WEBVTT

NOTE duration:"00:56:51.0800000"

NOTE recognizability:0.896

NOTE language:en-us

NOTE Confidence: 0.919951375

00:00:00.000 --> 00:00:01.215 Good morning, everybody.

NOTE Confidence: 0.919951375

00:00:01.215 --> 00:00:03.240 Thank you for being here.

NOTE Confidence: 0.919951375

00:00:03.240 --> 00:00:06.072 Welcome to Grand Rounds.

NOTE Confidence: 0.919951375

00:00:06.072 --> 00:00:09.240 This is the this Grand Rounds is

NOTE Confidence: 0.919951375

00:00:09.240 --> 00:00:10.693 in a special location, obviously,

NOTE Confidence: 0.919951375

00:00:10.693 --> 00:00:13.304 because we are linked today to the

NOTE Confidence: 0.919951375

00:00:13.304 --> 00:00:16.190 first of what we hope will be a

NOTE Confidence: 0.919951375

00:00:16.190 --> 00:00:18.283 really successful series of annual

NOTE Confidence: 0.919951375

00:00:18.283 --> 00:00:20.200 translational science retreats

NOTE Confidence: 0.919951375

00:00:20.200 --> 00:00:22.810 meant to highlight the amazing

NOTE Confidence: 0.919951375

00:00:22.810 --> 00:00:25.955 resources that are present at Yale

NOTE Confidence: 0.919951375

00:00:25.955 --> 00:00:28.637 Cancer Centre for people who do

NOTE Confidence: 0.919951375

00:00:28.640 --> 00:00:32.590 translational science and also to

NOTE Confidence: 0.919951375

00:00:32.590 --> 00:00:34.720 highlight some of the amazing stories

NOTE Confidence: 0.919951375

00:00:34.720 --> 00:00:37.236 that that have come out of this work.

NOTE Confidence: 0.919951375

00:00:37.240 --> 00:00:40.831 And so no one better to to be our

NOTE Confidence: 0.919951375

00:00:40.831 --> 00:00:44.396 inaugural speaker than Doctor Katie Politi.

NOTE Confidence: 0.919951375

00:00:44.400 --> 00:00:47.046 Katie studied biology at the University of

NOTE Confidence: 0.919951375

00:00:47.046 --> 00:00:50.036 Pavia in Italy and then moved to New York,

NOTE Confidence: 0.919951375

00:00:50.040 --> 00:00:52.640 obtaining her PhD in genetics

NOTE Confidence: 0.919951375

00:00:52.640 --> 00:00:54.200 at Columbia University.

NOTE Confidence: 0.919951375

00:00:54.200 --> 00:00:56.180 She then joined Harold Varmus's

NOTE Confidence: 0.919951375

00:00:56.180 --> 00:00:58.355 lab at Memorial Sloan Kettering

NOTE Confidence: 0.919951375

00:00:58.355 --> 00:01:01.292 and began her life's work on the

NOTE Confidence: 0.919951375

00:01:01.292 --> 00:01:03.557 molecular basis of lung cancer.

NOTE Confidence: 0.919951375

00:01:03.560 --> 00:01:05.120 She continues this work at Yale,

NOTE Confidence: 0.919951375

00:01:05.120 --> 00:01:07.458 now as a professor in the Departments

NOTE Confidence: 0.919951375

00:01:07.458 --> 00:01:09.340 of Pathology and Internal Medicine

NOTE Confidence: 0.919951375

00:01:09.340 --> 00:01:11.794 in the section of Medical Oncology.

NOTE Confidence: 0.919951375

00:01:11.800 --> 00:01:13.834 Her laboratory is focused on studying

NOTE Confidence: 0.919951375

00:01:13.834 --> 00:01:16.108 the biology of lung cancer and

NOTE Confidence: 0.919951375

00:01:16.108 --> 00:01:18.248 uncovering mechanisms of resistance to

NOTE Confidence: 0.919951375

00:01:18.248 --> 00:01:20.013 targeted therapies and immunotherapies

NOTE Confidence: 0.919951375

00:01:20.013 --> 00:01:21.677 in in this disease.

NOTE Confidence: 0.919951375

00:01:21.680 --> 00:01:25.665 She's also got a keen knowledge of

NOTE Confidence: 0.919951375

00:01:25.665 --> 00:01:26.933 essentially every mutation that's

NOTE Confidence: 0.919951375

00:01:26.933 --> 00:01:28.840 ever been described in lung cancer.

NOTE Confidence: 0.919951375

00:01:28.840 --> 00:01:31.031 And I know that doctors often call

NOTE Confidence: 0.919951375

00:01:31.031 --> 00:01:33.919 her up and say what drug should I use.

NOTE Confidence: 0.919951375

00:01:33.920 --> 00:01:36.368 She Co leads the cancer signaling

NOTE Confidence: 0.919951375

00:01:36.368 --> 00:01:37.592 networks research program.

NOTE Confidence: 0.919951375

00:01:37.600 --> 00:01:39.700 She's the scientific director of

NOTE Confidence: 0.919951375

00:01:39.700 --> 00:01:41.800 the Center for Thoracic Cancers,

NOTE Confidence: 0.919951375

00:01:41.800 --> 00:01:43.900 Co Director of the Yale Sport in

NOTE Confidence: 0.919951375

00:01:43.900 --> 00:01:45.597 Lung Cancer and recently elected

NOTE Confidence: 0.919951375

00:01:45.597 --> 00:01:47.799 to the ACR Board of Directors.

NOTE Confidence: 0.919951375

00:01:47.800 --> 00:01:50.010 So we're really appreciative that

NOTE Confidence: 0.919951375

00:01:50.010 --> 00:01:52.999 you're going to kick us off today

NOTE Confidence: 0.919951375

00:01:53.000 --> 00:01:56.968 the the ID number there is to record

NOTE Confidence: 0.919951375

00:01:56.968 --> 00:01:59.145 your attendance and then we'll

NOTE Confidence: 0.919951375

00:01:59.145 --> 00:02:01.515 have questions both in the room

NOTE Confidence: 0.919951375

00:02:01.520 --> 00:02:05.360 and online when when we're done.

NOTE Confidence: 0.919951375

00:02:05.360 --> 00:02:05.680 Thank you.

