

WEBVTT

NOTE duration:"01:03:30.8800000"

NOTE recognizability:0.826

NOTE language:en-us

NOTE Confidence: 0.89328481

00:00:00.000 --> 00:00:00.768 Good morning everybody.

NOTE Confidence: 0.89328481

00:00:00.768 --> 00:00:02.560 It's so nice to see everybody here.

NOTE Confidence: 0.89328481

00:00:02.560 --> 00:00:03.856 So let's get started.

NOTE Confidence: 0.89328481

00:00:03.856 --> 00:00:05.800 So this is a special occasion

NOTE Confidence: 0.89328481

00:00:05.870 --> 00:00:07.875 and actually nobody better than

NOTE Confidence: 0.89328481

00:00:07.875 --> 00:00:09.880 Doctor Armstrong to present the

NOTE Confidence: 0.89328481

00:00:09.880 --> 00:00:12.238 Lecturer in honour of Lance Tallman.

NOTE Confidence: 0.89328481

00:00:12.240 --> 00:00:14.540 So this series was established

NOTE Confidence: 0.89328481

00:00:14.540 --> 00:00:17.320 in 2012 by Doctor Marvin Sears.

NOTE Confidence: 0.89328481

00:00:17.320 --> 00:00:19.231 Dr. Sears was a long time chair

NOTE Confidence: 0.89328481

00:00:19.231 --> 00:00:20.890 and founder of the Ophthalmology

NOTE Confidence: 0.89328481

00:00:20.890 --> 00:00:22.840 and Visual Sciences at Yale,

NOTE Confidence: 0.89328481

00:00:22.840 --> 00:00:24.465 and he established this lecture

NOTE Confidence: 0.89328481

00:00:24.465 --> 00:00:26.560 series series in honour of his mother,
NOTE Confidence: 0.89328481

00:00:26.560 --> 00:00:27.120 Lance Tallman,
NOTE Confidence: 0.89328481

00:00:27.120 --> 00:00:29.240 who passed away from leukemia.
NOTE Confidence: 0.89328481

00:00:29.240 --> 00:00:31.320 And it really was the first lecture series
NOTE Confidence: 0.89328481

00:00:31.320 --> 00:00:33.118 dedicated solely to hematologic malignancies.
NOTE Confidence: 0.89328481

00:00:33.120 --> 00:00:35.136 So hematologists are always
NOTE Confidence: 0.89328481

00:00:35.136 --> 00:00:37.272 delighted and it's really intended
NOTE Confidence: 0.89328481

00:00:37.272 --> 00:00:39.312 to bring to Yale pioneers,
NOTE Confidence: 0.89328481

00:00:39.320 --> 00:00:40.272 you know,
NOTE Confidence: 0.89328481

00:00:40.272 --> 00:00:42.652 who study malignant hematologic diseases
NOTE Confidence: 0.89328481

00:00:42.652 --> 00:00:45.560 and then bring treatments to the patient.
NOTE Confidence: 0.89328481

00:00:45.560 --> 00:00:48.244 There's actually nobody better than to give
NOTE Confidence: 0.89328481

00:00:48.244 --> 00:00:50.638 today's lecture than Doctor Scott Armstrong.
NOTE Confidence: 0.89328481

00:00:50.640 --> 00:00:52.140 Doctor Armstrong is the
NOTE Confidence: 0.89328481

00:00:52.140 --> 00:00:53.640 President of Dana Farber,
NOTE Confidence: 0.89328481

00:00:53.640 --> 00:00:56.325 Boston Children's Cancer and Blood

NOTE Confidence: 0.89328481

00:00:56.325 --> 00:00:58.692 Disorder Center and the Chairman of

NOTE Confidence: 0.89328481

00:00:58.692 --> 00:01:00.307 the Department of Pediatric Oncology

NOTE Confidence: 0.89328481

00:01:00.307 --> 00:01:02.278 at Dana Farber Cancer Institute.

NOTE Confidence: 0.89328481

00:01:02.280 --> 00:01:04.920 And since 2016,

NOTE Confidence: 0.89328481

00:01:04.920 --> 00:01:07.048 he serves as the Associate Chief of

NOTE Confidence: 0.89328481

00:01:07.048 --> 00:01:08.960 the Division of Hematology Oncology

NOTE Confidence: 0.89328481

00:01:08.960 --> 00:01:11.307 at Boston Children's Hospital and

NOTE Confidence: 0.89328481

00:01:11.307 --> 00:01:13.389 was previously the Director of the

NOTE Confidence: 0.89328481

00:01:13.389 --> 00:01:15.295 Center for Abidinex Research at

NOTE Confidence: 0.89328481

00:01:15.295 --> 00:01:16.899 Memorial Sloan Kettering Cancer

NOTE Confidence: 0.89328481

00:01:16.899 --> 00:01:19.004 Center and Professor of Pediatrics

NOTE Confidence: 0.89328481

00:01:19.004 --> 00:01:21.199 at Weill Cornell Medical College.

NOTE Confidence: 0.89328481

00:01:21.200 --> 00:01:22.908 I'm not going to go back to

NOTE Confidence: 0.89328481

00:01:22.908 --> 00:01:24.159 medical degrees and all this,

NOTE Confidence: 0.89328481

00:01:24.160 --> 00:01:25.198 so good to have you here.

NOTE Confidence: 0.89328481

00:01:25.200 --> 00:01:28.353 So Roger Armstrong really has you know

NOTE Confidence: 0.89328481

00:01:28.353 --> 00:01:32.518 pioneered research in in epigenetics

NOTE Confidence: 0.89328481

00:01:32.520 --> 00:01:34.184 and studying pediatric cancers,

NOTE Confidence: 0.89328481

00:01:34.184 --> 00:01:34.600 right.

NOTE Confidence: 0.89328481

00:01:34.600 --> 00:01:36.646 And we always learn that studying

NOTE Confidence: 0.89328481

00:01:36.646 --> 00:01:38.914 cancer for example in Pediatrics can

NOTE Confidence: 0.89328481

00:01:38.914 --> 00:01:40.598 then really enlightened mechanism

NOTE Confidence: 0.89328481

00:01:40.598 --> 00:01:43.280 of disease also for adult patients.

NOTE Confidence: 0.89328481

00:01:43.280 --> 00:01:44.400 And I think it's super,

NOTE Confidence: 0.89328481

00:01:44.400 --> 00:01:46.338 super exciting to hear your talk

NOTE Confidence: 0.89328481

00:01:46.338 --> 00:01:47.945 today really bringing basic mechanism

NOTE Confidence: 0.89328481

00:01:47.945 --> 00:01:50.009 all the way from the lab to benefit

NOTE Confidence: 0.89328481

00:01:50.009 --> 00:01:52.170 so many of our patients and we're

NOTE Confidence: 0.89328481

00:01:52.170 --> 00:01:53.720 incredibly excited to have you here.

NOTE Confidence: 0.843636681764706

00:02:00.520 --> 00:02:02.380 Thank you for the nice introduction

NOTE Confidence: 0.843636681764706

00:02:02.380 --> 00:02:04.447 and and for the lectureship and

NOTE Confidence: 0.843636681764706
00:02:04.447 --> 00:02:06.357 the plaque that's very nice.
NOTE Confidence: 0.843636681764706
00:02:06.360 --> 00:02:07.716 And thank you for coming today.
NOTE Confidence: 0.843636681764706
00:02:07.720 --> 00:02:08.850 It's not the most beautiful
NOTE Confidence: 0.843636681764706
00:02:08.850 --> 00:02:10.360 day to be out walking around.
NOTE Confidence: 0.843636681764706
00:02:10.360 --> 00:02:13.120 So I appreciate you you making it here.
NOTE Confidence: 0.843636681764706
00:02:13.120 --> 00:02:14.652 And as Stephanie said,
NOTE Confidence: 0.843636681764706
00:02:14.652 --> 00:02:17.467 I'm going to talk to you today
NOTE Confidence: 0.843636681764706
00:02:17.467 --> 00:02:20.023 about work we've been doing over
NOTE Confidence: 0.843636681764706
00:02:20.023 --> 00:02:23.332 the past couple of decades now
NOTE Confidence: 0.843636681764706
00:02:23.332 --> 00:02:25.838 focused on originally a relatively
NOTE Confidence: 0.843636681764706
00:02:25.838 --> 00:02:28.394 rare subset of leukemia and then
NOTE Confidence: 0.843636681764706
00:02:28.394 --> 00:02:30.663 move to more common leukemias
NOTE Confidence: 0.843636681764706
00:02:30.663 --> 00:02:32.873 and maybe even beyond leukemias.
NOTE Confidence: 0.843636681764706
00:02:32.880 --> 00:02:34.994 And as many of you probably know
NOTE Confidence: 0.843636681764706
00:02:34.994 --> 00:02:36.811 that the concept of targeting
NOTE Confidence: 0.843636681764706

00:02:36.811 --> 00:02:38.511 chromatin or epigenetic based
NOTE Confidence: 0.843636681764706

00:02:38.511 --> 00:02:40.584 mechanisms been around for quite
NOTE Confidence: 0.843636681764706

00:02:40.584 --> 00:02:42.600 some time and there have been some
NOTE Confidence: 0.843636681764706

00:02:42.600 --> 00:02:44.000 therapeutic advances in that regard.
NOTE Confidence: 0.843636681764706

00:02:44.000 --> 00:02:45.746 But it's been it's stops and
NOTE Confidence: 0.843636681764706

00:02:45.746 --> 00:02:47.946 starts I would say along the road
NOTE Confidence: 0.843636681764706

00:02:47.946 --> 00:02:49.878 and hopefully I can convince you
NOTE Confidence: 0.843636681764706

00:02:49.878 --> 00:02:51.914 that we're maybe finally starting
NOTE Confidence: 0.843636681764706

00:02:51.914 --> 00:02:54.332 to make some significant go get
NOTE Confidence: 0.843636681764706

00:02:54.332 --> 00:02:55.876 some significant insights there.
NOTE Confidence: 0.843636681764706

00:02:55.880 --> 00:02:57.000 So these are my disclosures.
NOTE Confidence: 0.843636681764706

00:02:57.000 --> 00:02:59.120 I do consult for a number of biotech
NOTE Confidence: 0.843636681764706

00:02:59.120 --> 00:03:00.988 companies trying to convince them that
NOTE Confidence: 0.843636681764706

00:03:00.988 --> 00:03:02.598 these mechanisms are relevant that's
NOTE Confidence: 0.843636681764706

00:03:02.600 --> 00:03:05.316 and sometimes I'm able to do that.
NOTE Confidence: 0.843636681764706

00:03:05.320 --> 00:03:07.560 And then this patent on amended inhibition,

NOTE Confidence: 0.843636681764706
00:03:07.560 --> 00:03:08.475 NPM one AML.
NOTE Confidence: 0.843636681764706
00:03:08.475 --> 00:03:10.960 I'm going to talk about NPM one AML.
NOTE Confidence: 0.843636681764706
00:03:10.960 --> 00:03:12.466 And more important disclosure is these
NOTE Confidence: 0.843636681764706
00:03:12.466 --> 00:03:14.038 are the people that do the work.
NOTE Confidence: 0.843636681764706
00:03:14.040 --> 00:03:17.028 I don't do the work and I'm very lucky
NOTE Confidence: 0.843636681764706
00:03:17.028 --> 00:03:19.520 to have tremendous fellows in the lab.
NOTE Confidence: 0.843636681764706
00:03:19.520 --> 00:03:21.879 And actually all of these fellows other
NOTE Confidence: 0.843636681764706
00:03:21.879 --> 00:03:24.027 than Emily who soon will leave the
NOTE Confidence: 0.843636681764706
00:03:24.027 --> 00:03:26.554 lab to go start her own have started
NOTE Confidence: 0.843636681764706
00:03:26.554 --> 00:03:29.753 their own independent lab based careers now.
NOTE Confidence: 0.843636681764706
00:03:29.760 --> 00:03:31.426 So this is the outline of the
NOTE Confidence: 0.843636681764706
00:03:31.426 --> 00:03:33.120 talk I'm going to introduce you.
NOTE Confidence: 0.843636681764706
00:03:33.120 --> 00:03:36.640 Many of you probably know a lot of
NOTE Confidence: 0.843636681764706
00:03:36.640 --> 00:03:40.665 this to the MLL or CAT or MLL or KMT
NOTE Confidence: 0.843636681764706
00:03:40.665 --> 00:03:43.507 two ACI can't even remember what the
NOTE Confidence: 0.843636681764706

00:03:43.507 --> 00:03:46.984 other name is for complex and MLL
NOTE Confidence: 0.843636681764706

00:03:46.984 --> 00:03:49.736 rearranged leukemias and then move to
NOTE Confidence: 0.843636681764706

00:03:49.736 --> 00:03:51.556 the therapeutic development of small
NOTE Confidence: 0.843636681764706

00:03:51.556 --> 00:03:53.597 molecules that target those complexes.
NOTE Confidence: 0.843636681764706

00:03:53.600 --> 00:03:56.001 Talk a little bit about the clinical
NOTE Confidence: 0.843636681764706

00:03:56.001 --> 00:03:57.421 translation and resistance mechanisms
NOTE Confidence: 0.843636681764706

00:03:57.421 --> 00:03:59.710 that we're starting to see to those
NOTE Confidence: 0.843636681764706

00:03:59.710 --> 00:04:01.660 molecules and then talk about the
NOTE Confidence: 0.843636681764706

00:04:01.660 --> 00:04:03.291 potential role in other cancers.
NOTE Confidence: 0.843636681764706

00:04:03.291 --> 00:04:05.313 And as I already mentioned the,
NOTE Confidence: 0.843636681764706

00:04:05.320 --> 00:04:08.116 the concept of the OR the
NOTE Confidence: 0.843636681764706

00:04:08.116 --> 00:04:09.514 relevance of epigenetics.
NOTE Confidence: 0.843636681764706

00:04:09.520 --> 00:04:11.424 And just for those of you that
NOTE Confidence: 0.843636681764706

00:04:11.424 --> 00:04:13.095 are that are purists in the
NOTE Confidence: 0.843636681764706

00:04:13.095 --> 00:04:14.235 epigenetic and chromatin space,
NOTE Confidence: 0.843636681764706

00:04:14.240 --> 00:04:15.860 I will interchangeably use

NOTE Confidence: 0.843636681764706
00:04:15.860 --> 00:04:17.480 epigenetic and chromatin biology.
NOTE Confidence: 0.843636681764706
00:04:17.480 --> 00:04:19.601 Actually there there is a group of
NOTE Confidence: 0.843636681764706
00:04:19.601 --> 00:04:21.704 people that think those two things are
NOTE Confidence: 0.843636681764706
00:04:21.704 --> 00:04:23.848 not the same thing and the concept
NOTE Confidence: 0.843636681764706
00:04:23.848 --> 00:04:25.864 that these mechanisms are relevant and
NOTE Confidence: 0.843636681764706
00:04:25.864 --> 00:04:28.237 cancer has been around for quite some time.
NOTE Confidence: 0.843636681764706
00:04:28.240 --> 00:04:31.476 This is not a new idea and epigenetics
NOTE Confidence: 0.843636681764706
00:04:31.476 --> 00:04:33.468 really encompasses many different
NOTE Confidence: 0.843636681764706
00:04:33.468 --> 00:04:36.200 types of modifications of chromatin,
NOTE Confidence: 0.843636681764706
00:04:36.200 --> 00:04:37.320 DNA methylation,
NOTE Confidence: 0.843636681764706
00:04:37.320 --> 00:04:38.440 histone modifications,
NOTE Confidence: 0.843636681764706
00:04:38.440 --> 00:04:40.680 complexes have proteins that
NOTE Confidence: 0.843636681764706
00:04:40.680 --> 00:04:43.440 read those histone modifications.
NOTE Confidence: 0.843636681764706
00:04:43.440 --> 00:04:44.086 The nucleos,
NOTE Confidence: 0.843636681764706
00:04:44.086 --> 00:04:45.378 there's nucleosome remodeling complexes
NOTE Confidence: 0.843636681764706

00:04:45.378 --> 00:04:46.960 that you've probably heard about.
NOTE Confidence: 0.843636681764706

00:04:46.960 --> 00:04:48.800 The bath complex also are
NOTE Confidence: 0.843636681764706

00:04:48.800 --> 00:04:50.272 frequently mutated in cancer.
NOTE Confidence: 0.843636681764706

00:04:50.280 --> 00:04:52.317 So we've known that this is relevant,
NOTE Confidence: 0.843636681764706

00:04:52.320 --> 00:04:54.352 but what to do about it has been
NOTE Confidence: 0.843636681764706

00:04:54.352 --> 00:04:56.192 a little bit harder to understand
NOTE Confidence: 0.843636681764706

00:04:56.192 --> 00:04:58.088 and the the kind of simple
NOTE Confidence: 0.846459086818182

00:04:58.157 --> 00:05:00.064 concept is, is these mechanisms
NOTE Confidence: 0.846459086818182

00:05:00.064 --> 00:05:01.696 control developmental gene expression
NOTE Confidence: 0.846459086818182

00:05:01.696 --> 00:05:04.524 and if we were smart enough we'd
NOTE Confidence: 0.846459086818182

00:05:04.524 --> 00:05:06.444 figure out how to therapeutically
NOTE Confidence: 0.846459086818182

00:05:06.444 --> 00:05:08.962 target them and reverse those cancer
NOTE Confidence: 0.846459086818182

00:05:08.962 --> 00:05:11.032 causing gene expression mechanisms and
NOTE Confidence: 0.846459086818182

00:05:11.040 --> 00:05:12.756 hopefully we're starting to get there.
NOTE Confidence: 0.846459086818182

00:05:12.760 --> 00:05:15.245 There are some FDA approved drugs that
NOTE Confidence: 0.846459086818182

00:05:15.245 --> 00:05:17.714 you probably know about H TAC inhibitors

NOTE Confidence: 0.846459086818182
00:05:17.714 --> 00:05:19.454 and DNA methyl transferase inhibitors.
NOTE Confidence: 0.846459086818182
00:05:19.454 --> 00:05:22.390 I would say whether or not those molecules
NOTE Confidence: 0.846459086818182
00:05:22.446 --> 00:05:24.556 are working via epigenetic mechanisms,
NOTE Confidence: 0.846459086818182
00:05:24.560 --> 00:05:26.478 still a little bit of a question,
NOTE Confidence: 0.846459086818182
00:05:26.480 --> 00:05:29.035 but indeed those were the first ones
NOTE Confidence: 0.846459086818182
00:05:29.035 --> 00:05:31.801 that could be working via these some of
NOTE Confidence: 0.846459086818182
00:05:31.801 --> 00:05:34.000 these mechanisms that were FDA approved.
NOTE Confidence: 0.846459086818182
00:05:34.000 --> 00:05:36.856 So this is the leukemia that I became
NOTE Confidence: 0.846459086818182
00:05:36.856 --> 00:05:38.775 most interested in as a fellow
NOTE Confidence: 0.846459086818182
00:05:38.775 --> 00:05:40.195 back in the late 1990s.
NOTE Confidence: 0.846459086818182
00:05:40.200 --> 00:05:42.500 Now those are leukemias with
NOTE Confidence: 0.846459086818182
00:05:42.500 --> 00:05:45.632 rearrangements of the KMT 2A or
NOTE Confidence: 0.846459086818182
00:05:45.632 --> 00:05:49.260 or MLL gene and in Pediatrics as
NOTE Confidence: 0.846459086818182
00:05:49.260 --> 00:05:51.720 mentioned I'm a pediatric oncologist.
NOTE Confidence: 0.846459086818182
00:05:51.720 --> 00:05:53.455 This rearrangement when found in
NOTE Confidence: 0.846459086818182

00:05:53.455 --> 00:05:56.044 infants with AOL predicts a very poor
NOTE Confidence: 0.846459086818182

00:05:56.044 --> 00:05:58.014 prognosis and in pediatric leukemia
NOTE Confidence: 0.846459086818182

00:05:58.014 --> 00:06:00.239 therapy we're actually not used to that.
NOTE Confidence: 0.846459086818182

00:06:00.240 --> 00:06:02.193 We cure most of our patients with
NOTE Confidence: 0.846459086818182

00:06:02.193 --> 00:06:04.711 AOL and we find a subset that has a
NOTE Confidence: 0.846459086818182

00:06:04.711 --> 00:06:06.690 less than 40% long term survival.
NOTE Confidence: 0.846459086818182

00:06:06.690 --> 00:06:09.030 We that's unusual and this subset
NOTE Confidence: 0.846459086818182

00:06:09.030 --> 00:06:11.585 is that if an infant comes in that
NOTE Confidence: 0.846459086818182

00:06:11.585 --> 00:06:14.061 has ALL and has a rearrangement of
NOTE Confidence: 0.846459086818182

00:06:14.061 --> 00:06:16.317 this gene that it's probably in
NOTE Confidence: 0.846459086818182

00:06:16.320 --> 00:06:19.278 the 4050% long term survival now.
NOTE Confidence: 0.743930284666667

00:06:23.160 --> 00:06:25.680 And so back in the late 90s I joined
NOTE Confidence: 0.743930284666667

00:06:25.680 --> 00:06:28.198 Stan course Meyer's lab to start to
NOTE Confidence: 0.743930284666667

00:06:28.198 --> 00:06:30.106 learn about that and then obviously
NOTE Confidence: 0.743930284666667

00:06:30.106 --> 00:06:31.720 ultimately to start my own lab.
NOTE Confidence: 0.743930284666667

00:06:31.720 --> 00:06:34.114 So this is the the wild

NOTE Confidence: 0.743930284666667

00:06:34.114 --> 00:06:36.718 type MLL or KMT 2A protein.

NOTE Confidence: 0.743930284666667

00:06:36.720 --> 00:06:39.359 It's very large, it's in the nucleus,

NOTE Confidence: 0.743930284666667

00:06:39.360 --> 00:06:40.944 it's about 500K Daltons,

NOTE Confidence: 0.743930284666667

00:06:40.944 --> 00:06:44.040 makes it has made it difficult to study.

NOTE Confidence: 0.743930284666667

00:06:44.040 --> 00:06:45.774 It has a number of different

NOTE Confidence: 0.743930284666667

00:06:45.774 --> 00:06:47.760 domains and is bound to chromatin.

NOTE Confidence: 0.743930284666667

00:06:47.760 --> 00:06:50.000 We've known that for over 20 years.

NOTE Confidence: 0.743930284666667

00:06:50.000 --> 00:06:51.962 And when the translocation occurs that

NOTE Confidence: 0.743930284666667

00:06:51.962 --> 00:06:54.483 in terminus of MLL is fused to the

NOTE Confidence: 0.743930284666667

00:06:54.483 --> 00:06:56.205 C terminus of what's 100 different

NOTE Confidence: 0.743930284666667

00:06:56.268 --> 00:06:58.578 fusion proteins also making a little

NOTE Confidence: 0.743930284666667

00:06:58.578 --> 00:07:00.118 bit complicated to understand.

NOTE Confidence: 0.743930284666667

00:07:00.120 --> 00:07:01.891 And this is just the history that

NOTE Confidence: 0.743930284666667

00:07:01.891 --> 00:07:03.832 I won't go through in too much

NOTE Confidence: 0.743930284666667

00:07:03.832 --> 00:07:05.827 detail other than to say that the

NOTE Confidence: 0.743930284666667

00:07:05.827 --> 00:07:07.692 wild type MLL protein is was shown

NOTE Confidence: 0.743930284666667

00:07:07.692 --> 00:07:09.920 in the mid 90s by Stan Course,

NOTE Confidence: 0.743930284666667

00:07:09.920 --> 00:07:12.542 Mars Group and others to control

NOTE Confidence: 0.743930284666667

00:07:12.542 --> 00:07:14.952 development of blood system of

NOTE Confidence: 0.743930284666667

00:07:14.952 --> 00:07:16.451 hematopoiesis through presumably

NOTE Confidence: 0.743930284666667

00:07:16.451 --> 00:07:18.437 control of the homeotic or hox

NOTE Confidence: 0.743930284666667

00:07:18.437 --> 00:07:20.472 genes that are important in many

NOTE Confidence: 0.743930284666667

00:07:20.472 --> 00:07:22.097 types of development and but

NOTE Confidence: 0.743930284666667

00:07:22.097 --> 00:07:24.000 in blood development as well.

NOTE Confidence: 0.743930284666667

00:07:24.000 --> 00:07:26.440 And that was really actually

NOTE Confidence: 0.743930284666667

00:07:26.440 --> 00:07:28.456 pointed to that concept by studies

NOTE Confidence: 0.743930284666667

00:07:28.456 --> 00:07:30.280 done even before that in fly,

NOTE Confidence: 0.743930284666667

00:07:30.280 --> 00:07:32.000 in fruit flies and Drosophila,

NOTE Confidence: 0.743930284666667

00:07:32.000 --> 00:07:33.480 showing that the trithorax gene,

NOTE Confidence: 0.743930284666667

00:07:33.480 --> 00:07:35.760 which is the Drosophila homologue is

NOTE Confidence: 0.743930284666667

00:07:35.760 --> 00:07:37.640 important for development as well.

