Got it. So it’s my distinct pleasure to introduce Chen Yan to us today. He’s one of the invited speakers for this year for the Melanoma program. So for those that don’t know, Melanoma program is a fairly well established 1 going back to the 1980s when we started the first interdisciplinary disease team, John Kirkwood and Steve Arians specifically. And then as the years went by, other folks started the first interdisciplinary disease team, John Kirkwood and Steve Arians specifically. And then as the years went by, Ruth Taliban, who’s sitting here,
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
the sport in its previous iteration.

And that subsequently blossomed to a full project.

We are thrilled to have Chen working with us.

We couldn’t, we couldn’t ask for a better collaborator, both in terms of his scientific depth and in terms of his personality.

He’s definitely one of us.

And I actually don’t care that he’s the scientific Co director of the breast unit. As far as we’re concerned, he’s ours.

So without further ado, chin, the floor is yours.

Thank you.
Well, thank you Harry for your kind introduction and I was also like to thank my normal program for nominating me here to present here. I would say Cancer Center ground is one of the event that actually led me to work on Melanoma and on my way back from Grandma’s talks and I was working together with Marcus Bosenberg. I bought a decade ago and we were talking about Jerry 1B who might be important in Melanoma. I was working on Jerry one. Because I generally knockout my and well, we just started the collaboration and it’s a very fun collaboration and this is
00:02:07.963 --> 00:02:09.900 something I'm going to tell you today.

00:02:13.350 --> 00:02:16.590 So let me get this started.

00:02:16.590 --> 00:02:17.880 Fixed the pointer.

00:02:22.450 --> 00:02:24.810 So this is my disclosure.

00:02:24.810 --> 00:02:26.722 So what I'm going to do is first

00:02:26.722 --> 00:02:28.891 you give you a very quick overview

00:02:28.891 --> 00:02:30.938 of cancer epigenetics and then you

00:02:30.938 --> 00:02:35.348 how it recognizes drug resistance

00:02:35.348 --> 00:02:38.493 and immune evasion.

00:02:38.493 --> 00:02:40.380 So as many of you know,

00:02:40.380 --> 00:02:42.528 the epigenetics is study of

00:02:42.530 --> 00:02:44.620 health heroical traits that does

00:02:44.620 --> 00:02:46.710 not depend on the underlying DNA
sequences and the major epigenetic mechanisms include DNA methylation.

Put his own structure, histone modifications and non-coding on it.

There's a number of regulators of IPG netting mechanism including the coronary modernness which are involved in moving the nuclear zones around.

So what I'm going to tell you today mainly focus on KDM 5B which is an eraser which is involved in removing a certain modification and sandbag one which I'm touched upon which is the right approach.
So many of you are quite familiar with this hallmarks of cancer and what I'm going to tell you a little bit about is the immune invasion that cancer cells have to achieve. And if you look at it on the right side, this is a new, those are new hallmarks that have been added to the hallmarks of cancer and two of which actually quite related to epigenetics, including unlocking phenotypic. Plasticity and epigenetic reprogramming. So that’s what I’m going to tell you today.
So as many of you know epigenetics can regulate many of the cell fate and also a lot of mechanisms are involved in anti tumor immunity and just on the tumor cells for example, it has been shown DNA machination, histone modifications have been involved in regulating tumor antigen expression and cytokine secretion, PDL one expression and also chromatin structure. Have been shown to be important to response to cytotoxic attack, and those modifications are also important on other immune cells, including cytotoxic T cells.
dendritic cells and macrophages, which is not duplicated here.

