First grand rounds of 2021 and once again continuing our mission doing this. Whether it be in person or by zoom, we're sticking to the schedule and making sure that we advance the mission of disseminating and knowledge through this form.

Today is a really special occasion because it represents something I think we all look forward to the annual Frisbee lectureship and actually to begin the forum I'm going to turn it over to Ed Snider, Doctor Schneider, as you know,
is a professor of laboratory medicine.

Can’t send director for.

For membership director of membership for the Cancer Center,

Leader of blood banking.

Certainly has done a lot of work over the years in that domain and has really been the Shepherd for this lectureship for the past 18 years.

And I want to turn it over to Ed to share some perspectives and as well introduce members of the family.

Thank you very much Charlie to pleasure to introduce the Frisbees for this lectureship.

Rick and Chris Frisby, son Richie,
developed leukemia as a young man that’s a teenager and was the first bone marrow transplant done in the Connecticut. It was done by the late Jill Rappaport, who was running the program at the time. Richie did not survive first transplant failed and didn’t survive to have a second transplant, which was to be his sister. And in honor of him, in his memory, the family Rick and Christine set up the Frisby Foundation. So in 1990 they’ve given millions of dollars in Cancer Research and cancer education. They established the first stem cell processing lab at Yale,
New Haven long before Smilow had the first brick lay down the foundation and that was the precursor of the HCT lab, which is currently supporting SMILLOW in through Department of Laboratory Medicine. Went by Diet Doctor Diane Kraus. This lectureship was established 18 years ago and the current speaker doctor Marcus Motion is therefore the 18th speaker and we welcome him. And we would like to turn it over to Christine to do or say a few words. Of I’ll be brief, I just wanted to really thank Yale Dr Mnuchin, and in particular at Snyder,
who’s been very close to us for many
many years and been very supportive
of the foundation and the work we do.
And we love this lectureship. We don’t.
Foundations must smaller now.
We don’t do that many things,
but this is one thing that we continue doing,
and we’re going to continue to fund
this for years to come because we
think it’s just very rewarding.
So thank you very much, Ed.
Doctor Fox and Marcus as well at
the Commission.
Thank you Rick and Chris for all
that you’ve done and for so much
of the work that is being done for
the patients that smile.

Oh well, we can thank you for setting the foundation for this, so I'll now turn it over to Doctor Fuchs to introduce our 18th. It has been a wonderful tradition. What this lectureship has done is brought to Yale.

It thank you, Ann and Rick and Christine, thank you for your continued support of this important leadership over the past 18 years. I think this is really been a wonderful tradition.
Really rich cadre of innovators in developing understanding new approaches to human logic, which I think is a fitting legacy and this year’s annual Frisbee lecture is no exception to that. Impressive in August, Doctor Marcus musician was previously the chair of the Department of Systems Biology and the Lee Professor. Oh, at the City of Hope Cancer Center, as well as the associate director of Basic Science we were very privileged in the fall of 2020 to bring and recruit Doctor Mission to Yale.
As our inaugural director for the Center of Molecular and Cellular Oncology at the Yale Cancer Center and Smilow Cancer Hospital as well as the author and Isabel Bunker, Professor of Medicine, focused in hematology. Doctor Mission, trained in hematology oncology. His work as his training was both in the biology of human like you put in season Immunobiology. And frankly, over the past decade or really longer, he has been a leading innovator in understanding the evolution of
B cell malignancy's understanding

biology in terms of delivering

new approaches to drug discovery

in these cancers,

Ann and really now advancing that

beyond in terms of the immunobiology

immunotherapy that would be available

for lymphomas and human logic legacies.

Most notably narrow,

even in terms of novel car T therapies,

and I think all of that really

speaks to in many respects what’s so

relevant for the Frisby lectureship

Marcus for his many accomplishments

and impressive publication record

has been received countless awards.
I wouldn’t want to take too much time annunciating all of them, but they include the NCI outstanding Investigator award. Howard, You scholar award, leukemia, Lymphoma Society scholar award. Welcome Trust scholar award. Among many other awards that recognize his accomplishment, an innovative and record of innovation and accomplishment across all of these cancers. So it’s really a pleasure to introduce Marcus and an in many respects. Welcome to the faculty of Ovvio Cancer Center. Orchis, thank you.
Thank you, I’m not sharing my screen.

So first of all, I would like to thank the Frisby family and Charlie for having me here. And since I came to your Cancer Center last year for like I came to experience that many of us who are devoted to the cause of leukemia and young tires. That legacy of Richard D. Frisbie has inspired many of us and today I would like to text opportunity to present a few new findings from our lab that over the past recent years have led to
a new concept that I hope will help us in the future to treat this disease is more efficiently than. We were able to do in the past. And many of our try to leukemias are actually derived from lymphocytes and is a leukemia. In fact, represents the most frequent type of cancer in children and young adults, and one potential reason for that is that B cells during the early development have to go through a series of genetic modifications in error combination class.
switching hypermutation with the end

Generating Pi affinity antibodies

drawn by Powell, Ellie.

She was sitting here in his office

and for those reasons B cells

are an extremely high risk for

500 times higher than any other somatic cell,

and for this reason and also because

humans can actually live without

the lymphocytes for quite some time.

And we developed a research program

that is centered on specific
00:08:43.208 --> 00:08:46.874 vulnerabilities of this very cell type.

00:08:46.880 --> 00:08:48.436 So as cancer researchers,

00:08:48.436 --> 00:08:50.770 we are always looking for vulnerabilities,

00:08:50.770 --> 00:08:54.506 for vulnerabilities.

00:08:53.572 --> 00:08:54.506 and in this case we’re looking

00:08:54.510 --> 00:08:56.628 the nature of the sales making

00:08:56.628 --> 00:09:01.498 antibodies and are selected and

00:08:59.268 --> 00:09:01.498 ANVISA selection is a scene that

00:09:01.498 --> 00:09:04.506 that I hope I will be able

00:09:04.510 --> 00:09:09.805 to present to you on the occasion

00:09:09.805 --> 00:09:14.406 And the reason is that just by the

00:09:14.406 --> 00:09:16.699 random nature of recombination,

00:09:16.700 --> 00:09:18.520 events of antibody encoding
molecules vast majority, about 75% of oil newly generated
visas are initially autoreactive, meaning that their directed against himself and in these cells have to be removed from the repertoire, and this means they have to be powerful mechanisms in place to normal development to destroy and delete yourself from the repertoire. And although arching theme for our research in recent years is, can we actually leverage these mechanisms that are indeed in the life and selection and development of normally lymphocytes for the
00:09:55.781 --> 00:09:59.649 treatment of Pisa, leukemia and lymphoma?