NOTE Confidence: 0.743930284666667
00:07:37.640 --> 00:07:39.596 And then Mike Cleary and Terry,
NOTE Confidence: 0.743930284666667
00:07:39.600 --> 00:07:41.754 rabbits showed in very nice mouse
NOTE Confidence: 0.743930284666667
00:07:41.754 --> 00:07:44.051 studies in the late 90s that
NOTE Confidence: 0.743930284666667
00:07:44.051 --> 00:07:46.016 the MLL fusion proteins indeed
NOTE Confidence: 0.743930284666667
00:07:46.016 --> 00:07:47.880 do directly induce leukemia.
NOTE Confidence: 0.743930284666667
00:07:47.880 --> 00:07:49.710 And then David Alice's group showed
NOTE Confidence: 0.743930284666667
00:07:49.710 --> 00:07:52.689 that in the wild type MLL is a histone
NOTE Confidence: 0.743930284666667
00:07:52.689 --> 00:07:54.389 modifying enzyme modifies histone H3
NOTE Confidence: 0.743930284666667
00:07:54.451 --> 00:07:56.311 on lysine 4 through this enzymatic
NOTE Confidence: 0.743930284666667
00:07:56.311 --> 00:07:58.508 domain here at the C terminus.
NOTE Confidence: 0.743930284666667
00:07:58.508 --> 00:08:01.826 So this was really the first well
NOTE Confidence: 0.743930284666667
00:08:01.826 --> 00:08:03.397 characterized chromatin regulator
NOTE Confidence: 0.743930284666667
00:08:03.397 --> 00:08:06.953 that is known to drive tumor genesis.
NOTE Confidence: 0.743930284666667
00:08:06.960 --> 00:08:09.520 And so that was really why in the
NOTE Confidence: 0.743930284666667
00:08:09.520 --> 00:08:11.556 early early 2000s a lot of labs
NOTE Confidence: 0.743930284666667

00:08:11.556 --> 00:08:13.581 jumped on this to thinking maybe
NOTE Confidence: 0.743930284666667

00:08:13.581 --> 00:08:16.423 this would give us some insight into
NOTE Confidence: 0.743930284666667

00:08:16.423 --> 00:08:18.760 chromatin based mechanisms and cancer.
NOTE Confidence: 0.743930284666667

00:08:18.760 --> 00:08:21.096 So to summarize a lot of work that
NOTE Confidence: 0.743930284666667

00:08:21.096 --> 00:08:22.812 we did talk thinking about cells
NOTE Confidence: 0.743930284666667

00:08:22.812 --> 00:08:24.876 of origin of of this type and
NOTE Confidence: 0.743930284666667

00:08:24.876 --> 00:08:26.116 other types of leukemia.
NOTE Confidence: 0.743930284666667

00:08:26.120 --> 00:08:27.457 Not going to get into that too
NOTE Confidence: 0.743930284666667

00:08:27.457 --> 00:08:28.630 much today because I want to
NOTE Confidence: 0.743930284666667

00:08:28.630 --> 00:08:29.555 get to the therapeutic part.
NOTE Confidence: 0.743930284666667

00:08:29.560 --> 00:08:31.336 But we were able to show that the
NOTE Confidence: 0.743930284666667

00:08:31.336 --> 00:08:33.374 MLO fusion when we put it into either
NOTE Confidence: 0.743930284666667

00:08:33.374 --> 00:08:34.760 stem cells or progenitor cells,
NOTE Confidence: 0.743930284666667

00:08:34.760 --> 00:08:35.944 either mouse or human,
NOTE Confidence: 0.743930284666667

00:08:35.944 --> 00:08:37.720 that the MLO fusion can drive
NOTE Confidence: 0.743930284666667

00:08:37.786 --> 00:08:39.641 the development of leukemia from

NOTE Confidence: 0.743930284666667
00:08:39.641 --> 00:08:41.125 multiple different cell types
NOTE Confidence: 0.743930284666667
00:08:41.125 --> 00:08:43.039 in hematopoietic development.
NOTE Confidence: 0.743930284666667
00:08:43.040 --> 00:08:44.528 And these concepts have now been
NOTE Confidence: 0.743930284666667
00:08:44.528 --> 00:08:46.039 shown in other types of tumors.
NOTE Confidence: 0.743930284666667
00:08:46.040 --> 00:08:48.028 But at the time that was a
NOTE Confidence: 0.743930284666667
00:08:48.028 --> 00:08:48.880 relatively new concept.
NOTE Confidence: 0.743930284666667
00:08:48.880 --> 00:08:50.494 But what more importantly what it
NOTE Confidence: 0.743930284666667
00:08:50.494 --> 00:08:52.445 let us do is really characterize
NOTE Confidence: 0.743930284666667
00:08:52.445 --> 00:08:54.465 the gene expression program that's
NOTE Confidence: 0.743930284666667
00:08:54.465 --> 00:08:56.549 driven by this MLL fusion protein
NOTE Confidence: 0.743930284666667
00:08:56.549 --> 00:08:58.832 when we put it into in this case
NOTE Confidence: 0.743930284666667
00:08:58.832 --> 00:09:00.400 a mouse progenitor cell.
NOTE Confidence: 0.743930284666667
00:09:00.400 --> 00:09:02.430 And we could look very quickly to
NOTE Confidence: 0.743930284666667
00:09:02.430 --> 00:09:04.915 see what types of gene expression and
NOTE Confidence: 0.743930284666667
00:09:04.915 --> 00:09:06.850 chromatin based changes happened when
NOTE Confidence: 0.743930284666667

00:09:06.850 --> 00:09:09.118 the MLL fusion binds to chromatin.
NOTE Confidence: 0.743930284666667

00:09:09.120 --> 00:09:11.200 And our work and many,
NOTE Confidence: 0.743930284666667

00:09:11.200 --> 00:09:12.805 many people's work across the
NOTE Confidence: 0.743930284666667

00:09:12.805 --> 00:09:14.410 the world with this model
NOTE Confidence: 0.842150046666667

00:09:14.474 --> 00:09:16.224 originally developed by Mike Cleary's
NOTE Confidence: 0.842150046666667

00:09:16.224 --> 00:09:18.648 group have I would say that MLO
NOTE Confidence: 0.842150046666667

00:09:18.648 --> 00:09:20.472 fusion driven leukemia now is about
NOTE Confidence: 0.842150046666667

00:09:20.472 --> 00:09:21.940 as well characterized mechanistically
NOTE Confidence: 0.842150046666667

00:09:21.940 --> 00:09:24.520 this as any type of leukemia,
NOTE Confidence: 0.842150046666667

00:09:24.520 --> 00:09:26.545 probably any type of cancer
NOTE Confidence: 0.842150046666667

00:09:26.545 --> 00:09:28.404 largely because of this model.
NOTE Confidence: 0.842150046666667

00:09:28.404 --> 00:09:31.206 So we know where the fusion binds throughout
NOTE Confidence: 0.842150046666667

00:09:31.206 --> 00:09:33.036 chromatin, which genes it controls.
NOTE Confidence: 0.842150046666667

00:09:33.040 --> 00:09:34.832 We now have mechanisms of turning the fusion
NOTE Confidence: 0.842150046666667

00:09:34.832 --> 00:09:36.833 off and we can see what genes get shut off.
NOTE Confidence: 0.842150046666667

00:09:36.840 --> 00:09:39.078 We understand now quite a bit

NOTE Confidence: 0.842150046666667
00:09:39.080 --> 00:09:42.080 about what the MLL fusion does.
NOTE Confidence: 0.842150046666667
00:09:42.080 --> 00:09:44.048 Exactly how it does it is
NOTE Confidence: 0.842150046666667
00:09:44.048 --> 00:09:45.693 still a little bit unclear,
NOTE Confidence: 0.842150046666667
00:09:45.693 --> 00:09:48.024 but that is what we and others
NOTE Confidence: 0.842150046666667
00:09:48.024 --> 00:09:49.759 are really working on now.
NOTE Confidence: 0.842150046666667
00:09:49.760 --> 00:09:51.370 And of course that is what we
NOTE Confidence: 0.842150046666667
00:09:51.370 --> 00:09:53.456 need to know and under in order
NOTE Confidence: 0.842150046666667
00:09:53.456 --> 00:09:54.792 to develop hopefully therapeutics
NOTE Confidence: 0.842150046666667
00:09:54.792 --> 00:09:56.840 that can target these mechanisms.
NOTE Confidence: 0.842150046666667
00:09:56.840 --> 00:09:59.619 So this is a very simple actually
NOTE Confidence: 0.842150046666667
00:09:59.619 --> 00:10:02.640 summary of how the MLL fusion works.
NOTE Confidence: 0.842150046666667
00:10:02.640 --> 00:10:06.438 So here in Gray is the ML AF9 fusion,
NOTE Confidence: 0.842150046666667
00:10:06.440 --> 00:10:08.379 the in terminus of MLL bound to
NOTE Confidence: 0.842150046666667
00:10:08.379 --> 00:10:10.401 some of the proteins normally found
NOTE Confidence: 0.842150046666667
00:10:10.401 --> 00:10:13.019 in the MLL complex Menon and Ledge
NOTE Confidence: 0.842150046666667

00:10:13.085 --> 00:10:15.095 F here and those help localize
NOTE Confidence: 0.842150046666667

00:10:15.095 --> 00:10:16.748 the fusion protein to chromatin.
NOTE Confidence: 0.842150046666667

00:10:16.748 --> 00:10:19.212 And then the C terminal part of the
NOTE Confidence: 0.842150046666667

00:10:19.212 --> 00:10:21.706 fusion brings in a number of complexes
NOTE Confidence: 0.842150046666667

00:10:21.706 --> 00:10:23.479 is histone methyl transferase .1 L,
NOTE Confidence: 0.842150046666667

00:10:23.480 --> 00:10:25.592 which is a histone H3 lysine
NOTE Confidence: 0.842150046666667

00:10:25.592 --> 00:10:27.591 79 methyl transferase And this
NOTE Confidence: 0.842150046666667

00:10:27.591 --> 00:10:29.679 so-called super elongation complex,
NOTE Confidence: 0.842150046666667

00:10:29.680 --> 00:10:32.752 which is really a fundamental complex
NOTE Confidence: 0.842150046666667

00:10:32.752 --> 00:10:34.800 for controlling transcription broadly,
NOTE Confidence: 0.842150046666667

00:10:34.800 --> 00:10:36.360 not just in this setting.
NOTE Confidence: 0.842150046666667

00:10:36.360 --> 00:10:39.726 Certainly the MLL fusion drags these
NOTE Confidence: 0.842150046666667

00:10:39.726 --> 00:10:41.970 chromatin regulatory and transcriptional
NOTE Confidence: 0.842150046666667

00:10:42.049 --> 00:10:44.730 control proteins and complexes to its
NOTE Confidence: 0.842150046666667

00:10:44.730 --> 00:10:47.840 target genes to drive gene expression.
NOTE Confidence: 0.842150046666667

00:10:47.840 --> 00:10:50.876 So with that level of understanding,

NOTE Confidence: 0.842150046666667

00:10:50.880 --> 00:10:52.976 it became easier to go to pharma and

NOTE Confidence: 0.842150046666667

00:10:52.976 --> 00:10:54.931 biotech and to get them interested

NOTE Confidence: 0.842150046666667

00:10:54.931 --> 00:10:56.651 in developing small molecules that

NOTE Confidence: 0.842150046666667

00:10:56.651 --> 00:10:58.358 might target these mechanisms.

NOTE Confidence: 0.842150046666667

00:10:58.360 --> 00:11:00.958 Even though at the time no one knew

NOTE Confidence: 0.842150046666667

00:11:00.958 --> 00:11:02.794 if these were mechanisms be relevant

NOTE Confidence: 0.842150046666667

00:11:02.794 --> 00:11:04.586 beyond this relatively rare disease

NOTE Confidence: 0.842150046666667

00:11:04.586 --> 00:11:06.722 which is probably A couple thousand

NOTE Confidence: 0.842150046666667

00:11:06.786 --> 00:11:08.956 patients per year in the United States.

NOTE Confidence: 0.842150046666667

00:11:08.960 --> 00:11:10.088 But I'll show you,

NOTE Confidence: 0.842150046666667

00:11:10.088 --> 00:11:12.104 I think we think that indeed and

NOTE Confidence: 0.842150046666667

00:11:12.104 --> 00:11:14.216 in fact we have now shown in in

NOTE Confidence: 0.842150046666667

00:11:14.216 --> 00:11:15.920 patients that it it actually is.

NOTE Confidence: 0.842150046666667

00:11:15.920 --> 00:11:16.880 So each, as I mentioned,

NOTE Confidence: 0.842150046666667

00:11:16.880 --> 00:11:20.438 each of these labels in red is a small

NOTE Confidence: 0.842150046666667

00:11:20.438 --> 00:11:22.432 molecule that's been developed to target
NOTE Confidence: 0.842150046666667

00:11:22.432 --> 00:11:24.988 various components of this large complex.
NOTE Confidence: 0.842150046666667

00:11:24.988 --> 00:11:28.265 And to summarize broadly on molecules
NOTE Confidence: 0.842150046666667

00:11:28.265 --> 00:11:30.400 that target the complexes on the right,
NOTE Confidence: 0.842150046666667

00:11:30.400 --> 00:11:32.104 the kind of general
NOTE Confidence: 0.842150046666667

00:11:32.104 --> 00:11:32.956 transcriptional complexes,
NOTE Confidence: 0.842150046666667

00:11:32.960 --> 00:11:35.156 the problem there has primarily been
NOTE Confidence: 0.842150046666667

00:11:35.156 --> 00:11:37.520 toxicity that actually not too surprising
NOTE Confidence: 0.842150046666667

00:11:37.520 --> 00:11:39.600 you turn off transcription broadly,
NOTE Confidence: 0.842150046666667

00:11:39.600 --> 00:11:41.168 we can do that with some of
NOTE Confidence: 0.842150046666667

00:11:41.168 --> 00:11:41.840 our chemotherapeutic drugs.
NOTE Confidence: 0.842150046666667

00:11:41.840 --> 00:11:44.040 It's relatively toxic on the
NOTE Confidence: 0.842150046666667

00:11:44.040 --> 00:11:47.052 left side and to date the problem
NOTE Confidence: 0.842150046666667

00:11:47.052 --> 00:11:48.676 has actually been efficacy,
NOTE Confidence: 0.842150046666667

00:11:48.680 --> 00:11:51.067 meaning we can do pre clinical studies
NOTE Confidence: 0.842150046666667

00:11:51.067 --> 00:11:53.150 and I'll briefly load to this with

NOTE Confidence: 0.842150046666667

00:11:53.150 --> 00:11:54.840 .1 actually get really impressive

NOTE Confidence: 0.842150046666667

00:11:54.840 --> 00:11:57.000 changes in gene expression and such.

NOTE Confidence: 0.842150046666667

00:11:57.000 --> 00:11:59.261 But then we go into patients with

NOTE Confidence: 0.842150046666667

00:11:59.261 --> 00:12:01.589 the .1 inhibitor get a little bit

NOTE Confidence: 0.842150046666667

00:12:01.589 --> 00:12:04.075 of clinical signal and but unable

NOTE Confidence: 0.842150046666667

00:12:04.075 --> 00:12:06.600 to maintain that clinical response.

NOTE Confidence: 0.842150046666667

00:12:06.600 --> 00:12:08.718 But but toxicity has not primarily

NOTE Confidence: 0.842150046666667

00:12:08.718 --> 00:12:10.866 been a problem for the molecules

NOTE Confidence: 0.842150046666667

00:12:10.866 --> 00:12:13.040 on the left side of this figures

NOTE Confidence: 0.842150046666667

00:12:13.040 --> 00:12:14.720 and that's kind of where we've

NOTE Confidence: 0.777851471538462

00:12:14.720 --> 00:12:17.051 focused. And I'm going to talk a

NOTE Confidence: 0.777851471538462

00:12:17.051 --> 00:12:19.480 lot about this protein Menon here,

NOTE Confidence: 0.777851471538462

00:12:19.480 --> 00:12:21.514 which is really a scaffolding protein

NOTE Confidence: 0.777851471538462

00:12:21.514 --> 00:12:23.561 that's bound to the MLL fusion

NOTE Confidence: 0.777851471538462

00:12:23.561 --> 00:12:25.433 and helps keep it on chromatin.

NOTE Confidence: 0.777851471538462

00:12:25.440 --> 00:12:27.555 I'll show you more about that in a minute.

NOTE Confidence: 0.777851471538462

00:12:27.560 --> 00:12:29.960 Men and as an important part of the

NOTE Confidence: 0.777851471538462

00:12:29.960 --> 00:12:31.776 Amylo complex was first demonstrated

NOTE Confidence: 0.777851471538462

00:12:31.776 --> 00:12:34.040 in 2004 by Michael Cleary's group.

NOTE Confidence: 0.777851471538462

00:12:34.040 --> 00:12:36.196 And now there are many small molecules.

NOTE Confidence: 0.777851471538462

00:12:36.200 --> 00:12:38.377 I'll talk about the one we've been

NOTE Confidence: 0.777851471538462

00:12:38.377 --> 00:12:40.124 working on that disrupt this interaction.

NOTE Confidence: 0.777851471538462

00:12:40.124 --> 00:12:42.240 I'll show you how in a minute.

NOTE Confidence: 0.777851471538462

00:12:42.240 --> 00:12:44.080 And that really that concept,

NOTE Confidence: 0.777851471538462

00:12:44.080 --> 00:12:45.964 the first chemical biology done around

NOTE Confidence: 0.777851471538462

00:12:45.964 --> 00:12:48.654 this was done by Yolanda Grimbeck is due

NOTE Confidence: 0.777851471538462

00:12:48.654 --> 00:12:50.712 in Michigan where they developed the

NOTE Confidence: 0.777851471538462

00:12:50.770 --> 00:12:52.996 first small molecule to bind to minute.

NOTE Confidence: 0.777851471538462

00:12:53.000 --> 00:12:54.554 So just quickly I'm going to

NOTE Confidence: 0.777851471538462

00:12:54.554 --> 00:12:56.480 this is kind of jumping ahead,

NOTE Confidence: 0.777851471538462

00:12:56.480 --> 00:12:58.608 but it's a concept that I think is

NOTE Confidence: 0.777851471538462

00:12:58.608 --> 00:13:00.725 important in terms when we think

NOTE Confidence: 0.777851471538462

00:13:00.725 --> 00:13:02.245 about targeting chromatin complexes

NOTE Confidence: 0.777851471538462

00:13:02.245 --> 00:13:03.874 in leukemia or other diseases.

NOTE Confidence: 0.777851471538462

00:13:03.874 --> 00:13:06.706 So if this is a even more simplified

NOTE Confidence: 0.777851471538462

00:13:06.706 --> 00:13:09.518 view of the ML AF9 bound to chromatin

NOTE Confidence: 0.777851471538462

00:13:09.518 --> 00:13:11.151 through its adapter proteins and

NOTE Confidence: 0.777851471538462

00:13:11.151 --> 00:13:13.960 bring it in this case the .1 complex.

NOTE Confidence: 0.777851471538462

00:13:13.960 --> 00:13:16.214 I told you that we worked actually

NOTE Confidence: 0.777851471538462

00:13:16.214 --> 00:13:18.619 over a decade ago now with a

NOTE Confidence: 0.777851471538462

00:13:18.619 --> 00:13:20.671 company called Epizyme to make small

NOTE Confidence: 0.777851471538462

00:13:20.742 --> 00:13:23.157 molecule enzymatic inhibitors of .1.

NOTE Confidence: 0.777851471538462

00:13:23.160 --> 00:13:24.805 We've shown with genetic studies

NOTE Confidence: 0.777851471538462

00:13:24.805 --> 00:13:26.872 that that is an important component

NOTE Confidence: 0.777851471538462

00:13:26.872 --> 00:13:29.020 of this complex and that histone

NOTE Confidence: 0.777851471538462

00:13:29.020 --> 00:13:30.720 modification that it put places

NOTE Confidence: 0.777851471538462

00:13:30.720 --> 00:13:33.005 is important for controlling MLO

NOTE Confidence: 0.777851471538462

00:13:33.005 --> 00:13:34.833 fusion driven gene expression.

NOTE Confidence: 0.777851471538462

00:13:34.840 --> 00:13:36.898 And that went into clinical trials and

NOTE Confidence: 0.777851471538462

00:13:36.898 --> 00:13:39.431 we were able to a couple of patients

NOTE Confidence: 0.777851471538462

00:13:39.431 --> 00:13:41.016 actually went into to remission

NOTE Confidence: 0.777851471538462

00:13:41.083 --> 00:13:42.980 and many had some response but it

NOTE Confidence: 0.777851471538462

00:13:42.980 --> 00:13:44.496 they were all pretty transient.

NOTE Confidence: 0.777851471538462

00:13:44.496 --> 00:13:46.932 And I'm going to show you that

NOTE Confidence: 0.777851471538462

00:13:46.932 --> 00:13:49.436 that's not the case with the min an

NOTE Confidence: 0.777851471538462

00:13:49.436 --> 00:13:50.998 inhibitor and this summarizes why

NOTE Confidence: 0.777851471538462

00:13:50.998 --> 00:13:53.764 we think that is that if you the .1

NOTE Confidence: 0.777851471538462

00:13:53.764 --> 00:13:55.374 L inhibitor inhibits the enzymatic

NOTE Confidence: 0.777851471538462

00:13:55.374 --> 00:13:56.840 activity of this protein,

NOTE Confidence: 0.777851471538462

00:13:56.840 --> 00:13:59.240 but the whole complex remains stuck

NOTE Confidence: 0.777851471538462

00:13:59.240 --> 00:14:00.040 on chromatin.

NOTE Confidence: 0.777851471538462

00:14:00.040 --> 00:14:01.720 So it's actually doesn't take a

NOTE Confidence: 0.777851471538462
00:14:01.720 --> 00:14:03.929 lot for the cell to figure out how
NOTE Confidence: 0.777851471538462
00:14:03.929 --> 00:14:05.887 to deal with the fact that that
NOTE Confidence: 0.777851471538462
00:14:05.887 --> 00:14:08.035 enzymatic activity is no longer there.
NOTE Confidence: 0.777851471538462
00:14:08.040 --> 00:14:09.096 Whereas what I'm going to show
NOTE Confidence: 0.777851471538462
00:14:09.096 --> 00:14:10.440 you with the MLL Menin inhibitor,
NOTE Confidence: 0.777851471538462
00:14:10.440 --> 00:14:12.534 it actually disrupts the whole complex
NOTE Confidence: 0.777851471538462
00:14:12.534 --> 00:14:15.141 and much of the complex lifts and
NOTE Confidence: 0.777851471538462
00:14:15.141 --> 00:14:17.427 the fusion protein lifts off of
NOTE Confidence: 0.777851471538462
00:14:17.427 --> 00:14:19.400 chromatin and we think that probably
NOTE Confidence: 0.777851471538462
00:14:19.400 --> 00:14:21.512 is why the the Menin inhibitor
NOTE Confidence: 0.777851471538462
00:14:21.512 --> 00:14:23.880 approach is more dramatic.
NOTE Confidence: 0.777851471538462
00:14:23.880 --> 00:14:26.162 So in 2019 we published the small
NOTE Confidence: 0.777851471538462
00:14:26.162 --> 00:14:28.484 molecule that we were working on which
NOTE Confidence: 0.777851471538462
00:14:28.484 --> 00:14:30.708 was at the time called BTP 5O469.
NOTE Confidence: 0.777851471538462
00:14:30.708 --> 00:14:33.220 The version of it that's in the clinic
NOTE Confidence: 0.777851471538462

00:14:33.292 --> 00:14:35.408 is called Syndex 5613 or Revu Minib.
NOTE Confidence: 0.777851471538462

00:14:35.408 --> 00:14:37.040 Get to that in a minute.
NOTE Confidence: 0.777851471538462

00:14:37.040 --> 00:14:38.937 And this is a very potent small
NOTE Confidence: 0.777851471538462

00:14:38.937 --> 00:14:40.679 molecule that binds to this pocket on
NOTE Confidence: 0.777851471538462

00:14:40.679 --> 00:14:42.680 men and this is the men and protein.
NOTE Confidence: 0.777851471538462

00:14:42.680 --> 00:14:44.997 This is the crystal structure of this
NOTE Confidence: 0.777851471538462

00:14:45.000 --> 00:14:48.048 protein here in purple and blocks
NOTE Confidence: 0.777851471538462

00:14:48.048 --> 00:14:50.533 the interaction between men and
NOTE Confidence: 0.777851471538462

00:14:50.533 --> 00:14:52.786 and the MLL fusion and that leads
NOTE Confidence: 0.777851471538462

00:14:52.786 --> 00:14:55.075 to as I mentioned the loss of this
NOTE Confidence: 0.777851471538462

00:14:55.075 --> 00:14:56.239 complex on chromatin,
NOTE Confidence: 0.777851471538462

00:14:56.240 --> 00:14:57.888 but interestingly enough only
NOTE Confidence: 0.777851471538462

00:14:57.888 --> 00:15:00.360 does it at very selected sites.
NOTE Confidence: 0.89274465

00:15:00.360 --> 00:15:02.976 This complex actually remains on on
NOTE Confidence: 0.89274465

00:15:02.976 --> 00:15:05.995 chromatin and the wild type complex which
NOTE Confidence: 0.89274465

00:15:05.995 --> 00:15:08.146 would also be potentially disrupted

NOTE Confidence: 0.89274465

00:15:08.146 --> 00:15:10.984 by this molecule remains on chromatin

NOTE Confidence: 0.89274465

00:15:10.984 --> 00:15:13.416 at many sites throughout the genome.

NOTE Confidence: 0.89274465

00:15:13.416 --> 00:15:15.528 But there's a very selected group

NOTE Confidence: 0.89274465

00:15:15.528 --> 00:15:17.556 of genes loci where it's lost.