So just a brief introduction on my laboratory and we are interested in cancer epigenetics of course. And one of the area we are interested in is a cancer metastasis shown here. Just one of the example where we showed one of the target called CCR two is a driver of breast cancer metastasis. And you can look at here, if you knock down CCR two, you can suppress the ability of those breast cancer cells to metastasis to the lung and if you overexpress CCR two,
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.
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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
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00:05:30.637 --> 00:05:32.997 this is something that I will mention later.
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00:05:33.000 --> 00:05:35.690 And so I’m not going to go over this figure.
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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,
if you combine that with transfusion level, you can actually regress the tumor formation by the drug resistant cells. As a matter of because we are interested in the area, we are also interested in developing epigenetic drugs. And I will tell you some of the work on KDM 5 inhibitor development. And this is a some work that we have done a couple years ago where we characterized a potent bromodomain inhibitor where we show that this bromodomain inhibitor and HW 870 can not only inhibit the ability of the
cell tumor cells to grow but you can. Also hit on the macrophages by suppressing the expression of CSF 1A, critical regulator of macrophage polarization and the macrophage proliferation and this drug actually have entered the phase one clinical trial in China and moving into phase two very soon. So my laboratory had been focusing on a group of England called KDM 5 histone demethylase and as you can see here this group of vendors have four of them and they are called KDM 5 ABC D or Jared 1A1B1C and 1D
and all of those have this team JC domain which is the Jumanji C domain, it's hydroxylase domain and the by hydroxylation of the methanation. Group and the removal of formaldehyde.

They actually can demate the histones.

So this group of landline can demonstrate, try and demonstrate nice thing.

And because those machination marks are critical marks for actually transcribed genes, so by doing so this group of online can silence transcription. But that’s not the whole story.
And all those proteins actually have other domains including 80 rich interactive domain which is involved in DNA binding and some of the PhD fingers which are involved in binding specific histone modifications. In addition, they can interact with many other proteins involved in chromatin remodeling and transcription recognition. So they have. It has been documented that this group cannot only. The transcription repressor they can be transcription activated in some other settings.
So today’s talk we’ll be focusing on this protein called Kadian 5B or Jerry 1B. Also another known name is called the PLU One. Because there’s a number of evidence showing that Kadian 5B has oncogenic role. Initially was identified as a downstream gene downstream of her 2IN breast cancer because it was shown to be downregulated by anti to 15
anybody in her two overexpression cells.

And these have been shown by 90 points group that is amplified in luminal breast cancer and it’s a potential luminal linearity driving oncogene and we have shown in any in mouse. Jerry 1B can recruit Gallant St to regulate Fox A1 expression and that contribute to estrogen receptor target gene expression and in fact if you look at the estrogen. Except the positive tumors in for breast cancer, higher activity of Jerry won’t be OK and 5B is correlated with
poor prognosis of those patients. And then you point out group has also shown that Kadian 5B can promote transcriptomic heterogeneity and this actually contribute to the therapeutic resistance and this is just one of the mechanism that this could contribute to resistance. I will tell you more about our work on a different angle. In addition, when we deplete KDM 5B first initially in breast cancer cells in syngeneic mouse model, you can see down regulation of
KADIAN 5B can decrease the ability of those tumor cells to grow. And it was shown by Mihan honing scope that if you suppress, those tumor cells actually grow faster. However, after you serial transplantation, those cells still crash, so suggesting that it’s required for Melanoma maintenance instead of putting refreshing initial proliferation. And they were shown in multiple groups including ours that KADIAN file be involved in drug resistance and is shown here just one of the example by actually by a company constellation.
where they showed in multiple cancer cell lines including Melanoma. Here if you compare the effect of Canadian five inhibitor on parental cells or drug tolerant persister cells if you actually in this case they did a pre treatment of. Both S and and they should have shown that the KADIAN 5 inhibitor cannot inhibit the growth of the parental cells, but they can prevent the emergence of the drug resistant tolerant. Would DP cells or drug tolerant persister cells or drug resistant cells? In prostate cancer if we cost the
KADIAN file be knockout model to

the P-10 knockout model in process

specific deletion and where you
can see P-10 knockout model can
form a prostate cancer.

But if you get relocation 5B you can
normalize the those prostate
tumors basically you can see the
the size is much smaller.