00:09:59.650 --> 00:10:00.376 So in.

00:10:00.376 --> 00:10:00.739 Fact,

00:10:00.739 --> 00:10:02.917 the principle of the cell selection

00:10:02.917 --> 00:10:05.993 is driven by signals from the B cell

00:10:05.993 --> 00:10:08.270 receptor or surface immunolabeling,

00:10:08.270 --> 00:10:11.266 and we like to think of this.

Like I said, Goldilocks principle.

Because only if the signal strength

00:10:11.270 --> 00:10:16.692 that is elicited from this unit

00:10:16.692 --> 00:10:19.290 here is just right,

00:10:19.290 --> 00:10:20.790 then this says receive a positive

00:10:20.790 --> 00:10:23.208 signal and proliferate and survive,

00:10:23.208 --> 00:10:25.430 and this is usually the case

00:10:25.430 --> 00:10:27.788 when we have a
balance between activation signals.

Namely, kinase and phosphatase is.

That achieve this balance.

So if the signal is too weak,

for instance,

gives the first parties are just wrong,

or the receptor itself is not

functional and he says die by neglect.

Now we’re focusing here on

the other end of the scale,

where the signals overwhelmingly strong,

which is typically the case when this

receptor he is engaged by self antigen,

meaning that these receptors

are out reactive.

And these cells could give rise to autoimmune
disease and have to be eliminated.

And so this principle is not only relevant to normal B cell development.

In this cartoon here from a recent publication, shows that in transformed B cells and leukemia and lymphoma the signaling pathway downstream of the beasts are receptors engaged permutations. Every step of the way.

And so today I would like to divide my talk in three areas where we gain information of how we can leverage selection for therapeutic benefits.

One comes from inside that we glean.
from mutations and deletions and visa humorists such as leukemia and lymphoma.

Then inside some clinical trials. So we collaborate with large clinical trial groups in the United States and internationally and look for predictors of clinical outcomes and what we can learn in terms of therapeutic targeting options. And then finally how these complicated oncogenic signaling pathways intersect and how we can leverage these interactions again to undermine oncogenic signaling in these diseases.

So in the first part I’m going to talk about genetic lesions and what
we have done here based on mutation
data from cosmic and other sources
assembled a set of more than 5 million
somatic mutations in 39 different
types of cancer and look at these
mutations from the angle of whether
the mutation introduce a replacement.
Or effect according capacity of the
gene or whether they are silent,
meaning they are not selected for.
And then in all these diseases we
rank the mutations based on these
replacement over silent ratios.
And we do that in a way that ranks US
based on the cell specific ratios.
We end up with typically mutated genes, and these are widely known in B cell tumors like my D8820 and so forth, but was interesting to us that here at the top of the list they actually molecules in the PS3 kindness pass visit our frequently mutated throughout cancer, but are unexpectedly exempted from in B cell tumors, and this activating mutations of the PS3 kinase pathway. And P-10 and then ship one night in inventory. Phosphatases in this pathway. And this is the catalytic subunit.
00:13:45.890 --> 00:13:47.910 of peers with kindness itself.

00:13:47.910 --> 00:13:50.292 So we studied this in multiple different directions,

00:13:50.292 --> 00:13:51.086 but I would like to focus your content because it was just such a subset of striking example and then as we know for a long time, pretend deletions and mutations widely occur throughout many cancer types, but in 925 cases of B cell image leukemia, we didn’t find any of these mutations. And pretending opposers peers to kindness signaling by.
I am targeting Pep 3 which is a central initiator of the PS3 kinase signaling pathway and I will come back later in my talk.

And to study hyperactivation of the PS3 kindness pathway by dilution of 10, we develop the mouse model in our lab based on conditional deletion of the P 10 gene in our leukemia model and unlike what we know and solid tumors, conditional deletion of P. Then we basically compromise malignant.
transformation and then most importantly,
when we wait for leukemia to establish and miles at bear these
tumors and then delete speech engine,
this leads to remission and the mice survive for indefinite periods of time.
We also confirmed that the biochemistry or the premise here is correct because we actually do see increased activity,
increased output of the PSC kindness increased phosphorylation of AKT.
And most importantly,
we used inhibitors that block the PS3 kinase signaling pathways at multiple levels.
Here,
activation of PS3 kinese bicec using the
NOTE Confidence: 0.8061034
sick kinase inhibitor and it's platinum.
NOTE Confidence: 0.8061034
BKM 120 is a pan PSD.
NOTE Confidence: 0.8061034
Kindness never turn easy.
NOTE Confidence: 0.8061034
D 53 E 63 inhibits AKT and all
three of them have in common.
NOTE Confidence: 0.8061034
That’s actually rescuer protect
leukemia cells from sad as that
NOTE Confidence: 0.8061034
Dapon deletion of the P-10 phosphatase?
NOTE Confidence: 0.8061034
So this doesn’t mean that these
compounds are counterproductive in
leukemia because actually quite useful.
NOTE Confidence: 0.8061034
Our interpretation of this
NOTE Confidence: 0.8061034
unexpected result is that.
NOTE Confidence: 0.8061034
I was introduction of those inhibitors
restores signaling equilibrium again, the Goldilocks principle that these cells need, whereas deletion of the 10 alone here introduce a drastic perturbation which engages negative selection just as it does for the elimination of Hartree active users. We are hopeful that these ideas these concepts will eventually make their way into the clinic, and as an early indication that might indeed be the case, I’m showing you two promising preclinical results in our lab,
both based on small molecule inhibitors

00:17:00.843 -> 00:17:04.067 ship one inhibited by 3A amino color stain,

00:17:10.949 -> 00:17:13.873 inhibitor and both of them have

00:17:20.652 -> 00:17:23.939 burden control for long periods of time,

00:17:25.056 -> 00:17:27.846 extension or prolongation of overall

00:17:35.810 -> 00:17:38.552 So we’re hoping that this approach

00:17:41.210 can be developed further in and
00:17:41.210 --> 00:17:43.442 that some of these compounds will
make it into the clinical arena.

00:17:43.442 --> 00:17:48.830 Now the central premise of this
idea is that this is a mechanism.

00:17:48.830 --> 00:18:01.176 and to test this premise we performed
a reprogramming experience.

00:18:05.590 --> 00:18:09.325 And in which we should use the VPI flower,
just a transcription factor that can
transform besides into macrophages.