NOTE Confidence: 0.89274465

00:15:17.560 --> 00:15:19.240 The importance of that is,

NOTE Confidence: 0.89274465

00:15:19.240 --> 00:15:22.536 is that we know genetic inactivation of MLL

NOTE Confidence: 0.89274465

00:15:22.536 --> 00:15:26.037 broadly is toxic that to hematopoietic cells.

NOTE Confidence: 0.89274465

00:15:26.040 --> 00:15:28.182 But there's some reason that this

NOTE Confidence: 0.89274465

00:15:28.182 --> 00:15:30.651 mechanism seems to be only important

NOTE Confidence: 0.89274465

00:15:30.651 --> 00:15:32.599 at certain developmental loci.

NOTE Confidence: 0.89274465

00:15:32.600 --> 00:15:34.877 And we think that may be why we're not

NOTE Confidence: 0.89274465

00:15:34.877 --> 00:15:36.714 seeing tremendous toxicity that you

NOTE Confidence: 0.89274465

00:15:36.714 --> 00:15:39.006 could imagine by lifting this chromatin

NOTE Confidence: 0.89274465

00:15:39.065 --> 00:15:40.920 complexes off the genome broadly.

NOTE Confidence: 0.89274465

00:15:40.920 --> 00:15:43.370 And this is just one example of

NOTE Confidence: 0.89274465

00:15:43.370 --> 00:15:45.570 a preclinical PDX study that we
NOTE Confidence: 0.89274465

00:15:45.570 --> 00:15:47.712 did with an MLL rearranged AML.
NOTE Confidence: 0.89274465

00:15:47.720 --> 00:15:49.160 All of you probably know what
NOTE Confidence: 0.89274465

00:15:49.160 --> 00:15:49.880 PDX studies are,
NOTE Confidence: 0.89274465

00:15:49.880 --> 00:15:51.940 inject the human leukemia into
NOTE Confidence: 0.89274465

00:15:51.940 --> 00:15:54.608 immunodeficient mice and treat the mice here
NOTE Confidence: 0.89274465

00:15:54.608 --> 00:15:57.360 with two cycles if you will of of therapy.
NOTE Confidence: 0.89274465

00:15:57.360 --> 00:16:00.314 And the beauty of this experiment is
NOTE Confidence: 0.89274465

00:16:00.320 --> 00:16:03.339 from a technical standpoint is Syndax
NOTE Confidence: 0.89274465

00:16:03.339 --> 00:16:05.853 actually supplies us with mouse chow
NOTE Confidence: 0.89274465

00:16:05.853 --> 00:16:07.800 that's impregnated with the drugs.
NOTE Confidence: 0.89274465

00:16:07.800 --> 00:16:10.716 So you don't actually have to dose the mice.
NOTE Confidence: 0.89274465

00:16:10.720 --> 00:16:13.317 People in the lab love that fact.
NOTE Confidence: 0.89274465

00:16:13.320 --> 00:16:15.156 So basically you inject the leukemia,
NOTE Confidence: 0.89274465

00:16:15.160 --> 00:16:16.308 change the food and come back in
NOTE Confidence: 0.89274465

00:16:16.308 --> 00:16:17.518 a month and see what happened.

NOTE Confidence: 0.89274465

00:16:17.520 --> 00:16:18.955 And it's obviously not quite that simple,

NOTE Confidence: 0.89274465

00:16:18.960 --> 00:16:22.164 but so we were able to do these experiments

NOTE Confidence: 0.89274465

00:16:22.164 --> 00:16:25.278 with much more speed and much less pain

NOTE Confidence: 0.89274465

00:16:25.280 --> 00:16:27.198 than they than they often can take.

NOTE Confidence: 0.89274465

00:16:27.200 --> 00:16:29.054 And so you can see here that the the

NOTE Confidence: 0.89274465

00:16:29.054 --> 00:16:31.080 mice that were treated with the the MIN,

NOTE Confidence: 0.89274465

00:16:31.080 --> 00:16:33.170 an inhibitor essentially the AML

NOTE Confidence: 0.89274465

00:16:33.170 --> 00:16:36.200 in this PDX model was eradicated,

NOTE Confidence: 0.89274465

00:16:36.200 --> 00:16:38.027 which as most of you know who

NOTE Confidence: 0.89274465

00:16:38.027 --> 00:16:39.760 do these types of experiments.

NOTE Confidence: 0.89274465

00:16:39.760 --> 00:16:42.220 That's not the how these experiments

NOTE Confidence: 0.89274465

00:16:42.220 --> 00:16:43.040 usually go.

NOTE Confidence: 0.89274465

00:16:43.040 --> 00:16:45.945 You might see a prolongation of survival

NOTE Confidence: 0.89274465

00:16:45.945 --> 00:16:48.759 but not this degree of response.

NOTE Confidence: 0.89274465

00:16:48.760 --> 00:16:51.104 Same thing in a model that a lot

NOTE Confidence: 0.89274465

00:16:51.104 --> 00:16:52.040 of people use,
NOTE Confidence: 0.89274465

00:16:52.040 --> 00:16:53.648 this retroviral model of ML AF9
NOTE Confidence: 0.89274465

00:16:53.648 --> 00:16:55.439 that we've used a lot as well,
NOTE Confidence: 0.89274465

00:16:55.440 --> 00:16:58.996 which does lead to a very aggressive
NOTE Confidence: 0.89274465

00:16:59.000 --> 00:16:59.764 mouse AML.
NOTE Confidence: 0.89274465

00:16:59.764 --> 00:17:01.674 And you can see here,
NOTE Confidence: 0.89274465

00:17:01.680 --> 00:17:03.804 we've treated mice that have gotten
NOTE Confidence: 0.89274465

00:17:03.804 --> 00:17:05.520 these cells injected with the,
NOTE Confidence: 0.89274465

00:17:05.520 --> 00:17:06.020 the min,
NOTE Confidence: 0.89274465

00:17:06.020 --> 00:17:07.520 an inhibitor for this period of
NOTE Confidence: 0.89274465

00:17:07.520 --> 00:17:08.480 time and in fact,
NOTE Confidence: 0.89274465

00:17:08.480 --> 00:17:11.399 it eradicated the disease in this model.
NOTE Confidence: 0.89274465

00:17:11.400 --> 00:17:13.444 So that is again very different from
NOTE Confidence: 0.89274465

00:17:13.444 --> 00:17:15.902 what most of the graphs will look like
NOTE Confidence: 0.89274465

00:17:15.902 --> 00:17:18.080 when you do an experiment like this.
NOTE Confidence: 0.89274465

00:17:18.080 --> 00:17:20.456 So really indicating that

NOTE Confidence: 0.89274465

00:17:20.456 --> 00:17:22.238 there's significant potential.

NOTE Confidence: 0.89274465

00:17:22.240 --> 00:17:24.354 So I'm going to switch diseases or

NOTE Confidence: 0.89274465

00:17:24.354 --> 00:17:26.217 switch subtypes of leukemia and tell

NOTE Confidence: 0.89274465

00:17:26.217 --> 00:17:28.296 you a little bit about a different

NOTE Confidence: 0.89274465

00:17:28.354 --> 00:17:31.092 subtype that one is interesting and

NOTE Confidence: 0.89274465

00:17:31.092 --> 00:17:33.432 two actually kind of changed the

NOTE Confidence: 0.89274465

00:17:33.432 --> 00:17:35.400 level of interest from biotech and

NOTE Confidence: 0.89274465

00:17:35.469 --> 00:17:37.599 pharma because it's way more common

NOTE Confidence: 0.89274465

00:17:37.600 --> 00:17:40.396 and that's NPM one mutant AML.

NOTE Confidence: 0.89274465

00:17:40.400 --> 00:17:42.563 And I keep saying that because as

NOTE Confidence: 0.89274465

00:17:42.563 --> 00:17:44.452 you can probably tell in paediatrics

NOTE Confidence: 0.89274465

00:17:44.452 --> 00:17:45.756 and other rare cancers,

NOTE Confidence: 0.89274465

00:17:45.760 --> 00:17:47.944 we're constantly and many of you

NOTE Confidence: 0.89274465

00:17:47.944 --> 00:17:49.690 probably recognize this when we're

NOTE Confidence: 0.89274465

00:17:49.690 --> 00:17:51.640 talking about drug discovery and development,

NOTE Confidence: 0.89274465

00:17:51.640 --> 00:17:53.518 having to convince people to work
NOTE Confidence: 0.89274465

00:17:53.518 --> 00:17:55.608 on the diseases we're interested in
NOTE Confidence: 0.89274465

00:17:55.608 --> 00:17:57.558 because they're indeed quite rare.
NOTE Confidence: 0.926010796

00:17:57.560 --> 00:18:00.296 When you go from 1000 to 2000 patients per
NOTE Confidence: 0.926010796

00:18:00.296 --> 00:18:02.976 year in the United States to 15 into 17,000
NOTE Confidence: 0.926010796

00:18:02.976 --> 00:18:04.880 patients per year in the United States,
NOTE Confidence: 0.926010796

00:18:04.880 --> 00:18:07.155 you actually get a lot more interest.
NOTE Confidence: 0.926010796

00:18:07.160 --> 00:18:09.176 And so that's one of the
NOTE Confidence: 0.926010796

00:18:09.176 --> 00:18:10.880 reasons beyond just the the,
NOTE Confidence: 0.926010796

00:18:10.880 --> 00:18:12.352 the mechanistic interest that
NOTE Confidence: 0.926010796

00:18:12.352 --> 00:18:14.192 I think this is important.
NOTE Confidence: 0.926010796

00:18:14.200 --> 00:18:16.792 So Michael Kuhn, when we were in New York,
NOTE Confidence: 0.926010796

00:18:16.800 --> 00:18:19.944 a fellow at the time asked
NOTE Confidence: 0.926010796

00:18:19.944 --> 00:18:21.090 the question of well, OK,
NOTE Confidence: 0.926010796

00:18:21.090 --> 00:18:22.840 we know that the MLO rearranged leukemias.
NOTE Confidence: 0.926010796

00:18:22.840 --> 00:18:25.288 This is a gene expression data for

NOTE Confidence: 0.926010796

00:18:25.288 --> 00:18:27.560 the HOX genes and MIS ones from Tim

NOTE Confidence: 0.926010796

00:18:27.633 --> 00:18:29.633 LAYS group in a bunch of AM LS,

NOTE Confidence: 0.926010796

00:18:29.640 --> 00:18:31.000 and you probably know how to read these.

NOTE Confidence: 0.926010796

00:18:31.000 --> 00:18:32.967 Each row here is AG in each

NOTE Confidence: 0.926010796

00:18:32.967 --> 00:18:34.280 column with leukemia sample.

NOTE Confidence: 0.926010796

00:18:34.280 --> 00:18:36.730 And here's the MLL rearranged group OX,

NOTE Confidence: 0.926010796

00:18:36.730 --> 00:18:39.320 A cluster we know that's long known.

NOTE Confidence: 0.926010796

00:18:39.320 --> 00:18:41.301 In fact, some of the microarray data

NOTE Confidence: 0.926010796

00:18:41.301 --> 00:18:43.201 that I did as a fellow demonstrated

NOTE Confidence: 0.926010796

00:18:43.201 --> 00:18:45.769 that the Hox A cluster is expressed in

NOTE Confidence: 0.926010796

00:18:45.769 --> 00:18:48.200 MLL rearranged leukemias as is MIS one.

NOTE Confidence: 0.926010796

00:18:48.200 --> 00:18:50.840 Those are two targets of the ML effusion

NOTE Confidence: 0.926010796

00:18:50.840 --> 00:18:53.679 that have been worked on for many decades.

NOTE Confidence: 0.926010796

00:18:53.680 --> 00:18:55.936 It turns out in the NPM one mutant

NOTE Confidence: 0.926010796

00:18:55.936 --> 00:18:58.395 leukemia as you can see here on the right,

NOTE Confidence: 0.926010796

00:18:58.400 --> 00:19:00.948 they have the Hox A cluster as
NOTE Confidence: 0.926010796

00:19:00.948 --> 00:19:02.360 well and B cluster,
NOTE Confidence: 0.926010796

00:19:02.360 --> 00:19:04.400 another Hox cluster and MIS one.
NOTE Confidence: 0.926010796

00:19:04.400 --> 00:19:06.568 So this has also been known for some
NOTE Confidence: 0.926010796

00:19:06.568 --> 00:19:09.112 time that this subset of AML and PM one
NOTE Confidence: 0.926010796

00:19:09.112 --> 00:19:11.480 mutant also tends to express the Hox genes.
NOTE Confidence: 0.926010796

00:19:11.480 --> 00:19:14.798 So Michael using CRISPR which in
NOTE Confidence: 0.926010796

00:19:14.798 --> 00:19:17.657 2016 was still relatively new did
NOTE Confidence: 0.926010796

00:19:17.657 --> 00:19:19.199 a what's called a domain scan.
NOTE Confidence: 0.926010796

00:19:19.200 --> 00:19:20.920 I won't get into the details of that,
NOTE Confidence: 0.926010796

00:19:20.920 --> 00:19:23.916 but the point being that the inactivation
NOTE Confidence: 0.926010796

00:19:23.916 --> 00:19:27.165 of MLL and ultimately I mean of men
NOTE Confidence: 0.926010796

00:19:27.165 --> 00:19:29.708 and MLL led to differentiation and
NOTE Confidence: 0.926010796

00:19:29.708 --> 00:19:33.199 ultimately death of NPM one mutant AML cells.
NOTE Confidence: 0.926010796

00:19:33.200 --> 00:19:36.000 And the concept being at the time
NOTE Confidence: 0.926010796

00:19:36.000 --> 00:19:38.213 that the disruption of MLL and

NOTE Confidence: 0.926010796

00:19:38.213 --> 00:19:40.556 Menon in the NPM one state somehow

NOTE Confidence: 0.926010796

00:19:40.556 --> 00:19:44.364 leads to a decrease in the Hox gene

NOTE Confidence: 0.926010796

00:19:44.364 --> 00:19:46.319 expression and therefore ultimately

NOTE Confidence: 0.926010796

00:19:46.319 --> 00:19:49.277 a enemies one expression and therefore

NOTE Confidence: 0.926010796

00:19:49.277 --> 00:19:51.640 ultimately changes in gene expression.

NOTE Confidence: 0.926010796

00:19:51.640 --> 00:19:52.124 Hannah Okleman,

NOTE Confidence: 0.926010796

00:19:52.124 --> 00:19:54.403 who was a a fellow in the lab just

NOTE Confidence: 0.926010796

00:19:54.403 --> 00:19:55.803 recently moved back to Germany

NOTE Confidence: 0.926010796

00:19:55.803 --> 00:19:57.200 to start her own lab,

NOTE Confidence: 0.926010796

00:19:57.200 --> 00:20:00.000 then demonstrated that similar to

NOTE Confidence: 0.926010796

00:20:00.000 --> 00:20:03.576 the MLL fusions that NPM 1 mutations

NOTE Confidence: 0.926010796

00:20:03.576 --> 00:20:06.456 in mouse models could transform

NOTE Confidence: 0.926010796

00:20:06.456 --> 00:20:08.760 multiple hematopoietic cell types,

NOTE Confidence: 0.926010796

00:20:08.760 --> 00:20:10.853 stem cells a little bit more significantly

NOTE Confidence: 0.926010796

00:20:10.853 --> 00:20:12.360 more efficiently than progenitors,

NOTE Confidence: 0.926010796

00:20:12.360 --> 00:20:15.445 but also could transform progenitors
NOTE Confidence: 0.926010796

00:20:15.445 --> 00:20:17.022 as well and.
NOTE Confidence: 0.926010796

00:20:17.022 --> 00:20:18.048 Needless to say,
NOTE Confidence: 0.926010796

00:20:18.048 --> 00:20:21.481 there was still a question as to kind of
NOTE Confidence: 0.926010796

00:20:21.481 --> 00:20:23.440 mechanistically how all this was working.
NOTE Confidence: 0.926010796

00:20:23.440 --> 00:20:26.114 I'm going to summarize some chip seek
NOTE Confidence: 0.926010796

00:20:26.114 --> 00:20:29.040 data here that really shows that at
NOTE Confidence: 0.926010796

00:20:29.040 --> 00:20:31.596 least at this level of understanding,
NOTE Confidence: 0.926010796

00:20:31.600 --> 00:20:34.134 it's quite similar to what we see
NOTE Confidence: 0.926010796

00:20:34.134 --> 00:20:36.880 with the MLL rearranged leukemia.
NOTE Confidence: 0.926010796

00:20:36.880 --> 00:20:39.106 So these are NPM one mutant cell
NOTE Confidence: 0.926010796

00:20:39.106 --> 00:20:41.063 lines where we're doing chromatin
NOTE Confidence: 0.926010796

00:20:41.063 --> 00:20:43.408 immunoprecipitation for men and for
NOTE Confidence: 0.926010796

00:20:43.408 --> 00:20:47.066 example either in a control setting in
NOTE Confidence: 0.926010796

00:20:47.066 --> 00:20:49.238 black PMSO treated cells or the min
NOTE Confidence: 0.926010796

00:20:49.238 --> 00:20:51.070 inhibitor treated cells and you can see

NOTE Confidence: 0.926010796

00:20:51.070 --> 00:20:52.680 that min and comes off of chromatin.

NOTE Confidence: 0.926010796

00:20:52.680 --> 00:20:54.252 We know that when we treat

NOTE Confidence: 0.926010796

00:20:54.252 --> 00:20:55.300 with the min inhibitor

NOTE Confidence: 0.80620684625

00:20:55.355 --> 00:20:56.690 min and lifts off of

NOTE Confidence: 0.80620684625

00:20:56.690 --> 00:20:58.004 chromatin MLL shown here.

NOTE Confidence: 0.80620684625

00:20:58.004 --> 00:21:00.440 Now this is wild type MLL because

NOTE Confidence: 0.80620684625

00:21:00.516 --> 00:21:02.714 it's a mutant in PM one setting

NOTE Confidence: 0.80620684625

00:21:02.720 --> 00:21:04.238 doesn't come off the Hawks loci.

NOTE Confidence: 0.80620684625

00:21:04.240 --> 00:21:06.760 We'd seen that in the MLL fusion setting

NOTE Confidence: 0.80620684625

00:21:06.760 --> 00:21:09.235 as well but does come off of MES 1.

NOTE Confidence: 0.80620684625

00:21:09.240 --> 00:21:11.688 So this is that concept that I show you

NOTE Confidence: 0.80620684625

00:21:11.688 --> 00:21:13.988 that certain loci respond differently to

NOTE Confidence: 0.80620684625

00:21:13.988 --> 00:21:17.072 the min and inhibitor and this is showing

NOTE Confidence: 0.80620684625

00:21:17.072 --> 00:21:20.400 the RNA SEC or the gene expression.

NOTE Confidence: 0.80620684625

00:21:20.400 --> 00:21:22.360 And you can see that when there's

NOTE Confidence: 0.80620684625

00:21:22.360 --> 00:21:24.062 a correlation between loss of MLL
NOTE Confidence: 0.80620684625

00:21:24.062 --> 00:21:25.682 occupancy and loss of gene expression
NOTE Confidence: 0.80620684625

00:21:25.682 --> 00:21:27.815 and this is that looking at that more
NOTE Confidence: 0.80620684625

00:21:27.815 --> 00:21:29.904 broadly by what's called a GSDA analysis.
NOTE Confidence: 0.80620684625

00:21:29.904 --> 00:21:32.987 So the point being that much like what we saw
NOTE Confidence: 0.80620684625

00:21:32.987 --> 00:21:35.639 in the MLL fusions in the NPM one setting,
NOTE Confidence: 0.80620684625

00:21:35.640 --> 00:21:37.062 you treat with the men inhibitor
NOTE Confidence: 0.80620684625

00:21:37.062 --> 00:21:38.680 men and comes off of chromatin.
NOTE Confidence: 0.80620684625

00:21:38.680 --> 00:21:41.053 The MLL protein itself comes off of
NOTE Confidence: 0.80620684625

00:21:41.053 --> 00:21:43.400 chromatin at about 100 to 150 loci
NOTE Confidence: 0.80620684625

00:21:43.400 --> 00:21:46.040 and those genes lose their expression
NOTE Confidence: 0.80620684625

00:21:46.040 --> 00:21:47.656 when the cells differentiate.
NOTE Confidence: 0.80620684625

00:21:47.656 --> 00:21:51.160 And then if we go into PDX studies to
NOTE Confidence: 0.80620684625

00:21:51.160 --> 00:21:54.120 NPM one mutant flip 3 ITD Co mutant,
NOTE Confidence: 0.80620684625

00:21:54.120 --> 00:21:57.438 these are relatively aggressive AM LS.
NOTE Confidence: 0.80620684625

00:21:57.440 --> 00:21:59.786 You can see again pretty impressive

NOTE Confidence: 0.80620684625

00:21:59.786 --> 00:22:02.000 response in the PDX setting.

NOTE Confidence: 0.80620684625

00:22:02.000 --> 00:22:04.432 And for the people who start do these

NOTE Confidence: 0.80620684625

00:22:04.432 --> 00:22:06.960 types of experiments in the audience,

NOTE Confidence: 0.80620684625

00:22:06.960 --> 00:22:08.822 we actually as you probably know the

NOTE Confidence: 0.80620684625

00:22:08.822 --> 00:22:11.137 standard way to do this is put in

NOTE Confidence: 0.80620684625

00:22:11.137 --> 00:22:12.597 leukemia into an immunodeficient mouse,

NOTE Confidence: 0.80620684625

00:22:12.600 --> 00:22:14.175 the first sign of any leukemia in

NOTE Confidence: 0.80620684625

00:22:14.175 --> 00:22:15.478 the peripheral blood of those mice,

NOTE Confidence: 0.80620684625

00:22:15.480 --> 00:22:16.972 you start treating them.

NOTE Confidence: 0.80620684625

00:22:16.972 --> 00:22:19.210 We actually waited in this experiment

NOTE Confidence: 0.80620684625

00:22:19.273 --> 00:22:21.433 on the right until the mice were ill

NOTE Confidence: 0.80620684625

00:22:21.440 --> 00:22:24.560 and started treating them and actually

NOTE Confidence: 0.80620684625

00:22:24.560 --> 00:22:27.070 we could recover essentially 4 out of

NOTE Confidence: 0.80620684625

00:22:27.070 --> 00:22:29.920 five of the mice and eradicate the disease.

NOTE Confidence: 0.80620684625

00:22:29.920 --> 00:22:32.144 So we stacked the deck against us and

NOTE Confidence: 0.80620684625

00:22:32.144 --> 00:22:34.652 we're still able to to make that or
NOTE Confidence: 0.80620684625

00:22:34.652 --> 00:22:37.360 extend the the survival of those mice.
NOTE Confidence: 0.80620684625

00:22:37.360 --> 00:22:39.446 So to summarize this at this point
NOTE Confidence: 0.80620684625

00:22:39.446 --> 00:22:42.307 we the MIN inhibitor and NPM one
NOTE Confidence: 0.80620684625

00:22:42.307 --> 00:22:44.199 mutant AML induces differentiation,
NOTE Confidence: 0.80620684625

00:22:44.200 --> 00:22:45.506 reverses leukemia,
NOTE Confidence: 0.80620684625

00:22:45.506 --> 00:22:48.118 genic leukemic gene expression,
NOTE Confidence: 0.80620684625

00:22:48.120 --> 00:22:50.514 certain genes like MIS one removes
NOTE Confidence: 0.80620684625

00:22:50.514 --> 00:22:53.513 MLL from those loci and we get
NOTE Confidence: 0.80620684625

00:22:53.513 --> 00:22:54.399 dramatic responses.
NOTE Confidence: 0.80620684625

00:22:54.400 --> 00:22:56.864 So that was exciting and that was
NOTE Confidence: 0.80620684625

00:22:56.864 --> 00:22:59.093 enough to get Janssen and Ichi
NOTE Confidence: 0.80620684625

00:22:59.093 --> 00:23:01.048 and the various other large
NOTE Confidence: 0.80620684625

00:23:01.048 --> 00:23:02.679 pharmaceutical companies interested in,
NOTE Confidence: 0.80620684625

00:23:02.680 --> 00:23:04.508 in small molecule development
NOTE Confidence: 0.80620684625

00:23:04.508 --> 00:23:05.879 of Menon inhibitors.