Now I want to move back to Melanoma
because this is a focus on our talk today.
because this was done by Goran, a tenant in
the graduate student at that time.
the graduate student at that time.
In exposing like who is final right now?
Where he showed that high
expression is associated with poor survival of Melanoma patients. So now we decided to look at the Melanoma when we followed some of the work from Marcus Bosenberg. I have about my normal propagating cells. Was published more than a decade ago that if you look at the mouse Melanoma cells, you can sort them to three different populations, the P75P-75 positive cells, the CD 34 positive cells or the double negative cells. If you look at the ability of the cells to form tumors,
the CD 34 positive cells can form tumors very efficiently and the double negative cells can do so. With less efficacy but still works and the PDP 75 positive cells do not actually form tumors if they put them into modern mice. So we decided to look at this more systematically and when this is just a diagram show a table showing and many of the Yale University mouseman normal cell lines generated by Marcus Bosenberg Snapstory and those cell lines are generated were fun back six animals and you can do use those and use those cells for
syngeneic transplantation experiments.

And two of the cell lines we.

Used here uh Young 11.7 which will

actually I will use it also later

on for e-mail invasion studies

and also young ones 3.3 cells.

The reason why we chose those cells

because they only have two populations

so these 34 positive and city 34

negative both of them can form too much.

So this provide a nice system to look at

the population changes and when we put.

Drugs on onto them.

So we used the because those

are mutant tumors and we treat

23
those cells with rough inhibitor.

In this case we use actually use the PX4 or three, two over.

Stephanie.

Umm, as you can see here,

if you compare the parental cells and you have more CD 34 positive cells.

if you look at the resistance the drug resistant cells you have which we delicate as the Yom Young.

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If you look at the resistance the drug resistant cells you have which we deliberate as the Young.
00:15:25.700 --> 00:15:27.970 you can see 3034 negative.

00:15:27.970 --> 00:15:31.588 Those are more resistant to be off inhibitor treatment because there's less growth inhibition.

00:15:31.588 --> 00:15:34.000 And this phenomenon is also reversible.

00:15:34.102 --> 00:15:42.120 If we treat those, you can see that they shifted to the left side, meaning CD 34 negative cells.

00:15:44.579 --> 00:15:45.979 However, if you remove the drug after a couple passages and they will shift it back to the parental cell population.

00:15:56.100 --> 00:15:58.158 So one of the things that was actually who it was a graduate student
Once Marcus and I basically should notice that there’s an increased expression of KDM 5B if we treat those cells with BRAF inhibitor. And this is shown in young 1.7 cells, 3.377 cells. But also when you compare the parental with the resistance cells you see the similar increase of KADIAN fab expression. And this is reversible if you take out an inhibitor and the expression drops down and it’s showing 1.7 cells as well as 3.3 cells. So when we did the genetic experiment when we knocked down kidding 5 expression by a as shown here.
We can see in the one point 11.7 cells, there's a decrease of CD34 negative cells after we deplete eighteen 5B. When we look at the phenotype and it's consistent to what other people have seen in other Melanoma setting, if you knock down killing five, you actually increase the ability of them to grow in vitro. And then those cells are actually more sensitive to inhibitor treatment? Two in most cells but also in human cells, this is your Max cells. If you knock down Killian 5B
and you can see induction HPK

NOTE Confidence: 0.739691652727273

4 trimethylation which is the

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substrate of the enzyme and you

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can see those cells grow faster.

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However, they are less sensitive,

NOTE Confidence: 0.739691652727273

they’re more sensitive to BF inhibitor treatment.

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And if you look at this in animal models,

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uh, similar things happens when we treat

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cells with borough inhibitor and you can

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see KADIAN file being level increase

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And if you take away the inhibitor,

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you can see the level drops down.

