WEBVTT

NOTE duration:"00:54:20"

NOTE recognizability:0.852

NOTE language:en-us

NOTE Confidence: 0.8770731

00:00:00.000 --> 00:00:04.105 Good morning. So for those of you who

NOTE Confidence: 0.8770731

00:00:04.105 --> 00:00:06.598 either can't see me or don't know me,

NOTE Confidence: 0.8770731

00:00:06.600 --> 00:00:09.911 I'm Eric Weiner and I'm really pleased

NOTE Confidence: 0.8770731

00:00:09.911 --> 00:00:13.557 to be here to introduce Kathy Wu.

NOTE Confidence: 0.8770731

00:00:13.560 --> 00:00:18.600 This is the inaugural lecture of what we

NOTE Confidence: 0.8770731

00:00:18.600 --> 00:00:22.996 hope will be a new series and many of us

NOTE Confidence: 0.8770731

00:00:22.996 --> 00:00:25.598 in the Cancer Center spent a lot of time

NOTE Confidence: 0.8770731

00:00:25.598 --> 00:00:27.989 thinking about how we want to do conferences.

NOTE Confidence: 0.8770731

00:00:27.989 --> 00:00:31.101 And we looked at attendance and we looked

NOTE Confidence: 0.8770731

00:00:31.101 --> 00:00:34.048 at who goes to what and ultimately came

NOTE Confidence: 0.8770731

00:00:34.048 --> 00:00:36.960 to the decision that Grand runs as it was,

NOTE Confidence: 0.8770731

00:00:36.960 --> 00:00:39.452 which is now trying to be in

NOTE Confidence: 0.8770731

00:00:39.452 --> 00:00:41.600 person as much as possible,

NOTE Confidence: 0.8770731

00:00:41.600 --> 00:00:43.440 was largely attended by clinically

NOTE Confidence: 0.8770731

00:00:43.440 --> 00:00:44.912 oriented people in population,

NOTE Confidence: 0.8770731

00:00:44.920 --> 00:00:47.770 scientists and people who are otherwise

NOTE Confidence: 0.8770731

00:00:47.770 --> 00:00:50.406 looking for lunch and or breakfast.

NOTE Confidence: 0.8770731

00:00:50.406 --> 00:00:54.125 And and that there was really a need for

NOTE Confidence: 0.8770731

00:00:54.125 --> 00:00:56.995 a conference that focused a bit more

NOTE Confidence: 0.8770731

00:00:57.000 --> 00:01:01.040 on translational and basic questions.

NOTE Confidence: 0.8770731

00:01:01.040 --> 00:01:03.200 And so after some thought,

NOTE Confidence: 0.8770731

00:01:03.200 --> 00:01:06.140 a small committee of people that

NOTE Confidence: 0.8770731

00:01:06.140 --> 00:01:09.040 included Katie Politi and Megan King

NOTE Confidence: 0.8770731

00:01:09.040 --> 00:01:11.792 came up with the idea of trying a

NOTE Confidence: 0.8770731

00:01:11.792 --> 00:01:14.239 conference like this on a monthly basis.

NOTE Confidence: 0.8770731

00:01:14.240 --> 00:01:17.236 And this is the first of those.

NOTE Confidence: 0.8770731

00:01:17.240 --> 00:01:19.832 So I'm really pleased to have Kathy Wu here.

NOTE Confidence: 0.8770731

00:01:19.840 --> 00:01:22.996 I've known Kathy for many years.

NOTE Confidence: 0.8770731

00:01:23.000 --> 00:01:26.924 She was a fellow at Dana Farber and of

NOTE Confidence: 0.8770731

00:01:26.924 --> 00:01:30.856 course it's still with Dana Farber when

NOTE Confidence: 0.8770731

00:01:30.856 --> 00:01:35.056 I was a substantially younger attending.

NOTE Confidence: 0.8770731

00:01:35.056 --> 00:01:39.440 And in fact we worked together in clinic,

NOTE Confidence: 0.8770731

00:01:39.440 --> 00:01:40.278 yes, briefly.

NOTE Confidence: 0.8770731

00:01:40.278 --> 00:01:43.630 She dabbled a little bit in seeing a

NOTE Confidence: 0.8770731

00:01:43.720 --> 00:01:47.160 patient with breast cancer or one or two.

NOTE Confidence: 0.8770731

00:01:47.160 --> 00:01:50.520 And so I've known Kathy now for 20

NOTE Confidence: 0.8770731

00:01:50.520 --> 00:01:53.805 plus years and Kathy has built really

NOTE Confidence: 0.8770731

00:01:53.805 --> 00:01:57.480 a phenomenal career at at Dana Farber.

NOTE Confidence: 0.8770731

00:01:57.480 --> 00:01:59.960 Her own interests are broad.

NOTE Confidence: 0.8770731

00:01:59.960 --> 00:02:01.600 I learned last night something

NOTE Confidence: 0.8770731

00:02:01.600 --> 00:02:02.912 I didn't know before,

NOTE Confidence: 0.8770731

00:02:02.920 --> 00:02:05.349 which is that she even had an

NOTE Confidence: 0.8770731

00:02:05.349 --> 00:02:07.898 interest in sickle cell disease and

NOTE Confidence: 0.8770731

00:02:07.898 --> 00:02:09.806 therapeutic approaches to sickle

NOTE Confidence: 0.8770731

00:02:09.806 --> 00:02:12.040 cell disease way back when,

NOTE Confidence: 0.8770731

00:02:12.040 --> 00:02:14.070 but ultimately decided that some

NOTE Confidence: 0.8770731

00:02:14.070 --> 00:02:16.680 some amount of focus was needed.

NOTE Confidence: 0.8770731

00:02:16.680 --> 00:02:18.960 And her interests have really

NOTE Confidence: 0.8770731

00:02:18.960 --> 00:02:21.240 focused on immunotherapy and Col.

NOTE Confidence: 0.8770731

00:02:21.240 --> 00:02:23.836 and and beyond that,

NOTE Confidence: 0.8770731

00:02:23.836 --> 00:02:27.081 the development of vaccines and

NOTE Confidence: 0.8770731

00:02:27.081 --> 00:02:30.639 and tumor specific vaccines.

NOTE Confidence: 0.8770731

00:02:30.640 --> 00:02:33.040 She is presently a Professor of

NOTE Confidence: 0.8770731

00:02:33.040 --> 00:02:35.120 Medicine at Harvard Medical School

NOTE Confidence: 0.8770731

00:02:35.120 --> 00:02:38.480 and the chief of the Division of

NOTE Confidence: 0.8770731

00:02:38.480 --> 00:02:40.160 Let Me See If I Get This Right,

NOTE Confidence: 0.8770731

00:02:40.160 --> 00:02:42.092 Stem cell transplantation and

NOTE Confidence: 0.8770731

00:02:42.092 --> 00:02:44.507 cellular therapies at the the

NOTE Confidence: 0.8770731

00:02:44.507 --> 00:02:46.580 Dana Farber Cancer Institute.

NOTE Confidence: 0.8770731

00:02:46.580 --> 00:02:51.400 So it's really a pleasure to have you here.

NOTE Confidence: 0.8770731

00:02:51.400 --> 00:02:53.425 We're all looking forward to

NOTE Confidence: 0.8770731

00:02:53.425 --> 00:02:55.840 your talk on largely on CLL.

NOTE Confidence: 0.8770731

00:02:55.840 --> 00:02:57.676 And thanks so much for coming.

NOTE Confidence: 0.8770731

00:02:57.680 --> 00:02:58.592 We had I will,

NOTE Confidence: 0.8770731

00:02:58.592 --> 00:03:01.191 I will just say that a small group of us

NOTE Confidence: 0.8770731

00:03:01.191 --> 00:03:03.680 had a great dinner with Kathy last night.

NOTE Confidence: 0.8770731

00:03:03.680 --> 00:03:07.520 And in addition to being a great scientist,

NOTE Confidence: 0.8770731

00:03:07.520 --> 00:03:09.080 she's also just a delightful

NOTE Confidence: 0.8770731

00:03:09.080 --> 00:03:10.640 person to have dinner with.

NOTE Confidence: 0.826064656666667

00:03:19.240 --> 00:03:22.120 Well, it's really an honor to be here

NOTE Confidence: 0.826064656666667

00:03:22.120 --> 00:03:26.120 and and happy New Year, Happy Snow day.

NOTE Confidence: 0.826064656666667

00:03:26.120 --> 00:03:28.000 Thank you everyone in the

NOTE Confidence: 0.826064656666667

00:03:28.000 --> 00:03:29.880 room for trudging in this.

NOTE Confidence: 0.826064656666667

00:03:29.880 --> 00:03:33.680 It's really great to see you in person

NOTE Confidence: 0.826064656666667

00:03:33.680 --> 00:03:36.833 and and also to all the folks out in Zoom.

NOTE Confidence: 0.826064656666667

00:03:36.840 --> 00:03:38.919 I hope this is a successful series

NOTE Confidence: 0.826064656666667

00:03:38.919 --> 00:03:41.132 because I do think that the intersection

NOTE Confidence: 0.826064656666667

00:03:41.132 --> 00:03:43.364 between the clinical and the basic

NOTE Confidence: 0.826064656666667

00:03:43.364 --> 00:03:46.344 and really kind of being able to look

NOTE Confidence: 0.826064656666667

00:03:46.344 --> 00:03:47.784 at the translational opportunities

NOTE Confidence: 0.826064656666667

00:03:47.784 --> 00:03:49.976 that are afforded by the patients that

NOTE Confidence: 0.826064656666667

00:03:49.976 --> 00:03:52.228 we treat in the study are are are

NOTE Confidence: 0.826064656666667

00:03:52.228 --> 00:03:54.040 immense and so and very rewarding.

NOTE Confidence: 0.826064656666667

00:03:54.040 --> 00:03:58.240 So and as as Eric said I I do have many,

NOTE Confidence: 0.826064656666667

00:03:58.240 --> 00:03:59.720 many different different interests.

NOTE Confidence: 0.826064656666667

00:03:59.720 --> 00:04:03.636 I think that's a hallmark of a of a happy MD.

NOTE Confidence: 0.826064656666667

00:04:03.640 --> 00:04:05.901 So like we we're interested in a

NOTE Confidence: 0.826064656666667

00:04:05.901 --> 00:04:08.256 lot of things and and thank you for

NOTE Confidence: 0.826064656666667

00:04:08.256 --> 00:04:09.900 giving me the opportunity to maybe

NOTE Confidence: 0.826064656666667

00:04:09.953 --> 00:04:11.280 share some of the work that we've

NOTE Confidence: 0.826064656666667

00:04:11.280 --> 00:04:15.170 been doing in CLL Genomics. OK.

NOTE Confidence: 0.826064656666667

00:04:15.170 --> 00:04:17.120 So we'll start.

NOTE Confidence: 0.826064656666667

00:04:17.120 --> 00:04:17.480 Let's see

NOTE Confidence: 0.76337852

00:04:27.160 --> 00:04:29.800 here we go. Disclosure slide,

NOTE Confidence: 0.76337852

00:04:29.800 --> 00:04:31.396 OK, I thought I'd start here,

NOTE Confidence: 0.76337852

00:04:31.400 --> 00:04:34.460 which is you know I think just a a

NOTE Confidence: 0.76337852

00:04:34.460 --> 00:04:36.678 challenge to all of us in the cancer

NOTE Confidence: 0.76337852

00:04:36.678 --> 00:04:38.351 community whether or not we study

NOTE Confidence: 0.76337852

00:04:38.351 --> 00:04:40.439 CLL or not is really the challenge of

NOTE Confidence: 0.76337852

00:04:40.505 --> 00:04:42.437 tumor heterogeneity and evolution.

NOTE Confidence: 0.76337852

00:04:42.440 --> 00:04:44.906 This has really been kind of

NOTE Confidence: 0.76337852

00:04:44.906 --> 00:04:47.320 understood for quite some time now,

NOTE Confidence: 0.76337852

00:04:47.320 --> 00:04:49.427 made ever more clear through all the

NOTE Confidence: 0.76337852

00:04:49.427 --> 00:04:51.440 genomic studies that have been out there.

NOTE Confidence: 0.76337852

00:04:51.440 --> 00:04:54.177 But we know for sure that cancer

NOTE Confidence: 0.76337852

00:04:54.177 --> 00:04:56.280 is a heterogeneous population,

NOTE Confidence: 0.76337852

00:04:56.280 --> 00:04:57.320 for better or for worse.

NOTE Confidence: 0.76337852

00:04:57.320 --> 00:04:57.650 Unfortunately,

NOTE Confidence: 0.76337852

00:04:57.650 --> 00:04:59.960 by the time that we are diagnosing

NOTE Confidence: 0.76337852

00:04:59.960 --> 00:05:01.040 patients with cancer,

NOTE Confidence: 0.76337852

00:05:01.040 --> 00:05:03.301 we're really here at the time of

NOTE Confidence: 0.76337852

00:05:03.301 --> 00:05:05.600 escape where there's already so many

NOTE Confidence: 0.76337852

00:05:05.600 --> 00:05:06.863 different resistance mechanisms

NOTE Confidence: 0.76337852

00:05:06.863 --> 00:05:09.183 that have really come into play

NOTE Confidence: 0.76337852

00:05:09.183 --> 00:05:11.185 that make the tumor fit to expand

NOTE Confidence: 0.76337852

00:05:11.185 --> 00:05:14.120 and grow in the patient host.

NOTE Confidence: 0.76337852

00:05:14.120 --> 00:05:15.405 We also increasingly know that

NOTE Confidence: 0.76337852

00:05:15.405 --> 00:05:17.159 this is not happening in a vacuum,

NOTE Confidence: 0.76337852

00:05:17.160 --> 00:05:18.492 that there's an interaction

NOTE Confidence: 0.76337852

00:05:18.492 --> 00:05:20.157 with the host immune system.

NOTE Confidence: 0.76337852

00:05:20.160 --> 00:05:20.666 But again,

NOTE Confidence: 0.76337852

00:05:20.666 --> 00:05:22.437 by the time that we're seeing patients,

NOTE Confidence: 0.76337852

00:05:22.440 --> 00:05:24.780 there's so many different immune based

NOTE Confidence: 0.76337852

00:05:24.780 --> 00:05:27.360 escape mechanisms that are at play as well.

NOTE Confidence: 0.76337852

00:05:27.360 --> 00:05:29.176 And so a lot of the questions that

NOTE Confidence: 0.76337852

00:05:29.176 --> 00:05:31.091 I think as a field that we're

NOTE Confidence: 0.76337852

00:05:31.091 --> 00:05:32.496 really interested in asking is

NOTE Confidence: 0.76337852

00:05:32.554 --> 00:05:34.714 not only this question of tumor

NOTE Confidence: 0.76337852

00:05:34.714 --> 00:05:35.794 heterogeneity and evolution,

NOTE Confidence: 0.76337852

00:05:35.800 --> 00:05:38.278 but also how do we understand this,

NOTE Confidence: 0.76337852

00:05:38.280 --> 00:05:39.630 these heterogeneous tumor

NOTE Confidence: 0.76337852

00:05:39.630 --> 00:05:41.880 microenvironments are T cells there

NOTE Confidence: 0.76337852

00:05:41.880 --> 00:05:44.838 at the right place at the right time?

NOTE Confidence: 0.76337852

00:05:44.840 --> 00:05:46.770 How are we responding to

NOTE Confidence: 0.76337852

00:05:46.770 --> 00:05:47.431 diverse immunotherapies?

NOTE Confidence: 0.76337852

00:05:47.431 --> 00:05:49.870 And then what is the role of a tumor

NOTE Confidence: 0.76337852

00:05:49.930 --> 00:05:51.880 antigen in shaping the tumor response?

NOTE Confidence: 0.76337852

00:05:51.880 --> 00:05:53.609 I'm not going to talk today so

NOTE Confidence: 0.76337852

00:05:53.609 --> 00:05:55.184 much until the very, very end,

NOTE Confidence: 0.76337852

00:05:55.184 --> 00:05:56.948 but this is a very large area

NOTE Confidence: 0.76337852

00:05:56.948 --> 00:05:58.520 of interest in my group.

NOTE Confidence: 0.76337852

00:05:58.520 --> 00:05:59.288 And as I said,

NOTE Confidence: 0.76337852

00:05:59.288 --> 00:06:00.440 I'm going to focus on chronic

NOTE Confidence: 0.76337852

00:06:00.484 --> 00:06:01.400 lymphocytic leukemia,

NOTE Confidence: 0.76337852

00:06:01.400 --> 00:06:05.080 which honestly the questions that I'm

NOTE Confidence: 0.76337852

00:06:05.080 --> 00:06:07.960 asking could be in any sort of tumor system.

NOTE Confidence: 0.76337852

00:06:07.960 --> 00:06:10.216 But CLL really has a lot of very

NOTE Confidence: 0.76337852

00:06:10.216 --> 00:06:11.813 unique features about the disease

NOTE Confidence: 0.76337852

00:06:11.813 --> 00:06:13.428 that have made it exceptional

NOTE Confidence: 0.76337852

00:06:13.428 --> 00:06:15.199 for the study of genomics.

NOTE Confidence: 0.76337852

00:06:15.200 --> 00:06:16.920 First,

NOTE Confidence: 0.76337852

00:06:16.920 --> 00:06:18.928 in a small tube of blood you have

NOTE Confidence: 0.76337852

00:06:18.928 --> 00:06:21.365 very pure tumor that can is readily

NOTE Confidence: 0.76337852

00:06:21.365 --> 00:06:23.235 accessible directly from the patients.

NOTE Confidence: 0.76337852

00:06:23.240 --> 00:06:24.997 The other thing is for a cancer,

NOTE Confidence: 0.76337852

00:06:25.000 --> 00:06:26.488 it's quite indolent.

NOTE Confidence: 0.76337852

00:06:26.488 --> 00:06:28.910 And So what that means is that

NOTE Confidence: 0.76337852

00:06:28.910 --> 00:06:30.340 we really have really long

NOTE Confidence: 0.76337852

00:06:30.401 --> 00:06:32.117 disease histories of patients.

NOTE Confidence: 0.76337852

00:06:32.120 --> 00:06:35.018 We can really take snapshots in

NOTE Confidence: 0.76337852

00:06:35.018 --> 00:06:37.733 time and study evolution in real

NOTE Confidence: 0.76337852

00:06:37.733 --> 00:06:39.552 time along with the patient.

NOTE Confidence: 0.76337852

00:06:39.552 --> 00:06:41.760 And so for some time now,

NOTE Confidence: 0.76337852

00:06:41.760 --> 00:06:43.180 our group together with colleagues

NOTE Confidence: 0.76337852

00:06:43.180 --> 00:06:44.316 in the Boston area,

NOTE Confidence: 0.76337852

00:06:44.320 --> 00:06:45.750 we've actually had this program

NOTE Confidence: 0.76337852

00:06:45.750 --> 00:06:47.457 where we've been trying to study

NOTE Confidence: 0.76337852

00:06:47.457 --> 00:06:49.080 the link from genome to phenome.

NOTE Confidence: 0.76337852

00:06:49.080 --> 00:06:51.798 How can we genomically characterize CLL,

NOTE Confidence: 0.76337852

00:06:51.800 --> 00:06:53.594 how can we understand the clinical

NOTE Confidence: 0.76337852

00:06:53.594 --> 00:06:55.517 course in response to therapy and

NOTE Confidence: 0.76337852

00:06:55.517 --> 00:06:57.509 then how can we also functionally

NOTE Confidence: 0.76337852

00:06:57.509 --> 00:06:59.190 characterize the pathway dependencies and

NOTE Confidence: 0.76337852

00:06:59.190 --> 00:07:01.825 really thinking about how we can do better.