NOTE Confidence: 0.956115768

00:02:10.200 --> 00:02:11.880 Thank you very much, Barbara,

NOTE Confidence: 0.956115768

00:02:11.880 --> 00:02:14.600 for that wonderful introduction

NOTE Confidence: 0.956115768

00:02:14.600 --> 00:02:16.615 and thank you very much for

NOTE Confidence: 0.956115768

00:02:16.615 --> 00:02:18.360 having me as a speaker today.

NOTE Confidence: 0.956115768

00:02:18.360 --> 00:02:20.640 It really always is, I think,

NOTE Confidence: 0.956115768

00:02:20.640 --> 00:02:23.650 very special to speak at one's own

NOTE Confidence: 0.956115768

00:02:23.650 --> 00:02:25.574 institution and then especially

NOTE Confidence: 0.956115768

00:02:25.574 --> 00:02:28.064 also associated with this first

NOTE Confidence: 0.956115768

00:02:28.064 --> 00:02:29.680 translational science retreat.

NOTE Confidence: 0.956115768

00:02:29.680 --> 00:02:31.960 So I'm really excited about this.

NOTE Confidence: 0.956115768

00:02:31.960 --> 00:02:34.200 And today what I'm going to do is

NOTE Confidence: 0.956115768

00:02:34.200 --> 00:02:36.660 I'm going to tell you about some of

NOTE Confidence: 0.956115768

00:02:36.660 --> 00:02:39.212 the work that we've been doing over

NOTE Confidence: 0.956115768

00:02:39.212 --> 00:02:41.914 the past few years in the laboratory.

NOTE Confidence: 0.9136039925

00:02:45.800 --> 00:02:47.440 These are my disclosures.

NOTE Confidence: 0.924020505

00:02:49.840 --> 00:02:52.143 So we have a long standing interest

NOTE Confidence: 0.924020505

00:02:52.143 --> 00:02:54.919 in the lab on studying lung cancer.

NOTE Confidence: 0.924020505

00:02:54.920 --> 00:02:56.720 And as all of you know,

NOTE Confidence: 0.924020505

00:02:56.720 --> 00:02:58.480 there are several histological

NOTE Confidence: 0.924020505

00:02:58.480 --> 00:03:00.240 subtypes of lung cancer.

NOTE Confidence: 0.924020505

00:03:00.240 --> 00:03:02.680 But one of the things that we've learned

NOTE Confidence: 0.924020505

00:03:02.680 --> 00:03:05.037 over the past 20 or so years is that

NOTE Confidence: 0.924020505

00:03:05.040 --> 00:03:07.968 lung cancer is not one entity and that

NOTE Confidence: 0.924020505

00:03:07.968 --> 00:03:10.850 there are in addition to different

NOTE Confidence: 0.924020505

00:03:10.850 --> 00:03:13.435 histological subsets of the disease,

NOTE Confidence: 0.924020505

00:03:13.440 --> 00:03:17.841 there are also are a variety of laser

NOTE Confidence: 0.924020505

00:03:17.841 --> 00:03:20.967 pointer of molecular subsets and in

NOTE Confidence: 0.924020505

00:03:20.967 --> 00:03:23.920 particular in lung adenocarcinoma.

NOTE Confidence: 0.924020505

00:03:23.920 --> 00:03:26.416 Through various sequencing efforts,

NOTE Confidence: 0.924020505

00:03:26.416 --> 00:03:29.536 different mutations in genes that

NOTE Confidence: 0.924020505

00:03:29.536 --> 00:03:32.170 encode either receptor tyrosine

NOTE Confidence: 0.924020505

00:03:32.170 --> 00:03:34.850 kinases or downstream signaling

NOTE Confidence: 0.924020505

00:03:34.850 --> 00:03:37.116 components of receptor tyrosine

NOTE Confidence: 0.924020505

00:03:37.116 --> 00:03:39.244 kinase signaling pathways that

NOTE Confidence: 0.924020505

00:03:39.244 --> 00:03:41.771 regulate cell proliferation and cell

NOTE Confidence: 0.924020505

00:03:41.771 --> 00:03:43.702 survival have been identified as

NOTE Confidence: 0.924020505

00:03:43.702 --> 00:03:45.478 you can see here in this pie chart.

NOTE Confidence: 0.924020505

00:03:45.480 --> 00:03:48.061 And I think one of the things to

NOTE Confidence: 0.924020505

00:03:48.061 --> 00:03:49.766 really highlight is what we've

NOTE Confidence: 0.924020505

00:03:49.766 --> 00:03:51.897 learned over the years is that

NOTE Confidence: 0.924020505

00:03:51.897 --> 00:03:54.792 these mutations are in addition to

NOTE Confidence: 0.924020505

00:03:54.792 --> 00:03:56.826 being molecular to establishing

NOTE Confidence: 0.924020505

00:03:56.826 --> 00:03:58.756 molecular subsets of the disease.

NOTE Confidence: 0.924020505

00:03:58.760 --> 00:04:01.555 They really also are clinically

NOTE Confidence: 0.924020505

00:04:01.555 --> 00:04:03.791 relevant because different targeted

NOTE Confidence: 0.924020505

00:04:03.791 --> 00:04:06.279 agents have been developed that can

NOTE Confidence: 0.924020505

00:04:06.279 --> 00:04:09.084 you be used to block the activity

NOTE Confidence: 0.924020505

00:04:09.084 --> 00:04:10.958 of these mutated oncogenic drivers.

NOTE Confidence: 0.924020505

00:04:10.958 --> 00:04:12.911 And in particular and in the work

NOTE Confidence: 0.924020505

00:04:12.911 --> 00:04:14.520 that I'll tell you about today,

NOTE Confidence: 0.924020505

00:04:14.520 --> 00:04:15.480 for example,

NOTE Confidence: 0.924020505

00:04:15.480 --> 00:04:18.360 mutations were found 20 years ago

NOTE Confidence: 0.924020505

00:04:18.360 --> 00:04:20.788 now in Exxon's encoding the kinase

NOTE Confidence: 0.924020505

00:04:20.788 --> 00:04:22.990 domain of the epidermal growth factor

NOTE Confidence: 0.924020505

00:04:23.049 --> 00:04:28.399 receptor after in about 15 to 4050%

NOTE Confidence: 0.924020505

00:04:28.399 --> 00:04:31.394 of lung and nocarcinomas depending

NOTE Confidence: 0.924020505

00:04:31.394 --> 00:04:34.640 on which population you look at.

