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 --> 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 --> 00:00:11.265 we're sticking to the schedule

NOTE Confidence: 0.8616084

00:00:11.265 --> 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 --> 00:00:18.860 and knowledge through this form.

NOTE Confidence: 0.8616084

00:00:18.860 --> 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 --> 00:00:26.510 think we all look forward to the

NOTE Confidence: 0.8616084

00:00:26.510 --> 00:00:28.080 annual Frisbee lectureship and

NOTE Confidence: 0.8616084

00:00:28.080 --> 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 --> 00:00:40.578 is a professor of laboratory medicine.

NOTE Confidence: 0.8616084

00:00:40.580 --> 00:00:42.020 Can't send director for.

NOTE Confidence: 0.8616084

00:00:42.020 --> 00:00:43.460 For membership director of

NOTE Confidence: 0.8616084

00:00:43.460 --> 00:00:45.260 membership for the Cancer Center,

NOTE Confidence: 0.8616084

00:00:45.260 --> 00:00:46.688 Leader of blood banking.

NOTE Confidence: 0.8616084

00:00:46.688 --> 00:00:49.243 Certainly has done a lot of work

NOTE Confidence: 0.8616084

00:00:49.243 --> 00:00:51.602 over the years in that domain and

NOTE Confidence: 0.8616084

00:00:51.602 --> 00:00:54.200 has really been the Shepherd for this

NOTE Confidence: 0.8616084

00:00:54.200 --> 00:00:56.338 lectureship for the past 18 years.

NOTE Confidence: 0.8616084

00:00:56.338 --> 00:00:59.335 And I want to turn it over to Ed to

NOTE Confidence: 0.8616084

00:00:59.335 --> 00:01:01.861 share some perspectives and as well

NOTE Confidence: 0.8616084

00:01:01.861 --> 00:01:03.979 introduce members of the family.

NOTE Confidence: 0.7952434

00:01:04.790 --> 00:01:07.724 Thank you very much Charlie to pleasure to

NOTE Confidence: 0.7952434

00:01:07.724 --> 00:01:09.926 introduce the Frisbees for this lectureship.

NOTE Confidence: 0.7952434

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

NOTE Confidence: 0.7952434

00:01:12.130 --> 00:01:14.545 developed leukemia as a young man that's

NOTE Confidence: 0.7952434

00:01:14.545 --> 00:01:17.553 a teenager and was the first bone marrow

NOTE Confidence: 0.7952434

00:01:17.553 --> 00:01:19.463 transplant done in the Connecticut.

NOTE Confidence: 0.7952434

00:01:19.470 --> 00:01:22.406 It was done by the late Jill Rappaport,

NOTE Confidence: 0.7952434

00:01:22.410 --> 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 --> 00:01:29.540 transplant failed and didn't

NOTE Confidence: 0.7952434

00:01:29.540 --> 00:01:31.730 survive to have a second transplant,

NOTE Confidence: 0.7952434

00:01:31.730 --> 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 --> 00:01:39.580 the family rich Rick and Christine

NOTE Confidence: 0.7952434

00:01:39.580 --> 00:01:41.949 set up the Frisby Foundation.

NOTE Confidence: 0.7952434

00:01:41.950 --> 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 --> 00:01:51.390 They established the first stem

NOTE Confidence: 0.7952434

00:01:51.390 --> 00:01:53.480 cell processing lab at Yale,

NOTE Confidence: 0.7952434

00:01:53.480 --> 00:01:56.392 New Haven long before Smilow had the

NOTE Confidence: 0.7952434

00:01:56.392 --> 00:01:59.416 first brick lay down the foundation and

NOTE Confidence: 0.7952434

00:01:59.416 --> 00:02:02.680 that was the precursor of the HCT lab,

NOTE Confidence: 0.7952434

00:02:02.680 --> 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 --> 00:02:09.778 Went by Diet Doctor Diane Kraus.

NOTE Confidence: 0.7952434

00:02:09.780 --> 00:02:11.900 This lectureship was established 18

NOTE Confidence: 0.7952434

00:02:11.900 --> 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 --> 00:02:19.509 the 18th speaker and we welcome him.

NOTE Confidence: 0.7952434

00:02:19.510 --> 00:02:22.345 And we would like to turn it over to

NOTE Confidence: 0.7952434

00:02:22.345 --> 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,

NOTE Confidence: 0.7952434

00:02:30.310 --> 00:02:32.758 who's been very close to us for many

NOTE Confidence: 0.7952434

00:02:32.758 --> 00:02:34.871 many years and been very supportive

NOTE Confidence: 0.7952434

00:02:34.871 --> 00:02:37.479 of the foundation and the work we do.

NOTE Confidence: 0.7952434

00:02:37.480 --> 00:02:39.762 And we love this lectureship. We don't.

NOTE Confidence: 0.7952434

00:02:39.762 --> 00:02:41.066 Foundations must smaller now.

NOTE Confidence: 0.7952434

00:02:41.070 --> 00:02:43.020 We don't do that many things,

NOTE Confidence: 0.7952434

00:02:43.020 --> 00:02:45.954 but this is one thing that we continue doing,

NOTE Confidence: 0.7952434

00:02:45.960 --> 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 --> 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 --> 00:02:58.140 Doctor Fox and Marcus as well at

NOTE Confidence: 0.7952434

00:02:58.140 --> 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 --> 00:03:03.330 that you've done and for so much

NOTE Confidence: 0.7952434

00:03:03.330 --> 00:03:05.590 of the work that is being done for

NOTE Confidence: 0.7952434

00:03:05.590 --> 00:03:06.946 the patients that smile.

NOTE Confidence: 0.7952434

00:03:06.950 --> 00:03:07.476 Oh well,

NOTE Confidence: 0.7952434

00:03:07.476 --> 00:03:09.317 we can thank you for for setting

NOTE Confidence: 0.7952434

00:03:09.317 --> 00:03:10.810 the foundation for this,

NOTE Confidence: 0.7952434

00:03:10.810 --> 00:03:13.266 so I'll now turn it over to Doctor

NOTE Confidence: 0.7952434

00:03:13.266 --> 00:03:15.319 Fuchs to introduce our 18th.

NOTE Confidence: 0.7952434

00:03:15.320 --> 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 --> 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 --> 00:03:29.618 I think this is really been

NOTE Confidence: 0.7953831

00:03:29.618 --> 00:03:30.782 a wonderful tradition.

NOTE Confidence: 0.7953831

00:03:30.790 --> 00:03:32.910 Becausw, what this lectureship

NOTE Confidence: 0.7953831

00:03:32.910 --> 00:03:36.090 has done is brought to Yale.

NOTE Confidence: 0.7953831

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 --> 00:03:47.572 religion sees which I think is a fitting

NOTE Confidence: 0.7953831

00:03:47.572 --> 00:03:50.945 legacy and this year's annual Frisbee

NOTE Confidence: 0.7953831

00:03:50.945 --> 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 --> 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 --> 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 --> 00:04:13.540 as well as the associate director

NOTE Confidence: 0.7953831

00:04:13.540 --> 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 --> 00:04:25.122 As our inaugural director for the

NOTE Confidence: 0.7953831

00:04:25.122 --> 00:04:27.342 Center of Molecular and Cellular

NOTE Confidence: 0.7953831

00:04:27.342 --> 00:04:30.054 Oncology at the Yale Cancer Center

NOTE Confidence: 0.7953831

00:04:30.054 --> 00:04:32.696 and Smilow Cancer Hospital as well

NOTE Confidence: 0.7953831

00:04:32.696 --> 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 --> 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 --> 00:04:54.415 over the past decade or really longer,

NOTE Confidence: 0.7953831

00:04:54.420 --> 00:04:57.390 he has been a leading innovator

NOTE Confidence: 0.7953831

00:04:57.390 --> 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 --> 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 --> 00:05:08.870 in these cancers,

NOTE Confidence: 0.7953831

00:05:08.870 --> 00:05:11.384 Ann and really now advancing that

NOTE Confidence: 0.7953831

00:05:11.384 --> 00:05:14.322 beyond in terms of the immunobiology

NOTE Confidence: 0.7953831

00:05:14.322 --> 00:05:17.262 immunotherapy that would be available

NOTE Confidence: 0.7953831

00:05:17.262 --> 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 --> 00:05:25.540 even in terms of novel car T therapies,

NOTE Confidence: 0.7953831

00:05:25.540 --> 00:05:27.668 and I think all of that really

NOTE Confidence: 0.7953831

00:05:27.668 --> 00:05:30.527 speaks to in many respects what's so

NOTE Confidence: 0.7953831

00:05:30.527 --> 00:05:32.862 relevant for the Frisby lectureship

NOTE Confidence: 0.7953831

00:05:32.862 --> 00:05:35.420 Marcus for his many accomplishments

NOTE Confidence: 0.7953831

00:05:35.420 --> 00:05:37.432 and impressive publication record

NOTE Confidence: 0.7953831

00:05:37.432 --> 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

NOTE Confidence: 0.7953831

00:05:43.139 --> 00:05:45.319 time annunciating all of them,

NOTE Confidence: 0.7953831

00:05:45.320 --> 00:05:47.900 but they include the NCI outstanding

NOTE Confidence: 0.7953831

00:05:47.900 --> 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 --> 00:05:54.790 Welcome Trust scholar award.

NOTE Confidence: 0.7953831

00:05:54.790 --> 00:05:57.195 Among many other awards that

NOTE Confidence: 0.7953831

00:05:57.195 --> 00:05:58.638 recognize his accomplishment,

NOTE Confidence: 0.7953831

00:05:58.640 --> 00:06:02.105 an innovative and record of innovation and

NOTE Confidence: 0.7953831

00:06:02.105 --> 00:06:04.899 accomplishment across all of these cancers.

NOTE Confidence: 0.7953831

00:06:04.900 --> 00:06:08.148 So it's really a pleasure to introduce

NOTE Confidence: 0.7953831

00:06:08.148 --> 00:06:11.150 Marcus and an in many respects.

NOTE Confidence: 0.7953831

00:06:11.150 --> 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.

NOTE Confidence: 0.85380465

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

NOTE Confidence: 0.8221974

00:06:45.520 --> 00:06:48.425 So first of all, I would like

NOTE Confidence: 0.8221974

00:06:48.425 --> 00:06:51.251 to thank the Frisby family and

NOTE Confidence: 0.8221974

00:06:51.251 --> 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 --> 00:07:02.900 experience that many of us who

NOTE Confidence: 0.8221974

00:07:02.993 --> 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 --> 00:07:10.410 and leukemia and young tires.

NOTE Confidence: 0.8221974

00:07:10.410 --> 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 --> 00:07:24.286 findings from our lab that over

NOTE Confidence: 0.8221974

00:07:24.286 --> 00:07:27.330 the past recent years have led to

NOTE Confidence: 0.8221974

00:07:27.330 --> 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 --> 00:07:36.560 disease is more efficiently than.

NOTE Confidence: 0.8221974

00:07:36.560 --> 00:07:39.264 We were able to do in the past.

NOTE Confidence: 0.8221974

00:07:39.270 --> 00:07:42.590 And many of our try to leukemias are

NOTE Confidence: 0.8221974

00:07:42.590 --> 00:07:44.419 actually derived from lymphocytes

NOTE Confidence: 0.8221974

00:07:44.419 --> 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 --> 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 --> 00:07:54.522 and one potential reason for that

NOTE Confidence: 0.8221974

00:07:54.522 --> 00:07:57.293 is that B cells during the early

NOTE Confidence: 0.8221974

00:07:57.293 --> 00:07:59.777 development have to go through a

NOTE Confidence: 0.8221974

00:07:59.777 --> 00:08:01.918 series of genetic modifications

NOTE Confidence: 0.8221974

00:08:01.918 --> 00:08:04.114 in error combination class,

NOTE Confidence: 0.8221974

00:08:04.120 --> 00:08:06.560 switching hypermutation with the end

NOTE Confidence: 0.8221974

00:08:06.560 --> 00:08:09.529 goal for these cells protect us by.

NOTE Confidence: 0.8221974

00:08:09.530 --> 00:08:11.290 Generating Pi affinity antibodies

NOTE Confidence: 0.8221974

00:08:11.290 --> 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 --> 00:08:19.086 She was sitting here in his office

NOTE Confidence: 0.8221974

00:08:19.086 --> 00:08:21.645 and for those reasons B cells

NOTE Confidence: 0.8221974

00:08:21.645 --> 00:08:24.171 are an extremely high risk for

NOTE Confidence: 0.8221974

00:08:24.255 --> 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 --> 00:08:29.835 500 times higher than any other somatic cell,

NOTE Confidence: 0.8221974

00:08:29.840 --> 00:08:32.598 and for this reason and also becausw,

NOTE Confidence: 0.8221974

00:08:32.600 --> 00:08:34.880 humans can actually live without

NOTE Confidence: 0.8221974

00:08:34.880 --> 00:08:37.600 the lymphocytes for quite some time.

NOTE Confidence: 0.8221974

00:08:37.600 --> 00:08:40.540 And we developed a research program

NOTE Confidence: 0.8221974

00:08:40.540 --> 00:08:43.208 that is centered on specific

NOTE Confidence: 0.8221974

00:08:43.208 --> 00:08:46.874 vulnerabilities of this very cell type.

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

00:08:50.770 --> 00:08:53.572 and in this case we're looking

NOTE Confidence: 0.8221974

00:08:53.572 --> 00:08:54.506 for vulnerabilities.