NOTE Confidence: 0.76337852

00:07:01.825 --> 00:07:04.905 So what I'm going to talk about today

NOTE Confidence: 0.76337852

00:07:04.905 --> 00:07:08.125 is update the group on recent genomic

NOTE Confidence: 0.76337852

00:07:08.125 --> 00:07:11.164 studies and CLL driver discovery bid

NOTE Confidence: 0.76337852

00:07:11.164 --> 00:07:13.992 on our efforts in looking at tumor

NOTE Confidence: 0.76337852

00:07:13.992 --> 00:07:16.278 heterogeneity in our CLL GEM models.

NOTE Confidence: 0.76337852

00:07:16.280 --> 00:07:18.428 And then just a few perspectives

NOTE Confidence: 0.76337852

00:07:18.428 --> 00:07:19.860 of where we're going

NOTE Confidence: 0.964556758181818

00:07:19.930 --> 00:07:21.440 next in terms of the genomics.

NOTE Confidence: 0.964556758181818

00:07:21.440 --> 00:07:23.960 Again, as I said this is a

NOTE Confidence: 0.964556758181818

00:07:23.960 --> 00:07:27.005 very in general for cancer an

NOTE Confidence: 0.964556758181818

00:07:27.005 --> 00:07:29.080 indolent disease, it's typically

NOTE Confidence: 0.868007497777778

00:07:31.440 --> 00:07:32.788 marked initially by what

NOTE Confidence: 0.868007497777778

00:07:32.788 --> 00:07:34.473 we call watch and wait.

NOTE Confidence: 0.868007497777778

00:07:34.480 --> 00:07:37.040 So there can be a long lead time,

NOTE Confidence: 0.868007497777778

00:07:37.040 --> 00:07:40.208 but ultimately with treatment there can

NOTE Confidence: 0.868007497777778

00:07:40.208 --> 00:07:43.080 be cycles of recurrence that happen

NOTE Confidence: 0.868007497777778

00:07:43.080 --> 00:07:44.680 with shorter and shorter intervals,

NOTE Confidence: 0.868007497777778

00:07:44.680 --> 00:07:46.360 much like what we see in other tumors.

NOTE Confidence: 0.868007497777778

00:07:46.360 --> 00:07:48.502 I think a question that has

NOTE Confidence: 0.868007497777778

00:07:48.502 --> 00:07:50.366 always fascinated people in this

NOTE Confidence: 0.868007497777778

00:07:50.366 --> 00:07:52.550 field is how do we understand

NOTE Confidence: 0.868007497777778

00:07:52.550 --> 00:07:54.360 who progresses faster or slower?

NOTE Confidence: 0.868007497777778

00:07:54.360 --> 00:07:56.208 And what I mean by that is that

NOTE Confidence: 0.868007497777778

00:07:56.208 --> 00:07:58.084 there are some patients who succumb

NOTE Confidence: 0.868007497777778

00:07:58.084 --> 00:08:00.112 to their disease within two years.

NOTE Confidence: 0.868007497777778

00:08:00.120 --> 00:08:01.695 There are others that can have a

NOTE Confidence: 0.868007497777778

00:08:01.695 --> 00:08:03.348 little bit of therapy here and there

NOTE Confidence: 0.868007497777778

00:08:03.348 --> 00:08:05.080 go on for more than 1015 years.

NOTE Confidence: 0.868007497777778

00:08:05.080 --> 00:08:06.352 So why is that?

NOTE Confidence: 0.868007497777778

00:08:06.352 --> 00:08:07.942 What are the differences between

NOTE Confidence: 0.868007497777778

00:08:07.942 --> 00:08:10.011 the patients despite all their

NOTE Confidence: 0.868007497777778

00:08:10.011 --> 00:08:11.699 cells looking relatively similar

NOTE Confidence: 0.868007497777778

00:08:11.699 --> 00:08:13.280 under the microscope?

NOTE Confidence: 0.868007497777778

00:08:13.280 --> 00:08:15.416 And so for since forever there

NOTE Confidence: 0.868007497777778

00:08:15.416 --> 00:08:18.617 has been a long effort to try to

NOTE Confidence: 0.868007497777778

00:08:18.617 --> 00:08:21.167 understand those markers that we could

NOTE Confidence: 0.868007497777778

00:08:21.251 --> 00:08:23.956 use to distinguish amongst patients

NOTE Confidence: 0.868007497777778

00:08:23.960 --> 00:08:25.600 initially looking at clinical features,

NOTE Confidence: 0.868007497777778

00:08:25.600 --> 00:08:26.100 protein markers.

NOTE Confidence: 0.868007497777778

00:08:26.100 --> 00:08:28.475 But I would say over the past 10-15 years

NOTE Confidence: 0.868007497777778

00:08:28.475 --> 00:08:30.407 since there's been the next generation

NOTE Confidence: 0.868007497777778

00:08:30.407 --> 00:08:32.200 sequencing that's been available to us,

NOTE Confidence: 0.868007497777778

00:08:32.200 --> 00:08:33.988 there's really been an explosion of

NOTE Confidence: 0.868007497777778

00:08:33.988 --> 00:08:35.829 knowledge in terms of the genetic

NOTE Confidence: 0.868007497777778

00:08:35.829 --> 00:08:37.593 alterations later on top of that,

NOTE Confidence: 0.868007497777778

00:08:37.600 --> 00:08:39.440 the transcriptional alterations and

NOTE Confidence: 0.868007497777778

00:08:39.440 --> 00:08:41.625 even the epigenetic alterations so

NOTE Confidence: 0.868007497777778

00:08:41.625 --> 00:08:44.040 that we can understand what's going on.

NOTE Confidence: 0.868007497777778

00:08:44.040 --> 00:08:46.026 This slide really summarizes a lot

NOTE Confidence: 0.868007497777778

00:08:46.026 --> 00:08:48.590 of work that has been done since

NOTE Confidence: 0.868007497777778

00:08:48.590 --> 00:08:51.320 next generation sequencing has come upon us.

NOTE Confidence: 0.868007497777778

00:08:51.320 --> 00:08:53.959 I would say that the first studies

NOTE Confidence: 0.868007497777778

00:08:53.959 --> 00:08:58.020 in genomics arrived around 2010,

NOTE Confidence: 0.868007497777778

00:08:58.020 --> 00:08:59.240 2011.

NOTE Confidence: 0.868007497777778

00:08:59.240 --> 00:09:01.915 We were among the first

NOTE Confidence: 0.868007497777778

00:09:01.915 --> 00:09:03.799 to describe mutated SF3B1.

NOTE Confidence: 0.868007497777778

00:09:03.799 --> 00:09:05.473 So a splicing factor that kind

NOTE Confidence: 0.868007497777778

00:09:05.473 --> 00:09:07.399 of came out of the sequencing.

NOTE Confidence: 0.868007497777778

00:09:07.400 --> 00:09:10.018 No one had until then kind of

NOTE Confidence: 0.868007497777778

00:09:10.018 --> 00:09:12.361 puts altered splicing and and

NOTE Confidence: 0.868007497777778

00:09:12.361 --> 00:09:14.077 lymphoid malignancies together.

NOTE Confidence: 0.868007497777778

00:09:14.080 --> 00:09:17.080 There's been large scale studies

NOTE Confidence: 0.868007497777778

00:09:17.080 --> 00:09:19.208 in looking at clonal evolution.

NOTE Confidence: 0.868007497777778

00:09:19.208 --> 00:09:22.410 So again CLL was one of the first

NOTE Confidence: 0.868007497777778

00:09:22.410 --> 00:09:25.336 places that studied really this kind of

NOTE Confidence: 0.868007497777778

00:09:25.336 --> 00:09:28.479 concept of clonally evolving subpopulations.

NOTE Confidence: 0.868007497777778

00:09:28.480 --> 00:09:31.552 And then and you can see initially our

NOTE Confidence: 0.868007497777778

00:09:31.552 --> 00:09:34.550 studies were about 100 patients and then

NOTE Confidence: 0.868007497777778

00:09:34.550 --> 00:09:38.078 around 2015 about 500 patients per cohort.

NOTE Confidence: 0.868007497777778

00:09:38.080 --> 00:09:39.627 What I'm going to describe for you

NOTE Confidence: 0.868007497777778

00:09:39.627 --> 00:09:41.461 now is our recent work trying to

NOTE Confidence: 0.868007497777778

00:09:41.461 --> 00:09:43.141 put together all of these different

NOTE Confidence: 0.868007497777778

00:09:43.192 --> 00:09:44.632 studies together so that we could

NOTE Confidence: 0.868007497777778

00:09:44.632 --> 00:09:46.728 get a cohort of more than 1000.

NOTE Confidence: 0.868007497777778

00:09:46.728 --> 00:09:49.360 I want to say that during this

NOTE Confidence: 0.868007497777778

00:09:49.451 --> 00:09:51.670 time that we've kind of performed

NOTE Confidence: 0.868007497777778

00:09:51.670 --> 00:09:53.320 these sort of genomic studies,

NOTE Confidence: 0.868007497777778

00:09:53.320 --> 00:09:56.001 there has been vast changes in the

NOTE Confidence: 0.868007497777778

00:09:56.001 --> 00:09:58.000 therapeutic landscape of CLL therapy.

NOTE Confidence: 0.868007497777778

00:09:58.000 --> 00:10:03.670 So whereas previously it was very

NOTE Confidence: 0.868007497777778

00:10:03.670 --> 00:10:05.520 standard to get chemo immunotherapy.

NOTE Confidence: 0.868007497777778

00:10:05.520 --> 00:10:07.590 I would say that in the in the same

NOTE Confidence: 0.868007497777778

00:10:07.590 --> 00:10:09.672 time that time frame that I'm speaking

NOTE Confidence: 0.868007497777778

00:10:09.672 --> 00:10:11.339 there has been the introduction

NOTE Confidence: 0.868007497777778

00:10:11.339 --> 00:10:13.399 of targeted inhibitors of BCL,

NOTE Confidence: 0.868007497777778

00:10:13.400 --> 00:10:18.120 two of the B cell receptor signaling

NOTE Confidence: 0.868007497777778

00:10:18.120 --> 00:10:20.280 and also introduction of immunotherapy.

NOTE Confidence: 0.868007497777778

00:10:20.280 --> 00:10:22.360 So the really big changes,

NOTE Confidence: 0.868007497777778

00:10:22.360 --> 00:10:24.341 you know as we start to think

NOTE Confidence: 0.868007497777778

00:10:24.341 --> 00:10:26.320 about the the genomic lesions.

NOTE Confidence: 0.868007497777778

00:10:26.320 --> 00:10:29.956 So how do we build an integrative CLL map?

NOTE Confidence: 0.868007497777778

00:10:29.960 --> 00:10:30.416 Well,

NOTE Confidence: 0.868007497777778

00:10:30.416 --> 00:10:32.696 we joined forces between our

NOTE Confidence: 0.868007497777778

00:10:32.696 --> 00:10:34.987 colleagues in North America but

NOTE Confidence: 0.868007497777778

00:10:34.987 --> 00:10:37.327 also with our colleagues in Spain

NOTE Confidence: 0.868007497777778

00:10:37.327 --> 00:10:41.360 and Germany and together collected

NOTE Confidence: 0.868007497777778

00:10:41.360 --> 00:10:43.076 cases for which there was exomes,

NOTE Confidence: 0.890277493333333

00:10:43.080 --> 00:10:44.760 genomes, RNA sequencing

NOTE Confidence: 0.890277493333333

00:10:44.760 --> 00:10:46.440 and methylation profiling.

NOTE Confidence: 0.890277493333333

00:10:46.440 --> 00:10:49.768 And there was a nice overlap of these

NOTE Confidence: 0.890277493333333

00:10:49.768 --> 00:10:52.329 different platforms in in several hundreds

NOTE Confidence: 0.890277493333333

00:10:52.329 --> 00:10:55.060 of patients samples that we collected.

NOTE Confidence: 0.890277493333333

00:10:55.060 --> 00:10:58.706 And this is a kind of a

NOTE Confidence: 0.890277493333333

00:10:58.706 --> 00:11:00.153 intimidating commute plot,

NOTE Confidence: 0.890277493333333

00:11:00.153 --> 00:11:02.064 but I think it just speaks of

NOTE Confidence: 0.890277493333333

00:11:02.064 --> 00:11:03.919 a number of different things.

NOTE Confidence: 0.890277493333333

00:11:03.920 --> 00:11:06.118 First, I want to acknowledge the young

NOTE Confidence: 0.890277493333333

00:11:06.118 --> 00:11:08.757 people who were the leaders of this project.

NOTE Confidence: 0.890277493333333

00:11:08.760 --> 00:11:10.998 It was really an international collaboration.

NOTE Confidence: 0.890277493333333

00:11:11.000 --> 00:11:14.280 So I had the pleasure of working with

NOTE Confidence: 0.890277493333333

00:11:14.280 --> 00:11:16.943 Binyamin Nisbacher and Ziao Lin and

NOTE Confidence: 0.890277493333333

00:11:16.943 --> 00:11:19.143 Gaddy Goetz's group computational gurus

NOTE Confidence: 0.890277493333333

00:11:19.143 --> 00:11:22.077 and then Cindy Hahn from Dana Farber.

NOTE Confidence: 0.890277493333333

00:11:22.080 --> 00:11:25.048 Awesome lymphoma oriented fellow

NOTE Confidence: 0.890277493333333

00:11:25.048 --> 00:11:27.274 and then Ferran,

NOTE Confidence: 0.890277493333333

00:11:27.280 --> 00:11:30.880 Nadeau and Marty from the group in Spain,

NOTE Confidence: 0.890277493333333

00:11:30.880 --> 00:11:33.160 the Spanish CLL group in Barcelona,

NOTE Confidence: 0.890277493333333

00:11:33.160 --> 00:11:33.516 Barcelona.

NOTE Confidence: 0.890277493333333

00:11:33.516 --> 00:11:36.008 And then when we looked at these

NOTE Confidence: 0.890277493333333

00:11:36.008 --> 00:11:38.199 more than 1000 patient samples,

NOTE Confidence: 0.890277493333333

00:11:38.200 --> 00:11:41.461 in fact we were able to have

NOTE Confidence: 0.890277493333333

00:11:41.461 --> 00:11:42.143 greater sensitivity.

NOTE Confidence: 0.890277493333333

00:11:42.143 --> 00:11:44.530 In the magenta are all the new

NOTE Confidence: 0.890277493333333

00:11:44.594 --> 00:11:46.238 drivers that we identified.

NOTE Confidence: 0.890277493333333

00:11:46.240 --> 00:11:49.620 So each row is a driver alteration,

NOTE Confidence: 0.890277493333333

00:11:49.620 --> 00:11:52.661 each column is a different case and

NOTE Confidence: 0.890277493333333

00:11:52.661 --> 00:11:54.650 what you can see is in fact there is

NOTE Confidence: 0.890277493333333

00:11:54.714 --> 00:11:56.740 a a list of recurrent alterations,

NOTE Confidence: 0.890277493333333

00:11:56.740 --> 00:11:58.600 but a long tail.

NOTE Confidence: 0.890277493333333

00:11:58.600 --> 00:12:01.138 You can see that a lot of our discovery

NOTE Confidence: 0.890277493333333

00:12:01.138 --> 00:12:04.000 is down here at the one 1% or less level.

NOTE Confidence: 0.890277493333333

00:12:04.000 --> 00:12:04.640 So many,

NOTE Confidence: 0.890277493333333

00:12:04.640 --> 00:12:08.034 many different sort of driver

NOTE Confidence: 0.890277493333333

00:12:08.034 --> 00:12:10.804 alterations that we had greater

NOTE Confidence: 0.890277493333333

00:12:10.804 --> 00:12:13.526 sensitivity to identify because of

NOTE Confidence: 0.890277493333333

00:12:13.526 --> 00:12:16.040 the increased power of our cohort.

NOTE Confidence: 0.890277493333333

00:12:16.040 --> 00:12:18.792 Just to make a a really beautiful

NOTE Confidence: 0.890277493333333

00:12:18.792 --> 00:12:21.000 Long story short,

NOTE Confidence: 0.890277493333333

00:12:21.000 --> 00:12:23.338 we were able to double the number

NOTE Confidence: 0.890277493333333

00:12:23.338 --> 00:12:25.765 of CLL drivers that we were able

NOTE Confidence: 0.890277493333333

00:12:25.765 --> 00:12:26.888 to identify previously.

NOTE Confidence: 0.890277493333333

00:12:26.888 --> 00:12:29.434 There were about 10% of patients

NOTE Confidence: 0.890277493333333

00:12:29.434 --> 00:12:31.319 that we couldn't account for.

NOTE Confidence: 0.890277493333333

00:12:31.320 --> 00:12:32.904 There wasn't any sort of driver

NOTE Confidence: 0.890277493333333

00:12:32.904 --> 00:12:34.227 alteration that we could point

NOTE Confidence: 0.890277493333333

00:12:34.227 --> 00:12:35.746 to that was this is the reason

NOTE Confidence: 0.890277493333333

00:12:35.746 --> 00:12:37.314 that they have CLL and we've been

NOTE Confidence: 0.890277493333333

00:12:37.314 --> 00:12:38.960 able to close that gap so that

NOTE Confidence: 0.890277493333333

00:12:38.960 --> 00:12:41.520 there's only by now 3.8% that we

NOTE Confidence: 0.890277493333333

00:12:41.520 --> 00:12:44.403 can't account for the two large

NOTE Confidence: 0.890277493333333

00:12:44.403 --> 00:12:47.289 categories of CLL that are well

NOTE Confidence: 0.890277493333333

00:12:47.289 --> 00:12:50.564 known in the clinical arena on the

NOTE Confidence: 0.890277493333333

00:12:50.564 --> 00:12:53.096 basis of their immunoglobulin locus,

NOTE Confidence: 0.890277493333333

00:12:53.096 --> 00:12:56.036 the mutated and unmutated IGHV.

NOTE Confidence: 0.890277493333333

00:12:56.040 --> 00:12:58.032 We finally had enough power to

NOTE Confidence: 0.890277493333333

00:12:58.032 --> 00:12:59.749 actually break those two groups

NOTE Confidence: 0.890277493333333

00:12:59.749 --> 00:13:01.989 apart and look and look at them

NOTE Confidence: 0.890277493333333

00:13:01.989 --> 00:13:03.887 separately and they really look

NOTE Confidence: 0.890277493333333

00:13:03.887 --> 00:13:05.475 like very different diseases.

NOTE Confidence: 0.890277493333333

00:13:05.480 --> 00:13:08.078 They each have distinct molecular landscapes.

NOTE Confidence: 0.890277493333333

00:13:08.080 --> 00:13:09.800 It highlights the diverse

NOTE Confidence: 0.890277493333333

00:13:09.800 --> 00:13:11.520 trajectories of clonal evolution.