NOTE Confidence: 0.924020505

00:04:34.640 --> 00:04:38.960 And these are mutations that

NOTE Confidence: 0.924020505

00:04:38.960 --> 00:04:41.470 confer sensitivity to EGFR tyrosine

NOTE Confidence: 0.924020505

00:04:41.470 --> 00:04:42.474 kinase inhibitors.

NOTE Confidence: 0.924020505

00:04:42.480 --> 00:04:44.080 But there are many other

NOTE Confidence: 0.924020505

00:04:44.080 --> 00:04:45.360 targeted therapies as well.

NOTE Confidence: 0.924020505

00:04:45.360 --> 00:04:48.948 So you can have rearrangements in

NOTE Confidence: 0.924020505

00:04:48.948 --> 00:04:51.720 the anaplastic lymphoma kinase and

NOTE Confidence: 0.924020505

00:04:51.720 --> 00:04:53.645 targeted therapies that are effective

NOTE Confidence: 0.924020505

00:04:53.645 --> 00:04:57.047 in that and so on for a number of

NOTE Confidence: 0.924020505

00:04:57.047 --> 00:04:59.520 different oncogenic drivers and lung cancer.

NOTE Confidence: 0.924020505

00:04:59.520 --> 00:05:02.160 And so this has really transformed the field.

NOTE Confidence: 0.924020505

00:05:02.160 --> 00:05:06.870 And so if we look at this diagram here of

NOTE Confidence: 0.924020505

00:05:06.870 --> 00:05:10.445 approved FDA approvals for lung cancer in,

NOTE Confidence: 0.924020505

00:05:10.445 --> 00:05:11.420 in recent years,

NOTE Confidence: 0.924020505

00:05:11.420 --> 00:05:13.816 what you'll see is it really has

NOTE Confidence: 0.924020505

00:05:13.816 --> 00:05:16.036 been an explosion in FDA approvals,

NOTE Confidence: 0.924020505

00:05:16.040 --> 00:05:19.036 especially from the early 2000s in the

NOTE Confidence: 0.924020505

00:05:19.036 --> 00:05:22.025 2000 and 10s and approvals now also

NOTE Confidence: 0.924020505

00:05:22.025 --> 00:05:24.640 in the first part of the twenty 20s.

NOTE Confidence: 0.924020505

00:05:24.640 --> 00:05:26.734 Most of these agents that were

NOTE Confidence: 0.924020505

00:05:26.734 --> 00:05:28.556 approved recently have been targeted

NOTE Confidence: 0.924020505

00:05:28.556 --> 00:05:31.083 agents and that really is linked to

NOTE Confidence: 0.924020505

00:05:31.083 --> 00:05:32.953 the discoveries of these molecular

NOTE Confidence: 0.924020505

00:05:32.953 --> 00:05:34.397 subsets of the disease.

NOTE Confidence: 0.924020505

00:05:34.400 --> 00:05:37.244 But also do I think one of the things

NOTE Confidence: 0.924020505

00:05:37.244 --> 00:05:39.270 that has been emerging also in the

NOTE Confidence: 0.924020505

00:05:39.270 --> 00:05:42.127 past 10 to 15 years really are the

NOTE Confidence: 0.924020505

00:05:42.127 --> 00:05:43.771 approvals of immunotherapies that

NOTE Confidence: 0.924020505

00:05:43.771 --> 00:05:46.693 we hear a lot about agents that

NOTE Confidence: 0.924020505

00:05:46.693 --> 00:05:48.313 are targeting immune checkpoints

NOTE Confidence: 0.924020505

00:05:48.313 --> 00:05:50.028 like the anti PD1,

NOTE Confidence: 0.924020505

00:05:50.028 --> 00:05:53.080 anti PDL ONE Access and CTLA 4.

NOTE Confidence: 0.924020505

00:05:53.080 --> 00:05:55.114 And so this has really been

NOTE Confidence: 0.924020505

00:05:55.114 --> 00:05:57.000 transformative in a lung cancer.

NOTE Confidence: 0.924020505

00:05:57.000 --> 00:05:59.736 And I'd like just like to point out

NOTE Confidence: 0.924020505

00:05:59.736 --> 00:06:02.600 how in recent analysis what we're

NOTE Confidence: 0.924020505

00:06:02.600 --> 00:06:05.120 seeing is that there's actually

NOTE Confidence: 0.924020505

00:06:05.205 --> 00:06:07.666 a decrease in mortality from lung

NOTE Confidence: 0.924020505

00:06:07.666 --> 00:06:09.514 cancer in recent years.

NOTE Confidence: 0.924020505

00:06:09.520 --> 00:06:11.272 And in the study published in the New

NOTE Confidence: 0.924020505

00:06:11.272 --> 00:06:12.917 England Journal of Medicine a few years ago,

NOTE Confidence: 0.924020505

00:06:12.920 --> 00:06:15.195 it was really shown that the

NOTE Confidence: 0.924020505

00:06:15.195 --> 00:06:17.370 decrease in mortality from lung

NOTE Confidence: 0.924020505

00:06:17.370 --> 00:06:19.110 cancer can't be accounted

NOTE Confidence: 0.929720887619048

00:06:19.187 --> 00:06:21.329 for just because of a decrease

NOTE Confidence: 0.929720887619048

00:06:21.329 --> 00:06:23.400 in incidence of the disease.

NOTE Confidence: 0.929720887619048

00:06:23.400 --> 00:06:25.730 But is likely reflects actually

NOTE Confidence: 0.929720887619048

00:06:25.730 --> 00:06:29.641 advances in the care and in the new

NOTE Confidence: 0.929720887619048

00:06:29.641 --> 00:06:31.637 therapeutics that have emerged,

NOTE Confidence: 0.929720887619048

00:06:31.640 --> 00:06:33.355 including in particular in the

NOTE Confidence: 0.929720887619048

00:06:33.355 --> 00:06:35.070 years that were studied in

NOTE Confidence: 0.929720887619048

00:06:35.133 --> 00:06:36.998 this paper for targeted agents.