NOTE Confidence: 0.80620684625
00:23:05.880 --> 00:23:08.238 But it's still there was still
NOTE Confidence: 0.80620684625
00:23:08.240 --> 00:23:11.607 something here we don't quite or didn't
NOTE Confidence: 0.80620684625
00:23:11.607 --> 00:23:14.444 quite understand is why is it that
NOTE Confidence: 0.80620684625
00:23:14.444 --> 00:23:16.927 the NPM one mutant AML is depending
NOTE Confidence: 0.80620684625
00:23:16.927 --> 00:23:20.000 so much on the MLL Menon complex.
NOTE Confidence: 0.80620684625
00:23:20.000 --> 00:23:22.359 So Hannah dug into that as well.
NOTE Confidence: 0.80620684625
00:23:22.360 --> 00:23:23.480 You guys probably know this,
NOTE Confidence: 0.80620684625
00:23:23.480 --> 00:23:25.440 but this is just a little bit
NOTE Confidence: 0.80620684625
00:23:25.440 --> 00:23:27.320 about the mutant NPM one protein.
NOTE Confidence: 0.80620684625
00:23:27.320 --> 00:23:28.958 It's shown here.
NOTE Confidence: 0.80620684625
00:23:28.958 --> 00:23:29.504 Schematically,
NOTE Confidence: 0.80620684625
00:23:29.504 --> 00:23:32.580 it's found mostly in the nucleolus
NOTE Confidence: 0.80620684625
00:23:32.580 --> 00:23:34.893 in the wild type setting,
NOTE Confidence: 0.80620684625
00:23:34.893 --> 00:23:36.558 but when the mutation occurs,
NOTE Confidence: 0.80620684625
00:23:36.560 --> 00:23:38.708 it's a mutation in this nuclear
NOTE Confidence: 0.80620684625

00:23:38.708 --> 00:23:40.539 or localization signal that then
NOTE Confidence: 0.80620684625

00:23:40.539 --> 00:23:42.519 leads to a nuclear export signal.
NOTE Confidence: 0.80620684625

00:23:42.520 --> 00:23:44.832 So the mutant in PM one is largely
NOTE Confidence: 0.80620684625

00:23:44.832 --> 00:23:46.966 found in the cytoplasm and that
NOTE Confidence: 0.80620684625

00:23:46.966 --> 00:23:49.186 was recognized by the people who
NOTE Confidence: 0.80620684625

00:23:49.262 --> 00:23:51.448 initially described this mutation.
NOTE Confidence: 0.80620684625

00:23:51.448 --> 00:23:52.016 However,
NOTE Confidence: 0.80620684625

00:23:52.016 --> 00:23:53.720 there is some
NOTE Confidence: 0.825611378

00:23:53.720 --> 00:23:56.576 that remains the mutant in PM one
NOTE Confidence: 0.825611378

00:23:56.576 --> 00:23:58.883 in the nucleus and we've taken
NOTE Confidence: 0.825611378

00:23:58.883 --> 00:24:01.410 advantage of a system that many of
NOTE Confidence: 0.825611378

00:24:01.490 --> 00:24:03.698 you probably know about where you
NOTE Confidence: 0.825611378

00:24:03.698 --> 00:24:06.318 can now by CRISPR mediated homologous
NOTE Confidence: 0.825611378

00:24:06.318 --> 00:24:09.516 recombination actually tag if you will,
NOTE Confidence: 0.825611378

00:24:09.520 --> 00:24:13.456 whatever gene or protein of interest with a
NOTE Confidence: 0.825611378

00:24:13.456 --> 00:24:15.976 degradable version of FK PP12 shown here.

NOTE Confidence: 0.825611378

00:24:15.976 --> 00:24:18.310 And actually this cell line was made

NOTE Confidence: 0.825611378

00:24:18.310 --> 00:24:20.536 by Peggy Goodell's group in at Baylor

NOTE Confidence: 0.825611378

00:24:20.536 --> 00:24:23.299 and you have a mutant NPM one protein

NOTE Confidence: 0.825611378

00:24:23.299 --> 00:24:24.903 that has this degradable version

NOTE Confidence: 0.825611378

00:24:24.903 --> 00:24:26.910 of F KBP 12 and you can treat them

NOTE Confidence: 0.825611378

00:24:26.968 --> 00:24:28.756 with a small molecule Protac that

NOTE Confidence: 0.825611378

00:24:28.756 --> 00:24:30.320 will degrade the whole thing.

NOTE Confidence: 0.825611378

00:24:30.320 --> 00:24:32.602 So you can degrade the mutant oncoprotein

NOTE Confidence: 0.825611378

00:24:32.602 --> 00:24:34.728 and look fairly rapidly after degradation

NOTE Confidence: 0.825611378

00:24:34.728 --> 00:24:36.894 as to what's happening and here's

NOTE Confidence: 0.825611378

00:24:36.894 --> 00:24:38.919 how rapidly you get degradation.

NOTE Confidence: 0.825611378

00:24:38.920 --> 00:24:40.845 By 60 minutes you've got about half

NOTE Confidence: 0.825611378

00:24:40.845 --> 00:24:43.605 of the mutant protein gone and by 120

NOTE Confidence: 0.825611378

00:24:43.605 --> 00:24:45.075 minutes essentially all of us gone.

NOTE Confidence: 0.825611378

00:24:45.080 --> 00:24:47.144 So it's relatively rapid and these

NOTE Confidence: 0.825611378

00:24:47.144 --> 00:24:48.995 types of experiments are quite
NOTE Confidence: 0.825611378

00:24:48.995 --> 00:24:51.040 illuminating because you really have
NOTE Confidence: 0.825611378

00:24:51.040 --> 00:24:55.919 very tight control over over the system.
NOTE Confidence: 0.825611378

00:24:55.920 --> 00:24:58.688 And what we see is that we get
NOTE Confidence: 0.825611378

00:24:58.688 --> 00:25:00.717 differentiation when we degrade the
NOTE Confidence: 0.825611378

00:25:00.717 --> 00:25:02.822 mutant onca protein and ultimately
NOTE Confidence: 0.825611378

00:25:02.822 --> 00:25:04.957 apoptosis of the cells as well.
NOTE Confidence: 0.825611378

00:25:04.960 --> 00:25:07.080 And this is just the Western blot looking.
NOTE Confidence: 0.825611378

00:25:07.080 --> 00:25:08.790 We can actually separate the mutant
NOTE Confidence: 0.825611378

00:25:08.790 --> 00:25:10.613 protein from the wild type because
NOTE Confidence: 0.825611378

00:25:10.613 --> 00:25:11.239 it's tagged,
NOTE Confidence: 0.825611378

00:25:11.240 --> 00:25:13.960 it's here and you can see that here.
NOTE Confidence: 0.825611378

00:25:13.960 --> 00:25:15.480 This is the cytoplasmic prep,
NOTE Confidence: 0.825611378

00:25:15.480 --> 00:25:17.256 the nuclear prep and the chromatin
NOTE Confidence: 0.825611378

00:25:17.256 --> 00:25:19.444 prep and here's the mutant in PM one
NOTE Confidence: 0.825611378

00:25:19.444 --> 00:25:21.211 and we can control that by degrading

NOTE Confidence: 0.825611378

00:25:21.211 --> 00:25:23.283 it to show that that signal actually

NOTE Confidence: 0.825611378

00:25:23.283 --> 00:25:24.720 is what we think it is.

NOTE Confidence: 0.825611378

00:25:24.720 --> 00:25:26.500 And in fact there is a fair amount

NOTE Confidence: 0.825611378

00:25:26.500 --> 00:25:28.356 of the mutant in PM one in the

NOTE Confidence: 0.825611378

00:25:28.413 --> 00:25:29.580 nucleus and on chromatin.

NOTE Confidence: 0.825611378

00:25:29.580 --> 00:25:31.721 Then if we do chip seek to say

NOTE Confidence: 0.825611378

00:25:31.721 --> 00:25:33.541 where is it in the nucleus and

NOTE Confidence: 0.825611378

00:25:33.541 --> 00:25:35.597 where are where is it on chromatin.

NOTE Confidence: 0.825611378

00:25:35.600 --> 00:25:38.640 You can see here with with two different

NOTE Confidence: 0.825611378

00:25:38.640 --> 00:25:41.720 antibodies in black that the NPM one mutant,

NOTE Confidence: 0.825611378

00:25:41.720 --> 00:25:43.820 NPM one protein is bound to many

NOTE Confidence: 0.825611378

00:25:43.820 --> 00:25:45.867 of the similar genes that we've

NOTE Confidence: 0.825611378

00:25:45.867 --> 00:25:48.033 learned about with the MLL fusion,

NOTE Confidence: 0.825611378

00:25:48.040 --> 00:25:50.000 the Hox cluster MIS one.

NOTE Confidence: 0.825611378

00:25:50.000 --> 00:25:52.439 And when we degrade it that signal goes away.

NOTE Confidence: 0.825611378

00:25:52.440 --> 00:25:53.886 And I keep saying that because
NOTE Confidence: 0.825611378

00:25:53.886 --> 00:25:55.400 particularly with chip seek experiments,
NOTE Confidence: 0.825611378

00:25:55.400 --> 00:25:57.045 the opportunity for background signal
NOTE Confidence: 0.825611378

00:25:57.045 --> 00:25:59.692 is real and this is makes you feel
NOTE Confidence: 0.825611378

00:25:59.692 --> 00:26:01.564 much better that the signal that
NOTE Confidence: 0.825611378

00:26:01.564 --> 00:26:03.528 you're looking at is indeed the
NOTE Confidence: 0.825611378

00:26:03.528 --> 00:26:05.368 signal that you are interested in.
NOTE Confidence: 0.825611378

00:26:05.368 --> 00:26:07.352 And now you actually can go to primary
NOTE Confidence: 0.825611378

00:26:07.352 --> 00:26:08.789 patient samples with those antibodies
NOTE Confidence: 0.825611378

00:26:08.789 --> 00:26:10.808 and see the NPM one protein mutant
NOTE Confidence: 0.825611378

00:26:10.808 --> 00:26:12.677 NPM one protein bound there as well.
NOTE Confidence: 0.825611378

00:26:12.680 --> 00:26:14.528 And here's the list of the top 50
NOTE Confidence: 0.825611378

00:26:14.528 --> 00:26:16.564 or so genes to which the mutant
NOTE Confidence: 0.825611378

00:26:16.564 --> 00:26:18.074 NPM one protein is bound.
NOTE Confidence: 0.825611378

00:26:18.080 --> 00:26:19.898 And you can see as some of these genes
NOTE Confidence: 0.825611378

00:26:19.898 --> 00:26:21.518 that I've already talked about OX,

NOTE Confidence: 0.825611378

00:26:21.520 --> 00:26:23.776 A&B cluster and a number of other genes

NOTE Confidence: 0.825611378

00:26:23.776 --> 00:26:26.128 that we tend to pay attention to and

NOTE Confidence: 0.825611378

00:26:26.128 --> 00:26:28.756 stare at when we're talking about MLL or

NOTE Confidence: 0.825611378

00:26:28.756 --> 00:26:32.600 looking at MLL rearranged leukemias as well.

NOTE Confidence: 0.825611378

00:26:32.600 --> 00:26:34.120 So,

NOTE Confidence: 0.825611378

00:26:34.120 --> 00:26:36.040 but is it controlling gene expression.

NOTE Confidence: 0.825611378

00:26:36.040 --> 00:26:37.855 So now we have mutant

NOTE Confidence: 0.825611378

00:26:37.855 --> 00:26:39.670 NPM one protein bound to

NOTE Confidence: 0.829681794

00:26:39.753 --> 00:26:42.358 interesting sites in on chromatin

NOTE Confidence: 0.829681794

00:26:42.360 --> 00:26:44.418 and we can degrade it and show

NOTE Confidence: 0.829681794

00:26:44.418 --> 00:26:46.120 that that signal is specific.

NOTE Confidence: 0.829681794

00:26:46.120 --> 00:26:48.118 And now what happens to transcription?

NOTE Confidence: 0.829681794

00:26:48.120 --> 00:26:49.800 So this was 24 hours later,

NOTE Confidence: 0.829681794

00:26:49.800 --> 00:26:50.800 quite a bit later.

NOTE Confidence: 0.829681794

00:26:50.800 --> 00:26:52.927 Most of those genes that I just showed

NOTE Confidence: 0.829681794

00:26:52.927 --> 00:26:55.191 you where the NPM one protein is bound,

NOTE Confidence: 0.829681794

00:26:55.200 --> 00:26:56.750 their expression is down and

NOTE Confidence: 0.829681794

00:26:56.750 --> 00:26:58.620 this is an approach called pro

NOTE Confidence: 0.829681794

00:26:58.620 --> 00:27:00.433 seek which I won't get into the

NOTE Confidence: 0.829681794

00:27:00.433 --> 00:27:02.200 details as to how one does this.

NOTE Confidence: 0.829681794

00:27:02.200 --> 00:27:02.884 So many of you,

NOTE Confidence: 0.829681794

00:27:02.884 --> 00:27:04.331 some of you who work on transcription

NOTE Confidence: 0.829681794

00:27:04.331 --> 00:27:05.839 probably know this technique.

NOTE Confidence: 0.829681794

00:27:05.840 --> 00:27:07.685 But essentially it measures the

NOTE Confidence: 0.829681794

00:27:07.685 --> 00:27:10.118 amount of bound RNA polymerase 2 out

NOTE Confidence: 0.829681794

00:27:10.118 --> 00:27:12.214 throughout the length of the gene as a

NOTE Confidence: 0.829681794

00:27:12.276 --> 00:27:14.600 surrogate for transcriptional activity.

NOTE Confidence: 0.829681794

00:27:14.600 --> 00:27:16.632 And what we can see that as quickly

NOTE Confidence: 0.829681794

00:27:16.632 --> 00:27:18.952 as 30 minutes after treatment of the

NOTE Confidence: 0.829681794

00:27:18.952 --> 00:27:21.528 cells with the NPM one protein degrader,

NOTE Confidence: 0.829681794

00:27:21.528 --> 00:27:23.820 you're already seeing a decrease in
NOTE Confidence: 0.829681794

00:27:23.892 --> 00:27:25.802 transcription at those sites where
NOTE Confidence: 0.829681794

00:27:25.802 --> 00:27:28.160 the NPM one was previously bound.
NOTE Confidence: 0.829681794

00:27:28.160 --> 00:27:30.184 And and if you look at it across
NOTE Confidence: 0.829681794

00:27:30.184 --> 00:27:31.760 the the the all express genes
NOTE Confidence: 0.829681794

00:27:31.760 --> 00:27:33.080 you don't see those changes.
NOTE Confidence: 0.829681794

00:27:33.080 --> 00:27:37.300 So in fact it's the NPM one protein's
NOTE Confidence: 0.829681794

00:27:37.300 --> 00:27:40.000 bound there and somehow controlling
NOTE Confidence: 0.829681794

00:27:40.000 --> 00:27:42.400 transcription of these genes.
NOTE Confidence: 0.829681794

00:27:42.400 --> 00:27:43.996 And one of the ways it's doing
NOTE Confidence: 0.829681794

00:27:43.996 --> 00:27:45.919 it is by keeping RNA Pol two,
NOTE Confidence: 0.829681794

00:27:45.920 --> 00:27:47.744 CK nine that that super elongation
NOTE Confidence: 0.829681794

00:27:47.744 --> 00:27:50.396 complex that I told you is critical for
NOTE Confidence: 0.829681794

00:27:50.396 --> 00:27:52.116 transcription bound to those genes.
NOTE Confidence: 0.829681794

00:27:52.120 --> 00:27:54.066 So when we treat with the degrader
NOTE Confidence: 0.829681794

00:27:54.066 --> 00:27:56.356 NPM one comes off and then much

NOTE Confidence: 0.829681794

00:27:56.356 --> 00:27:57.748 of the transcriptional apparatus

NOTE Confidence: 0.829681794

00:27:57.748 --> 00:27:59.840 comes off of those genes as well.

NOTE Confidence: 0.829681794

00:27:59.840 --> 00:28:03.445 So it's maintaining a state that allows

NOTE Confidence: 0.829681794

00:28:03.445 --> 00:28:06.232 for those critical complexes including

NOTE Confidence: 0.829681794

00:28:06.232 --> 00:28:09.437 pole two to to bind to those low side.

NOTE Confidence: 0.829681794

00:28:09.440 --> 00:28:11.920 I'm going to go through the details of

NOTE Confidence: 0.829681794

00:28:11.920 --> 00:28:14.550 this but just to kind of summarize it

NOTE Confidence: 0.829681794

00:28:14.550 --> 00:28:17.037 that when we degrade mutant in PM one,

NOTE Confidence: 0.829681794

00:28:17.040 --> 00:28:19.104 we lose RNA polymerase two occupancy

NOTE Confidence: 0.829681794

00:28:19.104 --> 00:28:21.309 where the NPM one was previously

NOTE Confidence: 0.829681794

00:28:21.309 --> 00:28:22.837 bound within an hour.

NOTE Confidence: 0.829681794

00:28:22.840 --> 00:28:24.120 So off goes NPM one,

NOTE Confidence: 0.829681794

00:28:24.120 --> 00:28:26.486 off comes pole two and a number

NOTE Confidence: 0.829681794

00:28:26.486 --> 00:28:28.206 of other histone modifications

NOTE Confidence: 0.829681794

00:28:28.206 --> 00:28:29.492 like H3K27 acceleration,

NOTE Confidence: 0.829681794

00:28:29.492 --> 00:28:31.853 some of you know associated with various
NOTE Confidence: 0.829681794

00:28:31.853 --> 00:28:33.608 types of gene expression decreases
NOTE Confidence: 0.829681794

00:28:33.608 --> 00:28:35.679 and then the histone modification,
NOTE Confidence: 0.829681794

00:28:35.680 --> 00:28:37.500 other histone modifications start
NOTE Confidence: 0.829681794

00:28:37.500 --> 00:28:39.320 to decrease somewhat later.
NOTE Confidence: 0.829681794

00:28:39.320 --> 00:28:41.119 For those of you interested in transcription,
NOTE Confidence: 0.829681794

00:28:41.120 --> 00:28:43.478 we can talk more about this in detail later,
NOTE Confidence: 0.829681794

00:28:43.480 --> 00:28:45.160 but it looks like it's like when
NOTE Confidence: 0.829681794

00:28:45.160 --> 00:28:46.800 we degrade the mutant in PM one,
NOTE Confidence: 0.829681794

00:28:46.800 --> 00:28:48.325 the decrease in gene expression
NOTE Confidence: 0.829681794

00:28:48.325 --> 00:28:49.240 is actually biphasic.
NOTE Confidence: 0.829681794

00:28:49.240 --> 00:28:51.742 There's so initially there's a decrease
NOTE Confidence: 0.829681794

00:28:51.742 --> 00:28:54.960 of about 50% probably because pole 2
NOTE Confidence: 0.829681794

00:28:54.960 --> 00:28:58.216 is not quite as there's not as much
NOTE Confidence: 0.829681794

00:28:58.216 --> 00:29:00.160 pull two and other complex occupancy.
NOTE Confidence: 0.829681794

00:29:00.160 --> 00:29:02.330 And then after about 3 days we

NOTE Confidence: 0.829681794
00:29:02.330 --> 00:29:04.369 see a dramatic another dramatic
NOTE Confidence: 0.829681794
00:29:04.369 --> 00:29:06.437 decrease in gene expression.
NOTE Confidence: 0.829681794
00:29:06.440 --> 00:29:09.458 We think that's because now the
NOTE Confidence: 0.829681794
00:29:09.458 --> 00:29:11.470 histone modifications are starting
NOTE Confidence: 0.829681794
00:29:11.548 --> 00:29:13.574 to come in and and work together
NOTE Confidence: 0.829681794
00:29:13.574 --> 00:29:15.209 with whatever the previous mechanism
NOTE Confidence: 0.829681794
00:29:15.209 --> 00:29:17.439 was to fully shut off transcription.
NOTE Confidence: 0.971745945
00:29:19.640 --> 00:29:23.280 So how does this connect to to Menon?
NOTE Confidence: 0.9037175
00:29:26.280 --> 00:29:27.320 So
NOTE Confidence: 0.861922117692308
00:29:30.880 --> 00:29:33.480 there we go. So we now if you
NOTE Confidence: 0.861922117692308
00:29:33.480 --> 00:29:35.680 treat with the MIN inhibitor,
NOTE Confidence: 0.861922117692308
00:29:35.680 --> 00:29:38.774 what happens to this chromatin bound in
NOTE Confidence: 0.861922117692308
00:29:38.774 --> 00:29:41.832 mutant in PM one and I'll just quickly
NOTE Confidence: 0.861922117692308
00:29:41.832 --> 00:29:44.591 summarize it by saying you can see here
NOTE Confidence: 0.861922117692308
00:29:44.591 --> 00:29:46.934 here's the mutant in PM one we treat
NOTE Confidence: 0.861922117692308

00:29:46.934 --> 00:29:48.536 with the MIN inhibitor doesn't come
NOTE Confidence: 0.861922117692308

00:29:48.536 --> 00:29:50.327 off the hogs locus but it actually
NOTE Confidence: 0.861922117692308

00:29:50.327 --> 00:29:52.418 does come off of the mis one locus
NOTE Confidence: 0.861922117692308

00:29:52.418 --> 00:29:54.357 exactly where we're seeing MLL come off,
NOTE Confidence: 0.861922117692308

00:29:54.360 --> 00:29:56.696 same thing down here and if you compare
NOTE Confidence: 0.861922117692308

00:29:56.696 --> 00:29:59.085 that the gene expression again those are
NOTE Confidence: 0.861922117692308

00:29:59.085 --> 00:30:01.560 the genes that are losing expression.
NOTE Confidence: 0.861922117692308

00:30:01.560 --> 00:30:04.232 So to summarize what I'm saying here is
NOTE Confidence: 0.861922117692308

00:30:04.232 --> 00:30:07.266 that when we degrade the mutant NPM one
NOTE Confidence: 0.861922117692308

00:30:07.266 --> 00:30:09.480 protein with this degrader molecule,
NOTE Confidence: 0.861922117692308

00:30:09.480 --> 00:30:12.272 we lose RNA pole two CDK 9 and
NOTE Confidence: 0.861922117692308

00:30:12.272 --> 00:30:14.159 ultimately .1 at those loci.
NOTE Confidence: 0.861922117692308

00:30:14.160 --> 00:30:16.408 When we treat with the min inhibitor we
NOTE Confidence: 0.861922117692308

00:30:16.408 --> 00:30:18.921 do the same thing but at a subset of
NOTE Confidence: 0.861922117692308

00:30:18.921 --> 00:30:21.079 the loci where the NPM one is bound.
NOTE Confidence: 0.861922117692308

00:30:21.080 --> 00:30:23.504 So very similar to what's happening

NOTE Confidence: 0.861922117692308
00:30:23.504 --> 00:30:25.120 with the MLL fusion.
NOTE Confidence: 0.861922117692308
00:30:25.120 --> 00:30:27.696 However, we're now looking to see if
NOTE Confidence: 0.861922117692308
00:30:27.696 --> 00:30:29.760 indeed the mechanisms are identical.
NOTE Confidence: 0.861922117692308
00:30:29.760 --> 00:30:31.482 And it turns out that while some
NOTE Confidence: 0.861922117692308
00:30:31.482 --> 00:30:33.079 of the complexes are overlapping,
NOTE Confidence: 0.861922117692308
00:30:33.080 --> 00:30:35.380 these are the mechanisms are
NOTE Confidence: 0.861922117692308
00:30:35.380 --> 00:30:36.656 not perfectly identical.
NOTE Confidence: 0.861922117692308
00:30:36.656 --> 00:30:37.472 That is,
NOTE Confidence: 0.861922117692308
00:30:37.472 --> 00:30:39.104 some complexes are important
NOTE Confidence: 0.861922117692308
00:30:39.104 --> 00:30:40.679 in the MLO fusion,
NOTE Confidence: 0.861922117692308
00:30:40.680 --> 00:30:42.437 not an NPM one and vice versa.
NOTE Confidence: 0.861922117692308
00:30:42.440 --> 00:30:44.565 So we're trying to work through those
NOTE Confidence: 0.861922117692308
00:30:44.565 --> 00:30:46.515 details because as you can imagine,
NOTE Confidence: 0.861922117692308
00:30:46.520 --> 00:30:48.072 the next step that we want to do
NOTE Confidence: 0.861922117692308
00:30:48.072 --> 00:30:50.077 is come in and target some of these
NOTE Confidence: 0.861922117692308

00:30:50.077 --> 00:30:51.464 other complexes with small molecules.

NOTE Confidence: 0.861922117692308

00:30:51.464 --> 00:30:53.192 So to summarize this part before,

NOTE Confidence: 0.861922117692308

00:30:53.200 --> 00:30:56.315 now I move to the clinical translation.

NOTE Confidence: 0.861922117692308

00:30:56.320 --> 00:30:58.512 There are a subset of leukemias that have

NOTE Confidence: 0.861922117692308

00:30:58.512 --> 00:31:00.600 high level Hox gene expression MIS one,

NOTE Confidence: 0.861922117692308

00:31:00.600 --> 00:31:02.439 another transcription factor

NOTE Confidence: 0.861922117692308

00:31:02.439 --> 00:31:04.278 called PBX three.

NOTE Confidence: 0.861922117692308

00:31:04.280 --> 00:31:06.000 This actually accounts for about

NOTE Confidence: 0.861922117692308

00:31:06.000 --> 00:31:09.773 40% of human AML and it's ones

NOTE Confidence: 0.861922117692308

00:31:09.773 --> 00:31:13.040 with these genetic abnormalities,

NOTE Confidence: 0.861922117692308

00:31:13.040 --> 00:31:14.284 MLO rearrangement,

NOTE Confidence: 0.861922117692308

00:31:14.284 --> 00:31:18.638 NPM 1 mutation and I'm actually more

NOTE Confidence: 0.861922117692308

00:31:18.640 --> 00:31:21.094 relatively rare but more common than

NOTE Confidence: 0.861922117692308

00:31:21.094 --> 00:31:23.580 in adults rearrangement called Newt 98

NOTE Confidence: 0.861922117692308

00:31:23.580 --> 00:31:25.920 rearrangements in both pediatric and adult.

NOTE Confidence: 0.861922117692308

00:31:25.920 --> 00:31:28.292 So again accounting for

NOTE Confidence: 0.861922117692308

00:31:28.292 --> 00:31:31.080 about 40% of patients.

