WEBVTT NOTE duration:"00:56:25.0880000" NOTE language:en-us NOTE Confidence: 0.8616084 00:00:00.000 --> 00:00:03.296 First grand rounds of 2021 and once again NOTE Confidence: 0.8616084 $00{:}00{:}03.296 \dashrightarrow 00{:}00{:}05.889$ continuing our our mission doing this. NOTE Confidence: 0.8616084 00:00:05.890 - 00:00:09.218 Whether it be in person or by zoom, NOTE Confidence: 0.8616084 $00:00:09.220 \rightarrow 00:00:11.265$ we're sticking to the schedule NOTE Confidence: 0.8616084 $00{:}00{:}11.265 \dashrightarrow 00{:}00{:}14.397$ and making sure that we we advance NOTE Confidence: 0.8616084 00:00:14.397 - 00:00:16.401 the mission of disseminating NOTE Confidence: 0.8616084 $00{:}00{:}16{.}401 \dashrightarrow 00{:}00{:}18{.}860$ and knowledge through this form. NOTE Confidence: 0.8616084 $00{:}00{:}18.860 \dashrightarrow 00{:}00{:}21.710$ Today is a really special occasion NOTE Confidence: 0.8616084 00:00:21.710 --> 00:00:24.039 because it represents something I NOTE Confidence: 0.8616084 $00:00:24.039 \rightarrow 00:00:26.510$ think we all look forward to the NOTE Confidence: 0.8616084 $00{:}00{:}26.510 \dashrightarrow 00{:}00{:}28.080$ annual Frisbee lectures hip and NOTE Confidence: 0.8616084 $00:00:28.080 \dashrightarrow 00:00:30.852$ actually to begin the forum I I'm NOTE Confidence: 0.8616084 00:00:30.852 --> 00:00:34.134 going to turn it over to Ed Snider, NOTE Confidence: 0.8616084 00:00:34.140 --> 00:00:36.210 Doctor Schneider, as you know,

- NOTE Confidence: 0.8616084
- $00:00:36.210 \rightarrow 00:00:40.578$ is a professor of laboratory medicine.

 $00:00:40.580 \longrightarrow 00:00:42.020$ Can't send director for.

NOTE Confidence: 0.8616084

 $00:00:42.020 \longrightarrow 00:00:43.460$ For membership director of

NOTE Confidence: 0.8616084

 $00:00:43.460 \rightarrow 00:00:45.260$ membership for the Cancer Center,

NOTE Confidence: 0.8616084

 $00:00:45.260 \longrightarrow 00:00:46.688$ Leader of blood banking.

NOTE Confidence: 0.8616084

 $00:00:46.688 \rightarrow 00:00:49.243$ Certainly has done a lot of work

NOTE Confidence: 0.8616084

 $00:00:49.243 \rightarrow 00:00:51.602$ over the years in that domain and

NOTE Confidence: 0.8616084

 $00:00:51.602 \rightarrow 00:00:54.200$ has really been the Shepherd for this

NOTE Confidence: 0.8616084

 $00:00:54.200 \longrightarrow 00:00:56.338$ lectureship for the past 18 years.

NOTE Confidence: 0.8616084

 $00{:}00{:}56.338 \dashrightarrow 00{:}00{:}59.335$ And I want to turn it over to Ed to

NOTE Confidence: 0.8616084

 $00{:}00{:}59{.}335 \dashrightarrow 00{:}01{:}01{.}861$ share some perspectives and as well

NOTE Confidence: 0.8616084

 $00{:}01{:}01{.}861 \dashrightarrow 00{:}01{:}03{.}979$ introduce members of the family.

NOTE Confidence: 0.7952434

 $00{:}01{:}04.790 \dashrightarrow 00{:}01{:}07.724$ Thank you very much Charlie to pleasure to

NOTE Confidence: 0.7952434

 $00{:}01{:}07{.}724 \dashrightarrow 00{:}01{:}09{.}926$ introduce the Frisbees for this lecture ship.

NOTE Confidence: 0.7952434

00:01:09.930 --> 00:01:12.126 Rick and Chris Frisby, son Richie,

 $00{:}01{:}12{.}130 \dashrightarrow 00{:}01{:}14{.}545$ developed leukemia as a young man that's

NOTE Confidence: 0.7952434

 $00{:}01{:}14.545 \dashrightarrow 00{:}01{:}17.553$ a teenager and was the first bone marrow

NOTE Confidence: 0.7952434

 $00:01:17.553 \dashrightarrow 00:01:19.463$ transplant done in the Connecticut.

NOTE Confidence: 0.7952434

 $00:01:19.470 \dashrightarrow 00:01:22.406$ It was done by the late Jill Rappaport,

NOTE Confidence: 0.7952434

 $00:01:22.410 \rightarrow 00:01:25.938$ who was running the program at the time.

NOTE Confidence: 0.7952434

00:01:25.940 --> 00:01:27.940 Richie did not survive first

NOTE Confidence: 0.7952434

 $00{:}01{:}27{.}940 \dashrightarrow 00{:}01{:}29{.}540$ transplant failed and didn't

NOTE Confidence: 0.7952434

 $00:01:29.540 \rightarrow 00:01:31.730$ survive to have a second transplant,

NOTE Confidence: 0.7952434

 $00{:}01{:}31{.}730 \dashrightarrow 00{:}01{:}34{.}046$ which was to be his sister.

NOTE Confidence: 0.7952434

00:01:34.050 --> 00:01:37.180 And in honor of him, in his memory,

NOTE Confidence: 0.7952434

 $00{:}01{:}37{.}180 \dashrightarrow 00{:}01{:}39{.}580$ the family rich Rick and Christine

NOTE Confidence: 0.7952434

 $00:01:39.580 \longrightarrow 00:01:41.949$ set up the Frisby Foundation.

NOTE Confidence: 0.7952434

 $00:01:41.950 \longrightarrow 00:01:45.678$ So in 1990 they've given millions of dollars

NOTE Confidence: 0.7952434

 $00{:}01{:}45.678$ --> $00{:}01{:}49.298$ in Cancer Research and cancer education.

NOTE Confidence: 0.7952434

 $00:01:49.300 \rightarrow 00:01:51.390$ They established the first stem

NOTE Confidence: 0.7952434

 $00:01:51.390 \rightarrow 00:01:53.480$ cell processing lab at Yale,

 $00:01:53.480 \rightarrow 00:01:56.392$ New Haven long before Smilow had the

NOTE Confidence: 0.7952434

 $00{:}01{:}56{.}392 \dashrightarrow 00{:}01{:}59{.}416$ first brick lay down the foundation and

NOTE Confidence: 0.7952434

 $00:01:59.416 \rightarrow 00:02:02.680$ that was the precursor of the HCT lab,

NOTE Confidence: 0.7952434

 $00{:}02{:}02{.}680 \dashrightarrow 00{:}02{:}05{.}098$ which is currently supporting SMILOW in

NOTE Confidence: 0.7952434

00:02:05.098 --> 00:02:07.270 through Department of Laboratory Medicine.

NOTE Confidence: 0.7952434

 $00:02:07.270 \dashrightarrow 00:02:09.778$ Went by Diet Doctor Diane Kraus.

NOTE Confidence: 0.7952434

 $00:02:09.780 \longrightarrow 00:02:11.900$ This lectureship was established 18

NOTE Confidence: 0.7952434

 $00:02:11.900 \dashrightarrow 00:02:14.519$ years ago and the current speaker

NOTE Confidence: 0.7952434

00:02:14.519 $-\!\!>$ 00:02:16.669 doctor Marcus Motion is therefore

NOTE Confidence: 0.7952434

 $00{:}02{:}16.669 \dashrightarrow 00{:}02{:}19.509$ the 18th speaker and we welcome him.

NOTE Confidence: 0.7952434

 $00{:}02{:}19{.}510 \dashrightarrow 00{:}02{:}22{.}345$ And we would like to turn it over to

NOTE Confidence: 0.7952434

 $00{:}02{:}22{.}345 \dashrightarrow 00{:}02{:}24{.}436$ Christine to do or say a few words.

NOTE Confidence: 0.7952434

00:02:24.440 --> 00:02:25.684 Of I'll be brief,

NOTE Confidence: 0.7952434

00:02:25.684 --> 00:02:28.326 I just wanted to really thank Yale Dr

NOTE Confidence: 0.7952434

00:02:28.326 --> 00:02:30.310 Mnuchin, and in particular at Snyder,

 $00:02:30.310 \longrightarrow 00:02:32.758$ who's been very close to us for many

NOTE Confidence: 0.7952434

 $00{:}02{:}32.758 \dashrightarrow 00{:}02{:}34.871$ many years and been very supportive

NOTE Confidence: 0.7952434

 $00{:}02{:}34.871 \dashrightarrow 00{:}02{:}37.479$ of the foundation and the work we do.

NOTE Confidence: 0.7952434

 $00{:}02{:}37{.}480 \dashrightarrow 00{:}02{:}39{.}762$ And we love this lectures hip. We don't.

NOTE Confidence: 0.7952434

 $00:02:39.762 \dashrightarrow 00:02:41.066$ Foundations must smaller now.

NOTE Confidence: 0.7952434

 $00:02:41.070 \longrightarrow 00:02:43.020$ We don't do that many things,

NOTE Confidence: 0.7952434

 $00:02:43.020 \rightarrow 00:02:45.954$ but this is one thing that we continue doing,

NOTE Confidence: 0.7952434

 $00:02:45.960 \dashrightarrow 00:02:48.102$ and we're going to continue to fund

NOTE Confidence: 0.7952434

00:02:48.102 --> 00:02:50.446 this for years to come because we

NOTE Confidence: 0.7952434

 $00:02:50.446 \longrightarrow 00:02:52.146$ think it's just very rewarding.

NOTE Confidence: 0.7952434

00:02:52.150 --> 00:02:54.325 So thank you very much, Ed.

NOTE Confidence: 0.7952434

 $00{:}02{:}54{.}325 \dashrightarrow 00{:}02{:}58{.}140$ Doctor Fox and Marcus as well at

NOTE Confidence: 0.7952434

 $00{:}02{:}58{.}140 \dashrightarrow 00{:}02{:}59{.}230$ the Commission.

NOTE Confidence: 0.7952434

00:02:59.230 --> 00:03:01.344 Thank you Rick and Chris for all

NOTE Confidence: 0.7952434

 $00{:}03{:}01{.}344 \dashrightarrow 00{:}03{:}03{.}330$ that you've done and for so much

NOTE Confidence: 0.7952434

 $00:03:03.330 \longrightarrow 00:03:05.590$ of the work that is being done for

- NOTE Confidence: 0.7952434
- $00{:}03{:}05{.}590 \dashrightarrow 00{:}03{:}06{.}946$ the patients that smile.

 $00:03:06.950 \longrightarrow 00:03:07.476$ Oh well,

NOTE Confidence: 0.7952434

 $00:03:07.476 \longrightarrow 00:03:09.317$ we can thank you for for setting

NOTE Confidence: 0.7952434

 $00:03:09.317 \longrightarrow 00:03:10.810$ the foundation for this,

NOTE Confidence: 0.7952434

 $00{:}03{:}10.810 \dashrightarrow 00{:}03{:}13.266$ so I'll now turn it over to Doctor

NOTE Confidence: 0.7952434

 $00:03:13.266 \longrightarrow 00:03:15.319$ Fuchs to introduce our 18th.

NOTE Confidence: 0.7952434

 $00:03:15.320 \dashrightarrow 00:03:17.820$ Frisbee lecturer Doctor Marcus machine.

NOTE Confidence: 0.7953831

00:03:18.370 --> 00:03:21.466 It thank you, Ann and Rick and Christine,

NOTE Confidence: 0.7953831

00:03:21.470 --> 00:03:23.595 thank you for your continued

NOTE Confidence: 0.7953831

 $00{:}03{:}23.595 \dashrightarrow 00{:}03{:}25.295$ support of this important

NOTE Confidence: 0.7953831

00:03:25.295 -> 00:03:27.286 leadership over the past 18 years.

NOTE Confidence: 0.7953831

 $00{:}03{:}27.290 \dashrightarrow 00{:}03{:}29.618$ I think this is really been

NOTE Confidence: 0.7953831

 $00{:}03{:}29{.}618 \dashrightarrow 00{:}03{:}30{.}782$ a wonderful tradition.

NOTE Confidence: 0.7953831

 $00{:}03{:}30{.}790 \dashrightarrow 00{:}03{:}32{.}910$ Because, what this lectures hip

NOTE Confidence: 0.7953831

 $00:03:32.910 \longrightarrow 00:03:36.090$ has done is brought to Yale.

00:03:36.090 --> 00:03:38.760 Really rich cadre of innovators NOTE Confidence: 0.7953831 00:03:38.760 --> 00:03:40.896 in developing understanding an NOTE Confidence: 0.7953831 00:03:40.896 --> 00:03:43.619 new approaches to human logic, NOTE Confidence: 0.7953831 $00:03:43.620 \rightarrow 00:03:47.572$ religion sees which I think is a fitting NOTE Confidence: 0.7953831 $00:03:47.572 \rightarrow 00:03:50.945$ legacy and this year's annual Frisbee NOTE Confidence: 0.7953831 $00:03:50.945 \rightarrow 00:03:54.371$ lecture is no exception to that. NOTE Confidence: 0.7953831 00:03:54.380 --> 00:03:55.994 Impressive in August, NOTE Confidence: 0.7953831 $00:03:55.994 \rightarrow 00:03:57.608$ List of lecturers. NOTE Confidence: 0.7953831 00:03:57.610 --> 00:04:00.605 Doctor Marcus musician was previously NOTE Confidence: 0.7953831 00:04:00.605 - 00:04:04.231 the chair of the Department of NOTE Confidence: 0.7953831 $00:04:04.231 \rightarrow 00:04:07.465$ Systems Biology and the Lee Professor. NOTE Confidence: 0.7953831 00:04:07.470 --> 00:04:10.926 Oh, at the City of Hope Cancer Center, NOTE Confidence: 0.7953831 $00:04:10.930 \longrightarrow 00:04:13.540$ as well as the associate director NOTE Confidence: 0.7953831 $00:04:13.540 \longrightarrow 00:04:16.495$ of Basic Science an we were very NOTE Confidence: 0.7953831 00:04:16.495 --> 00:04:19.704 privileged in the fall of 2020 to bring NOTE Confidence: 0.7953831 00:04:19.704 --> 00:04:22.590 and recruit Doctor Mission to Yale.

- NOTE Confidence: 0.7953831
- $00:04:22.590 \dashrightarrow 00:04:25.122$ As our inaugural director for the
- NOTE Confidence: 0.7953831
- $00{:}04{:}25{.}122 \dashrightarrow 00{:}04{:}27{.}342$ Center of Molecular and Cellular
- NOTE Confidence: 0.7953831
- $00:04:27.342 \rightarrow 00:04:30.054$ Oncology at the Yale Cancer Center
- NOTE Confidence: 0.7953831
- $00:04:30.054 \rightarrow 00:04:32.696$ and Smilow Cancer Hospital as well
- NOTE Confidence: 0.7953831
- $00:04:32.696 \rightarrow 00:04:35.114$ as the author and Isabel Bunker,
- NOTE Confidence: 0.7953831
- 00:04:35.120 --> 00:04:37.988 Professor of Medicine, focused in hematology.
- NOTE Confidence: 0.7953831
- 00:04:37.990 --> 00:04:38.916 Doctor Mission,
- NOTE Confidence: 0.7953831
- 00:04:38.916 --> 00:04:40.768 trained in hematology oncology.
- NOTE Confidence: 0.7953831
- $00{:}04{:}40.770 \dashrightarrow 00{:}04{:}43.955$ His work as his training was both
- NOTE Confidence: 0.7953831
- 00:04:43.955 --> 00:04:47.597 in the biology of human like you
- NOTE Confidence: 0.7953831
- 00:04:47.597 --> 00:04:49.777 put in season Immunobiology.
- NOTE Confidence: 0.7953831
- 00:04:49.780 --> 00:04:50.810 And frankly,
- NOTE Confidence: 0.7953831
- $00:04:50.810 \longrightarrow 00:04:54.415$ over the past decade or really longer,
- NOTE Confidence: 0.7953831
- $00:04:54.420 \longrightarrow 00:04:57.390$ he has been a leading innovator
- NOTE Confidence: 0.7953831
- $00:04:57.390 \rightarrow 00:04:59.984$ in understanding the evolution of
- NOTE Confidence: 0.7953831

00:04:59.984 --> 00:05:02.120 B cell malignancy's understanding

NOTE Confidence: 0.7953831

 $00:05:02.120 \longrightarrow 00:05:04.790$ biology in terms of delivering

NOTE Confidence: 0.7953831

00:05:04.878 - 00:05:07.373 new approaches to drug discovery

NOTE Confidence: 0.7953831

 $00:05:07.373 \longrightarrow 00:05:08.870$ in these cancers,

NOTE Confidence: 0.7953831

 $00{:}05{:}08.870 \dashrightarrow 00{:}05{:}11.384$ Ann and really now advancing that

NOTE Confidence: 0.7953831

 $00{:}05{:}11{.}384 \dashrightarrow 00{:}05{:}14{.}322$ beyond in terms of the immunobiology

NOTE Confidence: 0.7953831

 $00{:}05{:}14.322 \dashrightarrow 00{:}05{:}17.262$ immuno therapy that would be available

NOTE Confidence: 0.7953831

 $00:05:17.262 \rightarrow 00:05:20.808$ for lymphomas and human logic legacies.

NOTE Confidence: 0.7953831

00:05:20.810 --> 00:05:21.968 Most notably narrow,

NOTE Confidence: 0.7953831

 $00{:}05{:}21.968 \dashrightarrow 00{:}05{:}25.540$ even in terms of novel car T the rapies,

NOTE Confidence: 0.7953831

 $00{:}05{:}25{.}540 \dashrightarrow 00{:}05{:}27{.}668$ and I think all of that really

NOTE Confidence: 0.7953831

 $00{:}05{:}27.668 \dashrightarrow 00{:}05{:}30.527$ speaks to in many respects what's so

NOTE Confidence: 0.7953831

 $00{:}05{:}30{.}527 \dashrightarrow 00{:}05{:}32{.}862$ relevant for the Frisby lectures hip

NOTE Confidence: 0.7953831

 $00{:}05{:}32.862 \dashrightarrow 00{:}05{:}35.420$ Marcus for his many accomplishments

NOTE Confidence: 0.7953831

 $00{:}05{:}35{.}420 \dashrightarrow 00{:}05{:}37{.}432$ and impressive publication record

NOTE Confidence: 0.7953831

 $00:05:37.432 \rightarrow 00:05:39.694$ has been received countless awards.

- NOTE Confidence: 0.7953831
- 00:05:39.694 --> 00:05:43.139 I I wouldn't want to take too much

 $00:05:43.139 \longrightarrow 00:05:45.319$ time annunciating all of them,

NOTE Confidence: 0.7953831

 $00:05:45.320 \rightarrow 00:05:47.900$ but they include the NCI outstanding

NOTE Confidence: 0.7953831

 $00:05:47.900 \longrightarrow 00:05:48.760$ Investigator award.

NOTE Confidence: 0.7953831

00:05:48.760 --> 00:05:50.910 Howard, You scholar award, leukemia,

NOTE Confidence: 0.7953831

00:05:50.910 --> 00:05:52.850 Lymphoma Society scholar award.

NOTE Confidence: 0.7953831

 $00{:}05{:}52.850 \dashrightarrow 00{:}05{:}54.790$ Welcome Trust scholar award.

NOTE Confidence: 0.7953831

 $00:05:54.790 \longrightarrow 00:05:57.195$ Among many other awards that

NOTE Confidence: 0.7953831

 $00{:}05{:}57{.}195 \dashrightarrow 00{:}05{:}58{.}638$ recognize his accomplishment,

NOTE Confidence: 0.7953831

 $00{:}05{:}58{.}640 \dashrightarrow 00{:}06{:}02{.}105$ an innovative and record of innovation and

NOTE Confidence: 0.7953831

 $00:06:02.105 \rightarrow 00:06:04.899$ accomplishment across all of these cancers.

NOTE Confidence: 0.7953831

 $00{:}06{:}04{.}900 \dashrightarrow 00{:}06{:}08{.}148$ So it's really a pleasure to introduce

NOTE Confidence: 0.7953831

 $00:06:08.148 \dashrightarrow 00:06:11.150$ Marcus and an in many respects.

NOTE Confidence: 0.7953831

 $00{:}06{:}11.150 \dashrightarrow 00{:}06{:}15.206$ Welcome to the faculty of Ovvio

NOTE Confidence: 0.7953831

00:06:15.206 --> 00:06:17.499 Cancer Center. Orchis, thank you.

00:06:19.810 --> 00:06:22.225 Thank you, I'm not sharing my screen.

NOTE Confidence: 0.8221974

 $00{:}06{:}45{.}520 \dashrightarrow 00{:}06{:}48{.}425$ So first of all, I would like

NOTE Confidence: 0.8221974

 $00:06:48.425 \longrightarrow 00:06:51.251$ to thank the Frisby family and

NOTE Confidence: 0.8221974

 $00:06:51.251 \rightarrow 00:06:54.709$ Charlie an ad for me being here.

NOTE Confidence: 0.8221974

00:06:54.710 --> 00:06:57.608 And since I came to your Cancer

NOTE Confidence: 0.8221974

00:06:57.608 --> 00:07:00.524 Center last for like I came to

NOTE Confidence: 0.8221974

00:07:00.524 $\operatorname{-->}$ 00:07:02.900 experience that many of us who

NOTE Confidence: 0.8221974

 $00:07:02.993 \longrightarrow 00:07:05.459$ are devoted to the cause of.

NOTE Confidence: 0.8221974

00:07:05.460 --> 00:07:08.082 Now titled can try to leukemia

NOTE Confidence: 0.8221974

 $00:07:08.082 \rightarrow 00:07:10.410$ and leukemia and young tires.

NOTE Confidence: 0.8221974

 $00:07:10.410 \longrightarrow 00:07:12.660$ That legacy of Richard D.