NOTE Confidence: 0.890277493333333

00:13:11.520 --> 00:13:13.182 So maybe by virtue of where

NOTE Confidence: 0.890277493333333

00:13:13.182 --> 00:13:14.680 you start as AB cell,

NOTE Confidence: 0.890277493333333

00:13:14.680 --> 00:13:16.246 maybe there's a path of different

NOTE Confidence: 0.890277493333333

00:13:16.246 --> 00:13:17.751 paths of least resistance that gets

NOTE Confidence: 0.890277493333333

00:13:17.751 --> 00:13:19.193 you to where you're going to be.

NOTE Confidence: 0.890277493333333

00:13:19.200 --> 00:13:21.126 And what was super interesting is

NOTE Confidence: 0.890277493333333

00:13:21.126 --> 00:13:23.678 that at least for the unmutated CLLS,

NOTE Confidence: 0.890277493333333

00:13:23.680 --> 00:13:26.165 their their source of heterogeneity

NOTE Confidence: 0.890277493333333

00:13:26.165 --> 00:13:27.159 was genetic.

NOTE Confidence: 0.890277493333333

00:13:27.160 --> 00:13:29.312 There was a lot of lot more putative

NOTE Confidence: 0.890277493333333

00:13:29.312 --> 00:13:31.118 drivers in this unmutated group,

NOTE Confidence: 0.890277493333333

00:13:31.120 --> 00:13:33.960 but in the mutated group,

NOTE Confidence: 0.890277493333333

00:13:33.960 --> 00:13:35.013 relatively few drivers,

NOTE Confidence: 0.890277493333333

00:13:35.013 --> 00:13:37.119 but a lot of transcriptional diversity.

NOTE Confidence: 0.890277493333333

00:13:37.120 --> 00:13:39.352 So really a different path to

NOTE Confidence: 0.890277493333333

00:13:39.352 --> 00:13:41.920 achieving that type of heterogeneity.

NOTE Confidence: 0.890277493333333

00:13:41.920 --> 00:13:44.629 And then what I want to show you is

NOTE Confidence: 0.890277493333333

00:13:44.629 --> 00:13:46.988 that when we looked at the expression,

NOTE Confidence: 0.890277493333333

00:13:46.988 --> 00:13:47.764 you know,

NOTE Confidence: 0.890277493333333

00:13:47.764 --> 00:13:50.150 Benjamin was able to identify what

NOTE Confidence: 0.890277493333333

00:13:50.150 --> 00:13:52.640 he called E CS expression clusters.

NOTE Confidence: 0.890277493333333

00:13:52.640 --> 00:13:54.320 And then the nomenclature here is some

NOTE Confidence: 0.890277493333333

00:13:54.320 --> 00:13:56.359 of them were enriched for M for mutated,

NOTE Confidence: 0.926483031666667

00:13:56.360 --> 00:13:57.482 some for unmutated.

NOTE Confidence: 0.926483031666667

00:13:57.482 --> 00:14:00.611 And what you can see is that it

NOTE Confidence: 0.926483031666667

00:14:00.611 --> 00:14:02.440 actually breaks down the group's

NOTE Confidence: 0.926483031666667

00:14:02.440 --> 00:14:04.993 more or less based on mutated on

NOTE Confidence: 0.926483031666667

00:14:04.993 --> 00:14:06.918 mutator or by their epigenetics.

NOTE Confidence: 0.926483031666667

00:14:06.920 --> 00:14:08.600 But you can also see by the fact

NOTE Confidence: 0.926483031666667

00:14:08.600 --> 00:14:10.235 that there's two colors within each

NOTE Confidence: 0.926483031666667

00:14:10.235 --> 00:14:11.685 column that there was contribution

NOTE Confidence: 0.926483031666667

00:14:11.685 --> 00:14:13.742 from both mutated and unmutated to

NOTE Confidence: 0.926483031666667

00:14:13.742 --> 00:14:15.114 these different expression clusters.

NOTE Confidence: 0.926483031666667

00:14:15.120 --> 00:14:17.598 And one example in one one.

NOTE Confidence: 0.926483031666667

00:14:17.600 --> 00:14:19.232 One thing that was really interesting

NOTE Confidence: 0.926483031666667

00:14:19.232 --> 00:14:21.860 is that by the yellow asterisks we could

NOTE Confidence: 0.926483031666667

00:14:21.860 --> 00:14:23.715 see that certain genetic alterations

NOTE Confidence: 0.926483031666667

00:14:23.715 --> 00:14:25.404 actually also segregated together

NOTE Confidence: 0.926483031666667

00:14:25.404 --> 00:14:27.080 with these expression clusters,

NOTE Confidence: 0.926483031666667

00:14:27.080 --> 00:14:28.845 suggesting that they were a

NOTE Confidence: 0.926483031666667

00:14:28.845 --> 00:14:30.610 cohesive entity each of these

NOTE Confidence: 0.926483031666667

00:14:30.681 --> 00:14:32.335 different expression cluster group.

NOTE Confidence: 0.926483031666667

00:14:32.335 --> 00:14:34.160 So for example trisomy 12,

NOTE Confidence: 0.926483031666667

00:14:34.160 --> 00:14:37.485 which is a very well known cytogenetic

NOTE Confidence: 0.926483031666667

00:14:37.485 --> 00:14:39.280 abnormality associated with CLL,

NOTE Confidence: 0.926483031666667

00:14:39.280 --> 00:14:41.210 but for which there's great

NOTE Confidence: 0.926483031666667

00:14:41.210 --> 00:14:43.140 heterogeneity in kind of the

NOTE Confidence: 0.926483031666667

00:14:43.214 --> 00:14:45.559 behavior of those trisomy twelves.

NOTE Confidence: 0.926483031666667

00:14:45.560 --> 00:14:47.954 They actually split out into two groups,

NOTE Confidence: 0.926483031666667

00:14:47.960 --> 00:14:49.835 one that's in a more

NOTE Confidence: 0.926483031666667

00:14:49.835 --> 00:14:50.960 predominantly unmutated group,

NOTE Confidence: 0.926483031666667

00:14:50.960 --> 00:14:52.760 another in a predominantly mutated group.

NOTE Confidence: 0.926483031666667

00:14:52.760 --> 00:14:55.760 And this maybe provides us with

NOTE Confidence: 0.926483031666667

00:14:55.760 --> 00:14:58.200 some understanding for why some

NOTE Confidence: 0.926483031666667

00:14:58.200 --> 00:15:00.450 samples with the same sort of

NOTE Confidence: 0.926483031666667

00:15:00.450 --> 00:15:01.774 cytogenetics might behave differently.

NOTE Confidence: 0.926483031666667

00:15:01.774 --> 00:15:03.783 And what was super interesting is when

NOTE Confidence: 0.926483031666667

00:15:03.783 --> 00:15:06.037 when Benjamin started to look at these

NOTE Confidence: 0.926483031666667

00:15:06.037 --> 00:15:07.313 different expression cluster groups,

NOTE Confidence: 0.926483031666667

00:15:07.320 --> 00:15:09.032 they actually did display

NOTE Confidence: 0.926483031666667

00:15:09.032 --> 00:15:10.744 different clinical outcome because

NOTE Confidence: 0.926483031666667

00:15:10.744 --> 00:15:12.878 we had very long clinical.

NOTE Confidence: 0.926483031666667

00:15:12.880 --> 00:15:14.740 These were also clinically

NOTE Confidence: 0.926483031666667

00:15:14.740 --> 00:15:16.600 annotated samples as well.

NOTE Confidence: 0.926483031666667

00:15:16.600 --> 00:15:17.874 And this is just kind of the

NOTE Confidence: 0.926483031666667

00:15:17.874 --> 00:15:19.118 final data slide related to this,

NOTE Confidence: 0.926483031666667

00:15:19.120 --> 00:15:21.535 which is indeed when we kind of

NOTE Confidence: 0.926483031666667

00:15:21.535 --> 00:15:23.504 breakdown the samples based on

NOTE Confidence: 0.926483031666667

00:15:23.504 --> 00:15:25.240 their classical clinical group,

NOTE Confidence: 0.926483031666667

00:15:25.240 --> 00:15:26.760 based on the expression clusters,

NOTE Confidence: 0.926483031666667

00:15:26.760 --> 00:15:29.225 whether they were concordant or

NOTE Confidence: 0.926483031666667

00:15:29.225 --> 00:15:31.197 discordant to that classification,

NOTE Confidence: 0.926483031666667

00:15:31.200 --> 00:15:33.984 we could actually see differences in

NOTE Confidence: 0.926483031666667

00:15:33.984 --> 00:15:35.840 their clinical outcomes suggesting

NOTE Confidence: 0.926483031666667

00:15:35.907 --> 00:15:38.157 that our expression cluster system

NOTE Confidence: 0.926483031666667

00:15:38.157 --> 00:15:40.280 was actually increasing the accuracy

NOTE Confidence: 0.926483031666667

00:15:40.280 --> 00:15:42.520 of what we're trying to do in

NOTE Confidence: 0.926483031666667

00:15:42.520 --> 00:15:44.320 terms of prognostication.

NOTE Confidence: 0.926483031666667

00:15:44.320 --> 00:15:46.240 So we've been really excited to,

NOTE Confidence: 0.926483031666667

00:15:46.240 --> 00:15:47.440 I mean this is really,

NOTE Confidence: 0.926483031666667

00:15:47.440 --> 00:15:49.064 this was really a Tour de force

NOTE Confidence: 0.926483031666667

00:15:49.064 --> 00:15:50.438 effort to bring together not

NOTE Confidence: 0.926483031666667

00:15:50.438 --> 00:15:51.993 only all these different groups

NOTE Confidence: 0.926483031666667

00:15:51.993 --> 00:15:53.480 together and their expertise,

NOTE Confidence: 0.926483031666667

00:15:53.480 --> 00:15:57.000 but also to layer on all of these

NOTE Confidence: 0.926483031666667

00:15:57.000 --> 00:15:59.440 different genomic layers to kind of

NOTE Confidence: 0.926483031666667

00:15:59.440 --> 00:16:00.988 identify unique molecular subtypes.

NOTE Confidence: 0.926483031666667

00:16:00.988 --> 00:16:04.079 And I do want to say that this,

NOTE Confidence: 0.926483031666667

00:16:04.080 --> 00:16:06.072 these studies were samples that were

NOTE Confidence: 0.926483031666667

00:16:06.072 --> 00:16:08.798 collected in the era of chemo immunotherapy.

NOTE Confidence: 0.926483031666667

00:16:08.800 --> 00:16:11.635 We are actively trying to look now

NOTE Confidence: 0.926483031666667

00:16:11.635 --> 00:16:14.753 how these relate to the modern era

NOTE Confidence: 0.926483031666667

00:16:14.753 --> 00:16:16.819 of targeted inhibition and we also

NOTE Confidence: 0.926483031666667

00:16:16.819 --> 00:16:18.450 are interested in in trying to look

NOTE Confidence: 0.926483031666667

00:16:18.506 --> 00:16:20.324 at whether or not the different

NOTE Confidence: 0.926483031666667

00:16:20.324 --> 00:16:22.430 molecular subtypes have differences

NOTE Confidence: 0.926483031666667

00:16:22.430 --> 00:16:26.000 in therapeutic vulnerabilities.

NOTE Confidence: 0.926483031666667

00:16:26.000 --> 00:16:28.008 Now I think you know as we've gotten

NOTE Confidence: 0.926483031666667

00:16:28.008 --> 00:16:29.598 better with our therapies we we

NOTE Confidence: 0.926483031666667

00:16:29.598 --> 00:16:31.428 always have to kind of reckon what

NOTE Confidence: 0.926483031666667

00:16:31.428 --> 00:16:33.080 is the area of most unmet need.

NOTE Confidence: 0.926483031666667

00:16:33.080 --> 00:16:35.330 And I think right now clinically

NOTE Confidence: 0.926483031666667

00:16:35.330 --> 00:16:38.132 for the for CLL there are so many

NOTE Confidence: 0.926483031666667

00:16:38.132 --> 00:16:39.158 different therapies available,

NOTE Confidence: 0.926483031666667

00:16:39.160 --> 00:16:41.267 but we are still really faced with

NOTE Confidence: 0.926483031666667

00:16:41.267 --> 00:16:43.239 the conundrum of Richter syndrome.

NOTE Confidence: 0.926483031666667

00:16:43.240 --> 00:16:46.448 This is really it's a rare,

NOTE Confidence: 0.926483031666667

00:16:46.448 --> 00:16:49.492 it occurs in five to 10% of patients

NOTE Confidence: 0.926483031666667

00:16:49.492 --> 00:16:52.334 with CLL but it is a transformation

NOTE Confidence: 0.926483031666667

00:16:52.334 --> 00:16:55.160 of a small indolent histological type

NOTE Confidence: 0.926483031666667

00:16:55.160 --> 00:16:58.288 into a high grade lymphoid malignancy.

NOTE Confidence: 0.926483031666667

00:16:58.288 --> 00:17:00.384 90% have Histology similar

NOTE Confidence: 0.926483031666667

00:17:00.384 --> 00:17:02.960 to diffuse large B cell,

NOTE Confidence: 0.926483031666667

00:17:02.960 --> 00:17:05.004 large B cell lymphoma.

NOTE Confidence: 0.926483031666667

00:17:05.004 --> 00:17:07.559 The majority are clonally unrelated.

NOTE Confidence: 0.923745231111111

00:17:07.560 --> 00:17:09.582 We know that because if we

NOTE Confidence: 0.923745231111111

00:17:09.582 --> 00:17:10.593 follow their immunoglobulin,

NOTE Confidence: 0.923745231111111

00:17:10.600 --> 00:17:11.455 the clonal immunoglobulin,

NOTE Confidence: 0.923745231111111

00:17:11.455 --> 00:17:13.920 we could see the same in the patient.

NOTE Confidence: 0.923745231111111

00:17:13.920 --> 00:17:18.113 Shown here is a micrograph that shows a

NOTE Confidence: 0.923745231111111

00:17:18.113 --> 00:17:20.024 sample where you can see the coexistence

NOTE Confidence: 0.923745231111111

00:17:20.024 --> 00:17:21.992 of these two entities within the same

NOTE Confidence: 0.923745231111111

00:17:21.992 --> 00:17:24.457 sample and you can see the really the

NOTE Confidence: 0.923745231111111

00:17:24.457 --> 00:17:26.197 big kind of histological differences.

NOTE Confidence: 0.923745231111111

00:17:26.200 --> 00:17:28.000 These are the patients that we typically say.

NOTE Confidence: 0.923745231111111

00:17:28.000 --> 00:17:30.128 I'm so sorry. Please get your affairs

NOTE Confidence: 0.923745231111111

00:17:30.128 --> 00:17:31.904 and orders that there's really not

NOTE Confidence: 0.923745231111111

00:17:31.904 --> 00:17:34.080 much more that we can do for you.

NOTE Confidence: 0.923745231111111

00:17:34.080 --> 00:17:36.582 And it's been very difficult to

NOTE Confidence: 0.923745231111111

00:17:36.582 --> 00:17:38.748 understand molecularly much about this

NOTE Confidence: 0.923745231111111

00:17:38.748 --> 00:17:40.898 entity because there's been limitations

NOTE Confidence: 0.923745231111111

00:17:40.898 --> 00:17:43.912 of tissue sampling and and and it's

NOTE Confidence: 0.923745231111111

00:17:43.912 --> 00:17:45.957 really based on morphologic diagnosis.

NOTE Confidence: 0.923745231111111

00:17:45.960 --> 00:17:48.578 There's been a lack of markers and

NOTE Confidence: 0.923745231111111

00:17:48.578 --> 00:17:50.429 understanding of genetics and for

NOTE Confidence: 0.923745231111111

00:17:50.429 --> 00:17:52.300 a blood based malignancy like CLL,

NOTE Confidence: 0.923745231111111

00:17:52.300 --> 00:17:53.840 Richter's is really like a solid tumor.

NOTE Confidence: 0.923745231111111

00:17:53.840 --> 00:17:57.130 I mean, this is really so unlike

NOTE Confidence: 0.923745231111111

00:17:57.130 --> 00:17:59.405 what I said before where there's ease

NOTE Confidence: 0.923745231111111

00:17:59.405 --> 00:18:01.880 in kind of having blood draws here.

NOTE Confidence: 0.923745231111111

00:18:01.880 --> 00:18:04.052 We have to get biopsies often

NOTE Confidence: 0.923745231111111

00:18:04.052 --> 00:18:06.199 FFP specimens in order to study.

NOTE Confidence: 0.923745231111111

00:18:06.200 --> 00:18:09.598 And and this has not been, not been easy.

NOTE Confidence: 0.923745231111111

00:18:09.600 --> 00:18:13.479 But I would say that over the past couple

NOTE Confidence: 0.923745231111111

00:18:13.479 --> 00:18:15.393 years that because of the availability

NOTE Confidence: 0.923745231111111

00:18:15.393 --> 00:18:17.678 of all these nice genomic platforms,

NOTE Confidence: 0.923745231111111

00:18:17.680 --> 00:18:19.435 there's there's been really an

NOTE Confidence: 0.923745231111111

00:18:19.435 --> 00:18:21.503 explosion of new studies that have

NOTE Confidence: 0.923745231111111

00:18:21.503 --> 00:18:23.717 come out in the past year and a half.

NOTE Confidence: 0.923745231111111

00:18:23.720 --> 00:18:26.368 And at the same time there's been

NOTE Confidence: 0.923745231111111

00:18:26.368 --> 00:18:28.388 modeling that's been done trying

NOTE Confidence: 0.923745231111111

00:18:28.388 --> 00:18:30.400 to really put our attention to

NOTE Confidence: 0.923745231111111

00:18:30.400 --> 00:18:32.200 how we can generate mouse models,

NOTE Confidence: 0.923745231111111

00:18:32.200 --> 00:18:33.556 whether they're PDXS or or Gem

NOTE Confidence: 0.923745231111111

00:18:33.556 --> 00:18:35.280 models to try to understand this.

NOTE Confidence: 0.923745231111111

00:18:35.280 --> 00:18:37.639 And there's been actually a lot of

NOTE Confidence: 0.923745231111111

00:18:37.639 --> 00:18:39.430 progress in understanding the genome

NOTE Confidence: 0.923745231111111

00:18:39.430 --> 00:18:41.650 that the genetics looking at the

NOTE Confidence: 0.923745231111111

00:18:41.650 --> 00:18:43.360 epigenetics and the transcriptomics.

NOTE Confidence: 0.923745231111111

00:18:43.360 --> 00:18:45.138 And So what I'm going to demonstrate

NOTE Confidence: 0.923745231111111

00:18:45.138 --> 00:18:47.002 for you in the next couple slides

NOTE Confidence: 0.923745231111111

00:18:47.002 --> 00:18:49.160 is some of our efforts in this area.

NOTE Confidence: 0.923745231111111

00:18:49.160 --> 00:18:51.274 This is really work that's been that

NOTE Confidence: 0.923745231111111

00:18:51.274 --> 00:18:53.538 was led by Aaron Perry who is now

NOTE Confidence: 0.923745231111111

00:18:53.538 --> 00:18:55.660 a new junior faculty member at the

NOTE Confidence: 0.923745231111111

00:18:55.660 --> 00:18:57.879 Dana Farber in the lymphoma group,

NOTE Confidence: 0.923745231111111

00:18:57.880 --> 00:19:01.030 Roman Guiz who's part of Philo back

NOTE Confidence: 0.923745231111111

00:19:01.030 --> 00:19:04.736 in in France and Ignot Lechner who is

NOTE Confidence: 0.923745231111111

00:19:04.736 --> 00:19:07.032 now a junior faculty member at BU.

