidence: 0.78673038625

00:16:42.952 --> 00:16:46.237 when we knocked down kiding 5
NOTE Confidence: 0.78673038625

00:16:46.237 --> 00:16:49.258 expression by a as shown here.

NOTE Confidence: 0.78673038625

00:16:49.258 --> 00:16:54.286 We can see in the one point 11.7 cells,

NOTE Confidence: 0.78673038625

00:16:54.286 --> 00:16:57.442 there's a decrease of CD34 negative

NOTE Confidence: 0.78673038625

00:16:57.442 --> 00:16:59.706 cells after we deplete eighteen 5B.

NOTE Confidence: 0.78673038625

00:16:59.706 --> 00:17:02.142 When we look at the phenotype and

NOTE Confidence: 0.78673038625

00:17:02.142 --> 00:17:04.571 it's consistent to what other people

NOTE Confidence: 0.78673038625

00:17:04.571 --> 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 --> 00:17:13.780 of them to grow in vitro.

NOTE Confidence: 0.739691652727273

00:17:16.590 --> 00:17:21.024 And then those cells are actually

NOTE Confidence: 0.739691652727273

00:17:21.024 --> 00:17:25.320 more sensitive to inhibitor treatment?

NOTE Confidence: 0.739691652727273

00:17:25.320 --> 00:17:28.430 So this is not only.

NOTE Confidence: 0.739691652727273

00:17:28.430 --> 00:17:31.616 Two in most cells but also in human cells,

NOTE Confidence: 0.739691652727273

00:17:31.620 --> 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

NOTE Confidence: 0.739691652727273

00:17:36.786 --> 00:17:39.364 and you can see induction HPK
NOTE Confidence: 0.739691652727273

00:17:39.364 --> 00:17:41.889 4 trimethylation which is the
NOTE Confidence: 0.739691652727273

00:17:41.889 --> 00:17:44.817 substrate of the enzyme and you
NOTE Confidence: 0.739691652727273

00:17:44.817 --> 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 --> 00:17:53.212 they're they're more sensitive
NOTE Confidence: 0.739691652727273

00:17:53.212 --> 00:17:55.164 to BF inhibitor treatment.
NOTE Confidence: 0.801970116666667

00:17:57.480 --> 00:18:00.099 And if you look at this in animal models,
NOTE Confidence: 0.801970116666667

00:18:00.100 --> 00:18:03.426 uh, similar things happens when we treat
NOTE Confidence: 0.801970116666667

00:18:03.426 --> 00:18:06.268 cells with borough inhibitor and you can
NOTE Confidence: 0.801970116666667

00:18:06.268 --> 00:18:08.577 see KADIAN file being level increase
NOTE Confidence: 0.801970116666667

00:18:08.577 --> 00:18:11.500 and if you take away the inhibitor,
NOTE Confidence: 0.801970116666667

00:18:11.500 --> 00:18:14.055 you can see the level drops down.
NOTE Confidence: 0.874118252941176

00:18:17.570 --> 00:18:20.330 So Umm, and then we look at the if you
NOTE Confidence: 0.874118252941176

00:18:20.404 --> 00:18:23.015 look at the population of the cells,
NOTE Confidence: 0.874118252941176

00:18:23.020 --> 00:18:26.048 you can see increased.

NOTE Confidence: 0.874118252941176
00:18:26.050 --> 00:18:30.470 City City for negative cells.
NOTE Confidence: 0.874118252941176
00:18:30.470 --> 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 --> 00:18:37.302 when you take out the inhibit that way
NOTE Confidence: 0.874118252941176
00:18:37.302 --> 00:18:40.238 and then those would not normalize.
NOTE Confidence: 0.874118252941176
00:18:40.240 --> 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 --> 00:18:50.890 Hebetor can suppress the emergence
NOTE Confidence: 0.874118252941176
00:18:50.890 --> 00:18:53.210 of drug resistance cells.
NOTE Confidence: 0.874118252941176
00:18:53.210 --> 00:18:54.610 So to summarize this part,
NOTE Confidence: 0.874118252941176
00:18:54.610 --> 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 --> 00:19:02.177 to BRF inhibitor treatment and BF
NOTE Confidence: 0.874118252941176

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 --> 00:19:13.329 this is reversible and kadian Fabian
NOTE Confidence: 0.874118252941176

00:19:13.419 --> 00:19:16.870 N can reduce this population cells and
NOTE Confidence: 0.874118252941176

00:19:16.870 --> 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 --> 00:19:24.635 to talk about uh immune evasion
NOTE Confidence: 0.874118252941176

00:19:24.635 --> 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 --> 00:19:35.080 Basically this is a diagram showing
NOTE Confidence: 0.874118252941176

00:19:35.166 --> 00:19:38.058 that the cancer cells interact with
NOTE Confidence: 0.874118252941176

00:19:38.058 --> 00:19:41.242 the immune system and and there are
NOTE Confidence: 0.874118252941176

00:19:41.242 --> 00:19:43.840 many ways that cancer cells have
NOTE Confidence: 0.874118252941176

00:19:43.932 --> 00:19:46.572 adopted to evade immune evasion

NOTE Confidence: 0.874118252941176
00:19:46.572 --> 00:19:49.212 to evade the immune response.
NOTE Confidence: 0.874118252941176
00:19:49.220 --> 00:19:50.456 So as a matter of fact,
NOTE Confidence: 0.874118252941176
00:19:50.460 --> 00:19:53.659 because of this mechanism and some drugs
NOTE Confidence: 0.874118252941176
00:19:53.659 --> 00:19:56.860 have been developed including the anti PD1,
NOTE Confidence: 0.874118252941176
00:19:56.860 --> 00:20:01.686 PDL one anti 4 antibodies as well as the
NOTE Confidence: 0.874118252941176
00:20:01.686 --> 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 --> 00:20:08.506 there's not much he's really actually
NOTE Confidence: 0.874118252941176
00:20:08.506 --> 00:20:10.559 known about the trafficking of T
NOTE Confidence: 0.874118252941176
00:20:10.559 --> 00:20:12.449 cells to tumors and the infiltration
NOTE Confidence: 0.874118252941176
00:20:12.449 --> 00:20:14.950 of the T cells into the tumor
NOTE Confidence: 0.874118252941176
00:20:14.950 --> 00:20:17.730 at that time when we started.
NOTE Confidence: 0.874118252941176
00:20:17.730 --> 00:20:19.830 And what's known about epigenetics,
NOTE Confidence: 0.874118252941176
00:20:19.830 --> 00:20:21.654 uh, in this setting,
NOTE Confidence: 0.874118252941176
00:20:21.654 --> 00:20:24.870 many of you are quite familiar with
NOTE Confidence: 0.874118252941176

00:20:24.870 --> 00:20:27.609 this concept about code tumor and
NOTE Confidence: 0.874118252941176

00:20:27.609 --> 00:20:30.665 hot tumor code tumor are not really
NOTE Confidence: 0.874118252941176

00:20:30.665 --> 00:20:32.549 responsive to another treatment,
NOTE Confidence: 0.874118252941176

00:20:32.550 --> 00:20:36.766 but the hot tumor will enable them to
NOTE Confidence: 0.874118252941176

00:20:36.766 --> 00:20:40.520 be responsive to even checkpoint block.
NOTE Confidence: 0.874118252941176

00:20:40.520 --> 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 --> 00:20:48.450 to be critical for this.
NOTE Confidence: 0.757766613

00:20:50.470 --> 00:20:53.578 Code to how the transition and
NOTE Confidence: 0.757766613

00:20:53.578 --> 00:20:57.207 if we treat this the tumors with
NOTE Confidence: 0.757766613

00:20:57.207 --> 00:20:59.802 a couple of inhibitors against
NOTE Confidence: 0.757766613

00:20:59.802 --> 00:21:02.660 those targets like DMT inhibitors.
NOTE Confidence: 0.757766613

00:21:02.660 --> 00:21:05.838 Two inhibitors. You can ship them to
NOTE Confidence: 0.757766613

00:21:05.838 --> 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 --> 00:21:14.500 not in all the settings.