NOTE Confidence: 0.8221974

00:07:12.660 --> 00:07:15.144 Frisbie has inspired many of us

NOTE Confidence: 0.8221974

00:07:15.144 --> 00:07:18.695 and and today I would like to text

NOTE Confidence: 0.8221974

00:07:18.695 --> 00:07:21.395 opportunity to present a few new

NOTE Confidence: 0.8221974

 $00{:}07{:}21.484 \dashrightarrow 00{:}07{:}24.286$ findings from our lab that over

NOTE Confidence: 0.8221974

 $00:07:24.286 \longrightarrow 00:07:27.330$ the past recent years have led to

- NOTE Confidence: 0.8221974
- $00:07:27.330 \longrightarrow 00:07:30.060$ a new concept that I hope will
- NOTE Confidence: 0.8221974
- 00:07:30.153 --> 00:07:33.569 help us in the future to treat this
- NOTE Confidence: 0.8221974
- $00:07:33.569 \rightarrow 00:07:36.560$ disease is more efficiently than.
- NOTE Confidence: 0.8221974
- $00:07:36.560 \longrightarrow 00:07:39.264$ We were able to do in the past.
- NOTE Confidence: 0.8221974
- $00:07:39.270 \longrightarrow 00:07:42.590$ And many of our try to leukemias are
- NOTE Confidence: 0.8221974
- $00:07:42.590 \rightarrow 00:07:44.419$ actually derived from lymphocytes
- NOTE Confidence: 0.8221974
- $00:07:44.419 \longrightarrow 00:07:46.247$ and is a leukemia.
- NOTE Confidence: 0.8221974
- 00:07:46.250 --> 00:07:47.068 In fact,
- NOTE Confidence: 0.8221974
- $00{:}07{:}47.068 \dashrightarrow 00{:}07{:}49.522$ represents the most frequent type of
- NOTE Confidence: 0.8221974
- 00:07:49.522 --> 00:07:52.348 cancer in children and young adults,
- NOTE Confidence: 0.8221974
- $00:07:52.350 \rightarrow 00:07:54.522$ and one potential reason for that
- NOTE Confidence: 0.8221974
- $00{:}07{:}54{.}522 \dashrightarrow 00{:}07{:}57{.}293$ is that B cells during the early
- NOTE Confidence: 0.8221974
- $00:07:57.293 \dashrightarrow 00:07:59.777$ development have to go through a
- NOTE Confidence: 0.8221974
- $00:07:59.777 \longrightarrow 00:08:01.918$ series of genetic modifications
- NOTE Confidence: 0.8221974
- $00:08:01.918 \rightarrow 00:08:04.114$ in error combination class,
- NOTE Confidence: 0.8221974

 $00:08:04.120 \rightarrow 00:08:06.560$ switching hypermutation with the end

NOTE Confidence: 0.8221974

 $00:08:06.560 \dashrightarrow 00:08:09.529$ goal for these cells protect us by.

NOTE Confidence: 0.8221974

 $00:08:09.530 \rightarrow 00:08:11.290$ Generating Pi affinity antibodies

NOTE Confidence: 0.8221974

 $00{:}08{:}11.290 \dashrightarrow 00{:}08{:}14.384$ and this is a cartoon here from

NOTE Confidence: 0.8221974

00:08:14.384 --> 00:08:16.307 1905 drawn by Powell, Ellie.

NOTE Confidence: 0.8221974

 $00{:}08{:}16{.}307 \dashrightarrow 00{:}08{:}19{.}086$ She was sitting here in his office

NOTE Confidence: 0.8221974

 $00{:}08{:}19.086 \dashrightarrow 00{:}08{:}21.645$ and for those reasons B cells

NOTE Confidence: 0.8221974

 $00:08:21.645 \longrightarrow 00:08:24.171$ are an extremely high risk for

NOTE Confidence: 0.8221974

 $00{:}08{:}24.255 \dashrightarrow 00{:}08{:}26.279$ malignant transformation.

NOTE Confidence: 0.8221974

00:08:26.280 --> 00:08:26.675 Actually,

NOTE Confidence: 0.8221974

 $00{:}08{:}26.675 \dashrightarrow 00{:}08{:}29.835$ 500 times higher than any other somatic cell,

NOTE Confidence: 0.8221974

 $00:08:29.840 \rightarrow 00:08:32.598$ and for this reason and also because,

NOTE Confidence: 0.8221974

 $00:08:32.600 \rightarrow 00:08:34.880$ humans can actually live without

NOTE Confidence: 0.8221974

 $00:08:34.880 \rightarrow 00:08:37.600$ the lymphocytes for quite some time.

NOTE Confidence: 0.8221974

 $00{:}08{:}37{.}600 \dashrightarrow 00{:}08{:}40{.}540$ And we developed a research program

NOTE Confidence: 0.8221974

 $00{:}08{:}40.540 \dashrightarrow 00{:}08{:}43.208$ that is centered on specific

- NOTE Confidence: 0.8221974
- $00:08:43.208 \rightarrow 00:08:46.874$ vulnerabilities of this very cell type.

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

NOTE Confidence: 0.8221974

 $00:08:48.436 \rightarrow 00:08:50.770$ we are always looking for vulnerabilities,

NOTE Confidence: 0.8221974

 $00:08:50.770 \longrightarrow 00:08:53.572$ and in this case we're looking

NOTE Confidence: 0.8221974

 $00{:}08{:}53{.}572 \dashrightarrow 00{:}08{:}54{.}506$ for vulnerabilities.

NOTE Confidence: 0.8221974

 $00:08:54.510 \longrightarrow 00:08:56.625$ That are intrinsically encoded in

NOTE Confidence: 0.8221974

 $00:08:56.625 \rightarrow 00:08:59.268$ the nature of the sales making

NOTE Confidence: 0.8221974

 $00{:}08{:}59{.}268 \dashrightarrow 00{:}09{:}01{.}498$ antibodies and are selected and

NOTE Confidence: 0.8221974

 $00{:}09{:}01{.}498 \dashrightarrow 00{:}09{:}03{.}981$ ANVISA selection is a scene that

NOTE Confidence: 0.8221974

 $00:09:03.981 \longrightarrow 00:09:06.477$ that that I hope I will be able

NOTE Confidence: 0.8221974

 $00:09:06.480 \dashrightarrow 00:09:09.805$ to present to you on the occasion

NOTE Confidence: 0.8221974

 $00{:}09{:}09{.}805 \dashrightarrow 00{:}09{:}11{.}230$ of this lecture.

NOTE Confidence: 0.8221974

 $00{:}09{:}11.230 \dashrightarrow 00{:}09{:}14.406$ And the reason is that just by the

NOTE Confidence: 0.8221974

 $00{:}09{:}14.406 \dashrightarrow 00{:}09{:}16.699$ random nature of recombination,

NOTE Confidence: 0.8221974

00:09:16.700 --> 00:09:18.520 events of antibody encoding

 $00:09:18.520 \rightarrow 00:09:19.885$ molecules vast majority,

NOTE Confidence: 0.8221974

 $00:09:19.890 \longrightarrow 00:09:22.626$ about 75% of oil newly generated

NOTE Confidence: 0.8221974

 $00:09:22.626 \rightarrow 00:09:24.450$ visas are initially autoreactive,

NOTE Confidence: 0.8221974

 $00{:}09{:}24.450 \dashrightarrow 00{:}09{:}26.805$ meaning that their directed against

NOTE Confidence: 0.8221974

 $00{:}09{:}26.805 \dashrightarrow 00{:}09{:}30.089$ himself and in these cells have to

NOTE Confidence: 0.8221974

 $00:09:30.089 \dashrightarrow 00:09:32.204$ be removed from the repertoire,

NOTE Confidence: 0.8221974

00:09:32.210
 $-\!>$ 00:09:35.234 and this means they have to be

NOTE Confidence: 0.8221974

 $00{:}09{:}35{.}234 \dashrightarrow 00{:}09{:}37{.}643$ powerful mechanisms in place to

NOTE Confidence: 0.8221974

 $00:09:37.643 \dashrightarrow 00:09:40.213$ normal development to destroy and NOTE Confidence: 0.8221974

 $00:09:40.213 \dashrightarrow 00:09:43.060$ delete yourself from the repertoire.

NOTE Confidence: 0.8221974

00:09:43.060 --> 00:09:45.080 And although arching theme for

NOTE Confidence: 0.8221974

 $00{:}09{:}45{.}080 \dashrightarrow 00{:}09{:}47{.}380$ our research in recent years is,

NOTE Confidence: 0.8221974

 $00{:}09{:}47.380 \dashrightarrow 00{:}09{:}49.265$ can we actually leverage these

NOTE Confidence: 0.8221974

 $00{:}09{:}49{.}265 \dashrightarrow 00{:}09{:}51{.}634$ mechanisms that are indeed in the

NOTE Confidence: 0.8221974

00:09:51.634 --> 00:09:53.709 life and selection and development

NOTE Confidence: 0.8221974

 $00:09:53.709 \longrightarrow 00:09:55.781$ of normally lymphocytes for the

 $00:09:55.781 \rightarrow 00:09:59.649$ treatment of Pisa, leukemia and lymphoma?

NOTE Confidence: 0.8221974

 $00{:}09{:}59.650 \dashrightarrow 00{:}10{:}00.376$ So in.

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

 $00:10:00.739 \rightarrow 00:10:02.917$ the principle of the cell selection

NOTE Confidence: 0.8221974

 $00{:}10{:}02{.}917 \dashrightarrow 00{:}10{:}05{.}993$ is driven by signals from the B cell

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

 $00:10:08.270 \longrightarrow 00:10:11.266$ and we like to think of this.

NOTE Confidence: 0.8221974

00:10:11.270 --> 00:10:14.040 Like I said, Goldilocks principle.

NOTE Confidence: 0.8221974

 $00{:}10{:}14.040 \dashrightarrow 00{:}10{:}16.692$ Because only if the signal strength

NOTE Confidence: 0.8221974

 $00:10:16.692 \longrightarrow 00:10:19.290$ that is elicited from this unit

NOTE Confidence: 0.8221974

00:10:19.290 --> 00:10:20.790 here is just right,

NOTE Confidence: 0.8221974

 $00{:}10{:}20.790 \dashrightarrow 00{:}10{:}23.208$ then this says receive a positive

NOTE Confidence: 0.8221974

 $00:10:23.208 \rightarrow 00:10:25.430$ signal and proliferate and survive,

NOTE Confidence: 0.8221974

 $00{:}10{:}25{.}430 \dashrightarrow 00{:}10{:}27{.}788$ and this is usually the case

NOTE Confidence: 0.8221974

 $00{:}10{:}27.788 \dashrightarrow 00{:}10{:}29.360$ when we have a

 $00:10:29.457 \rightarrow 00:10:32.657$ balance between activation signals.

NOTE Confidence: 0.8480648

 $00{:}10{:}32.660 \dashrightarrow 00{:}10{:}35.980$ Namely, kinase and phosphatase is.

NOTE Confidence: 0.8480648

 $00:10:35.980 \longrightarrow 00:10:37.424$ That achieve this balance.

NOTE Confidence: 0.8480648

00:10:37.424 --> 00:10:40.030 So if the signal is too weak,

NOTE Confidence: 0.8480648

 $00:10:40.030 \longrightarrow 00:10:40.764$ for instance,

NOTE Confidence: 0.8480648

 $00:10:40.764 \rightarrow 00:10:43.333$ gives the first parties are just wrong,

NOTE Confidence: 0.8480648

 $00:10:43.340 \longrightarrow 00:10:45.530$ or the receptor itself is not

NOTE Confidence: 0.8480648

 $00:10:45.530 \rightarrow 00:10:48.119$ functional and he says die by neglect.

NOTE Confidence: 0.8480648

 $00{:}10{:}48{.}120 \dashrightarrow 00{:}10{:}49{.}880$ Now we're focusing here on

NOTE Confidence: 0.8480648

 $00:10:49.880 \longrightarrow 00:10:52.170$ the other end of the scale,

NOTE Confidence: 0.8480648

 $00:10:52.170 \rightarrow 00:10:54.010$ where the signals overwhelmingly strong,

NOTE Confidence: 0.8480648

 $00{:}10{:}54.010 \dashrightarrow 00{:}10{:}56.439$ which is typically the case when this

NOTE Confidence: 0.8480648

 $00:10:56.439 \rightarrow 00:10:59.159$ receptor he is engaged by self antigen,

NOTE Confidence: 0.8480648

 $00:10:59.160 \longrightarrow 00:11:00.976$ meaning that these receptors

NOTE Confidence: 0.8480648

 $00{:}11{:}00{.}976 \dashrightarrow 00{:}11{:}02{.}338$ are out reactive.

NOTE Confidence: 0.8480648

 $00:11:02.340 \rightarrow 00:11:05.540$ And these cells could give rise to autoimmune

- NOTE Confidence: 0.8480648
- $00:11:05.540 \rightarrow 00:11:07.958$ disease and have to be eliminated.

 $00{:}11{:}07{.}960 \dashrightarrow 00{:}11{:}12{.}384$ And so this principle is not only

NOTE Confidence: 0.8480648

 $00:11:12.384 \rightarrow 00:11:16.600$ relevant to normal B cell evelopment.

NOTE Confidence: 0.8480648

 $00:11:16.600 \longrightarrow 00:11:18.735$ In this cartoon here from

NOTE Confidence: 0.8480648

00:11:18.735 --> 00:11:20.016 a recent publication,

NOTE Confidence: 0.8480648

 $00{:}11{:}20{.}020 \dashrightarrow 00{:}11{:}22{.}631$ shows that in transformed B cells and

NOTE Confidence: 0.8480648

 $00:11:22.631 \rightarrow 00:11:24.679$ leukemia and lymphoma the signaling

NOTE Confidence: 0.8480648

 $00:11:24.679 \rightarrow 00:11:26.829$ pathway downstream of the beasts

NOTE Confidence: 0.8480648

 $00{:}11{:}26.829 \dashrightarrow 00{:}11{:}29.010$ are receptors engaged permutations.

NOTE Confidence: 0.8480648

 $00:11:29.010 \longrightarrow 00:11:31.770$ Every step of the way.

NOTE Confidence: 0.8480648

00:11:31.770 --> 00:11:34.498 And so today I would like to divide

NOTE Confidence: 0.8480648

 $00{:}11{:}34{.}498 \dashrightarrow 00{:}11{:}37{.}647$ my talk in three areas where we gain NOTE Confidence: 0.8480648

00:11:37.647 --> 00:11:40.587 information of how we can leverage

NOTE Confidence: 0.8480648

 $00{:}11{:}40.587 \dashrightarrow 00{:}11{:}43.127$ selection for the rapeutic benefits.

NOTE Confidence: 0.8480648

 $00{:}11{:}43{.}130 \dashrightarrow 00{:}11{:}45{.}881$ One comes from inside that we gle an

 $00{:}11{:}45{.}881 \dashrightarrow 00{:}11{:}48{.}570$ from mutations and deletions and visa

NOTE Confidence: 0.8480648

 $00{:}11{:}48{.}570$ --> $00{:}11{:}51{.}432$ humorists such as leukemia and lymphoma.

NOTE Confidence: 0.8480648

 $00{:}11{:}51{.}440 \dashrightarrow 00{:}11{:}53{.}620$ Then inside some clinical trials.

NOTE Confidence: 0.8480648

 $00:11:53.620 \longrightarrow 00:11:55.590$ So we collaborate with large

NOTE Confidence: 0.8480648

 $00:11:55.590 \rightarrow 00:11:58.114$ clinical trial groups in the United

NOTE Confidence: 0.8480648

 $00{:}11{:}58{.}114 \dashrightarrow 00{:}12{:}00{.}050$ States and internationally and

NOTE Confidence: 0.8480648

 $00:12:00.050 \longrightarrow 00:12:02.470$ look for predictors of clinical.

NOTE Confidence: 0.8480648

 $00{:}12{:}02{.}470 \dashrightarrow 00{:}12{:}05{.}312$ Outcomes and what we can learn in

NOTE Confidence: 0.8480648

 $00{:}12{:}05{.}312 \dashrightarrow 00{:}12{:}07{.}970$ terms of the rapeutic targeting options.

NOTE Confidence: 0.8480648

 $00{:}12{:}07{.}970 \dashrightarrow 00{:}12{:}11{.}306$ And then finally how these complicated

NOTE Confidence: 0.8480648

00:12:11.306 --> 00:12:12.974 on cogenic signaling pathways

NOTE Confidence: 0.8480648

 $00:12:12.974 \rightarrow 00:12:15.805$ intersect and how we can leverage

NOTE Confidence: 0.8480648

 $00{:}12{:}15.805 \dashrightarrow 00{:}12{:}18.005$ these interactions again to undermine

NOTE Confidence: 0.8480648

 $00{:}12{:}18.085 \dashrightarrow 00{:}12{:}20.830$ on cogenic signaling in these diseases.

NOTE Confidence: 0.8480648

 $00:12:20.830 \longrightarrow 00:12:23.758$ So in the first part I'm going to

NOTE Confidence: 0.8480648

 $00:12:23.758 \rightarrow 00:12:26.273$ talk about genetic lesions and what

- NOTE Confidence: 0.8480648
- $00{:}12{:}26.273 \dashrightarrow 00{:}12{:}29.398$ we have done here based on mutation

 $00{:}12{:}29{.}398 \dashrightarrow 00{:}12{:}32{.}344$ data from cosmic and other sources

NOTE Confidence: 0.8480648

00:12:32.344 --> 00:12:36.065 assembled a set of more than 5 million

NOTE Confidence: 0.8480648

00:12:36.065 --> 00:12:38.310 somatic mutations in 39 different

NOTE Confidence: 0.8480648

00:12:38.397 - 00:12:41.316 types of cancer and look at these

NOTE Confidence: 0.8480648

 $00:12:41.316 \longrightarrow 00:12:44.280$ mutations from the angle of whether

NOTE Confidence: 0.8480648

 $00:12:44.280 \longrightarrow 00:12:46.990$ the mutation introduce a replacement.

NOTE Confidence: 0.8480648

00:12:46.990 --> 00:12:48.862 Or effect according capacity of the

NOTE Confidence: 0.8480648

 $00:12:48.862 \longrightarrow 00:12:50.789$ gene or whether they are silent,

NOTE Confidence: 0.8480648

 $00{:}12{:}50.790 \dashrightarrow 00{:}12{:}53.250$ meaning they are not selected for.

NOTE Confidence: 0.8480648

 $00{:}12{:}53{.}250 \dashrightarrow 00{:}12{:}55{.}791$ And then in all these diseases we

NOTE Confidence: 0.8480648

 $00{:}12{:}55{.}791 \dashrightarrow 00{:}12{:}58{.}332$ rank the mutations based on these

NOTE Confidence: 0.8480648

 $00{:}12{:}58{.}332 \dashrightarrow 00{:}13{:}00{.}168$ replacement over silent ratios.

NOTE Confidence: 0.8480648

 $00{:}13{:}00{.}170 \dashrightarrow 00{:}13{:}04{.}190$ And we do that in a way that ranks US

NOTE Confidence: 0.8480648

 $00{:}13{:}04{.}302 \dashrightarrow 00{:}13{:}07{.}998$ based on the cell specific ratios.

 $00{:}13{:}08{.}000 \dashrightarrow 00{:}13{:}10{.}310$ We end up with typically mutated genes,

NOTE Confidence: 0.8480648

00:13:10.310 $\operatorname{-->}$ 00:13:12.982 and these are widely known in B cell

NOTE Confidence: 0.8480648

00:13:12.982 --> 00:13:15.256 tumors like my D8820 and so forth,

NOTE Confidence: 0.8480648

 $00{:}13{:}15{.}260 \dashrightarrow 00{:}13{:}18{.}200$ But was interesting to us that here

NOTE Confidence: 0.8480648

 $00:13:18.200 \dashrightarrow 00:13:21.936$ at the top of the list they actually.

NOTE Confidence: 0.8480648

 $00{:}13{:}21{.}940 \dashrightarrow 00{:}13{:}24{.}215$ Molecules in the PS3 kindness

NOTE Confidence: 0.8480648

 $00:13:24.215 \longrightarrow 00:13:26.490$ pass visit our frequently mutated

NOTE Confidence: 0.8480648

 $00:13:26.568 \longrightarrow 00:13:27.870$ throughout cancer,

NOTE Confidence: 0.8480648

00:13:27.870 --> 00:13:30.245 but are unexpectedly spirit were

NOTE Confidence: 0.8480648

 $00:13:30.245 \rightarrow 00:13:33.300$ exempted from in B cell tumors,

NOTE Confidence: 0.8480648

 $00{:}13{:}33{.}300 \dashrightarrow 00{:}13{:}35{.}624$ and this activating mutations

NOTE Confidence: 0.8480648

 $00:13:35.624 \rightarrow 00:13:38.529$ of the PS3 kinase pathway.

NOTE Confidence: 0.8480648

 $00:13:38.530 \longrightarrow 00:13:40.558$ And P-10 and then ship one

NOTE Confidence: 0.8480648

 $00:13:40.558 \rightarrow 00:13:41.572$ night in inventory.

NOTE Confidence: 0.8480648

 $00:13:41.580 \dashrightarrow 00:13:43.276$ Phosphatases in this pathway.