NOTE Confidence: 0.8221974

00:08:54.510 --> 00:08:56.625 That are intrinsically encoded in

NOTE Confidence: 0.8221974

00:08:56.625 --> 00:08:59.268 the nature of the sales making

NOTE Confidence: 0.8221974

00:08:59.268 --> 00:09:01.498 antibodies and are selected and

NOTE Confidence: 0.8221974

00:09:01.498 --> 00:09:03.981 ANVISA selection is a scene that

NOTE Confidence: 0.8221974

00:09:03.981 --> 00:09:06.477 that that I hope I will be able

NOTE Confidence: 0.8221974

00:09:06.480 --> 00:09:09.805 to present to you on the occasion

NOTE Confidence: 0.8221974

00:09:09.805 --> 00:09:11.230 of this lecture.

NOTE Confidence: 0.8221974

00:09:11.230 --> 00:09:14.406 And the reason is that just by the

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

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

NOTE Confidence: 0.8221974

00:09:18.520 --> 00:09:19.885 molecules vast majority,

NOTE Confidence: 0.8221974

00:09:19.890 --> 00:09:22.626 about 75% of oil newly generated

NOTE Confidence: 0.8221974

00:09:22.626 --> 00:09:24.450 visas are initially autoreactive,

NOTE Confidence: 0.8221974

00:09:24.450 --> 00:09:26.805 meaning that their directed against

NOTE Confidence: 0.8221974

00:09:26.805 --> 00:09:30.089 himself and in these cells have to

NOTE Confidence: 0.8221974

00:09:30.089 --> 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 --> 00:09:37.643 powerful mechanisms in place to

NOTE Confidence: 0.8221974

00:09:37.643 --> 00:09:40.213 normal development to destroy and

NOTE Confidence: 0.8221974

00:09:40.213 --> 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 --> 00:09:47.380 our research in recent years is,

NOTE Confidence: 0.8221974

00:09:47.380 --> 00:09:49.265 can we actually leverage these

NOTE Confidence: 0.8221974

00:09:49.265 --> 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 --> 00:09:55.781 of normally lymphocytes for the

NOTE Confidence: 0.8221974

00:09:55.781 --> 00:09:59.649 treatment of Pisa, leukemia and lymphoma?

NOTE Confidence: 0.8221974

00:09:59.650 --> 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 --> 00:10:02.917 the principle of the cell selection

NOTE Confidence: 0.8221974

00:10:02.917 --> 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 --> 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 --> 00:10:16.692 Because only if the signal strength

NOTE Confidence: 0.8221974

00:10:16.692 --> 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 --> 00:10:23.208 then this says receive a positive

NOTE Confidence: 0.8221974

00:10:23.208 --> 00:10:25.430 signal and proliferate and survive,

NOTE Confidence: 0.8221974

00:10:25.430 --> 00:10:27.788 and this is usually the case

NOTE Confidence: 0.8221974

00:10:27.788 --> 00:10:29.360 when we have a

NOTE Confidence: 0.8480648

00:10:29.457 --> 00:10:32.657 balance between activation signals.

NOTE Confidence: 0.8480648

00:10:32.660 --> 00:10:35.980 Namely, kinase and phosphatase is.

NOTE Confidence: 0.8480648

00:10:35.980 --> 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 --> 00:10:40.764 for instance,

NOTE Confidence: 0.8480648

00:10:40.764 --> 00:10:43.333 gives the first parties are just wrong,

NOTE Confidence: 0.8480648

00:10:43.340 --> 00:10:45.530 or the receptor itself is not

NOTE Confidence: 0.8480648

00:10:45.530 --> 00:10:48.119 functional and he says die by neglect.

NOTE Confidence: 0.8480648

00:10:48.120 --> 00:10:49.880 Now we're focusing here on

NOTE Confidence: 0.8480648

00:10:49.880 --> 00:10:52.170 the other end of the scale,

NOTE Confidence: 0.8480648

00:10:52.170 --> 00:10:54.010 where the signals overwhelmingly strong,

NOTE Confidence: 0.8480648

00:10:54.010 --> 00:10:56.439 which is typically the case when this

NOTE Confidence: 0.8480648

00:10:56.439 --> 00:10:59.159 receptor he is engaged by self antigen,

NOTE Confidence: 0.8480648

00:10:59.160 --> 00:11:00.976 meaning that these receptors

NOTE Confidence: 0.8480648

00:11:00.976 --> 00:11:02.338 are out reactive.

NOTE Confidence: 0.8480648

00:11:02.340 --> 00:11:05.540 And these cells could give rise to autoimmune

NOTE Confidence: 0.8480648

00:11:05.540 --> 00:11:07.958 disease and have to be eliminated.

NOTE Confidence: 0.8480648

00:11:07.960 --> 00:11:12.384 And so this principle is not only

NOTE Confidence: 0.8480648

00:11:12.384 --> 00:11:16.600 relevant to normal B cell evelopment.

NOTE Confidence: 0.8480648

00:11:16.600 --> 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 --> 00:11:22.631 shows that in transformed B cells and

NOTE Confidence: 0.8480648

00:11:22.631 --> 00:11:24.679 leukemia and lymphoma the signaling

NOTE Confidence: 0.8480648

00:11:24.679 --> 00:11:26.829 pathway downstream of the beasts

NOTE Confidence: 0.8480648

00:11:26.829 --> 00:11:29.010 are receptors engaged permutations.

NOTE Confidence: 0.8480648

00:11:29.010 --> 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 --> 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 --> 00:11:43.127 selection for therapeutic benefits.

NOTE Confidence: 0.8480648

00:11:43.130 --> 00:11:45.881 One comes from inside that we glean

NOTE Confidence: 0.8480648

00:11:45.881 --> 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 --> 00:11:53.620 Then inside some clinical trials.

NOTE Confidence: 0.8480648

00:11:53.620 --> 00:11:55.590 So we collaborate with large

NOTE Confidence: 0.8480648

00:11:55.590 --> 00:11:58.114 clinical trial groups in the United

NOTE Confidence: 0.8480648

00:11:58.114 --> 00:12:00.050 States and internationally and

NOTE Confidence: 0.8480648

00:12:00.050 --> 00:12:02.470 look for predictors of clinical.

NOTE Confidence: 0.8480648

00:12:02.470 --> 00:12:05.312 Outcomes and what we can learn in

NOTE Confidence: 0.8480648

00:12:05.312 --> 00:12:07.970 terms of therapeutic targeting options.

NOTE Confidence: 0.8480648

00:12:07.970 --> 00:12:11.306 And then finally how these complicated

NOTE Confidence: 0.8480648

00:12:11.306 --> 00:12:12.974 oncogenic signaling pathways

NOTE Confidence: 0.8480648

00:12:12.974 --> 00:12:15.805 intersect and how we can leverage

NOTE Confidence: 0.8480648

00:12:15.805 --> 00:12:18.005 these interactions again to undermine

NOTE Confidence: 0.8480648

00:12:18.085 --> 00:12:20.830 oncogenic signaling in these diseases.

NOTE Confidence: 0.8480648

00:12:20.830 --> 00:12:23.758 So in the first part I'm going to

NOTE Confidence: 0.8480648

00:12:23.758 --> 00:12:26.273 talk about genetic lesions and what

NOTE Confidence: 0.8480648

00:12:26.273 --> 00:12:29.398 we have done here based on mutation

NOTE Confidence: 0.8480648

00:12:29.398 --> 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 --> 00:12:44.280 mutations from the angle of whether

NOTE Confidence: 0.8480648

00:12:44.280 --> 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 --> 00:12:50.789 gene or whether they are silent,

NOTE Confidence: 0.8480648

00:12:50.790 --> 00:12:53.250 meaning they are not selected for.

NOTE Confidence: 0.8480648

00:12:53.250 --> 00:12:55.791 And then in all these diseases we

NOTE Confidence: 0.8480648

00:12:55.791 --> 00:12:58.332 rank the mutations based on these

NOTE Confidence: 0.8480648

00:12:58.332 --> 00:13:00.168 replacement over silent ratios.

NOTE Confidence: 0.8480648

00:13:00.170 --> 00:13:04.190 And we do that in a way that ranks US

NOTE Confidence: 0.8480648

00:13:04.302 --> 00:13:07.998 based on the cell specific ratios.

NOTE Confidence: 0.8480648

00:13:08.000 --> 00:13:10.310 We end up with typically mutated genes,

NOTE Confidence: 0.8480648

00:13:10.310 --> 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 --> 00:13:18.200 But was interesting to us that here

NOTE Confidence: 0.8480648

00:13:18.200 --> 00:13:21.936 at the top of the list they actually.

NOTE Confidence: 0.8480648

00:13:21.940 --> 00:13:24.215 Molecules in the PS3 kindness

NOTE Confidence: 0.8480648

00:13:24.215 --> 00:13:26.490 pass visit our frequently mutated

NOTE Confidence: 0.8480648

00:13:26.568 --> 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 --> 00:13:33.300 exempted from in B cell tumors,

NOTE Confidence: 0.8480648

00:13:33.300 --> 00:13:35.624 and this activating mutations

NOTE Confidence: 0.8480648

00:13:35.624 --> 00:13:38.529 of the PS3 kinase pathway.

NOTE Confidence: 0.8480648

00:13:38.530 --> 00:13:40.558 And P-10 and then ship one

NOTE Confidence: 0.8480648

00:13:40.558 --> 00:13:41.572 night in inventory.

NOTE Confidence: 0.8480648

00:13:41.580 --> 00:13:43.276 Phosphatases in this pathway.

NOTE Confidence: 0.8480648

00:13:43.276 --> 00:13:45.820 And this is the catalytic subunit

NOTE Confidence: 0.8480648

00:13:45.890 --> 00:13:47.910 of peers with kindness itself.

NOTE Confidence: 0.8480648

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

NOTE Confidence: 0.8480648

00:13:50.292 --> 00:13:51.086 different directions,

NOTE Confidence: 0.8480648

00:13:51.090 --> 00:13:53.939 but I would like to focus your

NOTE Confidence: 0.8480648

00:13:53.939 --> 00:13:56.514 content because it was just such

NOTE Confidence: 0.8480648

00:13:56.514 --> 00:13:59.052 a subset of striking example and

NOTE Confidence: 0.8480648

00:13:59.052 --> 00:14:01.806 then as we know for a long time,

NOTE Confidence: 0.8480648

00:14:01.810 --> 00:14:03.795 pretend deletions and mutations widely

NOTE Confidence: 0.8480648

00:14:03.795 --> 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 --> 00:14:12.129 we didn't find any of these mutations.

NOTE Confidence: 0.8061034

00:14:12.130 --> 00:14:13.624 Again, highlighting the

NOTE Confidence: 0.8061034

00:14:13.624 --> 00:14:15.616 specificity of this mechanism.

NOTE Confidence: 0.8061034

00:14:15.620 --> 00:14:18.704 And pretending opposers peers

NOTE Confidence: 0.8061034

00:14:18.704 --> 00:14:21.788 to kindness signaling by.

NOTE Confidence: 0.8061034

00:14:21.790 --> 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 --> 00:14:28.761 signaling pathway and I will come

NOTE Confidence: 0.8061034

00:14:28.830 --> 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 --> 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 --> 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 --> 00:14:48.710 unlike what we know and solid tumors,

NOTE Confidence: 0.8061034

00:14:48.710 --> 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 --> 00:14:57.298 cells and if we change the sequence and

NOTE Confidence: 0.8061034

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

NOTE Confidence: 0.8061034

00:15:00.615 --> 00:15:03.266 then bring in transforming Uncle gene.

NOTE Confidence: 0.8061034

00:15:03.266 --> 00:15:05.561 Then we basically compromise malignant

NOTE Confidence: 0.8061034

00:15:05.561 --> 00:15:07.549 transformation and then most importantly,

NOTE Confidence: 0.8061034

00:15:07.550 --> 00:15:09.674 when we wait for leukemia to

NOTE Confidence: 0.8061034

00:15:09.674 --> 00:15:11.998 establish and miles at bear these

NOTE Confidence: 0.8061034

00:15:11.998 --> 00:15:14.500 tumors and then delete speech engine,

NOTE Confidence: 0.8061034

00:15:14.500 --> 00:15:17.937 this leads to remission and the mice

NOTE Confidence: 0.8061034

00:15:17.937 --> 00:15:20.829 survive for indefinite periods of time.

NOTE Confidence: 0.8061034

00:15:20.830 --> 00:15:23.236 We also confirmed that the biochemistry

NOTE Confidence: 0.8061034

00:15:23.236 --> 00:15:26.202 or the premise here is correct because

NOTE Confidence: 0.8061034

00:15:26.202 --> 00:15:28.782 we actually do see increased activity,

NOTE Confidence: 0.8061034

00:15:28.790 --> 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 --> 00:15:35.696 And most importantly,

NOTE Confidence: 0.8061034

00:15:35.696 --> 00:15:38.440 we used inhibitors that block the PS3

NOTE Confidence: 0.8061034

00:15:38.514 --> 00:15:41.508 kinase signaling pathways at multiple levels.

NOTE Confidence: 0.8061034

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

NOTE Confidence: 0.8061034

00:15:41.968 --> 00:15:45.174 activation of PS3 kinese bicec using the

NOTE Confidence: 0.8061034

00:15:45.174 --> 00:15:48.377 sick kinase inhibitor and it's platinum.