NOTE Confidence: 0.757766613

00:21:14.500 --> 00:21:18.340 And this is kind of related to what

NOTE Confidence: 0.757766613

00:21:18.340 --> 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 --> 00:21:28.790 that and we have looked at the cadian 5B.

NOTE Confidence: 0.757766613

00:21:28.790 --> 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 --> 00:21:43.225 shown to be negatively correlated with

NOTE Confidence: 0.757766613

00:21:43.225 --> 00:21:46.020 many of the immune related genes.

NOTE Confidence: 0.757766613

00:21:46.020 --> 00:21:47.826 And if you look at those top

NOTE Confidence: 0.757766613

00:21:47.826 --> 00:21:48.342 signaling pathway,

NOTE Confidence: 0.757766613

00:21:48.350 --> 00:21:50.264 those are all immune system related

NOTE Confidence: 0.757766613

00:21:50.264 --> 00:21:52.062 genes and those are negative

NOTE Confidence: 0.757766613

00:21:52.062 --> 00:21:53.372 coordinate with expression.

NOTE Confidence: 0.757766613

00:21:53.372 --> 00:21:56.046 If you look at the the identity
NOTE Confidence: 0.757766613

00:21:56.046 --> 00:21:57.330 of those genes,
NOTE Confidence: 0.757766613

00:21:57.330 --> 00:21:58.950 those shown here are the gene
NOTE Confidence: 0.757766613

00:21:58.950 --> 00:22:01.030 names and on the right side of
NOTE Confidence: 0.757766613

00:22:01.030 --> 00:22:03.158 the Spielman score and you can see
NOTE Confidence: 0.757766613

00:22:03.158 --> 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 --> 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 --> 00:22:16.492 coordinate with cadian fair expression.
NOTE Confidence: 0.751778822631579

00:22:16.500 --> 00:22:19.055 And some of the targets for immune
NOTE Confidence: 0.751778822631579

00:22:19.055 --> 00:22:21.062 checkpoint blockade PDL one CPT
NOTE Confidence: 0.751778822631579

00:22:21.062 --> 00:22:22.750 for also negative coordinate
NOTE Confidence: 0.751778822631579

00:22:22.750 --> 00:22:24.438 with KADIAN fabric expression.
NOTE Confidence: 0.751778822631579

00:22:24.440 --> 00:22:26.282 This will be important when we
NOTE Confidence: 0.751778822631579

00:22:26.282 --> 00:22:28.388 are trying to look at the e-mail

NOTE Confidence: 0.751778822631579
00:22:28.390 --> 00:22:32.230 checkpoint blockade resistant tumors.
NOTE Confidence: 0.751778822631579
00:22:32.230 --> 00:22:35.236 So when we looked at the KDM 5 be
NOTE Confidence: 0.751778822631579
00:22:35.236 --> 00:22:37.320 expression protein expression in
NOTE Confidence: 0.751778822631579
00:22:37.320 --> 00:22:40.650 melanomas and if you compare nonresponse
NOTE Confidence: 0.751778822631579
00:22:40.650 --> 00:22:42.809 boundaries with and responders,
NOTE Confidence: 0.751778822631579
00:22:42.810 --> 00:22:45.324 we can see increased expression location
NOTE Confidence: 0.751778822631579
00:22:45.324 --> 00:22:48.848 5B which is shown in red in those non
NOTE Confidence: 0.751778822631579
00:22:48.848 --> 00:22:51.078 responders compared to the responders
NOTE Confidence: 0.751778822631579
00:22:51.078 --> 00:22:54.590 and and the quantification is shown here.
NOTE Confidence: 0.751778822631579
00:22:54.590 --> 00:22:57.281 So this motivates us to look at the role
NOTE Confidence: 0.751778822631579
00:22:57.281 --> 00:23:00.228 of Canadian file be using animal models.
NOTE Confidence: 0.751778822631579
00:23:00.230 --> 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 --> 00:23:06.553 had generated a series of
NOTE Confidence: 0.751778822631579
00:23:06.553 --> 00:23:08.560 why UM or young models.
NOTE Confidence: 0.751778822631579

00:23:08.560 --> 00:23:11.232 Uh, one of the models that we started
NOTE Confidence: 0.751778822631579

00:23:11.232 --> 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 --> 00:23:18.980 for exposed to radiation,
NOTE Confidence: 0.751778822631579

00:23:18.980 --> 00:23:22.155 meaning those cells will radiate
NOTE Confidence: 0.751778822631579

00:23:22.155 --> 00:23:25.287 so that they have more mutations,
NOTE Confidence: 0.751778822631579

00:23:25.287 --> 00:23:27.741 they can generate more antigens that
NOTE Confidence: 0.751778822631579

00:23:27.741 --> 00:23:30.567 can be recognized by the immune system.
NOTE Confidence: 0.751778822631579

00:23:30.570 --> 00:23:33.138 So when we knocked out Kadian 5B in
NOTE Confidence: 0.751778822631579

00:23:33.138 --> 00:23:35.290 those cells, as you can see here,
NOTE Confidence: 0.751778822631579

00:23:35.290 --> 00:23:37.840 those cells can initially can grow,
NOTE Confidence: 0.751778822631579

00:23:37.840 --> 00:23:41.040 then they got fully rejected after a while.
NOTE Confidence: 0.751778822631579

00:23:41.040 --> 00:23:45.450 And the more importantly when we challenge
NOTE Confidence: 0.751778822631579

00:23:45.450 --> 00:23:48.190 those animals with the cells control
NOTE Confidence: 0.751778822631579

00:23:48.190 --> 00:23:51.080 cells which normally can grow very well,
NOTE Confidence: 0.751778822631579

00:23:51.080 --> 00:23:52.632 they never grow up.

NOTE Confidence: 0.751778822631579
00:23:52.632 --> 00:23:55.686 So this is very important imagine that if
NOTE Confidence: 0.751778822631579
00:23:55.686 --> 00:23:58.725 we have to treat patient with a drug and
NOTE Confidence: 0.751778822631579
00:23:58.725 --> 00:24:01.773 case for example in this case KADIAN 5
NOTE Confidence: 0.751778822631579
00:24:01.773 --> 00:24:06.258 targeting drug and those patient will not,
NOTE Confidence: 0.751778822631579
00:24:06.260 --> 00:24:08.425 will not have recurrence because
NOTE Confidence: 0.751778822631579
00:24:08.425 --> 00:24:11.559 they they will should never grow up
NOTE Confidence: 0.751778822631579
00:24:11.559 --> 00:24:13.779 because the immune memory response.
NOTE Confidence: 0.751778822631579
00:24:13.780 --> 00:24:15.365 So this is actually translated
NOTE Confidence: 0.751778822631579
00:24:15.365 --> 00:24:16.615 to 100% survival,
NOTE Confidence: 0.751778822631579
00:24:16.615 --> 00:24:20.305 which is uh, this is great.
NOTE Confidence: 0.751778822631579
00:24:20.310 --> 00:24:22.893 And then we look at the UM uh T
NOTE Confidence: 0.751778822631579
00:24:22.893 --> 00:24:25.239 cell infiltration when we compare
NOTE Confidence: 0.751778822631579
00:24:25.239 --> 00:24:28.691 the control cells and KADIAN file B
NOTE Confidence: 0.751778822631579
00:24:28.691 --> 00:24:31.550 knockout tumors at the very early stage,
NOTE Confidence: 0.751778822631579
00:24:31.550 --> 00:24:34.196 you can see the T cell infiltration
NOTE Confidence: 0.751778822631579

00:24:34.196 --> 00:24:35.330 either by e-mail,
NOTE Confidence: 0.751778822631579

00:24:35.330 --> 00:24:38.828 histochemistry as well as fax analysis.
NOTE Confidence: 0.751778822631579

00:24:38.830 --> 00:24:41.392 And there's another way to say that
NOTE Confidence: 0.751778822631579

00:24:41.392 --> 00:24:44.355 this is immune system dependent on we
NOTE Confidence: 0.751778822631579

00:24:44.355 --> 00:24:47.308 compared the ability of cells to grow
NOTE Confidence: 0.751778822631579

00:24:47.308 --> 00:24:50.360 in wild type cell wild type mice or rats.
NOTE Confidence: 0.751778822631579