NOTE Confidence: 0.929720887619048

00:06:37.000 --> 00:06:40.924 And so I think this is a really nice

NOTE Confidence: 0.929720887619048

00:06:40.924 --> 00:06:44.430 example of how what we've learned over

NOTE Confidence: 0.929720887619048

00:06:44.430 --> 00:06:47.484 the years from from the biology and

NOTE Confidence: 0.929720887619048

00:06:47.484 --> 00:06:49.830 from the genetic studies of tumors

NOTE Confidence: 0.929720887619048

00:06:49.904 --> 00:06:52.334 really is having a profound impact

NOTE Confidence: 0.929720887619048

00:06:52.334 --> 00:06:54.600 for patients with this disease.

NOTE Confidence: 0.929720887619048

00:06:54.600 --> 00:06:57.264 And of course I would be remiss if I

NOTE Confidence: 0.929720887619048

00:06:57.264 --> 00:06:59.693 didn't point out how immunotherapies

NOTE Confidence: 0.929720887619048

00:06:59.693 --> 00:07:01.757 have also been transformative.

NOTE Confidence: 0.929720887619048

00:07:01.760 --> 00:07:03.566 And I think the continued decrease

NOTE Confidence: 0.929720887619048

00:07:03.566 --> 00:07:05.387 in mortality that we are continuing

NOTE Confidence: 0.929720887619048

00:07:05.387 --> 00:07:07.619 to see is actually going to show how

NOTE Confidence: 0.929720887619048

00:07:07.678 --> 00:07:09.814 it isn't only the targeted therapies

NOTE Confidence: 0.929720887619048

00:07:09.814 --> 00:07:12.230 but also the immunotherapies that are

NOTE Confidence: 0.929720887619048

00:07:12.230 --> 00:07:14.705 really contributing to this decrease

NOTE Confidence: 0.929720887619048

00:07:14.705 --> 00:07:17.240 in and mortality from lung cancer.

NOTE Confidence: 0.929720887619048

00:07:17.240 --> 00:07:19.560 So if you know you look at this,

NOTE Confidence: 0.929720887619048

00:07:19.560 --> 00:07:21.068 there's really these advances

NOTE Confidence: 0.929720887619048

00:07:21.068 --> 00:07:22.199 have been tremendous.

NOTE Confidence: 0.929720887619048

00:07:22.200 --> 00:07:24.882 But what we do know is that both

NOTE Confidence: 0.929720887619048

00:07:24.882 --> 00:07:26.970 primary and acquired resistance

NOTE Confidence: 0.929720887619048

00:07:26.970 --> 00:07:29.580 to targeted therapies and to

NOTE Confidence: 0.929720887619048

00:07:29.668 --> 00:07:31.840 immunotherapies are common.

NOTE Confidence: 0.929720887619048

00:07:31.840 --> 00:07:35.004 And here you can see an example of

NOTE Confidence: 0.929720887619048

00:07:35.004 --> 00:07:38.112 scans from a patient with a tumors

NOTE Confidence: 0.929720887619048

00:07:38.112 --> 00:07:40.798 with AK Ras G12C mutation treated

NOTE Confidence: 0.929720887619048

00:07:40.798 --> 00:07:44.440 with AK Ras G12C inhibitor and

NOTE Confidence: 0.929720887619048

00:07:44.440 --> 00:07:46.600 you can see the tumor regresses

NOTE Confidence: 0.929720887619048

00:07:46.600 --> 00:07:48.917 but then comes back and you have

NOTE Confidence: 0.929720887619048

00:07:48.920 --> 00:07:50.700 this is acquired resistance.

NOTE Confidence: 0.929720887619048

00:07:50.700 --> 00:07:54.309 And here if we look at this plot

NOTE Confidence: 0.929720887619048

00:07:54.309 --> 00:07:56.520 taken from a review looking

NOTE Confidence: 0.929720887619048

00:07:56.520 --> 00:07:58.600 at studies of immunotherapies,

NOTE Confidence: 0.929720887619048

00:07:58.600 --> 00:08:01.378 you can see that across various

NOTE Confidence: 0.929720887619048

00:08:01.378 --> 00:08:03.230 different indications but including

NOTE Confidence: 0.929720887619048

00:08:03.301 --> 00:08:05.776 in lung cancer here that in clinical

NOTE Confidence: 0.929720887619048

00:08:05.776 --> 00:08:07.000 studies of immunotherapies,

NOTE Confidence: 0.929720887619048

00:08:07.000 --> 00:08:09.424 the response rates or to immune

NOTE Confidence: 0.929720887619048

00:08:09.424 --> 00:08:11.839 checkpoint inhibitors are not super high.

NOTE Confidence: 0.929720887619048

00:08:11.840 --> 00:08:14.010 We're not talking 7080% the way we're

NOTE Confidence: 0.929720887619048

00:08:14.010 --> 00:08:16.080 talking with some targeted therapies.

NOTE Confidence: 0.929720887619048

00:08:16.080 --> 00:08:17.166 Not only that,

NOTE Confidence: 0.929720887619048

00:08:17.166 --> 00:08:19.338 but also we see acquired resistance

NOTE Confidence: 0.929720887619048

00:08:19.338 --> 00:08:20.320 commonly emerging.

NOTE Confidence: 0.929720887619048

00:08:20.320 --> 00:08:22.488 So there's a lot of work that needs

NOTE Confidence: 0.929720887619048

00:08:22.488 --> 00:08:25.192 to be done to really understand and

NOTE Confidence: 0.929720887619048

00:08:25.192 --> 00:08:27.352 optimize treatments for both targeted

NOTE Confidence: 0.929720887619048

00:08:27.352 --> 00:08:29.566 agents and immunotherapies and to

NOTE Confidence: 0.929720887619048

00:08:29.566 --> 00:08:31.270 understand mechanisms of sensitivity

NOTE Confidence: 0.929720887619048

00:08:31.270 --> 00:08:33.400 and resistance to these agents.

NOTE Confidence: 0.929720887619048

00:08:33.400 --> 00:08:37.304 And So what do we do in my lab?

NOTE Confidence: 0.929720887619048

00:08:37.304 --> 00:08:40.560 And as part of the research program,

NOTE Confidence: 0.929720887619048

00:08:40.560 --> 00:08:45.004 we are really interested in understanding

NOTE Confidence: 0.929720887619048

00:08:45.004 --> 00:08:46.576 mechanistically biological processes

NOTE Confidence: 0.929720887619048

00:08:46.576 --> 00:08:49.196 that are involved in cancer.