NOTE Confidence: 0.8061034

00:15:48.380 --> 00:15:51.020 BKM 120 is a pan PSD.

NOTE Confidence: 0.8061034

00:15:51.020 --> 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 --> 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 --> 00:16:03.560 leukemia cells from sad as that

NOTE Confidence: 0.8061034

00:16:03.633 --> 00:16:05.538 would otherwise be in use.

NOTE Confidence: 0.8061034

00:16:05.540 --> 00:16:08.180 Dapon deletion of the P-10 phosphatase?

NOTE Confidence: 0.8061034

00:16:08.180 --> 00:16:10.640 So this doesn't mean that these

NOTE Confidence: 0.8061034

00:16:10.640 --> 00:16:12.280 compounds are counterproductive in

NOTE Confidence: 0.8061034

00:16:12.352 --> 00:16:14.777 leukemia because actually quite useful.

NOTE Confidence: 0.8061034

00:16:14.780 --> 00:16:16.712 Our interpretation of this

NOTE Confidence: 0.8061034

00:16:16.712 --> 00:16:18.644 unexpected result is that.

NOTE Confidence: 0.8061034

00:16:18.650 --> 00:16:21.290 I was introduction of those inhibitors

NOTE Confidence: 0.8061034

00:16:21.290 --> 00:16:23.050 restores signaling equilibrium again,

NOTE Confidence: 0.8061034

00:16:23.050 --> 00:16:24.370 the Goldilocks principle

NOTE Confidence: 0.8061034

00:16:24.370 --> 00:16:26.130 that these cells need,

NOTE Confidence: 0.8061034

00:16:26.130 --> 00:16:28.909 whereas deletion of the 10 alone here

NOTE Confidence: 0.8061034

00:16:28.909 --> 00:16:30.629 introduce a drastic perturbation

NOTE Confidence: 0.8061034

00:16:30.629 --> 00:16:32.441 which engages negative selection

NOTE Confidence: 0.8061034

00:16:32.441 --> 00:16:35.710 just as it does for the elimination

NOTE Confidence: 0.8061034

00:16:35.710 --> 00:16:37.570 of Hartree active users.

NOTE Confidence: 0.8028251

00:16:40.290 --> 00:16:42.840 We are hopeful that these ideas

NOTE Confidence: 0.8028251

00:16:42.840 --> 00:16:44.540 these concepts will eventually

NOTE Confidence: 0.8028251

00:16:44.613 --> 00:16:46.737 make their way into the clinic,

NOTE Confidence: 0.8028251

00:16:46.740 --> 00:16:49.170 and as an early indication that

NOTE Confidence: 0.8028251

00:16:49.170 --> 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 --> 00:16:55.600 preclinical results in our lab,

NOTE Confidence: 0.8028251

00:16:55.600 --> 00:16:57.964 both based on small molecule inhibitors

NOTE Confidence: 0.8028251

00:16:57.964 --> 00:17:00.843 of these key fast watch cases, namely,

NOTE Confidence: 0.8028251

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

NOTE Confidence: 0.8028251

00:17:04.070 --> 00:17:08.168 and then pretend which also is.

NOTE Confidence: 0.8028251

00:17:08.170 --> 00:17:10.949 Target if it was a small molecule

NOTE Confidence: 0.8028251

00:17:10.949 --> 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 --> 00:17:23.939 burden control for long periods of time,

NOTE Confidence: 0.8028251

00:17:23.940 --> 00:17:25.056 and she's,

NOTE Confidence: 0.8028251

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

NOTE Confidence: 0.8028251

00:17:27.846 --> 00:17:31.321 survival of mice that bear patient arrives

NOTE Confidence: 0.8028251

00:17:31.321 --> 00:17:35.810 in a graphs from B cell image leukemia cells.

NOTE Confidence: 0.8028251

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

NOTE Confidence: 0.8028251

00:17:38.552 --> 00:17:41.210 can be developed further in and

NOTE Confidence: 0.8028251

00:17:41.210 --> 00:17:43.442 that some of these compounds will

NOTE Confidence: 0.8028251

00:17:43.442 --> 00:17:46.128 make it into the clinical arena.

NOTE Confidence: 0.8028251

00:17:46.130 --> 00:17:48.830 Now the central premise of this

NOTE Confidence: 0.8028251

00:17:48.830 --> 00:17:52.099 idea is that this is a mechanism.

NOTE Confidence: 0.8028251

00:17:52.100 --> 00:17:53.004 Negative selection.

NOTE Confidence: 0.8028251

00:17:53.004 --> 00:17:56.168 Removal of art reactive says that is

NOTE Confidence: 0.8028251

00:17:56.168 --> 00:17:58.203 uniquely important in B lymphocytes

NOTE Confidence: 0.8028251

00:17:58.203 --> 00:18:01.176 and to test this premise we performed

NOTE Confidence: 0.8028251

00:18:01.176 --> 00:18:03.108 a reprogramming experience.

NOTE Confidence: 0.7699414

00:18:05.590 --> 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 --> 00:18:13.480 transform besides into macrophages.

NOTE Confidence: 0.7699414

00:18:13.480 --> 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 --> 00:18:23.437 after induction and in favor of Mach one,

NOTE Confidence: 0.7699414

00:18:23.440 --> 00:18:25.510 which is a macrophage marker.

NOTE Confidence: 0.7699414

00:18:25.510 --> 00:18:28.415 And indeed, after sometimes you say it,

NOTE Confidence: 0.7699414

00:18:28.420 --> 00:18:30.842 start to crawl around on the bottom

NOTE Confidence: 0.7699414

00:18:30.842 --> 00:18:33.463 LCS dishes and like macrophages and

NOTE Confidence: 0.7699414

00:18:33.463 --> 00:18:35.973 can even phagocytose and importantly.

NOTE Confidence: 0.7699414

00:18:35.980 --> 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 --> 00:18:43.340 10, Even though genetically identical.

NOTE Confidence: 0.7699414

00:18:43.340 --> 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 --> 00:18:51.660 removes the sensitivity of these cells

NOTE Confidence: 0.7699414

00:18:51.723 --> 00:18:53.848 to removal of source phosphatases,

NOTE Confidence: 0.7699414

00:18:53.850 --> 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 --> 00:19:00.898 there's no need for macrophages to be

NOTE Confidence: 0.7699414

00:19:00.898 --> 00:19:03.488 negatively selected as beast cells are.

NOTE Confidence: 0.7699414

00:19:03.490 --> 00:19:06.642 So this gives us confidence that this is

NOTE Confidence: 0.7699414

00:19:06.642 --> 00:19:09.861 a real mechanism that is reflective of

NOTE Confidence: 0.7699414

00:19:09.861 --> 00:19:13.639 the nature of the immune system to purge.

NOTE Confidence: 0.7699414

00:19:13.640 --> 00:19:17.252 Attractive sales and that is possible to

NOTE Confidence: 0.7699414

00:19:17.252 --> 00:19:19.380 selectively target this vulnerability

NOTE Confidence: 0.7699414

00:19:19.380 --> 00:19:21.376 in B cell tumors.

NOTE Confidence: 0.7699414

00:19:21.380 --> 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 --> 00:19:28.437 and when he worried that this is not

NOTE Confidence: 0.7699414

00:19:28.437 --> 00:19:30.185 just counterintuitive because you

NOTE Confidence: 0.7699414

00:19:30.185 --> 00:19:32.638 essentially doing the opposite from what

NOTE Confidence: 0.7699414

00:19:32.638 --> 00:19:34.885 everyone else is doing in this field,

NOTE Confidence: 0.7699414

00:19:34.890 --> 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 --> 00:19:39.628 But most importantly,

NOTE Confidence: 0.7699414

00:19:39.630 --> 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 --> 00:19:45.465 long periods of time,

NOTE Confidence: 0.7699414

00:19:45.470 --> 00:19:48.025 because that in itself could be dangerous,

NOTE Confidence: 0.7699414

00:19:48.030 --> 00:19:50.814 so he did an experiment to figure out

NOTE Confidence: 0.7699414

00:19:50.814 --> 00:19:53.757 what is the shortest period of time.

NOTE Confidence: 0.7699414

00:19:53.760 --> 00:19:56.970 Home to commit Visa is to say this and he

NOTE Confidence: 0.7699414

00:19:57.048 --> 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 --> 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 --> 00:20:11.899 remain constant,

NOTE Confidence: 0.7699414

00:20:11.900 --> 00:20:13.408 'cause there's no hyperactivation

NOTE Confidence: 0.7699414

00:20:13.408 --> 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 --> 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 --> 00:20:21.262 and he found that if there's

NOTE Confidence: 0.7699414

00:20:21.262 --> 00:20:23.589 a lapse of just three hours,

NOTE Confidence: 0.7699414

00:20:23.590 --> 00:20:26.187 so removal of simulator for three hours

NOTE Confidence: 0.7699414

00:20:26.187 --> 00:20:28.836 and then adding it right back that

NOTE Confidence: 0.7699414

00:20:28.836 --> 00:20:31.500 already is sufficient to commit the sales,

NOTE Confidence: 0.7699414

00:20:31.500 --> 00:20:34.916 that will be our goal going forward too.

NOTE Confidence: 0.7699414

00:20:34.920 --> 00:20:36.564 Target is short.

NOTE Confidence: 0.7699414

00:20:36.564 --> 00:20:38.756 Strong exposure to hyperactivation

NOTE Confidence: 0.7699414

00:20:38.756 --> 00:20:42.145 probably was click or only dated compounds

NOTE Confidence: 0.7699414

00:20:42.145 --> 00:20:45.110 that have a short plasma half life.

NOTE Confidence: 0.7699414

00:20:45.110 --> 00:20:48.414 Now in the second part of my talk,

NOTE Confidence: 0.7699414

00:20:48.420 --> 00:20:51.183 I'm going to give you 2 examples of how

NOTE Confidence: 0.7699414

00:20:51.183 --> 00:20:54.131 we can learn from information within

NOTE Confidence: 0.7699414

00:20:54.131 --> 00:20:56.691 clinical trials and gene expression,

NOTE Confidence: 0.7699414

00:20:56.700 --> 00:20:58.612 annotation related to outcome.

NOTE Confidence: 0.7699414

00:20:58.612 --> 00:21:01.480 So what approach is based on

NOTE Confidence: 0.7699414

00:21:01.566 --> 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 --> 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 --> 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 --> 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 --> 00:21:21.281 the two groups based on higher than

NOTE Confidence: 0.7699414

00:21:21.281 --> 00:21:23.146 median versus lower than median

NOTE Confidence: 0.7699414

00:21:23.146 --> 00:21:25.328 expression in these clinical trials.

NOTE Confidence: 0.7699414

00:21:25.330 --> 00:21:27.550 And then we asked the question,

NOTE Confidence: 0.7699414

00:21:27.550 --> 00:21:30.336 is there a difference between those two

NOTE Confidence: 0.7699414

00:21:30.336 --> 00:21:33.049 groups in terms of clinical outcome?

NOTE Confidence: 0.7699414

00:21:33.050 --> 00:21:35.416 And if the outcome is more favor

NOTE Confidence: 0.7699414

00:21:35.416 --> 00:21:36.430 we have here

NOTE Confidence: 0.8061022

00:21:36.507 --> 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 --> 00:21:43.535 For instance, we have a red annotation

NOTE Confidence: 0.8061022

00:21:43.535 --> 00:21:46.459 and if the group this heat map based

NOTE Confidence: 0.8061022

00:21:46.459 --> 00:21:48.835 on the site specific annotations we

NOTE Confidence: 0.8061022

00:21:48.835 --> 00:21:51.832 come up with a list of genes that

NOTE Confidence: 0.8061022

00:21:51.832 --> 00:21:54.124 became interesting to us and he at

NOTE Confidence: 0.8061022

00:21:54.124 --> 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 --> 00:22:03.588 also known as C25.

NOTE Confidence: 0.77276397

00:22:06.490 --> 00:22:08.800 So that was a bit unexpected.

NOTE Confidence: 0.77276397

00:22:08.800 --> 00:22:11.608 Becausw CD 25 is known as one of

NOTE Confidence: 0.77276397

00:22:11.608 --> 00:22:14.577 the three chains of the L2 receptor.

NOTE Confidence: 0.77276397

00:22:14.580 --> 00:22:16.836 Anna typically pairs with the better

NOTE Confidence: 0.77276397

00:22:16.836 --> 00:22:19.961 chain in the gamma chain to form a

NOTE Confidence: 0.77276397

00:22:19.961 --> 00:22:22.452 trimeric receptor, and this was step

NOTE Confidence: 0.77276397

00:22:22.452 --> 00:22:26.019 was active on T cells and in cases.

NOTE Confidence: 0.77276397

00:22:26.020 --> 00:22:28.280 And it's also important for

NOTE Confidence: 0.77276397

00:22:28.280 --> 00:22:31.010 formation of regulatory T cells or T.

NOTE Confidence: 0.77276397

00:22:31.010 --> 00:22:32.674 Rex, and therefore therefore

NOTE Confidence: 0.77276397

00:22:32.674 --> 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 --> 00:22:40.598 And here I'm showing you that.

NOTE Confidence: 0.77276397

00:22:40.600 --> 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,

NOTE Confidence: 0.77276397

00:22:50.440 --> 00:22:53.015 we see consistent pattern that

NOTE Confidence: 0.77276397

00:22:53.015 --> 00:22:55.590 the lower half of expression

NOTE Confidence: 0.77276397

00:22:55.678 --> 00:22:58.208 is related to better outcome.