00:24:50.360 --> 00:24:54.008 Deficient mice and as you can see here
NOTE Confidence: 0.751778822631579

00:24:54.008 --> 00:24:57.808 the the the the B6 is the wild type.
NOTE Confidence: 0.751778822631579

00:24:57.810 --> 00:25:00.029 Those two curves are what I have
NOTE Confidence: 0.751778822631579

00:25:00.029 --> 00:25:02.417 showed you before and if you look at
NOTE Confidence: 0.751778822631579

00:25:02.417 --> 00:25:04.918 the the ability of cells you grow in
NOTE Confidence: 0.751778822631579

00:25:04.918 --> 00:25:06.698 rectification mice the control goes
NOTE Confidence: 0.751778822631579

00:25:06.698 --> 00:25:10.662 here and then can be deficient once grow
NOTE Confidence: 0.751778822631579

00:25:10.662 --> 00:25:14.430 kind of similarly although slightly slower.
NOTE Confidence: 0.751778822631579

00:25:14.430 --> 00:25:17.280 So this basically set up the
NOTE Confidence: 0.751778822631579

00:25:17.280 --> 00:25:20.477 stage that Kadian 5B which is

NOTE Confidence: 0.751778822631579
00:25:20.477 --> 00:25:22.869 critical for immune evasion.
NOTE Confidence: 0.751778822631579
00:25:22.870 --> 00:25:26.110 So the next question is what's the mechanism,
NOTE Confidence: 0.751778822631579
00:25:26.110 --> 00:25:26.742 right?
NOTE Confidence: 0.751778822631579
00:25:26.742 --> 00:25:28.638 So how to?
NOTE Confidence: 0.751778822631579
00:25:28.640 --> 00:25:29.933 To understand this,
NOTE Confidence: 0.751778822631579
00:25:29.933 --> 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 --> 00:25:37.930 probably knockout versus wild type.
NOTE Confidence: 0.751778822631579
00:25:37.930 --> 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 --> 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 --> 00:25:53.972 can see there's an enrichment
NOTE Confidence: 0.769697436730769
00:25:53.972 --> 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 --> 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 --> 00:26:05.430 So now how does this actually work?
NOTE Confidence: 0.769697436730769

00:26:05.430 --> 00:26:07.430 And are those sensing pathway
NOTE Confidence: 0.769697436730769

00:26:07.430 --> 00:26:09.990 critical for the function of KDM 5B?
NOTE Confidence: 0.769697436730769

00:26:09.990 --> 00:26:12.366 As as many of you know that the
NOTE Confidence: 0.769697436730769

00:26:12.366 --> 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 --> 00:26:21.150 sensed through cgas sting pathway
NOTE Confidence: 0.769697436730769

00:26:21.150 --> 00:26:25.030 to big TV K1F3F7 and the interferon
NOTE Confidence: 0.769697436730769

00:26:25.030 --> 00:26:27.622 response and this need to induction
NOTE Confidence: 0.769697436730769

00:26:27.622 --> 00:26:29.587 interferon stimulated genes.
NOTE Confidence: 0.769697436730769

00:26:29.590 --> 00:26:31.977 And the double stranded on a could
NOTE Confidence: 0.769697436730769

00:26:31.977 --> 00:26:34.169 be sensed through regard MDA 5

NOTE Confidence: 0.769697436730769
00:26:34.169 --> 00:26:36.004 maps Altos three and basically
NOTE Confidence: 0.769697436730769
00:26:36.004 --> 00:26:38.269 also signals through and activate
NOTE Confidence: 0.769697436730769
00:26:38.269 --> 00:26:40.217 interference and steam engines.
NOTE Confidence: 0.769697436730769
00:26:40.220 --> 00:26:42.964 So what we did is we knock cloud
NOTE Confidence: 0.769697436730769
00:26:42.964 --> 00:26:44.732 each single component through
NOTE Confidence: 0.769697436730769
00:26:44.732 --> 00:26:47.720 this pathway and see what happens
NOTE Confidence: 0.769697436730769
00:26:47.720 --> 00:26:49.456 when we knock out the Canadian 5B.
NOTE Confidence: 0.769697436730769
00:26:49.460 --> 00:26:52.322 As you see it does not grow in the
NOTE Confidence: 0.769697436730769
00:26:52.322 --> 00:26:55.395 wild type cells do grow if we combine
NOTE Confidence: 0.769697436730769
00:26:55.395 --> 00:26:57.830 that with knockout of the mouse or
NOTE Confidence: 0.769697436730769
00:26:57.830 --> 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 --> 00:27:06.154 you can see partial rescue right here.
NOTE Confidence: 0.769697436730769
00:27:06.160 --> 00:27:08.552 If you get rid of both of them
NOTE Confidence: 0.769697436730769

00:27:08.552 --> 00:27:10.730 you see much better rescue.
NOTE Confidence: 0.769697436730769

00:27:10.730 --> 00:27:14.410 So we went on and when the upstream
NOTE Confidence: 0.769697436730769

00:27:14.410 --> 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 --> 00:27:31.308 in this case when in two independent.
NOTE Confidence: 0.769697436730769

00:27:31.310 --> 00:27:33.650 So how many established that?
NOTE Confidence: 0.769697436730769

00:27:33.650 --> 00:27:36.494 Now we want to understand why
NOTE Confidence: 0.769697436730769

00:27:36.494 --> 00:27:38.390 those pathways are activated.
NOTE Confidence: 0.769697436730769

00:27:38.390 --> 00:27:40.606 So why would the sense that we notice
NOTE Confidence: 0.769697436730769

00:27:40.610 --> 00:27:43.872 is that when we compare the control
NOTE Confidence: 0.769697436730769

00:27:43.872 --> 00:27:46.308 cells with the knockout cells,
NOTE Confidence: 0.769697436730769

00:27:46.308 --> 00:27:49.941 we can see the induction of double
NOTE Confidence: 0.769697436730769

00:27:49.941 --> 00:27:53.086 stranded on a in Kadian 5B knockout
NOTE Confidence: 0.769697436730769

00:27:53.086 --> 00:27:55.412 cells and then we have seen this

NOTE Confidence: 0.769697436730769
00:27:55.412 --> 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 --> 00:28:03.660 to realize our only sequencing data.
NOTE Confidence: 0.769697436730769
00:28:03.660 --> 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 --> 00:28:13.303 genome and then people are totally
NOTE Confidence: 0.769697436730769
00:28:13.303 --> 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 --> 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 --> 00:28:24.034 we can see induction of those
NOTE Confidence: 0.769697436730769
00:28:24.034 --> 00:28:26.030 retro elements and especially
NOTE Confidence: 0.769697436730769
00:28:26.121 --> 00:28:28.996 some of the endogenous retrovirus.
NOTE Confidence: 0.769697436730769
00:28:29.000 --> 00:28:29.420 Animals.
NOTE Confidence: 0.769697436730769
00:28:29.420 --> 00:28:33.702 And the one with which is called MOV 30 and
NOTE Confidence: 0.769697436730769

00:28:33.702 --> 00:28:37.068 you can see multiple of those showing up.

NOTE Confidence: 0.769697436730769

00:28:37.068 --> 00:28:39.732 And then we study is actually

NOTE Confidence: 0.769697436730769

00:28:39.732 --> 00:28:42.190 critical for the interferon response

NOTE Confidence: 0.769697436730769

00:28:42.190 --> 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 --> 00:28:50.938 you can see the down recognition or

NOTE Confidence: 0.769697436730769

00:28:50.938 --> 00:28:53.176 interference imagines suggesting that

NOTE Confidence: 0.769697436730769

00:28:53.176 --> 00:28:56.110 this is at least partially contribute

NOTE Confidence: 0.769697436730769

00:28:56.110 --> 00:28:59.218 to the interferon induction and maybe

NOTE Confidence: 0.769697436730769

00:28:59.218 --> 00:29:01.813 the response to e-mail evasion.