NOTE Confidence: 0.923745231111111

00:19:07.040 --> 00:19:09.536 And what we tried to do was assemble

NOTE Confidence: 0.923745231111111

00:19:09.536 --> 00:19:11.839 a nice paired matched cohort.

NOTE Confidence: 0.923745231111111

00:19:11.840 --> 00:19:13.512 So in other words,

NOTE Confidence: 0.923745231111111

00:19:13.512 --> 00:19:16.020 not just Richter samples in isolation

NOTE Confidence: 0.923745231111111

00:19:16.096 --> 00:19:18.292 but antecedent CLL matched together

NOTE Confidence: 0.923745231111111

00:19:18.292 --> 00:19:20.740 with the Richter's where we could track

NOTE Confidence: 0.923745231111111

00:19:20.740 --> 00:19:22.680 evolution in time across these patients.

NOTE Confidence: 0.923745231111111

00:19:22.680 --> 00:19:24.320 This was about 50 patients

NOTE Confidence: 0.923745231111111

00:19:24.320 --> 00:19:25.960 that we collected samples on.

NOTE Confidence: 0.923745231111111

00:19:25.960 --> 00:19:27.514 I think the point of emphasis that

NOTE Confidence: 0.923745231111111

00:19:27.514 --> 00:19:29.274 I want to show you on the left

NOTE Confidence: 0.923745231111111

00:19:29.274 --> 00:19:30.720 side here is the CLL course,

NOTE Confidence: 0.923745231111111

00:19:30.720 --> 00:19:33.000 the green is the different lines of therapy.

NOTE Confidence: 0.923745231111111

00:19:33.000 --> 00:19:34.681 On the right side is the Richter's

NOTE Confidence: 0.923745231111111

00:19:34.681 --> 00:19:36.490 and I want to show you that on the

NOTE Confidence: 0.923745231111111

00:19:36.542 --> 00:19:37.970 left side it's years where whereas

NOTE Confidence: 0.923745231111111

00:19:37.970 --> 00:19:39.520 on the right side it's months.

NOTE Confidence: 0.923745231111111

00:19:39.520 --> 00:19:41.710 So this kind of gives you a sense of kind

NOTE Confidence: 0.923745231111111

00:19:41.767 --> 00:19:43.959 of the the time course of these patients.

NOTE Confidence: 0.923745231111111

00:19:43.960 --> 00:19:45.941 The black dots are the different samples

NOTE Confidence: 0.923745231111111

00:19:45.941 --> 00:19:47.717 that we collected on the CLL course.

NOTE Confidence: 0.923745231111111

00:19:47.720 --> 00:19:50.360 The yellow here is the Richter

NOTE Confidence: 0.923745231111111

00:19:50.360 --> 00:19:51.240 diagnostic sample.

NOTE Confidence: 0.923745231111111

00:19:51.240 --> 00:19:51.491 Unfortunately,

NOTE Confidence: 0.923745231111111

00:19:51.491 --> 00:19:52.997 there's a lot of red here,

NOTE Confidence: 0.872428799

00:19:53.000 --> 00:19:54.600 which is that the patients

NOTE Confidence: 0.872428799

00:19:54.600 --> 00:19:56.200 did succumb to their disease.

NOTE Confidence: 0.872428799

00:19:56.200 --> 00:19:57.920 There's a number here with

NOTE Confidence: 0.872428799

00:19:57.920 --> 00:19:59.360 black arrows that are living.

NOTE Confidence: 0.872428799

00:19:59.360 --> 00:20:00.540 For the most part,

NOTE Confidence: 0.872428799

00:20:00.540 --> 00:20:01.720 these are patients who.

NOTE Confidence: 0.872428799

00:20:01.720 --> 00:20:03.304 We received therapy and then went

NOTE Confidence: 0.872428799

00:20:03.304 --> 00:20:05.003 on to stem cell transplant and

NOTE Confidence: 0.872428799

00:20:05.003 --> 00:20:08.320 really did a complete overhaul.

NOTE Confidence: 0.872428799

00:20:08.320 --> 00:20:10.864 So we we obtained eggsomes on most of

NOTE Confidence: 0.872428799

00:20:10.864 --> 00:20:12.919 these patients also had some genomes,

NOTE Confidence: 0.872428799

00:20:12.920 --> 00:20:14.712 RNA sequencing and single

NOTE Confidence: 0.872428799

00:20:14.712 --> 00:20:15.572 cell sequencing data.

NOTE Confidence: 0.872428799

00:20:15.572 --> 00:20:17.220 But I want to point out to you

NOTE Confidence: 0.872428799

00:20:17.269 --> 00:20:18.711 that you know a lot of these

NOTE Confidence: 0.872428799

00:20:18.711 --> 00:20:20.079 studies are really quite different.

NOTE Confidence: 0.872428799

00:20:20.080 --> 00:20:22.180 I think that the the conundrum that

NOTE Confidence: 0.872428799

00:20:22.180 --> 00:20:24.778 we've met with Richter's is that it's

NOTE Confidence: 0.872428799

00:20:24.778 --> 00:20:27.438 really two malignancies in the same sample.

NOTE Confidence: 0.872428799

00:20:27.440 --> 00:20:30.312 So how do you pull apart the genomic

NOTE Confidence: 0.872428799

00:20:30.312 --> 00:20:32.518 contributions of one versus the other.

NOTE Confidence: 0.872428799

00:20:32.520 --> 00:20:36.080 And for that we had a come up

NOTE Confidence: 0.872428799

00:20:36.080 --> 00:20:37.424 with a computational approach

NOTE Confidence: 0.872428799

00:20:37.424 --> 00:20:38.942 that was quite challenging,

NOTE Confidence: 0.872428799

00:20:38.942 --> 00:20:41.700 but we were able to succeed where

NOTE Confidence: 0.872428799

00:20:41.775 --> 00:20:44.139 we really optimize the copy number

NOTE Confidence: 0.872428799

00:20:44.139 --> 00:20:46.656 analysis to deal with FFPE artifact.

NOTE Confidence: 0.872428799

00:20:46.656 --> 00:20:49.932 We had a number of different filters

NOTE Confidence: 0.872428799

00:20:49.932 --> 00:20:52.582 that allowed us to kind of increase

NOTE Confidence: 0.872428799

00:20:52.582 --> 00:20:54.292 the sensitivity of our analysis

NOTE Confidence: 0.872428799

00:20:54.292 --> 00:20:56.110 and deal with contamination of

NOTE Confidence: 0.872428799

00:20:56.110 --> 00:20:58.480 whether tumor in the normal or

NOTE Confidence: 0.834635984444444

00:21:01.800 --> 00:21:02.536 the reverse.

NOTE Confidence: 0.834635984444444

00:21:02.536 --> 00:21:05.112 As I said the artifact from FFPE.

NOTE Confidence: 0.834635984444444

00:21:05.120 --> 00:21:07.532 And then we were able to put in our

NOTE Confidence: 0.834635984444444

00:21:07.532 --> 00:21:09.380 algorithms that allow us to identify

NOTE Confidence: 0.834635984444444

00:21:09.380 --> 00:21:12.495 clones and then also establish phylogeny.

NOTE Confidence: 0.834635984444444

00:21:12.495 --> 00:21:14.000 So at the end of the day,

NOTE Confidence: 0.834635984444444

00:21:14.000 --> 00:21:16.086 we were able to separate out the

NOTE Confidence: 0.834635984444444

00:21:16.086 --> 00:21:17.600 contributions of the CLL clones

NOTE Confidence: 0.834635984444444

00:21:17.600 --> 00:21:18.720 compared to the Richter's clones.

NOTE Confidence: 0.834635984444444

00:21:18.720 --> 00:21:20.680 And in doing so then we could look

NOTE Confidence: 0.834635984444444

00:21:20.680 --> 00:21:22.921 at start to look at phylogeny and

NOTE Confidence: 0.834635984444444

00:21:22.921 --> 00:21:24.606 understand which branches were CLL

NOTE Confidence: 0.834635984444444

00:21:24.667 --> 00:21:26.839 versus Richter's and look across time.

NOTE Confidence: 0.834635984444444

00:21:26.840 --> 00:21:29.440 So again, Long story short,

NOTE Confidence: 0.834635984444444

00:21:29.440 --> 00:21:31.465 I think one of the questions that has been

NOTE Confidence: 0.834635984444444

00:21:31.465 --> 00:21:33.237 asked in the field is it is Richter's,

NOTE Confidence: 0.834635984444444

00:21:33.240 --> 00:21:35.000 is it a distinct entity,

NOTE Confidence: 0.834635984444444

00:21:35.000 --> 00:21:38.248 is it similar or is it different

NOTE Confidence: 0.834635984444444

00:21:38.248 --> 00:21:39.955 from the Novo DLBCL?

NOTE Confidence: 0.834635984444444

00:21:39.955 --> 00:21:42.475 And here we had the advantage of being

NOTE Confidence: 0.834635984444444

00:21:42.475 --> 00:21:44.665 able to access older data of more

NOTE Confidence: 0.834635984444444

00:21:44.665 --> 00:21:47.286 than 300 samples of lymphoma that our

NOTE Confidence: 0.834635984444444

00:21:47.286 --> 00:21:49.916 colleague market ship had collected.

NOTE Confidence: 0.834635984444444

00:21:49.920 --> 00:21:54.648 And then using those data we

NOTE Confidence: 0.834635984444444

00:21:54.648 --> 00:21:56.607 performed unbiased NMF clustering.

NOTE Confidence: 0.834635984444444

00:21:56.607 --> 00:21:59.330 And you can see across the purple

NOTE Confidence: 0.834635984444444

00:21:59.401 --> 00:22:01.771 on the top that the Richter's

NOTE Confidence: 0.834635984444444

00:22:01.771 --> 00:22:02.956 really stand different.

NOTE Confidence: 0.834635984444444

00:22:02.960 --> 00:22:05.584 They're you know separately

NOTE Confidence: 0.834635984444444

00:22:05.584 --> 00:22:10.696 from DLBCL and so the the,

NOTE Confidence: 0.834635984444444

00:22:10.696 --> 00:22:14.140 so this is clonally unrelated Richter.

NOTE Confidence: 0.834635984444444

00:22:14.140 --> 00:22:17.360 So these are the few samples here

NOTE Confidence: 0.834635984444444

00:22:17.360 --> 00:22:21.240 do appear to be like de Novo DLBCL,

NOTE Confidence: 0.834635984444444

00:22:21.240 --> 00:22:23.000 but the vast majority,

NOTE Confidence: 0.834635984444444

00:22:23.000 --> 00:22:25.320 the clonally related stand separately

NOTE Confidence: 0.912607754827586

00:22:27.560 --> 00:22:28.912 among the Richter's itself.

NOTE Confidence: 0.912607754827586

00:22:28.912 --> 00:22:31.335 We were also because of all the

NOTE Confidence: 0.912607754827586

00:22:31.335 --> 00:22:33.291 genomic alterations that we found we

NOTE Confidence: 0.912607754827586

00:22:33.291 --> 00:22:35.688 were able to also perform unbiased

NOTE Confidence: 0.912607754827586

00:22:35.688 --> 00:22:37.943 clustering and discern that there's

NOTE Confidence: 0.912607754827586

00:22:37.943 --> 00:22:41.055 actually it appears to be molecular

NOTE Confidence: 0.912607754827586

00:22:41.055 --> 00:22:43.520 subtypes within Richter's itself

NOTE Confidence: 0.912607754827586

00:22:43.520 --> 00:22:47.205 and these TP 53 has long been

NOTE Confidence: 0.912607754827586

00:22:47.205 --> 00:22:49.060 associated with Richter's but we can

NOTE Confidence: 0.912607754827586

00:22:49.060 --> 00:22:50.235 see that there's different flavors.

NOTE Confidence: 0.912607754827586

00:22:50.240 --> 00:22:54.048 So this one here has enrichment in

NOTE Confidence: 0.912607754827586

00:22:54.048 --> 00:22:56.784 whole genome doubling this group.

NOTE Confidence: 0.912607754827586

00:22:56.784 --> 00:23:00.096 Here RS3 has Co occurrence with

NOTE Confidence: 0.912607754827586

00:23:00.096 --> 00:23:04.140 Notch one also deletion 15 Q which

NOTE Confidence: 0.912607754827586

00:23:04.140 --> 00:23:08.972 covers MGA which is effects Mick

NOTE Confidence: 0.912607754827586

00:23:08.972 --> 00:23:13.135 and then RS5 also has Notch one

NOTE Confidence: 0.912607754827586

00:23:13.135 --> 00:23:16.554 as well wild type Notch one and a

NOTE Confidence: 0.912607754827586

00:23:16.554 --> 00:23:18.239 lot of copy number alterations.

NOTE Confidence: 0.912607754827586

00:23:18.240 --> 00:23:19.460 There were also two other

NOTE Confidence: 0.912607754827586

00:23:19.460 --> 00:23:20.680 subtypes that did not have

NOTE Confidence: 0.76865602

00:23:22.720 --> 00:23:25.656 TP53K Ras S Pen, Notch one together with

NOTE Confidence: 0.76865602

00:23:25.656 --> 00:23:28.712 Trisomy 12 and also SF3B1 with EGR Two.

NOTE Confidence: 0.76865602

00:23:28.712 --> 00:23:30.802 And again these different subgroups

NOTE Confidence: 0.76865602

00:23:30.802 --> 00:23:32.904 appear to have different clinical

NOTE Confidence: 0.76865602

00:23:32.904 --> 00:23:35.328 behavior where the ones that have

NOTE Confidence: 0.76865602

00:23:35.400 --> 00:23:37.759 TP 53 seem to have worse prognosis.

NOTE Confidence: 0.76865602

00:23:37.760 --> 00:23:39.307 Now what is the meaning of kind

NOTE Confidence: 0.76865602

00:23:39.307 --> 00:23:41.405 of trying to look at all these

NOTE Confidence: 0.76865602

00:23:41.405 --> 00:23:42.440 different genomic alterations?

NOTE Confidence: 0.76865602

00:23:42.440 --> 00:23:44.589 Well one thing we realized is that

NOTE Confidence: 0.76865602

00:23:44.589 --> 00:23:46.836 maybe we could harness all of this

NOTE Confidence: 0.76865602

00:23:46.836 --> 00:23:48.720 and actually look to see this,

NOTE Confidence: 0.76865602

00:23:48.720 --> 00:23:51.600 whether this could help us devise a non

NOTE Confidence: 0.76865602

00:23:51.600 --> 00:23:54.296 invasive approach to identifying Richter's

NOTE Confidence: 0.76865602

00:23:54.296 --> 00:23:57.800 and getting us to earlier detection.

NOTE Confidence: 0.76865602

00:23:57.800 --> 00:24:01.226 And it turns out that with simply ultra

NOTE Confidence: 0.76865602

00:24:01.226 --> 00:24:04.915 low pass genome sequencing $150.00 a pop,

NOTE Confidence: 0.76865602

00:24:04.915 --> 00:24:08.170 you can focus on these different alterations

NOTE Confidence: 0.76865602

00:24:08.258 --> 00:24:10.736 that we identified and start to look.

NOTE Confidence: 0.76865602

00:24:10.736 --> 00:24:12.320 And in fact we were able

NOTE Confidence: 0.76865602

00:24:12.386 --> 00:24:13.796 to see in this example,

NOTE Confidence: 0.76865602

00:24:13.800 --> 00:24:16.124 this is a patient where we could

NOTE Confidence: 0.76865602

00:24:16.124 --> 00:24:17.518 identify the Richter's alterations

NOTE Confidence: 0.76865602

00:24:17.518 --> 00:24:19.842 even close to five to six months

NOTE Confidence: 0.76865602

00:24:19.842 --> 00:24:21.600 before the actual diagnosis.

NOTE Confidence: 0.76865602

00:24:21.600 --> 00:24:23.600 So if you follow this in the blood,

NOTE Confidence: 0.76865602

00:24:23.600 --> 00:24:26.470 the blood cells have CLL at this

NOTE Confidence: 0.76865602

00:24:26.470 --> 00:24:28.395 time early on and it's a very,

NOTE Confidence: 0.76865602

00:24:28.400 --> 00:24:31.746 very quiet genomic profile.

NOTE Confidence: 0.76865602

00:24:31.746 --> 00:24:34.344 Whereas the plasma shows all of

NOTE Confidence: 0.76865602

00:24:34.344 --> 00:24:36.135 these different alterations that

NOTE Confidence: 0.76865602

00:24:36.135 --> 00:24:38.691 match very similarly to what was

NOTE Confidence: 0.76865602

00:24:38.691 --> 00:24:41.038 detected much later when the actual

NOTE Confidence: 0.76865602

00:24:41.040 --> 00:24:43.398 the the tissue diagnosis was made.

NOTE Confidence: 0.76865602

00:24:43.400 --> 00:24:45.400 We've been able to see that in a

NOTE Confidence: 0.76865602

00:24:45.400 --> 00:24:47.278 number of different other cases.

NOTE Confidence: 0.76865602

00:24:47.280 --> 00:24:48.080 This is a nut.

NOTE Confidence: 0.76865602

00:24:48.080 --> 00:24:51.000 Whoopsie, this is another case.

NOTE Confidence: 0.76865602

00:24:51.000 --> 00:24:51.760 Well anyway,

NOTE Confidence: 0.76865602

00:24:51.760 --> 00:24:52.520 let's see

NOTE Confidence: 0.95134685

00:24:54.640 --> 00:24:59.920 where the in the plasma we were able

NOTE Confidence: 0.95134685

00:24:59.920 --> 00:25:02.719 to again follow find those kind of

NOTE Confidence: 0.95134685

00:25:02.720 --> 00:25:04.192 Richter's genomic alterations that

NOTE Confidence: 0.95134685

00:25:04.192 --> 00:25:08.320 was not evident in the blood cells.

NOTE Confidence: 0.95134685

00:25:08.320 --> 00:25:10.464 And finally, this is a case of a

NOTE Confidence: 0.95134685

00:25:10.464 --> 00:25:12.718 patient who went through transplant and

NOTE Confidence: 0.9313210728

00:25:15.200 --> 00:25:18.175 we were able to identify post transplant

NOTE Confidence: 0.9313210728

00:25:18.175 --> 00:25:20.740 relapse months before the actual diagnosis

NOTE Confidence: 0.9313210728

00:25:20.740 --> 00:25:23.170 and then institute therapy and you

NOTE Confidence: 0.9313210728

00:25:23.170 --> 00:25:25.838 see those alterations go away again.

NOTE Confidence: 0.9313210728

00:25:25.840 --> 00:25:26.872 So I think just to summarize

NOTE Confidence: 0.9313210728

00:25:26.872 --> 00:25:27.800 this part of the talk,

NOTE Confidence: 0.9313210728

00:25:27.800 --> 00:25:31.440 I I would say that we've been able to

NOTE Confidence: 0.9313210728

00:25:31.440 --> 00:25:33.510 actually find that the majority of

NOTE Confidence: 0.9313210728

00:25:33.510 --> 00:25:35.655 Richter's does evolve from CLS subclones

NOTE Confidence: 0.9313210728

00:25:35.655 --> 00:25:38.120 through acquisition of additional drivers.

NOTE Confidence: 0.9313210728

00:25:38.120 --> 00:25:40.240 Clonally related Richter's is

NOTE Confidence: 0.9313210728

00:25:40.240 --> 00:25:42.992 distinct from de Novo DLBCL.