NOTE Confidence: 0.77276397

00:22:58.210 --> 00:23:01.500 The top half towards outcome.

NOTE Confidence: 0.77276397

00:23:01.500 --> 00:23:03.636 The other reason we became interested

NOTE Confidence: 0.77276397

00:23:03.636 --> 00:23:06.498 is that if you bring in Uncle Gene,

NOTE Confidence: 0.77276397

00:23:06.500 --> 00:23:07.601 said drive, leukemia,

NOTE Confidence: 0.77276397

00:23:07.601 --> 00:23:10.430 lymphoma like these are able or LMP 2A.

NOTE Confidence: 0.77276397

00:23:10.430 --> 00:23:12.130 This leads to upregulation

NOTE Confidence: 0.77276397

00:23:12.130 --> 00:23:14.680 of C25 on the cell surface.

NOTE Confidence: 0.77276397

00:23:14.680 --> 00:23:17.216 And also it seems to play a role

NOTE Confidence: 0.77276397

00:23:17.216 --> 00:23:19.360 in resale developmented save.

NOTE Confidence: 0.77276397

00:23:19.360 --> 00:23:23.910 So he profile here see 25 M on A levels.

NOTE Confidence: 0.77276397

00:23:23.910 --> 00:23:26.058 Over the course of the sale

NOTE Confidence: 0.77276397

00:23:26.058 --> 00:23:28.263 evelopment we find here is striking

NOTE Confidence: 0.77276397

00:23:28.263 --> 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 --> 00:23:36.890 which we did in our lab.

NOTE Confidence: 0.77276397

00:23:36.890 --> 00:23:38.900 Compare this to the wild type

NOTE Confidence: 0.77276397

00:23:38.900 --> 00:23:41.032 animals and look at these fractions

NOTE Confidence: 0.77276397

00:23:41.032 --> 00:23:43.186 we see here is fraction D.

NOTE Confidence: 0.77276397

00:23:43.190 --> 00:23:45.518 But distractions entirely missing in the

NOTE Confidence: 0.77276397

00:23:45.518 --> 00:23:48.327 knockout mice and can also see this here.

NOTE Confidence: 0.77276397

00:23:48.330 --> 00:23:50.160 This is a defect here.

NOTE Confidence: 0.77276397

00:23:50.160 --> 00:23:53.096 We still don't know what this actually means,

NOTE Confidence: 0.77276397

00:23:53.100 --> 00:23:55.816 but we also find that later in

NOTE Confidence: 0.77276397

00:23:55.816 --> 00:23:58.038 development he says actually are

NOTE Confidence: 0.77276397

00:23:58.038 --> 00:24:00.478 over represented in fraction F.

NOTE Confidence: 0.77276397

00:24:00.480 --> 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

NOTE Confidence: 0.77276397

00:24:07.834 --> 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 --> 00:24:14.658 so we repeated this experiment with

NOTE Confidence: 0.77276397

00:24:14.658 --> 00:24:17.227 mice that have intact City 25,

NOTE Confidence: 0.77276397

00:24:17.230 --> 00:24:19.810 but are lacking the L2 cytokine.

NOTE Confidence: 0.77276397

00:24:19.810 --> 00:24:22.390 But contrary to our hypothesis fraction,

NOTE Confidence: 0.77276397

00:24:22.390 --> 00:24:25.934 D&F are just fine and be so developmen

NOTE Confidence: 0.77276397

00:24:25.934 --> 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 --> 00:24:32.252 ligation analysis,

NOTE Confidence: 0.77276397

00:24:32.260 --> 00:24:34.216 we find that C25 does actually

NOTE Confidence: 0.77276397

00:24:34.216 --> 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 --> 00:24:40.990 not respond to iron tools.

NOTE Confidence: 0.77276397

00:24:40.990 --> 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 --> 00:24:51.639 We found in our proximity ligation assay,

NOTE Confidence: 0.77276397

00:24:51.640 --> 00:24:54.460 said City 25 associate itself.

NOTE Confidence: 0.77276397

00:24:54.460 --> 00:24:56.842 With a signal image chain of

NOTE Confidence: 0.77276397

00:24:56.842 --> 00:24:58.430 the B cell receptor,

NOTE Confidence: 0.77276397

00:24:58.430 --> 00:25:00.602 which again is responsible for the

NOTE Confidence: 0.77276397

00:25:00.602 --> 00:25:02.542 Goldilocks principle to keep intact

NOTE Confidence: 0.77276397

00:25:02.542 --> 00:25:04.254 and equilibrium and intermediate

NOTE Confidence: 0.77276397

00:25:04.254 --> 00:25:05.966 ram of signaling intensity.

NOTE Confidence: 0.77276397

00:25:05.970 --> 00:25:08.721 And that's the case in resting B

NOTE Confidence: 0.77276397

00:25:08.721 --> 00:25:11.498 cells where prices are even more so

NOTE Confidence: 0.77276397

00:25:11.498 --> 00:25:14.252 the case after the visa receptor was

NOTE Confidence: 0.77276397

00:25:14.252 --> 00:25:17.087 stimulated with an anti IG M antibody.

NOTE Confidence: 0.77276397

00:25:17.090 --> 00:25:20.266 This is actually ongoing work in our lab,

NOTE Confidence: 0.77276397

00:25:20.270 --> 00:25:21.202 by Jay,

NOTE Confidence: 0.77276397

00:25:21.202 --> 00:25:23.532 wrongly with a research scientist

NOTE Confidence: 0.77276397

00:25:23.532 --> 00:25:24.930 in my group.

NOTE Confidence: 0.77276397

00:25:24.930 --> 00:25:27.906 And what he found is actually their CIA.

NOTE Confidence: 0.77276397

00:25:27.910 --> 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 --> 00:25:36.720 develop spontaneous germinal center,

NOTE Confidence: 0.80370665

00:25:36.720 --> 00:25:39.450 so even without any immunization,

NOTE Confidence: 0.80370665

00:25:39.450 --> 00:25:42.190 these B cells are autoreactive.

NOTE Confidence: 0.80370665

00:25:42.190 --> 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 --> 00:25:48.615 spontaneous germinal centers

NOTE Confidence: 0.80370665

00:25:48.615 --> 00:25:51.355 that are antigen independent.

NOTE Confidence: 0.80370665

00:25:51.360 --> 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 --> 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 --> 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 --> 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 --> 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 --> 00:26:22.680 in that competitive fitness,

NOTE Confidence: 0.80370665

00:26:22.680 --> 00:26:26.558 so we confirmed this here in a

NOTE Confidence: 0.80370665

00:26:26.558 --> 00:26:29.900 leukemia model whereby we transformed.

NOTE Confidence: 0.80370665

00:26:29.900 --> 00:26:33.524 25 mouse cells with the flux see 25

NOTE Confidence: 0.80370665

00:26:33.524 --> 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

NOTE Confidence: 0.80370665

00:26:40.201 --> 00:26:43.995 on the surface and then soon after

NOTE Confidence: 0.80370665

00:26:43.995 --> 00:26:46.484 this says disappear from culture.

NOTE Confidence: 0.80370665

00:26:46.484 --> 00:26:49.760 They failed to form any colonies that

NOTE Confidence: 0.80370665

00:26:49.843 --> 00:26:52.413 cannot initiate leukemia and mice

NOTE Confidence: 0.80370665

00:26:52.413 --> 00:26:55.538 that bears also leukemias recover and

NOTE Confidence: 0.80370665

00:26:55.538 --> 00:26:58.364 survive for indefinite periods of time.

NOTE Confidence: 0.80370665

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

NOTE Confidence: 0.80370665

00:26:59.240 --> 00:27:01.415 and that's coming back to

NOTE Confidence: 0.80370665

00:27:01.415 --> 00:27:02.720 signaling feedback control,

NOTE Confidence: 0.80370665

00:27:02.720 --> 00:27:04.910 we found that upon collisional

NOTE Confidence: 0.80370665

00:27:04.910 --> 00:27:08.032 City 25 in a similar way like

NOTE Confidence: 0.80370665

00:27:08.032 --> 00:27:10.546 deletion of P-10 and ship one,

NOTE Confidence: 0.80370665

00:27:10.550 --> 00:27:14.470 we see that the balance of ether

NOTE Confidence: 0.80370665

00:27:14.470 --> 00:27:16.150 receptor signaling strength.

NOTE Confidence: 0.80370665

00:27:16.150 --> 00:27:18.784 It's lost cause we have hyper

NOTE Confidence: 0.80370665

00:27:18.784 --> 00:27:20.540 activation of kinase substrates

NOTE Confidence: 0.80370665

00:27:20.615 --> 00:27:22.920 downstream of the visa receptor,

NOTE Confidence: 0.80370665

00:27:22.920 --> 00:27:27.078 including sick and then loss of phosphatase

NOTE Confidence: 0.80370665

00:27:27.078 --> 00:27:30.630 activity markers for P-10 and ship one.

NOTE Confidence: 0.80370665

00:27:30.630 --> 00:27:32.635 So we think those phenomena

NOTE Confidence: 0.80370665

00:27:32.635 --> 00:27:34.239 might actually be related,

NOTE Confidence: 0.80370665

00:27:34.240 --> 00:27:37.400 but CD 25 plays a role in maintaining

NOTE Confidence: 0.80370665

00:27:37.400 --> 00:27:39.514 the Goldilocks principle by

NOTE Confidence: 0.80370665

00:27:39.514 --> 00:27:41.998 regulating kinases and phosphatases.

NOTE Confidence: 0.80370665

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

NOTE Confidence: 0.80370665

00:27:42.336 --> 00:27:43.680 how is this possible?

NOTE Confidence: 0.80370665

00:27:43.680 --> 00:27:46.956 So the tail of CD 25 is very short

NOTE Confidence: 0.80370665

00:27:46.956 --> 00:27:50.497 here and it's just 13 amino acids and.

NOTE Confidence: 0.80370665

00:27:50.500 --> 00:27:55.000 So we looked at what City 25 might bind to.

NOTE Confidence: 0.80370665

00:27:55.000 --> 00:27:57.556 How does it interact with the

NOTE Confidence: 0.80370665

00:27:57.556 --> 00:28:00.086 cytoplasmic tail and as a negative

NOTE Confidence: 0.80370665

00:28:00.086 --> 00:28:02.306 control and using this for a

NOTE Confidence: 0.80370665

00:28:02.306 --> 00:28:04.899 lot of different experiments,

NOTE Confidence: 0.80370665

00:28:04.900 --> 00:28:07.450 we introduce a mutation of the

NOTE Confidence: 0.80370665

00:28:07.450 --> 00:28:09.150 central Seren residue which

NOTE Confidence: 0.80370665

00:28:09.229 --> 00:28:11.649 destroys the main protein kinase.

NOTE Confidence: 0.80370665

00:28:11.650 --> 00:28:13.618 He better consensus motive.

NOTE Confidence: 0.80370665

00:28:13.618 --> 00:28:17.698 And here we are using a bio ID

NOTE Confidence: 0.80370665

00:28:17.698 --> 00:28:20.770 approach which is based on fusions

NOTE Confidence: 0.80370665

00:28:20.770 --> 00:28:23.916 between the CD 25 tail and puree,

NOTE Confidence: 0.80370665

00:28:23.920 --> 00:28:26.800 which is a bacterial biotin ligase

NOTE Confidence: 0.80370665

00:28:26.800 --> 00:28:29.788 which attaches bio tends to approximate

NOTE Confidence: 0.80370665

00:28:29.788 --> 00:28:33.700 protein space on the mound and the proximity.

NOTE Confidence: 0.80370665

00:28:33.700 --> 00:28:34.688 And I,

NOTE Confidence: 0.80370665

00:28:34.688 --> 00:28:35.676 as expected,

NOTE Confidence: 0.80370665

00:28:35.676 --> 00:28:38.146 we found that two phosphatases

NOTE Confidence: 0.80370665

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

NOTE Confidence: 0.80370665

00:28:40.530 --> 00:28:43.085 Are in proximity of the tail of

NOTE Confidence: 0.80370665

00:28:43.085 --> 00:28:46.147 CD 25 and this is not the case.

NOTE Confidence: 0.80370665

00:28:46.150 --> 00:28:48.750 The tail here is mutated.

NOTE Confidence: 0.80370665

00:28:48.750 --> 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 --> 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 --> 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 --> 00:29:14.988 regulator of signaling strength.

NOTE Confidence: 0.80370665

00:29:14.990 --> 00:29:17.360 So if he abusively activate while

NOTE Confidence: 0.80370665

00:29:17.360 --> 00:29:20.130 types unify, we can block the kite.

NOTE Confidence: 0.80370665

00:29:20.130 --> 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 --> 00:29:25.265 So he expresses the 25

NOTE Confidence: 0.80370665

00:29:25.265 --> 00:29:27.240 and it's wild type form.

NOTE Confidence: 0.80370665

00:29:27.240 --> 00:29:29.110 The signal is delayed and

NOTE Confidence: 0.80370665

00:29:29.110 --> 00:29:30.980 almost entirely lost if they

NOTE Confidence: 0.80648685

00:29:31.053 --> 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 --> 00:29:37.205 but it's much less compared

NOTE Confidence: 0.80648685

00:29:37.205 --> 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 --> 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 --> 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 --> 00:30:05.548 seven 268 a mutant cannots again

NOTE Confidence: 0.80648685

00:30:05.548 --> 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 --> 00:30:13.107 regulate signaling is important for

NOTE Confidence: 0.80648685

00:30:13.107 --> 00:30:15.802 survival of these leukemia cells.