NOTE Confidence: 0.769697436730769

00:29:01.820 --> 00:29:03.899 And the one thing that we were

NOTE Confidence: 0.769697436730769

00:29:03.899 --> 00:29:05.734 puzzled about is that since I

NOTE Confidence: 0.769697436730769

00:29:05.734 --> 00:29:07.771 showed you that both DNA and only

NOTE Confidence: 0.769697436730769

00:29:07.839 --> 00:29:09.739 sensing password are required,

NOTE Confidence: 0.769697436730769

00:29:09.740 --> 00:29:12.260 where are those DNA coming from?

NOTE Confidence: 0.769697436730769

00:29:12.260 --> 00:29:14.220 And we postulated that those

NOTE Confidence: 0.769697436730769
00:29:14.220 --> 00:29:16.180 DNA will be coming from
NOTE Confidence: 0.762787830714286
00:29:16.257 --> 00:29:19.373 reverse transcription of those only
NOTE Confidence: 0.762787830714286
00:29:19.373 --> 00:29:22.844 species that that would generate
NOTE Confidence: 0.762787830714286
00:29:22.844 --> 00:29:27.400 through after we get rid of Kadian 5B.
NOTE Confidence: 0.762787830714286
00:29:27.400 --> 00:29:30.536 And one experiment we did is use
NOTE Confidence: 0.762787830714286
00:29:30.536 --> 00:29:31.880 reverse transcriptase inhibitor.
NOTE Confidence: 0.762787830714286
00:29:31.880 --> 00:29:34.778 This is a cocktail of reverse transcriptase
NOTE Confidence: 0.762787830714286
00:29:34.778 --> 00:29:37.010 inhibitors used for HIV treatment and
NOTE Confidence: 0.762787830714286
00:29:37.010 --> 00:29:40.312 where we see if you treat the cells with
NOTE Confidence: 0.762787830714286
00:29:40.312 --> 00:29:42.456 those reverse transcriptase inhibitor.
NOTE Confidence: 0.762787830714286
00:29:42.460 --> 00:29:46.289 You can see suppression of the interference
NOTE Confidence: 0.762787830714286
00:29:46.289 --> 00:29:48.876 imaging expression suggesting that this
NOTE Confidence: 0.762787830714286
00:29:48.876 --> 00:29:51.907 DNA might be created through this pathway.
NOTE Confidence: 0.762787830714286
00:29:51.910 --> 00:29:54.268 So now with all those mechanisms,
NOTE Confidence: 0.762787830714286
00:29:54.270 --> 00:29:56.532 now the question is can we
NOTE Confidence: 0.762787830714286

00:29:56.532 --> 00:29:58.480 translate it to targeting this?
NOTE Confidence: 0.762787830714286

00:29:58.480 --> 00:30:00.712 The quick question is that can
NOTE Confidence: 0.762787830714286

00:30:00.712 --> 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 --> 00:30:13.280 of evidence showing that KDM five are
NOTE Confidence: 0.762787830714286

00:30:13.280 --> 00:30:16.585 critical for cancer initiation progression.
NOTE Confidence: 0.762787830714286

00:30:16.590 --> 00:30:19.362 So we have started working on
NOTE Confidence: 0.762787830714286

00:30:19.362 --> 00:30:23.375 this on to by multiple methods to
NOTE Confidence: 0.762787830714286

00:30:23.375 --> 00:30:25.843 develop locating file inhibitors.
NOTE Confidence: 0.762787830714286

00:30:25.850 --> 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 --> 00:30:34.617 now called Yale Center for Monica.
NOTE Confidence: 0.762787830714286

00:30:34.620 --> 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 --> 00:30:39.630 biochemical screening for KADIAN

NOTE Confidence: 0.762787830714286
00:30:39.630 --> 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 --> 00:30:46.136 with those as a preliminary data we
NOTE Confidence: 0.762787830714286
00:30:46.136 --> 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 --> 00:30:54.579 were able to assemble a team about 30
NOTE Confidence: 0.762787830714286
00:30:54.579 --> 00:30:57.897 scientists to to develop those inhibitors.
NOTE Confidence: 0.762787830714286
00:30:57.900 --> 00:31:01.060 So we have done a high school screening
NOTE Confidence: 0.762787830714286
00:31:01.060 --> 00:31:03.405 about 200,000 compounds those are high
NOTE Confidence: 0.762787830714286
00:31:03.405 --> 00:31:05.872 quality compounds and have done extensive
NOTE Confidence: 0.762787830714286
00:31:05.872 --> 00:31:08.137 medicinal chemistry optimization of some
NOTE Confidence: 0.762787830714286
00:31:08.137 --> 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 --> 00:31:16.490 can you find a way with different inhibitors
NOTE Confidence: 0.762787830714286
00:31:16.490 --> 00:31:18.890 and shown here just the two of them,
NOTE Confidence: 0.762787830714286

00:31:18.890 --> 00:31:21.725 basically showing that they combined
NOTE Confidence: 0.762787830714286

00:31:21.725 --> 00:31:25.100 very tightly to the active site.
NOTE Confidence: 0.762787830714286

00:31:25.100 --> 00:31:27.485 One thing that I want to mention that those
NOTE Confidence: 0.762787830714286

00:31:27.485 --> 00:31:29.477 inhibitors are all pancaking from inhibitors.
NOTE Confidence: 0.762787830714286

00:31:29.480 --> 00:31:32.330 They hit both all Canadian five
NOTE Confidence: 0.762787830714286

00:31:32.330 --> 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 --> 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 --> 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 --> 00:31:55.670 And the one thing that we decided to do is
NOTE Confidence: 0.762787830714286

00:31:55.766 --> 00:31:59.598 we selected four KDM 5 and inhibitor here.
NOTE Confidence: 0.762787830714286

00:31:59.600 --> 00:32:01.750 Those are high quality specific
NOTE Confidence: 0.762787830714286

00:32:01.750 --> 00:32:03.040 calling from inhibitor.
NOTE Confidence: 0.762787830714286

00:32:03.040 --> 00:32:05.152 As you can see here they all induce

NOTE Confidence: 0.762787830714286
00:32:05.152 --> 00:32:07.233 HK for translation which is the
NOTE Confidence: 0.762787830714286
00:32:07.233 --> 00:32:09.459 substrate of the reaction and then
NOTE Confidence: 0.762787830714286
00:32:09.529 --> 00:32:11.601 did not do anything to the other
NOTE Confidence: 0.762787830714286
00:32:11.601 --> 00:32:14.430 of the histone modifications.
NOTE Confidence: 0.762787830714286
00:32:14.430 --> 00:32:17.294 And we did those actually in I'm 6-7
NOTE Confidence: 0.762787830714286
00:32:17.294 --> 00:32:19.579 and multiple human breast cancer cells
NOTE Confidence: 0.762787830714286
00:32:19.579 --> 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 --> 00:32:27.852 see the top pathway that's upregulate
NOTE Confidence: 0.762787830714286
00:32:27.852 --> 00:32:29.864 are those interference signaling
NOTE Confidence: 0.762787830714286
00:32:29.864 --> 00:32:32.122 pathway at that time I was like
NOTE Confidence: 0.762787830714286
00:32:32.122 --> 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 --> 00:32:41.220 so when we see there's an induction
NOTE Confidence: 0.762787830714286

00:32:41.296 --> 00:32:43.301 interfering pathway and we have
NOTE Confidence: 0.762787830714286

00:32:43.301 --> 00:32:45.790 seen this in multiple cell lines,
NOTE Confidence: 0.762787830714286

00:32:45.790 --> 00:32:47.110 multiple drugs.
NOTE Confidence: 0.762787830714286

00:32:47.110 --> 00:32:50.410 And we were able to.
NOTE Confidence: 0.762787830714286

00:32:50.410 --> 00:32:52.410 Understand how this actually worked.
NOTE Confidence: 0.762787830714286

00:32:52.410 --> 00:32:55.162 And at the end we were able to
NOTE Confidence: 0.762787830714286

00:32:55.162 --> 00:32:57.840 show that KADIAN 5 inhibitor can
NOTE Confidence: 0.762787830714286

00:32:57.840 --> 00:32:59.920 induce H3K4 termination at the
NOTE Confidence: 0.762787830714286

00:32:59.920 --> 00:33:02.000 stem promoter and by doing
NOTE Confidence: 0.693358643272727