NOTE Confidence: 0.9313210728

00:25:42.992 --> 00:25:45.520 There are molecular subtypes

NOTE Confidence: 0.9313210728

00:25:45.520 --> 00:25:48.088 of Richter's that have and and

NOTE Confidence: 0.9313210728

00:25:48.088 --> 00:25:49.800 these different subcategories do

NOTE Confidence: 0.9313210728

00:25:49.869 --> 00:25:51.840 have prognostic significance.

NOTE Confidence: 0.9313210728

00:25:51.840 --> 00:25:54.136 And then the we're very excited about

NOTE Confidence: 0.9313210728

00:25:54.136 --> 00:25:56.895 the self free DNA as a way to get us

NOTE Confidence: 0.9313210728

00:25:56.895 --> 00:25:58.470 to non invasive earlier diagnosis

NOTE Confidence: 0.9313210728

00:25:58.470 --> 00:26:01.172 because I think this could be really

NOTE Confidence: 0.9313210728

00:26:01.172 --> 00:26:04.880 quite impactful for our patients.

NOTE Confidence: 0.9313210728

00:26:04.880 --> 00:26:06.356 I think we're always trying to.

NOTE Confidence: 0.9313210728

00:26:06.360 --> 00:26:09.525 So I'm going to transition now in

NOTE Confidence: 0.9313210728

00:26:09.525 --> 00:26:13.155 terms of talking about the immune

NOTE Confidence: 0.9313210728

00:26:13.155 --> 00:26:14.312 microenvironment for Richter's.

NOTE Confidence: 0.9313210728

00:26:14.312 --> 00:26:14.864 You know,

NOTE Confidence: 0.9313210728

00:26:14.864 --> 00:26:16.820 I think we're always trying to gain

NOTE Confidence: 0.9313210728

00:26:16.820 --> 00:26:18.570 a bird's eye view of the landscape

NOTE Confidence: 0.9313210728

00:26:18.570 --> 00:26:20.615 and really the advent of single

NOTE Confidence: 0.9313210728

00:26:20.615 --> 00:26:22.840 cell analysis has really been

NOTE Confidence: 0.9313210728

00:26:22.840 --> 00:26:24.640 so impactful all around.

NOTE Confidence: 0.9313210728

00:26:24.640 --> 00:26:26.656 This is something I put together with

NOTE Confidence: 0.9313210728

00:26:26.656 --> 00:26:28.637 one of my postdoctoral fellows where

NOTE Confidence: 0.9313210728

00:26:28.637 --> 00:26:31.498 we tried to look at across the field.

NOTE Confidence: 0.9313210728

00:26:31.498 --> 00:26:33.694 You know single cell sequencing was

NOTE Confidence: 0.9313210728

00:26:33.694 --> 00:26:36.379 named the method of the year in 2013

NOTE Confidence: 0.9313210728

00:26:36.379 --> 00:26:38.346 and then subsequently 2019 in multi

NOTE Confidence: 0.9313210728

00:26:38.346 --> 00:26:40.747 ohmic analysis was the method of the year.

NOTE Confidence: 0.9313210728

00:26:40.747 --> 00:26:43.120 CLL has had a bit of a lag time in

NOTE Confidence: 0.9313210728

00:26:43.120 --> 00:26:45.200 terms of the the rest of the field,

NOTE Confidence: 0.9313210728

00:26:45.200 --> 00:26:47.853 but again the easy access to material

NOTE Confidence: 0.9313210728

00:26:47.853 --> 00:26:50.381 has really kind of stimulated us to

NOTE Confidence: 0.9313210728

00:26:50.381 --> 00:26:53.359 start to look a little bit more closely.

NOTE Confidence: 0.9313210728

00:26:53.360 --> 00:26:55.236 We've been able to apply this approach.

NOTE Confidence: 0.9313210728

00:26:55.240 --> 00:26:57.240 Again I mentioned that Richter's

NOTE Confidence: 0.9313210728

00:26:57.240 --> 00:27:00.800 is this area where the therapeutic

NOTE Confidence: 0.9313210728

00:27:00.800 --> 00:27:04.706 opportunities are not great,

NOTE Confidence: 0.9313210728

00:27:04.706 --> 00:27:07.972 but what has caught the attention of

NOTE Confidence: 0.9313210728

00:27:07.972 --> 00:27:10.746 many is that it turns out that there is

NOTE Confidence: 0.9313210728

00:27:10.746 --> 00:27:12.775 a response to immune checkpoint blockade.

NOTE Confidence: 0.9313210728

00:27:12.775 --> 00:27:16.062 So fit 42 to 65% responses to

NOTE Confidence: 0.9313210728

00:27:16.062 --> 00:27:18.278 PD1 blockade in Richter's.

NOTE Confidence: 0.9313210728

00:27:18.280 --> 00:27:20.248 This is really quite remarkable because

NOTE Confidence: 0.9313210728

00:27:20.248 --> 00:27:22.549 a lot of blood B cell malignancies

NOTE Confidence: 0.9313210728

00:27:22.549 --> 00:27:24.712 do not have a great response to

NOTE Confidence: 0.9313210728

00:27:24.720 --> 00:27:30.364 to PD anti PD one and so this sort

NOTE Confidence: 0.9313210728

00:27:30.364 --> 00:27:31.874 of across these many studies.

NOTE Confidence: 0.9313210728

00:27:31.880 --> 00:27:33.415 This raises the question are

NOTE Confidence: 0.9313210728

00:27:33.415 --> 00:27:34.643 there determinants of response

NOTE Confidence: 0.9313210728

00:27:34.643 --> 00:27:36.294 and resistance to PD1 blockade.

NOTE Confidence: 0.9313210728

00:27:36.294 --> 00:27:38.256 We were able to partner together

NOTE Confidence: 0.9313210728

00:27:38.256 --> 00:27:40.517 with our colleagues at MD Anderson.

NOTE Confidence: 0.9313210728

00:27:40.520 --> 00:27:42.879 Again this is the work of Aaron

NOTE Confidence: 0.9313210728

00:27:42.879 --> 00:27:45.180 Perry where they had already started

NOTE Confidence: 0.9313210728

00:27:45.180 --> 00:27:47.690 a trial where they had patients

NOTE Confidence: 0.9313210728

00:27:47.690 --> 00:27:50.270 initially on nivolumab and then then

NOTE Confidence: 0.9313210728

00:27:50.270 --> 00:27:52.370 after the first cycle then ibrutinib

NOTE Confidence: 0.9313210728

00:27:52.370 --> 00:27:54.364 was started and then response

NOTE Confidence: 0.9313210728

00:27:54.364 --> 00:27:56.559 assessment happened at three months.

NOTE Confidence: 0.9313210728

00:27:56.560 --> 00:27:59.032 And so we were able to collect bone

NOTE Confidence: 0.9313210728

00:27:59.032 --> 00:28:00.960 marrow samples from these patients,

NOTE Confidence: 0.9313210728

00:28:00.960 --> 00:28:03.472 a number in the green that had either

NOTE Confidence: 0.9313210728

00:28:03.472 --> 00:28:05.742 a partial or complete response to

NOTE Confidence: 0.9313210728

00:28:05.742 --> 00:28:07.490 patients that had progression even

NOTE Confidence: 0.9313210728

00:28:07.490 --> 00:28:09.200 at the three month time point.

NOTE Confidence: 0.9313210728

00:28:09.200 --> 00:28:12.004 And then just for comparison to CLL,

NOTE Confidence: 0.9313210728

00:28:12.004 --> 00:28:14.296 patients were treated on the same

NOTE Confidence: 0.9313210728

00:28:14.296 --> 00:28:16.283 trial and what Erin did was she was

NOTE Confidence: 0.9313210728

00:28:16.283 --> 00:28:18.098 able to take marrow samples from

NOTE Confidence: 0.9313210728

00:28:18.098 --> 00:28:19.873 these patients and through flow

NOTE Confidence: 0.9313210728

00:28:19.873 --> 00:28:21.520 cytometry you can see that the

NOTE Confidence: 0.759661734285714

00:28:23.560 --> 00:28:25.394 the small cells were the CLL cells,

NOTE Confidence: 0.759661734285714

00:28:25.400 --> 00:28:27.364 the large cells were the Richter's

NOTE Confidence: 0.759661734285714

00:28:27.364 --> 00:28:29.184 and then there was another

NOTE Confidence: 0.759661734285714

00:28:29.184 --> 00:28:31.003 population here which was neither

NOTE Confidence: 0.759661734285714

00:28:31.003 --> 00:28:32.765 and this was the immune cells

NOTE Confidence: 0.759661734285714

00:28:32.765 --> 00:28:34.235 that were in the bone marrow.

NOTE Confidence: 0.759661734285714

00:28:34.240 --> 00:28:35.950 And then she was able to

NOTE Confidence: 0.759661734285714

00:28:35.950 --> 00:28:37.200 perform a single cell

NOTE Confidence: 0.896807332

00:28:39.240 --> 00:28:39.628 characterization.

NOTE Confidence: 0.896807332

00:28:39.628 --> 00:28:43.120 And again to summarize a large body of work,

NOTE Confidence: 0.896807332

00:28:43.120 --> 00:28:45.150 what was really clear is that the

NOTE Confidence: 0.896807332

00:28:45.150 --> 00:28:46.599 responders compared to the non

NOTE Confidence: 0.896807332

00:28:46.599 --> 00:28:48.153 responders when you started to look

NOTE Confidence: 0.896807332

00:28:48.153 --> 00:28:50.600 at all of those single cell transcriptomes,

NOTE Confidence: 0.896807332

00:28:50.600 --> 00:28:52.632 those there was a kind of a cluster

NOTE Confidence: 0.896807332

00:28:52.632 --> 00:28:54.442 of cells that kind of segregated

NOTE Confidence: 0.896807332

00:28:54.442 --> 00:28:55.997 with a unique phenotype and

NOTE Confidence: 0.896807332

00:28:55.997 --> 00:28:57.758 we called this cluster one.

NOTE Confidence: 0.896807332

00:28:57.760 --> 00:29:00.634 It turns out it was high

NOTE Confidence: 0.896807332

00:29:00.634 --> 00:29:02.550 expression for a transcriptional

NOTE Confidence: 0.896807332

00:29:02.638 --> 00:29:04.994 factor called Hobbit ZNF 683.

NOTE Confidence: 0.896807332

00:29:04.994 --> 00:29:07.016 And as she started to look

NOTE Confidence: 0.896807332

00:29:07.016 --> 00:29:08.640 at this population,

NOTE Confidence: 0.896807332

00:29:08.640 --> 00:29:11.300 she was able to perform some functional

NOTE Confidence: 0.896807332

00:29:11.300 --> 00:29:13.198 studies and demonstrate through cut

NOTE Confidence: 0.896807332

00:29:13.198 --> 00:29:15.606 and cut and run and various various

NOTE Confidence: 0.896807332

00:29:15.606 --> 00:29:17.940 different sort of over expression and

NOTE Confidence: 0.896807332

00:29:17.940 --> 00:29:20.842 knockout kind of analysis that ZNF

NOTE Confidence: 0.896807332

00:29:20.842 --> 00:29:23.656 683 does appear to regulate T cell

NOTE Confidence: 0.896807332

00:29:23.656 --> 00:29:26.400 pathways with activation cytotoxicity.

NOTE Confidence: 0.896807332

00:29:26.400 --> 00:29:28.542 When we started to look at the

NOTE Confidence: 0.896807332

00:29:28.542 --> 00:29:30.249 trajectories the ZNF 683 high

NOTE Confidence: 0.896807332

00:29:30.249 --> 00:29:32.427 seemed to be a divergent pathway

NOTE Confidence: 0.896807332

00:29:32.427 --> 00:29:34.320 from terminal exhaustion.

NOTE Confidence: 0.896807332

00:29:34.320 --> 00:29:37.278 We also looked across other different

NOTE Confidence: 0.896807332

00:29:37.278 --> 00:29:40.060 solid tumor till settings and it turns

NOTE Confidence: 0.896807332

00:29:40.060 --> 00:29:42.915 out that the ZNF 683 high does mark

NOTE Confidence: 0.896807332

00:29:42.915 --> 00:29:45.244 a population that's of patients that

NOTE Confidence: 0.896807332

00:29:45.244 --> 00:29:47.918 have better response to PD one therapy.

NOTE Confidence: 0.896807332

00:29:47.920 --> 00:29:50.160 Notably we looked at Melanoma

NOTE Confidence: 0.896807332

00:29:50.160 --> 00:29:52.826 across and other settings and also

NOTE Confidence: 0.896807332

00:29:52.826 --> 00:29:56.290 in she was also able to see that

NOTE Confidence: 0.896807332

00:29:56.400 --> 00:29:59.851 you know we did our analysis in

NOTE Confidence: 0.896807332

00:29:59.851 --> 00:30:02.660 the marrow but to make it more

NOTE Confidence: 0.896807332

00:30:02.660 --> 00:30:04.480 clinically facile could could this

NOTE Confidence: 0.896807332

00:30:04.548 --> 00:30:06.840 be actually detected in the blood.

NOTE Confidence: 0.896807332

00:30:06.840 --> 00:30:09.468 And so she was able to look at independent

NOTE Confidence: 0.896807332

00:30:09.468 --> 00:30:11.300 patients who are responders or non

NOTE Confidence: 0.896807332

00:30:11.300 --> 00:30:13.240 responders on the MD Anderson trial.

NOTE Confidence: 0.896807332

00:30:13.240 --> 00:30:15.697 And in fact the responders have a

NOTE Confidence: 0.896807332

00:30:15.697 --> 00:30:18.125 very distinct profile in the blood T

NOTE Confidence: 0.896807332

00:30:18.125 --> 00:30:20.081 cells compared to the non responders

NOTE Confidence: 0.896807332

00:30:20.146 --> 00:30:22.012 where there is high expression of

NOTE Confidence: 0.896807332

00:30:22.012 --> 00:30:24.880 Z and F683 and and other cluster

NOTE Confidence: 0.896807332

00:30:24.880 --> 00:30:30.888 one genes as well and this is we.

NOTE Confidence: 0.896807332

00:30:30.888 --> 00:30:33.680 So we were very proud of Aaron and

NOTE Confidence: 0.896807332

00:30:33.680 --> 00:30:36.350 Camila to get this into cancer cell.

NOTE Confidence: 0.896807332

00:30:36.350 --> 00:30:40.760 We actually tried to for a cover.

NOTE Confidence: 0.896807332

00:30:40.760 --> 00:30:42.008 It did not work.

NOTE Confidence: 0.896807332

00:30:42.008 --> 00:30:44.388 So you will never see this published

NOTE Confidence: 0.896807332

00:30:44.388 --> 00:30:46.998 only here in the seminar series.

NOTE Confidence: 0.896807332

00:30:47.000 --> 00:30:50.159 But we were trying to make a play on

NOTE Confidence: 0.896807332

00:30:50.160 --> 00:30:52.608 ZNF 683 and The Hobbit and the idea

NOTE Confidence: 0.896807332

00:30:52.608 --> 00:30:55.662 that if those of you were Middle

NOTE Confidence: 0.896807332

00:30:55.662 --> 00:30:58.760 Earth aficionados or token lovers,

NOTE Confidence: 0.896807332

00:30:58.760 --> 00:31:00.080 you know,

NOTE Confidence: 0.896807332

00:31:00.080 --> 00:31:03.744 the idea that you can either take

NOTE Confidence: 0.896807332

00:31:03.744 --> 00:31:06.143 a path and get to the valley of

NOTE Confidence: 0.896807332

00:31:06.143 --> 00:31:08.120 death with exhaustion or you can

NOTE Confidence: 0.896807332

00:31:08.120 --> 00:31:10.091 take a divergent pathway and end

NOTE Confidence: 0.896807332

00:31:10.091 --> 00:31:11.675 up back in the Shire happy.

NOTE Confidence: 0.896807332

00:31:11.680 --> 00:31:15.172 So that was our idea. Didn't work.

NOTE Confidence: 0.896807332

00:31:15.172 --> 00:31:15.838 Whatever.

NOTE Confidence: 0.896807332

00:31:15.838 --> 00:31:17.836 So, so that.

NOTE Confidence: 0.896807332

00:31:17.840 --> 00:31:20.054 I'm going to move on to

NOTE Confidence: 0.896807332

00:31:20.054 --> 00:31:22.160 the second set of study,

NOTE Confidence: 0.896807332

00:31:22.160 --> 00:31:24.175 second chapter shall we say

NOTE Confidence: 0.896807332

00:31:24.175 --> 00:31:27.040 in trying to look at function.

NOTE Confidence: 0.896807332

00:31:27.040 --> 00:31:28.909 And here you know in the same

NOTE Confidence: 0.896807332

00:31:28.909 --> 00:31:30.040 way that in the,

NOTE Confidence: 0.896807332

00:31:30.040 --> 00:31:33.050 in the genetic realm we've been able

NOTE Confidence: 0.896807332

00:31:33.050 --> 00:31:36.456 to study heterogeneity in patients.

NOTE Confidence: 0.896807332

00:31:36.456 --> 00:31:37.200 Well,

NOTE Confidence: 0.896807332

00:31:37.200 --> 00:31:40.520 can we not actually generate mice

NOTE Confidence: 0.896807332

00:31:40.520 --> 00:31:43.912 that are actually faithful to the

NOTE Confidence: 0.896807332

00:31:43.912 --> 00:31:46.406 disease through the by mimicking

NOTE Confidence: 0.896807332

00:31:46.406 --> 00:31:48.321 some of these genetic alterations

NOTE Confidence: 0.896807332

00:31:48.321 --> 00:31:50.211 that we've identified And then

NOTE Confidence: 0.896807332

00:31:50.211 --> 00:31:52.239 that provides us a platform with

NOTE Confidence: 0.896807332

00:31:52.239 --> 00:31:53.611 studying mechanism of disease

NOTE Confidence: 0.896807332

00:31:53.611 --> 00:31:54.885 and testing novel therapies.

NOTE Confidence: 0.896807332

00:31:54.885 --> 00:31:57.485 And I just want to point out that

NOTE Confidence: 0.896807332

00:31:57.485 --> 00:31:59.958 there are different flavors of models.

NOTE Confidence: 0.726405345384615

00:31:59.960 --> 00:32:01.800 I I don't need to tell this audience

NOTE Confidence: 0.726405345384615

00:32:01.800 --> 00:32:03.440 or folks that yelled at, but

NOTE Confidence: 0.648140945

00:32:05.560 --> 00:32:07.360 the GEM models in general in,

NOTE Confidence: 0.648140945

00:32:07.360 --> 00:32:08.977 in particular I just want to point

NOTE Confidence: 0.648140945

00:32:08.977 --> 00:32:10.823 out have the advantage that this is

NOTE Confidence: 0.648140945

00:32:10.823 --> 00:32:12.473 kind of in a physiologic setting.

NOTE Confidence: 0.648140945

00:32:12.480 --> 00:32:16.449 It does allow us to look at tumor evolution

NOTE Confidence: 0.648140945

00:32:16.449 --> 00:32:19.960 and also immune micro environment analysis.