NOTE Confidence: 0.861922117692308

00:31:31.080 --> 00:31:35.236 So that all while all that was happening,

NOTE Confidence: 0.861922117692308

00:31:35.240 --> 00:31:37.340 Syndax and another company called cure

NOTE Confidence: 0.861922117692308

00:31:37.340 --> 00:31:39.680 oncology that many of you know about,

NOTE Confidence: 0.861922117692308

00:31:39.680 --> 00:31:41.572 we're developing small molecules

NOTE Confidence: 0.861922117692308

00:31:41.572 --> 00:31:43.720 here Syndax 5613 and here Cure's

NOTE Confidence: 0.841225401818182

00:31:45.760 --> 00:31:47.430 what's now Zytominib and these

NOTE Confidence: 0.841225401818182

00:31:47.430 --> 00:31:49.480 I'll show you some of this,

NOTE Confidence: 0.841225401818182

00:31:49.480 --> 00:31:51.604 the data from the Cindex trial

NOTE Confidence: 0.841225401818182

00:31:51.604 --> 00:31:53.840 and some mechanism of resistance.

NOTE Confidence: 0.841225401818182

00:31:53.840 --> 00:31:56.060 And as I mentioned essentially

NOTE Confidence: 0.841225401818182

00:31:56.060 --> 00:31:59.120 when the NPM one story came out,

NOTE Confidence: 0.841225401818182

00:31:59.120 --> 00:32:01.087 we were called by Janssen and actually

NOTE Confidence: 0.841225401818182

00:32:01.087 --> 00:32:02.629 another couple of other pharmaceutical

NOTE Confidence: 0.841225401818182

00:32:02.629 --> 00:32:04.555 companies and at least these three

NOTE Confidence: 0.841225401818182

00:32:04.555 --> 00:32:06.240 now have MIN inhibitors that are
NOTE Confidence: 0.841225401818182

00:32:06.240 --> 00:32:08.462 right on the tails if you will of
NOTE Confidence: 0.841225401818182

00:32:08.462 --> 00:32:10.908 the cure of development and Cindex.
NOTE Confidence: 0.841225401818182

00:32:10.908 --> 00:32:15.024 So this is so now we're into
NOTE Confidence: 0.841225401818182

00:32:15.024 --> 00:32:17.246 patients with the Syndex 5613.
NOTE Confidence: 0.841225401818182

00:32:17.246 --> 00:32:18.944 This is just date some of
NOTE Confidence: 0.841225401818182

00:32:18.944 --> 00:32:20.718 the data from the phase one.
NOTE Confidence: 0.841225401818182

00:32:20.720 --> 00:32:23.408 This is one of the first patients
NOTE Confidence: 0.841225401818182

00:32:23.408 --> 00:32:25.780 that was treated at Dana Farber and
NOTE Confidence: 0.841225401818182

00:32:25.780 --> 00:32:27.320 we were able to get the peripheral
NOTE Confidence: 0.841225401818182

00:32:27.364 --> 00:32:28.636 blood and here are the blast.
NOTE Confidence: 0.841225401818182

00:32:28.640 --> 00:32:30.635 And you can see this is with
NOTE Confidence: 0.841225401818182

00:32:30.635 --> 00:32:31.706 Revumenib that day three,
NOTE Confidence: 0.841225401818182

00:32:31.706 --> 00:32:32.754 not much has happened.
NOTE Confidence: 0.841225401818182

00:32:32.760 --> 00:32:35.084 Day seven start to see a decrease
NOTE Confidence: 0.841225401818182

00:32:35.084 --> 00:32:36.080 in peripheral blast,

NOTE Confidence: 0.841225401818182
00:32:36.080 --> 00:32:38.592 day 14 further decrease and by day 30
NOTE Confidence: 0.841225401818182
00:32:38.592 --> 00:32:40.980 at least the peripheral blood blasts
NOTE Confidence: 0.841225401818182
00:32:40.980 --> 00:32:43.518 are in this case essentially gone.
NOTE Confidence: 0.841225401818182
00:32:43.520 --> 00:32:45.075 Florian Perner is a postdoc
NOTE Confidence: 0.841225401818182
00:32:45.075 --> 00:32:46.319 who was doing this.
NOTE Confidence: 0.841225401818182
00:32:46.320 --> 00:32:48.036 He sorted these cells and looked
NOTE Confidence: 0.841225401818182
00:32:48.036 --> 00:32:50.045 at gene expression and in fact the
NOTE Confidence: 0.841225401818182
00:32:50.045 --> 00:32:51.665 gene expression changes that we see
NOTE Confidence: 0.841225401818182
00:32:51.665 --> 00:32:53.434 here look very similar to what we
NOTE Confidence: 0.841225401818182
00:32:53.434 --> 00:32:55.856 had seen in the preclinical studies
NOTE Confidence: 0.841225401818182
00:32:55.856 --> 00:32:58.276 not being a clinical trialist.
NOTE Confidence: 0.841225401818182
00:32:58.280 --> 00:33:00.152 I'm going to summarize the whole
NOTE Confidence: 0.841225401818182
00:33:00.152 --> 00:33:02.149 phase one right here with a lot
NOTE Confidence: 0.841225401818182
00:33:02.149 --> 00:33:04.233 of work from a lot of people and
NOTE Confidence: 0.841225401818182
00:33:04.233 --> 00:33:06.598 this was published last year.
NOTE Confidence: 0.841225401818182

00:33:06.600 --> 00:33:08.520 This is the Revue Minib Phase

NOTE Confidence: 0.841225401818182

00:33:08.520 --> 00:33:10.010 one with Syndex 5613.

NOTE Confidence: 0.841225401818182

00:33:10.010 --> 00:33:11.960 The other name for it,

NOTE Confidence: 0.841225401818182

00:33:11.960 --> 00:33:14.520 68 patients with relapsed

NOTE Confidence: 0.841225401818182

00:33:14.520 --> 00:33:15.800 refractory leukemia.

NOTE Confidence: 0.841225401818182

00:33:15.800 --> 00:33:17.152 As you probably know,

NOTE Confidence: 0.841225401818182

00:33:17.152 --> 00:33:19.180 many of these patients have had

NOTE Confidence: 0.841225401818182

00:33:19.245 --> 00:33:21.220 tremendous numbers of cycles of

NOTE Confidence: 0.841225401818182

00:33:21.220 --> 00:33:23.558 various types of therapies and the

NOTE Confidence: 0.841225401818182

00:33:23.558 --> 00:33:25.609 CR rate depending on how you count

NOTE Confidence: 0.841225401818182

00:33:25.609 --> 00:33:27.364 CRS and for those of you who do

NOTE Confidence: 0.841225401818182

00:33:27.364 --> 00:33:28.979 clinical trials and A and all we can

NOTE Confidence: 0.841225401818182

00:33:28.979 --> 00:33:30.369 talk about that is somewhere in the

NOTE Confidence: 0.841225401818182

00:33:30.369 --> 00:33:32.495 40% range with an overall response

NOTE Confidence: 0.841225401818182

00:33:32.495 --> 00:33:35.013 rate of about 50% and a median

NOTE Confidence: 0.841225401818182

00:33:35.013 --> 00:33:36.879 duration of response about nine months.

NOTE Confidence: 0.841225401818182
00:33:36.880 --> 00:33:39.400 So for in relapse refractory setting,
NOTE Confidence: 0.841225401818182
00:33:39.400 --> 00:33:41.810 these are actually pretty impressive
NOTE Confidence: 0.841225401818182
00:33:41.810 --> 00:33:44.220 numbers and the cure oncology
NOTE Confidence: 0.841225401818182
00:33:44.293 --> 00:33:46.921 small molecule seems to be doing
NOTE Confidence: 0.841225401818182
00:33:46.921 --> 00:33:48.287 something having similar activity.
NOTE Confidence: 0.841225401818182
00:33:48.287 --> 00:33:50.823 And in fact some of that data from
NOTE Confidence: 0.841225401818182
00:33:50.823 --> 00:33:52.707 Janssen was also just printed presented
NOTE Confidence: 0.841225401818182
00:33:52.707 --> 00:33:55.115 at ASH and it looks like the activity
NOTE Confidence: 0.841225401818182
00:33:55.115 --> 00:33:56.991 of that molecule is is similar.
NOTE Confidence: 0.841225401818182
00:33:56.991 --> 00:33:59.346 So indeed there looks like
NOTE Confidence: 0.841225401818182
00:33:59.346 --> 00:34:00.759 there's significant clinical
NOTE Confidence: 0.841225401818182
00:34:00.759 --> 00:34:02.400 activity of this approach.
NOTE Confidence: 0.841225401818182
00:34:02.400 --> 00:34:05.200 This lot slide just reminds me to
NOTE Confidence: 0.841225401818182
00:34:05.200 --> 00:34:07.686 point out and and then now I'm talking
NOTE Confidence: 0.841225401818182
00:34:07.686 --> 00:34:09.878 to people who are doing AML clinical
NOTE Confidence: 0.841225401818182

00:34:09.878 --> 00:34:11.876 trials in the in the audience.
NOTE Confidence: 0.841225401818182

00:34:11.880 --> 00:34:13.352 An interesting phenomenon that
NOTE Confidence: 0.841225401818182

00:34:13.352 --> 00:34:15.560 you know better than I do,
NOTE Confidence: 0.841225401818182

00:34:15.560 --> 00:34:17.246 but that is influencing how these
NOTE Confidence: 0.841225401818182

00:34:17.246 --> 00:34:19.249 drugs are are able to be developed
NOTE Confidence: 0.841225401818182

00:34:19.249 --> 00:34:21.174 and that is when you treat patients
NOTE Confidence: 0.841225401818182

00:34:21.235 --> 00:34:22.640 with them in an inhibitor,
NOTE Confidence: 0.841225401818182

00:34:22.640 --> 00:34:25.412 many of them will develop this syndrome
NOTE Confidence: 0.841225401818182

00:34:25.412 --> 00:34:26.600 called differentiation syndrome.
NOTE Confidence: 0.841225401818182

00:34:26.600 --> 00:34:29.520 But in this setting it looks a little
NOTE Confidence: 0.841225401818182

00:34:29.520 --> 00:34:30.880 different clinically I'm told,
NOTE Confidence: 0.841225401818182

00:34:30.880 --> 00:34:32.220 than the differentiation syndrome
NOTE Confidence: 0.841225401818182

00:34:32.220 --> 00:34:34.230 that you usually see when you
NOTE Confidence: 0.841225401818182

00:34:34.286 --> 00:34:36.056 treat patients with acute per
NOTE Confidence: 0.841225401818182

00:34:36.056 --> 00:34:37.472 myelocytic leukemia with ATRA.
NOTE Confidence: 0.8399656933333333

00:34:37.480 --> 00:34:40.012 In fact patients have died from

NOTE Confidence: 0.8399656933333333

00:34:40.012 --> 00:34:41.581 this differentiation syndrome and

NOTE Confidence: 0.8399656933333333

00:34:41.581 --> 00:34:43.688 so that has prompted the FDA to

NOTE Confidence: 0.8399656933333333

00:34:43.688 --> 00:34:46.040 call this a dose limiting toxicity.

NOTE Confidence: 0.8399656933333333

00:34:46.040 --> 00:34:47.440 Think about what that means.

NOTE Confidence: 0.8399656933333333

00:34:47.440 --> 00:34:50.504 It means that your your your dose limiting

NOTE Confidence: 0.8399656933333333

00:34:50.504 --> 00:34:53.079 toxicity is actually occurring as a

NOTE Confidence: 0.8399656933333333

00:34:53.079 --> 00:34:55.677 result of efficacy of your molecules.

NOTE Confidence: 0.8399656933333333

00:34:55.680 --> 00:34:58.099 So we can talk about what So I think

NOTE Confidence: 0.8399656933333333

00:34:58.099 --> 00:35:00.240 the FDA is fighting against the the

NOTE Confidence: 0.8399656933333333

00:35:00.240 --> 00:35:02.240 the some things that they shouldn't be,

NOTE Confidence: 0.8399656933333333

00:35:02.240 --> 00:35:04.616 but that's a that's a whole other soapbox

NOTE Confidence: 0.8399656933333333

00:35:04.616 --> 00:35:07.035 that we can talk about if we want to.

NOTE Confidence: 0.8399656933333333

00:35:07.040 --> 00:35:08.392 That would be like for those of you

NOTE Confidence: 0.8399656933333333

00:35:08.392 --> 00:35:09.711 who treat patients with ALL saying you

NOTE Confidence: 0.8399656933333333

00:35:09.711 --> 00:35:11.479 start to see a little tumor lysis syndrome,

NOTE Confidence: 0.8399656933333333

00:35:11.480 --> 00:35:12.630 we'd better stop treating them
NOTE Confidence: 0.8399656933333333

00:35:12.630 --> 00:35:15.960 because that's bad. No, that's good.
NOTE Confidence: 0.8399656933333333

00:35:15.960 --> 00:35:18.528 So with all this in mind and the
NOTE Confidence: 0.8399656933333333

00:35:18.528 --> 00:35:20.519 clinical activity looking interesting,
NOTE Confidence: 0.8399656933333333

00:35:20.520 --> 00:35:22.858 we figured that it was much like
NOTE Confidence: 0.8399656933333333

00:35:22.858 --> 00:35:24.320 any single targeted agent,
NOTE Confidence: 0.8399656933333333

00:35:24.320 --> 00:35:26.553 there was likely to be some mechanism
NOTE Confidence: 0.8399656933333333

00:35:26.553 --> 00:35:28.758 of resistance to that targeted agent.
NOTE Confidence: 0.8399656933333333

00:35:28.760 --> 00:35:31.000 And right about the time we started
NOTE Confidence: 0.8399656933333333

00:35:31.000 --> 00:35:33.166 thinking about this the Broad Institute
NOTE Confidence: 0.8399656933333333

00:35:33.166 --> 00:35:35.578 developed this screening based on or
NOTE Confidence: 0.8399656933333333

00:35:35.578 --> 00:35:37.539 screening approach based on single
NOTE Confidence: 0.8399656933333333

00:35:37.539 --> 00:35:40.293 nucleotide base editing which in fact
NOTE Confidence: 0.8399656933333333

00:35:40.293 --> 00:35:43.972 what you can do is tile in this case
NOTE Confidence: 0.8399656933333333

00:35:43.972 --> 00:35:46.744 Menon the whole length of the gene
NOTE Confidence: 0.8399656933333333

00:35:46.744 --> 00:35:49.062 with guides that will mutate not

NOTE Confidence: 0.8399656933333333

00:35:49.062 --> 00:35:50.874 every nucleotide because of the way

NOTE Confidence: 0.8399656933333333

00:35:50.874 --> 00:35:52.920 that it's designed but where you can

NOTE Confidence: 0.8399656933333333

00:35:52.920 --> 00:35:54.546 mutate the majority of amino acids

NOTE Confidence: 0.8399656933333333

00:35:54.599 --> 00:35:56.315 across the length of that protein

NOTE Confidence: 0.647701627142857

00:35:59.240 --> 00:36:01.634 to to basically do an in a

NOTE Confidence: 0.647701627142857

00:36:01.640 --> 00:36:03.005 cellular mutagenesis screen

NOTE Confidence: 0.647701627142857

00:36:03.005 --> 00:36:05.603 to see if you can phenotypes.

NOTE Confidence: 0.647701627142857

00:36:05.603 --> 00:36:08.187 So what Florian decided to do is to

NOTE Confidence: 0.647701627142857

00:36:08.187 --> 00:36:10.313 get that base editor library made

NOTE Confidence: 0.647701627142857

00:36:10.313 --> 00:36:12.780 for the minute gene treat cells with

NOTE Confidence: 0.647701627142857

00:36:12.780 --> 00:36:15.775 the min an inhibitor and see if there

NOTE Confidence: 0.647701627142857

00:36:15.775 --> 00:36:18.157 were mutations that made the cells

NOTE Confidence: 0.647701627142857

00:36:18.157 --> 00:36:20.517 resistant to the min an inhibitor.

NOTE Confidence: 0.647701627142857

00:36:20.520 --> 00:36:22.888 And in fact there were there shown here

NOTE Confidence: 0.647701627142857

00:36:22.888 --> 00:36:25.480 in two different MLL rearranged lines

NOTE Confidence: 0.647701627142857

00:36:25.480 --> 00:36:29.358 and interestingly enough we we kind of
NOTE Confidence: 0.647701627142857

00:36:29.360 --> 00:36:31.400 looking back this was probably silly.
NOTE Confidence: 0.647701627142857

00:36:31.400 --> 00:36:32.460 We looked at this,
NOTE Confidence: 0.647701627142857

00:36:32.460 --> 00:36:34.050 the new technique and there's a
NOTE Confidence: 0.647701627142857

00:36:34.106 --> 00:36:35.996 little bit of noise and we didn't
NOTE Confidence: 0.647701627142857

00:36:35.996 --> 00:36:37.678 know exactly what to make of
NOTE Confidence: 0.647701627142857

00:36:37.678 --> 00:36:39.033 it looked kind of interesting.
NOTE Confidence: 0.647701627142857

00:36:39.040 --> 00:36:41.232 Florian put it in the drawer and kind
NOTE Confidence: 0.647701627142857

00:36:41.232 --> 00:36:43.238 of didn't do too much more with it
NOTE Confidence: 0.647701627142857

00:36:43.240 --> 00:36:45.544 until we got a call from Ross Levine
NOTE Confidence: 0.647701627142857

00:36:45.544 --> 00:36:48.359 and Etan Stein at Memorial Sloan Kettering.
NOTE Confidence: 0.647701627142857

00:36:48.360 --> 00:36:48.619 Actually,
NOTE Confidence: 0.647701627142857

00:36:48.619 --> 00:36:50.691 I got a like emergent text from Ross
NOTE Confidence: 0.647701627142857

00:36:50.691 --> 00:36:52.376 which I thought something really bad
NOTE Confidence: 0.647701627142857

00:36:52.376 --> 00:36:54.797 had happened and he said we have to talk now.
NOTE Confidence: 0.647701627142857

00:36:54.800 --> 00:36:57.232 So I called him and he said we

NOTE Confidence: 0.647701627142857
00:36:57.232 --> 00:36:59.421 found mutations in Menin in samples
NOTE Confidence: 0.647701627142857
00:36:59.421 --> 00:37:01.306 from patients that have progressed
NOTE Confidence: 0.647701627142857
00:37:01.306 --> 00:37:03.078 on the Menin inhibitor.
NOTE Confidence: 0.647701627142857
00:37:03.080 --> 00:37:04.792 And great, you know,
NOTE Confidence: 0.647701627142857
00:37:04.792 --> 00:37:06.076 what are they?
NOTE Confidence: 0.647701627142857
00:37:06.080 --> 00:37:08.456 And in fact the first one was this
NOTE Confidence: 0.647701627142857
00:37:08.456 --> 00:37:09.925 mutation 3 andine 349.
NOTE Confidence: 0.647701627142857
00:37:09.925 --> 00:37:12.608 So we dug Florian's data out and
NOTE Confidence: 0.647701627142857
00:37:12.608 --> 00:37:13.600 we're like holy cow,
NOTE Confidence: 0.647701627142857
00:37:13.600 --> 00:37:15.808 the patients are getting the same
NOTE Confidence: 0.647701627142857
00:37:15.808 --> 00:37:18.200 mutation that the base header screen
NOTE Confidence: 0.647701627142857
00:37:18.200 --> 00:37:20.573 had suggested they might get even though
NOTE Confidence: 0.647701627142857
00:37:20.573 --> 00:37:22.765 we weren't confident in our in our data
NOTE Confidence: 0.647701627142857
00:37:22.765 --> 00:37:24.720 to go ahead and start studying that.
NOTE Confidence: 0.647701627142857
00:37:24.720 --> 00:37:26.960 But Needless to say with that information,
NOTE Confidence: 0.647701627142857

00:37:26.960 --> 00:37:29.544 we started studying this in quite a bit
NOTE Confidence: 0.647701627142857

00:37:29.544 --> 00:37:32.203 of detail and we went to send X and
NOTE Confidence: 0.647701627142857

00:37:32.203 --> 00:37:34.400 got samples from a number of patients.
NOTE Confidence: 0.647701627142857

00:37:34.400 --> 00:37:36.999 And it looks like within two to
NOTE Confidence: 0.647701627142857

00:37:36.999 --> 00:37:39.560 three months about 40% of the
NOTE Confidence: 0.647701627142857

00:37:39.560 --> 00:37:40.880 patients had developed.
NOTE Confidence: 0.647701627142857

00:37:40.880 --> 00:37:42.160 They weren't in fluorid
NOTE Confidence: 0.647701627142857

00:37:42.160 --> 00:37:43.120 relapse or progression,
NOTE Confidence: 0.647701627142857

00:37:43.120 --> 00:37:45.892 but had developed a clone with
NOTE Confidence: 0.647701627142857

00:37:45.892 --> 00:37:48.520 this a min and mutation in them.
NOTE Confidence: 0.647701627142857

00:37:48.520 --> 00:37:50.123 That's what this is showing here and
NOTE Confidence: 0.647701627142857

00:37:50.123 --> 00:37:51.736 here is like and those mutations
NOTE Confidence: 0.647701627142857

00:37:51.736 --> 00:37:53.196 were not present at screening.
NOTE Confidence: 0.647701627142857

00:37:53.200 --> 00:37:54.816 So this is just a pie chart in
NOTE Confidence: 0.647701627142857

00:37:54.816 --> 00:37:56.627 red here showing you the size of
NOTE Confidence: 0.647701627142857

00:37:56.627 --> 00:37:58.301 the clone that has developed the

NOTE Confidence: 0.647701627142857
00:37:58.301 --> 00:37:59.117 min and mutation.
NOTE Confidence: 0.647701627142857
00:37:59.120 --> 00:38:01.780 So this is acquired selective
NOTE Confidence: 0.647701627142857
00:38:01.780 --> 00:38:04.440 mutational resistance to the men,
NOTE Confidence: 0.647701627142857
00:38:04.440 --> 00:38:06.150 an inhibitor which as most of
NOTE Confidence: 0.647701627142857
00:38:06.150 --> 00:38:07.746 you probably know is considered
NOTE Confidence: 0.647701627142857
00:38:07.746 --> 00:38:09.716 a validation of the therapeutic
NOTE Confidence: 0.647701627142857
00:38:09.716 --> 00:38:11.995 targeting the kinase world when this
NOTE Confidence: 0.647701627142857
00:38:11.995 --> 00:38:13.632 happens and essentially we think
NOTE Confidence: 0.647701627142857
00:38:13.632 --> 00:38:15.961 it's saying the same thing here and
NOTE Confidence: 0.647701627142857
00:38:15.961 --> 00:38:18.353 we found a both in patients with MLO
NOTE Confidence: 0.647701627142857
00:38:18.353 --> 00:38:20.000 rearranged an NPM one mutant AML.
NOTE Confidence: 0.647701627142857
00:38:20.000 --> 00:38:21.799 So this is the, if you will,
NOTE Confidence: 0.647701627142857
00:38:21.800 --> 00:38:24.290 the gold standard for that validation
NOTE Confidence: 0.647701627142857
00:38:24.290 --> 00:38:26.453 of a therapeutic target in patients
NOTE Confidence: 0.647701627142857
00:38:26.453 --> 00:38:28.797 that that that you put so much pressure
NOTE Confidence: 0.647701627142857

00:38:28.797 --> 00:38:30.870 on the target that the cancer mutates.
NOTE Confidence: 0.647701627142857

00:38:30.870 --> 00:38:33.075 It's such that it's no longer effective.
NOTE Confidence: 0.647701627142857

00:38:33.080 --> 00:38:35.117 I'll show you why in a minute.
NOTE Confidence: 0.647701627142857

00:38:35.120 --> 00:38:37.280 And of course as most of you know,
NOTE Confidence: 0.647701627142857

00:38:37.280 --> 00:38:39.368 we can have to have combinations
NOTE Confidence: 0.647701627142857

00:38:39.368 --> 00:38:41.029 anyway and we were able to show that
NOTE Confidence: 0.647701627142857

00:38:41.029 --> 00:38:43.037 we can do the same thing in PDX models.
NOTE Confidence: 0.71167688

00:38:43.040 --> 00:38:44.660 So we take our MLL rearranged
NOTE Confidence: 0.71167688

00:38:44.660 --> 00:38:46.200 or NPM one mutant models,
NOTE Confidence: 0.71167688

00:38:46.200 --> 00:38:48.671 treat them with in an inhibitor and
NOTE Confidence: 0.71167688

00:38:48.671 --> 00:38:51.624 in some cases but not all they will
NOTE Confidence: 0.71167688

00:38:51.624 --> 00:38:54.896 develop the mutations that we see in
NOTE Confidence: 0.71167688

00:38:54.896 --> 00:38:56.760 in the patients and mechanistically
NOTE Confidence: 0.71167688

00:38:56.760 --> 00:38:58.720 we we know how this is working.
NOTE Confidence: 0.71167688

00:38:58.720 --> 00:39:00.560 I won't go into all the details but
NOTE Confidence: 0.71167688

00:39:00.560 --> 00:39:02.680 this is just one chip seek experiment.

NOTE Confidence: 0.71167688

00:39:02.680 --> 00:39:04.507 In the wild type setting you can

NOTE Confidence: 0.71167688

00:39:04.507 --> 00:39:06.280 see Menin comes off of chromatin,

NOTE Confidence: 0.71167688

00:39:06.280 --> 00:39:08.086 this is chip seek increase in

NOTE Confidence: 0.71167688

00:39:08.086 --> 00:39:09.880 concentrations of the Menin inhibitor.

NOTE Confidence: 0.71167688

00:39:09.880 --> 00:39:12.280 But if you have mutated Menin in that

NOTE Confidence: 0.71167688

00:39:12.280 --> 00:39:14.160 cell line, it no longer comes off.

NOTE Confidence: 0.71167688

00:39:14.160 --> 00:39:16.632 And we know now biochemically it's

NOTE Confidence: 0.71167688

00:39:16.632 --> 00:39:19.105 because the binding affinity of the

NOTE Confidence: 0.71167688

00:39:19.105 --> 00:39:21.000 Menin inhibitor has been shifted

NOTE Confidence: 0.71167688

00:39:21.000 --> 00:39:23.299 significantly as a result of those mutations.