00:33:02.075 --> 00:33:06.360 so, it actually induce Stein expression.
NOTE Confidence: 0.693358643272727

00:33:06.360 --> 00:33:08.916 And this need to the interferon
NOTE Confidence: 0.693358643272727

00:33:08.920 --> 00:33:10.520 stimulated gene expression and
NOTE Confidence: 0.693358643272727

00:33:10.520 --> 00:33:12.920 listening to the T cell infiltration.
NOTE Confidence: 0.876932511333333

00:33:15.070 --> 00:33:18.390 So this is a little bit different from
NOTE Confidence: 0.876932511333333

00:33:18.390 --> 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

NOTE Confidence: 0.876932511333333
00:33:23.700 --> 00:33:25.800 through either using Steam agonist,
NOTE Confidence: 0.876932511333333
00:33:25.800 --> 00:33:31.209 which the limitation of those drugs and is.
NOTE Confidence: 0.876932511333333
00:33:31.210 --> 00:33:33.208 Many of the cancer cells you
NOTE Confidence: 0.876932511333333
00:33:33.208 --> 00:33:34.540 actually have Stein silence.
NOTE Confidence: 0.876932511333333
00:33:34.540 --> 00:33:37.144 So by inducing Stein and this
NOTE Confidence: 0.876932511333333
00:33:37.144 --> 00:33:39.436 provide another mechanism how we
NOTE Confidence: 0.876932511333333
00:33:39.436 --> 00:33:41.826 can activate this signaling pathway.
NOTE Confidence: 0.876932511333333
00:33:41.830 --> 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 --> 00:33:51.069 cells and we can see induction of
NOTE Confidence: 0.876932511333333
00:33:51.156 --> 00:33:54.061 sting and in this case in Western
NOTE Confidence: 0.876932511333333
00:33:54.061 --> 00:33:56.466 border here and the induction
NOTE Confidence: 0.876932511333333
00:33:56.466 --> 00:33:58.778 of interference steam engines.
NOTE Confidence: 0.876932511333333
00:33:58.780 --> 00:34:00.724 And so we thought this is the shoe
NOTE Confidence: 0.876932511333333
00:34:00.724 --> 00:34:02.576 bat and the Canadian five inhibitor
NOTE Confidence: 0.876932511333333

00:34:02.576 --> 00:34:03.880 is going to work.
NOTE Confidence: 0.876932511333333

00:34:03.880 --> 00:34:07.360 And to our surprise, nothing happened.
NOTE Confidence: 0.876932511333333

00:34:07.360 --> 00:34:09.089 And when we took put this in
NOTE Confidence: 0.876932511333333

00:34:09.089 --> 00:34:10.200 the mouseman normal cells,
NOTE Confidence: 0.876932511333333

00:34:10.200 --> 00:34:11.584 the Yammer 1.7 cells,
NOTE Confidence: 0.876932511333333

00:34:11.584 --> 00:34:14.210 the model system that we have tested.
NOTE Confidence: 0.876932511333333

00:34:14.210 --> 00:34:18.690 2 into 2 Canadian farm inhibitor and
NOTE Confidence: 0.876932511333333

00:34:18.690 --> 00:34:22.806 the retro element was were not induced,
NOTE Confidence: 0.876932511333333

00:34:22.810 --> 00:34:25.888 the interference images were not induced,
NOTE Confidence: 0.876932511333333

00:34:25.890 --> 00:34:26.654 nothing happened.
NOTE Confidence: 0.876932511333333

00:34:26.654 --> 00:34:29.710 So we did not want to give up
NOTE Confidence: 0.876932511333333

00:34:29.710 --> 00:34:31.840 because we thought maybe there's
NOTE Confidence: 0.876932511333333

00:34:31.840 --> 00:34:34.782 some limitation of the drugs and so
NOTE Confidence: 0.876932511333333

00:34:34.782 --> 00:34:37.006 we did those rescue experiment to
NOTE Confidence: 0.876932511333333

00:34:37.006 --> 00:34:38.886 understand whether the critical the
NOTE Confidence: 0.876932511333333

00:34:38.886 --> 00:34:40.830 community activity is required or not.

NOTE Confidence: 0.876932511333333
00:34:40.830 --> 00:34:44.064 So what we did is that for.
NOTE Confidence: 0.876932511333333
00:34:44.070 --> 00:34:45.420 I'll call it Yama cells.
NOTE Confidence: 0.876932511333333
00:34:45.420 --> 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 --> 00:34:54.820 Those mutant are dead Canadian 5B.
NOTE Confidence: 0.876932511333333
00:34:54.820 --> 00:34:56.848 And as you can see here,
NOTE Confidence: 0.876932511333333
00:34:56.850 --> 00:34:59.338 in both cases you can see wild type
NOTE Confidence: 0.876932511333333
00:34:59.338 --> 00:35:01.778 or mutant Canadian 5B can suppress
NOTE Confidence: 0.876932511333333
00:35:01.778 --> 00:35:04.450 the expression of retro elements and
NOTE Confidence: 0.876932511333333
00:35:04.450 --> 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 --> 00:35:09.828 both of those can induce the
NOTE Confidence: 0.876932511333333
00:35:09.828 --> 00:35:12.050 growth of those tumors.
NOTE Confidence: 0.876932511333333
00:35:12.050 --> 00:35:13.136 So now what?
NOTE Confidence: 0.876932511333333
00:35:13.136 --> 00:35:16.096 Now we are back to the starting point
NOTE Confidence: 0.876932511333333

00:35:16.096 --> 00:35:18.847 and kind of depressed right at time.

NOTE Confidence: 0.876932511333333

00:35:18.850 --> 00:35:21.722 So we went on and decided to look

NOTE Confidence: 0.876932511333333

00:35:21.722 --> 00:35:24.160 at all the repressive mechanisms

NOTE Confidence: 0.876932511333333

00:35:24.160 --> 00:35:26.750 and to see which one might work.

NOTE Confidence: 0.876932511333333

00:35:26.750 --> 00:35:27.962 And one of the things that

NOTE Confidence: 0.876932511333333

00:35:27.962 --> 00:35:29.090 we decided to look at is,

NOTE Confidence: 0.876932511333333

00:35:29.090 --> 00:35:30.254 is actually inhibitor for

NOTE Confidence: 0.876932511333333

00:35:30.254 --> 00:35:32.000 example and those are two higher

NOTE Confidence: 0.876932511333333

00:35:32.053 --> 00:35:33.609 quantities that true inhibitor,

NOTE Confidence: 0.876932511333333

00:35:33.610 --> 00:35:35.680 it did not do much either.

NOTE Confidence: 0.876932511333333

00:35:35.680 --> 00:35:38.504 Umm, and then uh,

NOTE Confidence: 0.876932511333333

00:35:38.504 --> 00:35:39.210 it.

NOTE Confidence: 0.876932511333333

00:35:39.210 --> 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 --> 00:35:44.612 and we use a pretty dirty

NOTE Confidence: 0.876932511333333

00:35:44.612 --> 00:35:45.920 actually actually canine method.