00:18:13.480 --> 00:18:16.640 And this is shown here besides expressed in
and this marker here is lost overtime

00:18:20.163 --> 00:18:23.437 after induction and in favor of Mach one,
which is a macrophage marker. And indeed, after sometimes you say it, start to crawl around on the bottom LCS dishes and like macrophages and can even phagocytose and importantly. Coming back to our hypothesis, if you genetically delete P, The reprogramming from B to Milo to be 2. Macrophage fade almost entirely removes the sensitivity of these cells to removal of source phosphatases, which makes sense because fact macrophages don’t make autoantibodies, there’s no need for macrophages to be negatively selected as beast cells are.
So this gives us confidence that this is a real mechanism that is reflective of the nature of the immune system to purge. Attractive sales and that is possible to selectively target this vulnerability in B cell tumors. Now in this work was done by Gen. John Shannon, our lab, and when he worried that this is not just counterintuitive because you essentially doing the opposite from what everyone else is doing in this field, namely by instead of inhibiting kinases. VR Pro activating kinases. But most importantly,
what was worried about what happens
NOTE Confidence: 0.7699414
if he hyper activate kinases for
NOTE Confidence: 0.7699414
long periods of time,
NOTE Confidence: 0.7699414
because that in itself could be dangerous,
NOTE Confidence: 0.7699414
so he did an experiment to figure out
NOTE Confidence: 0.7699414
what is the shortest period of time.
NOTE Confidence: 0.7699414
Home to commit Visa is to say this and he
NOTE Confidence: 0.7699414
did this with an engineered hyperactive.
NOTE Confidence: 0.7699414
Formosa sick kinase.
NOTE Confidence: 0.7699414
Labeled here as GFP.
NOTE Confidence: 0.7699414
If you bring in this hyper active
NOTE Confidence: 0.7699414
kinase in the presence of stickiness,
NOTE Confidence: 0.7699414
inhibitors of GFP labeled cells
NOTE Confidence: 0.7699414
remain constant,
NOTE Confidence: 0.7699414
’cause there’s no hyperactivation
NOTE Confidence: 0.7699414
of the pathway.
Now, if we wash out the inhibitor cells as expected, rapidly die, and he found that if there's a lapse of just three hours, so removal of simulator for three hours and then adding it right back that already is sufficient to commit the sales, that will be our goal going forward too. Target is short. Strong exposure to hyperactivation probably was click or only dated compounds that have a short plasma half life. Now in the second part of my talk, I’m going to give you 2 examples of how
we can learn from information within clinical trials and gene expression, annotation related to outcome. So what approach is based on microarray data that we obtain? Collaboration was a clinical study. Groups and much of this works also publicly available. And for each of these micro area probe sets that measure expression of individual transcripts, we divide the patient courts and the two groups based on higher than median versus lower than median expression in these clinical trials. And then we asked the question,
is there a difference between those two groups in terms of clinical outcome? And if the outcome is more favorable, we have here a blue annotation and its outcome is more poor, shorter overall survival. For instance, we have a red annotation and if the group this heat map based on the site specific annotations we come up with a list of genes that became interesting to us and he at the very top is 1 molecule that I’m going to spend the next couple minutes on the L2 receptor Alpha chain, also known as C25.
So that was a bit unexpected.

Becausw CD 25 is known as one of the three chains of the L2 receptor.

Anna typically pairs with the better chain in the gamma chain to form a trimeric receptor, and this was step was active on T cells and in cases.

And it’s also important for formation of regulatory T cells or T. Rex, and therefore therefore important to prevent autoimmunity.

Again, important to be self selection.

Then if you look at individual visa diseases, pediatric B cell, leukemia, CLL, Podiatry, pizza, leukemia,
NOTE Confidence: 0.77276397
00:22:48.884 --> 00:22:50.438 mantle cell lymphoma,
NOTE Confidence: 0.77276397
00:22:50.440 --> 00:22:53.015 we see consistent pattern that
NOTE Confidence: 0.77276397
00:22:53.015 --> 00:22:55.590 the lower half of expression
NOTE Confidence: 0.77276397
00:22:55.678 --> 00:22:58.208 is related to better outcome.
NOTE Confidence: 0.77276397
00:22:58.210 --> 00:23:01.500 The top half towards outcome.
NOTE Confidence: 0.77276397
00:23:01.500 --> 00:23:03.636 The other reason we became interested
NOTE Confidence: 0.77276397
00:23:03.636 --> 00:23:06.498 is that if you bring in Uncle Gene,
NOTE Confidence: 0.77276397
00:23:06.500 --> 00:23:07.601 said drive, leukemia,
NOTE Confidence: 0.77276397
00:23:07.601 --> 00:23:10.430 lymphoma like these are able or LMP 2A.
NOTE Confidence: 0.77276397
00:23:10.430 --> 00:23:12.130 This leads to upregulation
NOTE Confidence: 0.77276397
NOTE Confidence: 0.77276397
00:23:14.680 --> 00:23:17.216 And also it seems to play a role
NOTE Confidence: 0.77276397
00:23:17.216 --> 00:23:19.360 in resale developmented save.
NOTE Confidence: 0.77276397
00:23:19.360 --> 00:23:23.910 So he profile here see 25 M on A levels.
NOTE Confidence: 0.77276397
00:23:23.910 --> 00:23:26.058 Over the course of the sale
NOTE Confidence: 0.77276397
development we find here is striking. And that's interesting, because if you look at C25 knockout mice, which we did in our lab. Compare this to the wild type. But distractions entirely missing in the knockout mice and can also see this here. This is a defect here. We still don't know what this actually means, but we also find that later in development he says actually are over represented in fraction F. So our initial hypothesis was this might
reflect previously unrecognized role of IL two signaling in B cells and. I mean, so we repeated this experiment with mice that have intact City 25, but are lacking the L2 cytokine. But contrary to our hypothesis fraction, D&F are just fine and be so development is completely unperturbed in these mice. And I’ll see you in this proximity ligation analysis, we find that C25 does actually not bind to any of those other change of the L2 receptor and does not respond to iron tools.
So it’s not true that C.

We found in our proximity ligation assay, we found City 25 associate itself. With a signal image chain of the B cell receptor, which again is responsible for the Goldilocks principle to keep intact and equilibrium and intermediate ram of signaling intensity.

This is actually ongoing work in our lab.
by Jay,

wrongly with a research scientist

And what he found is actually their CIA.

25 negatively regulates B cell

activation and in the absence of CD 25.

Miles,

so even without any immunization,

these B cells are autoreactive.

Their escape negative selection

and therefore more attractive,

spontaneous germinal centers

that are antigen independent.