NOTE Confidence: 0.874118252941176

So Umm, and then we look at the if you

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look at the population of the cells,

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you can see increased.
00:18:26.050 --> 00:18:30.470 City City for negative cells.
00:18:30.470 --> 00:18:32.845 When we treat the cells
00:18:32.845 --> 00:18:34.270 with Burrough inhibitor,
00:18:34.270 --> 00:18:37.302 when you take out the inhibit that way
00:18:37.302 --> 00:18:40.238 and then those would not normalize.
00:18:40.240 --> 00:18:42.886 So Umm, and this is all consistent
00:18:42.886 --> 00:18:45.837 with our data and others have shown,
00:18:45.840 --> 00:18:46.792 which you’re not showing
00:18:46.792 --> 00:18:47.982 here on that KADIAN filing.
00:18:47.990 --> 00:18:50.890 Hebetor can suppress the emergence
00:18:50.890 --> 00:18:53.210 of drug resistance cells.
00:18:53.210 --> 00:18:54.610 So to summarize this part,
00:18:54.610 --> 00:18:57.203 we see we have showed that 634
00:18:57.203 --> 00:18:59.468 negative cells are more resistant
00:18:59.468 --> 00:19:02.177 to BRF inhibitor treatment and BF
inhibitor can increase C30 four negative cells and you can induce KADIAN file be up recognition and this is reversible and kadian Fabian N can reduce this population cells and induce drug resistance sensitivity.

So now I want to switch gear to talk about uh immune evasion and firstly I want to start with this cancer immunity cycle on which many of you know have seen before. Basically this is a diagram showing that the cancer cells interact with the immune system and and there are many ways that cancer cells have adopted to evade immune evasion.
to evade the immune response.

So as a matter of fact, because of this mechanism and some drugs have been developed including the anti PD1, PDL one anti 4 antibodies as well as the ways to push the effect of on the T cells. However, there’s not much he’s really actually known about the trafficking of T cells to tumors and the infiltration of the T cells into the tumor at that time when we started. And what’s known about epigenetics, many of you are quite familiar with.
this concept about code tumor and hot tumor code tumor are not really responsive to another treatment, but the hot tumor will enable them to be responsive to even checkpoint block. And a sub couple for epigenetic. Uh regulators have been shown to be critical for this.

Code to how the transition and if we treat this the tumors with a couple of inhibitors against those targets like DMT inhibitors. You can ship them to be more hard to become more hot hot. Um, in some of the settings, not in all the settings.
And this is kind of related to what we are trying to do and at that time actually a couple of years ago before that and we have looked at the cadian 5B. And how it’s related to other genes when we look at the TCA Melanoma data set? And to our surprise, actually KADIAN 5 expression was shown to be negatively correlated with many of the immune related genes. And if you look at those top signaling pathway, those are all immune system related genes and those are negative coordinate with expression.
If you look at the identity of those genes, those shown here are the gene names and on the right side of the Spielman score and you can see many of the silo kinds, for example interferon gamma and TNF A6796 O 10 which are involved in T cell recruitment are all negative coordinate with cadian fabric expression. And some of the targets for immune checkpoint blockade PDL one CPT for also negative coordinate with KADIAN fabric expression. This will be important when we are trying to look at the e-mail
checkpoint blockade resistant tumors.

So when we looked at the KDM 5 be expression protein expression in melanomas and if you compare nonresponse boundaries with and responders, we can see increased expression location which is shown in red in those non responders compared to the responders and the quantification is shown here. So this motivates us to look at the role of Canadian file be using animal models. As I mentioned earlier.