NOTE Confidence: 0.876932511333333
00:35:45.920 --> 00:35:48.350 Transfers inhibit the code channel thing
NOTE Confidence: 0.876932511333333
00:35:48.350 --> 00:35:51.688 and it can inhibit actually K9 translation.
NOTE Confidence: 0.876932511333333
00:35:51.690 --> 00:35:55.020 You can see induction of MOV 30 and some
NOTE Confidence: 0.876932511333333
00:35:55.020 --> 00:35:58.228 of the interferon stimulated genes.
NOTE Confidence: 0.876932511333333
00:35:58.230 --> 00:36:00.919 So now there are multiple HK9
NOTE Confidence: 0.876932511333333
00:36:00.919 --> 00:36:03.013 methyltransferase and so we knocked out
NOTE Confidence: 0.876932511333333
00:36:03.013 --> 00:36:05.597 each single one of them to see which one.
NOTE Confidence: 0.876932511333333
00:36:05.600 --> 00:36:10.235 Is critical when we knock out the G9A or
NOTE Confidence: 0.876932511333333
00:36:10.240 --> 00:36:12.336 SO39H1 and it did not really do anything.
NOTE Confidence: 0.876932511333333
00:36:12.340 --> 00:36:14.220 But when we knockout set
NOTE Confidence: 0.876932511333333
00:36:14.220 --> 00:36:16.100 B1 which is shown here,
NOTE Confidence: 0.876932511333333
00:36:16.100 --> 00:36:19.956 you can see robust induction on mobile 30.
NOTE Confidence: 0.876932511333333
00:36:19.960 --> 00:36:22.480 So this is what was a great news.
NOTE Confidence: 0.876932511333333
00:36:22.480 --> 00:36:25.056 So at that time we're quite excited.
NOTE Confidence: 0.876932511333333
00:36:25.060 --> 00:36:28.196 And then when we did call e-mail
NOTE Confidence: 0.876932511333333

00:36:28.196 --> 00:36:29.092 precipitation experiment,
NOTE Confidence: 0.876932511333333

00:36:29.100 --> 00:36:31.422 we actually can see that KADIAN
NOTE Confidence: 0.876932511333333

00:36:31.422 --> 00:36:34.039 file B can interact with set DB1.
NOTE Confidence: 0.876932511333333

00:36:34.040 --> 00:36:35.900 When we did set DB1 IP,
NOTE Confidence: 0.876932511333333

00:36:35.900 --> 00:36:42.490 that's the pull down of Kadian 5B by Sade 1.
NOTE Confidence: 0.779074838571429

00:36:42.490 --> 00:36:45.626 And then uh, this is quite exciting.
NOTE Confidence: 0.779074838571429

00:36:45.630 --> 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 --> 00:36:57.675 the the the heat map where we ranked
NOTE Confidence: 0.779074838571429

00:36:57.675 --> 00:37:00.090 those KADIAN file B target genes where
NOTE Confidence: 0.779074838571429

00:37:00.090 --> 00:37:02.447 you can see KADIAN file B combined
NOTE Confidence: 0.779074838571429

00:37:02.447 --> 00:37:04.829 them very well in wild type cells,
NOTE Confidence: 0.779074838571429

00:37:04.830 --> 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 --> 00:37:12.460 you can see amazingly overlapping
NOTE Confidence: 0.779074838571429

00:37:12.460 --> 00:37:16.963 binding of the set DB1 and the HTK 9

NOTE Confidence: 0.779074838571429
00:37:16.963 --> 00:37:20.160 formation which is the product of set
NOTE Confidence: 0.722333791
00:37:22.320 --> 00:37:25.194 DB1H3K9 formation is a repressible mark
NOTE Confidence: 0.722333791
00:37:25.194 --> 00:37:28.040 that can suppress gene expression.
NOTE Confidence: 0.722333791
00:37:28.040 --> 00:37:30.848 And to our surprise, when we look at
NOTE Confidence: 0.722333791
00:37:30.848 --> 00:37:33.148 the HK4 translation and imagination,
NOTE Confidence: 0.722333791
00:37:33.148 --> 00:37:36.919 which are the substrate of the Kadian 5B,
NOTE Confidence: 0.722333791
00:37:36.920 --> 00:37:39.728 you can actually do not see much effect.
NOTE Confidence: 0.722333791
00:37:39.730 --> 00:37:42.610 Suppress a suggestion that KDM 5B
NOTE Confidence: 0.722333791
00:37:42.610 --> 00:37:45.086 function add message function is
NOTE Confidence: 0.722333791
00:37:45.086 --> 00:37:47.436 probably silenced in this setting.
NOTE Confidence: 0.722333791
00:37:47.440 --> 00:37:50.820 So now those are all.
NOTE Confidence: 0.806272241
00:37:53.360 --> 00:37:58.320 Important and now we want to look at this in.
NOTE Confidence: 0.806272241
00:37:58.320 --> 00:38:00.060 Drug resistance setting and
NOTE Confidence: 0.806272241
00:38:00.060 --> 00:38:02.235 in this case e-mail checkpoint
NOTE Confidence: 0.806272241
00:38:02.235 --> 00:38:03.980 blockade resistance setting.
NOTE Confidence: 0.806272241

00:38:03.980 --> 00:38:06.338 When you look at the KTM 5 be expression,
NOTE Confidence: 0.806272241

00:38:06.340 --> 00:38:08.914 it's actually lower in the patient
NOTE Confidence: 0.806272241

00:38:08.914 --> 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 --> 00:38:15.580 with the progressive disease.
NOTE Confidence: 0.806272241

00:38:15.580 --> 00:38:17.620 So this is suggesting that if
NOTE Confidence: 0.806272241

00:38:17.620 --> 00:38:20.155 we can lower expression you can
NOTE Confidence: 0.806272241

00:38:20.155 --> 00:38:22.724 make the reason tumor sensitive.
NOTE Confidence: 0.806272241

00:38:22.724 --> 00:38:25.444 Indeed that's actually true and
NOTE Confidence: 0.806272241

00:38:25.444 --> 00:38:28.498 we use this young 1.7 model.
NOTE Confidence: 0.806272241

00:38:28.498 --> 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 --> 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 --> 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 --> 00:38:47.399 on then nothing happens.

NOTE Confidence: 0.806272241

00:38:47.400 --> 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 --> 00:38:54.838 you can see if you get relocating 5

NOTE Confidence: 0.806272241

00:38:54.838 --> 00:38:56.889 you can already see some response.

NOTE Confidence: 0.806272241

00:38:56.890 --> 00:38:59.710 If you combine with PD1 blockade

NOTE Confidence: 0.806272241

00:38:59.710 --> 00:39:01.590 you see synergistic response.

NOTE Confidence: 0.806272241

00:39:01.590 --> 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 --> 00:39:09.182 survival of those animals.

NOTE Confidence: 0.806272241

00:39:09.190 --> 00:39:11.214 And this is just one of the PD1

NOTE Confidence: 0.806272241

00:39:11.214 --> 00:39:13.022 resistant model and when we look at

NOTE Confidence: 0.806272241

00:39:13.022 --> 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 --> 00:39:26.236 So lastly, is this also true in humans?
NOTE Confidence: 0.806272241

00:39:26.240 --> 00:39:29.138 When we compare the the KADIAN 5
NOTE Confidence: 0.806272241

00:39:29.138 --> 00:39:31.130 expression with the indulgence
NOTE Confidence: 0.806272241

00:39:31.130 --> 00:39:33.888 retro elements part of the category
NOTE Confidence: 0.806272241

00:39:33.888 --> 00:39:35.316 of the retro elements,
NOTE Confidence: 0.806272241

00:39:35.320 --> 00:39:37.480 you can see the the ones with high
NOTE Confidence: 0.806272241

00:39:37.480 --> 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 --> 00:39:41.950 of some of the.
NOTE Confidence: 0.712199291428571

00:39:44.420 --> 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 --> 00:39:53.193 with Kaden 5 expression and the
NOTE Confidence: 0.712199291428571

00:39:53.193 --> 00:39:55.259 expression is correlated with the
NOTE Confidence: 0.712199291428571

00:39:55.259 --> 00:39:57.737 better response to PD1 blockade is
NOTE Confidence: 0.712199291428571

00:39:57.737 --> 00:40:00.256 opposite to what we see with PKD and 5B.
NOTE Confidence: 0.712199291428571

00:40:00.260 --> 00:40:03.522 So to basically to summarize this part

NOTE Confidence: 0.712199291428571
00:40:03.522 --> 00:40:06.791 of my talk which I showed you that Kadian
NOTE Confidence: 0.712199291428571
00:40:06.791 --> 00:40:09.791 5B can interact with set DB1 and and
NOTE Confidence: 0.712199291428571
00:40:09.791 --> 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 --> 00:40:17.194 to silence retroelements,
NOTE Confidence: 0.712199291428571
00:40:17.200 --> 00:40:19.419 if you gather with locating 5B you
NOTE Confidence: 0.712199291428571
00:40:19.419 --> 00:40:21.200 can activate endogenous retroelements.
NOTE Confidence: 0.712199291428571
00:40:21.200 --> 00:40:23.020 You can activate double stranded
NOTE Confidence: 0.712199291428571
00:40:23.020 --> 00:40:24.840 on Ascension pathway and double
NOTE Confidence: 0.712199291428571
00:40:24.903 --> 00:40:27.118 strand DNA sensing pathways through
NOTE Confidence: 0.712199291428571
00:40:27.118 --> 00:40:28.890 the reverse transcription process.
NOTE Confidence: 0.712199291428571
00:40:28.890 --> 00:40:31.459 It I need to the better representation
NOTE Confidence: 0.712199291428571
00:40:31.459 --> 00:40:35.030 of the MHC one and the cytokine secretion
NOTE Confidence: 0.712199291428571
00:40:35.030 --> 00:40:38.078 lead to higher immunogenicity and better
NOTE Confidence: 0.712199291428571
00:40:38.078 --> 00:40:40.948 response to e-mail checkpoint blockade.
NOTE Confidence: 0.712199291428571