NOTE Confidence: 0.80648685

00:30:15.810 --> 00:30:18.648 So we have modeled the interaction

NOTE Confidence: 0.80648685

00:30:18.648 --> 00:30:21.444 between these molecules and came up

NOTE Confidence: 0.80648685

00:30:21.444 --> 00:30:23.904 with the structural model for this,

NOTE Confidence: 0.80648685

00:30:23.910 --> 00:30:27.168 which has rank one PKC better

NOTE Confidence: 0.80648685

00:30:27.168 --> 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 --> 00:30:32.876 and this interaction,

NOTE Confidence: 0.80648685

00:30:32.880 --> 00:30:35.802 he has facilitated by the C25

NOTE Confidence: 0.80648685

00:30:35.802 --> 00:30:38.300 tear which insert itself here.

NOTE Confidence: 0.80648685

00:30:38.300 --> 00:30:41.506 So overall we think that he says.

NOTE Confidence: 0.80648685

00:30:41.510 --> 00:30:43.910 Activate CD 25 downstream of the

NOTE Confidence: 0.80648685

00:30:43.910 --> 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 --> 00:30:51.552 which then forms a complex with Raekwon

NOTE Confidence: 0.80648685

00:30:51.552 --> 00:30:54.740 to recruit first parties here to surface.

NOTE Confidence: 0.80648685

00:30:54.740 --> 00:30:57.085 Which then again provide negative

NOTE Confidence: 0.80648685

00:30:57.085 --> 00:31:00.014 feedback control so it's like a

NOTE Confidence: 0.80648685

00:31:00.014 --> 00:31:03.050 circle that goes back to maintain

NOTE Confidence: 0.80648685

00:31:03.050 --> 00:31:04.568 equilibrium Goldilocks principle

NOTE Confidence: 0.80648685

00:31:04.648 --> 00:31:07.329 again for the survival of the cells.

NOTE Confidence: 0.80648685

00:31:07.330 --> 00:31:11.170 So our conclusion is that we think that

NOTE Confidence: 0.80648685

00:31:11.170 --> 00:31:14.209 negative selection can be leveraged indeed.

NOTE Confidence: 0.80648685

00:31:14.210 --> 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 --> 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 --> 00:31:26.204 interference proceeding 25.

NOTE Confidence: 0.80648685

00:31:26.210 --> 00:31:27.050 Feedback control.

NOTE Confidence: 0.80648685

00:31:27.050 --> 00:31:29.990 So the goal here would be to.

NOTE Confidence: 0.80648685

00:31:29.990 --> 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 --> 00:31:38.076 powerful activation signal over the

NOTE Confidence: 0.80648685

00:31:38.156 --> 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 --> 00:31:46.822 selection of what looks like at the

NOTE Confidence: 0.80648685

00:31:46.822 --> 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 --> 00:31:54.260 Coming back to our.

NOTE Confidence: 0.80648685

00:31:54.260 --> 00:31:57.860 Database which we find us a very rich

NOTE Confidence: 0.80648685

00:31:57.860 --> 00:32:00.918 resource for new ideas and concepts.

NOTE Confidence: 0.80648685

00:32:00.920 --> 00:32:02.364 You found another interesting

NOTE Confidence: 0.80648685

00:32:02.364 --> 00:32:04.169 outcome predictor that I would

NOTE Confidence: 0.80648685

00:32:04.169 --> 00:32:06.196 like to introduce to you with the.

NOTE Confidence: 0.80648685

00:32:06.200 --> 00:32:08.642 It's a recent publication that just

NOTE Confidence: 0.80648685

00:32:08.642 --> 00:32:12.189 came out a couple weeks ago and that is

NOTE Confidence: 0.80648685

00:32:12.189 --> 00:32:15.188 focused here on a molecule called IIT M3.

NOTE Confidence: 0.80648685

00:32:15.190 --> 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 --> 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 --> 00:32:30.900 He said leukemia and lymphoma

NOTE Confidence: 0.80648685

00:32:30.900 --> 00:32:34.572 subtypes and it's known for long time

NOTE Confidence: 0.80648685

00:32:34.572 --> 00:32:37.716 initially was found as a specifying

NOTE Confidence: 0.80648685

00:32:37.716 --> 00:32:40.808 molecules for primordial germ cells.

NOTE Confidence: 0.80648685

00:32:40.810 --> 00:32:42.766 And then more recently it was

NOTE Confidence: 0.80648685

00:32:42.766 --> 00:32:45.074 found as an antiviral protein that

NOTE Confidence: 0.80648685

00:32:45.074 --> 00:32:46.950 can restrict viral replication.

NOTE Confidence: 0.80648685

00:32:46.950 --> 00:32:48.186 He is shown HIV,

NOTE Confidence: 0.80648685

00:32:48.186 --> 00:32:50.541 but more recent data shows it also

NOTE Confidence: 0.80648685

00:32:50.541 --> 00:32:52.691 important for the restriction of

NOTE Confidence: 0.80648685

00:32:52.691 --> 00:32:55.020 coronavirus and many other viruses,

NOTE Confidence: 0.80648685

00:32:55.020 --> 00:32:57.812 and what was important to us is that

NOTE Confidence: 0.80648685

00:32:57.812 --> 00:33:00.221 is actually used as a diagnostic

NOTE Confidence: 0.80648685

00:33:00.221 --> 00:33:02.669 tool for pediatric leukemia to find

NOTE Confidence: 0.80648685

00:33:02.742 --> 00:33:04.998 patients that are at high risk.

NOTE Confidence: 0.80648685

00:33:05.000 --> 00:33:08.546 So it's one probe set on a low density

NOTE Confidence: 0.80648685

00:33:08.546 --> 00:33:12.075 array to identify patients at high risk.

NOTE Confidence: 0.80648685

00:33:12.080 --> 00:33:14.270 So we started the function of

NOTE Confidence: 0.80648685

00:33:14.270 --> 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 --> 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 --> 00:33:29.585 And they are prone to

NOTE Confidence: 0.7593378

00:33:29.585 --> 00:33:31.470 cell death as shown by P.

NOTE Confidence: 0.7593378

00:33:31.470 --> 00:33:34.417 53 activation and loss of PCL too.

NOTE Confidence: 0.7593378

00:33:34.420 --> 00:33:36.580 And importantly, these cells actually

NOTE Confidence: 0.7593378

00:33:36.580 --> 00:33:38.740 cannot be properly activated to

NOTE Confidence: 0.7593378

00:33:38.806 --> 00:33:40.558 undergo affinity maturation.

NOTE Confidence: 0.7593378

00:33:40.560 --> 00:33:44.187 So here is PNA is a German center marker

NOTE Confidence: 0.7593378

00:33:44.187 --> 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 --> 00:33:54.636 So if he smiles are immunized and

NOTE Confidence: 0.7593378

00:33:54.636 --> 00:33:57.789 nicely form germinal centres but if.

NOTE Confidence: 0.7593378

00:33:57.790 --> 00:34:00.160 He says that by Adoptively

NOTE Confidence: 0.7593378

00:34:00.160 --> 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 --> 00:34:06.553 or German centre visa is and

NOTE Confidence: 0.7593378

00:34:06.553 --> 00:34:08.209 subsequent affinity maturation.

NOTE Confidence: 0.7593378

00:34:08.210 --> 00:34:10.938 Is this drastically reduced?

NOTE Confidence: 0.7593378

00:34:10.940 --> 00:34:13.635 And the same is true in leukemia,

NOTE Confidence: 0.7593378

00:34:13.640 --> 00:34:16.328 so I have items with efficient leukemia.

NOTE Confidence: 0.7593378

00:34:16.330 --> 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 --> 00:34:22.980 There also lacks ability

NOTE Confidence: 0.7593378

00:34:22.980 --> 00:34:24.165 to initiate leukemia,

NOTE Confidence: 0.7593378

00:34:24.170 --> 00:34:25.942 and those two models.

NOTE Confidence: 0.7593378

00:34:25.942 --> 00:34:29.394 And they have a similar phenotype as I

NOTE Confidence: 0.7593378

00:34:29.394 --> 00:34:32.226 showed you in normally says in terms of

NOTE Confidence: 0.7593378

00:34:32.315 --> 00:34:35.375 lack of peers with kindness signaling.

NOTE Confidence: 0.7593378

00:34:35.380 --> 00:34:38.624 Survival and strong expression

NOTE Confidence: 0.7593378

00:34:38.624 --> 00:34:42.679 of death related or checkpoint

NOTE Confidence: 0.7593378

00:34:42.679 --> 00:34:45.850 related molecules like P53.

NOTE Confidence: 0.7593378

00:34:45.850 --> 00:34:48.615 So in terms of structure and mechanism,

NOTE Confidence: 0.7593378

00:34:48.620 --> 00:34:51.620 we were able to figure out how I've

NOTE Confidence: 0.7593378

00:34:51.620 --> 00:34:54.168 item three is regulated in Indy.

NOTE Confidence: 0.7593378

00:34:54.170 --> 00:34:56.410 Lymphocytes is actually very short

NOTE Confidence: 0.7593378

00:34:56.410 --> 00:34:59.465 protein or 433 amino acids in length

NOTE Confidence: 0.7593378

00:34:59.465 --> 00:35:02.034 and we found that it can actually

NOTE Confidence: 0.7593378

00:35:02.034 --> 00:35:04.688 insert itself into the cell membrane.

NOTE Confidence: 0.7593378

00:35:04.690 --> 00:35:07.630 And this happens when I'm downstream.

NOTE Confidence: 0.7593378

00:35:07.630 --> 00:35:09.661 Also visa receptor.

NOTE Confidence: 0.7593378

00:35:09.661 --> 00:35:10.338 Lynn,

NOTE Confidence: 0.7593378

00:35:10.338 --> 00:35:13.723 another sack family kinases phosphorylate.

NOTE Confidence: 0.7593378

00:35:13.730 --> 00:35:16.145 I've item three at this tyrosine 20s

NOTE Confidence: 0.7593378

00:35:16.145 --> 00:35:18.310 that's really a central tiersen,

NOTE Confidence: 0.7593378

00:35:18.310 --> 00:35:20.220 which leads to recruitment to

NOTE Confidence: 0.7593378

00:35:20.220 --> 00:35:21.366 the cell membrane,

NOTE Confidence: 0.7593378

00:35:21.370 --> 00:35:23.998 and then it can easily interact

NOTE Confidence: 0.7593378

00:35:23.998 --> 00:35:26.902 with the visa receptor or it

NOTE Confidence: 0.7593378

00:35:26.902 --> 00:35:28.507 becomes internalised again.

NOTE Confidence: 0.7593378

00:35:28.510 --> 00:35:31.128 So for this reason we studied this

NOTE Confidence: 0.7593378

00:35:31.128 --> 00:35:33.476 mutation here and actually found that

NOTE Confidence: 0.7593378

00:35:33.476 --> 00:35:36.150 it can function as an Uncle gene.

NOTE Confidence: 0.7593378

00:35:36.150 --> 00:35:38.733 So when we introduce us for cinematic

NOTE Confidence: 0.7593378

00:35:38.733 --> 00:35:41.745 form of white 20 which mimics the

NOTE Confidence: 0.7593378

00:35:41.745 --> 00:35:44.481 confirmation that is always was formulated.

NOTE Confidence: 0.7593378

00:35:44.490 --> 00:35:46.565 Into a mouse strain that

NOTE Confidence: 0.7593378

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

NOTE Confidence: 0.7593378

00:35:48.230 --> 00:35:52.318 which has a very long latency to disease.

NOTE Confidence: 0.7593378

00:35:52.320 --> 00:35:54.906 We actually found that this leads

NOTE Confidence: 0.7593378

00:35:54.906 --> 00:35:57.370 to increased formation of colonies.

NOTE Confidence: 0.7593378

00:35:57.370 --> 00:36:00.140 Increased PS3 kinase activity and

NOTE Confidence: 0.7593378

00:36:00.140 --> 00:36:02.910 also increased activity of the

NOTE Confidence: 0.7593378

00:36:03.006 --> 00:36:05.778 visa receptor signaling pathway.

NOTE Confidence: 0.7593378

00:36:05.780 --> 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 --> 00:36:12.119 we could show the poisoner interactome

NOTE Confidence: 0.7593378

00:36:12.119 --> 00:36:14.581 analysis that this form of items

NOTE Confidence: 0.7593378

00:36:14.581 --> 00:36:16.546 three intersects with multiple central

NOTE Confidence: 0.7593378

00:36:16.611 --> 00:36:18.927 components of both the PS3 kinase

NOTE Confidence: 0.7593378

00:36:18.927 --> 00:36:20.855 and visa receptor signaling pathway.

NOTE Confidence: 0.7593378

00:36:20.855 --> 00:36:23.855 And there's also shown here by these red

NOTE Confidence: 0.7593378

00:36:23.855 --> 00:36:26.600 dots in this proximity ligation assay,

NOTE Confidence: 0.7593378

00:36:26.600 --> 00:36:30.436 where if I can three molecules come

NOTE Confidence: 0.7593378

00:36:30.436 --> 00:36:34.360 in close proximity. And he says.