Um, Marcus Bosenberg snapped, had generated a series of why UM or young models.
Uh, one of the models that we started to use is this Yamaha 1.7 models. Yeah, this stand for ER stands for exposed to radiation, meaning those cells will radiate so that they have more mutations, they can generate more antigens that can be recognized by the immune system. So when we knocked out Kadian 5B in those cells, as you can see here, those cells can initially grow, then they got fully rejected after a while. And the more importantly when we challenge those animals with the cells control those animals with the cells control which normally can grow very well, they never grow up.
So this is very important imagine that if we have to treat patient with a drug and case for example in this case KADIAN 5 targeting drug and those patient will not, will not have recurrence because because the immune memory response. So this is actually translated to 100% survival, which is uh, this is great. And then we look at the UM uh T cell infiltration when we compare the control cells and KADIAN file B the control cells and KADIAN file B the control cells and KADIAN file B the control cells and KADIAN file B the control cells and KADIAN file B knockout tumors at the very early stage, you can see the T cell infiltration.
either by e-mail, histochemistry as well as fax analysis. And there's another way to say that this is immune system dependent on we compared the ability of cells to grow in wild type cell wild type mice or rats. Deficient mice and as you can see here the B6 is the wild type. Those two curves are what I have showed you before and if you look at the ability of cells you grow in rectification mice the control goes here and then can be deficient once grow kind of similarly although slightly slower. So this basically set up the stage that Kadian 5B which is
00:25:20.477 --> 00:25:22.869 critical for immune evasion.
00:25:22.870 --> 00:25:26.110 So the next question is what's the mechanism,
00:25:26.110 --> 00:25:26.742 right?
00:25:26.742 --> 00:25:28.638 So how to?
00:25:28.640 --> 00:25:29.933 To understand this,
00:25:29.933 --> 00:25:32.950 we are look dead on a sequencing
00:25:33.034 --> 00:25:35.380 comparing Yammer 1.7 cells,
00:25:35.380 --> 00:25:37.930 probably knockout versus wild type.
00:25:37.930 --> 00:25:40.303 And we can see there's an induction
00:25:40.303 --> 00:25:42.717 of a lot of signaling pathway
00:25:42.717 --> 00:25:45.790 involved in DNA on a sensing pathway
00:25:45.872 --> 00:25:49.106 and showing here that generation analysis,
00:25:49.110 --> 00:25:51.735 the instrument parts where you
00:25:51.735 --> 00:25:53.972 can see there's an enrichment
00:25:53.972 --> 00:25:55.548 regarding like research pathways
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
double strand DNA sensed through those
NOTE Confidence: 0.769697436730769
00:26:12.366 --> 00:26:14.716 pathways and double strand DNA is
NOTE Confidence: 0.769697436730769
00:26:14.716 --> 00:26:16.826 sensed through cgas sting pathway
NOTE Confidence: 0.769697436730769
00:26:16.826 --> 00:26:19.235 double strand DNA double strand on
NOTE Confidence: 0.769697436730769
00:26:19.235 --> 00:26:21.150 the Ascension sensed through those
NOTE Confidence: 0.769697436730769
00:26:21.150 --> 00:26:25.030 pathways and double strand DNA is
NOTE Confidence: 0.769697436730769
00:26:25.030 --> 00:26:27.622 sensed through cgas sting pathway
NOTE Confidence: 0.769697436730769
00:26:27.622 --> 00:26:29.587 double TV K1F3F7 and the interferon
NOTE Confidence: 0.769697436730769
00:26:29.590 --> 00:26:34.169 And the double stranded on a could
NOTE Confidence: 0.769697436730769
00:26:34.169 --> 00:26:34.169 be sensed through regard MDA 5
00:26:34.169 --> 00:26:36.004 maps Altos three and basically
00:26:36.004 --> 00:26:38.269 also signals through and activate
00:26:38.269 --> 00:26:40.217 interference and steam engines.
00:26:40.220 --> 00:26:42.964 So what we did is we knock cloud
00:26:42.964 --> 00:26:44.732 each single component through
00:26:44.732 --> 00:26:47.720 this pathway and see what happens
00:26:47.720 --> 00:26:49.456 when we knock out the Canadian 5B.
00:26:49.460 --> 00:26:52.322 As you see it does not grow in the
00:26:52.322 --> 00:26:55.395 wild type cells do grow if we combine
00:26:55.395 --> 00:26:57.830 that with knockout of the mouse or
00:26:57.830 --> 00:26:59.740 steam and the important mediator of.
00:26:59.740 --> 00:27:01.680 Christian Arnie or double Strand
00:27:01.680 --> 00:27:02.844 DNA sensing pathway,
00:27:02.850 --> 00:27:06.154 you can see partial rescue right here.
00:27:06.160 --> 00:27:08.552 If you get rid of both of them
00:27:08.565 --> 00:27:10.226...
you see much better rescue.