NOTE Confidence: 0.8480648

 $00:13:43.276 \longrightarrow 00:13:45.820$ And this is the catalytic subunit

- NOTE Confidence: 0.8480648
- $00{:}13{:}45{.}890 \dashrightarrow 00{:}13{:}47{.}910$ of peers with kindness itself.
- NOTE Confidence: 0.8480648
- $00:13:47.910 \longrightarrow 00:13:50.292$ So we studied this in multiple
- NOTE Confidence: 0.8480648
- $00:13:50.292 \longrightarrow 00:13:51.086$ different directions,
- NOTE Confidence: 0.8480648
- $00:13:51.090 \longrightarrow 00:13:53.939$ but I would like to focus your
- NOTE Confidence: 0.8480648
- $00{:}13{:}53{.}939 \dashrightarrow 00{:}13{:}56{.}514$ content because it was just such
- NOTE Confidence: 0.8480648
- $00{:}13{:}56{.}514 \dashrightarrow 00{:}13{:}59{.}052$ a subset of striking example and
- NOTE Confidence: 0.8480648
- $00:13:59.052 \rightarrow 00:14:01.806$ then as we know for a long time,
- NOTE Confidence: 0.8480648
- $00:14:01.810 \longrightarrow 00:14:03.795$ pretend deletions and mutations widely
- NOTE Confidence: 0.8480648
- $00{:}14{:}03.795 \dashrightarrow 00{:}14{:}05.780$ occur throughout many cancer types,
- NOTE Confidence: 0.8480648
- 00:14:05.780 --> 00:14:09.344 but in 925 cases of B cell image leukemia,
- NOTE Confidence: 0.8061034
- $00:14:09.350 \rightarrow 00:14:12.129$ we didn't find any of these mutations.
- NOTE Confidence: 0.8061034
- $00{:}14{:}12{.}130 \dashrightarrow 00{:}14{:}13{.}624$ Again, highlighting the
- NOTE Confidence: 0.8061034
- $00{:}14{:}13.624 \dashrightarrow 00{:}14{:}15.616$ specificity of this mechanism.
- NOTE Confidence: 0.8061034
- $00{:}14{:}15.620 \dashrightarrow 00{:}14{:}18.704$ And pretending opposers peers
- NOTE Confidence: 0.8061034
- $00:14:18.704 \rightarrow 00:14:21.788$ to kindness signaling by.
- NOTE Confidence: 0.8061034

 $00:14:21.790 \longrightarrow 00:14:24.494$ I am targeting Pep 3 which is a

NOTE Confidence: 0.8061034

00:14:24.494 --> 00:14:26.649 central initiator of the PS3 kinase

NOTE Confidence: 0.8061034

 $00{:}14{:}26.649 \dashrightarrow 00{:}14{:}28.761$ signaling pathway and I will come

NOTE Confidence: 0.8061034

 $00{:}14{:}28{.}830 \dashrightarrow 00{:}14{:}30{.}895$ to that back later in my talk.

NOTE Confidence: 0.8061034

00:14:30.900 --> 00:14:33.931 And to study hyperactivation of the PS3

NOTE Confidence: 0.8061034

 $00:14:33.931 \longrightarrow 00:14:36.409$ kindness pathway by dilution of 10,

NOTE Confidence: 0.8061034

00:14:36.410 --> 00:14:39.466 we develop the mouse model in our lab

NOTE Confidence: 0.8061034

 $00:14:39.466 \rightarrow 00:14:42.076$ based on conditional deletion of the

NOTE Confidence: 0.8061034

00:14:42.076 --> 00:14:45.672 P 10 gene in our leukemia model and

NOTE Confidence: 0.8061034

 $00{:}14{:}45{.}672 \dashrightarrow 00{:}14{:}48{.}710$ unlike what we know and solid tumors,

NOTE Confidence: 0.8061034

 $00:14:48.710 \longrightarrow 00:14:50.426$ conditional deletion of P.

NOTE Confidence: 0.8061034

00:14:50.426 --> 00:14:53.930 10 result in Rapid City S of leukemia

NOTE Confidence: 0.8061034

 $00{:}14{:}53{.}930 \dashrightarrow 00{:}14{:}57{.}298$ cells and if we change the sequence and

NOTE Confidence: 0.8061034

00:14:57.383 --> 00:15:00.615 1
st delete return a normal B cells and

NOTE Confidence: 0.8061034

 $00:15:00.615 \rightarrow 00:15:03.266$ then bring in transforming Uncle gene.

NOTE Confidence: 0.8061034

 $00:15:03.266 \rightarrow 00:15:05.561$ Then we basically compromise malignant

- NOTE Confidence: 0.8061034
- $00:15:05.561 \rightarrow 00:15:07.549$ transformation and then most importantly,

 $00{:}15{:}07{.}550 \dashrightarrow 00{:}15{:}09{.}674$ when we wait for leukemia to

NOTE Confidence: 0.8061034

 $00{:}15{:}09{.}674 \dashrightarrow 00{:}15{:}11{.}998$ establish and miles at bear these

NOTE Confidence: 0.8061034

 $00:15:11.998 \rightarrow 00:15:14.500$ tumors and then delete speech engine,

NOTE Confidence: 0.8061034

 $00{:}15{:}14.500 \dashrightarrow 00{:}15{:}17.937$ this leads to remission and the mice

NOTE Confidence: 0.8061034

 $00{:}15{:}17{.}937 \dashrightarrow 00{:}15{:}20{.}829$ survive for indefinite periods of time.

NOTE Confidence: 0.8061034

 $00:15:20.830 \rightarrow 00:15:23.236$ We also confirmed that the biochemistry

NOTE Confidence: 0.8061034

 $00:15:23.236 \rightarrow 00:15:26.202$ or the premise here is correct because

NOTE Confidence: 0.8061034

 $00{:}15{:}26.202 \dashrightarrow 00{:}15{:}28.782$ we actually do see increased activity,

NOTE Confidence: 0.8061034

 $00{:}15{:}28.790 \dashrightarrow 00{:}15{:}31.886$ increased output of the PSC kindness

NOTE Confidence: 0.8061034

00:15:31.886 --> 00:15:34.519 pathway by increased phosphorylation of AKT.

NOTE Confidence: 0.8061034

 $00:15:34.520 \longrightarrow 00:15:35.696$ And most importantly,

NOTE Confidence: 0.8061034

 $00{:}15{:}35{.}696 \dashrightarrow 00{:}15{:}38{.}440$ we used inhibitors that block the PS3

NOTE Confidence: 0.8061034

 $00:15:38.514 \rightarrow 00:15:41.508$ kinase signaling pathways at multiple levels.

NOTE Confidence: 0.8061034

00:15:41.510 --> 00:15:41.968 Here,

 $00:15:41.968 \rightarrow 00:15:45.174$ activation of PS3 kinese bicec using the

NOTE Confidence: 0.8061034

 $00:15:45.174 \rightarrow 00:15:48.377$ sick kinase inhibitor and it's platinum.

NOTE Confidence: 0.8061034

 $00:15:48.380 \longrightarrow 00:15:51.020$ BKM 120 is a pan PSD.

NOTE Confidence: 0.8061034

 $00:15:51.020 \longrightarrow 00:15:52.788$ Kindness never turn easy.

NOTE Confidence: 0.8061034

00:15:52.788 --> 00:15:56.383 D 53 E 63 inhibits AKT and all

NOTE Confidence: 0.8061034

 $00:15:56.383 \rightarrow 00:15:58.933$ three of them have in common.

NOTE Confidence: 0.8061034

00:15:58.940 --> 00:16:00.788 That's actually rescuer protect

NOTE Confidence: 0.8061034

 $00{:}16{:}00{.}788 \dashrightarrow 00{:}16{:}03{.}560$ leukemia cells from sad as that

NOTE Confidence: 0.8061034

 $00{:}16{:}03{.}633 \dashrightarrow 00{:}16{:}05{.}538$ would otherwise be in use.

NOTE Confidence: 0.8061034

 $00:16:05.540 \rightarrow 00:16:08.180$ Dapon deletion of the P-10 phosphatase?

NOTE Confidence: 0.8061034

 $00{:}16{:}08{.}180 \dashrightarrow 00{:}16{:}10{.}640$ So this doesn't mean that these

NOTE Confidence: 0.8061034

 $00:16:10.640 \rightarrow 00:16:12.280$ compounds are counterproductive in

NOTE Confidence: 0.8061034

 $00{:}16{:}12.352 \dashrightarrow 00{:}16{:}14.777$ leukemia because actually quite useful.

NOTE Confidence: 0.8061034

 $00:16:14.780 \longrightarrow 00:16:16.712$ Our interpretation of this

NOTE Confidence: 0.8061034

 $00:16:16.712 \longrightarrow 00:16:18.644$ unexpected result is that.

NOTE Confidence: 0.8061034

 $00{:}16{:}18.650 \dashrightarrow 00{:}16{:}21.290$ I was introduction of those inhibitors

- NOTE Confidence: 0.8061034
- $00:16:21.290 \rightarrow 00:16:23.050$ restores signaling equilibrium again,

 $00:16:23.050 \longrightarrow 00:16:24.370$ the Goldilocks principle

NOTE Confidence: 0.8061034

 $00:16:24.370 \longrightarrow 00:16:26.130$ that these cells need,

NOTE Confidence: 0.8061034

 $00{:}16{:}26{.}130 \dashrightarrow 00{:}16{:}28{.}909$ whereas deletion of the 10 alone here

NOTE Confidence: 0.8061034

 $00{:}16{:}28{.}909 \dashrightarrow 00{:}16{:}30{.}629$ introduce a drastic perturbation

NOTE Confidence: 0.8061034

 $00:16:30.629 \rightarrow 00:16:32.441$ which engages negative selection

NOTE Confidence: 0.8061034

 $00:16:32.441 \longrightarrow 00:16:35.710$ just as it does for the elimination

NOTE Confidence: 0.8061034

 $00:16:35.710 \longrightarrow 00:16:37.570$ of Hartree active users.

NOTE Confidence: 0.8028251

 $00{:}16{:}40.290 \dashrightarrow 00{:}16{:}42.840$ We are hopeful that these ideas

NOTE Confidence: 0.8028251

 $00:16:42.840 \longrightarrow 00:16:44.540$ these concepts will eventually

NOTE Confidence: 0.8028251

 $00:16:44.613 \rightarrow 00:16:46.737$ make their way into the clinic,

NOTE Confidence: 0.8028251

 $00{:}16{:}46{.}740 \dashrightarrow 00{:}16{:}49{.}170$ and as an early indication that NOTE Confidence: 0.8028251

 $00:16:49.170 \rightarrow 00:16:51.569$ that might indeed be the case,

NOTE Confidence: 0.8028251

00:16:51.570 --> 00:16:53.585 I'm showing you two promising

NOTE Confidence: 0.8028251

 $00:16:53.585 \rightarrow 00:16:55.600$ preclinical results in our lab,

 $00{:}16{:}55{.}600 \dashrightarrow 00{:}16{:}57{.}964$ both based on small molecule inhibitors

NOTE Confidence: 0.8028251

 $00:16:57.964 \rightarrow 00:17:00.843$ of these key fast watch cases, namely,

NOTE Confidence: 0.8028251

 $00{:}17{:}00{.}843 \dashrightarrow 00{:}17{:}04{.}067$ ship one inhibited by 3A amino color stain,

NOTE Confidence: 0.8028251

 $00:17:04.070 \longrightarrow 00:17:08.168$ and then pretend which also is.

NOTE Confidence: 0.8028251

00:17:08.170 $\operatorname{-->}$ 00:17:10.949 Target if it was a small molecule

NOTE Confidence: 0.8028251

 $00{:}17{:}10{.}949 \dashrightarrow 00{:}17{:}13{.}873$ inhibitor and both of them have

NOTE Confidence: 0.8028251

00:17:13.873 -> 00:17:16.073 desirable on target activity

NOTE Confidence: 0.8028251

00:17:16.073 --> 00:17:17.723 biochemically and importantly,

NOTE Confidence: 0.8028251

00:17:17.730 --> 00:17:20.652 their chief Disease Control or disease

NOTE Confidence: 0.8028251

 $00{:}17{:}20.652 \dashrightarrow 00{:}17{:}23.939$ burden control for long periods of time,

NOTE Confidence: 0.8028251

 $00{:}17{:}23{.}940 \dashrightarrow 00{:}17{:}25{.}056$ and she's,

NOTE Confidence: 0.8028251

 $00{:}17{:}25.056 \dashrightarrow 00{:}17{:}27.846$ extension or prolongation of overall

NOTE Confidence: 0.8028251

 $00{:}17{:}27.846 \dashrightarrow 00{:}17{:}31.321$ survival of mice that bear patient arrives

NOTE Confidence: 0.8028251

 $00{:}17{:}31{.}321 \dashrightarrow 00{:}17{:}35{.}810$ in a graphs from B cell image leukemia cells.

NOTE Confidence: 0.8028251

 $00{:}17{:}35{.}810 \dashrightarrow 00{:}17{:}38{.}552$ So we're hoping that this approach

NOTE Confidence: 0.8028251

 $00:17:38.552 \longrightarrow 00:17:41.210$ can be developed further in and

- NOTE Confidence: 0.8028251
- $00{:}17{:}41{.}210 \dashrightarrow 00{:}17{:}43{.}442$ that some of these compounds will

 $00:17:43.442 \longrightarrow 00:17:46.128$ make it into the clinical arena.

NOTE Confidence: 0.8028251

 $00:17:46.130 \longrightarrow 00:17:48.830$ Now the central premise of this

NOTE Confidence: 0.8028251

 $00:17:48.830 \longrightarrow 00:17:52.099$ idea is that this is a mechanism.

NOTE Confidence: 0.8028251

 $00:17:52.100 \longrightarrow 00:17:53.004$ Negative selection.

NOTE Confidence: 0.8028251

 $00{:}17{:}53.004 \dashrightarrow 00{:}17{:}56.168$ Removal of art reactive says that is

NOTE Confidence: 0.8028251

 $00{:}17{:}56.168 \dashrightarrow 00{:}17{:}58.203$ uniquely important in B lymphocytes

NOTE Confidence: 0.8028251

 $00:17:58.203 \rightarrow 00:18:01.176$ and to test this premise we performed

NOTE Confidence: 0.8028251

 $00{:}18{:}01{.}176 \dashrightarrow 00{:}18{:}03{.}108$ a reprogramming experience.

NOTE Confidence: 0.7699414

 $00{:}18{:}05{.}590 \dashrightarrow 00{:}18{:}09{.}325$ And in which we should use the VPI flower,

NOTE Confidence: 0.7699414

00:18:09.330 --> 00:18:11.820 just a transcription factor that can

NOTE Confidence: 0.7699414

 $00{:}18{:}11.820 \dashrightarrow 00{:}18{:}13.480$ transform besides into macrophages.

NOTE Confidence: 0.7699414

 $00{:}18{:}13{.}480 \dashrightarrow 00{:}18{:}16{.}640$ And this is shown here besides expressed in

NOTE Confidence: 0.7699414

00:18:16.640 --> 00:18:20.163 19 and this marker here is lost overtime

NOTE Confidence: 0.7699414

 $00{:}18{:}20{.}163 \dashrightarrow 00{:}18{:}23{.}437$ after induction and in favor of Mach one,

 $00:18:23.440 \longrightarrow 00:18:25.510$ which is a macrophage marker.

NOTE Confidence: 0.7699414

 $00:18:25.510 \rightarrow 00:18:28.415$ And indeed, after sometimes you say it,

NOTE Confidence: 0.7699414

 $00{:}18{:}28{.}420 \dashrightarrow 00{:}18{:}30{.}842$ start to crawl around on the bottom

NOTE Confidence: 0.7699414

 $00{:}18{:}30{.}842 \dashrightarrow 00{:}18{:}33{.}463$ LCS dishes and like macrophages and

NOTE Confidence: 0.7699414

 $00{:}18{:}33{.}463 \dashrightarrow 00{:}18{:}35{.}973$ can even phagocytose and importantly.

NOTE Confidence: 0.7699414

 $00{:}18{:}35{.}980 \dashrightarrow 00{:}18{:}37{.}990$ Coming back to our hypothesis,

NOTE Confidence: 0.7699414

00:18:37.990 --> 00:18:40.000 if you genetically delete P.

NOTE Confidence: 0.7699414

 $00:18:40.000 \rightarrow 00:18:43.340 \ 10$, Even though genetically identical.

NOTE Confidence: 0.7699414

 $00{:}18{:}43{.}340 \dashrightarrow 00{:}18{:}47{.}273$ The reprogramming from B to Milo to be 2.

NOTE Confidence: 0.7699414

00:18:47.280 --> 00:18:49.032 Macrophage fade almost entirely

NOTE Confidence: 0.7699414

 $00{:}18{:}49.032 \dashrightarrow 00{:}18{:}51.660$ removes the sensitivity of these cells

NOTE Confidence: 0.7699414

 $00{:}18{:}51{.}723 \dashrightarrow 00{:}18{:}53{.}848$ to removal of source phosphatases,

NOTE Confidence: 0.7699414

 $00{:}18{:}53.850 \dashrightarrow 00{:}18{:}56.035$ which makes sense because fact

NOTE Confidence: 0.7699414

00:18:56.035 --> 00:18:57.783 macrophages don't make autoantibodies,

NOTE Confidence: 0.7699414

 $00{:}18{:}57{.}790 \dashrightarrow 00{:}19{:}00{.}898$ there's no need for macrophages to be

NOTE Confidence: 0.7699414

 $00:19:00.898 \rightarrow 00:19:03.488$ negatively selected as beast cells are.

- NOTE Confidence: 0.7699414
- $00:19:03.490 \longrightarrow 00:19:06.642$ So this gives us confidence that this is

 $00{:}19{:}06.642 \dashrightarrow 00{:}19{:}09.861$ a real mechanism that is reflective of

NOTE Confidence: 0.7699414

 $00:19:09.861 \rightarrow 00:19:13.639$ the nature of the immune system to purge.

NOTE Confidence: 0.7699414

 $00:19:13.640 \longrightarrow 00:19:17.252$ Attractive sales and that is possible to

NOTE Confidence: 0.7699414

 $00:19:17.252 \rightarrow 00:19:19.380$ selectively target this vulnerability

NOTE Confidence: 0.7699414

 $00:19:19.380 \longrightarrow 00:19:21.376$ in B cell tumors.

NOTE Confidence: 0.7699414

 $00:19:21.380 \longrightarrow 00:19:24.300$ Now in this work was done by Gen.

NOTE Confidence: 0.7699414

00:19:24.300 --> 00:19:25.580 John Shannon, our lab,

NOTE Confidence: 0.7699414

 $00{:}19{:}25{.}580 \dashrightarrow 00{:}19{:}28{.}437$ and when he worried that this is not

NOTE Confidence: 0.7699414

 $00{:}19{:}28{.}437 \dashrightarrow 00{:}19{:}30{.}185$ just counterintuitive because you

NOTE Confidence: 0.7699414

 $00{:}19{:}30{.}185 \dashrightarrow 00{:}19{:}32{.}638$ essentially doing the opposite from what

NOTE Confidence: 0.7699414

 $00{:}19{:}32.638 \dashrightarrow 00{:}19{:}34.885$ every one else is doing in this field,

NOTE Confidence: 0.7699414

 $00:19:34.890 \rightarrow 00:19:37.080$ namely by instead of inhibiting kinases.

NOTE Confidence: 0.7699414

00:19:37.080 --> 00:19:38.536 VR Pro activating kinases.

NOTE Confidence: 0.7699414

 $00:19:38.536 \rightarrow 00:19:39.628$ But most importantly,

 $00:19:39.630 \longrightarrow 00:19:41.808$ what was worried about what happens

NOTE Confidence: 0.7699414

00:19:41.808 --> 00:19:44.041 if he hyper activate kinases for

NOTE Confidence: 0.7699414

 $00:19:44.041 \longrightarrow 00:19:45.465$ long periods of time,

NOTE Confidence: 0.7699414

 $00:19:45.470 \rightarrow 00:19:48.025$ because that in itself could be dangerous,

NOTE Confidence: 0.7699414

 $00{:}19{:}48.030 \dashrightarrow 00{:}19{:}50.814$ so he did an experiment to figure out

NOTE Confidence: 0.7699414

 $00{:}19{:}50{.}814 \dashrightarrow 00{:}19{:}53{.}757$ what is the shortest period of time.

NOTE Confidence: 0.7699414

 $00{:}19{:}53.760 \dashrightarrow 00{:}19{:}56.970$ Home to commit Visa is to say this and he

NOTE Confidence: 0.7699414

 $00:19:57.048 \rightarrow 00:20:00.180$ did this with an engineered hyperactive.

NOTE Confidence: 0.7699414

00:20:00.180 --> 00:20:01.971 Formosa sick kinase.

NOTE Confidence: 0.7699414

00:20:01.971 - > 00:20:04.359 Labeled here as GFP.

NOTE Confidence: 0.7699414

 $00:20:04.360 \longrightarrow 00:20:06.628$ If you bring in this hyper active

NOTE Confidence: 0.7699414

00:20:06.628 --> 00:20:09.260 kinase in the presence of stickiness,

NOTE Confidence: 0.7699414

00:20:09.260 --> 00:20:11.145 inhibitors of GFP labeled cells

NOTE Confidence: 0.7699414

 $00:20:11.145 \longrightarrow 00:20:11.899$ remain constant,

NOTE Confidence: 0.7699414

 $00{:}20{:}11{.}900 \dashrightarrow 00{:}20{:}13{.}408$ 'cause there's no hyperactivation

NOTE Confidence: 0.7699414

 $00:20:13.408 \longrightarrow 00:20:14.539$ of the pathway.

- NOTE Confidence: 0.7699414
- 00:20:14.540 --> 00:20:14.917 Now,
- NOTE Confidence: 0.7699414
- $00:20:14.917 \longrightarrow 00:20:17.179$ if we wash out the inhibitor
- NOTE Confidence: 0.7699414
- 00:20:17.179 --> 00:20:19.048 cells as expected, rapidly die,
- NOTE Confidence: 0.7699414
- $00:20:19.048 \longrightarrow 00:20:21.262$ and he found that if there's
- NOTE Confidence: 0.7699414
- $00:20:21.262 \longrightarrow 00:20:23.589$ a lapse of just three hours,
- NOTE Confidence: 0.7699414
- $00{:}20{:}23.590 \dashrightarrow 00{:}20{:}26.187$ so removal of simulator for three hours
- NOTE Confidence: 0.7699414
- $00{:}20{:}26.187 \dashrightarrow 00{:}20{:}28.836$ and then adding it right back that
- NOTE Confidence: 0.7699414
- $00:20:28.836 \rightarrow 00:20:31.500$ already is sufficient to commit the sales,
- NOTE Confidence: 0.7699414
- $00{:}20{:}31{.}500 \dashrightarrow 00{:}20{:}34{.}916$ that will be our goal going forward too.
- NOTE Confidence: 0.7699414
- $00:20:34.920 \longrightarrow 00:20:36.564$ Target is short.
- NOTE Confidence: 0.7699414
- $00:20:36.564 \rightarrow 00:20:38.756$ Strong exposure to hyperactivation
- NOTE Confidence: 0.7699414
- $00{:}20{:}38.756 \dashrightarrow 00{:}20{:}42.145$ probably was click or only dated compounds
- NOTE Confidence: 0.7699414
- $00{:}20{:}42.145 \dashrightarrow 00{:}20{:}45.110$ that have a short plasma half life.
- NOTE Confidence: 0.7699414
- $00{:}20{:}45.110 \dashrightarrow 00{:}20{:}48.414$ Now in the second part of my talk,
- NOTE Confidence: 0.7699414
- $00:20:48.420 \rightarrow 00:20:51.183$ I'm going to give you 2 examples of how
- NOTE Confidence: 0.7699414

 $00:20:51.183 \longrightarrow 00:20:54.131$ we can learn from information within

NOTE Confidence: 0.7699414

 $00:20:54.131 \rightarrow 00:20:56.691$ clinical trials and gene expression,

NOTE Confidence: 0.7699414

 $00{:}20{:}56{.}700 \dashrightarrow 00{:}20{:}58{.}612$ annotation related to outcome.