The other observation here was that if
Jerome deleted 325 in human lymphoma sales, they undergo a particular pattern of autonomous calcium signaling. They have autonomous activation. Do sales are proliferating very fast, but also for short half life and I quickly, which is reflected here by expression of PG restore parenting. These cells are. Just easily exhausted and in that competitive fitness, so we confirmed this here in a leukemia model whereby we transformed. 25 mouse cells with the flux see 25 every year and then after activation of query is illusia CD 25 expression.
00:26:40.201 --> 00:26:43.995 on the surface and then soon after
NOTE Confidence: 0.80370665
00:26:43.995 --> 00:26:46.484 this says disappear from culture.
NOTE Confidence: 0.80370665
00:26:46.484 --> 00:26:49.760 They failed to form any colonies that
NOTE Confidence: 0.80370665
00:26:49.843 --> 00:26:52.413 cannot initiate leukemia and mice
NOTE Confidence: 0.80370665
00:26:52.413 --> 00:26:55.538 that bears also leukemias recover and
NOTE Confidence: 0.80370665
00:26:55.538 --> 00:26:58.364 survive for indefinite periods of time.
NOTE Confidence: 0.80370665
00:26:58.370 --> 00:26:59.240 Now, Interestingly,
NOTE Confidence: 0.80370665
00:26:59.240 --> 00:27:01.415 and that’s coming back to
NOTE Confidence: 0.80370665
00:27:01.415 --> 00:27:04.910 signaling feedback control,
NOTE Confidence: 0.80370665
00:27:04.910 --> 00:27:08.032 City 25 in a similar way like
NOTE Confidence: 0.80370665
00:27:08.032 --> 00:27:10.546 deletion of P-10 and ship one,
NOTE Confidence: 0.80370665
00:27:10.550 --> 00:27:14.470 we see that the balance of ether
NOTE Confidence: 0.80370665
00:27:14.470 --> 00:27:16.150 receptor signaling strength.
NOTE Confidence: 0.80370665
00:27:16.150 --> 00:27:18.784 It’s lost cause we have hyper
NOTE Confidence: 0.80370665
00:27:18.784 --> 00:27:20.540 activation of kinase substrates
NOTE Confidence: 0.80370665
00:27:20.615 --> 00:27:22.920 downstream of the visa receptor,
NOTE Confidence: 0.80370665
00:27:22.920 --> 00:27:27.078 including sick and then loss of phosphatase
NOTE Confidence: 0.80370665
00:27:27.078 --> 00:27:30.630 activity markers for P-10 and ship one.
NOTE Confidence: 0.80370665
00:27:30.630 --> 00:27:32.635 So we think those phenomena
NOTE Confidence: 0.80370665
00:27:32.635 --> 00:27:34.239 might actually be related,
NOTE Confidence: 0.80370665
00:27:34.240 --> 00:27:37.400 but CD 25 plays a role in maintaining
NOTE Confidence: 0.80370665
00:27:37.400 --> 00:27:39.514 the Goldilocks principle by
NOTE Confidence: 0.80370665
00:27:39.514 --> 00:27:41.998 regulating kinases and phosphatases.
NOTE Confidence: 0.80370665
00:27:42.000 --> 00:27:42.336 Now,
NOTE Confidence: 0.80370665
00:27:42.336 --> 00:27:43.680 how is this possible?
NOTE Confidence: 0.80370665
00:27:43.680 --> 00:27:46.956 So the tail of CD 25 is very short
NOTE Confidence: 0.80370665
00:27:46.956 --> 00:27:50.497 here and it’s just 13 amino acids and.
NOTE Confidence: 0.80370665
00:27:50.500 --> 00:27:55.000 So we looked at what City 25 might bind to.
NOTE Confidence: 0.80370665
00:27:55.000 --> 00:27:57.556 How does it interact with the
NOTE Confidence: 0.80370665
00:27:57.556 --> 00:28:00.086 cytoplasmic tail and as a negative
control and using this for a lot of different experiments, we introduce a mutation of the central Seren residue which destroys the main protein kinase. He better consensus motive. And here we are using a bio ID approach which is based on fusions between the CD 25 tail and purée, which is a bacterial biotin ligase which attaches bio tends to approximate protein space on the mound and the proximity. And I, as expected, we found that two phosphatases
ship one and PTPN 6 here.

NOTE Confidence: 0.80370665

Are in proximity of the tail of

NOTE Confidence: 0.80370665

CD 25 and this is not the case.

NOTE Confidence: 0.80370665

The tail here is mutated.

NOTE Confidence: 0.80370665

And this is also confirmed here in

NOTE Confidence: 0.80370665

a more traditional experiment based

NOTE Confidence: 0.80370665

on pull down and quiet peace or

NOTE Confidence: 0.80370665

ship 1P-10 and PTPN 6 can or bind.

NOTE Confidence: 0.80370665

But binding this weekend or entirely

NOTE Confidence: 0.80370665

lost when the stay here is mutated.

NOTE Confidence: 0.80370665

So in terms of function,

NOTE Confidence: 0.80370665

this could be confirmed that indeed see

NOTE Confidence: 0.80370665

functioned as a powerful negative

NOTE Confidence: 0.80370665

regulated of signaling strength.

NOTE Confidence: 0.80370665

So if he abusively activate while

NOTE Confidence: 0.80370665

types unify, we can block the kite.
Some signal here that would otherwise be elicited. So he expresses the 25 and it’s wild type form. The signal is delayed and almost entirely lost if they express the mutant. This depression can still be seen, but it’s much less compared to the wild type form. And then in terms of leukemia, survival and growth be used here, cameras between the extracellular part of CD 19, which is a B cell specific
transmembrane protein and tale of users via type or is mutant and wild type form can rescue. Survival of leukemia cells but seven a mutant cannots again showing that ability to recruit phosphatases to negatively regulate signaling is important for survival of these leukemia cells. So we have modeled the interaction between these molecules and came up with the structural model for this, which has rank one scaffold at the center. Wrapped around by PKC better and this interaction,
NOTE Confidence: 0.80648685
00:30:32.880 --> 00:30:35.802 he has facilitated by the C25
NOTE Confidence: 0.80648685
00:30:35.802 --> 00:30:38.300 tear which insert itself here.
NOTE Confidence: 0.80648685
00:30:38.300 --> 00:30:41.506 So overall we think that he says.
NOTE Confidence: 0.80648685
00:30:41.510 --> 00:30:43.910 Activate CD 25 downstream of the
NOTE Confidence: 0.80648685
00:30:46.083 --> 00:30:48.568 visa receptor via sick because
NOTE Confidence: 0.80648685
00:30:48.570 --> 00:30:51.552 which then forms a complex with Raekwon
NOTE Confidence: 0.80648685
00:30:51.552 --> 00:30:54.740 to recruit first parties here to surface.
NOTE Confidence: 0.80648685
00:30:54.740 --> 00:30:57.085 Which then again provide negative
NOTE Confidence: 0.80648685
00:30:57.085 --> 00:31:00.014 feedback control so it’s like a
NOTE Confidence: 0.80648685
00:31:00.014 --> 00:31:03.050 circle that goes back to maintain
NOTE Confidence: 0.80648685
00:31:03.050 --> 00:31:04.568 equilibrium Goldilocks principle
NOTE Confidence: 0.80648685
00:31:04.648 --> 00:31:07.329 again for the survival of the cells.
NOTE Confidence: 0.80648685
00:31:07.330 --> 00:31:11.170 So our conclusion is that we think that
NOTE Confidence: 0.80648685
00:31:11.170 --> 00:31:14.209 negative selection can be leveraged indeed.
NOTE Confidence: 0.80648685

48
For potential therapeutic benefits of.

He said leukemia and lymphoma is avoided because of phosphatases.