NOTE Confidence: 0.7593378

00:36:34.360 --> 00:36:36.622 Now the structural basis for data

NOTE Confidence: 0.7593378

00:36:36.622 --> 00:36:39.361 set and that was very surprising to

NOTE Confidence: 0.7593378

00:36:39.361 --> 00:36:42.049 us that I've item 3 can directly

NOTE Confidence: 0.7593378

00:36:42.134 --> 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 --> 00:36:52.702 And that is unexpected because this

NOTE Confidence: 0.7593378

00:36:52.702 --> 00:36:55.148 interaction is usually mediated by a

NOTE Confidence: 0.7593378

00:36:55.148 --> 00:36:57.224 so-called pH domain in larger proteins.

NOTE Confidence: 0.7593378

00:36:57.230 --> 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 --> 00:37:07.600 so we were looking here for and you

NOTE Confidence: 0.7593378

00:37:07.600 --> 00:37:09.833 structure basis of houses interaction

NOTE Confidence: 0.7593378

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 --> 00:37:18.265 conserved intracellular loop of

NOTE Confidence: 0.83150226

00:37:18.265 --> 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 --> 00:37:29.775 and in doing so we found a cluster of.

NOTE Confidence: 0.83150226

00:37:29.780 --> 00:37:32.923 Five basic amino acids and of particular

NOTE Confidence: 0.83150226

00:37:32.923 --> 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 --> 00:37:41.549 104 and even though they are 21

NOTE Confidence: 0.83150226

00:37:41.549 --> 00:37:43.811 amino acids apart from each other,

NOTE Confidence: 0.83150226

00:37:43.811 --> 00:37:46.013 they come very close here in

NOTE Confidence: 0.83150226

00:37:46.013 --> 00:37:47.880 the structure analysis,

NOTE Confidence: 0.83150226

00:37:47.880 --> 00:37:49.604 and they're basically former

NOTE Confidence: 0.83150226

00:37:49.604 --> 00:37:51.759 clamp to directly interact here.

NOTE Confidence: 0.83150226

00:37:51.760 --> 00:37:54.920 With this pit three molecule.

NOTE Confidence: 0.83150226

00:37:54.920 --> 00:37:58.128 So by mutation analysis we were able to

NOTE Confidence: 0.83150226

00:37:58.128 --> 00:38:01.306 show that the whites are morally cure.

NOTE Confidence: 0.83150226

00:38:01.310 --> 00:38:03.710 Was this bracket of lice and

NOTE Confidence: 0.83150226

00:38:03.710 --> 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 --> 00:38:11.740 and peace a receptor signaling?

NOTE Confidence: 0.83150226

00:38:11.740 --> 00:38:13.900 But when these two amino acids

NOTE Confidence: 0.83150226

00:38:13.900 --> 00:38:15.798 here are mutated through the

NOTE Confidence: 0.83150226

00:38:15.798 --> 00:38:17.366 brackets along the active,

NOTE Confidence: 0.83150226

00:38:17.370 --> 00:38:20.140 the entire Lee loses ability.

NOTE Confidence: 0.83150226

00:38:20.140 --> 00:38:21.880 So that's something that became

NOTE Confidence: 0.83150226

00:38:21.880 --> 00:38:24.047 really interested in that we hope

NOTE Confidence: 0.83150226

00:38:24.047 --> 00:38:25.872 to pursue further in collaboration

NOTE Confidence: 0.83150226

00:38:25.872 --> 00:38:27.332 with our colleagues at.

NOTE Confidence: 0.83150226

00:38:27.340 --> 00:38:27.654 Yeah,

NOTE Confidence: 0.83150226

00:38:27.654 --> 00:38:29.852 like a new way of how proteins

NOTE Confidence: 0.83150226

00:38:29.852 --> 00:38:32.081 can make contact with Pepsi to

NOTE Confidence: 0.83150226

00:38:32.081 --> 00:38:33.996 initiate PSV kind of signaling

NOTE Confidence: 0.83150226

00:38:33.996 --> 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 --> 00:38:39.670 How model is that in the

NOTE Confidence: 0.83150226

00:38:39.749 --> 00:38:41.377 absence of five items,

NOTE Confidence: 0.83150226

00:38:41.380 --> 00:38:45.028 we and normal cells also modeling and says.

NOTE Confidence: 0.83150226

00:38:45.030 --> 00:38:47.340 The molecules that initiate PSU

NOTE Confidence: 0.83150226

00:38:47.340 --> 00:38:49.650 kind of signaling are scattered

NOTE Confidence: 0.83150226

00:38:49.723 --> 00:38:51.847 throughout the cell membrane.

NOTE Confidence: 0.83150226

00:38:51.850 --> 00:38:52.966 Only five items,

NOTE Confidence: 0.83150226

00:38:52.966 --> 00:38:55.570 three is there acting as a molecular

NOTE Confidence: 0.83150226

00:38:55.643 --> 00:38:58.198 glues are drawn together and form a

NOTE Confidence: 0.83150226

00:38:58.198 --> 00:39:00.699 tight complex to initiate signaling.

NOTE Confidence: 0.83150226

00:39:00.700 --> 00:39:05.120 I'm not coming to the last part of my talk,

NOTE Confidence: 0.83150226

00:39:05.120 --> 00:39:06.888 which was quite surprising

NOTE Confidence: 0.83150226

00:39:06.888 --> 00:39:09.540 to some of us and Mr.

NOTE Confidence: 0.83150226

00:39:09.540 --> 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 --> 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 --> 00:39:21.029 question of how do oncogenic pathways,

NOTE Confidence: 0.83150226

00:39:21.030 --> 00:39:22.798 once activated by mutations?

NOTE Confidence: 0.83150226

00:39:22.798 --> 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 --> 00:39:33.420 that is to malignant transformation.

NOTE Confidence: 0.825705850909091

00:39:33.420 --> 00:39:37.108 And this idea is based on a concept

NOTE Confidence: 0.825705850909091

00:39:37.108 --> 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 --> 00:39:48.640 step malignant transformation by

NOTE Confidence: 0.825705850909091

00:39:48.640 --> 00:39:50.754 sequential acquisition of Driver

NOTE Confidence: 0.825705850909091

00:39:50.754 --> 00:39:53.790 Uncle Gene set together, then form

NOTE Confidence: 0.825705850909091

00:39:53.790 --> 00:39:56.465 the development of colorectal cancer.

NOTE Confidence: 0.825705850909091

00:39:56.470 --> 00:40:00.000 So the question here is, is this.

NOTE Confidence: 0.825705850909091

00:40:00.000 --> 00:40:02.550 Same in visa is do we.

NOTE Confidence: 0.825705850909091

00:40:02.550 --> 00:40:04.804 Is it true that acquisition of addition

NOTE Confidence: 0.825705850909091

00:40:04.804 --> 00:40:07.300 mutations lead to more malignant phenotypes?

NOTE Confidence: 0.825705850909091

00:40:07.300 --> 00:40:09.525 And how do these oncogenic

NOTE Confidence: 0.825705850909091

00:40:09.525 --> 00:40:11.750 pathways interact with each other?

NOTE Confidence: 0.825705850909091

00:40:11.750 --> 00:40:13.400 So to answer this question,

NOTE Confidence: 0.825705850909091

00:40:13.400 --> 00:40:15.902 we formed a collaboration with Children

NOTE Confidence: 0.825705850909091

00:40:15.902 --> 00:40:17.950 psychology Group and Saint Jude.

NOTE Confidence: 0.825705850909091

00:40:17.950 --> 00:40:20.380 And studied.

NOTE Confidence: 0.825705850909091

00:40:20.380 --> 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 --> 00:40:29.962 And what we did first was what you

NOTE Confidence: 0.825705850909091

00:40:29.962 --> 00:40:32.769 would call a mapping analysis of

NOTE Confidence: 0.825705850909091

00:40:32.769 --> 00:40:35.319 affinity versus repulsion of pathways.

NOTE Confidence: 0.825705850909091

00:40:35.320 --> 00:40:37.460 So basically asking the question.

NOTE Confidence: 0.825705850909091

00:40:37.460 --> 00:40:40.616 So activating lesions in one pathway.

NOTE Confidence: 0.825705850909091

00:40:40.620 --> 00:40:41.648 Are they?

NOTE Confidence: 0.825705850909091

00:40:41.648 --> 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 --> 00:40:52.012 Or is there like relationships of mutual

NOTE Confidence: 0.8212341

00:40:52.012 --> 00:40:54.497 exclusivity and we found a number of

NOTE Confidence: 0.8212341

00:40:54.497 --> 00:40:56.770 interactions that we are still working on?

NOTE Confidence: 0.8212341

00:40:56.770 --> 00:40:58.450 But one was really striking to

NOTE Confidence: 0.8212341

00:40:58.450 --> 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 --> 00:41:04.726 as shown here in this cartoon.

NOTE Confidence: 0.8212341

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

NOTE Confidence: 0.8212341

00:41:08.100 --> 00:41:11.396 The Jack Stat 5 Path pathway and IIRC

NOTE Confidence: 0.8212341

00:41:11.396 --> 00:41:14.600 home up kinase signaling pathway.

NOTE Confidence: 0.8212341

00:41:14.600 --> 00:41:17.816 And here I'm showing you the

NOTE Confidence: 0.8212341

00:41:17.816 --> 00:41:21.250 result based on these 1148 cases.

NOTE Confidence: 0.8212341

00:41:21.250 --> 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 --> 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 --> 00:41:33.550 but these are activating lesions and only

NOTE Confidence: 0.8212341

00:41:33.621 --> 00:41:36.456 in 35 cases which is just feed the spend.

NOTE Confidence: 0.8212341

00:41:36.460 --> 00:41:38.800 We found activation of both pathways,

NOTE Confidence: 0.8212341

00:41:38.800 --> 00:41:43.248 which which is much lower than than random.

NOTE Confidence: 0.8212341

00:41:43.250 --> 00:41:45.056 Also, when we look at individual

NOTE Confidence: 0.8212341

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

NOTE Confidence: 0.8212341

00:41:47.152 --> 00:41:49.636 Erk or phosphorylation of stat five,

NOTE Confidence: 0.8212341

00:41:49.640 --> 00:41:52.503 we have a clear cut negative or

NOTE Confidence: 0.8212341

00:41:52.503 --> 00:41:54.077 inverse relationship between them

NOTE Confidence: 0.8212341

00:41:54.077 --> 00:41:56.534 and you can also see here I have to

NOTE Confidence: 0.8212341

00:41:56.603 --> 00:41:58.811 level off Western blot that that

NOTE Confidence: 0.8212341

00:41:58.811 --> 00:42:00.882 you have either force relation or

NOTE Confidence: 0.8212341

00:42:00.882 --> 00:42:02.954 step file for false for work and

NOTE Confidence: 0.8212341

00:42:02.954 --> 00:42:04.806 this leads to different profiles

NOTE Confidence: 0.8212341

00:42:04.806 --> 00:42:07.050 in terms of correct sensitivity so

NOTE Confidence: 0.8212341

00:42:07.116 --> 00:42:09.166 traumatic Nip is American emitter.

NOTE Confidence: 0.8212341

00:42:09.170 --> 00:42:11.330 It was in the herb signaling

NOTE Confidence: 0.8212341

00:42:11.330 --> 00:42:13.260 pathway that effects on these.

NOTE Confidence: 0.8212341

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

NOTE Confidence: 0.8212341

00:42:17.806 --> 00:42:18.272 mainly,

NOTE Confidence: 0.8212341

00:42:18.272 --> 00:42:21.068 the stat 5 signaling pathway which

NOTE Confidence: 0.8212341

00:42:21.068 --> 00:42:23.609 is affecting those leukemias here.

NOTE Confidence: 0.8212341

00:42:23.610 --> 00:42:25.770 And I'm.

NOTE Confidence: 0.8212341

00:42:25.770 --> 00:42:28.486 So we became interested in this small

NOTE Confidence: 0.8212341

00:42:28.486 --> 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 --> 00:42:35.920 even though they seem to

NOTE Confidence: 0.8212341

00:42:35.920 --> 00:42:37.138 be mutually exclusive.

NOTE Confidence: 0.8212341

00:42:37.140 --> 00:42:40.356 So wanted to know who they occur in

NOTE Confidence: 0.8212341

00:42:40.356 --> 00:42:43.629 the same say or how does this work?

NOTE Confidence: 0.8212341

00:42:43.630 --> 00:42:45.660 And to answer this question,

NOTE Confidence: 0.8212341

00:42:45.660 --> 00:42:48.220 or we developed in our lap a single

NOTE Confidence: 0.8212341

00:42:48.220 --> 00:42:50.899 self also protein analysis that allows

NOTE Confidence: 0.8212341

00:42:50.899 --> 00:42:53.354 us to interrogate her phosphorylation

NOTE Confidence: 0.8212341

00:42:53.354 --> 00:42:56.337 of STAT 5 and phosphorylation of Erk.

NOTE Confidence: 0.8212341

00:42:56.340 --> 00:42:58.372 Concurrently in single cells,

NOTE Confidence: 0.8212341

00:42:58.372 --> 00:43:02.480 and this is here based on the gel

NOTE Confidence: 0.8212341

00:43:02.480 --> 00:43:05.854 matrix where we can deposit 6400 cells,

NOTE Confidence: 0.8212341

00:43:05.860 --> 00:43:09.010 single cells and then look at STAT

NOTE Confidence: 0.8212341

00:43:09.010 --> 00:43:11.685 5 and workforce relations events

NOTE Confidence: 0.8212341

00:43:11.685 --> 00:43:14.750 individually and this year or

NOTE Confidence: 0.8212341

00:43:14.750 --> 00:43:16.589 four patient arrived.