So we went on and when the upstream

when we get rid of the sea gas or

MDA 5 and you can also see partial

rescue if you get rid of both of them.

You can see pretty good rescue response

in this case when in two independent.

So how many established that?

Now we want to understand why

those pathways are activated.

So why would the sense that we notice

is that when we compare the control

cells with the knockout cells,

we can see the induction of double

stranded on a in Kadian 5B knockout

and then we have seen this
also in two months as well.

And this motivated us to go back and realize our only sequencing data. For expressing those retro elements and those retirement are part of junk genome and then people are totally normally ignore and it turned out to be very important in this case. And what we have seen is that we knock out Kadian 5B, we can see induction of those some of the endogenous retrovirus. And the one with which is called MOV 30 and Animals.
you can see multiple of those showing up.

And then we study is actually critical for the interferon response.

because if we knock down M30 with SRAM as you can see here,

you can see the down recognition or interference imagines suggesting that this is at least partially contribute

to the interferon induction and maybe this is at least partially contribute

to the interferon induction and maybe

the response to e-mail evasion.

And the one thing that we were puzzled about is that since I showed you that both DNA and only sensing password are required,

where are those DNA coming from?

And we postulated that those
DNA will be coming from reverse transcription of those only species that would generate through after we get rid of Kadian 5B. And one experiment we did is use reverse transcriptase inhibitor. This is a cocktail of reverse transcriptase inhibitors used for HIV treatment and where we see if you treat the cells with those reverse transcriptase inhibitor. You can see suppression of the interference imaging expression suggesting that this DNA might be created through this pathway. So now with all those mechanisms, now the question is can we
The quick question is that can we induce under tumor immune response with KDM 5 inhibitors? So as I mentioned because there’s a lot of evidence showing that KDM five are critical for cancer initiation progression. So we have started working on this on to by multiple methods to develop locating file inhibitors. So initially with that panel ground from the Yale Small Molecule Screening Center now called Yale Center for Monica. We have done some screening, biochemical screening for KADIAN
00:30:39.630 --> 00:30:41.355 5D methods inhibitor.
00:30:41.360 --> 00:30:43.520 And initially we did 100,000 compounds
00:30:43.520 --> 00:30:46.136 with those as a preliminary data we
00:30:46.136 --> 00:30:48.705 were able to obtain support for NCI
00:30:48.777 --> 00:30:50.847 experimental security program where we
00:30:50.847 --> 00:30:54.579 were able to assemble a team about 30
00:30:54.579 --> 00:30:57.897 scientists to to develop those inhibitors.
00:30:57.900 --> 00:31:01.060 So we have done a high school screening
00:31:01.060 --> 00:31:03.405 about 200,000 compounds those are high
00:31:03.405 --> 00:31:05.872 quality compounds and have done extensive
00:31:05.872 --> 00:31:08.137 medicinal chemistry optimization of some
00:31:08.137 --> 00:31:11.664 of the compounds and we have solved.
00:31:11.664 --> 00:31:13.828 25 uh crystal structures,
00:31:13.830 --> 00:31:16.490 can you find a way with different inhibitors
00:31:16.490 --> 00:31:18.890 and shown here just the two of them,
basically showing that they combined very tightly to the active site. One thing that I want to mention that those inhibitors are all pancaking from inhibitors. They hit both all Canadian five family members because the Catholic side is very similar, very similar for all those Canadian 5A family members. So even with with those and we decided to ask what the Canadian five inhibitor can do. And the one thing that we decided to do is we selected four KDM 5 and inhibitor here. Those are high quality specific calling from inhibitor. As you can see here they all induce
HK for translation which is the substrate of the reaction and then did not do anything to the other of the histone modifications. And we did those actually in I'm 6-7 and multiple human breast cancer cells and when we looked at the gene expression changes to our surprise we see the top pathway that's upregulate are those interference signaling pathway at that time I was like interfering pathway is not something I want to work on not so much now. So, so anyway, so when we see there's an induction
interfering pathway and we have seen this in multiple cell lines, multiple drugs. And we were able to understand how this actually worked. And at the end we were able to show that KADIAN 5 inhibitor can induce H3K4 termination at the steam promoter and by doing so, it actually induce Stein expression. And this need to the interferon stimulated gene expression and listening to the T cell infiltration. So this is a little bit different from what other people have been trying to. Uh, to activate this pathway.
through either using Steam agonist, which the limitation of those drugs and is. Many of the cancer cells you actually have Stein silence. So by inducing Stein and this provide another mechanism how we can activate this signaling pathway. So now and we actually tested KADIAN 5 inhibitor in multiple human Melanoma and we can see induction of sting and in this case in Western border here and the induction of interference steam engines. And so we thought this is the shoe bat and the Canadian five inhibitor
is going to work.
And to our surprise, nothing happened.
And when we took put this in the mouseman normal cells,
the Y ammer 1.7 cells, the model system that we have tested.
2 into 2 Canadian farm inhibitor and the retro element was were not induced,
the interference images were not induced, nothing happened.
So we did not want to give up because we thought maybe there’s some limitation of the drugs and so we did those rescue experiment to understand whether the critical the community activity is required or not.
So what we did is that for... I'll call it Yama cells.