NOTE Confidence: 0.7699414

 $00:20:58.612 \longrightarrow 00:21:01.480$ So what approach is based on

NOTE Confidence: 0.7699414

 $00:21:01.566 \rightarrow 00:21:04.076$ microarray data that we obtain?

NOTE Confidence: 0.7699414

00:21:04.080 --> 00:21:06.380 Collaboration was a clinical study.

NOTE Confidence: 0.7699414

 $00:21:06.380 \longrightarrow 00:21:09.608$ Groups and much of this works

NOTE Confidence: 0.7699414

00:21:09.608 --> 00:21:11.222 also publicly available.

NOTE Confidence: 0.7699414

 $00{:}21{:}11{.}230 \dashrightarrow 00{:}21{:}13{.}218$ And for each of these micro area

NOTE Confidence: 0.7699414

00:21:13.218 --> 00:21:15.200 probe sets that measure expression

NOTE Confidence: 0.7699414

 $00:21:15.200 \longrightarrow 00:21:16.799$ of individual transcripts,

NOTE Confidence: 0.7699414

00:21:16.800 - 00:21:18.780 we divide the patient courts and

NOTE Confidence: 0.7699414

00:21:18.780 $\operatorname{-->}$ 00:21:21.281 the two groups based on higher than

NOTE Confidence: 0.7699414

 $00{:}21{:}21{.}281 \dashrightarrow 00{:}21{:}23.146$ median versus lower than median

NOTE Confidence: 0.7699414

 $00{:}21{:}23.146 \dashrightarrow 00{:}21{:}25.328$ expression in these clinical trials.

NOTE Confidence: 0.7699414

 $00:21:25.330 \longrightarrow 00:21:27.550$ And then we asked the question,

- NOTE Confidence: 0.7699414
- $00{:}21{:}27{.}550 \dashrightarrow 00{:}21{:}30{.}336$ is there a difference between those two

 $00:21:30.336 \rightarrow 00:21:33.049$ groups in terms of clinical outcome?

NOTE Confidence: 0.7699414

 $00{:}21{:}33.050 \dashrightarrow 00{:}21{:}35.416$ And if the outcome is more favor

NOTE Confidence: 0.7699414

 $00:21:35.416 \longrightarrow 00:21:36.430$ we have here

NOTE Confidence: 0.8061022

 $00{:}21{:}36{.}507 \dashrightarrow 00{:}21{:}39{.}251$ a blue annotation and its outcome is

NOTE Confidence: 0.8061022

00:21:39.251 --> 00:21:41.144 more poor, shorter overall survival.

NOTE Confidence: 0.8061022

 $00{:}21{:}41{.}144 \dashrightarrow 00{:}21{:}43{.}535$ For instance, we have a red annotation

NOTE Confidence: 0.8061022

 $00{:}21{:}43.535 \dashrightarrow 00{:}21{:}46.459$ and if the group this heat map based

NOTE Confidence: 0.8061022

 $00{:}21{:}46{.}459 \dashrightarrow 00{:}21{:}48{.}835$ on the site specific annotations we

NOTE Confidence: 0.8061022

 $00{:}21{:}48.835 \dashrightarrow 00{:}21{:}51.832$ come up with a list of genes that

NOTE Confidence: 0.8061022

 $00{:}21{:}51{.}832 \dashrightarrow 00{:}21{:}54{.}124$ became interesting to us and he at

NOTE Confidence: 0.8061022

 $00{:}21{:}54{.}124 \dashrightarrow 00{:}21{:}56{.}784$ the very top is 1 molecule that I'm

NOTE Confidence: 0.8061022

00:21:56.784 --> 00:21:59.486 going to spend the next couple minutes

NOTE Confidence: 0.8061022

00:21:59.486 --> 00:22:02.120 on the L2 receptor Alpha chain,

NOTE Confidence: 0.8061022

 $00:22:02.120 \longrightarrow 00:22:03.588$ also known as C25.

 $00:22:06.490 \longrightarrow 00:22:08.800$ So that was a bit unexpected.

NOTE Confidence: 0.77276397

00:22:08.800 --> 00:22:11.608 Becaus
w ${\rm CD}$ 25 is known as one of

NOTE Confidence: 0.77276397

 $00{:}22{:}11.608 \dashrightarrow 00{:}22{:}14.577$ the three chains of the L2 receptor. NOTE Confidence: 0.77276397

 $00:22:14.580 \rightarrow 00:22:16.836$ Anna typically pairs with the better NOTE Confidence: 0.77276397

 $00{:}22{:}16.836 \dashrightarrow 00{:}22{:}19.961$ chain in the gamma chain to form a NOTE Confidence: 0.77276397

 $00{:}22{:}19{.}961 \dashrightarrow 00{:}22{:}22{.}452$ trimeric receptor, and this was step NOTE Confidence: 0.77276397

 $00{:}22{:}22{.}452 \dashrightarrow 00{:}22{:}26.019$ was active on T cells and in cases.

NOTE Confidence: 0.77276397

 $00:22:26.020 \longrightarrow 00:22:28.280$ And it's also important for

NOTE Confidence: 0.77276397

 $00{:}22{:}28.280 \dashrightarrow 00{:}22{:}31.010$ formation of regulatory T cells or T.

NOTE Confidence: 0.77276397

 $00{:}22{:}31.010 \dashrightarrow 00{:}22{:}32.674$ Rex, and therefore therefore

NOTE Confidence: 0.77276397

 $00{:}22{:}32.674 \dashrightarrow 00{:}22{:}34.338$ important to prevent autoimmunity.

NOTE Confidence: 0.77276397

00:22:34.340 --> 00:22:37.490 Again, important to be self selection.

NOTE Confidence: 0.77276397

 $00:22:37.490 \longrightarrow 00:22:40.598$ And here I'm showing you that.

NOTE Confidence: 0.77276397

 $00:22:40.600 \rightarrow 00:22:44.736$ Then if you look at individual visa diseases,

NOTE Confidence: 0.77276397

00:22:44.740 --> 00:22:46.812 pediatric B cell, leukemia,

NOTE Confidence: 0.77276397

00:22:46.812 --> 00:22:48.884 CLL, Podiatry, pizza, leukemia,

- NOTE Confidence: 0.77276397
- 00:22:48.884 --> 00:22:50.438 mantle cell lymphoma,

 $00:22:50.440 \longrightarrow 00:22:53.015$ 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

 $00{:}22{:}55.678 \dashrightarrow 00{:}22{:}58.208$ is related to better outcome.

NOTE Confidence: 0.77276397

 $00{:}22{:}58{.}210 \dashrightarrow 00{:}23{:}01{.}500$ The top half towards outcome.

NOTE Confidence: 0.77276397

 $00{:}23{:}01{.}500 \dashrightarrow 00{:}23{:}03{.}636$ 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

 $00{:}23{:}07.601 \dashrightarrow 00{:}23{:}10.430$ lymphoma like these are able or LMP 2A.

NOTE Confidence: 0.77276397

 $00:23:10.430 \longrightarrow 00:23:12.130$ This leads to upregulation

NOTE Confidence: 0.77276397

 $00:23:12.130 \longrightarrow 00:23:14.680$ of C25 on the cell surface.

NOTE Confidence: 0.77276397

 $00{:}23{:}14.680 \dashrightarrow 00{:}23{:}17.216$ 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

 $00{:}23{:}19{.}360 \dashrightarrow 00{:}23{:}23{.}910$ So he profile here see 25 M on A levels.

NOTE Confidence: 0.77276397

 $00:23:23.910 \longrightarrow 00:23:26.058$ Over the course of the sale
$00:23:26.058 \rightarrow 00:23:28.263$ evelopment we find here is striking

NOTE Confidence: 0.77276397

 $00{:}23{:}28{.}263 \dashrightarrow 00{:}23{:}30{.}720$ peak and the so called Faction D.

NOTE Confidence: 0.77276397

00:23:30.720 --> 00:23:31.623 And that's interesting,

NOTE Confidence: 0.77276397

00:23:31.623 --> 00:23:34.040 because if you look at C25 knockout mice,

NOTE Confidence: 0.77276397

 $00:23:34.040 \longrightarrow 00:23:36.890$ which we did in our lab.

NOTE Confidence: 0.77276397

 $00:23:36.890 \longrightarrow 00:23:38.900$ Compare this to the wild type

NOTE Confidence: 0.77276397

 $00{:}23{:}38{.}900 \dashrightarrow 00{:}23{:}41{.}032$ animals and look at these fractions

NOTE Confidence: 0.77276397

 $00:23:41.032 \longrightarrow 00:23:43.186$ we see here is fraction D.

NOTE Confidence: 0.77276397

 $00{:}23{:}43.190 \dashrightarrow 00{:}23{:}45.518$ But distractions entirely missing in the

NOTE Confidence: 0.77276397

 $00{:}23{:}45{.}518 \dashrightarrow 00{:}23{:}48{.}327$ knock out mice and can also see this here.

NOTE Confidence: 0.77276397

 $00{:}23{:}48{.}330 \dashrightarrow 00{:}23{:}50{.}160$ This is a defect here.

NOTE Confidence: 0.77276397

 $00:23:50.160 \rightarrow 00:23:53.096$ We still don't know what this actually means,

NOTE Confidence: 0.77276397

 $00{:}23{:}53{.}100 \dashrightarrow 00{:}23{:}55{.}816$ but we also find that later in

NOTE Confidence: 0.77276397

 $00{:}23{:}55{.}816 \dashrightarrow 00{:}23{:}58{.}038$ development he says actually are

NOTE Confidence: 0.77276397

 $00{:}23{:}58{.}038 \dashrightarrow 00{:}24{:}00{.}478$ over represented in fraction F.

NOTE Confidence: 0.77276397

 $00:24:00.480 \rightarrow 00:24:05.261$ So our initial hypothesis was this might

- NOTE Confidence: 0.77276397
- 00:24:05.261 --> 00:24:07.834 reflect previously unrecognized role

 $00:24:07.834 \rightarrow 00:24:11.210$ of IL two signaling in B cells and.

NOTE Confidence: 0.77276397

00:24:11.210 --> 00:24:12.072 I mean,

NOTE Confidence: 0.77276397

 $00:24:12.072 \rightarrow 00:24:14.658$ so we repeated this experiment with

NOTE Confidence: 0.77276397

 $00:24:14.658 \rightarrow 00:24:17.227$ mice that have intact City 25,

NOTE Confidence: 0.77276397

 $00:24:17.230 \longrightarrow 00:24:19.810$ but are lacking the L2 cytokine.

NOTE Confidence: 0.77276397

 $00{:}24{:}19{.}810 \dashrightarrow 00{:}24{:}22{.}390$ But contrary to our hypothesis fraction,

NOTE Confidence: 0.77276397

 $00:24:22.390 \rightarrow 00:24:25.934$ D&F are just fine and be so developmen

NOTE Confidence: 0.77276397

 $00:24:25.934 \rightarrow 00:24:29.117$ is completely unperturbed in these mice.

NOTE Confidence: 0.77276397

00:24:29.120 --> 00:24:31.556 And I'll see you in this proximity

NOTE Confidence: 0.77276397

 $00:24:31.556 \longrightarrow 00:24:32.252$ ligation analysis,

NOTE Confidence: 0.77276397

 $00{:}24{:}32{.}260 \dashrightarrow 00{:}24{:}34{.}216$ we find that C25 does actually

NOTE Confidence: 0.77276397

 $00:24:34.216 \longrightarrow 00:24:36.637$ not bind to any of those other

NOTE Confidence: 0.77276397

00:24:36.637 --> 00:24:39.066 change of the L2 receptor and does

NOTE Confidence: 0.77276397

 $00:24:39.145 \longrightarrow 00:24:40.990$ not respond to iron tools.

 $00:24:40.990 \longrightarrow 00:24:43.078$ So it's not true that C.

NOTE Confidence: 0.77276397

00:24:43.080 --> 00:24:46.064 25 is in any way related to I

NOTE Confidence: 0.77276397

00:24:46.064 --> 00:24:48.510 L2 signaling and visas instead.

NOTE Confidence: 0.77276397

 $00:24:48.510 \rightarrow 00:24:51.639$ We found in our proximity ligation assay,

NOTE Confidence: 0.77276397

 $00{:}24{:}51{.}640 \dashrightarrow 00{:}24{:}54{.}460$ said City 25 associate itself.

NOTE Confidence: 0.77276397

 $00:24:54.460 \longrightarrow 00:24:56.842$ With a signal image chain of

NOTE Confidence: 0.77276397

 $00:24:56.842 \longrightarrow 00:24:58.430$ the B cell receptor,

NOTE Confidence: 0.77276397

 $00{:}24{:}58{.}430 \dashrightarrow 00{:}25{:}00{.}602$ which again is responsible for the

NOTE Confidence: 0.77276397

 $00{:}25{:}00.602 \dashrightarrow 00{:}25{:}02.542$ Goldilocks principle to keep intact

NOTE Confidence: 0.77276397

 $00{:}25{:}02{.}542 \dashrightarrow 00{:}25{:}04{.}254$ and equilibrium and intermediate

NOTE Confidence: 0.77276397

 $00:25:04.254 \longrightarrow 00:25:05.966$ ram of signaling intensity.

NOTE Confidence: 0.77276397

 $00{:}25{:}05{.}970 \dashrightarrow 00{:}25{:}08{.}721$ And that's the case in resting B

NOTE Confidence: 0.77276397

 $00{:}25{:}08{.}721 \dashrightarrow 00{:}25{:}11{.}498$ cells where prices are even more so

NOTE Confidence: 0.77276397

 $00{:}25{:}11{.}498 \dashrightarrow 00{:}25{:}14{.}252$ the case after the visa receptor was

NOTE Confidence: 0.77276397

 $00{:}25{:}14.252 \dashrightarrow 00{:}25{:}17.087$ stimulated with an anti IG M antibody.

NOTE Confidence: 0.77276397

 $00:25:17.090 \rightarrow 00:25:20.266$ This is actually ongoing work in our lab,

- NOTE Confidence: 0.77276397
- $00:25:20.270 \longrightarrow 00:25:21.202$ by Jay,
- NOTE Confidence: 0.77276397
- $00:25:21.202 \rightarrow 00:25:23.532$ wrongly with a research scientist
- NOTE Confidence: 0.77276397
- $00{:}25{:}23.532 \dashrightarrow 00{:}25{:}24.930$ in my group.
- NOTE Confidence: 0.77276397
- $00:25:24.930 \rightarrow 00:25:27.906$ And what he found is actually their CIA.
- NOTE Confidence: 0.77276397
- $00{:}25{:}27{.}910 \dashrightarrow 00{:}25{:}30{.}510$ 25 negatively regulates B cell
- NOTE Confidence: 0.77276397
- $00{:}25{:}30{.}510$ --> $00{:}25{:}33{.}980$ activation and in the absence of CD 25.
- NOTE Confidence: 0.77276397
- 00:25:33.980 --> 00:25:34.528 Miles,
- NOTE Confidence: 0.77276397
- $00{:}25{:}34{.}528 \dashrightarrow 00{:}25{:}36{.}720$ develop spontaneous germinal center,
- NOTE Confidence: 0.80370665
- $00{:}25{:}36{.}720 \dashrightarrow 00{:}25{:}39{.}450$ so even without any immunization,
- NOTE Confidence: 0.80370665
- $00{:}25{:}39{.}450 \dashrightarrow 00{:}25{:}42{.}190$ these B cells are autoreactive.
- NOTE Confidence: 0.80370665
- $00{:}25{:}42.190 \dashrightarrow 00{:}25{:}44.374$ Their escape negative selection
- NOTE Confidence: 0.80370665
- $00{:}25{:}44{.}374$ --> $00{:}25{:}46{.}558$ and therefore more attractive,
- NOTE Confidence: 0.80370665
- $00{:}25{:}46.560 \dashrightarrow 00{:}25{:}48.615$ spontaneous germinal centers
- NOTE Confidence: 0.80370665
- $00{:}25{:}48.615 \dashrightarrow 00{:}25{:}51.355$ that are antigen independent.
- NOTE Confidence: 0.80370665
- $00{:}25{:}51{.}360 \dashrightarrow 00{:}25{:}54{.}692$ The other observation here was that if
- NOTE Confidence: 0.80370665

00:25:54.692 --> 00:25:58.220 Jerome deleted 325 in human lymphoma sales,

NOTE Confidence: 0.80370665

 $00{:}25{:}58{.}220 \dashrightarrow 00{:}26{:}00{.}670$ they undergo a particular pattern

NOTE Confidence: 0.80370665

00:26:00.670 --> 00:26:02.630 of autonomous calcium signaling.

NOTE Confidence: 0.80370665

 $00:26:02.630 \rightarrow 00:26:04.590$ They have autonomous activation.

NOTE Confidence: 0.80370665

00:26:04.590 --> 00:26:07.530 Do sales are proliferating very fast,

NOTE Confidence: 0.80370665

00:26:07.530 --> 00:26:11.940 but also for short half life and I quickly,

NOTE Confidence: 0.80370665

 $00:26:11.940 \longrightarrow 00:26:14.390$ which is reflected here by

NOTE Confidence: 0.80370665

00:26:14.390 --> 00:26:16.840 expression of PG restore parenting.

NOTE Confidence: 0.80370665

 $00{:}26{:}16.840 \dashrightarrow 00{:}26{:}18.370$ These cells are.

NOTE Confidence: 0.80370665

00:26:18.370 --> 00:26:20.410 Just easily exhausted and

NOTE Confidence: 0.80370665

 $00:26:20.410 \longrightarrow 00:26:22.680$ in that competitive fitness,

NOTE Confidence: 0.80370665

 $00{:}26{:}22.680 \dashrightarrow 00{:}26{:}26.558$ so we confirmed this here in a

NOTE Confidence: 0.80370665

 $00:26:26.558 \rightarrow 00:26:29.900$ leukemia model whereby we transformed.

NOTE Confidence: 0.80370665

 $00{:}26{:}29{.}900 \dashrightarrow 00{:}26{:}33{.}524$ 25 mouse cells with the flux see 25

NOTE Confidence: 0.80370665

 $00:26:33.524 \rightarrow 00:26:36.541$ every year and then after activation

NOTE Confidence: 0.80370665

00:26:36.541 --> 00:26:40.201 of query is illusia CD 25 expression

 $00:26:40.201 \rightarrow 00:26:43.995$ on the surface and then soon after

NOTE Confidence: 0.80370665

 $00{:}26{:}43.995 \dashrightarrow 00{:}26{:}46.484$ this says disappear from culture.

NOTE Confidence: 0.80370665

 $00{:}26{:}46{.}484 \dashrightarrow 00{:}26{:}49{.}760$ They failed to form any colonies that

NOTE Confidence: 0.80370665

 $00{:}26{:}49{.}843 \dashrightarrow 00{:}26{:}52{.}413$ cannot initiate leukemia and mice

NOTE Confidence: 0.80370665

 $00{:}26{:}52{.}413 \dashrightarrow 00{:}26{:}55{.}538$ that bears also leukemias recover and

NOTE Confidence: 0.80370665

 $00{:}26{:}55{.}538 \dashrightarrow 00{:}26{:}58{.}364$ survive for indefinite periods of time.

NOTE Confidence: 0.80370665

00:26:58.370 --> 00:26:59.240 Now, Interestingly,

NOTE Confidence: 0.80370665

 $00{:}26{:}59{.}240 \dashrightarrow 00{:}27{:}01{.}415$ and that's coming back to

NOTE Confidence: 0.80370665

 $00:27:01.415 \longrightarrow 00:27:02.720$ signaling feedback control,

NOTE Confidence: 0.80370665

 $00{:}27{:}02{.}720 \dashrightarrow 00{:}27{:}04{.}910$ we found that upon collisional

NOTE Confidence: 0.80370665

 $00:27:04.910 \longrightarrow 00:27:08.032$ City 25 in a similar way like

NOTE Confidence: 0.80370665

 $00{:}27{:}08{.}032 \dashrightarrow 00{:}27{:}10{.}546$ deletion of P-10 and ship one,

NOTE Confidence: 0.80370665

 $00{:}27{:}10.550 \dashrightarrow 00{:}27{:}14.470$ we see that the balance of ether

NOTE Confidence: 0.80370665

 $00{:}27{:}14.470 \dashrightarrow 00{:}27{:}16.150$ receptor signaling strength.

NOTE Confidence: 0.80370665

 $00:27:16.150 \longrightarrow 00:27:18.784$ It's lost cause we have hyper

 $00{:}27{:}18.784 \dashrightarrow 00{:}27{:}20.540$ 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

 $00:27:22.920 \longrightarrow 00:27:27.078$ 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

 $00{:}27{:}30{.}630 \dashrightarrow 00{:}27{:}32{.}635$ So we think those phenomena

NOTE Confidence: 0.80370665

 $00:27:32.635 \longrightarrow 00:27:34.239$ might actually be related,

NOTE Confidence: 0.80370665

 $00:27:34.240 \longrightarrow 00:27:37.400$ but CD 25 plays a role in maintaining

NOTE Confidence: 0.80370665

 $00:27:37.400 \longrightarrow 00:27:39.514$ the Goldilocks principle by

NOTE Confidence: 0.80370665

 $00{:}27{:}39{.}514 \dashrightarrow 00{:}27{:}41{.}998$ regulating kinases and phosphatases.

NOTE Confidence: 0.80370665

00:27:42.000 --> 00:27:42.336 Now,

NOTE Confidence: 0.80370665

 $00:27:42.336 \longrightarrow 00:27:43.680$ how is this possible?

NOTE Confidence: 0.80370665

 $00:27:43.680 \longrightarrow 00:27:46.956$ So the tail of CD 25 is very short

NOTE Confidence: 0.80370665

 $00:27:46.956 \longrightarrow 00:27:50.497$ here and it's just 13 amino acids and.

NOTE Confidence: 0.80370665

 $00:27:50.500 \rightarrow 00:27:55.000$ So we looked at what City 25 might bind to.