NOTE Confidence: 0.71167688

00:39:23.299 --> 00:39:23.998 And in fact,

NOTE Confidence: 0.71167688

00:39:24.000 --> 00:39:26.044 we know this now at the crystal

NOTE Confidence: 0.71167688

00:39:26.044 --> 00:39:27.566 structure level and we know

NOTE Confidence: 0.71167688

00:39:27.566 --> 00:39:29.036 exactly why that's the case.

NOTE Confidence: 0.71167688

00:39:29.040 --> 00:39:32.316 So here's revuminib bound to Menin.

NOTE Confidence: 0.71167688

00:39:32.320 --> 00:39:34.720 You can see over here on the right,
NOTE Confidence: 0.71167688

00:39:34.720 --> 00:39:35.719 these amino acids
NOTE Confidence: 0.958237584444445

00:39:38.520 --> 00:39:40.385 M327T349-G331, all these are mutations
NOTE Confidence: 0.958237584444445

00:39:40.385 --> 00:39:43.840 that have been found in patients.
NOTE Confidence: 0.958237584444445

00:39:43.840 --> 00:39:45.264 Interestingly enough,
NOTE Confidence: 0.958237584444445

00:39:45.264 --> 00:39:48.784 the wild type MLL protein does not
NOTE Confidence: 0.958237584444445

00:39:48.784 --> 00:39:50.860 use those amino acids to anchor
NOTE Confidence: 0.958237584444445

00:39:50.933 --> 00:39:53.033 and that's actually an important
NOTE Confidence: 0.958237584444445

00:39:53.033 --> 00:39:55.133 concept because if you develop
NOTE Confidence: 0.958237584444445

00:39:55.200 --> 00:39:57.632 the mutation that where men and
NOTE Confidence: 0.958237584444445

00:39:57.632 --> 00:40:00.080 the MLL can no longer interact,
NOTE Confidence: 0.958237584444445

00:40:00.080 --> 00:40:01.760 those cells won't survive that.
NOTE Confidence: 0.958237584444445

00:40:01.760 --> 00:40:03.128 So that that that's not an
NOTE Confidence: 0.958237584444445

00:40:03.128 --> 00:40:04.040 option for the cells.
NOTE Confidence: 0.958237584444445

00:40:04.040 --> 00:40:06.044 They have to mutate something that
NOTE Confidence: 0.958237584444445

00:40:06.044 --> 00:40:08.099 doesn't affect MLL but does affect

NOTE Confidence: 0.958237584444445

00:40:08.099 --> 00:40:10.073 the the binding of the inhibitor.

NOTE Confidence: 0.958237584444445

00:40:10.080 --> 00:40:12.400 And in fact that's exactly what they've done.

NOTE Confidence: 0.958237584444445

00:40:12.400 --> 00:40:14.906 They've mutated this region of men and

NOTE Confidence: 0.958237584444445

00:40:14.906 --> 00:40:17.516 that has plays no role in MLL binding.

NOTE Confidence: 0.958237584444445

00:40:17.516 --> 00:40:19.840 And the way that that happens is

NOTE Confidence: 0.958237584444445

00:40:19.911 --> 00:40:21.886 essentially right here the yellow

NOTE Confidence: 0.958237584444445

00:40:21.886 --> 00:40:24.105 is the the min inhibitor bound to

NOTE Confidence: 0.958237584444445

00:40:24.105 --> 00:40:26.538 wild type min and the purple is the

NOTE Confidence: 0.958237584444445

00:40:26.538 --> 00:40:28.434 min inhibitor bound to mutant min.

NOTE Confidence: 0.958237584444445

00:40:28.440 --> 00:40:30.568 And and you can see essentially what's

NOTE Confidence: 0.958237584444445

00:40:30.568 --> 00:40:32.838 called a steric clash which so the the,

NOTE Confidence: 0.958237584444445

00:40:32.840 --> 00:40:35.157 the min inhibitor is pushed out a

NOTE Confidence: 0.958237584444445

00:40:35.157 --> 00:40:37.250 little bit here because of these

NOTE Confidence: 0.958237584444445

00:40:37.250 --> 00:40:39.658 changes in the amino acid and that

NOTE Confidence: 0.958237584444445

00:40:39.732 --> 00:40:42.212 leads to a 10 to 100 fold decrease

NOTE Confidence: 0.958237584444445

00:40:42.212 --> 00:40:43.998 in affinity of this molecule.
NOTE Confidence: 0.958237584444445

00:40:43.998 --> 00:40:46.508 So this is I find this amazing
NOTE Confidence: 0.958237584444445

00:40:46.508 --> 00:40:49.517 because it's rare that you get to see
NOTE Confidence: 0.958237584444445

00:40:49.517 --> 00:40:51.357 molecularly the difference between
NOTE Confidence: 0.958237584444445

00:40:51.360 --> 00:40:54.048 response and resistance which is really
NOTE Confidence: 0.958237584444445

00:40:54.048 --> 00:40:56.896 essentially a few angstroms here of
NOTE Confidence: 0.958237584444445

00:40:56.896 --> 00:41:00.592 this Menon inhibitor binding to to Menon.
NOTE Confidence: 0.958237584444445

00:41:00.600 --> 00:41:04.495 So this we're we're continuing to work
NOTE Confidence: 0.958237584444445

00:41:04.495 --> 00:41:06.440 on mechanisms of resistance in the past
NOTE Confidence: 0.958237584444445

00:41:06.440 --> 00:41:08.192 five or last five or 10 minutes here.
NOTE Confidence: 0.958237584444445

00:41:08.200 --> 00:41:10.876 I'll tell you about some others,
NOTE Confidence: 0.958237584444445

00:41:10.880 --> 00:41:12.980 but just getting back to a little
NOTE Confidence: 0.958237584444445

00:41:12.980 --> 00:41:15.279 bit to that comment I made about
NOTE Confidence: 0.958237584444445

00:41:15.280 --> 00:41:17.685 dose escalation and stopping your
NOTE Confidence: 0.958237584444445

00:41:17.685 --> 00:41:20.090 dose escalation before you perhaps
NOTE Confidence: 0.958237584444445

00:41:20.165 --> 00:41:22.360 get to full potential efficacy.

NOTE Confidence: 0.958237584444445

00:41:22.360 --> 00:41:25.184 And now we see that we're developing or

NOTE Confidence: 0.958237584444445

00:41:25.184 --> 00:41:27.290 patients are developing mutations that

NOTE Confidence: 0.958237584444445

00:41:27.290 --> 00:41:30.719 all they do is shift the curve a little bit.

NOTE Confidence: 0.958237584444445

00:41:30.720 --> 00:41:33.267 It does make you wonder if you'd had a

NOTE Confidence: 0.958237584444445

00:41:33.267 --> 00:41:35.146 higher dose and a higher concentration

NOTE Confidence: 0.958237584444445

00:41:35.146 --> 00:41:37.540 earlier on if you might have prevented

NOTE Confidence: 0.958237584444445

00:41:37.602 --> 00:41:39.960 the cells from developing those mutations.

NOTE Confidence: 0.958237584444445

00:41:39.960 --> 00:41:43.230 So we with send X luckily providing

NOTE Confidence: 0.958237584444445

00:41:43.230 --> 00:41:45.090 us food now with varying amounts

NOTE Confidence: 0.958237584444445

00:41:45.090 --> 00:41:46.839 of the min an inhibitor.

NOTE Confidence: 0.958237584444445

00:41:46.840 --> 00:41:49.368 We were able to do a dose response

NOTE Confidence: 0.958237584444445

00:41:49.368 --> 00:41:51.907 experiment in a PDX model with increasing

NOTE Confidence: 0.958237584444445

00:41:51.907 --> 00:41:54.480 concentrations of the min an inhibitor.

NOTE Confidence: 0.958237584444445

00:41:54.480 --> 00:41:56.454 And you can see here that at

NOTE Confidence: 0.958237584444445

00:41:56.454 --> 00:41:57.680 the lowest concentration point,

NOTE Confidence: 0.958237584444445

00:41:57.680 --> 00:42:00.680 O3 3%, you see no response.
NOTE Confidence: 0.958237584444445

00:42:00.680 --> 00:42:02.738 At the minimal the medium concentration
NOTE Confidence: 0.958237584444445

00:42:02.738 --> 00:42:05.648 here you do see a response and the
NOTE Confidence: 0.958237584444445

00:42:05.648 --> 00:42:07.856 leukemias progress and the vast majority
NOTE Confidence: 0.958237584444445

00:42:07.921 --> 00:42:10.476 of them will have developed the mutation.
NOTE Confidence: 0.958237584444445

00:42:10.480 --> 00:42:11.925 If you then go threefold
NOTE Confidence: 0.958237584444445

00:42:11.925 --> 00:42:14.120 more of them in an inhibitor,
NOTE Confidence: 0.958237584444445

00:42:14.120 --> 00:42:15.680 you get a much longer response.
NOTE Confidence: 0.958237584444445

00:42:15.680 --> 00:42:16.226 In fact,
NOTE Confidence: 0.958237584444445

00:42:16.226 --> 00:42:18.843 maybe some of them here are cured of the
NOTE Confidence: 0.958237584444445

00:42:18.843 --> 00:42:21.075 disease and when the resistance occurs,
NOTE Confidence: 0.958237584444445

00:42:21.080 --> 00:42:23.040 it occurs without the min and mutations.
NOTE Confidence: 0.958237584444445

00:42:23.040 --> 00:42:24.051 So in fact,
NOTE Confidence: 0.958237584444445

00:42:24.051 --> 00:42:25.736 a higher concentration does at
NOTE Confidence: 0.958237584444445

00:42:25.736 --> 00:42:28.101 least in this model prevent the
NOTE Confidence: 0.958237584444445

00:42:28.101 --> 00:42:29.571 development of those mutations.

NOTE Confidence: 0.958237584444445
00:42:29.571 --> 00:42:31.830 So you can see if you stop your dose
NOTE Confidence: 0.958237584444445
00:42:31.893 --> 00:42:34.088 escalation right here because you're
NOTE Confidence: 0.958237584444445
00:42:34.088 --> 00:42:35.405 getting differentiation syndrome
NOTE Confidence: 0.958237584444445
00:42:35.405 --> 00:42:37.516 and somebody tells you you have to,
NOTE Confidence: 0.958237584444445
00:42:37.520 --> 00:42:39.150 you're actually setting up a
NOTE Confidence: 0.958237584444445
00:42:39.150 --> 00:42:40.780 situation where you're going to
NOTE Confidence: 0.905408497272727
00:42:40.837 --> 00:42:43.799 get acquired resistance mutations.
NOTE Confidence: 0.905408497272727
00:42:43.800 --> 00:42:45.036 Having said all that,
NOTE Confidence: 0.905408497272727
00:42:45.036 --> 00:42:46.890 we're still getting resistance way out
NOTE Confidence: 0.905408497272727
00:42:46.944 --> 00:42:49.160 here with the single agent at higher doses.
NOTE Confidence: 0.905408497272727
00:42:49.160 --> 00:42:51.624 So what's that all about and
NOTE Confidence: 0.905408497272727
00:42:51.624 --> 00:42:53.640 I'll quickly summarize this.
NOTE Confidence: 0.905408497272727
00:42:53.640 --> 00:42:55.315 Essentially what we're seeing here
NOTE Confidence: 0.905408497272727
00:42:55.315 --> 00:42:57.382 is that the leukemia cells and
NOTE Confidence: 0.905408497272727
00:42:57.382 --> 00:42:59.057 this is another phenomenon that's
NOTE Confidence: 0.905408497272727

00:42:59.057 --> 00:43:01.089 known in other settings now are
NOTE Confidence: 0.905408497272727

00:43:01.089 --> 00:43:02.997 not mutating the men and they're
NOTE Confidence: 0.905408497272727

00:43:02.997 --> 00:43:04.348 actually changing their state
NOTE Confidence: 0.905408497272727

00:43:04.348 --> 00:43:06.826 significantly to lead to a state that
NOTE Confidence: 0.905408497272727

00:43:06.826 --> 00:43:09.440 we don't understand completely yet,
NOTE Confidence: 0.905408497272727

00:43:09.440 --> 00:43:11.474 but where they're now no longer
NOTE Confidence: 0.905408497272727

00:43:11.474 --> 00:43:13.760 dependent on that Hawks niece program.
NOTE Confidence: 0.905408497272727

00:43:13.760 --> 00:43:15.512 And and in fact interestingly they
NOTE Confidence: 0.905408497272727

00:43:15.512 --> 00:43:16.680 look much more differentiated.
NOTE Confidence: 0.905408497272727

00:43:16.680 --> 00:43:19.563 The leukemias themselves almost
NOTE Confidence: 0.905408497272727

00:43:19.563 --> 00:43:21.778 look like monocytes in terms
NOTE Confidence: 0.905408497272727

00:43:21.778 --> 00:43:24.440 of their their flow cytometry,
NOTE Confidence: 0.905408497272727

00:43:24.440 --> 00:43:25.810 but definitely will transplant the
NOTE Confidence: 0.905408497272727

00:43:25.810 --> 00:43:27.680 disease from 1 bow to the next.
NOTE Confidence: 0.905408497272727

00:43:27.680 --> 00:43:30.000 So they're not monocytes,
NOTE Confidence: 0.905408497272727

00:43:30.000 --> 00:43:31.782 but so we're trying to understand

NOTE Confidence: 0.905408497272727

00:43:31.782 --> 00:43:33.386 this mechanism mode of adaptive

NOTE Confidence: 0.905408497272727

00:43:33.386 --> 00:43:35.156 resistance a little bit better.

NOTE Confidence: 0.905408497272727

00:43:35.160 --> 00:43:37.200 Now have developed a model,

NOTE Confidence: 0.905408497272727

00:43:37.200 --> 00:43:39.616 a cell line model for it and have

NOTE Confidence: 0.905408497272727

00:43:39.616 --> 00:43:41.480 developed some PDX models as well.

NOTE Confidence: 0.905408497272727

00:43:41.480 --> 00:43:44.456 But the cell line model actually

NOTE Confidence: 0.905408497272727

00:43:44.456 --> 00:43:46.938 lets us move to what everyone

NOTE Confidence: 0.905408497272727

00:43:46.938 --> 00:43:48.930 likes to do now which is a genome

NOTE Confidence: 0.905408497272727

00:43:48.983 --> 00:43:50.519 wide CRISPR screen to say OK,

NOTE Confidence: 0.905408497272727

00:43:50.520 --> 00:43:52.614 how did the dependence do the

NOTE Confidence: 0.905408497272727

00:43:52.614 --> 00:43:54.010 dependencies change when you

NOTE Confidence: 0.905408497272727

00:43:54.073 --> 00:43:55.879 go from one state to the next?

NOTE Confidence: 0.905408497272727

00:43:55.880 --> 00:43:56.942 And to summarize,

NOTE Confidence: 0.905408497272727

00:43:56.942 --> 00:43:59.851 a lot of analysis in fact they do

NOTE Confidence: 0.905408497272727

00:43:59.851 --> 00:44:02.683 appear to and this is on a subtle

NOTE Confidence: 0.905408497272727

00:44:02.683 --> 00:44:04.976 transferase CAT6A or MAZ which
NOTE Confidence: 0.905408497272727

00:44:04.976 --> 00:44:07.396 also rearranged rarely in some
NOTE Confidence: 0.905408497272727

00:44:07.396 --> 00:44:10.580 leukemias now becomes seems to become
NOTE Confidence: 0.905408497272727

00:44:10.580 --> 00:44:13.040 relevant in this in this setting.
NOTE Confidence: 0.905408497272727

00:44:13.040 --> 00:44:15.464 So here is just an experiment
NOTE Confidence: 0.905408497272727

00:44:15.464 --> 00:44:16.676 showing you that.
NOTE Confidence: 0.905408497272727

00:44:16.680 --> 00:44:19.596 So we developed resistant leukemia cells
NOTE Confidence: 0.905408497272727

00:44:19.600 --> 00:44:21.357 that don't have the MIN in mutation.
NOTE Confidence: 0.905408497272727

00:44:21.360 --> 00:44:22.878 They're resents to the MIN inhibitor.
NOTE Confidence: 0.905408497272727

00:44:22.880 --> 00:44:24.320 Here it is in blue.
NOTE Confidence: 0.905408497272727

00:44:24.320 --> 00:44:26.301 But if you treat with the cat
NOTE Confidence: 0.905408497272727

00:44:26.301 --> 00:44:28.000 6A in this case guide,
NOTE Confidence: 0.905408497272727

00:44:28.000 --> 00:44:31.300 it re sensitizes the the cell
NOTE Confidence: 0.905408497272727

00:44:31.300 --> 00:44:33.930 line to the MIN inhibitor.
NOTE Confidence: 0.905408497272727

00:44:33.930 --> 00:44:36.480 But interestingly and interestingly enough,
NOTE Confidence: 0.905408497272727

00:44:36.480 --> 00:44:38.125 the CAT 6A by itself in the

NOTE Confidence: 0.905408497272727

00:44:38.125 --> 00:44:39.714 absence of the MIN inhibitor has

NOTE Confidence: 0.905408497272727

00:44:39.714 --> 00:44:41.358 a little bit of an effect.

NOTE Confidence: 0.905408497272727

00:44:41.360 --> 00:44:44.750 It's really something about the relationship

NOTE Confidence: 0.905408497272727

00:44:44.750 --> 00:44:47.516 between CAT6A and Menon that is important.

NOTE Confidence: 0.905408497272727

00:44:47.520 --> 00:44:48.612 So what's CAT6A?

NOTE Confidence: 0.905408497272727

00:44:48.612 --> 00:44:50.796 It's a histone has still transferase

NOTE Confidence: 0.905408497272727

00:44:50.796 --> 00:44:53.073 as well modifies histone H3

NOTE Confidence: 0.905408497272727

00:44:53.073 --> 00:44:55.438 on various lysine shown here.

NOTE Confidence: 0.905408497272727

00:44:55.440 --> 00:44:58.180 And if you do now chip seek in either O

NOTE Confidence: 0.905408497272727

00:44:58.254 --> 00:45:01.278 sensitive leukemia cell lines or resistant,

NOTE Confidence: 0.905408497272727

00:45:01.280 --> 00:45:05.706 the MLL Menon and CAT6A chip seek

NOTE Confidence: 0.905408497272727

00:45:05.706 --> 00:45:08.344 data looks very similar and in so here

NOTE Confidence: 0.905408497272727

00:45:08.344 --> 00:45:10.201 both in the sensitive or the resistant

NOTE Confidence: 0.905408497272727

00:45:10.201 --> 00:45:12.406 and this is just showing that more

NOTE Confidence: 0.905408497272727

00:45:12.406 --> 00:45:14.477 broadly so men and Catsix is there,

NOTE Confidence: 0.905408497272727

00:45:14.480 --> 00:45:17.240 it's on the scene and it becomes seems
NOTE Confidence: 0.905408497272727

00:45:17.240 --> 00:45:19.843 to become much more important when the
NOTE Confidence: 0.905408497272727

00:45:19.843 --> 00:45:22.760 cells adapt to the men and inhibitor.
NOTE Confidence: 0.905408497272727

00:45:22.760 --> 00:45:23.768 Needless to say,
NOTE Confidence: 0.905408497272727

00:45:23.768 --> 00:45:25.784 we're now doing the experiments to
NOTE Confidence: 0.905408497272727

00:45:25.784 --> 00:45:28.594 see if this combination in mice will
NOTE Confidence: 0.905408497272727

00:45:28.594 --> 00:45:33.118 reverse the resistance in patient samples.
NOTE Confidence: 0.905408497272727

00:45:33.120 --> 00:45:34.995 It won't reverse the resistance
NOTE Confidence: 0.905408497272727

00:45:34.995 --> 00:45:36.120 to the mutations,
NOTE Confidence: 0.905408497272727

00:45:36.120 --> 00:45:38.230 but it might reverse the
NOTE Confidence: 0.905408497272727

00:45:38.230 --> 00:45:40.076 resistance to the adapted form.
NOTE Confidence: 0.905408497272727

00:45:40.076 --> 00:45:42.400 But the men inhibitor works well enough,
NOTE Confidence: 0.905408497272727

00:45:42.400 --> 00:45:44.115 it's hard to generate that adaptive form,
NOTE Confidence: 0.905408497272727

00:45:44.120 --> 00:45:46.997 so it's taking us a little while.
NOTE Confidence: 0.905408497272727

00:45:47.000 --> 00:45:50.393 I'm going to skip this just for time's sake,
NOTE Confidence: 0.847159214545455

00:45:50.400 --> 00:45:54.064 but to and just to summarize saying that

NOTE Confidence: 0.847159214545455

00:45:54.064 --> 00:45:56.644 these complexes here, the .1 complex,

NOTE Confidence: 0.847159214545455

00:45:56.644 --> 00:45:58.196 the Super elongation complex,

NOTE Confidence: 0.847159214545455

00:45:58.200 --> 00:46:01.856 I've been talking about MLL and CAT6A.

NOTE Confidence: 0.847159214545455

00:46:01.856 --> 00:46:03.680 If you look broadly,

NOTE Confidence: 0.847159214545455

00:46:03.680 --> 00:46:06.088 some of you probably know that Broad

NOTE Confidence: 0.847159214545455

00:46:06.088 --> 00:46:07.843 Institute's been doing broad CRISPR

NOTE Confidence: 0.847159214545455

00:46:07.843 --> 00:46:10.153 screens on five 600 cancer cell lines,

NOTE Confidence: 0.847159214545455

00:46:10.160 --> 00:46:12.015 and they make all this data publicly

NOTE Confidence: 0.847159214545455

00:46:12.015 --> 00:46:13.599 available in many different ways.

NOTE Confidence: 0.847159214545455

00:46:13.600 --> 00:46:15.120 You can search that data.

NOTE Confidence: 0.847159214545455

00:46:15.120 --> 00:46:18.410 If you ask what genes have a

NOTE Confidence: 0.847159214545455

00:46:18.410 --> 00:46:20.499 similar dependency to Menin

NOTE Confidence: 0.847159214545455

00:46:20.499 --> 00:46:23.399 throughout all of cancer space,

NOTE Confidence: 0.847159214545455

00:46:23.400 --> 00:46:25.600 .1 is the next thing on the list.

NOTE Confidence: 0.847159214545455

00:46:25.600 --> 00:46:28.090 And then and then these other

NOTE Confidence: 0.847159214545455

00:46:28.090 --> 00:46:30.475 proteins here E&L which is part of
NOTE Confidence: 0.847159214545455

00:46:30.475 --> 00:46:32.520 the Super elongation complex CAT6.
NOTE Confidence: 0.847159214545455

00:46:32.520 --> 00:46:34.619 A point being these,
NOTE Confidence: 0.847159214545455

00:46:34.619 --> 00:46:36.784 it's clear that these complexes
NOTE Confidence: 0.847159214545455

00:46:36.784 --> 00:46:38.840 are working together somehow
NOTE Confidence: 0.847159214545455

00:46:38.840 --> 00:46:41.360 throughout many cancer cell lines,
NOTE Confidence: 0.847159214545455

00:46:41.360 --> 00:46:43.160 Leukemia for sure,
NOTE Confidence: 0.847159214545455

00:46:43.160 --> 00:46:46.412 but also probably others as well.
NOTE Confidence: 0.847159214545455

00:46:46.412 --> 00:46:49.756 And in fact that led us to this
NOTE Confidence: 0.847159214545455

00:46:49.756 --> 00:46:51.180 publication for actually for
NOTE Confidence: 0.847159214545455

00:46:51.180 --> 00:46:53.918 about a year and a half ago now.
NOTE Confidence: 0.847159214545455

00:46:53.920 --> 00:46:56.240 Matt Hemming,
NOTE Confidence: 0.847159214545455

00:46:56.240 --> 00:46:58.460 a paediatric or medical oncology
NOTE Confidence: 0.847159214545455

00:46:58.460 --> 00:47:00.236 fellow was interested in
NOTE Confidence: 0.847159214545455

00:47:00.236 --> 00:47:01.409 gastrointestinal stromal tumors
NOTE Confidence: 0.847159214545455

00:47:01.409 --> 00:47:03.719 and just did a genome wide CRISPR

NOTE Confidence: 0.847159214545455
00:47:03.719 --> 00:47:05.816 screen because that's how you start
NOTE Confidence: 0.847159214545455
00:47:05.816 --> 00:47:07.800 every project these days it seems.
NOTE Confidence: 0.847159214545455
00:47:07.800 --> 00:47:10.184 And in fact cat 6A was one of
NOTE Confidence: 0.847159214545455
00:47:10.184 --> 00:47:12.478 the top hits in that screen.
NOTE Confidence: 0.847159214545455
00:47:12.480 --> 00:47:15.680 And then we looked a little bit more in more
NOTE Confidence: 0.847159214545455
00:47:15.762 --> 00:47:18.400 detail .1 and Menin were in there as well.
NOTE Confidence: 0.847159214545455
00:47:18.400 --> 00:47:19.400 And the bottom line is,
NOTE Confidence: 0.847159214545455
00:47:19.400 --> 00:47:23.072 is it appears that this CAT6,
NOTE Confidence: 0.847159214545455
00:47:23.072 --> 00:47:27.688 A .1 Menin complex cooperation is
NOTE Confidence: 0.847159214545455
00:47:27.688 --> 00:47:31.560 important in this type of cancer as well.
NOTE Confidence: 0.847159214545455
00:47:31.560 --> 00:47:33.240 And we don't understand,
NOTE Confidence: 0.847159214545455
00:47:33.240 --> 00:47:36.018 you might ask why should ask why?
NOTE Confidence: 0.847159214545455
00:47:36.018 --> 00:47:37.482 We don't completely understand
NOTE Confidence: 0.847159214545455
00:47:37.482 --> 00:47:38.960 why it's the case.
NOTE Confidence: 0.847159214545455
00:47:38.960 --> 00:47:41.725 But it does appear that when we
NOTE Confidence: 0.847159214545455

00:47:41.725 --> 00:47:44.160 inhibit CAT6A and men and in cell

NOTE Confidence: 0.847159214545455

00:47:44.160 --> 00:47:47.688 lines or in mice or in PDX or

NOTE Confidence: 0.847159214545455

00:47:47.688 --> 00:47:50.172 xenograft models that a program

NOTE Confidence: 0.847159214545455

00:47:50.172 --> 00:47:52.302 that Matt had described earlier

NOTE Confidence: 0.847159214545455

00:47:52.302 --> 00:47:54.046 driven by transcription factors

NOTE Confidence: 0.847159214545455

00:47:54.046 --> 00:47:55.924 like one called hand one,

NOTE Confidence: 0.847159214545455

00:47:55.924 --> 00:47:58.150 which is known to be important

NOTE Confidence: 0.847159214545455

00:47:58.227 --> 00:48:00.280 for controlling lineage associated

NOTE Confidence: 0.847159214545455

00:48:00.280 --> 00:48:02.680 gene expression in this cancer,

NOTE Confidence: 0.847159214545455

00:48:02.680 --> 00:48:04.560 certain goes down pretty rapidly.