NOTE Confidence: 0.8212341

00:43:16.590 --> 00:43:19.050 Cases where we looked at individual

NOTE Confidence: 0.8212341

00:43:19.050 --> 00:43:21.612 sales and were then actually able

NOTE Confidence: 0.8212341

00:43:21.612 --> 00:43:24.156 to determine that even though for

NOTE Confidence: 0.8212341

00:43:24.156 --> 00:43:27.278 all those four cases we get to dual

NOTE Confidence: 0.8212341

00:43:27.278 --> 00:43:29.652 signal by Western blot, if he.

NOTE Confidence: 0.8212341

00:43:29.652 --> 00:43:32.844 Use our single cell for supporting analysis.

NOTE Confidence: 0.8212341

00:43:32.850 --> 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 --> 00:43:41.780 and that goes for all four cases and we

NOTE Confidence: 0.8212341

00:43:41.780 --> 00:43:44.114 don't see any double expressing cells.

NOTE Confidence: 0.8212341

00:43:44.120 --> 00:43:46.255 So our conclusion is at least are

NOTE Confidence: 0.8212341

00:43:46.255 --> 00:43:48.339 actually rare by colonial diseases,

NOTE Confidence: 0.8212341

00:43:48.340 --> 00:43:51.682 in which two clones are competing

NOTE Confidence: 0.8212341

00:43:51.682 --> 00:43:53.353 against each other.

NOTE Confidence: 0.8212341

00:43:53.360 --> 00:43:56.753 Then we asked what is the reason for that?

NOTE Confidence: 0.8212341

00:43:56.760 --> 00:43:59.028 So what is the underlying mechanism

NOTE Confidence: 0.8212341

00:43:59.028 --> 00:44:01.716 that these two pathways just can't go

NOTE Confidence: 0.8212341

00:44:01.716 --> 00:44:03.936 together and to address this question,

NOTE Confidence: 0.8212341

00:44:03.940 --> 00:44:05.532 we actually voiced it.

NOTE Confidence: 0.8212341

00:44:05.532 --> 00:44:07.920 The alternative pathway on the leukemia

NOTE Confidence: 0.8212341

00:44:07.991 --> 00:44:10.364 said are driven by the other pathway,

NOTE Confidence: 0.8212341

00:44:10.370 --> 00:44:13.394 meaning that here is a visa able or

NOTE Confidence: 0.8212341

00:44:13.394 --> 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

NOTE Confidence: 0.65469474

00:44:19.282 --> 00:44:22.257 able and use different models for that.

NOTE Confidence: 0.65469474

00:44:22.260 --> 00:44:24.534 And here, this colony forming assay

NOTE Confidence: 0.65469474

00:44:24.534 --> 00:44:27.420 shows if you have one single driver,

NOTE Confidence: 0.65469474

00:44:27.420 --> 00:44:29.410 either in the rason start.

NOTE Confidence: 0.65469474

00:44:29.410 --> 00:44:30.994 Five pathways is dramatically

NOTE Confidence: 0.65469474

00:44:30.994 --> 00:44:32.578 increases number of colonies,

NOTE Confidence: 0.65469474

00:44:32.580 --> 00:44:34.956 but if we have posed together,

NOTE Confidence: 0.65469474

00:44:34.960 --> 00:44:37.415 we basically lose or colony

NOTE Confidence: 0.65469474

00:44:37.415 --> 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 --> 00:44:44.664 so single driver nicely lead to outgrows,

NOTE Confidence: 0.65469474

00:44:44.670 --> 00:44:48.280 but combination of Bosa suppressive.

NOTE Confidence: 0.65469474

00:44:48.280 --> 00:44:50.716 What was really surprising to us?

NOTE Confidence: 0.65469474

00:44:50.720 --> 00:44:51.412 This actually,

NOTE Confidence: 0.65469474

00:44:51.412 --> 00:44:53.834 that if we use genetic ablation of

NOTE Confidence: 0.65469474

00:44:53.834 --> 00:44:56.398 the diverging or alternative pathway,

NOTE Confidence: 0.65469474

00:44:56.400 --> 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 --> 00:45:02.080 this actually Slack celebration of

NOTE Confidence: 0.65469474

00:45:02.080 --> 00:45:04.110 leukemia initiation in this model.

NOTE Confidence: 0.65469474

00:45:04.110 --> 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 --> 00:45:14.270 leukemia and we remove perk. This.

NOTE Confidence: 0.65469474

00:45:14.270 --> 00:45:16.430 Accelerates development of leukemia.

NOTE Confidence: 0.65469474

00:45:16.430 --> 00:45:19.670 Likewise in a chaos driven leukemia.

NOTE Confidence: 0.65469474

00:45:19.670 --> 00:45:22.950 Removal of stat 5.

NOTE Confidence: 0.65469474

00:45:22.950 --> 00:45:25.794 Come initiates faster development

NOTE Confidence: 0.65469474

00:45:25.794 --> 00:45:28.638 of looking more Genesis.

NOTE Confidence: 0.65469474

00:45:28.640 --> 00:45:29.408 And biochemically,

NOTE Confidence: 0.65469474

00:45:29.408 --> 00:45:32.096 we were able to recover too late.

NOTE Confidence: 0.65469474

00:45:32.100 --> 00:45:34.790 This was small molecule inhibitors

NOTE Confidence: 0.65469474

00:45:34.790 --> 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 --> 00:45:41.206 activity as expected.

NOTE Confidence: 0.65469474

00:45:41.210 --> 00:45:43.320 But it also induces phosphorylation

NOTE Confidence: 0.65469474

00:45:43.320 --> 00:45:45.432 of STAT 5, and rocks.

NOTE Confidence: 0.65469474

00:45:45.432 --> 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 --> 00:45:51.344 but increases per activity.

NOTE Confidence: 0.65469474

00:45:51.350 --> 00:45:53.950 And so to end here,

NOTE Confidence: 0.65469474

00:45:53.950 --> 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 --> 00:46:03.828 reactivation of diverging pathways.

NOTE Confidence: 0.65469474

00:46:03.830 --> 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 --> 00:46:15.730 Strongly activates falsework at the

NOTE Confidence: 0.65469474

00:46:15.730 --> 00:46:19.818 expense of start 5 and then DPH here.

NOTE Confidence: 0.65469474

00:46:19.820 --> 00:46:22.725 Is the stat 5 agonist drive start

NOTE Confidence: 0.65469474

00:46:22.725 --> 00:46:24.848 five phosphorylation but at the

NOTE Confidence: 0.65469474

00:46:24.848 --> 00:46:27.254 expense of work and this has

NOTE Confidence: 0.65469474

00:46:27.254 --> 00:46:29.320 interesting activity on the clonal

NOTE Confidence: 0.65469474

00:46:29.320 --> 00:46:31.702 dynamics of these leukemias in vivo.

NOTE Confidence: 0.65469474

00:46:31.710 --> 00:46:34.990 So start five leukemia can be converted into,

NOTE Confidence: 0.65469474

00:46:34.990 --> 00:46:37.040 IIRC, leukemia, and most importantly,

NOTE Confidence: 0.65469474

00:46:37.040 --> 00:46:39.090 if you combine these pathway

NOTE Confidence: 0.65469474

00:46:39.090 --> 00:46:40.730 agonist was conventional treatment.

NOTE Confidence: 0.65469474

00:46:40.730 --> 00:46:41.951 So, for instance,

NOTE Confidence: 0.65469474

00:46:41.951 --> 00:46:43.986 here on Earth inhibitor with

NOTE Confidence: 0.65469474

00:46:43.986 --> 00:46:45.649 a Step 5 agonist,

NOTE Confidence: 0.65469474

00:46:45.650 --> 00:46:47.658 we achieve a dramatic

NOTE Confidence: 0.65469474

00:46:47.658 --> 00:46:49.666 prolongation of overall survival.

NOTE Confidence: 0.65469474

00:46:49.670 --> 00:46:51.600 So.

NOTE Confidence: 0.65469474

00:46:51.600 --> 00:46:55.037 The final conclusion here is that we

NOTE Confidence: 0.65469474

00:46:55.037 --> 00:46:58.178 propose that diversity of signaling input.

NOTE Confidence: 0.65469474

00:46:58.180 --> 00:47:00.765 Is actually an important barrier

NOTE Confidence: 0.65469474

00:47:00.765 --> 00:47:02.833 of malignant transformation and

NOTE Confidence: 0.65469474

00:47:02.833 --> 00:47:04.292 centralization and convergence

NOTE Confidence: 0.65469474

00:47:04.292 --> 00:47:06.036 onto one single pathway.

NOTE Confidence: 0.65469474

00:47:06.040 --> 00:47:09.568 Inactivation of all the other pathways.

NOTE Confidence: 0.65469474

00:47:09.570 --> 00:47:12.030 Is an early and critical step

NOTE Confidence: 0.65469474

00:47:12.030 --> 00:47:13.260 of malignant transformation,

NOTE Confidence: 0.65469474

00:47:13.260 --> 00:47:15.260 and if we achieve.

NOTE Confidence: 0.65469474

00:47:15.260 --> 00:47:18.260 To reinstate at the very signaling

NOTE Confidence: 0.65469474

00:47:18.357 --> 00:47:19.490 environment.

NOTE Confidence: 0.65469474

00:47:19.490 --> 00:47:21.835 That would resemble the interactions

NOTE Confidence: 0.65469474

00:47:21.835 --> 00:47:25.143 of normal cells were sent by him

NOTE Confidence: 0.65469474

00:47:25.143 --> 00:47:27.358 and which have multiple receptors.

NOTE Confidence: 0.65469474

00:47:27.360 --> 00:47:29.680 Multiple cues from the environment.

NOTE Confidence: 0.65469474

00:47:29.680 --> 00:47:32.045 So we're proposing a strategy

NOTE Confidence: 0.65469474

00:47:32.045 --> 00:47:33.464 of pharmacological reactivation

NOTE Confidence: 0.65469474

00:47:33.464 --> 00:47:36.221 that would restore their diverse

NOTE Confidence: 0.65469474

00:47:36.221 --> 00:47:37.379 signaling environment.

NOTE Confidence: 0.65469474

00:47:37.380 --> 00:47:39.924 And we hope that this approach can also

NOTE Confidence: 0.65469474

00:47:39.924 --> 00:47:42.040 be leveraged to overcome convention

NOTE Confidence: 0.65469474

00:47:42.040 --> 00:47:43.928 mechanisms of black resistance.

NOTE Confidence: 0.65469474

00:47:43.930 --> 00:47:46.240 So here we have passed their

NOTE Confidence: 0.65469474

00:47:46.240 --> 00:47:47.010 convergence minimal.

NOTE Confidence: 0.65469474

00:47:47.010 --> 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 --> 00:47:53.165 But here if you have divergent pathways,

NOTE Confidence: 0.65469474

00:47:53.170 --> 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.

NOTE Confidence: 0.65469474

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 --> 00:48:06.080 Farber at yeah.

NOTE Confidence: 0.65469474

00:48:06.080 --> 00:48:07.840 And would like to acknowledge

NOTE Confidence: 0.65469474

00:48:07.840 --> 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 --> 00:48:13.738 who did most of the conceptual

NOTE Confidence: 0.76657015

00:48:13.738 --> 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 --> 00:48:22.034 Marcus that's amazing. Collection

NOTE Confidence: 0.8229462

00:48:22.034 --> 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 --> 00:48:34.357 intuitive alot of these pathways are

NOTE Confidence: 0.8229462

00:48:34.357 --> 00:48:37.647 in B cells and be some legacies.

NOTE Confidence: 0.8229462

00:48:37.650 --> 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.

NOTE Confidence: 0.8229462

00:48:43.990 --> 00:48:46.615 That I guess are principally

NOTE Confidence: 0.8229462

00:48:46.615 --> 00:48:49.240 designed for B cell elimination.

NOTE Confidence: 0.8229462

00:48:49.240 --> 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 --> 00:48:55.140 target those pathways?

NOTE Confidence: 0.8229462

00:48:55.140 --> 00:48:57.108 Or could you target those pathways

NOTE Confidence: 0.8229462

00:48:57.108 --> 00:48:58.901 in conjunction with the growing

NOTE Confidence: 0.8229462

00:48:58.901 --> 00:49:00.173 armamentarium of available

NOTE Confidence: 0.8229462

00:49:00.173 --> 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 --> 00:49:07.104 could you leverage that combination?

NOTE Confidence: 0.86497533

00:49:09.170 --> 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

NOTE Confidence: 0.86497533

00:49:13.830 --> 00:49:15.846 hyperactivation of Visa receptor

NOTE Confidence: 0.86497533

00:49:15.846 --> 00:49:18.600 signaling to engage negative selection,

NOTE Confidence: 0.86497533

00:49:18.600 --> 00:49:24.290 and I think we have two options, one is.

NOTE Confidence: 0.86497533

00:49:24.290 --> 00:49:26.660 Already available, but less attractive,

NOTE Confidence: 0.86497533

00:49:26.660 --> 00:49:29.882 that would be April inhibition or

NOTE Confidence: 0.86497533

00:49:29.882 --> 00:49:32.930 phosphatases like Ship One and P-10.