NOTE Confidence: 0.80370665

 $00{:}27{:}55{.}000 \dashrightarrow 00{:}27{:}57{.}556$ How does it interact with the

NOTE Confidence: 0.80370665

 $00:27:57.556 \rightarrow 00:28:00.086$ cytoplasmic tail and as a negative

 $00:28:00.086 \longrightarrow 00:28:02.306$ control and using this for a

NOTE Confidence: 0.80370665

 $00{:}28{:}02{.}306 \dashrightarrow 00{:}28{:}04{.}899$ lot of different experiments,

NOTE Confidence: 0.80370665

 $00:28:04.900 \longrightarrow 00:28:07.450$ we introduce a mutation of the

NOTE Confidence: 0.80370665

 $00:28:07.450 \longrightarrow 00:28:09.150$ central Seren residue which

NOTE Confidence: 0.80370665

 $00{:}28{:}09{.}229 \dashrightarrow 00{:}28{:}11{.}649$ destroys the main protein kinase.

NOTE Confidence: 0.80370665

 $00{:}28{:}11.650 \dashrightarrow 00{:}28{:}13.618$ He better consensus motive.

NOTE Confidence: 0.80370665

 $00{:}28{:}13.618 \dashrightarrow 00{:}28{:}17.698$ And here we are using a bio ID

NOTE Confidence: 0.80370665

 $00:28:17.698 \longrightarrow 00:28:20.770$ approach which is based on fusions

NOTE Confidence: 0.80370665

 $00{:}28{:}20{.}770 \dashrightarrow 00{:}28{:}23{.}916$ between the CD 25 tail and puree,

NOTE Confidence: 0.80370665

 $00{:}28{:}23{.}920 \dashrightarrow 00{:}28{:}26{.}800$ which is a bacterial biotin ligase

NOTE Confidence: 0.80370665

 $00{:}28{:}26.800 \dashrightarrow 00{:}28{:}29.788$ which attaches bio tends to approximate

NOTE Confidence: 0.80370665

 $00:28:29.788 \rightarrow 00:28:33.700$ protein space on the mound and the proximity.

NOTE Confidence: 0.80370665

 $00{:}28{:}33{.}700 \dashrightarrow 00{:}28{:}34{.}688$ And I,

NOTE Confidence: 0.80370665

 $00:28:34.688 \longrightarrow 00:28:35.676$ as expected,

NOTE Confidence: 0.80370665

 $00{:}28{:}35{.}676 \dashrightarrow 00{:}28{:}38{.}146$ we found that two phosphatases

00:28:38.146 --> 00:28:40.528 ship one and PTPN 6 here.

NOTE Confidence: 0.80370665

 $00:28:40.530 \longrightarrow 00:28:43.085$ Are in proximity of the tail of

NOTE Confidence: 0.80370665

 $00{:}28{:}43.085 \dashrightarrow 00{:}28{:}46.147$ CD 25 and this is not the case.

NOTE Confidence: 0.80370665

 $00:28:46.150 \longrightarrow 00:28:48.750$ The tail here is mutated.

NOTE Confidence: 0.80370665

 $00{:}28{:}48.750 \dashrightarrow 00{:}28{:}51.774$ And this is also confirmed here in

NOTE Confidence: 0.80370665

 $00{:}28{:}51{.}774$ --> $00{:}28{:}54{.}017$ a more traditional experiment based NOTE Confidence: 0.80370665

00:28:54.017 --> 00:28:57.041 on pull down and quiet peace or

NOTE Confidence: 0.80370665

00:28:57.041 --> 00:28:59.915 ship 1P-10 and PTPN 6 can or bind.

NOTE Confidence: 0.80370665

 $00{:}28{:}59{.}920 \dashrightarrow 00{:}29{:}02{.}842$ But binding this weekend or entirely NOTE Confidence: 0.80370665

00:29:02.842 --> 00:29:06.298 lost when the stay here is mutated.

NOTE Confidence: 0.80370665

00:29:06.300 --> 00:29:08.280 So in terms of function,

NOTE Confidence: 0.80370665

 $00{:}29{:}08{.}280 \dashrightarrow 00{:}29{:}10{.}688$ this could be confirmed that indeed see

NOTE Confidence: 0.80370665

00:29:10.688 --> 00:29:13.160 25 functioned as a powerful negative

NOTE Confidence: 0.80370665

 $00{:}29{:}13.160 \dashrightarrow 00{:}29{:}14.988$ regulator of signaling strength.

NOTE Confidence: 0.80370665

 $00:29:14.990 \longrightarrow 00:29:17.360$ So if he abusively activate while

NOTE Confidence: 0.80370665

 $00:29:17.360 \rightarrow 00:29:20.130$ types unify, we can block the kite.

- NOTE Confidence: 0.80370665
- $00{:}29{:}20{.}130 \dashrightarrow 00{:}29{:}22{.}105$ Some signal here that would
- NOTE Confidence: 0.80370665
- 00:29:22.105 --> 00:29:23.290 otherwise be elicited.
- NOTE Confidence: 0.80370665
- $00{:}29{:}23.290 \dashrightarrow 00{:}29{:}25.265$ So he expresses the 25
- NOTE Confidence: 0.80370665
- $00:29:25.265 \rightarrow 00:29:27.240$ and it's wild type form.
- NOTE Confidence: 0.80370665
- $00:29:27.240 \longrightarrow 00:29:29.110$ The signal is delayed and
- NOTE Confidence: 0.80370665
- $00:29:29.110 \longrightarrow 00:29:30.980$ almost entirely lost if they
- NOTE Confidence: 0.80648685
- $00:29:31.053 \rightarrow 00:29:32.370$ express the mutant.
- NOTE Confidence: 0.80648685
- 00:29:32.370 00:29:34.740 This depression can still be seen,
- NOTE Confidence: 0.80648685
- $00{:}29{:}34.740 \dashrightarrow 00{:}29{:}37.205$ but it's much less compared
- NOTE Confidence: 0.80648685
- $00:29:37.205 \longrightarrow 00:29:39.670$ to the wild type form.
- NOTE Confidence: 0.80648685
- 00:29:39.670 --> 00:29:42.466 And then in terms of leukemia,
- NOTE Confidence: 0.80648685
- $00:29:42.470 \longrightarrow 00:29:45.260$ survival and growth be used here,
- NOTE Confidence: 0.80648685
- 00:29:45.260 --> 00:29:46.658 cameras between the
- NOTE Confidence: 0.80648685
- 00:29:46.658 --> 00:29:48.988 extracellular part of CD 19,
- NOTE Confidence: 0.80648685
- $00:29:48.990 \longrightarrow 00:29:52.122$ which is a B cell specific
- NOTE Confidence: 0.80648685

00:29:52.122 --> 00:29:54.698 transmembrane protein and tale of NOTE Confidence: 0.80648685 00:29:54.698 --> 00:29:57.456 225 users via type or is mutant NOTE Confidence: 0.80648685 00:29:57.456 - > 00:30:00.260 and wild type form can rescue. NOTE Confidence: 0.80648685 00:30:00.260 -> 00:30:02.565 Survival of leukemia cells but NOTE Confidence: 0.80648685 $00{:}30{:}02{.}565 \dashrightarrow 00{:}30{:}05{.}548$ seven 268 a mutant cannots again NOTE Confidence: 0.80648685 $00:30:05.548 \rightarrow 00:30:08.503$ showing that ability to recruit NOTE Confidence: 0.80648685 00:30:08.503 --> 00:30:10.276 phosphatases to negatively NOTE Confidence: 0.80648685 $00:30:10.276 \longrightarrow 00:30:13.107$ regulate signaling is important for NOTE Confidence: 0.80648685 $00:30:13.107 \rightarrow 00:30:15.802$ survival of these leukemia cells. NOTE Confidence: 0.80648685 $00:30:15.810 \longrightarrow 00:30:18.648$ So we have modeled the interaction NOTE Confidence: 0.80648685 $00{:}30{:}18.648 \dashrightarrow 00{:}30{:}21.444$ between these molecules and came up NOTE Confidence: 0.80648685 $00:30:21.444 \rightarrow 00:30:23.904$ with the structural model for this, NOTE Confidence: 0.80648685 $00:30:23.910 \longrightarrow 00:30:27.168$ which has rank one PKC better NOTE Confidence: 0.80648685 $00:30:27.168 \longrightarrow 00:30:29.340$ scaffold at the center. NOTE Confidence: 0.80648685 00:30:29.340 --> 00:30:31.550 Wrapped around by PKC better NOTE Confidence: 0.80648685 $00:30:31.550 \longrightarrow 00:30:32.876$ and this interaction,

- NOTE Confidence: 0.80648685
- $00:30:32.880 \longrightarrow 00:30:35.802$ he has facilitated by the C25

 $00:30:35.802 \longrightarrow 00:30:38.300$ tear which insert itself here.

NOTE Confidence: 0.80648685

 $00:30:38.300 \longrightarrow 00:30:41.506$ So overall we think that he says.

NOTE Confidence: 0.80648685

 $00:30:41.510 \longrightarrow 00:30:43.910$ Activate CD 25 downstream of the

NOTE Confidence: 0.80648685

00:30:43.910 --> 00:30:46.083 visa receptor via sick because

NOTE Confidence: 0.80648685

00:30:46.083 - 00:30:48.568 he better phosphorylation of C25,

NOTE Confidence: 0.80648685

 $00:30:48.570 \longrightarrow 00:30:51.552$ which then forms a complex with Raekwon

NOTE Confidence: 0.80648685

 $00{:}30{:}51{.}552 \dashrightarrow 00{:}30{:}54{.}740$ to recruit first parties here to surface.

NOTE Confidence: 0.80648685

 $00{:}30{:}54.740 \dashrightarrow 00{:}30{:}57.085$ Which then again provide negative

NOTE Confidence: 0.80648685

 $00{:}30{:}57.085 \dashrightarrow 00{:}31{:}00.014$ feedback control so it's like a

NOTE Confidence: 0.80648685

 $00:31:00.014 \rightarrow 00:31:03.050$ circle that goes back to maintain

NOTE Confidence: 0.80648685

 $00:31:03.050 \dashrightarrow 00:31:04.568$ 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

 $00{:}31{:}07{.}330 \dashrightarrow 00{:}31{:}11{.}170$ So our conclusion is that we think that

NOTE Confidence: 0.80648685

 $00:31:11.170 \rightarrow 00:31:14.209$ negative selection can be leveraged indeed.

 $00:31:14.210 \longrightarrow 00:31:17.250$ For potential therapeutic benefits of.

NOTE Confidence: 0.80648685

00:31:17.250 --> 00:31:20.136 He said leukemia and lymphoma is

NOTE Confidence: 0.80648685

 $00{:}31{:}20{.}136 \dashrightarrow 00{:}31{:}22{.}060$ avoided because of phosphatases

NOTE Confidence: 0.80648685

00:31:22.144 --> 00:31:24.464 hyperactivation of sick or

NOTE Confidence: 0.80648685

 $00:31:24.464 \longrightarrow 00:31:26.204$ interference proceeding 25.

NOTE Confidence: 0.80648685

 $00:31:26.210 \longrightarrow 00:31:27.050$ Feedback control.

NOTE Confidence: 0.80648685

 $00{:}31{:}27.050 \dashrightarrow 00{:}31{:}29.990$ So the goal here would be to.

NOTE Confidence: 0.80648685

 $00:31:29.990 \dashrightarrow 00:31:32.686$ Push says that I had the upper limit

NOTE Confidence: 0.80648685

00:31:32.686 --> 00:31:35.756 there or it transformed the after a

NOTE Confidence: 0.80648685

 $00{:}31{:}35{.}756 \dashrightarrow 00{:}31{:}38{.}076$ powerful activation signal over the

NOTE Confidence: 0.80648685

 $00:31:38.156 \dashrightarrow 00:31:41.030$ edge by removing feedback control and

NOTE Confidence: 0.80648685

00:31:41.030 --> 00:31:43.434 balance which will trigger negative

NOTE Confidence: 0.80648685

 $00{:}31{:}43{.}434 \dashrightarrow 00{:}31{:}46{.}822$ selection of what looks like at the

NOTE Confidence: 0.80648685

 $00{:}31{:}46.822 \dashrightarrow 00{:}31{:}50.718$ level of signaling autoreactive B cells.

NOTE Confidence: 0.80648685

00:31:50.720 --> 00:31:51.428 Um?

NOTE Confidence: 0.80648685

 $00:31:51.428 \longrightarrow 00:31:54.260$ Coming back to our.

- NOTE Confidence: 0.80648685
- $00:31:54.260 \rightarrow 00:31:57.860$ Database which we find us a very rich

 $00:31:57.860 \rightarrow 00:32:00.918$ resource for new ideas and concepts.

NOTE Confidence: 0.80648685

 $00:32:00.920 \longrightarrow 00:32:02.364$ You found another interesting

NOTE Confidence: 0.80648685

 $00:32:02.364 \longrightarrow 00:32:04.169$ outcome predictor that I would

NOTE Confidence: 0.80648685

 $00:32:04.169 \longrightarrow 00:32:06.196$ like to introduce to you with the.

NOTE Confidence: 0.80648685

 $00:32:06.200 \longrightarrow 00:32:08.642$ It's a recent publication that just

NOTE Confidence: 0.80648685

 $00:32:08.642 \rightarrow 00:32:12.189$ came out a couple weeks ago and that is

NOTE Confidence: 0.80648685

 $00:32:12.189 \dashrightarrow 00:32:15.188$ focused here on a molecule called IIT M3.

NOTE Confidence: 0.80648685

 $00{:}32{:}15{.}190 \dashrightarrow 00{:}32{:}18{.}054$ And it's interfering inducible

NOTE Confidence: 0.80648685

00:32:18.054 --> 00:32:19.486 transmembrane protein.

NOTE Confidence: 0.80648685

00:32:19.490 --> 00:32:23.550 And as I showed you for C25

NOTE Confidence: 0.80648685

 $00{:}32{:}23{.}550 \dashrightarrow 00{:}32{:}25{.}830$ to smaller cure is.

NOTE Confidence: 0.80648685

00:32:25.830 --> 00:32:28.370 An outcome predictor in various.

NOTE Confidence: 0.80648685

 $00{:}32{:}28{.}370 \dashrightarrow 00{:}32{:}30{.}900$ He said leukemia and lymphoma

NOTE Confidence: 0.80648685

 $00{:}32{:}30{.}900 \dashrightarrow 00{:}32{:}34{.}572$ subtypes and it's known for long time

 $00:32:34.572 \rightarrow 00:32:37.716$ initially was found as a specifying

NOTE Confidence: 0.80648685

 $00:32:37.716 \rightarrow 00:32:40.808$ molecules for primordial germ cells.

NOTE Confidence: 0.80648685

 $00{:}32{:}40{.}810 \dashrightarrow 00{:}32{:}42{.}766$ And then more recently it was

NOTE Confidence: 0.80648685

 $00:32:42.766 \longrightarrow 00:32:45.074$ found as an antiviral protein that

NOTE Confidence: 0.80648685

 $00{:}32{:}45.074 \dashrightarrow 00{:}32{:}46.950$ can restrict viral replication.

NOTE Confidence: 0.80648685

 $00:32:46.950 \rightarrow 00:32:48.186$ He is shown HIV,

NOTE Confidence: 0.80648685

 $00{:}32{:}48.186 \dashrightarrow 00{:}32{:}50.541$ but more recent data shows it also

NOTE Confidence: 0.80648685

 $00{:}32{:}50{.}541 \dashrightarrow 00{:}32{:}52{.}691$ important for the restriction of

NOTE Confidence: 0.80648685

 $00:32:52.691 \dashrightarrow 00:32:55.020$ coronavirus and many other viruses,

NOTE Confidence: 0.80648685

 $00:32:55.020 \dashrightarrow 00:32:57.812$ and what was important to us is that NOTE Confidence: 0.80648685

 $00:32:57.812 \rightarrow 00:33:00.221$ is actually used as a diagnostic

NOTE Confidence: 0.80648685

 $00:33:00.221 \dashrightarrow 00:33:02.669$ tool for pediatric leukemia to find

NOTE Confidence: 0.80648685

 $00:33:02.742 \longrightarrow 00:33:04.998$ patients that are at high risk.

NOTE Confidence: 0.80648685

 $00{:}33{:}05{.}000 \dashrightarrow 00{:}33{:}08{.}546$ So it's one probe set on a low density

NOTE Confidence: 0.80648685

 $00:33:08.546 \rightarrow 00:33:12.075$ array to identify patients at high risk.

NOTE Confidence: 0.80648685

 $00:33:12.080 \longrightarrow 00:33:14.270$ So we started the function of

- NOTE Confidence: 0.80648685
- $00:33:14.270 \rightarrow 00:33:16.845$ items three in a genetic mouse
- NOTE Confidence: 0.80648685
- 00:33:16.845 --> 00:33:18.909 model and found actually.
- NOTE Confidence: 0.80648685
- 00:33:18.910 --> 00:33:20.395 Happy says surprisingly,
- NOTE Confidence: 0.80648685
- $00{:}33{:}20{.}395 \dashrightarrow 00{:}33{:}22{.}870$ that are lacking this interferon
- NOTE Confidence: 0.80648685
- 00:33:22.870 --> 00:33:23.860 inducible transmembrane
- NOTE Confidence: 0.7593378
- 00:33:23.921 --> 00:33:25.974 protein. I have a defect
- NOTE Confidence: 0.7593378
- 00:33:25.974 --> 00:33:27.929 in PS3 kind of signaling.
- NOTE Confidence: 0.7593378
- $00{:}33{:}27{.}930 \dashrightarrow 00{:}33{:}29{.}585$ And they are prone to
- NOTE Confidence: 0.7593378
- $00{:}33{:}29{.}585 \dashrightarrow 00{:}33{:}31{.}470$ cell death as shown by P.
- NOTE Confidence: 0.7593378
- $00{:}33{:}31{.}470 \dashrightarrow 00{:}33{:}34{.}417$ 53 activation and loss of PCL too.
- NOTE Confidence: 0.7593378
- $00:33:34.420 \longrightarrow 00:33:36.580$ And importantly, these cells actually
- NOTE Confidence: 0.7593378
- $00{:}33{:}36{.}580 \dashrightarrow 00{:}33{:}38{.}740$ cannot be properly activated to
- NOTE Confidence: 0.7593378
- $00{:}33{:}38.806 \dashrightarrow 00{:}33{:}40.558$ undergo affinity maturation.
- NOTE Confidence: 0.7593378
- $00{:}33{:}40{.}560 \dashrightarrow 00{:}33{:}44{.}187$ So here is PNA is a German center marker
- NOTE Confidence: 0.7593378
- $00:33:44.187 \rightarrow 00:33:48.106$ which is a throwback for affinity maturation.
- NOTE Confidence: 0.7593378

00:33:48.110 -> 00:33:50.936 In in in, in visa here.

NOTE Confidence: 0.7593378

 $00{:}33{:}50{.}940 \dashrightarrow 00{:}33{:}54{.}636$ So if he smiles are immunized and

NOTE Confidence: 0.7593378

 $00:33:54.636 \rightarrow 00:33:57.789$ nicely form germinal centres but if.

NOTE Confidence: 0.7593378

 $00:33:57.790 \longrightarrow 00:34:00.160$ He says that by Adoptively

NOTE Confidence: 0.7593378

 $00:34:00.160 \longrightarrow 00:34:02.530$ transferred are lacking item 3.

NOTE Confidence: 0.7593378

00:34:02.530 --> 00:34:04.230 The amount of general centers

NOTE Confidence: 0.7593378

 $00{:}34{:}04{.}230 \dashrightarrow 00{:}34{:}06{.}553$ or German centre visa is and

NOTE Confidence: 0.7593378

 $00:34:06.553 \rightarrow 00:34:08.209$ subsequent affinity maturation.

NOTE Confidence: 0.7593378

 $00:34:08.210 \longrightarrow 00:34:10.938$ Is this drastically reduced?

NOTE Confidence: 0.7593378

 $00{:}34{:}10{.}940 \dashrightarrow 00{:}34{:}13{.}635$ And the same is true in leukemia,

NOTE Confidence: 0.7593378

 $00{:}34{:}13.640 \dashrightarrow 00{:}34{:}16.328$ so I have items with efficient leukemia.

NOTE Confidence: 0.7593378

 $00:34:16.330 \longrightarrow 00:34:18.358$ Says cannot form colonies.

NOTE Confidence: 0.7593378

00:34:18.358 --> 00:34:21.400 If Transformers disable or N Ross.

NOTE Confidence: 0.7593378

 $00:34:21.400 \longrightarrow 00:34:22.980$ There also lacks ability

NOTE Confidence: 0.7593378

 $00{:}34{:}22{.}980 \dashrightarrow 00{:}34{:}24{.}165$ to initiate leukemia,

NOTE Confidence: 0.7593378

 $00:34:24.170 \longrightarrow 00:34:25.942$ and those two models.

- NOTE Confidence: 0.7593378
- $00:34:25.942 \rightarrow 00:34:29.394$ And they have a similar phenotype as I

 $00:34:29.394 \rightarrow 00:34:32.226$ showed you in normally says in terms of

NOTE Confidence: 0.7593378

 $00:34:32.315 \longrightarrow 00:34:35.375$ lack of peers with kindness signaling.

NOTE Confidence: 0.7593378

 $00:34:35.380 \longrightarrow 00:34:38.624$ Survival and strong expression

NOTE Confidence: 0.7593378

 $00:34:38.624 \longrightarrow 00:34:42.679$ of death related or checkpoint

NOTE Confidence: 0.7593378

 $00:34:42.679 \longrightarrow 00:34:45.850$ related molecules like P53.

NOTE Confidence: 0.7593378

 $00{:}34{:}45.850 \dashrightarrow 00{:}34{:}48.615$ So in terms of structure and mechanism,

NOTE Confidence: 0.7593378

 $00:34:48.620 \rightarrow 00:34:51.620$ we were able to figure out how I've

NOTE Confidence: 0.7593378

 $00{:}34{:}51{.}620 \dashrightarrow 00{:}34{:}54{.}168$ item three is regulated in Indy.