00:40:40.950 --> 00:40:43.476 So although with the first group
NOTE Confidence: 0.712199291428571

00:40:43.476 --> 00:40:46.562 that show that Kadian 5B is critical
NOTE Confidence: 0.712199291428571

00:40:46.562 --> 00:40:47.885 for immune evasion,
NOTE Confidence: 0.712199291428571

00:40:47.890 --> 00:40:50.026 we are not the first group to so
NOTE Confidence: 0.712199291428571

00:40:50.026 --> 00:40:52.429 shows that B1 has this function and
NOTE Confidence: 0.712199291428571

00:40:52.429 --> 00:40:54.229 multiple groups about the similar
NOTE Confidence: 0.712199291428571

00:40:54.301 --> 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 --> 00:41:05.826 and and this is just multiple papers
NOTE Confidence: 0.712199291428571

00:41:05.826 --> 00:41:08.358 basically by multiple groups and this
NOTE Confidence: 0.712199291428571

00:41:08.358 --> 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 --> 00:41:15.170 What do we know about epigenetic
NOTE Confidence: 0.712199291428571

00:41:15.170 --> 00:41:17.980 regulation of the viral mimicry pathway?
NOTE Confidence: 0.720328561666667

00:41:20.000 --> 00:41:22.520 Basically I've showed before that double
NOTE Confidence: 0.720328561666667

00:41:22.520 --> 00:41:25.690 DMT and SD one can do this and here we

NOTE Confidence: 0.720328561666667
00:41:25.780 --> 00:41:29.326 just showed up and said one can do this
NOTE Confidence: 0.720328561666667
00:41:29.326 --> 00:41:32.276 and all those inhibitors will be able
NOTE Confidence: 0.720328561666667
00:41:32.276 --> 00:41:34.910 to induce those biometric response and
NOTE Confidence: 0.720328561666667
00:41:34.982 --> 00:41:37.574 the firm response and better response
NOTE Confidence: 0.720328561666667
00:41:37.574 --> 00:41:40.010 to e-mail checkable and blockade.
NOTE Confidence: 0.720328561666667
00:41:40.010 --> 00:41:42.242 So now I would like to thank all
NOTE Confidence: 0.720328561666667
00:41:42.242 --> 00:41:44.537 the people involved in this and
NOTE Confidence: 0.720328561666667
00:41:44.537 --> 00:41:46.617 especially Marcus Bosenberg group and
NOTE Confidence: 0.720328561666667
00:41:46.617 --> 00:41:48.988 where we had the fun collaboration.
NOTE Confidence: 0.720328561666667
00:41:48.990 --> 00:41:52.721 A decade on collaboration and and the
NOTE Confidence: 0.720328561666667
00:41:52.721 --> 00:41:56.104 drug resistant work is led by Shawnee
NOTE Confidence: 0.720328561666667
00:41:56.104 --> 00:41:59.338 anew and Sami Zang and the immune
NOTE Confidence: 0.720328561666667
00:41:59.338 --> 00:42:02.950 evasion they walked the net by Samin
NOTE Confidence: 0.720328561666667
00:42:03.056 --> 00:42:06.596 Jan and Samin has actually started.
NOTE Confidence: 0.720328561666667
00:42:06.600 --> 00:42:08.980 Isn't Professor Ship at
NOTE Confidence: 0.720328561666667

00:42:08.980 --> 00:42:10.765 Shanghai Tech University?
NOTE Confidence: 0.720328561666667

00:42:10.770 --> 00:42:13.146 And on the some of the bad formatting works
NOTE Confidence: 0.720328561666667

00:42:13.146 --> 00:42:15.723 are done by Western East High and the glory,
NOTE Confidence: 0.720328561666667

00:42:15.730 --> 00:42:19.125 and also like to thank all the
NOTE Confidence: 0.720328561666667

00:42:19.130 --> 00:42:23.225 youthful members for the kind of help
NOTE Confidence: 0.720328561666667

00:42:23.225 --> 00:42:26.790 through the course of this project.
NOTE Confidence: 0.720328561666667

00:42:26.790 --> 00:42:30.310 And when I try to start on Melanoma,
NOTE Confidence: 0.720328561666667

00:42:30.310 --> 00:42:33.115 the SPORE members welcomed me
NOTE Confidence: 0.720328561666667

00:42:33.115 --> 00:42:36.337 with open arms and that's how
NOTE Confidence: 0.720328561666667

00:42:36.337 --> 00:42:38.890 I can get where we are here.
NOTE Confidence: 0.720328561666667

00:42:38.890 --> 00:42:41.077 And I'd also like to thank all the other.
NOTE Confidence: 0.720328561666667

00:42:41.080 --> 00:42:42.675 Funding agencies for their support
NOTE Confidence: 0.720328561666667

00:42:42.675 --> 00:42:45.599 as you can see in a couple of
NOTE Confidence: 0.720328561666667

00:42:45.599 --> 00:42:46.859 Melanoma Research Foundation,
NOTE Confidence: 0.720328561666667

00:42:46.860 --> 00:42:48.452 Melanoma research alliance have
NOTE Confidence: 0.720328561666667

00:42:48.452 --> 00:42:50.840 been very helpful in supporting our

NOTE Confidence: 0.720328561666667
00:42:50.900 --> 00:42:52.682 research in Melanoma and I would
NOTE Confidence: 0.720328561666667
00:42:52.682 --> 00:42:54.938 like to thank you all for your
NOTE Confidence: 0.720328561666667
00:42:54.938 --> 00:42:56.954 attention and I welcome any questions.
NOTE Confidence: 0.71509299
00:43:09.220 --> 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 --> 00:43:38.670 So the question is whether we
NOTE Confidence: 0.7468024765
00:43:38.745 --> 00:43:41.205 have tried to combine KDM 5
NOTE Confidence: 0.7468024765
00:43:41.205 --> 00:43:42.845 inhibitor with sting agonist,
NOTE Confidence: 0.7468024765
00:43:42.850 --> 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 --> 00:43:47.642 but we have not had the
NOTE Confidence: 0.7468024765
00:43:47.642 --> 00:43:50.180 time to do this experiment.
NOTE Confidence: 0.7468024765
00:43:50.180 --> 00:43:51.710 Yeah, which we should have done, yeah.
NOTE Confidence: 0.81533074
00:43:54.440 --> 00:43:54.930 OK.
NOTE Confidence: 0.811770852
00:43:56.040 --> 00:43:58.288 That was a great job. Thank you so much.
NOTE Confidence: 0.811770852

00:43:58.290 --> 00:44:01.020 And went back and forth a little bit
NOTE Confidence: 0.811770852

00:44:01.020 --> 00:44:03.182 between 10:20 and five inhibition
NOTE Confidence: 0.811770852

00:44:03.182 --> 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 --> 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 --> 00:44:22.780 also some other cancer types where
NOTE Confidence: 0.52550698

00:44:22.780 --> 00:44:26.588 we have seen is that in actually
NOTE Confidence: 0.52550698

00:44:26.588 --> 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 --> 00:44:34.946 this is MC38 with the colorectal
NOTE Confidence: 0.52550698

00:44:34.946 --> 00:44:38.649 cancer where when we treated those.
NOTE Confidence: 0.52550698

00:44:38.650 --> 00:44:40.642 So those animals, uh tumor bearing
NOTE Confidence: 0.52550698

00:44:40.642 --> 00:44:42.670 animals with KDM 5 inhibitor,
NOTE Confidence: 0.52550698

00:44:42.670 --> 00:44:44.210 you can suppress the ability to grow.