So the goal here would be to. Push says that I had the upper limit there or it transformed the after a powerful activation signal over the edge by removing feedback control and balance which will trigger negative selection of what looks like at the level of signaling autoreactive B cells.

Coming back to our.
Database which we find us a very rich resource for new ideas and concepts. You found another interesting outcome predictor that I would like to introduce to you with. It’s a recent publication that just came out a couple weeks ago and that is focused here on a molecule called IIT M3. And it’s interfering inducible transmembrane protein. And as I showed you for C25 to smaller cure is. An outcome predictor in various. He said leukemia and lymphoma subtypes and it’s known for long time.
initially was found as a specifying molecules for primordial germ cells. And then more recently it was found as an antiviral protein that can restrict viral replication. He is shown HIV, but more recent data shows it also important for the restriction of coronavirus and many other viruses, and what was important to us is that is actually used as a diagnostic tool for pediatric leukemia to find patients that are at high risk. So it’s one probe set on a low density array to identify patients at high risk. So we started the function of
items three in a genetic mouse
model and found actually.
Happy says surprisingly,
that are lacking this interferon
ducible transmembrane
I have a defect
in PS3 kind of signaling.
And they are prone to
cell death as shown by P.
activation and loss of PCL too.
And importantly, these cells actually
cannot be properly activated to
undergo affinity maturation.
So here is PNA is a German center marker
which is a throwback for affinity maturation.
In in, in visa here.

So if he smiles are immunized and nicely form germinal centres but if.

He says that by Adoptively transferred are lacking item 3.

The amount of general centers or German centre visa is and subsequent affinity maturation.

Is this drastically reduced?

And the same is true in leukemia, so I have items with efficient leukemia.

Says cannot form colonies.

If Transformers disable or N Ross. There also lacks ability

to initiate leukemia,
And they have a similar phenotype as I showed you in normally says in terms of lack of peers with kindness signaling. Survival and strong expression of death related or checkpoint molecules like P53. So in terms of structure and mechanism, we were able to figure out how it’s regulated in Indy. Lymphocytes is actually very short protein or 433 amino acids in length and we found that it can actually insert itself into the cell membrane. And this happens when I’m downstream. Also visa receptor.
00:35:09.661 --> 00:35:10.338 Lynn,
NOTE Confidence: 0.7593378
00:35:10.338 --> 00:35:13.723 another sack family kinases phosphorylate.
NOTE Confidence: 0.7593378
00:35:13.730 --> 00:35:16.145 I’ve item three at this tyrosine 20s
NOTE Confidence: 0.7593378
00:35:16.145 --> 00:35:18.310 that’s really a central tiersen,
NOTE Confidence: 0.7593378
00:35:18.310 --> 00:35:20.220 which leads to recruitment to
NOTE Confidence: 0.7593378
00:35:20.220 --> 00:35:21.366 the cell membrane,
NOTE Confidence: 0.7593378
00:35:21.370 --> 00:35:23.998 and then it can easily interact
NOTE Confidence: 0.7593378
00:35:23.998 --> 00:35:26.902 with the visa receptor or it
NOTE Confidence: 0.7593378
00:35:26.902 --> 00:35:28.507 becomes internalised again.
NOTE Confidence: 0.7593378
00:35:28.510 --> 00:35:31.128 So for this reason we studied this
NOTE Confidence: 0.7593378
00:35:31.128 --> 00:35:33.476 mutation here and actually found that
NOTE Confidence: 0.7593378
00:35:33.476 --> 00:35:36.150 it can function as an Uncle gene.
NOTE Confidence: 0.7593378
00:35:36.150 --> 00:35:38.733 So when we introduce us for cinematic
NOTE Confidence: 0.7593378
00:35:38.733 --> 00:35:41.745 form of white 20 which mimics the
NOTE Confidence: 0.7593378
00:35:41.745 --> 00:35:44.481 confirmation that is always was formulated.
NOTE Confidence: 0.7593378
00:35:44.490 --> 00:35:46.565 Into a mouse strain that
carries transgenic BCR ABL, which has a very long latency to disease. We actually found that this leads to increased formation of colonies. Increased PS3 kinase activity and also increased activity of the visa receptor signaling pathway. And so structurally, we could show the poisoner interactome analysis that this form of items three intersects with multiple central components of both the PS3 kinase and visa receptor signaling pathway. And there’s also shown here by these red
dots in this proximity ligation assay,

where if I can three molecules come in close proximity. And he says.

Now the structural basis for data set and that was very surprising to us that I’ve item 3 can directly bind to PIP 3 which is initiating phospholipid and lipid rafts to initiate PS3 kinase signaling.

And that is unexpected because this interaction is usually mediated by a so-called pH domain in larger proteins. But I’ve item three is such a short party in that has no resemblance of the pH domain,

so we were looking here for and you
structure basis of houses interaction

could happen in the absence of a pH domain. And we looked at the conserved intracellular loop of five items free that is used to insert into the cell membrane, and in doing so we found a cluster of.

Five basic amino acids and of particular interest is this bracket here would call it between lysing 83 and license and even though they are 21 amino acids apart from each other, they come very close here in the structure analysis, and they’re basically former.
clamp to directly interact here.

With this pit three molecule.

So by mutation analysis we were able to show that the whites are morally cure.

Was this bracket of lice and 83 and license 104 intact?

Is a powerful initiator of PSV kindness and peace a receptor signaling?

But when these two amino acids here are mutated through the brackets along the active, the entire Lee loses ability.