NOTE Confidence: 0.7593378

 $00{:}34{:}54{.}170 \dashrightarrow 00{:}34{:}56{.}410$ Lymphocytes is actually very short

NOTE Confidence: 0.7593378

 $00:34:56.410 \longrightarrow 00:34:59.465$ protein or 433 amino acids in length

NOTE Confidence: 0.7593378

 $00{:}34{:}59{.}465 \dashrightarrow 00{:}35{:}02{.}034$ and we found that it can actually

NOTE Confidence: 0.7593378

 $00{:}35{:}02.034 \dashrightarrow 00{:}35{:}04.688$ insert itself into the cell membrane.

NOTE Confidence: 0.7593378

 $00{:}35{:}04.690 \dashrightarrow 00{:}35{:}07.630$ And this happens when I'm downstream.

NOTE Confidence: 0.7593378

 $00:35:07.630 \longrightarrow 00:35:09.661$ Also visa receptor.

- 00:35:09.661 --> 00:35:10.338 Lynn,
- NOTE Confidence: 0.7593378
- $00:35:10.338 \rightarrow 00:35:13.723$ another sack family kinases phosphorylate.
- NOTE Confidence: 0.7593378
- $00:35:13.730 \dashrightarrow 00:35:16.145$ 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
- $00{:}35{:}18{.}310 \dashrightarrow 00{:}35{:}20{.}220$ which leads to recruitment to
- NOTE Confidence: 0.7593378
- $00:35:20.220 \longrightarrow 00:35:21.366$ the cell membrane,
- NOTE Confidence: 0.7593378
- $00{:}35{:}21.370 \dashrightarrow 00{:}35{:}23.998$ and then it can easily interact
- NOTE Confidence: 0.7593378
- $00{:}35{:}23{.}998 \dashrightarrow 00{:}35{:}26{.}902$ 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
- $00{:}35{:}28{.}510 \dashrightarrow 00{:}35{:}31{.}128$ So for this reason we studied this
- NOTE Confidence: 0.7593378
- $00{:}35{:}31{.}128 \dashrightarrow 00{:}35{:}33{.}476$ 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
- $00:35:36.150 \longrightarrow 00:35:38.733$ So when we introduce us for cinematic
- NOTE Confidence: 0.7593378
- $00:35:38.733 \longrightarrow 00:35:41.745$ form of white 20 which mimics the
- NOTE Confidence: 0.7593378
- $00:35:41.745 \rightarrow 00:35:44.481$ confirmation that is always was formulated.
- NOTE Confidence: 0.7593378
- $00:35:44.490 \longrightarrow 00:35:46.565$ Into a mouse strain that

- NOTE Confidence: 0.7593378
- 00:35:46.565 --> 00:35:48.225 carries transgenic BCR ABL,

 $00{:}35{:}48{.}230 \dashrightarrow 00{:}35{:}52{.}318$ which has a very long latency to disease.

NOTE Confidence: 0.7593378

 $00:35:52.320 \rightarrow 00:35:54.906$ We actually found that this leads

NOTE Confidence: 0.7593378

 $00:35:54.906 \rightarrow 00:35:57.370$ to increased formation of colonies.

NOTE Confidence: 0.7593378

 $00{:}35{:}57{.}370 \dashrightarrow 00{:}36{:}00{.}140$ Increased PS3 kinase activity and

NOTE Confidence: 0.7593378

 $00{:}36{:}00{.}140 \dashrightarrow 00{:}36{:}02{.}910$ also increased activity of the

NOTE Confidence: 0.7593378

 $00:36:03.006 \dashrightarrow 00:36:05.778$ visa receptor signaling pathway.

NOTE Confidence: 0.7593378

 $00:36:05.780 \longrightarrow 00:36:08.240$ And.

NOTE Confidence: 0.7593378

00:36:08.240 --> 00:36:09.533 And so structurally,

NOTE Confidence: 0.7593378

 $00:36:09.533 \longrightarrow 00:36:12.119$ we could show the poisoner interactome

NOTE Confidence: 0.7593378

 $00:36:12.119 \longrightarrow 00:36:14.581$ analysis that this form of items

NOTE Confidence: 0.7593378

 $00{:}36{:}14.581 \dashrightarrow 00{:}36{:}16.546$ three intersects with multiple central

NOTE Confidence: 0.7593378

 $00{:}36{:}16.611 \dashrightarrow 00{:}36{:}18.927$ components of both the PS3 kinase

NOTE Confidence: 0.7593378

 $00{:}36{:}18.927 \dashrightarrow 00{:}36{:}20.855$ and visa receptor signaling pathway.

NOTE Confidence: 0.7593378

 $00:36:20.855 \dashrightarrow 00:36:23.855$ And there's also shown here by these red

 $00:36:23.855 \rightarrow 00:36:26.600$ dots in this proximity ligation assay, NOTE Confidence: 0.7593378 $00{:}36{:}26{.}600 \dashrightarrow 00{:}36{:}30{.}436$ where if I can three molecules come NOTE Confidence: 0.7593378 $00:36:30.436 \rightarrow 00:36:34.360$ in close proximity. And he says. NOTE Confidence: 0.7593378 $00:36:34.360 \longrightarrow 00:36:36.622$ Now the structural basis for data NOTE Confidence: 0.7593378 $00:36:36.622 \rightarrow 00:36:39.361$ set and that was very surprising to NOTE Confidence: 0.7593378 $00:36:39.361 \longrightarrow 00:36:42.049$ us that I've item 3 can directly NOTE Confidence: 0.7593378 $00:36:42.134 \longrightarrow 00:36:45.088$ bind to PIP 3 which is initiating NOTE Confidence: 0.7593378 00:36:45.088 --> 00:36:47.630 phospholipid and lipid rafts to NOTE Confidence: 0.7593378 00:36:47.630 --> 00:36:50.170 initiate PS3 kinase signaling. NOTE Confidence: 0.7593378 $00:36:50.170 \rightarrow 00:36:52.702$ And that is unexpected because this NOTE Confidence: 0.7593378 $00:36:52.702 \rightarrow 00:36:55.148$ interaction is usually mediated by a NOTE Confidence: 0.7593378 $00:36:55.148 \rightarrow 00:36:57.224$ so-called pH domain in larger proteins. NOTE Confidence: 0.7593378 $00:36:57.230 \longrightarrow 00:37:00.110$ But I've item three is such a short NOTE Confidence: 0.7593378 00:37:00.110 -> 00:37:02.599 party in that has no resemblance NOTE Confidence: 0.7593378 00:37:02.599 --> 00:37:04.279 of the pH domain, NOTE Confidence: 0.7593378 $00:37:04.280 \rightarrow 00:37:07.600$ so we were looking here for and you

- NOTE Confidence: 0.7593378
- $00:37:07.600 \rightarrow 00:37:09.833$ structure basis of houses interaction

00:37:09.833 --> 00:37:12.906 could happen in the absence of a

NOTE Confidence: 0.83150226

00:37:12.995 --> 00:37:16.285 pH domain. And we looked at the

NOTE Confidence: 0.83150226

 $00:37:16.285 \rightarrow 00:37:18.265$ conserved intracellular loop of

NOTE Confidence: 0.83150226

 $00{:}37{:}18.265 \dashrightarrow 00{:}37{:}21.299$ five items free that that is used

NOTE Confidence: 0.83150226

00:37:21.299 - > 00:37:24.239 to insert into the cell membrane,

NOTE Confidence: 0.83150226

 $00:37:24.240 \longrightarrow 00:37:29.775$ and in doing so we found a cluster of.

NOTE Confidence: 0.83150226

 $00{:}37{:}29{.}780 \dashrightarrow 00{:}37{:}32{.}923$ Five basic amino acids and of particular

NOTE Confidence: 0.83150226

 $00{:}37{:}32{.}923 \dashrightarrow 00{:}37{:}35{.}676$ interest is this bracket here would

NOTE Confidence: 0.83150226

00:37:35.676 --> 00:37:38.763 call it between lysing 83 and license

NOTE Confidence: 0.83150226

 $00{:}37{:}38{.}847 \dashrightarrow 00{:}37{:}41{.}549$ 104 and even though they are 21

NOTE Confidence: 0.83150226

 $00{:}37{:}41.549 \dashrightarrow 00{:}37{:}43.811$ amino acids apart from each other,

NOTE Confidence: 0.83150226

 $00{:}37{:}43.811 \dashrightarrow 00{:}37{:}46.013$ they come very close here in

NOTE Confidence: 0.83150226

 $00{:}37{:}46.013 \dashrightarrow 00{:}37{:}47.880$ the structure analysis,

NOTE Confidence: 0.83150226

 $00:37:47.880 \longrightarrow 00:37:49.604$ and they're basically former

 $00:37:49.604 \rightarrow 00:37:51.759$ clamp to directly interact here.

NOTE Confidence: 0.83150226

 $00{:}37{:}51{.}760 \dashrightarrow 00{:}37{:}54{.}920$ With this pit three molecule.

NOTE Confidence: 0.83150226

 $00{:}37{:}54{.}920 \dashrightarrow 00{:}37{:}58{.}128$ So by mutation analysis we were able to

NOTE Confidence: 0.83150226

 $00:37:58.128 \rightarrow 00:38:01.306$ show that the whites are morally cure.

NOTE Confidence: 0.83150226

 $00{:}38{:}01{.}310 \dashrightarrow 00{:}38{:}03{.}710$ Was this bracket of lice and

NOTE Confidence: 0.83150226

 $00:38:03.710 \longrightarrow 00:38:06.000$ 83 and license 104 intact?

NOTE Confidence: 0.83150226

00:38:06.000 --> 00:38:08.884 Is a powerful initiator of PSV kindness

NOTE Confidence: 0.83150226

 $00:38:08.884 \rightarrow 00:38:11.740$ and peace a receptor signaling?

NOTE Confidence: 0.83150226

 $00{:}38{:}11{.}740 \dashrightarrow 00{:}38{:}13{.}900$ But when these two amino acids

NOTE Confidence: 0.83150226

 $00:38:13.900 \longrightarrow 00:38:15.798$ here are mutated through the

NOTE Confidence: 0.83150226

 $00:38:15.798 \longrightarrow 00:38:17.366$ brackets along the active,

NOTE Confidence: 0.83150226

 $00:38:17.370 \longrightarrow 00:38:20.140$ the entire Lee loses ability.

NOTE Confidence: 0.83150226

 $00{:}38{:}20{.}140 \dashrightarrow 00{:}38{:}21{.}880$ So that's something that became

NOTE Confidence: 0.83150226

 $00{:}38{:}21.880 \dashrightarrow 00{:}38{:}24.047$ really interested in that we hope

NOTE Confidence: 0.83150226

 $00{:}38{:}24.047 \dashrightarrow 00{:}38{:}25.872$ to pursue further in collaboration

NOTE Confidence: 0.83150226

 $00:38:25.872 \rightarrow 00:38:27.332$ with our colleagues at.

- NOTE Confidence: 0.83150226
- $00:38:27.340 \longrightarrow 00:38:27.654$ Yeah,
- NOTE Confidence: 0.83150226
- $00:38:27.654 \longrightarrow 00:38:29.852$ like a new way of how proteins
- NOTE Confidence: 0.83150226
- $00{:}38{:}29{.}852 \dashrightarrow 00{:}38{:}32{.}081$ can make contact with Pepsi to
- NOTE Confidence: 0.83150226
- $00:38:32.081 \dashrightarrow 00:38:33.996$ initiate PSV kind of signaling
- NOTE Confidence: 0.83150226
- $00{:}38{:}33{.}996 \dashrightarrow 00{:}38{:}36{.}336$ in normal and Uncle Genic Lee.
- NOTE Confidence: 0.83150226
- 00:38:36.340 --> 00:38:37.672 Transform B says so.
- NOTE Confidence: 0.83150226
- $00{:}38{:}37.672 \dashrightarrow 00{:}38{:}39.670$ How model is that in the
- NOTE Confidence: 0.83150226
- $00:38:39.749 \longrightarrow 00:38:41.377$ absence of five items,
- NOTE Confidence: 0.83150226
- $00:38:41.380 \longrightarrow 00:38:45.028$ we and normal cells also modeling and says.
- NOTE Confidence: 0.83150226
- $00:38:45.030 \dashrightarrow 00:38:47.340$ The molecules that initiate PSU
- NOTE Confidence: 0.83150226
- $00{:}38{:}47{.}340 \dashrightarrow 00{:}38{:}49{.}650$ kind of signaling are scattered
- NOTE Confidence: 0.83150226
- $00{:}38{:}49{.}723 \dashrightarrow 00{:}38{:}51{.}847$ throughout the cell membrane.
- NOTE Confidence: 0.83150226
- $00:38:51.850 \rightarrow 00:38:52.966$ Only five items,
- NOTE Confidence: 0.83150226
- $00{:}38{:}52{.}966 \dashrightarrow 00{:}38{:}55{.}570$ three is there acting as a molecular
- NOTE Confidence: 0.83150226
- $00{:}38{:}55{.}643 \dashrightarrow 00{:}38{:}58{.}198$ glues are drawn together and form a
- NOTE Confidence: 0.83150226

 $00:38:58.198 \rightarrow 00:39:00.699$ tight complex to initiate signaling.

NOTE Confidence: 0.83150226

 $00{:}39{:}00{.}700 \dashrightarrow 00{:}39{:}05{.}120$ I'm not coming to the last part of my talk,

NOTE Confidence: 0.83150226

 $00:39:05.120 \rightarrow 00:39:06.888$ which was quite surprising

NOTE Confidence: 0.83150226

 $00{:}39{:}06{.}888 \dashrightarrow 00{:}39{:}09{.}540$ to some of us and Mr.

NOTE Confidence: 0.83150226

 $00:39:09.540 \longrightarrow 00:39:12.627$ Looking for ways to translate that knowledge.

NOTE Confidence: 0.83150226

00:39:12.630 --> 00:39:14.840 Looking for houses can be

NOTE Confidence: 0.83150226

 $00:39:14.840 \longrightarrow 00:39:15.724$ exploited therapeutically,

NOTE Confidence: 0.83150226

00:39:15.730 - 00:39:18.034 but it essentially starts from the

NOTE Confidence: 0.83150226

 $00{:}39{:}18.034 \dashrightarrow 00{:}39{:}21.029$ question of how do oncogenic pathways,

NOTE Confidence: 0.83150226

 $00:39:21.030 \longrightarrow 00:39:22.798$ once activated by mutations?

NOTE Confidence: 0.83150226

 $00:39:22.798 \longrightarrow 00:39:25.008$ How do they interact and?

NOTE Confidence: 0.825705850909091

00:39:27.090 --> 00:39:30.078 Becoming. Part of an orchestrated move

NOTE Confidence: 0.825705850909091

 $00:39:30.078 \longrightarrow 00:39:33.420$ that is to malignant transformation.

NOTE Confidence: 0.825705850909091

 $00{:}39{:}33{.}420 \dashrightarrow 00{:}39{:}37{.}108$ And this idea is based on a concept

NOTE Confidence: 0.825705850909091

 $00:39:37.108 \dashrightarrow 00:39:39.961$ that was formulated and long

NOTE Confidence: 0.825705850909091

00:39:39.961 - > 00:39:43.597 time ago by fear and Vogelstein.

- NOTE Confidence: 0.825705850909091
- 00:39:43.600 --> 00:39:46.400 Here's Arconic concept of Mikey
- NOTE Confidence: 0.825705850909091
- $00:39:46.400 \longrightarrow 00:39:48.640$ step malignant transformation by
- NOTE Confidence: 0.825705850909091
- $00{:}39{:}48.640 \dashrightarrow 00{:}39{:}50.754$ sequential acquisition of Driver
- NOTE Confidence: 0.825705850909091
- $00:39:50.754 \rightarrow 00:39:53.790$ Uncle Gene set together, then form
- NOTE Confidence: 0.825705850909091
- $00:39:53.790 \rightarrow 00:39:56.465$ the development of colorectal cancer.
- NOTE Confidence: 0.825705850909091
- $00:39:56.470 \longrightarrow 00:40:00.000$ So the question here is, is this.
- NOTE Confidence: 0.825705850909091
- $00:40:00.000 \longrightarrow 00:40:02.550$ Same in visa is do we.
- NOTE Confidence: 0.825705850909091
- $00:40:02.550 \longrightarrow 00:40:04.804$ Is it true that acquisition of addition
- NOTE Confidence: 0.825705850909091
- $00:40:04.804 \rightarrow 00:40:07.300$ mutations lead to more malignant phenotypes?
- NOTE Confidence: 0.825705850909091
- $00:40:07.300 \longrightarrow 00:40:09.525$ And how do these on cogenic
- NOTE Confidence: 0.825705850909091
- $00:40:09.525 \rightarrow 00:40:11.750$ pathways interact with each other?
- NOTE Confidence: 0.825705850909091
- $00:40:11.750 \longrightarrow 00:40:13.400$ So to answer this question,
- NOTE Confidence: 0.825705850909091
- $00{:}40{:}13.400 \dashrightarrow 00{:}40{:}15.902$ we formed a collaboration with Children
- NOTE Confidence: 0.825705850909091
- $00{:}40{:}15.902 \dashrightarrow 00{:}40{:}17.950$ psychology Group and Saint Jude.
- NOTE Confidence: 0.825705850909091
- $00:40:17.950 \longrightarrow 00:40:20.380$ And studied.
- NOTE Confidence: 0.825705850909091

 $00:40:20.380 \longrightarrow 00:40:23.795$ Mutation data from one 1148

NOTE Confidence: 0.825705850909091

00:40:23.795 - 00:40:27.210 cases of ecel image PLA.

NOTE Confidence: 0.825705850909091

 $00{:}40{:}27{.}210 \dashrightarrow 00{:}40{:}29{.}962$ And what we did first was what you

NOTE Confidence: 0.825705850909091

 $00{:}40{:}29{.}962 \dashrightarrow 00{:}40{:}32{.}769$ would call a mapping analysis of

NOTE Confidence: 0.825705850909091

 $00:40:32.769 \longrightarrow 00:40:35.319$ affinity versus repulsion of pathways.

NOTE Confidence: 0.825705850909091

 $00{:}40{:}35{.}320 \dashrightarrow 00{:}40{:}37{.}460$ So basically asking the question.

NOTE Confidence: 0.825705850909091

 $00:40:37.460 \longrightarrow 00:40:40.616$ So activating lesions in one pathway.

NOTE Confidence: 0.825705850909091

 $00:40:40.620 \rightarrow 00:40:41.648$ Are they?

NOTE Confidence: 0.825705850909091

 $00:40:41.648 \rightarrow 00:40:45.246$ Do they have affinity to activation of?

NOTE Confidence: 0.8212341

00:40:47.940 --> 00:40:49.520 Hidden in a different pathway?

NOTE Confidence: 0.8212341

 $00:40:49.520 \rightarrow 00:40:52.012$ Or is there like relationships of mutual NOTE Confidence: 0.8212341

 $00:40:52.012 \rightarrow 00:40:54.497$ exclusivity and we found a number of

NOTE Confidence: 0.8212341

 $00:40:54.497 \rightarrow 00:40:56.770$ interactions that we are still working on?

NOTE Confidence: 0.8212341

 $00:40:56.770 \longrightarrow 00:40:58.450$ But one was really striking to

NOTE Confidence: 0.8212341

 $00{:}40{:}58{.}450 \dashrightarrow 00{:}41{:}00{.}608$ us and it's an interaction of

NOTE Confidence: 0.8212341

00:41:00.608 --> 00:41:02.556 repulsion of mutual exclusivity,

- NOTE Confidence: 0.8212341
- $00{:}41{:}02{.}560 \dashrightarrow 00{:}41{:}04{.}726$ as shown here in this cartoon.

00:41:04.730 --> 00:41:08.097 And that involves a stat 5 pathway.

NOTE Confidence: 0.8212341

 $00{:}41{:}08{.}100 \dashrightarrow 00{:}41{:}11{.}396$ The Jack Stat 5 Path pathway and IIRC

NOTE Confidence: 0.8212341

 $00:41:11.396 \rightarrow 00:41:14.600$ home up kinase signaling pathway.

NOTE Confidence: 0.8212341

 $00:41:14.600 \longrightarrow 00:41:17.816$ And here I'm showing you the

NOTE Confidence: 0.8212341

 $00:41:17.816 \longrightarrow 00:41:21.250$ result based on these 1148 cases.

NOTE Confidence: 0.8212341

 $00{:}41{:}21{.}250 \dashrightarrow 00{:}41{:}23{.}810$ Many of them have shown here in Green

NOTE Confidence: 0.8212341

00:41:23.810 --> 00:41:25.886 Spot 5 activating lesions forming

NOTE Confidence: 0.8212341

 $00:41:25.886 \longrightarrow 00:41:29.050$ one large cluster up here and then.

NOTE Confidence: 0.8212341

00:41:29.050 --> 00:41:30.400 Here's another cluster,

NOTE Confidence: 0.8212341

 $00:41:30.400 \rightarrow 00:41:33.550$ but these are activating lesions and only

NOTE Confidence: 0.8212341

 $00:41:33.621 \longrightarrow 00:41:36.456$ in 35 cases which is just feed the spend.

NOTE Confidence: 0.8212341

 $00:41:36.460 \rightarrow 00:41:38.800$ We found activation of both pathways,

NOTE Confidence: 0.8212341

 $00{:}41{:}38.800 \dashrightarrow 00{:}41{:}43.248$ which which is much lower than than random.

NOTE Confidence: 0.8212341

 $00:41:43.250 \rightarrow 00:41:45.056$ Also, when we look at individual

00:41:45.056 --> 00:41:47.152 cases and look at phosphorylation of

NOTE Confidence: 0.8212341

 $00{:}41{:}47.152 \dashrightarrow 00{:}41{:}49.636$ Erk or phosphorylation of stat five,

NOTE Confidence: 0.8212341

 $00:41:49.640 \longrightarrow 00:41:52.503$ we have a clear cut negative or

NOTE Confidence: 0.8212341

 $00{:}41{:}52{.}503 \dashrightarrow 00{:}41{:}54{.}077$ 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

 $00{:}41{:}56{.}603 \dashrightarrow 00{:}41{:}58{.}811$ 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

 $00:42:00.882 \longrightarrow 00:42:02.954$ step file for false for work and

NOTE Confidence: 0.8212341

 $00{:}42{:}02{.}954 \dashrightarrow 00{:}42{:}04{.}806$ this leads to different profiles

NOTE Confidence: 0.8212341

 $00{:}42{:}04.806 \dashrightarrow 00{:}42{:}07.050$ 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

 $00:42:09.170 \longrightarrow 00:42:11.330$ It was in the herb signaling

NOTE Confidence: 0.8212341

 $00{:}42{:}11{.}330 \dashrightarrow 00{:}42{:}13{.}260$ pathway that effects on these.