We reintroduced either wild type or mutant KADIAN 5B into those cells. Those mutant are dead Canadian 5B. And as you can see here, in both cases you can see wild type or mutant Canadian 5B can suppress the expression of retro elements and those interference stimulate genes. Moreover, both of those can induce the growth of those tumors. So now what?

Now we are back to the starting point.
and kind of depressed right at time.

So we went on and decided to look at all the repressive mechanisms and to see which one might work. And one of the things that we decided to look at is, is actually inhibitor for example and those are two higher quantities that true inhibitor, it did not do much either. Umm, and then uh, there’s some clue that HK9 message transfers would work, and we use a pretty dirty actually canine method.
Transfers inhibit the code channel thing and it can inhibit actually K9 translation. You can see induction of MOV 30 and some of the interferon stimulated genes. So now there are multiple HK9 methyltransferase and so we knocked out each single one of them to see which one. Is critical when we knock out the G9A or SO39H1 and it did not really do anything. But when we knockout set B1 which is shown here, you can see robust induction on mobile 30. So this is what was a great news. So at that time we’re quite excited. And then when we did call e-mail
precipitation experiment,
we actually can see that KADIAN file B can interact with set DB1.
When we did set DB1 IP,
that’s the pull down of Kadian 5B by Sade 1.
Then we decided to map the binding of KDM 5B and set DB1 and shown here just the heat map where we ranked those KADIAN file B target genes where you can see KADIAN file B combined them very well in wild type cells, not so much in knockout cells. When we look at set DB1 binding, you can see amazingly overlapping binding of the set DB1 and the HTK 9
formation which is the product of set
DB1H3K9 formation is a repressible mark
that can suppress gene expression.
And to our surprise, when we look at
the HK4 translation and imagination,
which are the substrate of the Kadian 5B,
which is probably silenced in this setting.
So now those are all.
Important and now we want to look at this in.
Drug resistance setting and
in this case e-mail checkpoint
blockade resistance setting.
When you look at the KTM 5 be expression, it’s actually lower in the patient with computer response to anti-PD1 blockade compared to the ones with progressive disease. So this is suggesting that if we can lower expression, you can make the reason tumor sensitive. Indeed that’s actually true and we use this young 1.7 model, which is the parental model for the Yammer 1.7 I have showed you before. This model is resistant to all immune checkpoint blockade, PD1 blockade. If you look at this, nothing happens. If you throw CTO four anybody...
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
So lastly, is this also true in humans? When we compare the KADIAN 5 expression with the indulgence retro elements part of the category, you can see the ones with high Acadian 5 be expression was shown. On this you have no expression of some of the. You always showing here just one example RV 2637 and it’s anti correlated with Kaden 5 expression and the expression is correlated with the better response to PD1 blockade is opposite to what we see with PKD and 5B. So to basically to summarize this part
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
So although with the first group that show that Kadian 5B is critical for immune evasion,
we are not the first group to so shows that B1 has this function and multiple groups about the similar time show that said B1 is involved in. Suppressing tumor immunogenicity and and this is just multiple papers basically by multiple groups and this add to basically add to the what. Uh, what? What do we know about epigenetic regulation of the viral mimicry pathway? Basically I've showed before that double 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
Shanghai Tech University?