So that’s something that became really interested in that we hope to pursue further in collaboration with our colleagues at.
Yeah, like a new way of how proteins can make contact with Pepsi to initiate PSV kind of signaling in normal and Uncle Genic Lee. Transform B says so. How model is that in the absence of five items, we and normal cells also modeling and says. The molecules that initiate PSU kind of signaling are scattered throughout the cell membrane. Only five items, three is there acting as a molecular glues are drawn together and form a
tight complex to initiate signaling.

I'm not coming to the last part of my talk, which was quite surprising to some of us and Mr. Looking for ways to translate that knowledge.

Looking for houses can be exploited therapeutically, but it essentially starts from the question of how do oncogenic pathways, once activated by mutations? How do they interact and? And this idea is based on a concept that was formulated and long time ago by fear and Vogelstein.
Here’s Arconic concept of Mikey’s sequential acquisition of Driver gene set together, then form the development of colorectal cancer. So the question here is, is this. Is it true that acquisition of additional mutations lead to more malignant phenotypes? And how do these oncogenic pathways interact with each other? So to answer this question, we formed a collaboration with Children psychology Group and Saint Jude. And studied.
Mutation data from one 1148 cases of ecel image PLA.

And what we did first was what you would call a mapping analysis of affinity versus repulsion of pathways. So basically asking the question. Activating lesions in one pathway. Do they have affinity to activation of?

Hidden in a different pathway? Or is there like relationships of mutual exclusivity and we found a number of interactions that we are still working on? But one was really striking to us and it’s an interaction of repulsion of mutual exclusivity,
as shown here in this cartoon. And that involves a stat 5 pathway. The Jack Stat 5 Path pathway and IIRC home up kinase signaling pathway. And here I’m showing you the result based on these 1148 cases. Many of them have shown here in Green Spot 5 activating lesions forming one large cluster up here and then. Here’s another cluster, but these are activating lesions and only in 35 cases which is just feed the spend. We found activation of both pathways, which which is much lower than than random. Also, when we look at individual
00:41:45.056 --> 00:41:47.152 cases and look at phosphorylation of
NOTE Confidence: 0.8212341
00:41:47.152 --> 00:41:49.636 Erk or phosphorylation of stat five,
NOTE Confidence: 0.8212341
00:41:49.640 --> 00:41:52.503 we have a clear cut negative or
NOTE Confidence: 0.8212341
00:41:52.503 --> 00:41:54.077 inverse relationship between them
NOTE Confidence: 0.8212341
00:41:54.077 --> 00:41:56.534 and you can also see here I have to
NOTE Confidence: 0.8212341
00:41:56.603 --> 00:41:58.811 level off Western blot that that
NOTE Confidence: 0.8212341
00:41:58.811 --> 00:42:00.882 you have either force relation or
NOTE Confidence: 0.8212341
00:42:00.882 --> 00:42:02.954 step file for false for work and
NOTE Confidence: 0.8212341
00:42:02.954 --> 00:42:04.806 this leads to different profiles
NOTE Confidence: 0.8212341
00:42:04.806 --> 00:42:07.050 in terms of correct sensitivity so
NOTE Confidence: 0.8212341
00:42:07.116 --> 00:42:09.166 traumatic Nip is American emitter.
NOTE Confidence: 0.8212341
00:42:09.170 --> 00:42:11.330 It was in the herb signaling
NOTE Confidence: 0.8212341
00:42:11.330 --> 00:42:13.260 pathway that effects on these.
NOTE Confidence: 0.8212341
00:42:13.260 --> 00:42:17.806 Leukemias hear worse porn atnip effects,
NOTE Confidence: 0.8212341
00:42:17.806 --> 00:42:18.272 mainly,
NOTE Confidence: 0.8212341
00:42:18.272 --> 00:42:21.068 the stat 5 signaling pathway which
00:42:21.068 --> 00:42:23.609 is affecting those leukemias here.
00:42:23.610 --> 00:42:25.770 And I’m.
00:42:25.770 --> 00:42:28.486 So we became interested in this small
00:42:28.486 --> 00:42:31.388 minority of cases in which we have
00:42:31.388 --> 00:42:33.884 indication of activation of both pathways,
00:42:33.890 --> 00:42:35.920 even though they seem to
00:42:35.920 --> 00:42:37.138 be mutually exclusive.
00:42:37.140 --> 00:42:40.356 So wanted to know who they occur in
00:42:40.356 --> 00:42:43.629 the same say or how does this work?
00:42:43.630 --> 00:42:45.660 And to answer this question,
00:42:45.660 --> 00:42:48.220 or we developed in our lap a single
00:42:48.220 --> 00:42:50.899 self also protein analysis that allows
00:42:50.899 --> 00:42:53.354 us to interrogate her phosphorylation
00:42:53.354 --> 00:42:56.337 of STAT 5 and phosphorylation of Erk.
00:42:56.340 --> 00:42:58.372 Concurrently in single cells,
and this is here based on the gel matrix where we can deposit 6400 cells, single cells and then look at STAT workforce relations events individually and this year or four patient arrived. Cases where we looked at individual sales and were then actually able to determine that even though for all those four cases we get to dual signal by Western blot, if we. Use our single cell for supporting analysis. We see that these are actually two competing clones, 1 colonial start, five Zelda clone, here's org, and that goes for all four cases and we
00:43:41.780 --> 00:43:44.114 don’t see any double expressing cells.
00:43:44.120 --> 00:43:46.255 So our conclusion is at least are
00:43:46.255 --> 00:43:48.339 actually rare by colonial diseases,
00:43:48.340 --> 00:43:51.682 in which two clones are competing
00:43:51.682 --> 00:43:53.353 against each other.
00:43:53.360 --> 00:43:56.753 Then we asked what is the reason for that?
00:43:56.760 --> 00:44:01.716 So what is the underlying mechanism
00:44:01.716 --> 00:44:03.936 that these two pathways just can’t go
00:44:03.940 --> 00:44:05.532 we actually voiced it.
00:44:05.532 --> 00:44:07.920 The alternative pathway on the leukemia
00:44:07.991 --> 00:44:10.364 said are driven by the other pathway,
00:44:10.370 --> 00:44:13.394 meaning that here is a visa able or
00:44:13.394 --> 00:44:16.290 start five driven leukemia then was.
00:44:16.290 --> 00:44:19.282 And Ross, when Ross driven leukemia was VCR
able and use different models for that.

And here, this colony forming assay shows if you have one single driver,

Five pathways is dramatically increases number of colonies,

but if we have posed together, we basically lose or colony formation capability.