NOTE Confidence: 0.8212341

00:42:13.260 --> 00:42:17.806 Leukemias hear worse porn at nip effects,

NOTE Confidence: 0.8212341

 $00{:}42{:}17.806 \dashrightarrow 00{:}42{:}18.272$ mainly,

NOTE Confidence: 0.8212341

 $00:42:18.272 \rightarrow 00:42:21.068$ the stat 5 signaling pathway which

- NOTE Confidence: 0.8212341
- $00:42:21.068 \rightarrow 00:42:23.609$ is affecting those leukemias here.

 $00{:}42{:}23.610 \dashrightarrow 00{:}42{:}25.770$ And I'm.

NOTE Confidence: 0.8212341

 $00{:}42{:}25{.}770 \dashrightarrow 00{:}42{:}28{.}486$ So we became interested in this small

NOTE Confidence: 0.8212341

 $00:42:28.486 \rightarrow 00:42:31.388$ minority of cases in which we have

NOTE Confidence: 0.8212341

00:42:31.388 --> 00:42:33.884 indication of activation of both pathways,

NOTE Confidence: 0.8212341

 $00:42:33.890 \longrightarrow 00:42:35.920$ even though they seem to

NOTE Confidence: 0.8212341

 $00:42:35.920 \longrightarrow 00:42:37.138$ be mutually exclusive.

NOTE Confidence: 0.8212341

 $00{:}42{:}37{.}140 \dashrightarrow 00{:}42{:}40{.}356$ So wanted to know who they occur in

NOTE Confidence: 0.8212341

 $00{:}42{:}40{.}356 \dashrightarrow 00{:}42{:}43{.}629$ the same say or how does this work?

NOTE Confidence: 0.8212341

 $00:42:43.630 \longrightarrow 00:42:45.660$ And to answer this question,

NOTE Confidence: 0.8212341

 $00:42:45.660 \rightarrow 00:42:48.220$ or we developed in our lap a single

NOTE Confidence: 0.8212341

 $00{:}42{:}48{.}220 \dashrightarrow 00{:}42{:}50{.}899$ self also protein analysis that allows

NOTE Confidence: 0.8212341

 $00{:}42{:}50{.}899 \dashrightarrow 00{:}42{:}53{.}354$ us to interrogate her phosphorylation

NOTE Confidence: 0.8212341

 $00{:}42{:}53{.}354 \dashrightarrow 00{:}42{:}56{.}337$ of STAT 5 and phosphorylation of Erk.

NOTE Confidence: 0.8212341

 $00:42:56.340 \longrightarrow 00:42:58.372$ Concurrently in single cells,

 $00:42:58.372 \rightarrow 00:43:02.480$ and this is here based on the gel

NOTE Confidence: 0.8212341

 $00:43:02.480 \longrightarrow 00:43:05.854$ matrix where we can deposit 6400 cells,

NOTE Confidence: 0.8212341

 $00{:}43{:}05{.}860 \dashrightarrow 00{:}43{:}09{.}010$ single cells and then look at STAT

NOTE Confidence: 0.8212341

 $00{:}43{:}09{.}010 \dashrightarrow 00{:}43{:}11.685$ 5 and workforce relations events

NOTE Confidence: 0.8212341

 $00{:}43{:}11.685 \dashrightarrow 00{:}43{:}14.750$ individually and this year or

NOTE Confidence: 0.8212341

 $00:43:14.750 \longrightarrow 00:43:16.589$ four patient arrived.

NOTE Confidence: 0.8212341

 $00{:}43{:}16.590 \dashrightarrow 00{:}43{:}19.050$ Cases where we looked at individual

NOTE Confidence: 0.8212341

 $00{:}43{:}19.050 \dashrightarrow 00{:}43{:}21.612$ sales and were then actually able

NOTE Confidence: 0.8212341

 $00{:}43{:}21.612 \dashrightarrow 00{:}43{:}24.156$ to determine that even though for

NOTE Confidence: 0.8212341

 $00{:}43{:}24.156 \dashrightarrow 00{:}43{:}27.278$ all those four cases we get to dual

NOTE Confidence: 0.8212341

 $00:43:27.278 \longrightarrow 00:43:29.652$ signal by Western blot, if he.

NOTE Confidence: 0.8212341

 $00:43:29.652 \rightarrow 00:43:32.844$ Use our single cell for supporting analysis.

NOTE Confidence: 0.8212341

 $00{:}43{:}32{.}850 \dashrightarrow 00{:}43{:}35{.}314$ We see that these are actually two

NOTE Confidence: 0.8212341

00:43:35.314 --> 00:43:37.073 competing clones, 1 colonial start,

NOTE Confidence: 0.8212341

00:43:37.073 --> 00:43:38.768 five Zelda clone, here's org,

NOTE Confidence: 0.8212341

 $00:43:38.768 \longrightarrow 00:43:41.780$ and that goes for all four cases and we

- NOTE Confidence: 0.8212341
- $00:43:41.780 \rightarrow 00:43:44.114$ don't see any double expressing cells.

 $00:43:44.120 \longrightarrow 00:43:46.255$ So our conclusion is at least are

NOTE Confidence: 0.8212341

 $00:43:46.255 \rightarrow 00:43:48.339$ actually rare by colonial diseases,

NOTE Confidence: 0.8212341

 $00:43:48.340 \rightarrow 00:43:51.682$ in which two clones are competing

NOTE Confidence: 0.8212341

 $00:43:51.682 \longrightarrow 00:43:53.353$ against each other.

NOTE Confidence: 0.8212341

 $00:43:53.360 \longrightarrow 00:43:56.753$ Then we asked what is the reason for that?

NOTE Confidence: 0.8212341

 $00:43:56.760 \rightarrow 00:43:59.028$ So what is the underlying mechanism

NOTE Confidence: 0.8212341

 $00:43:59.028 \rightarrow 00:44:01.716$ that these two pathways just can't go

NOTE Confidence: 0.8212341

 $00:44:01.716 \rightarrow 00:44:03.936$ together and to address this question,

NOTE Confidence: 0.8212341

 $00:44:03.940 \longrightarrow 00:44:05.532$ we actually voiced it.

NOTE Confidence: 0.8212341

 $00{:}44{:}05{.}532 \dashrightarrow 00{:}44{:}07{.}920$ The alternative pathway on the leukemia

NOTE Confidence: 0.8212341

 $00{:}44{:}07{.}991 \dashrightarrow 00{:}44{:}10{.}364$ said are driven by the other pathway,

NOTE Confidence: 0.8212341

 $00{:}44{:}10{.}370 \dashrightarrow 00{:}44{:}13{.}394$ meaning that here is a visa able or

NOTE Confidence: 0.8212341

 $00{:}44{:}13{.}394 \dashrightarrow 00{:}44{:}16{.}290$ start five driven leukemia then was.

NOTE Confidence: 0.65469474

00:44:16.290 --> 00:44:19.282 And Ross, when Ross driven leukemia was VCR

 $00:44:19.282 \rightarrow 00:44:22.257$ able and use different models for that.

NOTE Confidence: 0.65469474

 $00:44:22.260 \rightarrow 00:44:24.534$ And here, this colony forming assay

NOTE Confidence: 0.65469474

 $00:44:24.534 \rightarrow 00:44:27.420$ shows if you have one single driver,

NOTE Confidence: 0.65469474

 $00:44:27.420 \longrightarrow 00:44:29.410$ either in the rason start.

NOTE Confidence: 0.65469474

 $00:44:29.410 \rightarrow 00:44:30.994$ Five pathways is dramatically

NOTE Confidence: 0.65469474

 $00:44:30.994 \longrightarrow 00:44:32.578$ increases number of colonies,

NOTE Confidence: 0.65469474

 $00:44:32.580 \longrightarrow 00:44:34.956$ but if we have posed together,

NOTE Confidence: 0.65469474

 $00:44:34.960 \longrightarrow 00:44:37.415$ we basically lose or colony

NOTE Confidence: 0.65469474

 $00{:}44{:}37{.}415 \dashrightarrow 00{:}44{:}38{.}397$ formation capability.

NOTE Confidence: 0.65469474

00:44:38.400 -> 00:44:41.286 The same holds true for growth,

NOTE Confidence: 0.65469474

 $00{:}44{:}41{.}290 \dashrightarrow 00{:}44{:}44{.}664$ so single driver nicely lead to outgrows,

NOTE Confidence: 0.65469474

 $00:44:44.670 \rightarrow 00:44:48.280$ but combination of Bosa suppressive.

NOTE Confidence: 0.65469474

 $00:44:48.280 \rightarrow 00:44:50.716$ What was really surprising to us?

NOTE Confidence: 0.65469474

 $00:44:50.720 \longrightarrow 00:44:51.412$ This actually,

NOTE Confidence: 0.65469474

 $00:44:51.412 \longrightarrow 00:44:53.834$ that if we use genetic ablation of

NOTE Confidence: 0.65469474

 $00:44:53.834 \rightarrow 00:44:56.398$ the diverging or alternative pathway,

- NOTE Confidence: 0.65469474
- $00:44:56.400 \longrightarrow 00:44:58.020$ even though we basically
- NOTE Confidence: 0.65469474
- 00:44:58.020 --> 00:45:00.045 remove an Uncle Genic driver,
- NOTE Confidence: 0.65469474
- $00:45:00.050 \rightarrow 00:45:02.080$ this actually Slack celebration of
- NOTE Confidence: 0.65469474
- $00:45:02.080 \rightarrow 00:45:04.110$ leukemia initiation in this model.
- NOTE Confidence: 0.65469474
- $00{:}45{:}04{.}110 \dashrightarrow 00{:}45{:}07{.}086$ So in this case we have here a
- NOTE Confidence: 0.65469474
- 00:45:07.086 --> 00:45:09.952 visa able or start five driven
- NOTE Confidence: 0.65469474
- $00:45:09.952 \longrightarrow 00:45:14.270$ leukemia and we remove perk. This.
- NOTE Confidence: 0.65469474
- $00:45:14.270 \rightarrow 00:45:16.430$ Accelerates development of leukemia.
- NOTE Confidence: 0.65469474
- $00{:}45{:}16{.}430 \dashrightarrow 00{:}45{:}19{.}670$ Likewise in a chaos driven leukemia.
- NOTE Confidence: 0.65469474
- $00:45:19.670 \longrightarrow 00:45:22.950$ Removal of stat 5.
- NOTE Confidence: 0.65469474
- $00:45:22.950 \longrightarrow 00:45:25.794$ Come initiates faster development
- NOTE Confidence: 0.65469474
- $00{:}45{:}25{.}794 \dashrightarrow 00{:}45{:}28{.}638$ of looking more Genesis.
- NOTE Confidence: 0.65469474
- $00:45:28.640 \longrightarrow 00:45:29.408$ And biochemically,
- NOTE Confidence: 0.65469474
- $00{:}45{:}29{.}408 \dashrightarrow 00{:}45{:}32{.}096$ we were able to recover too late.
- NOTE Confidence: 0.65469474
- $00{:}45{:}32.100 \dashrightarrow 00{:}45{:}34.790$ This was small molecule inhibitors
- NOTE Confidence: 0.65469474

- $00{:}45{:}34.790 \dashrightarrow 00{:}45{:}37.480$ that Rametta Nathan MacKinnon bitter.
- NOTE Confidence: 0.65469474
- 00:45:37.480 -> 00:45:39.343 Distinguishes her kindness
- NOTE Confidence: 0.65469474
- $00:45:39.343 \longrightarrow 00:45:41.206$ activity as expected.
- NOTE Confidence: 0.65469474
- $00:45:41.210 \longrightarrow 00:45:43.320$ But it also induces phosphorylation
- NOTE Confidence: 0.65469474
- $00{:}45{:}43{.}320 \dashrightarrow 00{:}45{:}45{.}432$ of STAT 5, and rocks.
- NOTE Confidence: 0.65469474
- $00{:}45{:}45{.}432 \dashrightarrow 00{:}45{:}47{.}116$ Litten appears opposite effect.
- NOTE Confidence: 0.65469474
- 00:45:47.120 --> 00:45:49.232 It distinguishes start 5,
- NOTE Confidence: 0.65469474
- $00:45:49.232 \longrightarrow 00:45:51.344$ but increases per activity.
- NOTE Confidence: 0.65469474
- $00{:}45{:}51{.}350 \dashrightarrow 00{:}45{:}53{.}950$ And so to end here,
- NOTE Confidence: 0.65469474
- $00:45:53.950 \longrightarrow 00:45:57.070$ this final chapter of my talk,
- NOTE Confidence: 0.65469474
- 00:45:57.070 00:45:59.595 we came across agonists that
- NOTE Confidence: 0.65469474
- 00:45:59.595 00:46:01.615 we use for pharmacological
- NOTE Confidence: 0.65469474
- $00:46:01.615 \rightarrow 00:46:03.828$ reactivation of diverging pathways.
- NOTE Confidence: 0.65469474
- $00:46:03.830 \longrightarrow 00:46:07.990$ So in this case BC I hear this,
- NOTE Confidence: 0.65469474
- 00:46:07.990 --> 00:46:12.430 I 215 is so powerful activator, IIRC agonist.
- NOTE Confidence: 0.65469474
- $00:46:12.430 \longrightarrow 00:46:15.730$ Strongly activates falsework at the

- NOTE Confidence: 0.65469474
- $00:46:15.730 \longrightarrow 00:46:19.818$ 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
- $00:46:22.725 \longrightarrow 00:46:24.848$ five phosphorylation but at the
- NOTE Confidence: 0.65469474
- $00:46:24.848 \longrightarrow 00:46:27.254$ expense of work and this has
- NOTE Confidence: 0.65469474
- $00:46:27.254 \rightarrow 00:46:29.320$ interesting activity on the clonal
- NOTE Confidence: 0.65469474
- $00{:}46{:}29{.}320 \dashrightarrow 00{:}46{:}31{.}702$ dynamics of these leukemias in vivo.
- NOTE Confidence: 0.65469474
- $00{:}46{:}31.710 \dashrightarrow 00{:}46{:}34.990$ 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
- $00:46:37.040 \longrightarrow 00:46:39.090$ if you combine these pathway
- NOTE Confidence: 0.65469474
- $00:46:39.090 \rightarrow 00:46:40.730$ agonist was conventional treatment.
- NOTE Confidence: 0.65469474
- 00:46:40.730 --> 00:46:41.951 So, for instance,
- NOTE Confidence: 0.65469474
- $00{:}46{:}41.951 \dashrightarrow 00{:}46{:}43.986$ here on Earth inhibitor with
- NOTE Confidence: 0.65469474
- $00{:}46{:}43.986 \dashrightarrow 00{:}46{:}45.649$ a Step 5 agonist,
- NOTE Confidence: 0.65469474
- $00{:}46{:}45{.}650 \dashrightarrow 00{:}46{:}47{.}658$ we achieve a dramatic
- NOTE Confidence: 0.65469474
- $00:46:47.658 \rightarrow 00:46:49.666$ prolongation of overall survival.
- NOTE Confidence: 0.65469474
- $00{:}46{:}49.670 \dashrightarrow 00{:}46{:}51.600$ So.
- NOTE Confidence: 0.65469474
- $00{:}46{:}51{.}600 \dashrightarrow 00{:}46{:}55{.}037$ The final conclusion here is that we
- NOTE Confidence: 0.65469474
- $00:46:55.037 \rightarrow 00:46:58.178$ propose that diversity of signaling input.
- NOTE Confidence: 0.65469474
- $00:46:58.180 \longrightarrow 00:47:00.765$ Is actually an important barrier
- NOTE Confidence: 0.65469474
- $00{:}47{:}00.765 \dashrightarrow 00{:}47{:}02.833$ of malignant transformation and
- NOTE Confidence: 0.65469474
- $00{:}47{:}02.833 \dashrightarrow 00{:}47{:}04.292$ centralization and convergence
- NOTE Confidence: 0.65469474
- $00{:}47{:}04.292 \dashrightarrow 00{:}47{:}06.036$ onto one single pathway.
- NOTE Confidence: 0.65469474
- $00:47:06.040 \longrightarrow 00:47:09.568$ Inactivation of all the other pathways.
- NOTE Confidence: 0.65469474
- $00{:}47{:}09{.}570 \dashrightarrow 00{:}47{:}12{.}030$ Is an early and critical step
- NOTE Confidence: 0.65469474
- $00:47:12.030 \longrightarrow 00:47:13.260$ of malignant transformation,
- NOTE Confidence: 0.65469474
- $00:47:13.260 \longrightarrow 00:47:15.260$ and if we achieve.
- NOTE Confidence: 0.65469474
- $00{:}47{:}15.260 \dashrightarrow 00{:}47{:}18.260$ To reinstate at the very signaling
- NOTE Confidence: 0.65469474
- $00{:}47{:}18.357 \dashrightarrow 00{:}47{:}19.490$ environment.
- NOTE Confidence: 0.65469474
- $00:47:19.490 \longrightarrow 00:47:21.835$ That would resemble the interactions
- NOTE Confidence: 0.65469474
- $00{:}47{:}21.835 \dashrightarrow 00{:}47{:}25.143$ of normal cells were sent by him
- NOTE Confidence: 0.65469474
- $00:47:25.143 \rightarrow 00:47:27.358$ and which have multiple receptors.

- NOTE Confidence: 0.65469474
- $00:47:27.360 \rightarrow 00:47:29.680$ Multiple cues from the environment.

 $00{:}47{:}29.680 \dashrightarrow 00{:}47{:}32.045$ So we're proposing a strategy

NOTE Confidence: 0.65469474

 $00{:}47{:}32.045 \dashrightarrow 00{:}47{:}33.464$ of pharmacological reactivation

NOTE Confidence: 0.65469474

 $00:47:33.464 \longrightarrow 00:47:36.221$ that would restore their diverse

NOTE Confidence: 0.65469474

 $00:47:36.221 \rightarrow 00:47:37.379$ signaling environment.

NOTE Confidence: 0.65469474

 $00{:}47{:}37{.}380 \dashrightarrow 00{:}47{:}39{.}924$ And we hope that this approach can also

NOTE Confidence: 0.65469474

 $00:47:39.924 \longrightarrow 00:47:42.040$ be leveraged to overcome convention

NOTE Confidence: 0.65469474

 $00{:}47{:}42.040 \dashrightarrow 00{:}47{:}43.928$ mechanisms of black resistance.

NOTE Confidence: 0.65469474

 $00{:}47{:}43{.}930 \dashrightarrow 00{:}47{:}46{.}240$ So here we have passed their

NOTE Confidence: 0.65469474

 $00:47:46.240 \longrightarrow 00:47:47.010$ convergence minimal.

NOTE Confidence: 0.65469474

 $00{:}47{:}47{.}010 \dashrightarrow 00{:}47{:}49{.}314$ What we called friction and permissive

NOTE Confidence: 0.65469474

00:47:49.314 --> 00:47:50.466 environment for transformation.

NOTE Confidence: 0.65469474

 $00:47:50.470 \rightarrow 00:47:53.165$ But here if you have divergent pathways,

NOTE Confidence: 0.65469474

 $00{:}47{:}53{.}170 \dashrightarrow 00{:}47{:}55{.}928$ we actually do have some friction and

NOTE Confidence: 0.65469474

 $00{:}47{:}55{.}928$ --> $00{:}47{:}59{.}009$ create a non permissive environment.

00:47:59.010 --> 00:48:01.899 And with that I would like to thank a

NOTE Confidence: 0.65469474

00:48:01.899 --> 00:48:04.409 number of collaborators at a dinner,

NOTE Confidence: 0.65469474

 $00:48:04.410 \longrightarrow 00:48:06.080$ Farber at yeah.

NOTE Confidence: 0.65469474

 $00:48:06.080 \longrightarrow 00:48:07.840$ And would like to acknowledge

NOTE Confidence: 0.65469474

 $00{:}48{:}07{.}840 \dashrightarrow 00{:}48{:}10{.}080$ particular 2 senior members of my lap.

NOTE Confidence: 0.76657015

00:48:10.080 --> 00:48:11.740 Linda Shannon and Jerome Lee,

NOTE Confidence: 0.76657015

 $00:48:11.740 \longrightarrow 00:48:13.738$ who did most of the conceptual

NOTE Confidence: 0.76657015

 $00:48:13.738 \longrightarrow 00:48:15.070$ innovation of this work.

NOTE Confidence: 0.76657015

00:48:15.070 --> 00:48:16.398 Thank you very much.

NOTE Confidence: 0.8229462

 $00{:}48{:}19{.}490 \dashrightarrow 00{:}48{:}22{.}034$ Marcus that's amazing. Collection

NOTE Confidence: 0.8229462

 $00{:}48{:}22.034 \dashrightarrow 00{:}48{:}26.570$ of studies and it is remarkable how

NOTE Confidence: 0.8229462

00:48:26.675 --> 00:48:30.225 complex and somewhat almost counter

NOTE Confidence: 0.8229462

 $00{:}48{:}30{.}225 \dashrightarrow 00{:}48{:}34{.}357$ intuitive alot of these pathways are

NOTE Confidence: 0.8229462

 $00:48:34.357 \rightarrow 00:48:37.647$ in B cells and be some legacies.

NOTE Confidence: 0.8229462

 $00{:}48{:}37.650 \dashrightarrow 00{:}48{:}39.468$ And it's obviously a delicate balance.

NOTE Confidence: 0.8229462

00:48:39.470 --> 00:48:41.732 And let me ask you, 'cause you?

- NOTE Confidence: 0.8229462
- 00:48:41.732 --> 00:48:43.988 You've identified a number of pathways.

00:48:43.990 --> 00:48:46.615 That I guess are principally

NOTE Confidence: 0.8229462

 $00:48:46.615 \rightarrow 00:48:49.240$ designed for B cell elimination.

NOTE Confidence: 0.8229462

 $00:48:49.240 \longrightarrow 00:48:51.276$ That you could leverage.

NOTE Confidence: 0.8229462

00:48:51.276 --> 00:48:53.312 How would you potentially

NOTE Confidence: 0.8229462

 $00:48:53.312 \rightarrow 00:48:55.140$ target those pathways?