And on the some of the bad formatting works are done by Western East High and the glory,

And also like to thank all the youthful members for the kind of help through the course of this project.

And when I try to start on Melanoma, the SPORE members welcomed me with open arms and that’s how I can get where we are here.

And I’d also like to thank all the other. Funding agencies for their support as you can see in a couple of

Melanoma Research Foundation, Melanoma research alliance have been very helpful in supporting our
research in Melanoma and I would like to thank you all for your attention and I welcome any questions.

Or maybe one back.

Yeah. That's a great. So the question is whether we have tried to combine KDM 5 inhibitor with sting agonist, that's a great suggestion. And we have thought about this, but we have not had the time to do this experiment.

Yeah, which we should have done, yeah.

That was a great job. Thank you so much.
And went back and forth a little bit between 10:20 and five inhibition and 25 B specific inhibition. And I know that you think the KDM 5B is the most important one. What about? And so we have, we actually have been working on breast cancer and also some other cancer types where we have seen is that in actually maybe I'll show you one slide here. This was just published basically this is MC38 with the colorectal cancer where when we treated those. So those animals, uh tumor bearing animals with KDM 5 inhibitor, you can suppress the ability to grow.
So it works incorrect cancer.

Also when we look at the breast cancer you can see they have some new efficacy. You can also combine that with PD1 blockade and we can have I would say additive effect. So it works in multiple cancer types. It's just where we need to find the correct cancer types and subtypes even so that we were able to use those inhibitors. Yeah, yeah. So, yeah, those are all planning. Can you invite me here with us? So, so one of the things that we
are trying to do is to develop KADIAN file family members, specific degraders. And with the protect or some other similar kind of mechanism or molecular glue type of mechanism you can develop a specific degraders against KDM 5 and we are actually working on that. We have some potential degraders that work specifically on Canadian 5B and some of them work on multiple all kidding 5A in different settings.
00:46:04.730 --> 00:46:08.613 So the question is, do I anticipate?
00:46:08.613 --> 00:46:12.612 Other epigenetic reader and writer
00:46:12.612 --> 00:46:15.002 to have similar effect, yes,
00:46:15.002 --> 00:46:17.612 because actually I have showed
00:46:17.612 --> 00:46:21.378 you one in one of the diagram.
00:46:21.380 --> 00:46:25.846 There are multiple other ones on this.
00:46:25.850 --> 00:46:30.176 OK. Yeah. Once which have been shown
00:46:30.176 --> 00:46:33.784 have similar effect and although I
00:46:33.784 --> 00:46:35.982 have to say in different cancer types
00:46:35.982 --> 00:46:37.984 and they have different effect and
00:46:37.984 --> 00:46:40.600 we just need to find the right one
00:46:40.600 --> 00:46:42.966 and that work in the in our setting.
00:46:42.966 --> 00:46:47.800 OK, that's.
00:46:46.570 --> 00:46:47.800 OK, that’s.
00:46:50.970 --> 00:46:51.720 Question for you.
00:46:54.980 --> 00:46:57.326 So you showed that Kenny M5
00:46:58.613 --> 00:46:58.613
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
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
said said B1 and then those inhibitors.

To have more specificity as you as you suggested to target this pathway and it’s probably better than getting 5 inhibitor or 71 inhibitor which might have some other off target effect that we don’t want to see.

That’s what interesting, because when you think of, for example, LC-1, there are requests that seem to be targeting the. But we know that they actually impact step folding effects, other proteins that play a role in one. I wonder if those types of indicators are out there.
Yeah, you could be made, but uh, we don’t have those yet.

Work in progress.

OK. If no more questions. Thank you.