NOTE Confidence: 0.929720887619048

00:08:49.200 --> 00:08:52.680 We like to integrate these with

NOTE Confidence: 0.929720887619048

00:08:52.680 --> 00:08:54.808 studying and addressing clinical

NOTE Confidence: 0.929720887619048

00:08:54.808 --> 00:08:56.936 challenges and investigating specimens

NOTE Confidence: 0.929720887619048

00:08:56.936 --> 00:08:59.798 and data from patients with cancer.

NOTE Confidence: 0.929720887619048

00:08:59.800 --> 00:09:01.832 And really the hope is that the work

NOTE Confidence: 0.929720887619048

00:09:01.832 --> 00:09:03.960 that we do collectively as a group,

NOTE Confidence: 0.929720887619048

00:09:03.960 --> 00:09:07.302 this is work that we do with many

NOTE Confidence: 0.929720887619048

00:09:07.302 --> 00:09:09.257 different people is to discover

NOTE Confidence: 0.929720887619048

00:09:09.257 --> 00:09:11.300 things that will discover findings

NOTE Confidence: 0.929720887619048

00:09:11.300 --> 00:09:14.086 that will lead to clinical trials and

NOTE Confidence: 0.929720887619048

00:09:14.086 --> 00:09:16.920 new therapeutic approaches to patients.

NOTE Confidence: 0.929720887619048

00:09:16.920 --> 00:09:20.190 Central to our research program is

NOTE Confidence: 0.929720887619048

00:09:20.190 --> 00:09:23.488 the use of biological specimens from

NOTE Confidence: 0.929720887619048

00:09:23.488 --> 00:09:26.800 patients and analysis of these specimens.

NOTE Confidence: 0.929720887619048

00:09:26.800 --> 00:09:28.632 And I think this slide is also going

NOTE Confidence: 0.929720887619048

00:09:28.632 --> 00:09:30.825 to be showed later in the day as an

NOTE Confidence: 0.929720887619048

00:09:30.825 --> 00:09:32.560 example of one of the resources that

NOTE Confidence: 0.929720887619048

00:09:32.560 --> 00:09:35.250 we have as part of the lung cancer

NOTE Confidence: 0.929720887619048

00:09:35.250 --> 00:09:39.560 program to really be able to collect

NOTE Confidence: 0.929720887619048

00:09:39.560 --> 00:09:42.360 and use specimens from patients.

NOTE Confidence: 0.929720887619048

00:09:42.360 --> 00:09:44.232 And this is just one of the examples

NOTE Confidence: 0.929720887619048

00:09:44.232 --> 00:09:46.154 of one of the resources I think

NOTE Confidence: 0.929720887619048

00:09:46.154 --> 00:09:47.544 you'll hear about a couple

NOTE Confidence: 0.969507246923077

00:09:47.605 --> 00:09:49.075 of others later on as well.

NOTE Confidence: 0.969507246923077

00:09:49.080 --> 00:09:51.194 But really an effort that started many,

NOTE Confidence: 0.969507246923077

00:09:51.200 --> 00:09:54.692 many years ago working initially

NOTE Confidence: 0.969507246923077

00:09:54.692 --> 00:09:57.834 with Scott Genger and Anna

NOTE Confidence: 0.969507246923077

00:09:57.834 --> 00:10:00.198 Wertz and Roy Herbst and many,

NOTE Confidence: 0.969507246923077

00:10:00.200 --> 00:10:03.160 many people in this room now with

NOTE Confidence: 0.969507246923077

00:10:03.160 --> 00:10:06.215 Sarah and many of all of the thoracic

NOTE Confidence: 0.969507246923077

00:10:06.215 --> 00:10:09.120 oncologists on the team and pathologists.

NOTE Confidence: 0.969507246923077

00:10:09.120 --> 00:10:10.593 Kurt for example,

NOTE Confidence: 0.969507246923077

00:10:10.593 --> 00:10:13.048 really working on collecting specimens

NOTE Confidence: 0.969507246923077

00:10:13.048 --> 00:10:15.551 from patients who have advanced

NOTE Confidence: 0.969507246923077

00:10:15.551 --> 00:10:17.475 lung cancer through treatment,

NOTE Confidence: 0.969507246923077

00:10:17.480 --> 00:10:19.076 especially at the time of resistance.

NOTE Confidence: 0.969507246923077

00:10:19.080 --> 00:10:20.907 So that then we can take these

NOTE Confidence: 0.969507246923077

00:10:20.907 --> 00:10:22.000 specimens and analyze them,

NOTE Confidence: 0.969507246923077

00:10:22.000 --> 00:10:24.100 generate patient derived models.

NOTE Confidence: 0.969507246923077

00:10:24.100 --> 00:10:27.250 And really these have contributed extensively

NOTE Confidence: 0.969507246923077

00:10:27.326 --> 00:10:30.356 to the work that I will tell you about today.

NOTE Confidence: 0.969507246923077

00:10:30.360 --> 00:10:33.524 And so I put a little cryovile here.

NOTE Confidence: 0.969507246923077

00:10:33.524 --> 00:10:37.100 And So what I'm going to do through the talk

NOTE Confidence: 0.969507246923077

00:10:37.100 --> 00:10:40.040 is when you see a cryovial on the slide,

NOTE Confidence: 0.969507246923077

00:10:40.040 --> 00:10:43.995 it actually is an example of data

NOTE Confidence: 0.969507246923077

00:10:44.000 --> 00:10:46.002 that we've been able to analyse and

NOTE Confidence: 0.969507246923077

00:10:46.002 --> 00:10:48.117 use because of the specimens that

NOTE Confidence: 0.969507246923077

00:10:48.117 --> 00:10:50.117 were collected through this approach.

NOTE Confidence: 0.969507246923077

00:10:50.120 --> 00:10:53.396 So you'll see that throughout the talk.

NOTE Confidence: 0.969507246923077

00:10:53.400 --> 00:10:55.504 So what what am I going to tell

NOTE Confidence: 0.969507246923077

00:10:55.504 --> 00:10:56.480 you about today.