NOTE Confidence: 0.8229462

 $00:48:55.140 \longrightarrow 00:48:57.108$ Or could you target those pathways

NOTE Confidence: 0.8229462

 $00:48:57.108 \longrightarrow 00:48:58.901$ in conjunction with the growing

NOTE Confidence: 0.8229462

00:48:58.901 --> 00:49:00.173 arm
amentarium of available

NOTE Confidence: 0.8229462

 $00:49:00.173 \longrightarrow 00:49:01.869$ therapies for be similar?

NOTE Confidence: 0.8229462

00:49:01.870 --> 00:49:04.120 Concedes that are now in practice?

NOTE Confidence: 0.8229462

00:49:04.120 --> 00:49:05.239 Or could you,

NOTE Confidence: 0.8229462

 $00:49:05.239 \rightarrow 00:49:07.104$ could you leverage that combination?

NOTE Confidence: 0.86497533

 $00:49:09.170 \longrightarrow 00:49:11.318$ Right in terms of potential for

NOTE Confidence: 0.86497533

 $00{:}49{:}11{.}318$ --> $00{:}49{:}13{.}830$ translation and how we would leverage

00:49:13.830 --> 00:49:15.846 hyperactivation of Visa receptor

NOTE Confidence: 0.86497533

 $00:49:15.846 \rightarrow 00:49:18.600$ signaling to engage negative selection,

NOTE Confidence: 0.86497533

 $00{:}49{:}18.600 \dashrightarrow 00{:}49{:}24.290$ and I think we have two options, one is.

NOTE Confidence: 0.86497533

 $00{:}49{:}24{.}290 \dashrightarrow 00{:}49{:}26{.}660$ Already available, but less attractive,

NOTE Confidence: 0.86497533

 $00{:}49{:}26.660 \dashrightarrow 00{:}49{:}29.882$ that would be April inhibition or

NOTE Confidence: 0.86497533

 $00:49:29.882 \longrightarrow 00:49:32.930$ phosphatases like Ship One and P-10.

NOTE Confidence: 0.86497533

 $00{:}49{:}32{.}930 \dashrightarrow 00{:}49{:}35{.}972$ I'm attractive cause in the field

NOTE Confidence: 0.86497533

 $00{:}49{:}35{.}972 \dashrightarrow 00{:}49{:}38{.}625$ phosphatase innovation raises a lot

NOTE Confidence: 0.86497533

 $00{:}49{:}38.625 \dashrightarrow 00{:}49{:}40.809$ of questions about specificity.

NOTE Confidence: 0.86497533

 $00{:}49{:}40.810 \dashrightarrow 00{:}49{:}43.288$ 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

 $00{:}49{:}46.705 \dashrightarrow 00{:}49{:}49.719$ would be to generate a direct agonist

NOTE Confidence: 0.86497533

 $00:49:49.719 \rightarrow 00:49:52.568$ 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

 $00{:}49{:}55{.}530 \dashrightarrow 00{:}49{:}57{.}898$ visa receptor signaling cascade.

NOTE Confidence: 0.86497533

 $00:49:57.900 \longrightarrow 00:50:01.068$ So actually yesterday.

00:50:01.070 --> 00:50:03.311 I was at at Mark CBI weekly meeting and

NOTE Confidence: 0.86497533

 $00{:}50{:}03{.}311 \dashrightarrow 00{:}50{:}05{.}457$ and there was some encouraging feedback

NOTE Confidence: 0.86497533

 $00:50:05.457 \longrightarrow 00:50:07.870$ that that might actually be feasable.

NOTE Confidence: 0.86497533

 $00{:}50{:}07{.}870 \dashrightarrow 00{:}50{:}10{.}131$ So that's an approach that I would

NOTE Confidence: 0.86497533

 $00:50:10.131 \longrightarrow 00:50:12.156$ definitely like to pursue in the

NOTE Confidence: 0.86497533

 $00:50:12.156 \longrightarrow 00:50:14.130$ future to develop a direct hyper

NOTE Confidence: 0.86497533

 $00:50:14.130 \longrightarrow 00:50:16.298$ agonist or one of these key kindness.

NOTE Confidence: 0.8305846

00:50:18.720 --> 00:50:20.860 Excellent, thank you so and

NOTE Confidence: 0.8305846

 $00{:}50{:}20{.}860 \dashrightarrow 00{:}50{:}23{.}481$ people should feel free to submit

NOTE Confidence: 0.8305846

 $00{:}50{:}23.481 \dashrightarrow 00{:}50{:}26.253$ questions on the on the chat box.

NOTE Confidence: 0.8305846

 $00:50:26.260 \longrightarrow 00:50:28.360$ Dying cross as a question.

NOTE Confidence: 0.8305846

 $00{:}50{:}28{.}360 \dashrightarrow 00{:}50{:}31{.}704$ I don't know if you can see it.

NOTE Confidence: 0.8305846

00:50:31.710 --> 00:50:33.800 Marcus, I'll just read it.

NOTE Confidence: 0.8305846

00:50:33.800 --> 00:50:35.750 PLA suggested that CD 25 C

NOTE Confidence: 0.8305846

00:50:35.750 --> 00:50:37.050 79 eight colocalization is

 $00:50:37.112 \rightarrow 00:50:38.830$ predominantly intracellular.

NOTE Confidence: 0.8305846

 $00:50:38.830 \longrightarrow 00:50:41.770$ What do you think that this indicates?

NOTE Confidence: 0.8182225

 $00:50:43.440 \longrightarrow 00:50:46.728$ Great questions so.

NOTE Confidence: 0.8182225

 $00{:}50{:}46{.}730 \dashrightarrow 00{:}50{:}50{.}270$ We have done an experiment with.

NOTE Confidence: 0.8182225

 $00{:}50{:}50{.}270 \dashrightarrow 00{:}50{:}53{.}049$ WGA, which is a surface marker and

NOTE Confidence: 0.8182225

 $00{:}50{:}53{.}049 \dashrightarrow 00{:}50{:}55{.}207$ we we actually find colocalization

NOTE Confidence: 0.8182225

 $00:50:55.207 \longrightarrow 00:50:58.426$ of about 60 to 70% of those

NOTE Confidence: 0.8182225

 $00{:}50{:}58.426 \dashrightarrow 00{:}51{:}01.474$ 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

 $00:51:03.560 \longrightarrow 00:51:05.212$ 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

 $00{:}51{:}07.758 \dashrightarrow 00{:}51{:}10.250$ 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

 $00:51:11.774 \rightarrow 00:51:13.298$ that is very strange,

NOTE Confidence: 0.8182225

 $00:51:13.300 \rightarrow 00:51:16.114$ because why would the visa receptor

NOTE Confidence: 0.8182225

 $00{:}51{:}16.114 \dashrightarrow 00{:}51{:}18.798$ be internalized or somewhat was in

- NOTE Confidence: 0.8182225
- $00{:}51{:}18.798 \dashrightarrow 00{:}51{:}20.976$ this area associated with CD 25?

 $00:51:20.980 \longrightarrow 00:51:24.018$ And so we can answer this fully.

NOTE Confidence: 0.8182225

 $00:51:24.020 \longrightarrow 00:51:26.771$ But in light of the recent study

NOTE Confidence: 0.8182225

 $00{:}51{:}26{.}771 \dashrightarrow 00{:}51{:}28{.}885$ by whose daughter was published

NOTE Confidence: 0.8182225

00:51:28.885 --> 00:51:31.020 in nature two years ago,

NOTE Confidence: 0.8182225

 $00{:}51{:}31{.}020 \dashrightarrow 00{:}51{:}33{.}449$ where he actually shows that in malignant

NOTE Confidence: 0.8182225

00:51:33.449 --> 00:51:35.547 lymphoma B cell receptor signaling

NOTE Confidence: 0.8182225

 $00:51:35.547 \rightarrow 00:51:38.027$ complexes form of endosomal membranes,

NOTE Confidence: 0.8182225

 $00:51:38.030 \longrightarrow 00:51:39.212$ his Tinder sale.

NOTE Confidence: 0.8182225

 $00:51:39.212 \longrightarrow 00:51:41.182$ We think that exact same

NOTE Confidence: 0.8182225

 $00:51:41.182 \longrightarrow 00:51:42.939$ thing might happen here.

NOTE Confidence: 0.8182225

00:51:42.940 --> 00:51:44.048 You don't know that,

NOTE Confidence: 0.8182225

 $00:51:44.048 \rightarrow 00:51:46.450$ but that's that would be our explanation,

NOTE Confidence: 0.8182225

00:51:46.450 --> 00:51:48.358 so I don't think it's predominant.

NOTE Confidence: 0.8182225

 $00{:}51{:}48{.}360 \dashrightarrow 00{:}51{:}50{.}383$ But I agree with Diane that let

 $00:51:50.383 \rightarrow 00:51:51.870$ me see intracellular complexes,

NOTE Confidence: 0.8182225

 $00{:}51{:}51{.}870 \dashrightarrow 00{:}51{:}54{.}110$ and we think they're an endo zones.

NOTE Confidence: 0.82619333

 $00:51:55.360 \rightarrow 00:51:57.556$ Thank you and Diana's second question,

NOTE Confidence: 0.82619333

 $00{:}51{:}57{.}560 \dashrightarrow 00{:}52{:}00{.}302$ which is CD 25 seems to

NOTE Confidence: 0.82619333

 $00{:}52{:}00{.}302 \dashrightarrow 00{:}52{:}01{.}216$ prevent autoreactivity.

NOTE Confidence: 0.82619333

 $00{:}52{:}01{.}220 \dashrightarrow 00{:}52{:}03{.}800$ Do you think this is related

NOTE Confidence: 0.82619333

 $00:52:03.800 \longrightarrow 00:52:06.820$ to CD-25 CD 79 interaction?

NOTE Confidence: 0.82619333

 $00:52:06.820 \longrightarrow 00:52:11.128$ 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

 $00:52:14.360 \longrightarrow 00:52:16.610$ 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

 $00:52:18.860 \longrightarrow 00:52:20.695$ 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

 $00:52:22.170 \longrightarrow 00:52:24.378$ so Eric told us at 3:25,

NOTE Confidence: 0.826858489

 $00:52:24.380 \longrightarrow 00:52:26.744$ and that's known by work from

NOTE Confidence: 0.826858489

 $00:52:26.744 \rightarrow 00:52:29.390$ from his group and also others.

- NOTE Confidence: 0.826858489
- $00{:}52{:}29{.}390 \dashrightarrow 00{:}52{:}31{.}690$ It is crucial to maintain

 $00:52:31.690 \longrightarrow 00:52:33.990$ central visa tolerance so that

NOTE Confidence: 0.826858489

 $00:52:34.074 \rightarrow 00:52:36.539$ molecule is not there anymore.

NOTE Confidence: 0.826858489

 $00:52:36.540 \rightarrow 00:52:40.050$ Then central tolerance mechanisms don't work.

NOTE Confidence: 0.826858489

 $00{:}52{:}40.050 \dashrightarrow 00{:}52{:}41.815$ I think our signaling studies

NOTE Confidence: 0.826858489

 $00:52:41.815 \longrightarrow 00:52:43.970$ just about to clarify how this.

NOTE Confidence: 0.826858489

00:52:43.970 --> 00:52:44.325 Actually,

NOTE Confidence: 0.826858489

 $00:52:44.325 \rightarrow 00:52:46.810$ you know what this mechanism of that?

NOTE Confidence: 0.826858489

 $00{:}52{:}46{.}810 \dashrightarrow 00{:}52{:}49{.}426$ I think the link or how C25 interferes

NOTE Confidence: 0.826858489

 $00:52:49.426 \longrightarrow 00:52:51.539$ with Visa receptor signaling is not

NOTE Confidence: 0.826858489

 $00{:}52{:}51{.}539 \dashrightarrow 00{:}52{:}54{.}650$ known in our paper is not published yet,

NOTE Confidence: 0.826858489

 $00:52:54.650 \longrightarrow 00:52:57.380$ so we're still working on that.

NOTE Confidence: 0.826858489

 $00{:}52{:}57{.}380 \dashrightarrow 00{:}52{:}57{.}786$ Honey.

NOTE Confidence: 0.826858489

00:52:57.786 --> 00:52:59.816 And I I do think,

NOTE Confidence: 0.826858489

 $00:52:59.820 \rightarrow 00:53:00.037$ actually,

 $00:53:00.037 \longrightarrow 00:53:01.122$ that it doesn't act in

NOTE Confidence: 0.826858489

 $00{:}53{:}01{.}122 \dashrightarrow 00{:}53{:}02{.}280$ service in the global India.

NOTE Confidence: 0.8513638

00:53:05.370 --> 00:53:06.798 And again, people should

NOTE Confidence: 0.8513638

 $00{:}53{:}06{.}798 \dashrightarrow 00{:}53{:}08{.}226$ submit their questions online.

NOTE Confidence: 0.8513638

00:53:08.230 --> 00:53:10.702 Marcus, I mean, could you ever

NOTE Confidence: 0.8513638

 $00{:}53{:}10.702 \dashrightarrow 00{:}53{:}13.649$ conceive of you know you identify a?

NOTE Confidence: 0.8513638

00:53:13.650 - 00:53:15.672 Be so malignancy that's driven by

NOTE Confidence: 0.8513638

00:53:15.672 --> 00:53:17.679 jackstadt and you would give them,

NOTE Confidence: 0.8513638

00:53:17.680 --> 00:53:18.330 IIRC activator.

NOTE Confidence: 0.8513638

00:53:18.330 --> 00:53:20.930 You know I obviously we focus on how

NOTE Confidence: 0.8513638

00:53:20.996 --> 00:53:23.060 to inhibit the pathway in cancer,

NOTE Confidence: 0.8513638

 $00:53:23.060 \dashrightarrow 00:53:25.075$ but is that something you could

NOTE Confidence: 0.8513638

 $00:53:25.075 \rightarrow 00:53:26.750$ conceive as a therapeutic approach?

NOTE Confidence: 0.8390908

00:53:28.770 --> 00:53:31.098 If I may quote back on my slides

NOTE Confidence: 0.8390908

 $00{:}53{:}31{.}098 \dashrightarrow 00{:}53{:}32{.}720$ because there's one that I want

NOTE Confidence: 0.8390908

 $00:53:32.720 \longrightarrow 00:53:34.269$ to show you. This is study.

- NOTE Confidence: 0.5958561
- $00:53:36.810 \rightarrow 00:53:40.461$ Yeah, this study heals. Come by Veronica.

 $00:53:40.461 \longrightarrow 00:53:42.540$ Sex is group so that did you

NOTE Confidence: 0.6687811

 $00:53:42.540 \rightarrow 00:53:45.640$ want to share your slide or? Yes,

NOTE Confidence: 0.767513

 $00:53:45.640 \rightarrow 00:53:47.327$ I'm going to show this slide again.

NOTE Confidence: 0.8439994

 $00{:}53{:}54{.}460 \dashrightarrow 00{:}53{:}56{.}777$ OK, so I I hope I'm I

NOTE Confidence: 0.8439994

 $00:53:56.777 \rightarrow 00:53:58.560$ got the question correct.

NOTE Confidence: 0.8439994

 $00{:}53{:}58{.}560 \dashrightarrow 00{:}54{:}01{.}917$ This is what I I would like to refer.

NOTE Confidence: 0.8439994

 $00:54:01.920 \longrightarrow 00:54:07.200$ It's a study by the only car sex is cool.

NOTE Confidence: 0.8439994

00:54:07.200 --> 00:54:10.640 That it's a trial for patients was NPN,

NOTE Confidence: 0.8439994

 $00:54:10.640 \rightarrow 00:54:12.360$ and they received rocks.

NOTE Confidence: 0.8439994

00:54:12.360 --> 00:54:14.110 Luton Airport, just Jack.

NOTE Confidence: 0.8439994

00:54:14.110 --> 00:54:17.225 Start fires inhibitor over long periods of

NOTE Confidence: 0.8439994

 $00{:}54{:}17{.}225 \dashrightarrow 00{:}54{:}20{.}589$ time is actually going opposite direction,

NOTE Confidence: 0.8439994

 $00{:}54{:}20{.}590 \dashrightarrow 00{:}54{:}23{.}254$ so they found that these patients

NOTE Confidence: 0.8439994

 $00:54:23.254 \longrightarrow 00:54:26.150$ developed in 6% of nine patients out

 $00:54:26.150 \longrightarrow 00:54:29.852$ of 157 was NP ND well developed hybrid

NOTE Confidence: 0.8439994

 $00:54:29.852 \rightarrow 00:54:34.262$ diesel lymphoma that were driven with Keras.

NOTE Confidence: 0.8439994

 $00{:}54{:}34{.}270 \dashrightarrow 00{:}54{:}37{.}910$ And that's a 15 fold increase risk.

NOTE Confidence: 0.8439994

 $00:54:37.910 \longrightarrow 00:54:40.773$ So what they said in this study

NOTE Confidence: 0.8439994

 $00:54:40.773 \longrightarrow 00:54:43.448$ is that actually find one reason.

NOTE Confidence: 0.8439994

 $00:54:43.450 \rightarrow 00:54:47.286$ Population of the Start 5 pathway enables.

NOTE Confidence: 0.8439994

 $00:54:47.290 \longrightarrow 00:54:48.905$ The transformation of the pre

NOTE Confidence: 0.8439994

 $00:54:48.905 \rightarrow 00:54:50.903$ malignant B cell tumor that carries

NOTE Confidence: 0.8439994

 $00{:}54{:}50{.}903 \dashrightarrow 00{:}54{:}52{.}493$ the Chaos Legion that essentially

NOTE Confidence: 0.8439994

 $00{:}54{:}52{.}493 \dashrightarrow 00{:}54{:}55{.}128$ what we did in our genetic experiment.

NOTE Confidence: 0.8439994

00:54:55.130 --> 00:54:57.640 So I think it can cut both ways so it

NOTE Confidence: 0.8439994

 $00{:}54{:}57{.}709 \dashrightarrow 00{:}55{:}00{.}421$ can be beneficial if he find ways to

NOTE Confidence: 0.8439994

 $00:55:00.421 \rightarrow 00:55:02.935$ leverage this activity to completely

NOTE Confidence: 0.8439994

 $00:55:02.935 \rightarrow 00:55:04.699$ suppress oncogenic signaling.

NOTE Confidence: 0.8439994

 $00:55:04.700 \dashrightarrow 00:55:07.028$ But like Veronicas NPN study shows,

NOTE Confidence: 0.8439994

00:55:07.030 - 00:55:09.403 it can also go in your opposite

- NOTE Confidence: 0.8439994
- $00:55:09.403 \longrightarrow 00:55:11.826$ direction if you try to achieve

 $00{:}55{:}11.826$ --> $00{:}55{:}14.036$ long-term suppression of 1 pathway,

NOTE Confidence: 0.8439994

 $00:55:14.040 \rightarrow 00:55:16.368$ you might inadvertently activate the other.

NOTE Confidence: 0.8375848

 $00:55:17.790 \longrightarrow 00:55:18.986$ So it's really interesting.

NOTE Confidence: 0.8375848

 $00:55:18.986 \longrightarrow 00:55:20.182$ 'cause obviously if you're

NOTE Confidence: 0.8375848

 $00:55:20.182 \longrightarrow 00:55:21.778$ going to use ruxolitinib you,

NOTE Confidence: 0.8375848

 $00:55:21.780 \rightarrow 00:55:23.616$ it's context may be very specific.

NOTE Confidence: 0.8375848

00:55:23.620 --> 00:55:26.076 I mean, I know it's a small proportion,

NOTE Confidence: 0.8375848

 $00:55:26.080 \longrightarrow 00:55:27.916$ but that's a pretty heart risk.

NOTE Confidence: 0.8601446

 $00{:}55{:}34.780 \dashrightarrow 00{:}55{:}38.868$ Just waiting to see if any other questions.

NOTE Confidence: 0.8601446

 $00{:}55{:}38{.}870 \dashrightarrow 00{:}55{:}40{.}418$ Well, I think we're you know,

NOTE Confidence: 0.8601446

 $00{:}55{:}40{.}420 \dashrightarrow 00{:}55{:}42{.}219$ really, at the top of the hour,

NOTE Confidence: 0.8601446

 $00{:}55{:}42{.}220 \dashrightarrow 00{:}55{:}44{.}443$ so you know, want to thank Mark is for

NOTE Confidence: 0.8601446

 $00{:}55{:}44{.}443 \dashrightarrow 00{:}55{:}46{.}676$ it really is an extraordinary talk.

NOTE Confidence: 0.8601446

 $00{:}55{:}46.680 \dashrightarrow 00{:}55{:}48.580$ That's creating so much insight

 $00:55:48.580 \rightarrow 00:55:50.980$ into the biology of AB cells.

NOTE Confidence: 0.8601446

 $00:55:50.980 \rightarrow 00:55:53.326$ Both respect to cancer and autoimmunity.

NOTE Confidence: 0.8601446

00:55:53.330 --> 00:55:54.738 Wanna thank Doctor, Snyder,

NOTE Confidence: 0.8601446

 $00:55:54.738 \longrightarrow 00:55:56.850$ and Snyder for sort of share

NOTE Confidence: 0.8601446

 $00{:}55{:}56{.}922 \dashrightarrow 00{:}55{:}59{.}187$ continuing to lead this lectures hip?

NOTE Confidence: 0.8601446

00:55:59.190 --> 00:56:01.815 And I want to thank the Frisbees

NOTE Confidence: 0.8601446

 $00{:}56{:}01{.}815 \dashrightarrow 00{:}56{:}03{.}768$ for their continued support of

NOTE Confidence: 0.8601446

 $00{:}56{:}03.768 \dashrightarrow 00{:}56{:}06.018$ our Cancer Center and the mission

NOTE Confidence: 0.8601446

 $00{:}56{:}06.018 \dashrightarrow 00{:}56{:}08.578$ and the support of this lecture.

NOTE Confidence: 0.91440165

00:56:10.820 --> 00:56:12.812 I wish you all a great

NOTE Confidence: 0.91440165

 $00{:}56{:}12.812 \dashrightarrow 00{:}56{:}14.640$ day and happy New year.

NOTE Confidence: 0.895135683333333

 $00{:}56{:}17{.}160 \dashrightarrow 00{:}56{:}18{.}558$ Thank you. Thank

NOTE Confidence: 0.90354365

 $00:56:18.560 \longrightarrow 00:56:20.620$ you, thank you very much.

NOTE Confidence: 0.90354365

00:56:20.620 --> 00:56:21.940 Thank you Marcus. Take care.