NOTE Confidence: 0.86497533

00:49:32.930 --> 00:49:35.972 I'm attractive cause in the field

NOTE Confidence: 0.86497533

00:49:35.972 --> 00:49:38.625 phosphatase innovation raises a lot

NOTE Confidence: 0.86497533

00:49:38.625 --> 00:49:40.809 of questions about specificity.

NOTE Confidence: 0.86497533

00:49:40.810 --> 00:49:43.288 An alternative approach is one that

NOTE Confidence: 0.86497533

00:49:43.288 --> 00:49:46.705 Mark Lemon and I have discussed and that

NOTE Confidence: 0.86497533

00:49:46.705 --> 00:49:49.719 would be to generate a direct agonist

NOTE Confidence: 0.86497533

00:49:49.719 --> 00:49:52.568 of picky kinase like sick or BDK.

NOTE Confidence: 0.86497533

00:49:52.570 --> 00:49:55.530 Something fairly upstream in the

NOTE Confidence: 0.86497533

00:49:55.530 --> 00:49:57.898 visa receptor signaling cascade.

NOTE Confidence: 0.86497533

00:49:57.900 --> 00:50:01.068 So actually yesterday.

NOTE Confidence: 0.86497533

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 --> 00:50:05.457 and there was some encouraging feedback

NOTE Confidence: 0.86497533

00:50:05.457 --> 00:50:07.870 that that might actually be feasable.

NOTE Confidence: 0.86497533

00:50:07.870 --> 00:50:10.131 So that's an approach that I would

NOTE Confidence: 0.86497533

00:50:10.131 --> 00:50:12.156 definitely like to pursue in the

NOTE Confidence: 0.86497533

00:50:12.156 --> 00:50:14.130 future to develop a direct hyper

NOTE Confidence: 0.86497533

00:50:14.130 --> 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 --> 00:50:23.481 people should feel free to submit

NOTE Confidence: 0.8305846

00:50:23.481 --> 00:50:26.253 questions on the on the chat box.

NOTE Confidence: 0.8305846

00:50:26.260 --> 00:50:28.360 Dying cross as a question.

NOTE Confidence: 0.8305846

00:50:28.360 --> 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

NOTE Confidence: 0.8305846

00:50:37.112 --> 00:50:38.830 predominantly intracellular.

NOTE Confidence: 0.8305846

00:50:38.830 --> 00:50:41.770 What do you think that this indicates?

NOTE Confidence: 0.8182225

00:50:43.440 --> 00:50:46.728 Great questions so.

NOTE Confidence: 0.8182225

00:50:46.730 --> 00:50:50.270 We have done an experiment with.

NOTE Confidence: 0.8182225

00:50:50.270 --> 00:50:53.049 WGA, which is a surface marker and

NOTE Confidence: 0.8182225

00:50:53.049 --> 00:50:55.207 we we actually find colocalization

NOTE Confidence: 0.8182225

00:50:55.207 --> 00:50:58.426 of about 60 to 70% of those

NOTE Confidence: 0.8182225

00:50:58.426 --> 00:51:01.474 interactions with the CD79A and B.

NOTE Confidence: 0.8182225

00:51:01.480 --> 00:51:03.556 So I don't think it's predominantly,

NOTE Confidence: 0.8182225

00:51:03.560 --> 00:51:05.212 but the question remains,

NOTE Confidence: 0.8182225

00:51:05.212 --> 00:51:07.690 there's still a significant amount of

NOTE Confidence: 0.8182225

00:51:07.758 --> 00:51:10.250 interactions that are was in the sale.

NOTE Confidence: 0.8182225

00:51:10.250 --> 00:51:11.774 And you thought, indeed,

NOTE Confidence: 0.8182225

00:51:11.774 --> 00:51:13.298 that is very strange,

NOTE Confidence: 0.8182225

00:51:13.300 --> 00:51:16.114 because why would the visa receptor

NOTE Confidence: 0.8182225

00:51:16.114 --> 00:51:18.798 be internalized or somewhat was in

NOTE Confidence: 0.8182225

00:51:18.798 --> 00:51:20.976 this area associated with CD 25?

NOTE Confidence: 0.8182225

00:51:20.980 --> 00:51:24.018 And so we can answer this fully.

NOTE Confidence: 0.8182225

00:51:24.020 --> 00:51:26.771 But in light of the recent study

NOTE Confidence: 0.8182225

00:51:26.771 --> 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 --> 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 --> 00:51:38.027 complexes form of endosomal membranes,

NOTE Confidence: 0.8182225

00:51:38.030 --> 00:51:39.212 his Tinder sale.

NOTE Confidence: 0.8182225

00:51:39.212 --> 00:51:41.182 We think that exact same

NOTE Confidence: 0.8182225

00:51:41.182 --> 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 --> 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 --> 00:51:50.383 But I agree with Diane that let

NOTE Confidence: 0.8182225

00:51:50.383 --> 00:51:51.870 me see intracellular complexes,

NOTE Confidence: 0.8182225

00:51:51.870 --> 00:51:54.110 and we think they're an endo zones.

NOTE Confidence: 0.82619333

00:51:55.360 --> 00:51:57.556 Thank you and Diana's second question,

NOTE Confidence: 0.82619333

00:51:57.560 --> 00:52:00.302 which is CD 25 seems to

NOTE Confidence: 0.82619333

00:52:00.302 --> 00:52:01.216 prevent autoreactivity.

NOTE Confidence: 0.82619333

00:52:01.220 --> 00:52:03.800 Do you think this is related

NOTE Confidence: 0.82619333

00:52:03.800 --> 00:52:06.820 to CD-25 CD 79 interaction?

NOTE Confidence: 0.82619333

00:52:06.820 --> 00:52:11.128 Does it? Does C25 interact with

NOTE Confidence: 0.82619333

00:52:11.128 --> 00:52:13.750 surface immuno globulin's? I'm.

NOTE Confidence: 0.826858489

00:52:14.360 --> 00:52:16.610 So. That's actually a question

NOTE Confidence: 0.826858489

00:52:16.610 --> 00:52:18.860 that I asked Eric Metra,

NOTE Confidence: 0.826858489

00:52:18.860 --> 00:52:20.695 who's my collaborator in the

NOTE Confidence: 0.826858489

00:52:20.695 --> 00:52:22.163 field of autoimmune diseases,

NOTE Confidence: 0.826858489

00:52:22.170 --> 00:52:24.378 so Eric told us at 3:25,

NOTE Confidence: 0.826858489

00:52:24.380 --> 00:52:26.744 and that's known by work from

NOTE Confidence: 0.826858489

00:52:26.744 --> 00:52:29.390 from his group and also others.

NOTE Confidence: 0.826858489

00:52:29.390 --> 00:52:31.690 It is crucial to maintain

NOTE Confidence: 0.826858489

00:52:31.690 --> 00:52:33.990 central visa tolerance so that

NOTE Confidence: 0.826858489

00:52:34.074 --> 00:52:36.539 molecule is not there anymore.

NOTE Confidence: 0.826858489

00:52:36.540 --> 00:52:40.050 Then central tolerance mechanisms don't work.

NOTE Confidence: 0.826858489

00:52:40.050 --> 00:52:41.815 I think our signaling studies

NOTE Confidence: 0.826858489

00:52:41.815 --> 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 --> 00:52:46.810 you know what this mechanism of that?

NOTE Confidence: 0.826858489

00:52:46.810 --> 00:52:49.426 I think the link or how C25 interferes

NOTE Confidence: 0.826858489

00:52:49.426 --> 00:52:51.539 with Visa receptor signaling is not

NOTE Confidence: 0.826858489

00:52:51.539 --> 00:52:54.650 known in our paper is not published yet,

NOTE Confidence: 0.826858489

00:52:54.650 --> 00:52:57.380 so we're still working on that.

NOTE Confidence: 0.826858489

00:52:57.380 --> 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 --> 00:53:00.037 actually,

NOTE Confidence: 0.826858489

00:53:00.037 --> 00:53:01.122 that it doesn't act in

NOTE Confidence: 0.826858489

00:53:01.122 --> 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 --> 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 --> 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 --> 00:53:25.075 but is that something you could

NOTE Confidence: 0.8513638

00:53:25.075 --> 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 --> 00:53:32.720 because there's one that I want

NOTE Confidence: 0.8390908

00:53:32.720 --> 00:53:34.269 to show you. This is study.

NOTE Confidence: 0.5958561

00:53:36.810 --> 00:53:40.461 Yeah, this study heals. Come by Veronica.

NOTE Confidence: 0.5958561

00:53:40.461 --> 00:53:42.540 Sex is group so that did you

NOTE Confidence: 0.6687811

00:53:42.540 --> 00:53:45.640 want to share your slide or? Yes,

NOTE Confidence: 0.767513

00:53:45.640 --> 00:53:47.327 I'm going to show this slide again.

NOTE Confidence: 0.8439994

00:53:54.460 --> 00:53:56.777 OK, so I I hope I'm I

NOTE Confidence: 0.8439994

00:53:56.777 --> 00:53:58.560 got the question correct.

NOTE Confidence: 0.8439994

00:53:58.560 --> 00:54:01.917 This is what I I would like to refer.

NOTE Confidence: 0.8439994

00:54:01.920 --> 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 --> 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 --> 00:54:20.589 time is actually going opposite direction,

NOTE Confidence: 0.8439994

00:54:20.590 --> 00:54:23.254 so they found that these patients

NOTE Confidence: 0.8439994

00:54:23.254 --> 00:54:26.150 developed in 6% of nine patients out

NOTE Confidence: 0.8439994

00:54:26.150 --> 00:54:29.852 of 157 was NP ND well developed hybrid

NOTE Confidence: 0.8439994

00:54:29.852 --> 00:54:34.262 diesel lymphoma that were driven with Keras.

NOTE Confidence: 0.8439994

00:54:34.270 --> 00:54:37.910 And that's a 15 fold increase risk.

NOTE Confidence: 0.8439994

00:54:37.910 --> 00:54:40.773 So what they said in this study

NOTE Confidence: 0.8439994

00:54:40.773 --> 00:54:43.448 is that actually find one reason.

NOTE Confidence: 0.8439994

00:54:43.450 --> 00:54:47.286 Population of the Start 5 pathway enables.

NOTE Confidence: 0.8439994

00:54:47.290 --> 00:54:48.905 The transformation of the pre

NOTE Confidence: 0.8439994

00:54:48.905 --> 00:54:50.903 malignant B cell tumor that carries

NOTE Confidence: 0.8439994

00:54:50.903 --> 00:54:52.493 the Chaos Legion that essentially

NOTE Confidence: 0.8439994

00:54:52.493 --> 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 --> 00:55:00.421 can be beneficial if he find ways to

NOTE Confidence: 0.8439994

00:55:00.421 --> 00:55:02.935 leverage this activity to completely

NOTE Confidence: 0.8439994

00:55:02.935 --> 00:55:04.699 suppress oncogenic signaling.

NOTE Confidence: 0.8439994

00:55:04.700 --> 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 --> 00:55:11.826 direction if you try to achieve

NOTE Confidence: 0.8439994

00:55:11.826 --> 00:55:14.036 long-term suppression of 1 pathway,

NOTE Confidence: 0.8439994

00:55:14.040 --> 00:55:16.368 you might inadvertently activate the other.

NOTE Confidence: 0.8375848

00:55:17.790 --> 00:55:18.986 So it's really interesting.

NOTE Confidence: 0.8375848

00:55:18.986 --> 00:55:20.182 'cause obviously if you're

NOTE Confidence: 0.8375848

00:55:20.182 --> 00:55:21.778 going to use ruxolitinib you,

NOTE Confidence: 0.8375848

00:55:21.780 --> 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 --> 00:55:27.916 but that's a pretty heart risk.

NOTE Confidence: 0.8601446

00:55:34.780 --> 00:55:38.868 Just waiting to see if any other questions.

NOTE Confidence: 0.8601446

00:55:38.870 --> 00:55:40.418 Well, I think we're you know,

NOTE Confidence: 0.8601446

00:55:40.420 --> 00:55:42.219 really, at the top of the hour,

NOTE Confidence: 0.8601446

00:55:42.220 --> 00:55:44.443 so you know, want to thank Mark is for

NOTE Confidence: 0.8601446

00:55:44.443 --> 00:55:46.676 it really is an extraordinary talk.

NOTE Confidence: 0.8601446

00:55:46.680 --> 00:55:48.580 That's creating so much insight

NOTE Confidence: 0.8601446

00:55:48.580 --> 00:55:50.980 into the biology of AB cells.

NOTE Confidence: 0.8601446

00:55:50.980 --> 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 --> 00:55:56.850 and Snyder for sort of share

NOTE Confidence: 0.8601446

00:55:56.922 --> 00:55:59.187 continuing to lead this lectureship?

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 --> 00:56:03.768 for their continued support of

NOTE Confidence: 0.8601446

00:56:03.768 --> 00:56:06.018 our Cancer Center and the mission

NOTE Confidence: 0.8601446

00:56:06.018 --> 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 --> 00:56:14.640 day and happy New year.

NOTE Confidence: 0.895135683333333

00:56:17.160 --> 00:56:18.558 Thank you. Thank

NOTE Confidence: 0.90354365

00:56:18.560 --> 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.