NOTE Confidence: 0.969507246923077

00:10:56.480 --> 00:10:59.680 So I think as most of you know

NOTE Confidence: 0.969507246923077

00:10:59.680 --> 00:11:01.882 we have a long standing interest

NOTE Confidence: 0.969507246923077

00:11:01.882 --> 00:11:04.188 in studying the biology of EGF

NOTE Confidence: 0.969507246923077

00:11:04.188 --> 00:11:05.720 receptor driven lung cancer.

NOTE Confidence: 0.969507246923077

00:11:05.720 --> 00:11:09.388 And so when patients and really the

NOTE Confidence: 0.969507246923077

00:11:09.388 --> 00:11:12.538 focus that we've had at least in

NOTE Confidence: 0.969507246923077

00:11:12.538 --> 00:11:14.344 the in the past or until recently

NOTE Confidence: 0.969507246923077

00:11:14.344 --> 00:11:16.409 has really been and because of the

NOTE Confidence: 0.969507246923077

00:11:16.409 --> 00:11:18.250 sort of the clinical landscape has

NOTE Confidence: 0.969507246923077

00:11:18.250 --> 00:11:19.960 really been on advanced metastatic

NOTE Confidence: 0.969507246923077

00:11:19.960 --> 00:11:22.560 EGF receptor driven lung cancer.

NOTE Confidence: 0.969507246923077

00:11:22.560 --> 00:11:26.032 And so when patients are diagnosed

NOTE Confidence: 0.969507246923077

00:11:26.032 --> 00:11:28.600 with EGF receptor driven lung cancer,

NOTE Confidence: 0.969507246923077

00:11:28.600 --> 00:11:32.602 now they're mostly treated with tyrosine

NOTE Confidence: 0.969507246923077

00:11:32.602 --> 00:11:34.612 kinase inhibitors most recently and

NOTE Confidence: 0.969507246923077

00:11:34.612 --> 00:11:37.296 in the United States especially the

NOTE Confidence: 0.969507246923077

00:11:37.296 --> 00:11:39.316 tyrosine kinase inhibitor awesome.

NOTE Confidence: 0.969507246923077

00:11:39.320 --> 00:11:41.936 Merton if this is one of the newer

NOTE Confidence: 0.969507246923077

00:11:41.936 --> 00:11:44.128 generation of agents that has more

NOTE Confidence: 0.969507246923077

00:11:44.128 --> 00:11:46.368 activity on mutant EGFR compared

NOTE Confidence: 0.969507246923077

00:11:46.368 --> 00:11:47.712 to wild type.

NOTE Confidence: 0.969507246923077

00:11:47.720 --> 00:11:49.745 So hopefully decreasing its toxicity

NOTE Confidence: 0.969507246923077

00:11:49.745 --> 00:11:52.850 and has been shown to have superior

NOTE Confidence: 0.969507246923077

00:11:52.850 --> 00:11:55.365 progression free survival and overall

NOTE Confidence: 0.969507246923077

00:11:55.365 --> 00:11:57.925 survival compared to standard of

NOTE Confidence: 0.969507246923077

00:11:57.925 --> 00:11:59.881 care earlier generation tyrosine

NOTE Confidence: 0.969507246923077

00:11:59.881 --> 00:12:02.189 kinase inhibitors in this disease.

NOTE Confidence: 0.969507246923077

00:12:02.189 --> 00:12:04.632 And so this was an A really

NOTE Confidence: 0.969507246923077

00:12:04.632 --> 00:12:06.239 important advance in the field.

NOTE Confidence: 0.969507246923077

00:12:06.240 --> 00:12:06.578 However,

NOTE Confidence: 0.969507246923077

00:12:06.578 --> 00:12:08.944 what we do know is that still

NOTE Confidence: 0.969507246923077

00:12:08.944 --> 00:12:12.013 resistance or acquired resistance two

NOTE Confidence: 0.969507246923077

00:12:12.013 --> 00:12:16.385 asamertinib occurs almost inevitably

NOTE Confidence: 0.969507246923077

00:12:16.385 --> 00:12:20.245 and it actually isn't very commonly

NOTE Confidence: 0.969507246923077

00:12:20.245 --> 00:12:24.000 associated with on target EGFR mutations.

NOTE Confidence: 0.969507246923077

00:12:24.000 --> 00:12:26.720 And this is different from some of the

NOTE Confidence: 0.969507246923077

00:12:26.720 --> 00:12:28.688 earlier generations of tyrosine kinase

NOTE Confidence: 0.969507246923077

00:12:28.688 --> 00:12:31.540 inhibitors that instead where we saw

NOTE Confidence: 0.969507246923077

00:12:31.540 --> 00:12:34.240 commonly one most frequently observed

NOTE Confidence: 0.969507246923077

00:12:34.240 --> 00:12:36.080 on target EGF receptor mutation,

NOTE Confidence: 0.969507246923077

00:12:36.080 --> 00:12:37.724 the T79 TM mutation.

NOTE Confidence: 0.969507246923077

00:12:37.724 --> 00:12:40.850 But you see additional mechanisms of

NOTE Confidence: 0.969507246923077

00:12:40.850 --> 00:12:44.000 resistance met amplification for example,

NOTE Confidence: 0.969507246923077

00:12:44.000 --> 00:12:45.640 so a bypass signaling pathway

NOTE Confidence: 0.969507246923077

00:12:45.640 --> 00:12:47.800 being one of the more common.

NOTE Confidence: 0.969507246923077

00:12:47.800 --> 00:12:50.502 Then we see a histologic changes in

NOTE Confidence: 0.969507246923077

00:12:50.502 --> 00:12:52.854 the tumors that occur quite frequently,

NOTE Confidence: 0.969507246923077

00:12:52.854 --> 00:12:55.056 but then most of the mechanisms

NOTE Confidence: 0.969507246923077

00:12:55.056 --> 00:12:57.284 of resistance are really not known

NOTE Confidence: 0.969507246923077

00:12:57.284 --> 00:12:58.358 and poorly understood.

NOTE Confidence: 0.969507246923077

00:12:58.360 --> 00:13:01.119 And so one of the things that we've

NOTE Confidence: 0.969507246923077

00:13:01.119 --> 00:13:04.233 been interested from when as we

NOTE Confidence: 0.969507246923077

00:13:04.233 --> 00:13:07.680 think about these problems is really,

NOTE Confidence: 0.969507246923077

00:13:07.680 --> 00:13:10.064 really understanding these tough

NOTE Confidence: 0.969507246923077

00:13:10.064 --> 00:13:12.448 challenges like really understanding

NOTE Confidence: 0.969507246923077

00:13:12.448 --> 00:13:15.325 this part of the pie chart, right.