NOTE Confidence: 0.648140945

00:32:19.960 --> 00:32:22.800 And so for the past period of time,

NOTE Confidence: 0.648140945

00:32:22.800 --> 00:32:23.930 my group has really been

NOTE Confidence: 0.648140945

00:32:23.930 --> 00:32:25.106 interested in this question, well,

NOTE Confidence: 0.648140945

00:32:25.106 --> 00:32:27.042 how do you get from AB cell,

NOTE Confidence: 0.648140945

00:32:27.042 --> 00:32:29.149 what are the kind of pathway hits

NOTE Confidence: 0.648140945

00:32:29.149 --> 00:32:31.316 that happen that gets you to CLL?

NOTE Confidence: 0.648140945

00:32:31.320 --> 00:32:33.720 And can we study some of these alterations

NOTE Confidence: 0.648140945

00:32:33.720 --> 00:32:36.326 that we spent a lot of time genomically

NOTE Confidence: 0.648140945

00:32:36.326 --> 00:32:40.853 identifying such as SF3B1 or IK,

NOTE Confidence: 0.648140945

00:32:40.853 --> 00:32:45.066 CF3 or DMT3A and so and so forth and

NOTE Confidence: 0.648140945

00:32:45.066 --> 00:32:47.194 can we start to look at these things.

NOTE Confidence: 0.648140945

00:32:47.200 --> 00:32:49.816 So I won't go over these past studies

NOTE Confidence: 0.648140945

00:32:49.816 --> 00:32:52.931 only to say that it has in fact been

NOTE Confidence: 0.648140945

00:32:52.931 --> 00:32:54.770 very gratifying to generate these

NOTE Confidence: 0.648140945

00:32:54.770 --> 00:32:57.200 mouse models and to demonstrate that,

NOTE Confidence: 0.648140945

00:32:57.200 --> 00:33:00.230 yes, these putative drivers that

NOTE Confidence: 0.648140945

00:33:00.230 --> 00:33:02.654 we've identified through sequencing

NOTE Confidence: 0.648140945

00:33:02.654 --> 00:33:04.997 actually generate CLL in mice.

NOTE Confidence: 0.648140945

00:33:05.000 --> 00:33:07.826 Most recently we had a very nice

NOTE Confidence: 0.648140945

00:33:07.826 --> 00:33:10.160 study ELISA 10 Hacken generated

NOTE Confidence: 0.808189956666667

00:33:12.560 --> 00:33:14.540 the setting where using CRISPR she

NOTE Confidence: 0.808189956666667

00:33:14.540 --> 00:33:16.435 was able to introduce combinations

NOTE Confidence: 0.808189956666667

00:33:16.435 --> 00:33:18.980 of different alterations and release

NOTE Confidence: 0.808189956666667

00:33:18.980 --> 00:33:21.032 combinatorial study the different models

NOTE Confidence: 0.808189956666667

00:33:21.032 --> 00:33:23.440 of CLL and Richter's that we identified.

NOTE Confidence: 0.808189956666667

00:33:23.440 --> 00:33:25.407 But for today, I'm going to talk

NOTE Confidence: 0.808189956666667

00:33:25.407 --> 00:33:26.817 about new unpublished data where

NOTE Confidence: 0.808189956666667

00:33:26.817 --> 00:33:28.602 we've been focused on one of the

NOTE Confidence: 0.808189956666667

00:33:28.602 --> 00:33:30.317 newer drivers that we identified,

NOTE Confidence: 0.808189956666667

00:33:30.320 --> 00:33:33.113 RPS 15 and some of the insights

NOTE Confidence: 0.808189956666667

00:33:33.113 --> 00:33:34.840 that we've identified there.

NOTE Confidence: 0.808189956666667

00:33:34.840 --> 00:33:38.200 So RPS 15, what is it?

NOTE Confidence: 0.808189956666667

00:33:38.200 --> 00:33:41.572 It is a ribosomal protein.

NOTE Confidence: 0.808189956666667

00:33:41.572 --> 00:33:45.099 It's identified in 5% of CLL patients.

NOTE Confidence: 0.808189956666667

00:33:45.099 --> 00:33:47.864 It's enriched in patients who

NOTE Confidence: 0.808189956666667

00:33:47.864 --> 00:33:50.759 are relapsed following therapy.

NOTE Confidence: 0.808189956666667

00:33:50.760 --> 00:33:53.260 It's associated with shorter

NOTE Confidence: 0.808189956666667

00:33:53.260 --> 00:33:56.385 progression free survival and it

NOTE Confidence: 0.808189956666667

00:33:56.385 --> 00:33:58.219 commonly Co expresses with TP53.

NOTE Confidence: 0.808189956666667

00:33:58.219 --> 00:34:00.410 One of the things that we found

NOTE Confidence: 0.808189956666667

00:34:00.477 --> 00:34:02.626 interesting about RPS 15 is that there

NOTE Confidence: 0.808189956666667

00:34:02.626 --> 00:34:04.758 does seem to be a hotspot region

NOTE Confidence: 0.808189956666667

00:34:04.760 --> 00:34:07.154 where a lot of the alterations happen.

NOTE Confidence: 0.808189956666667

00:34:07.160 --> 00:34:09.536 And so this kind of piqued our interest

NOTE Confidence: 0.808189956666667

00:34:09.536 --> 00:34:11.837 in trying to learn more about RPS 15.

NOTE Confidence: 0.808189956666667

00:34:11.840 --> 00:34:13.649 I do want to put this in the context

NOTE Confidence: 0.808189956666667

00:34:13.649 --> 00:34:15.517 that they're across different cancers.

NOTE Confidence: 0.808189956666667

00:34:15.520 --> 00:34:19.118 There's been a lot of different ribosomal

NOTE Confidence: 0.808189956666667

00:34:19.120 --> 00:34:22.344 mutations that have been found for CLLR.

NOTE Confidence: 0.808189956666667

00:34:22.344 --> 00:34:24.704 PS15 is the only ribosomal

NOTE Confidence: 0.808189956666667

00:34:24.704 --> 00:34:27.120 mutation that's been identified.

NOTE Confidence: 0.808189956666667

00:34:27.120 --> 00:34:28.700 But certainly across other

NOTE Confidence: 0.808189956666667

00:34:28.700 --> 00:34:30.280 cancers including breast cancer,

NOTE Confidence: 0.808189956666667

00:34:30.280 --> 00:34:31.784 Melanoma, myeloma,

NOTE Confidence: 0.808189956666667

00:34:31.784 --> 00:34:35.396 you see that this biology seems to be there.

NOTE Confidence: 0.808189956666667

00:34:35.400 --> 00:34:37.204 And carbosomopathies have been

NOTE Confidence: 0.808189956666667

00:34:37.204 --> 00:34:39.459 associated with a variety of

NOTE Confidence: 0.808189956666667

00:34:39.459 --> 00:34:41.160 different altered functions,

NOTE Confidence: 0.808189956666667

00:34:41.160 --> 00:34:44.580 so including DNA damage,

NOTE Confidence: 0.808189956666667

00:34:44.580 --> 00:34:46.900 proteasomal alteration and metabolic

NOTE Confidence: 0.808189956666667

00:34:46.900 --> 00:34:47.480 rewiring.

NOTE Confidence: 0.808189956666667

00:34:47.480 --> 00:34:50.352 So we were interested in trying to dig

NOTE Confidence: 0.808189956666667

00:34:50.352 --> 00:34:53.800 a little bit deeper about this in CLL.

NOTE Confidence: 0.808189956666667

00:34:53.800 --> 00:34:55.680 So we used our,

NOTE Confidence: 0.808189956666667

00:34:55.680 --> 00:34:57.568 we used this in a similar fashion to

NOTE Confidence: 0.808189956666667

00:34:57.568 --> 00:34:59.437 the other mice that we've generated.

NOTE Confidence: 0.808189956666667

00:34:59.440 --> 00:35:04.039 We introduced one of these hotspot mutations

NOTE Confidence: 0.808189956666667

00:35:04.040 --> 00:35:06.798 that was intercross with CD19 cream mice.

NOTE Confidence: 0.808189956666667

00:35:06.800 --> 00:35:09.448 So this alteration is only present in B

NOTE Confidence: 0.808189956666667

00:35:09.448 --> 00:35:12.316 cells in the context of CD19 expression.

NOTE Confidence: 0.808189956666667

00:35:12.320 --> 00:35:15.833 So in B cells we were able to generate both

NOTE Confidence: 0.808189956666667

00:35:15.833 --> 00:35:18.198 heterozygous and homozygous mutated mice.

NOTE Confidence: 0.808189956666667

00:35:18.200 --> 00:35:21.714 We also intercross also with deletion 15,

NOTE Confidence: 0.808189956666667

00:35:21.720 --> 00:35:23.592 sorry TP 53,

NOTE Confidence: 0.808189956666667

00:35:23.592 --> 00:35:27.140 so that they were also mice that

NOTE Confidence: 0.808189956666667

00:35:27.140 --> 00:35:30.880 had double mutations as well.

NOTE Confidence: 0.808189956666667

00:35:30.880 --> 00:35:32.320 And so this is just a bit of

NOTE Confidence: 0.808189956666667

00:35:32.320 --> 00:35:33.120 the targeting strategy.

NOTE Confidence: 0.808189956666667

00:35:33.120 --> 00:35:34.866 This was really studies led by

NOTE Confidence: 0.808189956666667

00:35:34.866 --> 00:35:37.954 an MDPHD student and currently

NOTE Confidence: 0.808189956666667

00:35:37.954 --> 00:35:40.873 at MGH as a as an intern.

NOTE Confidence: 0.808189956666667

00:35:40.880 --> 00:35:43.666 And then Marwan Kwok is a awesome postdoc

NOTE Confidence: 0.808189956666667

00:35:43.666 --> 00:35:45.297 in my group right now who's leading

NOTE Confidence: 0.808189956666667

00:35:45.297 --> 00:35:47.037 up on some of the functional studies.

NOTE Confidence: 0.808189956666667

00:35:47.040 --> 00:35:50.022 Neil Ruthin is in grad Graduate

NOTE Confidence: 0.808189956666667

00:35:50.022 --> 00:35:52.445 School in the New York area

NOTE Confidence: 0.808189956666667

00:35:52.445 --> 00:35:53.600 for computational biology.

NOTE Confidence: 0.808189956666667

00:35:53.600 --> 00:35:55.276 So RPS 15 mutations,

NOTE Confidence: 0.808189956666667

00:35:55.276 --> 00:35:58.383 we we're very able through our mouse

NOTE Confidence: 0.808189956666667

00:35:58.383 --> 00:36:01.897 models to confirm that it does have

NOTE Confidence: 0.808189956666667

00:36:01.897 --> 00:36:03.949 oncogenic potential because certainly

NOTE Confidence: 0.808189956666667

00:36:03.949 --> 00:36:07.586 over time we're able to identify that

NOTE Confidence: 0.808189956666667

00:36:07.586 --> 00:36:11.684 there is a population of RPS 15 mice

NOTE Confidence: 0.808189956666667

00:36:11.684 --> 00:36:14.840 that are do have expanded B cells.

NOTE Confidence: 0.808189956666667

00:36:14.840 --> 00:36:17.990 You can see this also in

NOTE Confidence: 0.808189956666667

00:36:17.990 --> 00:36:19.528 screen sizes over time.

NOTE Confidence: 0.808189956666667

00:36:19.528 --> 00:36:21.480 It does take quite a bit of time

NOTE Confidence: 0.808189956666667

00:36:21.545 --> 00:36:23.480 consistent with the human disease.

NOTE Confidence: 0.808189956666667

00:36:23.480 --> 00:36:27.560 It does take about 15,

NOTE Confidence: 0.808189956666667

00:36:27.560 --> 00:36:28.607 about 818 months,

NOTE Confidence: 0.808189956666667

00:36:28.607 --> 00:36:31.050 18 to 218 months to two years

NOTE Confidence: 0.808189956666667

00:36:31.133 --> 00:36:32.918 in order to see disease.

NOTE Confidence: 0.808189956666667

00:36:32.920 --> 00:36:35.840 So this is really a labor of love.

NOTE Confidence: 0.808189956666667

00:36:35.840 --> 00:36:39.065 But I would say that for sure with

NOTE Confidence: 0.808189956666667

00:36:39.065 --> 00:36:42.110 the RPS 15 mutations mutant mice we

NOTE Confidence: 0.917190518666667

00:36:42.198 --> 00:36:45.800 do see onset of disease less so with

NOTE Confidence: 0.917190518666667

00:36:45.800 --> 00:36:49.357 just the TP single mutant TP 53 but

NOTE Confidence: 0.917190518666667

00:36:49.357 --> 00:36:52.096 with a double mutant we also see not

NOTE Confidence: 0.917190518666667

00:36:52.096 --> 00:36:54.640 only CLL but evidence of Richter's.

NOTE Confidence: 0.917190518666667

00:36:54.640 --> 00:36:56.810 But what was interesting is in the

NOTE Confidence: 0.917190518666667

00:36:56.810 --> 00:36:58.467 setting of hypo hyper proliferation

NOTE Confidence: 0.917190518666667

00:36:58.467 --> 00:37:01.099 when we look early on it seems to

NOTE Confidence: 0.917190518666667

00:37:01.163 --> 00:37:03.398 there seems to be hypoproliferation.

NOTE Confidence: 0.917190518666667

00:37:03.400 --> 00:37:05.712 So if we measure the B cell percentages

NOTE Confidence: 0.917190518666667

00:37:05.712 --> 00:37:07.862 in the homozygous mice in the

NOTE Confidence: 0.917190518666667

00:37:07.862 --> 00:37:10.124 setting of pre leukemia it's actually

NOTE Confidence: 0.917190518666667

00:37:10.189 --> 00:37:12.199 depressed compared to wild type.

NOTE Confidence: 0.917190518666667

00:37:12.200 --> 00:37:13.640 So what is going on?

NOTE Confidence: 0.917190518666667

00:37:13.640 --> 00:37:16.622 How is this kind of hypoproliferation

NOTE Confidence: 0.917190518666667

00:37:16.622 --> 00:37:18.113 turning into hyper?

NOTE Confidence: 0.917190518666667

00:37:18.120 --> 00:37:20.000 And so to kind of gain some clues,

NOTE Confidence: 0.917190518666667

00:37:20.000 --> 00:37:22.328 we really focused on these pre

NOTE Confidence: 0.917190518666667

00:37:22.328 --> 00:37:24.410 leukemic mice for which we collected

NOTE Confidence: 0.917190518666667

00:37:24.410 --> 00:37:27.024 B cells and started off by just

NOTE Confidence: 0.917190518666667

00:37:27.024 --> 00:37:29.154 looking at gene expression profiling.

NOTE Confidence: 0.917190518666667

00:37:29.160 --> 00:37:31.120 And it became quite evident that there

NOTE Confidence: 0.917190518666667

00:37:31.120 --> 00:37:33.360 was quite a few different altered

NOTE Confidence: 0.917190518666667

00:37:33.360 --> 00:37:35.600 pathways including cell cycle checkpoints,

NOTE Confidence: 0.917190518666667

00:37:35.600 --> 00:37:37.624 MIC targets, DNA repair.

NOTE Confidence: 0.917190518666667

00:37:37.624 --> 00:37:40.154 And looking close more closely,

NOTE Confidence: 0.917190518666667

00:37:40.160 --> 00:37:42.302 we could see that this was related

NOTE Confidence: 0.917190518666667

00:37:42.302 --> 00:37:44.381 to either reduction in proliferative

NOTE Confidence: 0.917190518666667

00:37:44.381 --> 00:37:47.790 capacity as well as there was increased

NOTE Confidence: 0.917190518666667

00:37:47.865 --> 00:37:50.940 G1 checkpoint activity after mitogenic

NOTE Confidence: 0.917190518666667

00:37:50.940 --> 00:37:53.400 stimulation and increased apoptosis.

NOTE Confidence: 0.917190518666667

00:37:53.400 --> 00:37:57.648 Now these alterations in in cell

NOTE Confidence: 0.917190518666667

00:37:57.648 --> 00:38:00.880 cycle could be due to cell stress.

NOTE Confidence: 0.917190518666667

00:38:00.880 --> 00:38:03.600 So we started to look at the question

NOTE Confidence: 0.917190518666667

00:38:03.600 --> 00:38:06.518 of whether or not there was changes in

NOTE Confidence: 0.917190518666667

00:38:06.518 --> 00:38:09.510 oxidative stress and in fact using a

NOTE Confidence: 0.917190518666667

00:38:09.510 --> 00:38:13.080 Mitosox assay in our homozygous mice,

NOTE Confidence: 0.917190518666667

00:38:13.080 --> 00:38:15.691 we do see evidence both at baseline

NOTE Confidence: 0.917190518666667

00:38:15.691 --> 00:38:17.790 and with stimulation that there

NOTE Confidence: 0.917190518666667

00:38:17.790 --> 00:38:19.602 is increased enhanced oxidative

NOTE Confidence: 0.917190518666667

00:38:19.602 --> 00:38:22.126 stress which is supported by the

NOTE Confidence: 0.917190518666667

00:38:22.126 --> 00:38:24.352 fact that when we use the inhibitor,

NOTE Confidence: 0.917190518666667

00:38:24.360 --> 00:38:27.076 so that pro oxidant we actually see

NOTE Confidence: 0.917190518666667

00:38:27.076 --> 00:38:30.285 that the RPS 15 mice are more sensitive

NOTE Confidence: 0.917190518666667

00:38:30.285 --> 00:38:33.878 to this inhibitor than the wild type.

NOTE Confidence: 0.917190518666667

00:38:33.880 --> 00:38:35.560 Now because of the cellular stress,

NOTE Confidence: 0.917190518666667

00:38:35.560 --> 00:38:39.040 does this actually can this actually

NOTE Confidence: 0.917190518666667

00:38:39.040 --> 00:38:44.144 support acquisition of genotoxic injury?

NOTE Confidence: 0.917190518666667

00:38:44.144 --> 00:38:45.730 And in this case,

NOTE Confidence: 0.917190518666667

00:38:45.730 --> 00:38:48.300 we were able to use gamma H2 AX and

NOTE Confidence: 0.917190518666667

00:38:48.300 --> 00:38:50.421 we see in the homozygous mice that

NOTE Confidence: 0.917190518666667

00:38:50.421 --> 00:38:52.593 there is increase in gamma H2AX.

NOTE Confidence: 0.917190518666667

00:38:52.593 --> 00:38:55.158 And as we started to,

NOTE Confidence: 0.917190518666667

00:38:55.160 --> 00:38:56.636 there's a lot of westerns that

NOTE Confidence: 0.917190518666667

00:38:56.636 --> 00:38:57.880 I could have shown you.

NOTE Confidence: 0.917190518666667

00:38:57.880 --> 00:39:00.575 But suffice it to say that through

NOTE Confidence: 0.917190518666667

00:39:00.575 --> 00:39:02.679 examination of the mutant mice,

NOTE Confidence: 0.917190518666667

00:39:02.680 --> 00:39:04.948 we do see impaired cell cycle

NOTE Confidence: 0.917190518666667

00:39:04.948 --> 00:39:07.000 checkpoint response to DNA damage,

NOTE Confidence: 0.917190518666667

00:39:07.000 --> 00:39:08.431 impaired response signaling,

NOTE Confidence: 0.917190518666667

00:39:08.431 --> 00:39:11.293 abrogation of ATM and CHECK 2

NOTE Confidence: 0.917190518666667

00:39:11.293 --> 00:39:13.470 signaling and heightened intrinsic

NOTE Confidence: 0.917190518666667

00:39:13.470 --> 00:39:15.634 aberrant DNA damage response.