The same holds true for growth, so single driver nicely lead to outgrows,

but combination of Bosa suppressive. What was really surprising to us?

that if we use genetic ablation of the diverging or alternative pathway,
even though we basically remove an Uncle Genic driver, this actually Slack celebration of leukemia initiation in this model. So in this case we have here a visa able or start five driven leukemia and we remove perk. This. Accelerates development of leukemia. Likewise in a chaos driven leukemia. Removal of stat 5. Come initiates faster development of looking more Genesis. And biochemically, we were able to recover too late. This was small molecule inhibitors.
that Rametta Nathan MacKinnon bitter.

Distinguishes her kindness as expected.

But it also induces phosphorylation of STAT 5, and rocks.

Litten appears opposite effect.

It distinguishes start 5, but increases per activity.

And so to end here, this final chapter of my talk.

we came across agonists that we use for pharmacological reactivation of diverging pathways.

So in this case BC I hear this, I 215 is so powerful activator, IIRC agonist.

Strongly activates falsework at the
NOTE Confidence: 0.65469474
00:46:15.730 --> 00:46:19.818 expense of start 5 and then DPH here.
NOTE Confidence: 0.65469474
00:46:19.820 --> 00:46:22.725 Is the stat 5 agonist drive start
NOTE Confidence: 0.65469474
00:46:22.725 --> 00:46:24.848 five phosphorylation but at the
NOTE Confidence: 0.65469474
00:46:24.848 --> 00:46:27.254 expense of work and this has
NOTE Confidence: 0.65469474
00:46:27.254 --> 00:46:29.320 interesting activity on the clonal
NOTE Confidence: 0.65469474
00:46:29.320 --> 00:46:31.702 dynamics of these leukemias in vivo.
NOTE Confidence: 0.65469474
00:46:31.710 --> 00:46:34.990 So start five leukemia can be converted into,
NOTE Confidence: 0.65469474
00:46:34.990 --> 00:46:37.040 IIRC, leukemia, and most importantly,
NOTE Confidence: 0.65469474
00:46:37.040 --> 00:46:39.090 if you combine these pathway
NOTE Confidence: 0.65469474
00:46:39.090 --> 00:46:40.730 agonist was conventional treatment.
NOTE Confidence: 0.65469474
00:46:40.730 --> 00:46:41.951 So, for instance,
NOTE Confidence: 0.65469474
00:46:41.951 --> 00:46:43.986 here on Earth inhibitor with
NOTE Confidence: 0.65469474
00:46:43.986 --> 00:46:45.649 a Step 5 agonist,
NOTE Confidence: 0.65469474
00:46:45.650 --> 00:46:47.658 we achieve a dramatic
NOTE Confidence: 0.65469474
00:46:47.658 --> 00:46:49.666 prolongation of overall survival.
NOTE Confidence: 0.65469474
So.
The final conclusion here is that we propose that diversity of signaling input. Is actually an important barrier of malignant transformation and centralization and convergence onto one single pathway. Inactivation of all the other pathways. Is an early and critical step of malignant transformation, and if we achieve. To reinstate at the very signaling environment. That would resemble the interactions of normal cells were sent by him and which have multiple receptors.
Multiple cues from the environment. So we're proposing a strategy of pharmacological reactivation that would restore their diverse signaling environment. And we hope that this approach can also be leveraged to overcome convention mechanisms of black resistance. So here we have passed their convergence minimal. What we called friction and permissive environment for transformation. But here if you have divergent pathways, we actually do have some friction and create a non permissive environment.
And with that I would like to thank a number of collaborators at a dinner, Farber at yeah. And would like to acknowledge particular 2 senior members of my lab. Linda Shannon and Jerome Lee, who did most of the conceptual innovation of this work. Thank you very much. Marcus that’s amazing. Collection of studies and it is remarkable how complex and somewhat almost counter intuitive alot of these pathways are in B cells and be some legacies. And it’s obviously a delicate balance. And let me ask you, ’cause you?
You’ve identified a number of pathways. That I guess are principally designed for B cell elimination. That you could leverage. How would you potentially target those pathways? Or could you target those pathways in conjunction with the growing armamentarium of available therapies for be similar? Concedes that are now in practice? Or could you, could you leverage that combination? Right in terms of potential for translation and how we would leverage
00:49:13.830 --> 00:49:15.846 hyperactivation of Visa receptor
NOTE Confidence: 0.86497533
00:49:15.846 --> 00:49:18.600 signaling to engage negative selection,
NOTE Confidence: 0.86497533
00:49:18.600 --> 00:49:24.290 and I think we have two options, one is.
NOTE Confidence: 0.86497533
00:49:24.290 --> 00:49:26.660 Already available, but less attractive,
NOTE Confidence: 0.86497533
00:49:26.660 --> 00:49:29.882 that would be April inhibition or
NOTE Confidence: 0.86497533
00:49:29.882 --> 00:49:32.930 phosphatases like Ship One and P-10.
NOTE Confidence: 0.86497533
00:49:32.930 --> 00:49:35.972 I’m attractive cause in the field
NOTE Confidence: 0.86497533
00:49:35.972 --> 00:49:38.625 phosphatase innovation raises a lot
NOTE Confidence: 0.86497533
00:49:38.625 --> 00:49:40.809 of questions about specificity.
NOTE Confidence: 0.86497533
00:49:40.810 --> 00:49:43.288 An alternative approach is one that
NOTE Confidence: 0.86497533
00:49:43.288 --> 00:49:46.705 Mark Lemon and I have discussed and that
NOTE Confidence: 0.86497533
00:49:46.705 --> 00:49:49.719 would be to generate a direct agonist
NOTE Confidence: 0.86497533
00:49:49.719 --> 00:49:52.568 of picky kinase like sick or BDK.
NOTE Confidence: 0.86497533
00:49:52.570 --> 00:49:55.530 Something fairly upstream in the
NOTE Confidence: 0.86497533
00:49:55.530 --> 00:49:57.898 visa receptor signaling cascade.
NOTE Confidence: 0.86497533
00:49:57.900 --> 00:50:01.068 So actually yesterday.
I was at a Mark CBI weekly meeting and there was some encouraging feedback that might actually be feasible. So that’s an approach that I would definitely like to pursue in the future to develop a direct hyper agonist or one of these key kindness.

Excellent, thank you so and people should feel free to submit questions on the chat box. Dying cross as a question.

PLA suggested that CD 25 C 79 eight colocalization is

Marcus, I'll just read it.