NOTE Confidence: 0.969507246923077

00:13:15.325 --> 00:13:17.275 What are these mechanisms of resistance,

NOTE Confidence: 0.969507246923077

00:13:17.280 --> 00:13:19.896 What is happening in these tumors

NOTE Confidence: 0.969507246923077

00:13:19.896 --> 00:13:21.640 where we don't really

NOTE Confidence: 0.839592348

00:13:21.719 --> 00:13:24.287 have a key genetic alteration that

NOTE Confidence: 0.839592348

00:13:24.287 --> 00:13:26.932 has changed that or clear process

NOTE Confidence: 0.839592348

00:13:26.932 --> 00:13:30.194 that is happening that we can target.

NOTE Confidence: 0.839592348

00:13:30.200 --> 00:13:32.524 And so just a couple of thoughts

NOTE Confidence: 0.839592348

00:13:32.524 --> 00:13:34.998 that sort of guide our thinking.

NOTE Confidence: 0.839592348

00:13:35.000 --> 00:13:37.520 Targeted agents are probably not sufficient.

NOTE Confidence: 0.839592348

00:13:37.520 --> 00:13:40.970 We need to discover new untapped

NOTE Confidence: 0.839592348

00:13:40.970 --> 00:13:43.807 vulnerabilities of oncogene driven lung

NOTE Confidence: 0.839592348

00:13:43.807 --> 00:13:46.669 cancers and then the tackling resistance

NOTE Confidence: 0.839592348

00:13:46.669 --> 00:13:50.190 requires new knowledge of the links between

NOTE Confidence: 0.839592348

00:13:50.268 --> 00:13:53.273 cancer cell plasticity and the tumor

NOTE Confidence: 0.839592348

00:13:53.273 --> 00:13:55.077 microenvironment and tumor heterogeneity.

NOTE Confidence: 0.839592348

00:13:55.080 --> 00:13:56.750 And so these are some of the and so I

NOTE Confidence: 0.839592348

00:13:56.797 --> 00:13:58.579 think of these that like the the not the

NOTE Confidence: 0.839592348

00:13:58.579 --> 00:14:00.127 low hanging fruit but the fruit really

NOTE Confidence: 0.839592348

00:14:00.127 --> 00:14:03.840 at the top of the tree that we're trying

NOTE Confidence: 0.839592348

00:14:03.840 --> 00:14:07.228 to really grasp and understand when we.

NOTE Confidence: 0.839592348

00:14:07.228 --> 00:14:09.864 And and really if we look at EGF receptor

NOTE Confidence: 0.839592348

00:14:09.864 --> 00:14:12.840 driven lung cancer and we think about it,

NOTE Confidence: 0.839592348

00:14:12.840 --> 00:14:15.240 one of the things that we know is

NOTE Confidence: 0.839592348

00:14:15.240 --> 00:14:17.208 that with with the targeted agents

NOTE Confidence: 0.839592348

00:14:17.208 --> 00:14:19.616 that I've told you about today is

NOTE Confidence: 0.839592348

00:14:19.616 --> 00:14:21.680 we do see this acquired resistance.

NOTE Confidence: 0.839592348

00:14:21.680 --> 00:14:22.780 But not only that.

NOTE Confidence: 0.839592348

00:14:22.780 --> 00:14:25.284 We also know that when we use the

NOTE Confidence: 0.839592348

00:14:25.284 --> 00:14:27.254 targeted agents they don't completely

NOTE Confidence: 0.839592348

00:14:27.254 --> 00:14:29.645 eradicate all the tumor cells and

NOTE Confidence: 0.839592348

00:14:29.645 --> 00:14:31.931 there's variability in the depth and

NOTE Confidence: 0.839592348

00:14:31.931 --> 00:14:33.560 duration of responses in patients.

NOTE Confidence: 0.839592348

00:14:33.560 --> 00:14:36.192 And you can see this really in this

NOTE Confidence: 0.839592348

00:14:36.192 --> 00:14:37.952 waterfall plot where there's some

NOTE Confidence: 0.839592348

00:14:37.952 --> 00:14:39.477 tumors that shrink dramatically

NOTE Confidence: 0.839592348

00:14:39.477 --> 00:14:41.479 and others that shrink less.

NOTE Confidence: 0.839592348

00:14:41.479 --> 00:14:43.992 And so we've been interested in the

NOTE Confidence: 0.839592348

00:14:43.992 --> 00:14:46.843 question of what accounts for this

NOTE Confidence: 0.839592348

00:14:46.843 --> 00:14:49.418 heterogeneity and disease progression and

NOTE Confidence: 0.839592348

00:14:49.418 --> 00:14:52.037 sensitivity to tyrosine kinase inhibitors.

NOTE Confidence: 0.839592348

00:14:52.040 --> 00:14:53.818 And so the first thing that I'm

NOTE Confidence: 0.839592348

00:14:53.818 --> 00:14:56.007 going to go through is some of the

NOTE Confidence: 0.839592348

00:14:56.007 --> 00:14:58.248 work that we've done to study how

NOTE Confidence: 0.839592348

00:14:58.248 --> 00:15:00.288 different EGF receptor mutations can

NOTE Confidence: 0.839592348

00:15:00.288 --> 00:15:02.226 actually have distinct properties.

NOTE Confidence: 0.839592348

00:15:02.226 --> 00:15:05.756 And so first of all,

NOTE Confidence: 0.839592348

00:15:05.760 --> 00:15:07.587 I've sort of told you about EGF

NOTE Confidence: 0.839592348

00:15:07.587 --> 00:15:09.199 receptor mutations and one could think,

NOTE Confidence: 0.839592348

00:15:09.200 --> 00:15:11.475 oh, we can lump them all together.