NOTE Confidence: 0.7715616

00:39:18.720 --> 00:39:22.472 And Despite that, there's also

NOTE Confidence: 0.7715616

00:39:22.472 --> 00:39:23.636 increased proliferation signaling.

NOTE Confidence: 0.7715616

00:39:23.640 --> 00:39:26.800 So one of our highest hits in

NOTE Confidence: 0.7715616

00:39:26.800 --> 00:39:28.360 our gene expression was ZAP 70,

NOTE Confidence: 0.7715616

00:39:28.360 --> 00:39:30.480 which has relevance to CLL.

NOTE Confidence: 0.7715616

00:39:30.480 --> 00:39:31.720 So we see that here.

NOTE Confidence: 0.7715616

00:39:31.720 --> 00:39:34.276 And there's also enhanced ABCR signaling.

NOTE Confidence: 0.7715616

00:39:34.280 --> 00:39:36.165 So definitely a balance between

NOTE Confidence: 0.7715616

00:39:36.165 --> 00:39:37.673 different forces at play.

NOTE Confidence: 0.7715616

00:39:37.680 --> 00:39:41.766 Going on, our next question was that is

NOTE Confidence: 0.7715616

00:39:41.766 --> 00:39:44.159 seeing these different sort of phenotypes,

NOTE Confidence: 0.7715616

00:39:44.160 --> 00:39:46.800 since this is a ribosomal protein,

NOTE Confidence: 0.7715616

00:39:46.800 --> 00:39:48.948 is there actually alteration?

NOTE Confidence: 0.7715616

00:39:48.948 --> 00:39:51.666 Is there effects of mutant

NOTE Confidence: 0.7715616

00:39:51.666 --> 00:39:53.878 RPS 15 on translation?

NOTE Confidence: 0.7715616

00:39:53.880 --> 00:39:56.610 And so we asked could RPS 15

NOTE Confidence: 0.7715616

00:39:56.610 --> 00:39:58.482 mutation cause ribosomes to

NOTE Confidence: 0.7715616

00:39:58.482 --> 00:40:00.958 preferentially translate certain genes?

NOTE Confidence: 0.7715616

00:40:00.960 --> 00:40:02.940 Could the mutation cause ribosomes

NOTE Confidence: 0.7715616

00:40:02.940 --> 00:40:05.512 for example to stall at specific

NOTE Confidence: 0.7715616

00:40:05.512 --> 00:40:07.554 protein coding sequence motifs

NOTE Confidence: 0.7715616

00:40:07.554 --> 00:40:09.542 interrupting translation of certain

NOTE Confidence: 0.7715616

00:40:09.542 --> 00:40:11.895 genes or could it read through

NOTE Confidence: 0.7715616

00:40:11.895 --> 00:40:14.321 stop codons and then result in

NOTE Confidence: 0.7715616

00:40:14.321 --> 00:40:16.317 misfolded and degraded proteins?

NOTE Confidence: 0.7715616

00:40:16.320 --> 00:40:18.822 And so for this we performed

NOTE Confidence: 0.7715616

00:40:18.822 --> 00:40:20.073 A ribosomal profiling.

NOTE Confidence: 0.7715616

00:40:20.080 --> 00:40:22.719 And when we started to look at

NOTE Confidence: 0.7715616

00:40:22.720 --> 00:40:24.876 whether or not there was evidence of

NOTE Confidence: 0.7715616

00:40:24.876 --> 00:40:25.800 differential translation efficiency,

NOTE Confidence: 0.7715616

00:40:25.800 --> 00:40:28.404 there were certainly many genes that

NOTE Confidence: 0.7715616

00:40:28.404 --> 00:40:32.330 were appeared to be have enhanced or

NOTE Confidence: 0.7715616

00:40:32.330 --> 00:40:33.680 depressed translational efficiency.

NOTE Confidence: 0.7715616

00:40:33.680 --> 00:40:37.276 And as we started to look at the

NOTE Confidence: 0.7715616

00:40:37.276 --> 00:40:38.916 pathways that were impacted,

NOTE Confidence: 0.7715616

00:40:38.920 --> 00:40:40.654 these included many of those pathways

NOTE Confidence: 0.7715616

00:40:40.654 --> 00:40:42.620 that I already talked to you about

NOTE Confidence: 0.7715616

00:40:42.620 --> 00:40:43.875 in the pre leukemic setting.

NOTE Confidence: 0.7715616

00:40:43.880 --> 00:40:45.320 So cell cycle, MC target,

NOTE Confidence: 0.7715616

00:40:45.320 --> 00:40:48.560 cell cycle checkpoints and DNA replication.

NOTE Confidence: 0.7715616

00:40:48.560 --> 00:40:50.702 And specific examples that we could

NOTE Confidence: 0.7715616

00:40:50.702 --> 00:40:53.448 see were genes that are have very well

NOTE Confidence: 0.7715616

00:40:53.448 --> 00:40:57.880 known roles in these different pathways.

NOTE Confidence: 0.7715616

00:40:57.880 --> 00:41:00.820 We were able to support this this

NOTE Confidence: 0.7715616

00:41:00.820 --> 00:41:03.160 kind of ribosome Riboseek analysis

NOTE Confidence: 0.7715616

00:41:03.160 --> 00:41:05.860 by looking at protein expression

NOTE Confidence: 0.7715616

00:41:05.860 --> 00:41:09.559 and we can confirm that what we saw

NOTE Confidence: 0.7715616

00:41:09.559 --> 00:41:11.796 as as having depressed translation.

NOTE Confidence: 0.7715616

00:41:11.796 --> 00:41:15.147 So the GPX one we could actually

NOTE Confidence: 0.7715616

00:41:15.147 --> 00:41:18.570 confirm at the protein level for

NOTE Confidence: 0.7715616

00:41:18.570 --> 00:41:24.172 GPX 1 and O2O2 four and increase

NOTE Confidence: 0.7715616

00:41:24.172 --> 00:41:27.600 expression in PTP 4A2.

NOTE Confidence: 0.7715616

00:41:27.600 --> 00:41:30.624 So that was actually very nice to see

NOTE Confidence: 0.7715616

00:41:30.624 --> 00:41:32.877 that linkages between translation and

NOTE Confidence: 0.7715616

00:41:32.877 --> 00:41:36.195 the the pathways that we were impacting.

NOTE Confidence: 0.7715616

00:41:36.200 --> 00:41:41.320 When we started to look at,

NOTE Confidence: 0.7715616

00:41:41.320 --> 00:41:44.491 we were also able to see evidence

NOTE Confidence: 0.7715616

00:41:44.491 --> 00:41:47.360 not only in a in a murine cells

NOTE Confidence: 0.7715616

00:41:47.360 --> 00:41:50.160 but also in a human cell line.

NOTE Confidence: 0.7715616

00:41:50.160 --> 00:41:53.716 We saw evidence of stop codon stalling.

NOTE Confidence: 0.7715616

00:41:53.720 --> 00:41:56.184 So you can see kind of a pile

NOTE Confidence: 0.7715616

00:41:56.184 --> 00:41:58.820 up here in terms of the relative

NOTE Confidence: 0.7715616

00:41:58.820 --> 00:42:00.840 position to the stop codon,

NOTE Confidence: 0.7715616

00:42:00.840 --> 00:42:03.168 but we also saw evidence of

NOTE Confidence: 0.7715616

00:42:03.168 --> 00:42:04.720 stop codon read through.

NOTE Confidence: 0.7715616

00:42:04.720 --> 00:42:08.716 And so we do see that there's enrichment of

NOTE Confidence: 0.7715616

00:42:08.716 --> 00:42:13.440 certain codons in that kind of stop site,

NOTE Confidence: 0.7715616

00:42:13.440 --> 00:42:15.640 suggesting that this is not a random process,

NOTE Confidence: 0.7715616

00:42:15.640 --> 00:42:17.485 but there's actually motifs that

NOTE Confidence: 0.7715616

00:42:17.485 --> 00:42:19.920 are kind of guiding this process.

NOTE Confidence: 0.7715616

00:42:19.920 --> 00:42:20.624 And finally,

NOTE Confidence: 0.7715616

00:42:20.624 --> 00:42:23.088 as we started to look at the

NOTE Confidence: 0.7715616

00:42:23.088 --> 00:42:24.080 leukemic B cells,

NOTE Confidence: 0.7715616

00:42:24.080 --> 00:42:28.200 we could see up regulation of Mick targets.

NOTE Confidence: 0.7715616

00:42:28.200 --> 00:42:29.800 And I'm going to just skip over this,

NOTE Confidence: 0.7715616

00:42:29.800 --> 00:42:31.354 but only to say that as we

NOTE Confidence: 0.7715616

00:42:31.354 --> 00:42:32.911 start to go through our model

NOTE Confidence: 0.7715616

00:42:32.911 --> 00:42:34.836 of what we think is going on,

NOTE Confidence: 0.7715616

00:42:34.840 --> 00:42:38.438 we do see that in this mutated

NOTE Confidence: 0.7715616

00:42:38.440 --> 00:42:40.785 ribosomal protein that there is

NOTE Confidence: 0.7715616

00:42:40.785 --> 00:42:42.661 evidence of altered translation

NOTE Confidence: 0.7715616

00:42:42.661 --> 00:42:44.809 through a couple of different

NOTE Confidence: 0.7715616

00:42:44.809 --> 00:42:46.824 mechanisms that these do initially

NOTE Confidence: 0.7715616

00:42:46.824 --> 00:42:48.679 lead to hypoproliferation.

NOTE Confidence: 0.7715616

00:42:48.680 --> 00:42:53.800 There is elevated ZAP 70 and BCR

NOTE Confidence: 0.7715616

00:42:53.800 --> 00:42:55.760 signaling as well as make activation.

NOTE Confidence: 0.7715616

00:42:55.760 --> 00:42:58.305 But in initially there's P53

NOTE Confidence: 0.7715616

00:42:58.305 --> 00:43:00.850 mediated apoptosis and cell cycle

NOTE Confidence: 0.83020986

00:43:00.938 --> 00:43:03.340 checkpoint changes that are leading

NOTE Confidence: 0.83020986

00:43:03.340 --> 00:43:04.920 to that hyper proliferation,

NOTE Confidence: 0.83020986

00:43:04.920 --> 00:43:06.870 but that over time there's acquisition

NOTE Confidence: 0.83020986

00:43:06.870 --> 00:43:08.857 of DNA damage and genomic instability

NOTE Confidence: 0.83020986

00:43:08.857 --> 00:43:11.361 that tip the balance and get us to

NOTE Confidence: 0.83020986

00:43:11.426 --> 00:43:12.960 the state of hyper proliferation.

NOTE Confidence: 0.83020986

00:43:12.960 --> 00:43:15.760 So just to conclude this part of the talk,

NOTE Confidence: 0.83020986

00:43:15.760 --> 00:43:19.324 I'll just say that again our our new

NOTE Confidence: 0.83020986

00:43:19.324 --> 00:43:21.610 work suggests that RPS 15 mutation

NOTE Confidence: 0.83020986

00:43:21.687 --> 00:43:23.973 is ACL driver and reinforces the

NOTE Confidence: 0.83020986

00:43:23.973 --> 00:43:26.501 notion that CLL has these core

NOTE Confidence: 0.83020986

00:43:26.501 --> 00:43:28.357 pathways that are affected.

NOTE Confidence: 0.83020986

00:43:28.360 --> 00:43:30.436 So I didn't go into this,

NOTE Confidence: 0.83020986

00:43:30.440 --> 00:43:33.608 but across our different mouse models

NOTE Confidence: 0.83020986

00:43:33.608 --> 00:43:36.853 we are seeing common pathways through

NOTE Confidence: 0.83020986

00:43:36.853 --> 00:43:40.159 different mechanisms that appear to be

NOTE Confidence: 0.83020986

00:43:40.160 --> 00:43:43.680 involved and current ongoing work is

NOTE Confidence: 0.83020986

00:43:43.680 --> 00:43:46.015 starting to look at the immune micro

NOTE Confidence: 0.83020986

00:43:46.015 --> 00:43:48.346 environment so that we can start to

NOTE Confidence: 0.83020986

00:43:48.346 --> 00:43:52.254 link the genotype with whether or not

NOTE Confidence: 0.83020986

00:43:52.254 --> 00:43:53.544 they're related to distinct changes

NOTE Confidence: 0.83020986

00:43:53.544 --> 00:43:55.238 in the immune micro environment.

NOTE Confidence: 0.935381125

00:43:57.720 --> 00:43:59.368 In the final slides,

NOTE Confidence: 0.935381125

00:43:59.368 --> 00:44:02.671 I just want to say that you know I

NOTE Confidence: 0.935381125

00:44:02.671 --> 00:44:04.333 think that where we're going next

NOTE Confidence: 0.935381125

00:44:04.333 --> 00:44:06.319 in sort of sort of our studies,

NOTE Confidence: 0.935381125

00:44:06.320 --> 00:44:08.579 a lot of the CLO work until now I

NOTE Confidence: 0.935381125

00:44:08.579 --> 00:44:10.956 think across the field has been really

NOTE Confidence: 0.935381125

00:44:10.960 --> 00:44:13.756 focused on the blood easy access,

NOTE Confidence: 0.935381125

00:44:13.760 --> 00:44:14.988 lots of tumor there.

NOTE Confidence: 0.935381125

00:44:14.988 --> 00:44:16.830 But I think increasingly we do

NOTE Confidence: 0.935381125

00:44:16.892 --> 00:44:18.878 need to look at these specialized

NOTE Confidence: 0.935381125

00:44:18.880 --> 00:44:21.495 hematolymphoid organs where there is

NOTE Confidence: 0.935381125

00:44:21.495 --> 00:44:23.587 a specialized immune microenvironment

NOTE Confidence: 0.935381125

00:44:23.587 --> 00:44:25.839 that we can understand better.

NOTE Confidence: 0.935381125

00:44:25.840 --> 00:44:27.160 I think that there is a

NOTE Confidence: 0.864112503

00:44:29.200 --> 00:44:30.760 priority and interest in trying

NOTE Confidence: 0.864112503

00:44:30.760 --> 00:44:32.320 to go earlier in disease.

NOTE Confidence: 0.864112503

00:44:32.320 --> 00:44:35.560 So how can we understand those early events?

NOTE Confidence: 0.864112503

00:44:35.560 --> 00:44:37.880 How can we intervene early?

NOTE Confidence: 0.864112503

00:44:37.880 --> 00:44:39.920 How can we change Natural History?

NOTE Confidence: 0.864112503

00:44:39.920 --> 00:44:41.838 We're only going to get there by

NOTE Confidence: 0.864112503

00:44:41.840 --> 00:44:44.976 understanding a little bit more about this

NOTE Confidence: 0.864112503

00:44:44.976 --> 00:44:47.324 earlier time Multiomic profiling for sure.

NOTE Confidence: 0.864112503

00:44:47.324 --> 00:44:50.111 There's so much data out there and how

NOTE Confidence: 0.864112503

00:44:50.111 --> 00:44:52.327 can we link them all together and kind

NOTE Confidence: 0.864112503

00:44:52.390 --> 00:44:54.679 of not have them as separate entities,

NOTE Confidence: 0.864112503

00:44:54.680 --> 00:44:57.350 but really trying to coalesce

NOTE Confidence: 0.864112503

00:44:57.350 --> 00:45:00.636 into kind of archetypes that we

NOTE Confidence: 0.864112503

00:45:00.636 --> 00:45:02.562 can understand spatial analysis.

NOTE Confidence: 0.864112503

00:45:02.562 --> 00:45:05.208 So our group is actively working

NOTE Confidence: 0.864112503

00:45:05.208 --> 00:45:08.301 on efforts to try to look at the

NOTE Confidence: 0.864112503

00:45:08.301 --> 00:45:10.155 architecture of lymph nodes and

NOTE Confidence: 0.864112503

00:45:10.155 --> 00:45:14.068 bone marrow to see how malignant

NOTE Confidence: 0.864112503

00:45:14.068 --> 00:45:16.636 cells are organized and also in

NOTE Confidence: 0.864112503

00:45:16.636 --> 00:45:18.600 relationship to their genotype.

NOTE Confidence: 0.864112503

00:45:18.600 --> 00:45:22.104 So their mutations and do specific

NOTE Confidence: 0.864112503

00:45:22.104 --> 00:45:25.240 clones segregate with specific types

NOTE Confidence: 0.864112503

00:45:25.240 --> 00:45:29.490 of niches and and are they organized

NOTE Confidence: 0.864112503

00:45:29.490 --> 00:45:31.240 in certain type of neighborhoods.

NOTE Confidence: 0.864112503

00:45:31.240 --> 00:45:33.120 And finally I I touched upon with our

NOTE Confidence: 0.864112503

00:45:33.120 --> 00:45:35.113 self free DNA work some of the early

NOTE Confidence: 0.864112503

00:45:35.113 --> 00:45:37.121 detection I'm going to end with the

NOTE Confidence: 0.864112503

00:45:37.121 --> 00:45:39.071 last couple slides speaking about early

NOTE Confidence: 0.864112503

00:45:39.071 --> 00:45:41.280 intervention we hope in the future.

NOTE Confidence: 0.864112503

00:45:41.280 --> 00:45:43.688 But another big part of the work

NOTE Confidence: 0.864112503

00:45:43.688 --> 00:45:46.514 that my group does is think about

NOTE Confidence: 0.864112503

00:45:46.514 --> 00:45:47.798 cancer neo antigens.

NOTE Confidence: 0.864112503

00:45:47.800 --> 00:45:51.076 And from all the genomic studies

NOTE Confidence: 0.864112503

00:45:51.080 --> 00:45:52.632 that we've been doing,

NOTE Confidence: 0.864112503

00:45:52.632 --> 00:45:54.572 we've realized that there there

NOTE Confidence: 0.864112503

00:45:54.572 --> 00:45:56.805 is the opportunity for these

NOTE Confidence: 0.864112503

00:45:56.805 --> 00:45:59.020 mutations to generate epitopes that

NOTE Confidence: 0.864112503

00:45:59.020 --> 00:46:01.440 can be recognized by by T cells.

NOTE Confidence: 0.864112503

00:46:01.440 --> 00:46:03.800 I'm not going to go into this in

NOTE Confidence: 0.864112503

00:46:03.800 --> 00:46:06.038 great length only to say that there's

NOTE Confidence: 0.864112503

00:46:06.040 --> 00:46:07.400 straightforward algorithms by now

NOTE Confidence: 0.864112503

00:46:07.400 --> 00:46:10.170 that allow us to take start with the

NOTE Confidence: 0.864112503

00:46:10.170 --> 00:46:12.856 sequencing data and identify for us

NOTE Confidence: 0.864112503

00:46:12.856 --> 00:46:15.880 what those new antigens might be.

NOTE Confidence: 0.864112503

00:46:15.880 --> 00:46:17.995 I want to say that some of our earliest

NOTE Confidence: 0.864112503

00:46:17.995 --> 00:46:19.794 work in the new antigen field and

NOTE Confidence: 0.864112503

00:46:19.794 --> 00:46:21.413 kind of setting up these pipelines

NOTE Confidence: 0.864112503

00:46:21.413 --> 00:46:23.359 were in CLL because that is where

NOTE Confidence: 0.864112503

00:46:23.359 --> 00:46:28.200 we had the data and all the tools to

NOTE Confidence: 0.864112503

00:46:28.200 --> 00:46:31.380 help us construct some of the these

NOTE Confidence: 0.864112503

00:46:31.380 --> 00:46:33.120 first pipelines that were available.