NOTE Confidence: 0.52550698

00:44:44.210 --> 00:44:46.710 So it works incorrect cancer.

NOTE Confidence: 0.52550698

00:44:46.710 --> 00:44:48.974 Also when we look at the breast cancer

NOTE Confidence: 0.52550698

00:44:48.974 --> 00:44:51.575 you can see they have some new efficacy.

NOTE Confidence: 0.52550698

00:44:51.580 --> 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 --> 00:44:57.377 I would say additive effect.

NOTE Confidence: 0.52550698

00:44:57.380 --> 00:45:02.098 So it works in multiple cancer types.

NOTE Confidence: 0.52550698

00:45:02.100 --> 00:45:04.648 It's just where we need to find

NOTE Confidence: 0.52550698

00:45:04.648 --> 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 --> 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 --> 00:45:16.894 those are all planning.

NOTE Confidence: 0.86637986

00:45:16.900 --> 00:45:17.936 Can you invite me here with us?

NOTE Confidence: 0.86637986

00:45:17.940 --> 00:45:21.028 So, so one of the things that we

NOTE Confidence: 0.86637986

00:45:21.028 --> 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 --> 00:45:27.998 specific degraders.
NOTE Confidence: 0.86637986

00:45:28.000 --> 00:45:31.750 And with the.
NOTE Confidence: 0.86637986

00:45:31.750 --> 00:45:33.742 Because with the protect or some
NOTE Confidence: 0.86637986

00:45:33.742 --> 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 --> 00:45:42.206 degraders against KDM 5 and we
NOTE Confidence: 0.86637986

00:45:42.206 --> 00:45:44.460 are actually working on that.
NOTE Confidence: 0.86637986

00:45:44.460 --> 00:45:48.928 We have some potential degraders that
NOTE Confidence: 0.86637986

00:45:48.928 --> 00:45:51.544 work specifically on Canadian 5B and
NOTE Confidence: 0.86637986

00:45:51.544 --> 00:45:54.108 some of them work on multiple all
NOTE Confidence: 0.86637986

00:45:54.108 --> 00:45:56.150 kidding 5A in different settings.
NOTE Confidence: 0.555586011666667

00:45:58.370 --> 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 --> 00:46:12.612 Other epigenetic reader and writer
NOTE Confidence: 0.804168843333333
00:46:12.612 --> 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 --> 00:46:21.378 you one in one of the diagram.
NOTE Confidence: 0.804168843333333
00:46:21.380 --> 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 --> 00:46:33.784 have similar effect and although I
NOTE Confidence: 0.804168843333333
00:46:33.784 --> 00:46:35.982 have to say in different cancer types
NOTE Confidence: 0.804168843333333
00:46:35.982 --> 00:46:37.984 and they have different effect and
NOTE Confidence: 0.804168843333333
00:46:37.984 --> 00:46:40.600 we just need to find the right one
NOTE Confidence: 0.804168843333333
00:46:40.600 --> 00:46:42.966 and that work in the in our setting.
NOTE Confidence: 0.92254168
00:46:46.570 --> 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 --> 00:46:57.326 So you showed that Kenny M5
NOTE Confidence: 0.56578101625

00:46:57.340 --> 00:47:00.460 views anticorrelated with all sorts of
NOTE Confidence: 0.56578101625

00:47:00.460 --> 00:47:03.060 new vectors, both positive and negative.
NOTE Confidence: 0.837579152

00:47:05.700 --> 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 --> 00:47:14.650 Well, that's a great question.
NOTE Confidence: 0.789690956

00:47:14.650 --> 00:47:17.710 We have not looked. Yeah.
NOTE Confidence: 0.789690956

00:47:17.710 --> 00:47:20.610 So you just need to do something
NOTE Confidence: 0.789690956

00:47:20.610 --> 00:47:22.827 also analysis too or just analyze
NOTE Confidence: 0.789690956

00:47:22.827 --> 00:47:24.820 single cell data to see to see that.
NOTE Confidence: 0.789690956

00:47:24.820 --> 00:47:26.410 Yeah, it's great, great suggestion.
NOTE Confidence: 0.789690956

00:47:26.410 --> 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 --> 00:47:35.720 Wonderful mechanistic. Right.
NOTE Confidence: 0.736882002

00:47:40.140 --> 00:47:42.905 My question is regarding Katie M5B.
NOTE Confidence: 0.736882002

00:47:42.905 --> 00:47:46.550 And it's a deck that seemed to be asymmetric.
NOTE Confidence: 0.699299990333333

00:47:48.720 --> 00:47:51.149 You showed us. I was wondering whether

NOTE Confidence: 0.699299990333333

00:47:51.149 --> 00:47:53.495 they would be animators that could

NOTE Confidence: 0.699299990333333

00:47:53.495 --> 00:47:55.973 maybe the scaffolding effect of paying

NOTE Confidence: 0.699299990333333

00:47:55.973 --> 00:47:58.662 5D its interaction with 71 and whether

NOTE Confidence: 0.699299990333333

00:47:58.662 --> 00:48:01.442 those could be more appropriate for

NOTE Confidence: 0.699299990333333

00:48:01.442 --> 00:48:05.060 who gets PDL 1 increased response.

NOTE Confidence: 0.7466141296875

00:48:06.990 --> 00:48:10.308 Yeah, that so answer the question is

NOTE Confidence: 0.7466141296875

00:48:10.308 --> 00:48:13.663 whether we should inhibit the scaffold

NOTE Confidence: 0.7466141296875

00:48:13.663 --> 00:48:16.608 function location 5B, which is great.

NOTE Confidence: 0.7466141296875

00:48:16.608 --> 00:48:19.170 So that's something that we are thinking

NOTE Confidence: 0.7466141296875

00:48:19.243 --> 00:48:21.595 along the way because we have to first

NOTE Confidence: 0.7466141296875

00:48:21.595 --> 00:48:24.080 of all we need to identify the domains

NOTE Confidence: 0.7466141296875

00:48:24.080 --> 00:48:26.420 that are critical for those interaction.

NOTE Confidence: 0.7466141296875

00:48:26.420 --> 00:48:28.760 And then one of the things that we're trying

NOTE Confidence: 0.7466141296875

00:48:28.760 --> 00:48:31.020 to do is you to look for those domains

NOTE Confidence: 0.7466141296875

00:48:31.020 --> 00:48:33.894 that are involved in interacting with

NOTE Confidence: 0.7466141296875

00:48:33.894 --> 00:48:37.268 said said B1 and then those inhibitors.
NOTE Confidence: 0.7466141296875

00:48:37.270 --> 00:48:40.819 To have more specificity as you as
NOTE Confidence: 0.7466141296875

00:48:40.819 --> 00:48:43.768 you suggested to target this pathway
NOTE Confidence: 0.7466141296875

00:48:43.768 --> 00:48:46.565 and it's probably better than getting
NOTE Confidence: 0.7466141296875

00:48:46.565 --> 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 --> 00:48:53.486 effect that we don't want to see.
NOTE Confidence: 0.76170298375

00:48:54.870 --> 00:48:55.536 That's what interesting,
NOTE Confidence: 0.76170298375

00:48:55.536 --> 00:48:56.646 because when you think of,
NOTE Confidence: 0.76170298375

00:48:56.650 --> 00:48:58.318 for example, LC-1, there are requests
NOTE Confidence: 0.76170298375

00:48:58.318 --> 00:49:00.219 that seem to be targeting the.
NOTE Confidence: 0.777380149

00:49:03.860 --> 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 --> 00:49:12.540 other proteins that play a role in one.
NOTE Confidence: 0.820704649

00:49:14.840 --> 00:49:16.508 I wonder if those types of
NOTE Confidence: 0.820704649

00:49:16.508 --> 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 --> 00:49:23.206 we we don't have those yet.

NOTE Confidence: 0.88700327

00:49:23.210 --> 00:49:24.419 Work in progress.

NOTE Confidence: 0.9599048

00:49:30.210 --> 00:49:33.618 OK. If no more questions. Thank you.