NOTE Confidence: 0.847159214545455

00:48:04.560 --> 00:48:06.605 So there's something about the

NOTE Confidence: 0.847159214545455

00:48:06.605 --> 00:48:08.241 developmental program and this

NOTE Confidence: 0.847159214545455

00:48:08.241 --> 00:48:10.655 cancer as well that seems to be

NOTE Confidence: 0.847159214545455

00:48:10.655 --> 00:48:11.951 dependent on these complexes,

NOTE Confidence: 0.847159214545455

00:48:11.960 --> 00:48:14.897 but you don't really see it as

NOTE Confidence: 0.847159214545455

00:48:14.897 --> 00:48:16.679 dramatically as in leukemia until you

NOTE Confidence: 0.847159214545455
00:48:16.679 --> 00:48:18.879 start to combine the the small molecules.
NOTE Confidence: 0.847159214545455
00:48:18.880 --> 00:48:20.000 Many will do a little bit of it,
NOTE Confidence: 0.847159214545455
00:48:20.000 --> 00:48:21.800 Mos cats, XA will do a little bit,
NOTE Confidence: 0.847159214545455
00:48:21.800 --> 00:48:22.800 but when you combine them,
NOTE Confidence: 0.847159214545455
00:48:22.800 --> 00:48:25.474 you really get a a dramatic response.
NOTE Confidence: 0.847159214545455
00:48:25.480 --> 00:48:26.728 So the point being that we're
NOTE Confidence: 0.847159214545455
00:48:26.728 --> 00:48:28.000 looking at this in leukemia,
NOTE Confidence: 0.847159214545455
00:48:28.000 --> 00:48:30.266 but we're starting to move into
NOTE Confidence: 0.847159214545455
00:48:30.266 --> 00:48:33.942 some other cancers as well to see if
NOTE Confidence: 0.847159214545455
00:48:33.942 --> 00:48:35.998 indeed these developmental regulators,
NOTE Confidence: 0.847159214545455
00:48:36.000 --> 00:48:38.800 if you will, might be relevant there.
NOTE Confidence: 0.847159214545455
00:48:38.800 --> 00:48:41.896 I just summarized this data and
NOTE Confidence: 0.847159214545455
00:48:41.896 --> 00:48:43.960 I'll end with this.
NOTE Confidence: 0.847159214545455
00:48:43.960 --> 00:48:46.180 Pfizer just published a paper
NOTE Confidence: 0.847159214545455
00:48:46.180 --> 00:48:47.956 about six months ago.
NOTE Confidence: 0.847159214545455

00:48:47.960 --> 00:48:50.125 They've now developed a clinical
NOTE Confidence: 0.847159214545455

00:48:50.125 --> 00:48:52.240 grade CAT6A inhibitor and in fact
NOTE Confidence: 0.847159214545455

00:48:52.240 --> 00:48:54.436 this small molecule is in phase
NOTE Confidence: 0.847159214545455

00:48:54.436 --> 00:48:56.656 one clinical trials in estrogen
NOTE Confidence: 0.847159214545455

00:48:56.656 --> 00:48:58.432 receptor positive breast cancer.
NOTE Confidence: 0.847159214545455

00:48:58.440 --> 00:49:00.757 And it looks like from this paper
NOTE Confidence: 0.847159214545455

00:49:00.757 --> 00:49:03.373 and we've now done a number of
NOTE Confidence: 0.847159214545455

00:49:03.373 --> 00:49:05.308 experiments as well that somehow
NOTE Confidence: 0.847159214545455

00:49:05.308 --> 00:49:08.063 Menon is supporting the ER driven
NOTE Confidence: 0.847159214545455

00:49:08.063 --> 00:49:09.437 gene expression program.
NOTE Confidence: 0.8125254833333333

00:49:09.440 --> 00:49:12.554 And Needless to say, I mean sorry Cat 6A.
NOTE Confidence: 0.8125254833333333

00:49:12.560 --> 00:49:13.970 Needless to say, we're now looking
NOTE Confidence: 0.8125254833333333

00:49:13.970 --> 00:49:15.878 at this Cat 6A men in combination.
NOTE Confidence: 0.8125254833333333

00:49:15.880 --> 00:49:17.941 And again as much as like that we saw
NOTE Confidence: 0.8125254833333333

00:49:17.941 --> 00:49:20.674 in GIST, it looks like this the ER
NOTE Confidence: 0.8125254833333333

00:49:20.674 --> 00:49:23.009 driven program is highly dependent on

NOTE Confidence: 0.8125254833333333

00:49:23.009 --> 00:49:25.469 those two complexes and we're trying

NOTE Confidence: 0.8125254833333333

00:49:25.469 --> 00:49:28.156 to work through that now as well.

NOTE Confidence: 0.8125254833333333

00:49:28.160 --> 00:49:30.680 So to summarize what I've told you,

NOTE Confidence: 0.8125254833333333

00:49:30.680 --> 00:49:34.136 the MEN in MLO complex is a relevant

NOTE Confidence: 0.8125254833333333

00:49:34.136 --> 00:49:37.360 therapeutic target and snippet subset of

NOTE Confidence: 0.8125254833333333

00:49:37.360 --> 00:49:40.175 AM LS and that acquired somatic mutations

NOTE Confidence: 0.8125254833333333

00:49:40.175 --> 00:49:43.038 in men and are a mechanism of resistance,

NOTE Confidence: 0.8125254833333333

00:49:43.040 --> 00:49:45.206 not the only mechanism of resistance

NOTE Confidence: 0.8125254833333333

00:49:45.206 --> 00:49:47.646 but that clearly validates men and has

NOTE Confidence: 0.8125254833333333

00:49:47.646 --> 00:49:49.518 a therapeutic target in this disease.

NOTE Confidence: 0.8125254833333333

00:49:49.520 --> 00:49:51.991 We're continuing to work on the various

NOTE Confidence: 0.8125254833333333

00:49:51.991 --> 00:49:54.426 types of resistance and we do think

NOTE Confidence: 0.8125254833333333

00:49:54.426 --> 00:49:56.071 that rational combinations like men

NOTE Confidence: 0.8125254833333333

00:49:56.071 --> 00:49:58.003 and CAT6A or men and other things with

NOTE Confidence: 0.8125254833333333

00:49:58.003 --> 00:50:00.539 a lot going on in terms of trying to

NOTE Confidence: 0.8125254833333333

00:50:00.539 --> 00:50:01.760 understand which combinations may
NOTE Confidence: 0.8125254833333333

00:50:01.760 --> 00:50:03.040 prevent development of resistance.
NOTE Confidence: 0.8125254833333333

00:50:03.040 --> 00:50:05.147 And perhaps the most exciting in the
NOTE Confidence: 0.8125254833333333

00:50:05.147 --> 00:50:07.578 longer term is if we can understand
NOTE Confidence: 0.8125254833333333

00:50:07.578 --> 00:50:09.408 where these mechanisms might be
NOTE Confidence: 0.8125254833333333

00:50:09.408 --> 00:50:11.078 important even beyond leukemia.
NOTE Confidence: 0.8125254833333333

00:50:11.080 --> 00:50:12.160 And I think they're going to
NOTE Confidence: 0.8125254833333333

00:50:12.160 --> 00:50:12.520 be opportunities,
NOTE Confidence: 0.8125254833333333

00:50:12.520 --> 00:50:15.112 but we certainly still have work to do to,
NOTE Confidence: 0.8125254833333333

00:50:15.120 --> 00:50:16.056 to prove that.
NOTE Confidence: 0.8125254833333333

00:50:16.056 --> 00:50:18.240 So I've talked much about the people
NOTE Confidence: 0.8125254833333333

00:50:18.309 --> 00:50:20.640 in in the lab that have done the work.
NOTE Confidence: 0.8125254833333333

00:50:20.640 --> 00:50:22.800 These are our collaborators at Dana
NOTE Confidence: 0.8125254833333333

00:50:22.800 --> 00:50:24.972 Farber actually Nathaniel Gray now
NOTE Confidence: 0.8125254833333333

00:50:24.972 --> 00:50:28.040 at Stanford and Ross I mentioned and
NOTE Confidence: 0.8125254833333333

00:50:28.040 --> 00:50:30.961 Chang and Richard who work with Ross

NOTE Confidence: 0.8125254833333333
00:50:30.961 --> 00:50:34.095 at MSK and some of our collaborators
NOTE Confidence: 0.8125254833333333
00:50:34.095 --> 00:50:35.461 throughout HMS community.
NOTE Confidence: 0.8125254833333333
00:50:35.461 --> 00:50:36.604 So thank you,
NOTE Confidence: 0.8125254833333333
00:50:36.604 --> 00:50:38.890 happy to take any questions and
NOTE Confidence: 0.8125254833333333
00:50:38.959 --> 00:50:40.999 thanks for thanks for staying.
NOTE Confidence: 0.8125254833333333
00:50:41.000 --> 00:50:41.080 All
NOTE Confidence: 0.83906405
00:50:48.760 --> 00:50:50.820 right, absolutely spectacular grand
NOTE Confidence: 0.83906405
00:50:50.820 --> 00:50:53.645 rounds really going from basic science to
NOTE Confidence: 0.83906405
00:50:53.645 --> 00:50:55.946 the patient and back and forth and it's
NOTE Confidence: 0.83906405
00:50:55.946 --> 00:50:59.000 absolutely spectacular. Thank you. Yeah
NOTE Confidence: 0.53273008
00:50:59.000 --> 00:51:01.320 and and great talk. So I think
NOTE Confidence: 0.775831832777778
00:51:01.320 --> 00:51:03.816 the main issue and you know as a
NOTE Confidence: 0.775831832777778
00:51:03.816 --> 00:51:05.449 clinical investigator in my mind
NOTE Confidence: 0.775831832777778
00:51:05.449 --> 00:51:07.034 with all epigenetic therapies is,
NOTE Confidence: 0.775831832777778
00:51:07.040 --> 00:51:09.021 is the therapeutic window as you were
NOTE Confidence: 0.775831832777778

00:51:09.021 --> 00:51:11.157 saying like how do you actually disrupt
NOTE Confidence: 0.775831832777778

00:51:11.160 --> 00:51:12.540 translational or transcriptional
NOTE Confidence: 0.775831832777778

00:51:12.540 --> 00:51:15.300 programs that are relevant to the
NOTE Confidence: 0.775831832777778

00:51:15.300 --> 00:51:17.597 leukemia but not to the normal tissue.
NOTE Confidence: 0.775831832777778

00:51:17.600 --> 00:51:20.060 So for example with this index
NOTE Confidence: 0.775831832777778

00:51:20.060 --> 00:51:22.893 particular drug was this as a result
NOTE Confidence: 0.775831832777778

00:51:22.893 --> 00:51:25.085 of screening of thousands of molecules
NOTE Confidence: 0.775831832777778

00:51:25.085 --> 00:51:27.035 and because as you mentioned it,
NOTE Confidence: 0.775831832777778

00:51:27.040 --> 00:51:28.622 it seems like to disrupt only where
NOTE Confidence: 0.775831832777778

00:51:28.622 --> 00:51:29.919 it's relevant to the leukemia,
NOTE Confidence: 0.775831832777778

00:51:29.920 --> 00:51:32.086 but it's not disrupting the MLL
NOTE Confidence: 0.775831832777778

00:51:32.086 --> 00:51:33.760 interactions that are important for
NOTE Confidence: 0.775831832777778

00:51:33.760 --> 00:51:35.640 normal hematopoiesis and other functions.
NOTE Confidence: 0.775831832777778

00:51:35.640 --> 00:51:37.915 So that how did this transition happen?
NOTE Confidence: 0.775831832777778

00:51:37.920 --> 00:51:40.016 It's just a matter of luck or is
NOTE Confidence: 0.775831832777778

00:51:40.016 --> 00:51:42.116 it tons of screening of other yeah

NOTE Confidence: 0.8495477711111111

00:51:42.160 --> 00:51:43.400 you know the old saying

NOTE Confidence: 0.8495477711111111

00:51:43.400 --> 00:51:44.392 better lucky than good.

NOTE Confidence: 0.8495477711111111

00:51:44.400 --> 00:51:48.088 I I think that that's what we found here,

NOTE Confidence: 0.8495477711111111

00:51:48.088 --> 00:51:50.392 meaning that for some reason and

NOTE Confidence: 0.8495477711111111

00:51:50.392 --> 00:51:52.800 we're looking into this men and is

NOTE Confidence: 0.8495477711111111

00:51:52.800 --> 00:51:55.440 only critical for MLL wild type.

NOTE Confidence: 0.8495477711111111

00:51:55.440 --> 00:51:57.805 Obviously this mechanism probably wasn't

NOTE Confidence: 0.8495477711111111

00:51:57.805 --> 00:52:00.170 developed during evolution for MLL

NOTE Confidence: 0.8495477711111111

00:52:00.238 --> 00:52:03.080 fusions to localize to certain loci.

NOTE Confidence: 0.8495477711111111

00:52:03.080 --> 00:52:05.996 So MLL as I mentioned is a monstrous protein.

NOTE Confidence: 0.8495477711111111

00:52:06.000 --> 00:52:08.758 It has many domains that combine chromatin.

NOTE Confidence: 0.8495477711111111

00:52:08.760 --> 00:52:10.923 So it's very likely and there's some

NOTE Confidence: 0.8495477711111111

00:52:10.923 --> 00:52:13.335 data to support this that different

NOTE Confidence: 0.8495477711111111

00:52:13.335 --> 00:52:15.710 domains or different binding partners

NOTE Confidence: 0.8495477711111111

00:52:15.710 --> 00:52:17.697 determine localization to different

NOTE Confidence: 0.8495477711111111

00:52:17.697 --> 00:52:19.158 places throughout chromatin.
NOTE Confidence: 0.8495477711111111

00:52:19.160 --> 00:52:21.348 And it just so happens in this it
NOTE Confidence: 0.8495477711111111

00:52:21.348 --> 00:52:23.172 kind of was predicted by some of the
NOTE Confidence: 0.8495477711111111

00:52:23.172 --> 00:52:25.121 early Cleary work that Menon was a
NOTE Confidence: 0.8495477711111111

00:52:25.121 --> 00:52:26.800 unique dependency in these leukemias.
NOTE Confidence: 0.8495477711111111

00:52:26.800 --> 00:52:30.280 Well that's because it's really
NOTE Confidence: 0.8495477711111111

00:52:30.280 --> 00:52:33.728 intersecting exactly with the
NOTE Confidence: 0.8495477711111111

00:52:33.728 --> 00:52:36.970 important MLL fusion driven targets.
NOTE Confidence: 0.8495477711111111

00:52:36.970 --> 00:52:38.595 We don't know the molecular
NOTE Confidence: 0.8495477711111111

00:52:38.595 --> 00:52:39.840 mechanism for that yet,
NOTE Confidence: 0.8495477711111111

00:52:39.840 --> 00:52:41.611 but basically it's a long way of
NOTE Confidence: 0.8495477711111111

00:52:41.611 --> 00:52:43.444 saying we think there's a multi
NOTE Confidence: 0.8495477711111111

00:52:43.444 --> 00:52:45.134 valent interaction between MLL and
NOTE Confidence: 0.8495477711111111

00:52:45.134 --> 00:52:47.071 chromatin and Menon is only important
NOTE Confidence: 0.8495477711111111

00:52:47.071 --> 00:52:48.877 for a subset of that interaction.
NOTE Confidence: 0.611521578

00:52:50.360 --> 00:52:51.488 Scott, fantastic talk.

NOTE Confidence: 0.611521578

00:52:51.488 --> 00:52:52.942 And the the question about

NOTE Confidence: 0.611521578

00:52:52.942 --> 00:52:53.878 the solar cancer part,

NOTE Confidence: 0.611521578

00:52:53.880 --> 00:52:55.768 so you alluded to that you are it's

NOTE Confidence: 0.611521578

00:52:55.768 --> 00:52:57.752 great to see that you and other

NOTE Confidence: 0.611521578

00:52:57.752 --> 00:52:59.640 companies are looking into this aspect.

NOTE Confidence: 0.611521578

00:52:59.640 --> 00:53:02.076 So, so we know that oxygens are

NOTE Confidence: 0.611521578

00:53:02.076 --> 00:53:03.940 often deregulated in solar cancer

NOTE Confidence: 0.611521578

00:53:03.940 --> 00:53:06.196 as well in addition to leukemia.

NOTE Confidence: 0.611521578

00:53:06.200 --> 00:53:08.996 So what happens to men inhibitor,

NOTE Confidence: 0.611521578

00:53:09.000 --> 00:53:12.240 the men and MLL inhibitor monotherapies,

NOTE Confidence: 0.611521578

00:53:12.240 --> 00:53:13.566 do they have any efficacy in

NOTE Confidence: 0.611521578

00:53:13.566 --> 00:53:15.077 solar cancer or you have to

NOTE Confidence: 0.611521578

00:53:15.077 --> 00:53:16.221 really using combinations before

NOTE Confidence: 0.611521578

00:53:16.221 --> 00:53:17.880 you can see something happening?

NOTE Confidence: 0.60625714

00:53:17.880 --> 00:53:19.560 Yeah, it's good question.

NOTE Confidence: 0.60625714

00:53:19.560 --> 00:53:21.484 So actually it's a good point.
NOTE Confidence: 0.60625714

00:53:21.484 --> 00:53:23.746 There are a number of say subtypes of
NOTE Confidence: 0.60625714

00:53:23.746 --> 00:53:25.558 lung cancer that express HOX genes.
NOTE Confidence: 0.60625714

00:53:25.560 --> 00:53:27.280 We actually haven't looked
NOTE Confidence: 0.60625714

00:53:27.280 --> 00:53:29.000 at that probably should,
NOTE Confidence: 0.60625714

00:53:29.000 --> 00:53:31.758 but in the both in the gastrointestinal
NOTE Confidence: 0.60625714

00:53:31.758 --> 00:53:33.808 stromal tumors and the ER
NOTE Confidence: 0.60625714

00:53:33.808 --> 00:53:35.798 positive breast cancer cell lines,
NOTE Confidence: 0.60625714

00:53:35.800 --> 00:53:39.636 the men inhibitor will slow their growth.
NOTE Confidence: 0.60625714

00:53:39.640 --> 00:53:41.656 So they have some effect and that
NOTE Confidence: 0.60625714

00:53:41.656 --> 00:53:43.880 is it looks like through somehow
NOTE Confidence: 0.60625714

00:53:43.880 --> 00:53:46.040 modulating the ER driven program,
NOTE Confidence: 0.60625714

00:53:46.040 --> 00:53:48.146 but it's much more dramatic both
NOTE Confidence: 0.60625714

00:53:48.146 --> 00:53:49.966 the gene expression changes and
NOTE Confidence: 0.60625714

00:53:49.966 --> 00:53:51.746 the inhibition of proliferation if
NOTE Confidence: 0.60625714

00:53:51.746 --> 00:53:53.564 you combine the minute inhibitor

NOTE Confidence: 0.60625714

00:53:53.564 --> 00:53:55.520 and and the cat 6A inhibitor.

NOTE Confidence: 0.60625714

00:53:55.520 --> 00:53:58.480 So how that works, we don't,

NOTE Confidence: 0.60625714

00:53:58.480 --> 00:54:01.080 we don't completely understand yet.

NOTE Confidence: 0.60625714

00:54:01.080 --> 00:54:04.385 It's a way of saying and and predicting

NOTE Confidence: 0.60625714

00:54:04.385 --> 00:54:06.275 and hopefully get the word out

NOTE Confidence: 0.60625714

00:54:06.275 --> 00:54:08.280 before all the trials get shut down,

NOTE Confidence: 0.60625714

00:54:08.280 --> 00:54:10.005 that the single agents might

NOTE Confidence: 0.60625714

00:54:10.005 --> 00:54:11.040 have some activity,

NOTE Confidence: 0.60625714

00:54:11.040 --> 00:54:12.937 but I suspect they won't be home

NOTE Confidence: 0.60625714

00:54:12.937 --> 00:54:14.954 runs and the companies have to

NOTE Confidence: 0.60625714

00:54:14.954 --> 00:54:16.854 have the wherewithal to actually

NOTE Confidence: 0.60625714

00:54:16.854 --> 00:54:18.880 move forward to the combinations.

NOTE Confidence: 0.60625714

00:54:18.880 --> 00:54:21.620 And those of you who've done this

NOTE Confidence: 0.60625714

00:54:21.620 --> 00:54:23.120 before know that can be difficult.

NOTE Confidence: 0.60625714

00:54:23.120 --> 00:54:26.079 So we're going to try to get the

NOTE Confidence: 0.60625714

00:54:26.079 --> 00:54:27.752 word out that you should move
NOTE Confidence: 0.60625714

00:54:27.752 --> 00:54:29.920 the combinations quickly before
NOTE Confidence: 0.60625714

00:54:29.920 --> 00:54:32.200 people lose interest.
NOTE Confidence: 0.60625714

00:54:32.200 --> 00:54:34.234 There's a lot of psychology and
NOTE Confidence: 0.60625714

00:54:34.234 --> 00:54:36.116 sociology that goes into keeping
NOTE Confidence: 0.60625714

00:54:36.116 --> 00:54:37.956 the drug companies interested,
NOTE Confidence: 0.60625714

00:54:37.960 --> 00:54:39.976 so that's a little bit of a soapbox to
NOTE Confidence: 0.60625714

00:54:39.976 --> 00:54:41.916 say the single agents do something.
NOTE Confidence: 0.60625714

00:54:41.920 --> 00:54:44.280 The combination definitely looks better.
NOTE Confidence: 0.775965477222222

00:54:46.280 --> 00:54:47.612 Manoj, a great talk.
NOTE Confidence: 0.775965477222222

00:54:47.612 --> 00:54:49.610 My question is about the specificity
NOTE Confidence: 0.775965477222222

00:54:49.676 --> 00:54:51.671 of both the MLL fusion proteins and
NOTE Confidence: 0.775965477222222

00:54:51.671 --> 00:54:52.956 the NPM 1C that you alluded to.
NOTE Confidence: 0.775965477222222

00:54:52.960 --> 00:54:55.560 And Amar was also asking.
NOTE Confidence: 0.775965477222222

00:54:55.560 --> 00:54:58.074 So I think you probably worked on this
NOTE Confidence: 0.775965477222222

00:54:58.074 --> 00:54:59.838 on the cancer discovery latest paper,

NOTE Confidence: 0.775965477222222

00:54:59.840 --> 00:55:02.152 but most of them also seem to be

NOTE Confidence: 0.775965477222222

00:55:02.152 --> 00:55:03.830 overlapping with like say PRC 2

NOTE Confidence: 0.775965477222222

00:55:03.830 --> 00:55:05.782 targets or you know are there other

NOTE Confidence: 0.775965477222222

00:55:05.782 --> 00:55:07.762 mechanisms you think are relevant to

NOTE Confidence: 0.775965477222222

00:55:07.762 --> 00:55:09.900 why these are so tightly overlapping

NOTE Confidence: 0.775965477222222

00:55:09.900 --> 00:55:11.800 the fusion proteins and the

NOTE Confidence: 0.86876282

00:55:12.160 --> 00:55:13.798 yeah, so, so it's a good point.

NOTE Confidence: 0.86876282

00:55:13.800 --> 00:55:16.068 So they do overlap significantly with

NOTE Confidence: 0.86876282

00:55:16.068 --> 00:55:19.619 PRC 2 targets and you know as you may

NOTE Confidence: 0.86876282

00:55:19.619 --> 00:55:23.120 remember the the this has been predicted

NOTE Confidence: 0.86876282

00:55:23.120 --> 00:55:25.398 for 3 decades from the Drosophila work.