NOTE Confidence: 0.864112503

00:46:33.120 --> 00:46:37.504 And certainly our vaccine neo antigen

NOTE Confidence: 0.864112503

00:46:37.504 --> 00:46:40.671 work that Doctor Weiner alluded to has

NOTE Confidence: 0.864112503

00:46:40.671 --> 00:46:44.119 taken our group very far afield from CLL.

NOTE Confidence: 0.864112503

00:46:44.120 --> 00:46:46.528 We've gone into the solid tumors and

NOTE Confidence: 0.864112503

00:46:46.528 --> 00:46:48.792 we've been able to conduct some early
NOTE Confidence: 0.864112503
00:46:48.792 --> 00:46:50.856 proof of concept studies that such
NOTE Confidence: 0.864112503
00:46:50.856 --> 00:46:53.329 an approach of starting with tumor
NOTE Confidence: 0.864112503
00:46:53.329 --> 00:46:55.389 looking for genomic alterations and
NOTE Confidence: 0.864112503
00:46:55.455 --> 00:46:58.035 generating a personal vaccine is feasible.
NOTE Confidence: 0.864112503
00:46:58.040 --> 00:47:00.032 But I've always been super interested
NOTE Confidence: 0.864112503
00:47:00.032 --> 00:47:02.320 in trying to bring it back to CLL.
NOTE Confidence: 0.864112503
00:47:02.320 --> 00:47:04.368 And so I'm happy to say that right
NOTE Confidence: 0.864112503
00:47:04.368 --> 00:47:07.800 now we have a phase one study for
NOTE Confidence: 0.864112503
00:47:07.800 --> 00:47:11.190 patients with unmutated IGHV led by
NOTE Confidence: 0.864112503
00:47:11.190 --> 00:47:14.375 ine on and supported by Matt Davids
NOTE Confidence: 0.864112503
00:47:14.375 --> 00:47:17.745 and Jennifer Brown to study and
NOTE Confidence: 0.864112503
00:47:17.745 --> 00:47:21.070 look at the impact of this vaccine
NOTE Confidence: 0.864112503
00:47:21.174 --> 00:47:23.585 alone vaccine together with low dose
NOTE Confidence: 0.864112503
00:47:23.585 --> 00:47:26.305 cyclophosphamide as a way to kind of
NOTE Confidence: 0.864112503
00:47:26.305 --> 00:47:28.170 alter the immune micro environment

NOTE Confidence: 0.864112503

00:47:28.170 --> 00:47:30.048 and maybe address T regs.

NOTE Confidence: 0.864112503

00:47:30.048 --> 00:47:33.400 And then also a third cohort to actually

NOTE Confidence: 0.864112503

00:47:33.400 --> 00:47:37.040 add immune checkpoint blockade together and

NOTE Confidence: 0.839589959130435

00:47:39.480 --> 00:47:41.692 we already have enrolled in a number

NOTE Confidence: 0.839589959130435

00:47:41.692 --> 00:47:44.060 the first three patients we're already

NOTE Confidence: 0.839589959130435

00:47:44.060 --> 00:47:45.860 seeing interesting immune responses

NOTE Confidence: 0.839589959130435

00:47:45.860 --> 00:47:48.558 compared to our solid tumor settings.

NOTE Confidence: 0.839589959130435

00:47:48.560 --> 00:47:50.410 These are patients who actively

NOTE Confidence: 0.839589959130435

00:47:50.410 --> 00:47:51.520 have circulating disease.

NOTE Confidence: 0.839589959130435

00:47:51.520 --> 00:47:54.968 So is it possible to even vaccinate and

NOTE Confidence: 0.839589959130435

00:47:54.968 --> 00:47:57.518 generate meaningful responses when there's

NOTE Confidence: 0.839589959130435

00:47:57.520 --> 00:48:00.000 leukemia that's that's in circulation?

NOTE Confidence: 0.839589959130435

00:48:00.000 --> 00:48:01.400 And the the short answer,

NOTE Confidence: 0.839589959130435

00:48:01.400 --> 00:48:02.392 it seems like yes.

NOTE Confidence: 0.839589959130435

00:48:02.392 --> 00:48:04.256 So we're we we are actually seeing

NOTE Confidence: 0.839589959130435

00:48:04.256 --> 00:48:05.846 very nice brisk immune responses

NOTE Confidence: 0.839589959130435

00:48:05.846 --> 00:48:07.880 to actually some of our patients.

NOTE Confidence: 0.839589959130435

00:48:07.880 --> 00:48:10.162 So I hope you stay tuned and

NOTE Confidence: 0.839589959130435

00:48:10.162 --> 00:48:12.092 hopefully we'll have more to say

NOTE Confidence: 0.839589959130435

00:48:12.092 --> 00:48:14.000 about that in the time to come.

NOTE Confidence: 0.839589959130435

00:48:14.000 --> 00:48:15.620 I've tried to acknowledge

NOTE Confidence: 0.839589959130435

00:48:15.620 --> 00:48:17.240 folks along the way,

NOTE Confidence: 0.839589959130435

00:48:17.240 --> 00:48:19.760 but here's a more extensive

NOTE Confidence: 0.839589959130435

00:48:19.760 --> 00:48:22.280 list and I really appreciate

NOTE Confidence: 0.839589959130435

00:48:22.378 --> 00:48:24.400 your attention and thank you.

NOTE Confidence: 0.925431816666667

00:48:32.500 --> 00:48:34.576 Yes. So how do you think

NOTE Confidence: 0.832267378333333

00:48:34.620 --> 00:48:36.498 about driver mutations,

NOTE Confidence: 0.832267378333333

00:48:36.498 --> 00:48:38.376 specific driver mutations

NOTE Confidence: 0.832267378333333

00:48:38.380 --> 00:48:41.140 related to transformation,

NOTE Confidence: 0.832267378333333

00:48:41.140 --> 00:48:44.060 related to potential for

NOTE Confidence: 0.68811598

00:48:47.760 --> 00:48:49.252 these differentiation B cells

NOTE Confidence: 0.68811598

00:48:49.252 --> 00:48:51.117 leading to the clinical outcome?

NOTE Confidence: 0.68811598

00:48:51.120 --> 00:48:53.250 You listed a whole list of

NOTE Confidence: 0.68811598

00:48:53.250 --> 00:48:54.315 potential driver mutations.

NOTE Confidence: 0.68811598

00:48:54.320 --> 00:48:56.336 It's not clearly what the individual

NOTE Confidence: 0.68811598

00:48:56.336 --> 00:48:57.680 driver mutations are doing.

NOTE Confidence: 0.68811598

00:48:57.680 --> 00:48:59.018 And how you think about getting

NOTE Confidence: 0.68811598

00:48:59.018 --> 00:49:00.360 the answer to that question,

NOTE Confidence: 0.68811598

00:49:00.360 --> 00:49:01.560 if it is an important question,

NOTE Confidence: 0.831612027272727

00:49:03.760 --> 00:49:05.026 yeah, no, I think I skipped

NOTE Confidence: 0.831612027272727

00:49:05.026 --> 00:49:06.240 over a lot of stuff.

NOTE Confidence: 0.831612027272727

00:49:06.240 --> 00:49:08.427 And so I think one of the things that

NOTE Confidence: 0.831612027272727

00:49:08.427 --> 00:49:10.747 we can do when we have these driver

NOTE Confidence: 0.831612027272727

00:49:10.747 --> 00:49:13.944 lists because we can see whether they

NOTE Confidence: 0.831612027272727

00:49:13.944 --> 00:49:15.880 segregate into particular pathways.

NOTE Confidence: 0.831612027272727

00:49:15.880 --> 00:49:19.640 And by virtue of kind of separating

NOTE Confidence: 0.831612027272727

00:49:19.640 --> 00:49:22.240 out the CLL versus Richter clones,

NOTE Confidence: 0.831612027272727

00:49:22.240 --> 00:49:24.608 we were able to kind of identify which

NOTE Confidence: 0.831612027272727

00:49:24.608 --> 00:49:26.719 of those drivers seem to be CLL,

NOTE Confidence: 0.831612027272727

00:49:26.720 --> 00:49:29.555 which were Richter's and which were which

NOTE Confidence: 0.831612027272727

00:49:29.555 --> 00:49:33.680 were in a path on the way to transformation.

NOTE Confidence: 0.831612027272727

00:49:33.680 --> 00:49:38.384 And so some of those pathways that

NOTE Confidence: 0.831612027272727

00:49:38.384 --> 00:49:43.520 we see affected are related to Mick,

NOTE Confidence: 0.831612027272727

00:49:43.520 --> 00:49:47.280 for example, they're related to cell cycles.

NOTE Confidence: 0.831612027272727

00:49:47.280 --> 00:49:50.196 So this it's not a surprise,

NOTE Confidence: 0.831612027272727

00:49:50.200 --> 00:49:54.155 but it and metabolic rewiring as well.

NOTE Confidence: 0.831612027272727

00:49:54.160 --> 00:49:57.400 So there's many.

NOTE Confidence: 0.831612027272727

00:49:57.400 --> 00:50:00.970 So I think the drivers do help us think

NOTE Confidence: 0.831612027272727

00:50:00.970 --> 00:50:03.720 about the biology of what is going on,

NOTE Confidence: 0.831612027272727

00:50:03.720 --> 00:50:06.820 but I think that I hope that we can also

NOTE Confidence: 0.831612027272727

00:50:06.900 --> 00:50:11.120 use them as ways to for early detection.

NOTE Confidence: 0.831612027272727

00:50:11.120 --> 00:50:12.520 I don't know if this is answers

NOTE Confidence: 0.831612027272727

00:50:12.520 --> 00:50:12.920 your question,

NOTE Confidence: 0.831612027272727

00:50:12.920 --> 00:50:13.160 but

NOTE Confidence: 0.48386598

00:50:15.200 --> 00:50:16.960 yeah, I don't want the questions online,

NOTE Confidence: 0.887721206666667

00:50:16.960 --> 00:50:19.360 but what what do you think about the

NOTE Confidence: 0.887721206666667

00:50:19.360 --> 00:50:23.220 role of RGS 15 in normal CD5B cells?

NOTE Confidence: 0.887721206666667

00:50:23.220 --> 00:50:25.280 So it's there, yes.

NOTE Confidence: 0.887721206666667

00:50:25.280 --> 00:50:27.583 So the question is what is its

NOTE Confidence: 0.887721206666667

00:50:27.583 --> 00:50:29.279 function in thinking about what

NOTE Confidence: 0.887721206666667

00:50:29.280 --> 00:50:32.121 CD5B cells are doing in terms of

NOTE Confidence: 0.887721206666667

00:50:32.121 --> 00:50:33.189 maintenance and tolerance for

NOTE Confidence: 0.887721206666667

00:50:33.189 --> 00:50:34.631 example and their potential product

NOTE Confidence: 0.887721206666667

00:50:34.631 --> 00:50:36.116 activity and where they are,

NOTE Confidence: 0.911263191428571

00:50:36.320 --> 00:50:38.315 right. So we haven't looked into that.

NOTE Confidence: 0.911263191428571

00:50:38.320 --> 00:50:43.600 I mean I think we we have the tools and

NOTE Confidence: 0.911263191428571

00:50:43.600 --> 00:50:47.298 so we've we've really been focused on the,

NOTE Confidence: 0.911263191428571

00:50:47.298 --> 00:50:48.825 the mutant setting. Yeah.

NOTE Confidence: 0.911263191428571

00:50:48.825 --> 00:50:53.080 But I I think it's a really interesting

NOTE Confidence: 0.911263191428571

00:50:53.080 --> 00:50:57.960 question and I think that it would

NOTE Confidence: 0.911263191428571

00:50:57.960 --> 00:50:59.795 be a separate question where it

NOTE Confidence: 0.911263191428571

00:50:59.795 --> 00:51:01.839 could be like all of these different

NOTE Confidence: 0.803011412

00:51:04.160 --> 00:51:06.560 mutations that we're finding. Yes.

NOTE Confidence: 0.803011412

00:51:06.560 --> 00:51:08.480 Yes the the genes and and what are

NOTE Confidence: 0.803011412

00:51:08.480 --> 00:51:09.960 their roles in in normal business.

NOTE Confidence: 0.34478727

00:51:12.320 --> 00:51:14.754 I think I I I think you are

NOTE Confidence: 0.34478727

00:51:14.754 --> 00:51:17.320 absolutely correct. Yeah. Yes.

NOTE Confidence: 0.34478727

00:51:17.920 --> 00:51:21.210 Yeah I'm I'm getting discredited I think

NOTE Confidence: 0.34478727

00:51:21.210 --> 00:51:23.586 you said that the unmutated CLLS have

NOTE Confidence: 0.34478727

00:51:23.586 --> 00:51:25.637 a re urgent headed with the nursery

NOTE Confidence: 0.775221385555556

00:51:26.680 --> 00:51:30.624 so yeah so the quest so the unmutated

NOTE Confidence: 0.775221385555556

00:51:30.624 --> 00:51:34.444 has there are there's a far longer

NOTE Confidence: 0.775221385555556

00:51:34.444 --> 00:51:38.000 list of mutated drivers in unmutated

NOTE Confidence: 0.794600371111111

00:51:39.080 --> 00:51:41.816 CLLI see. So I guess the question then

NOTE Confidence: 0.794600371111111

00:51:41.816 --> 00:51:44.638 is do you think that the mechanism

NOTE Confidence: 0.794600371111111

00:51:44.638 --> 00:51:48.110 that's leading to the mutations of the

NOTE Confidence: 0.794600371111111

00:51:48.110 --> 00:51:51.512 IGH locus is unrelated to the genetic

NOTE Confidence: 0.794600371111111

00:51:51.512 --> 00:51:53.696 diversity that we're getting or is there

NOTE Confidence: 0.794600371111111

00:51:53.696 --> 00:51:55.720 a relations to them and how does that I

NOTE Confidence: 0.841131801428571

00:51:55.720 --> 00:51:57.078 I I think that's a great question.

NOTE Confidence: 0.841131801428571

00:51:57.080 --> 00:51:58.920 So the the question is whether or not

NOTE Confidence: 0.848722992

00:52:00.960 --> 00:52:06.640 how the immunoglobulin mutational status

NOTE Confidence: 0.848722992

00:52:06.640 --> 00:52:10.518 relates to kind of the genetic diversity.

NOTE Confidence: 0.848722992

00:52:10.520 --> 00:52:13.160 So. So yeah, it's been understood

NOTE Confidence: 0.848722992

00:52:13.160 --> 00:52:16.926 that whether or not the CL LS have a

NOTE Confidence: 0.848722992

00:52:16.926 --> 00:52:18.645 mutated or unmutated immunoglobulin

NOTE Confidence: 0.848722992

00:52:18.645 --> 00:52:22.035 relates to their cell of origin,

NOTE Confidence: 0.848722992

00:52:22.040 --> 00:52:25.152 kind of where are they in kind of B

NOTE Confidence: 0.848722992

00:52:25.152 --> 00:52:27.540 cell development and and whether or

NOTE Confidence: 0.848722992

00:52:27.628 --> 00:52:30.114 not those kind of normal physiological

NOTE Confidence: 0.848722992

00:52:30.114 --> 00:52:32.799 mutational processes are are present.

NOTE Confidence: 0.848722992

00:52:32.800 --> 00:52:36.352 So I think it does speak to the

NOTE Confidence: 0.848722992

00:52:36.352 --> 00:52:39.064 underlying biology of that cell

NOTE Confidence: 0.848722992

00:52:39.064 --> 00:52:42.220 of origin and probably it helps us

NOTE Confidence: 0.848722992

00:52:42.220 --> 00:52:44.716 understand why there there could be

NOTE Confidence: 0.848722992

00:52:44.716 --> 00:52:50.400 more mutations in in these different

NOTE Confidence: 0.848722992

00:52:50.400 --> 00:52:53.960 genes compared to the unmutated.

NOTE Confidence: 0.848722992

00:52:53.960 --> 00:52:55.280 So that that that would be a way

NOTE Confidence: 0.848722992

00:52:55.280 --> 00:52:56.160 to put it together.

NOTE Confidence: 0.504185542

00:52:59.200 --> 00:53:02.760 I have some questions. OK, yes.

NOTE Confidence: 0.504185542

00:53:02.760 --> 00:53:06.217 So Marcus Bosenberg asks are

NOTE Confidence: 0.504185542

00:53:06.217 --> 00:53:08.302 there any recurrent genetic or

NOTE Confidence: 0.504185542

00:53:08.302 --> 00:53:10.639 epigenetic changes in CLL arising

NOTE Confidence: 0.504185542

00:53:10.639 --> 00:53:13.600 at later time points in RPS 15?

NOTE Confidence: 0.873417537

00:53:15.720 --> 00:53:18.008 Marcus, hello, great question.

NOTE Confidence: 0.873417537

00:53:18.008 --> 00:53:21.440 We haven't actually looked at that.

NOTE Confidence: 0.873417537

00:53:21.440 --> 00:53:23.442 I think that's a great question and

NOTE Confidence: 0.873417537

00:53:23.442 --> 00:53:25.024 and probably something I should take

NOTE Confidence: 0.873417537

00:53:25.024 --> 00:53:26.880 back to the group and we should look,

NOTE Confidence: 0.873417537

00:53:26.880 --> 00:53:28.088 but we we haven't,

NOTE Confidence: 0.873417537

00:53:28.088 --> 00:53:29.598 we haven't looked at that.

NOTE Confidence: 0.873417537

00:53:29.600 --> 00:53:30.560 So thank you.

NOTE Confidence: 0.873190474285714

00:53:35.440 --> 00:53:36.811 One last question,

NOTE Confidence: 0.873190474285714

00:53:36.811 --> 00:53:38.639 there's George Miller asks,

NOTE Confidence: 0.873190474285714

00:53:38.640 --> 00:53:41.560 can you comment on the role of Epstein

NOTE Confidence: 0.873190474285714

00:53:41.560 --> 00:53:44.076 Barr virus in conversion of CLL to

NOTE Confidence: 0.6933937

00:53:46.520 --> 00:53:46.680 PLVCL?

NOTE Confidence: 0.72661042

00:53:50.960 --> 00:53:54.170 I really can't maybe yes,

NOTE Confidence: 0.72661042

00:53:54.170 --> 00:53:55.640 we we have not looked at that.

NOTE Confidence: 0.72661042

00:53:55.640 --> 00:53:58.680 It's a great question and certainly

NOTE Confidence: 0.709254776666667

00:54:01.640 --> 00:54:05.748 EBB does is does play a role in

NOTE Confidence: 0.709254776666667

00:54:05.748 --> 00:54:08.318 immortalization of B cell lines.

NOTE Confidence: 0.709254776666667

00:54:08.320 --> 00:54:10.917 But but I I don't have much

NOTE Confidence: 0.709254776666667

00:54:10.920 --> 00:54:12.884 deep thoughts about that.

NOTE Confidence: 0.709254776666667

00:54:12.884 --> 00:54:14.840 So my regrets. Thank you.

NOTE Confidence: 0.709254776666667

00:54:14.840 --> 00:54:16.838 Well, thank you very much for

NOTE Confidence: 0.709254776666667

00:54:16.840 --> 00:54:20.000 visiting us. Yes, thank you.