PLA suggested that CD 25 C

79 eight colocalization is
00:50:37.112 --> 00:50:38.830 predominantly intracellular.
NOTE Confidence: 0.8305846
00:50:38.830 --> 00:50:41.770 What do you think that this indicates?
NOTE Confidence: 0.8182225
00:50:43.440 --> 00:50:46.728 Great questions so.
NOTE Confidence: 0.8182225
00:50:46.730 --> 00:50:50.270 We have done an experiment with.
NOTE Confidence: 0.8182225
00:50:50.270 --> 00:50:53.049 WGA, which is a surface marker and
NOTE Confidence: 0.8182225
00:50:53.049 --> 00:50:55.207 we we actually find colocalization
NOTE Confidence: 0.8182225
00:50:55.207 --> 00:50:58.426 of about 60 to 70% of those
NOTE Confidence: 0.8182225
00:50:58.426 --> 00:51:01.474 interactions with the CD79A and B.
NOTE Confidence: 0.8182225
00:51:01.480 --> 00:51:03.556 So I don’t think it’s predominantly,
NOTE Confidence: 0.8182225
00:51:03.560 --> 00:51:05.212 but the question remains,
NOTE Confidence: 0.8182225
00:51:05.212 --> 00:51:07.690 there’s still a significant amount of
NOTE Confidence: 0.8182225
00:51:07.758 --> 00:51:10.250 interactions that are was in the sale.
NOTE Confidence: 0.8182225
00:51:10.250 --> 00:51:11.774 And you thought, indeed,
NOTE Confidence: 0.8182225
00:51:11.774 --> 00:51:13.298 that is very strange,
NOTE Confidence: 0.8182225
00:51:13.300 --> 00:51:16.114 because why would the visa receptor
NOTE Confidence: 0.8182225
00:51:16.114 --> 00:51:18.798 be internalized or somewhat was in

79
this area associated with CD 25?
And so we can answer this fully.
But in light of the recent study by whose daughter was published in nature two years ago, where he actually shows that in malignant lymphoma B cell receptor signaling forms of endosomal membranes, his Tinder sale. We think that exact same thing might happen here. You don’t know that, but that’s that would be our explanation, so I don’t think it’s predominant. But I agree with Diane that let
00:51:50.383 --> 00:51:51.870 me see intracellular complexes,
NOTE Confidence: 0.8182225
00:51:51.870 --> 00:51:54.110 and we think they’re an endo zones.
NOTE Confidence: 0.82619333
00:51:55.360 --> 00:51:57.556 Thank you and Diana’s second question,
NOTE Confidence: 0.82619333
00:51:57.560 --> 00:52:00.302 which is CD 25 seems to
NOTE Confidence: 0.82619333
00:52:00.302 --> 00:52:01.216 prevent autoreactivity.
NOTE Confidence: 0.82619333
00:52:01.220 --> 00:52:03.800 Do you think this is related
NOTE Confidence: 0.82619333
00:52:03.800 --> 00:52:06.820 to CD-25 CD 79 interaction?
NOTE Confidence: 0.82619333
00:52:06.820 --> 00:52:11.128 Does it? Does C25 interact with
NOTE Confidence: 0.82619333
00:52:11.128 --> 00:52:13.750 surface immuno globulin’s? I’m.
NOTE Confidence: 0.826858489
00:52:14.360 --> 00:52:16.610 So. That’s actually a question
NOTE Confidence: 0.826858489
00:52:16.610 --> 00:52:18.860 that I asked Eric Metra,
NOTE Confidence: 0.826858489
00:52:18.860 --> 00:52:20.695 who’s my collaborator in the
NOTE Confidence: 0.826858489
00:52:20.695 --> 00:52:22.163 field of autoimmune diseases,
NOTE Confidence: 0.826858489
00:52:22.170 --> 00:52:24.378 so Eric told us at 3:25,
NOTE Confidence: 0.826858489
00:52:24.380 --> 00:52:26.744 and that’s known by work from
NOTE Confidence: 0.826858489
00:52:26.744 --> 00:52:29.390 from his group and also others.
It is crucial to maintain central visa tolerance so that molecule is not there anymore. Then central tolerance mechanisms don’t work. I think our signaling studies just about to clarify how this. Actually, you know what this mechanism of that? I think the link or how C25 interferes with Visa receptor signaling is not known in our paper is not published yet, so we’re still working on that. Honey. And I do think, actually,
that it doesn’t act in
NOTE Confidence: 0.826858489
service in the global India.
NOTE Confidence: 0.8513638
And again, people should
NOTE Confidence: 0.8513638
submit their questions online.
NOTE Confidence: 0.8513638
Marcus, I mean, could you ever
conceive of you know you identify a?
NOTE Confidence: 0.8513638
Be so malignancy that’s driven by
NOTE Confidence: 0.8513638
jackstadt and you would give them,
NOTE Confidence: 0.8513638
IIRC activator.
NOTE Confidence: 0.8513638
You know I obviously we focus on how
NOTE Confidence: 0.8513638
to inhibit the pathway in cancer,
NOTE Confidence: 0.8513638
but is that something you could
NOTE Confidence: 0.8513638
conceive as a therapeutic approach?
NOTE Confidence: 0.8390908
If I may quote back on my slides
NOTE Confidence: 0.8390908
because there’s one that I want
NOTE Confidence: 0.8390908
to show you. This is study.
Yeah, this study heals. Come by Veronica.

Sex is group so that did you want to share your slide or? Yes, I'm going to show this slide again.

OK, so I hope I got the question correct. This is what I would like to refer. It's a study by the only car sex is cool. That it's a trial for patients was NPN, and they received rocks. Start fires inhibitor over long periods of time is actually going opposite direction, so they found that these patients developed in 6% of nine patients out.
of 157 was NP ND well developed hybrid
diesel lymphoma that were driven with Keras.
And that's a 15 fold increase risk.

So what they said in this study
Population of the Start 5 pathway enables.
The transformation of the pre
malignant B cell tumor that carries
the Chaos Legion that essentially
what we did in our genetic experiment.
So I think it can cut both ways so it
can be beneficial if he find ways to
leverage this activity to completely
suppress oncogenic signaling.
But like Veronicas NPN study shows,
it can also go in your opposite
direction if you try to achieve long-term suppression of 1 pathway, you might inadvertently activate the other. So it’s really interesting. ’cause obviously if you’re going to use ruxolitinib you, it’s context may be very specific. I mean, I know it’s a small proportion, but that’s a pretty heart risk. Just waiting to see if any other questions. Well, I think we’re you know, really, at the top of the hour, so you know, want to thank Mark is for it really is an extraordinary talk. That’s creating so much insight
into the biology of AB cells.

Both respect to cancer and autoimmunity.

Wanna thank Doctor, Snyder, and Snyder for sort of share continuing to lead this lectureship?

And I want to thank the Frisbees for their continued support of our Cancer Center and the mission and the support of this lecture.

I wish you all a great day and happy New year.

Thank you. Thank you very much. Thank you Marcus. Take care.