NOTE Confidence: 0.86876282

00:55:25.400 --> 00:55:27.775 The initial Drosophila work show

NOTE Confidence: 0.86876282

00:55:27.775 --> 00:55:30.050 Polycom and Trithorax actually are

NOTE Confidence: 0.86876282

00:55:30.050 --> 00:55:32.175 known to be genetically genetic

NOTE Confidence: 0.86876282

00:55:32.175 --> 00:55:35.425 antagonists of one another and the the

NOTE Confidence: 0.86876282

00:55:35.425 --> 00:55:37.800 trithorax slash MLL complex controls
NOTE Confidence: 0.86876282

00:55:37.800 --> 00:55:40.192 developmental genes that the PRC two
NOTE Confidence: 0.86876282

00:55:40.192 --> 00:55:42.600 or Polycom complex wants to shut off.
NOTE Confidence: 0.86876282

00:55:42.600 --> 00:55:46.211 So in absolutely this is A these
NOTE Confidence: 0.86876282

00:55:46.211 --> 00:55:48.655 proteins complexes MLL probably
NOTE Confidence: 0.86876282

00:55:48.655 --> 00:55:50.468 Catsix A are inventing.
NOTE Confidence: 0.86876282

00:55:50.468 --> 00:55:52.526 We've shown this in some other settings
NOTE Confidence: 0.86876282

00:55:52.526 --> 00:55:54.568 are preventing the Polycom complexes from
NOTE Confidence: 0.86876282

00:55:54.568 --> 00:55:56.880 coming in and repressing gene expression.
NOTE Confidence: 0.86876282

00:55:56.880 --> 00:55:58.872 So the the way we think that this
NOTE Confidence: 0.86876282

00:55:58.872 --> 00:56:00.473 is working is during hematopoietic
NOTE Confidence: 0.86876282

00:56:00.473 --> 00:56:03.344 development as you go from stem cells to
NOTE Confidence: 0.86876282

00:56:03.344 --> 00:56:05.678 progenitors to fully developed myeloid cells,
NOTE Confidence: 0.86876282

00:56:05.680 --> 00:56:08.228 the Polycom complex at least for a
NOTE Confidence: 0.86876282

00:56:08.228 --> 00:56:10.081 subset of developmental loci are
NOTE Confidence: 0.86876282

00:56:10.081 --> 00:56:12.151 shutting those programs off and the

NOTE Confidence: 0.86876282

00:56:12.151 --> 00:56:14.358 MLL fusion won't let them do that.

NOTE Confidence: 0.86876282

00:56:14.360 --> 00:56:16.590 So they're antagonizing and then

NOTE Confidence: 0.86876282

00:56:16.590 --> 00:56:19.311 Newt 98 fusions and probably NPM

NOTE Confidence: 0.86876282

00:56:19.311 --> 00:56:21.759 one are antagonizing PRC 2 section.

NOTE Confidence: 0.86876282

00:56:21.760 --> 00:56:22.000 Yeah,

NOTE Confidence: 0.8318617833333333

00:56:23.160 --> 00:56:24.205 awesome. I'm going to bring

NOTE Confidence: 0.8318617833333333

00:56:24.205 --> 00:56:25.719 it over to you in a second.

NOTE Confidence: 0.8318617833333333

00:56:25.720 --> 00:56:27.477 We have an online question which I

NOTE Confidence: 0.8318617833333333

00:56:27.477 --> 00:56:28.797 think you probably partially answered

NOTE Confidence: 0.8318617833333333

00:56:28.797 --> 00:56:30.877 and that is what is the mechanism of

NOTE Confidence: 0.8318617833333333

00:56:30.929 --> 00:56:32.758 gene specific targeting of MLL EF9

NOTE Confidence: 0.8318617833333333

00:56:32.758 --> 00:56:34.851 and similarly what you think is the

NOTE Confidence: 0.8318617833333333

00:56:34.851 --> 00:56:36.985 underlying mechanism for the gene target

NOTE Confidence: 0.8318617833333333

00:56:36.985 --> 00:56:38.760 specificity of men and inhibitors.

NOTE Confidence: 0.8318617833333333

00:56:38.760 --> 00:56:40.400 So for the online person, yeah.

NOTE Confidence: 0.8534905055555556

00:56:40.400 --> 00:56:42.632 So it's a good, it's a very good question.
NOTE Confidence: 0.853490505555556

00:56:42.640 --> 00:56:44.760 We do it. I don't the bottom line is,
NOTE Confidence: 0.853490505555556

00:56:44.760 --> 00:56:45.900 is we don't know the answer
NOTE Confidence: 0.853490505555556

00:56:45.946 --> 00:56:47.038 to the second part of that.
NOTE Confidence: 0.853490505555556

00:56:47.040 --> 00:56:50.200 I mean that's the that's at the moment.
NOTE Confidence: 0.853490505555556

00:56:50.200 --> 00:56:51.640 Probably the most critical question
NOTE Confidence: 0.853490505555556

00:56:51.640 --> 00:56:53.810 is why is it that Menon's only
NOTE Confidence: 0.853490505555556

00:56:53.810 --> 00:56:55.635 important for localization of the
NOTE Confidence: 0.853490505555556

00:56:55.635 --> 00:56:57.560 MLL compacts to certain loci.
NOTE Confidence: 0.853490505555556

00:56:57.560 --> 00:56:58.792 So Needless to say,
NOTE Confidence: 0.853490505555556

00:56:58.792 --> 00:57:00.332 we're looking at various aspects
NOTE Confidence: 0.853490505555556

00:57:00.332 --> 00:57:02.548 of those loci to try to understand
NOTE Confidence: 0.853490505555556

00:57:02.548 --> 00:57:04.399 what that's what that's all about.
NOTE Confidence: 0.853490505555556

00:57:04.400 --> 00:57:07.200 MLL targeting to chromatin broadly has many,
NOTE Confidence: 0.853490505555556

00:57:07.200 --> 00:57:08.600 probably has many mechanisms,
NOTE Confidence: 0.853490505555556

00:57:08.600 --> 00:57:11.052 some of its direct there's a domain

NOTE Confidence: 0.853490505555556

00:57:11.052 --> 00:57:13.040 on MLL that binds to what's called

NOTE Confidence: 0.853490505555556

00:57:13.040 --> 00:57:15.716 a CPG island which is upstream of

NOTE Confidence: 0.853490505555556

00:57:15.716 --> 00:57:17.352 many transcriptional start sites.

NOTE Confidence: 0.853490505555556

00:57:17.360 --> 00:57:18.596 Menon plays a role.

NOTE Confidence: 0.853490505555556

00:57:18.596 --> 00:57:20.141 There are other accessory proteins

NOTE Confidence: 0.853490505555556

00:57:20.141 --> 00:57:21.080 that play roles.

NOTE Confidence: 0.853490505555556

00:57:21.080 --> 00:57:23.424 So I think the cell has just given

NOTE Confidence: 0.853490505555556

00:57:23.424 --> 00:57:25.249 itself many options to figure out

NOTE Confidence: 0.853490505555556

00:57:25.249 --> 00:57:28.008 where to put MLL and and each of

NOTE Confidence: 0.853490505555556

00:57:28.008 --> 00:57:29.876 those mechanisms slightly different.

NOTE Confidence: 0.827995068

00:57:31.040 --> 00:57:32.480 We have a trainee question.

NOTE Confidence: 0.7926859

00:57:33.680 --> 00:57:34.680 So my name is trainee,

NOTE Confidence: 0.668171385714286

00:57:36.880 --> 00:57:38.171 I just wanted to follow my name used

NOTE Confidence: 0.668171385714286

00:57:38.171 --> 00:57:39.994 to be that at some point you graduated.

NOTE Confidence: 0.668171385714286

00:57:39.994 --> 00:57:42.210 I just want to follow up on your

NOTE Confidence: 0.668171385714286

00:57:42.274 --> 00:57:44.398 comment about combination therapies.

NOTE Confidence: 0.668171385714286

00:57:44.400 --> 00:57:45.992 So I specifically wanted to ask is there

NOTE Confidence: 0.668171385714286

00:57:45.992 --> 00:57:47.320 any thought that men and inhibition

NOTE Confidence: 0.668171385714286

00:57:47.320 --> 00:57:49.054 could convert these resistant like

NOTE Confidence: 0.668171385714286

00:57:49.054 --> 00:57:50.489 subtypes especially in the pediatric

NOTE Confidence: 0.668171385714286

00:57:50.489 --> 00:57:52.268 setting to a chemosensitive form if

NOTE Confidence: 0.668171385714286

00:57:52.268 --> 00:57:53.723 there's thought of combining with

NOTE Confidence: 0.668171385714286

00:57:53.723 --> 00:57:55.824 chemo to then re sensitize them and

NOTE Confidence: 0.668171385714286

00:57:55.824 --> 00:57:57.400 potentially cure those patients. Yeah,

NOTE Confidence: 0.888061219285714

00:57:57.400 --> 00:57:59.815 it's it's a good short answer is

NOTE Confidence: 0.888061219285714

00:57:59.815 --> 00:58:02.360 we don't know the answer to that.

NOTE Confidence: 0.888061219285714

00:58:02.360 --> 00:58:04.979 I I think there's a lot to be learned

NOTE Confidence: 0.888061219285714

00:58:04.979 --> 00:58:08.077 and the beauty of having now multiple

NOTE Confidence: 0.888061219285714

00:58:08.077 --> 00:58:10.680 small molecule selective small molecules,

NOTE Confidence: 0.888061219285714

00:58:10.680 --> 00:58:14.040 we can do those types of experiments,

NOTE Confidence: 0.888061219285714

00:58:14.040 --> 00:58:15.690 but the short answer is we

NOTE Confidence: 0.888061219285714
00:58:15.690 --> 00:58:17.040 haven't haven't gotten there yet.
NOTE Confidence: 0.86971958
00:58:20.000 --> 00:58:21.029 Yeah, great talk.
NOTE Confidence: 0.86971958
00:58:21.029 --> 00:58:22.744 Have you seen any phenotypic
NOTE Confidence: 0.86971958
00:58:22.744 --> 00:58:24.202 differences in the fusion
NOTE Confidence: 0.86971958
00:58:24.202 --> 00:58:25.800 partners with MML or MLL?
NOTE Confidence: 0.86971958
00:58:25.800 --> 00:58:26.800 You mentioned there's you know,
NOTE Confidence: 0.86971958
00:58:26.800 --> 00:58:27.454 100 different ones.
NOTE Confidence: 0.86971958
00:58:27.454 --> 00:58:29.160 Do they all have the same kind of,
NOTE Confidence: 0.86971958
00:58:29.160 --> 00:58:30.280 you know, break points?
NOTE Confidence: 0.86971958
00:58:30.280 --> 00:58:31.400 Does it change expression?
NOTE Confidence: 0.86971958
00:58:31.400 --> 00:58:32.200 Do you see any variability
NOTE Confidence: 0.86971958
00:58:32.200 --> 00:58:33.240 in the kind of those fusion
NOTE Confidence: 0.887931306111111
00:58:33.240 --> 00:58:35.724 partners? Yeah, it's a good question
NOTE Confidence: 0.887931306111111
00:58:35.724 --> 00:58:38.265 that's been asked for many decades
NOTE Confidence: 0.887931306111111
00:58:38.265 --> 00:58:40.677 and not been answered very well,
NOTE Confidence: 0.887931306111111

00:58:40.680 --> 00:58:42.144 at least in patient samples because
NOTE Confidence: 0.887931306111111

00:58:42.144 --> 00:58:43.716 it's hard to get enough patient
NOTE Confidence: 0.887931306111111

00:58:43.716 --> 00:58:45.620 samples of these subtypes to to ever
NOTE Confidence: 0.887931306111111

00:58:45.620 --> 00:58:47.080 really do that experiment. Well,
NOTE Confidence: 0.895308128

00:58:49.400 --> 00:58:50.880 at least for the fusion,
NOTE Confidence: 0.895308128

00:58:50.880 --> 00:58:52.518 the different fusion AM LS we've
NOTE Confidence: 0.895308128

00:58:52.518 --> 00:58:53.989 assessed and that have been
NOTE Confidence: 0.895308128

00:58:53.989 --> 00:58:55.670 assessed in patients, it doesn't.
NOTE Confidence: 0.895308128

00:58:55.670 --> 00:58:58.155 It's not clear that the fusion partner
NOTE Confidence: 0.895308128

00:58:58.160 --> 00:59:01.800 is determining men and responsiveness.
NOTE Confidence: 0.895308128

00:59:01.800 --> 00:59:03.740 Is the fusion partner influencing
NOTE Confidence: 0.895308128

00:59:03.740 --> 00:59:05.680 the phenotype of the leukemia?
NOTE Confidence: 0.895308128

00:59:05.680 --> 00:59:09.500 I think that question still still
NOTE Confidence: 0.895308128

00:59:09.500 --> 00:59:12.270 open and there's aren't enough good
NOTE Confidence: 0.895308128

00:59:12.270 --> 00:59:14.240 models to really answer that question.
NOTE Confidence: 0.69459664625

00:59:18.360 --> 00:59:20.560 If you delete the at least for AF9,

NOTE Confidence: 0.69459664625

00:59:20.560 --> 00:59:23.080 if you delete the C turn much of the AF9,

NOTE Confidence: 0.69459664625

00:59:23.080 --> 00:59:24.760 it will no longer be transforming.

NOTE Confidence: 0.69459664625

00:59:24.760 --> 00:59:26.800 So that fusion partner is important

NOTE Confidence: 0.68397459

00:59:29.080 --> 00:59:30.599 and and in in the AF9 setting,

NOTE Confidence: 0.68397459

00:59:30.600 --> 00:59:31.965 we think it's important because

NOTE Confidence: 0.68397459

00:59:31.965 --> 00:59:33.890 that's the anchor to drop to pull

NOTE Confidence: 0.68397459

00:59:33.890 --> 00:59:35.155 all those other complexes in.

NOTE Confidence: 0.68397459

00:59:35.160 --> 00:59:37.477 But it's that's a nice simple answer.

NOTE Confidence: 0.68397459

00:59:37.480 --> 00:59:38.945 It's not that simple because

NOTE Confidence: 0.68397459

00:59:38.945 --> 00:59:40.410 some of the fusion proteins

NOTE Confidence: 0.68397459

00:59:40.468 --> 00:59:42.038 don't bind to those complexes.

NOTE Confidence: 0.68397459

00:59:42.040 --> 00:59:44.520 So what they're doing is, is less clear,

NOTE Confidence: 0.9703975

00:59:46.560 --> 00:59:48.225 beautiful talk. Thank you.

NOTE Confidence: 0.9703975

00:59:48.225 --> 00:59:50.200 Obviously there are lots of

NOTE Confidence: 0.9703975

00:59:50.200 --> 00:59:51.720 other chromatin complexes,

NOTE Confidence: 0.751410632222222

00:59:51.720 --> 00:59:53.800 switch, sniff, polychrome, etcetera.
NOTE Confidence: 0.751410632222222

00:59:53.800 --> 00:59:56.400 Any any thoughts on those?
NOTE Confidence: 0.751410632222222

00:59:56.400 --> 00:59:58.110 Are you looking at any exploring
NOTE Confidence: 0.751410632222222

00:59:58.110 --> 01:00:01.600 any of those other chromatin?
NOTE Confidence: 0.751410632222222

01:00:02.080 --> 01:00:03.800 Yeah, accessibility.
NOTE Confidence: 0.751410632222222

01:00:03.800 --> 01:00:05.360 Epigenetic complexes?
NOTE Confidence: 0.760728562

01:00:05.360 --> 01:00:10.899 Sure. So we have over time looked at
NOTE Confidence: 0.760728562

01:00:10.899 --> 01:00:15.020 the Polycom complex mostly in leukemia
NOTE Confidence: 0.760728562

01:00:15.020 --> 01:00:17.778 and it for whatever reason and this is
NOTE Confidence: 0.760728562

01:00:17.778 --> 01:00:19.388 going to be right contradictory to how
NOTE Confidence: 0.760728562

01:00:19.388 --> 01:00:21.152 I answered one of my previous questions.
NOTE Confidence: 0.760728562

01:00:21.160 --> 01:00:23.645 The Polycom complex does seem
NOTE Confidence: 0.760728562

01:00:23.645 --> 01:00:26.864 to be important in the continued
NOTE Confidence: 0.760728562

01:00:26.864 --> 01:00:30.200 proliferation of many types of leukemia.
NOTE Confidence: 0.760728562

01:00:30.200 --> 01:00:34.004 How that's working and why hard to know,
NOTE Confidence: 0.760728562

01:00:34.004 --> 01:00:37.250 but the small molecule PRC 2

NOTE Confidence: 0.760728562

01:00:37.250 --> 01:00:40.400 inhibitors or or EZH 2 inhibitors

NOTE Confidence: 0.760728562

01:00:40.400 --> 01:00:41.856 don't have tremendous activity.

NOTE Confidence: 0.760728562

01:00:41.856 --> 01:00:44.474 So whether or not it's the enzymatic

NOTE Confidence: 0.760728562

01:00:44.474 --> 01:00:47.064 activity versus some other part of the

NOTE Confidence: 0.760728562

01:00:47.064 --> 01:00:49.439 complex at least in leukemia anyway,

NOTE Confidence: 0.760728562

01:00:49.440 --> 01:00:50.352 I don't know.

NOTE Confidence: 0.760728562

01:00:50.352 --> 01:00:52.480 And I think that probably it brings

NOTE Confidence: 0.760728562

01:00:52.548 --> 01:00:55.706 up a good point that and we've

NOTE Confidence: 0.760728562

01:00:55.706 --> 01:00:56.917 done this in the past as well,

NOTE Confidence: 0.760728562

01:00:56.920 --> 01:00:59.433 but we have to be careful about

NOTE Confidence: 0.760728562

01:00:59.433 --> 01:01:01.572 the thought process that enzymatic

NOTE Confidence: 0.760728562

01:01:01.572 --> 01:01:03.780 inhibition of a protein in one of

NOTE Confidence: 0.760728562

01:01:03.780 --> 01:01:05.780 these complexes is the same thing as

NOTE Confidence: 0.760728562

01:01:05.780 --> 01:01:07.595 complete interactivation of the protein.

NOTE Confidence: 0.760728562

01:01:07.600 --> 01:01:09.280 It's not and we now seen that

NOTE Confidence: 0.760728562

01:01:09.280 --> 01:01:10.000 many different times.
NOTE Confidence: 0.760728562

01:01:10.000 --> 01:01:12.982 So the enzymatic part of the
NOTE Confidence: 0.760728562

01:01:12.982 --> 01:01:14.473 proteins is important,
NOTE Confidence: 0.760728562

01:01:14.480 --> 01:01:16.030 but there's probably a structural
NOTE Confidence: 0.760728562

01:01:16.030 --> 01:01:17.895 component to this that when you
NOTE Confidence: 0.760728562

01:01:17.895 --> 01:01:19.449 take the protein completely out and
NOTE Confidence: 0.760728562

01:01:19.449 --> 01:01:21.514 this is the same way for EZH 2 the
NOTE Confidence: 0.760728562

01:01:21.514 --> 01:01:23.398 the changes are much more dramatic.
NOTE Confidence: 0.760728562

01:01:23.400 --> 01:01:25.452 So it gets to the question as to what
NOTE Confidence: 0.760728562

01:01:25.452 --> 01:01:27.274 his some modifications are doing and
NOTE Confidence: 0.760728562

01:01:27.274 --> 01:01:30.038 that gets to even more deep and complicated.
NOTE Confidence: 0.760728562

01:01:30.040 --> 01:01:31.840 But so long answer to yes,
NOTE Confidence: 0.760728562

01:01:31.840 --> 01:01:32.840 we've looked at the complexes,
NOTE Confidence: 0.760728562

01:01:32.840 --> 01:01:35.876 we haven't looked much at the
NOTE Confidence: 0.760728562

01:01:35.876 --> 01:01:37.394 chromatin remodeling complexes.
NOTE Confidence: 0.760728562

01:01:37.400 --> 01:01:40.316 Segal Kadosh who some of you may know is

NOTE Confidence: 0.760728562

01:01:40.320 --> 01:01:42.440 at Dana Farber and we just let her do that.

NOTE Confidence: 0.760728562

01:01:42.440 --> 01:01:46.240 She they're doing a lot in that regard.

NOTE Confidence: 0.760728562

01:01:46.240 --> 01:01:47.717 I'm sure they're playing a role here.

NOTE Confidence: 0.760728562

01:01:47.720 --> 01:01:50.480 What but how and what we don't know.

NOTE Confidence: 0.785801059333333

01:01:51.360 --> 01:01:53.648 We have one last question and after this

NOTE Confidence: 0.785801059333333

01:01:53.648 --> 01:01:55.760 is actually a session for the trainees,

NOTE Confidence: 0.785801059333333

01:01:55.760 --> 01:01:58.200 very private was Doctor Armstrong.

NOTE Confidence: 0.9075081125

01:01:58.880 --> 01:02:00.168 Yeah, one last question.

NOTE Confidence: 0.9075081125

01:02:00.168 --> 01:02:01.456 This is actually related

NOTE Confidence: 0.9075081125

01:02:01.456 --> 01:02:03.079 to the fusion partners,

NOTE Confidence: 0.9075081125

01:02:03.080 --> 01:02:04.718 but as you know we often get,

NOTE Confidence: 0.9075081125

01:02:04.720 --> 01:02:06.547 you know when we do the geneteach

NOTE Confidence: 0.9075081125

01:02:06.547 --> 01:02:08.120 sequencing we get MLL deletions,

NOTE Confidence: 0.9075081125

01:02:08.120 --> 01:02:09.346 MLL mutations,

NOTE Confidence: 0.9075081125

01:02:09.346 --> 01:02:13.637 sometimes Trisom 11 or you know PDD.

NOTE Confidence: 0.9075081125

01:02:13.640 --> 01:02:16.190 And is your sense that beyond
NOTE Confidence: 0.9075081125

01:02:16.190 --> 01:02:18.639 the fusion MLL Fusion's those
NOTE Confidence: 0.9075081125

01:02:18.639 --> 01:02:20.720 alterations also have susceptibility
NOTE Confidence: 0.9075081125

01:02:20.720 --> 01:02:23.160 to an inhibition or yeah,
NOTE Confidence: 0.888833029285714

01:02:23.280 --> 01:02:25.135 as you probably know since you've been
NOTE Confidence: 0.888833029285714

01:02:25.135 --> 01:02:26.840 important in running some of the trials,
NOTE Confidence: 0.888833029285714

01:02:26.840 --> 01:02:30.862 the MLLPTD subtype of AML for
NOTE Confidence: 0.888833029285714

01:02:30.862 --> 01:02:33.154 some of the trials is included.
NOTE Confidence: 0.888833029285714

01:02:33.160 --> 01:02:35.505 There's been an assumption to some extent
NOTE Confidence: 0.888833029285714

01:02:35.505 --> 01:02:37.830 that they should be responsive the PD.
NOTE Confidence: 0.888833029285714

01:02:37.830 --> 01:02:39.360 So we have generated some MLL.
NOTE Confidence: 0.888833029285714

01:02:39.360 --> 01:02:41.358 So MLLPTDS are actually a partial
NOTE Confidence: 0.888833029285714

01:02:41.358 --> 01:02:43.560 tandem duplication of a part of the
NOTE Confidence: 0.888833029285714

01:02:43.560 --> 01:02:45.824 MLL protein and that subset of AML is
NOTE Confidence: 0.888833029285714

01:02:45.824 --> 01:02:47.750 incredibly difficult to treat and it's
NOTE Confidence: 0.888833029285714

01:02:47.750 --> 01:02:51.558 also found in MD's those mutations,

NOTE Confidence: 0.888833029285714

01:02:51.560 --> 01:02:53.864 but that almost tells you immediately

NOTE Confidence: 0.888833029285714

01:02:53.864 --> 01:02:55.703 it's also found in MDSMLL.

NOTE Confidence: 0.888833029285714

01:02:55.703 --> 01:02:57.824 Rearrangements are not found in MDS that

NOTE Confidence: 0.888833029285714

01:02:57.824 --> 01:02:59.083 they're probably something different

NOTE Confidence: 0.888833029285714

01:02:59.083 --> 01:03:00.901 going on in the minute inhibitor

NOTE Confidence: 0.888833029285714

01:03:00.901 --> 01:03:02.555 doesn't have at least in our PDX

NOTE Confidence: 0.888833029285714

01:03:02.555 --> 01:03:04.422 models the same type of activity in

NOTE Confidence: 0.888833029285714

01:03:04.422 --> 01:03:07.439 those PDX as it does MLL rearranged.

NOTE Confidence: 0.888833029285714

01:03:07.440 --> 01:03:09.978 So I think it gets back to this issue

NOTE Confidence: 0.888833029285714

01:03:09.978 --> 01:03:12.349 that we've been discussing that in

NOTE Confidence: 0.888833029285714

01:03:12.349 --> 01:03:15.080 that setting either because of that

NOTE Confidence: 0.888833029285714

01:03:15.080 --> 01:03:17.816 duplication or otherwise the that MLL

NOTE Confidence: 0.888833029285714

01:03:17.816 --> 01:03:19.976 Oncoprotein sticks on chromatin through

NOTE Confidence: 0.888833029285714

01:03:19.976 --> 01:03:22.280 a different mechanism than Menon.

NOTE Confidence: 0.888833029285714

01:03:22.280 --> 01:03:24.560 So we're got a project looking

NOTE Confidence: 0.888833029285714

01:03:24.560 --> 01:03:25.760 at exactly that,

NOTE Confidence: 0.888833029285714

01:03:25.760 --> 01:03:28.400 trying to understand what that is.

NOTE Confidence: 0.888833029285714

01:03:28.400 --> 01:03:29.840 We haven't looked at the deletions.

NOTE Confidence: 0.888833029285714

01:03:29.840 --> 01:03:30.878 I wouldn't predict they would be.