NOTE Confidence: 0.839592348

00:15:11.480 --> 00:15:12.515 But in reality,

NOTE Confidence: 0.839592348

00:15:12.515 --> 00:15:15.965 what we do know and what is becoming I

NOTE Confidence: 0.839592348

00:15:15.965 --> 00:15:18.809 think increasingly clear in recent years

NOTE Confidence: 0.839592348

00:15:18.809 --> 00:15:21.595 is that you have their different EGF

NOTE Confidence: 0.839592348

00:15:21.595 --> 00:15:23.800 receptor mutations and not only that,

NOTE Confidence: 0.839592348

00:15:23.800 --> 00:15:27.640 the different EGF receptor mutations have

NOTE Confidence: 0.839592348

00:15:27.640 --> 00:15:29.756 different properties both biological,

NOTE Confidence: 0.839592348

00:15:29.756 --> 00:15:32.216 biochemical and also in terms

NOTE Confidence: 0.839592348

00:15:32.216 --> 00:15:34.200 of TKI sensitivity.

NOTE Confidence: 0.839592348

00:15:34.200 --> 00:15:35.880 And so when we look at

NOTE Confidence: 0.839592348

00:15:35.880 --> 00:15:36.720 EGF receptor mutations,

NOTE Confidence: 0.839592348

00:15:36.720 --> 00:15:39.639 there are two major categories of mutations.

NOTE Confidence: 0.839592348

00:15:39.640 --> 00:15:43.720 There's the L858R point mutation and then

NOTE Confidence: 0.839592348

00:15:43.720 --> 00:15:46.280 there's a set of small in frame deletion,

NOTE Confidence: 0.839592348

00:15:46.280 --> 00:15:49.640 some of them more complex and Exxon 19.

NOTE Confidence: 0.839592348

00:15:49.640 --> 00:15:52.022 The most common of these is

NOTE Confidence: 0.839592348

00:15:52.022 --> 00:15:54.498 this E 746 to a 750 mutation.

NOTE Confidence: 0.839592348

00:15:54.498 --> 00:15:56.584 But then there are these other in

NOTE Confidence: 0.839592348

00:15:56.584 --> 00:15:58.576 Dells that are found at, you know,

NOTE Confidence: 0.839592348

00:15:58.576 --> 00:16:00.116 variable frequencies in these tumors,

NOTE Confidence: 0.839592348

00:16:00.120 --> 00:16:01.704 but they exist.

NOTE Confidence: 0.839592348

00:16:01.704 --> 00:16:03.896 And So what does it mean?

NOTE Confidence: 0.839592348

00:16:03.896 --> 00:16:05.316 Are all these mutations alike?

NOTE Confidence: 0.839592348

00:16:05.320 --> 00:16:05.621 Well,

NOTE Confidence: 0.839592348

00:16:05.621 --> 00:16:08.330 one of the things that we know is that

NOTE Confidence: 0.839592348

00:16:08.406 --> 00:16:10.698 even if you just broadly categorize

NOTE Confidence: 0.839592348

00:16:10.698 --> 00:16:13.985 the L858R mutations and the e.g FRXN 19

NOTE Confidence: 0.839592348

00:16:13.985 --> 00:16:16.911 deletion mutations and you look at the

NOTE Confidence: 0.839592348

00:16:16.911 --> 00:16:18.916 survival curves on ossumertinib from

NOTE Confidence: 0.839592348

00:16:18.916 --> 00:16:21.992 the trial of frontline osumertinib,

NOTE Confidence: 0.839592348

00:16:21.992 --> 00:16:25.095 you see that even just the

NOTE Confidence: 0.839592348

00:16:25.095 --> 00:16:26.555 Exxon 19 deletion mutations,

NOTE Confidence: 0.839592348

00:16:26.560 --> 00:16:28.480 the overall survival is about

NOTE Confidence: 0.839592348

00:16:28.480 --> 00:16:30.400 40 months in that study.

NOTE Confidence: 0.839592348

00:16:30.400 --> 00:16:31.840 But for the L858 Rs,

NOTE Confidence: 0.839592348

00:16:31.840 --> 00:16:33.356 it's about 33 months.

NOTE Confidence: 0.839592348

00:16:33.356 --> 00:16:35.630 And this is consistent over across

NOTE Confidence: 0.867878751764706

00:16:35.703 --> 00:16:37.182 different tyrosine kinase

NOTE Confidence: 0.867878751764706

00:16:37.182 --> 00:16:39.154 inhibitors that are used.

NOTE Confidence: 0.867878751764706

00:16:39.160 --> 00:16:42.758 So the L858R subset does worse with

NOTE Confidence: 0.867878751764706

00:16:42.760 --> 00:16:45.637 TKIS compared to the Exxon 19 subset.

NOTE Confidence: 0.867878751764706

00:16:45.640 --> 00:16:49.720 We also found several years ago in

NOTE Confidence: 0.867878751764706

00:16:49.720 --> 00:16:52.850 work that we did together with Sarah

NOTE Confidence: 0.867878751764706

00:16:52.850 --> 00:16:55.964 Goldberg and Mark Lemon is that that

NOTE Confidence: 0.867878751764706

00:16:55.964 --> 00:16:58.772 there's a small in frame deletion

NOTE Confidence: 0.867878751764706

00:16:58.772 --> 00:17:02.400 in a Proline insertion mutation and

NOTE Confidence: 0.867878751764706

00:17:02.400 --> 00:17:04.815 one of the Exxon 19 deletions that

NOTE Confidence: 0.867878751764706

00:17:04.815 --> 00:17:07.272 actually if you look at that mutation

NOTE Confidence: 0.867878751764706

00:17:07.272 --> 00:17:09.448 and you look in upon treatment with

NOTE Confidence: 0.867878751764706

00:17:09.448 --> 00:17:11.480 irlatinib this was a few years ago.

NOTE Confidence: 0.867878751764706

00:17:11.480 --> 00:17:13.646 So one of the early generation

NOTE Confidence: 0.867878751764706

00:17:13.646 --> 00:17:15.566 tyrosine kinase inhibitors that the

NOTE Confidence: 0.867878751764706

00:17:15.566 --> 00:17:17.198 progression free survival duration

NOTE Confidence: 0.867878751764706

00:17:17.198 --> 00:17:19.575 of a treatment overall survival were

NOTE Confidence: 0.867878751764706

00:17:19.575 --> 00:17:22.160 all worse for the for erlontinib in

NOTE Confidence: 0.867878751764706

00:17:22.160 --> 00:17:24.777 that subset compared to the more

NOTE Confidence: 0.867878751764706

00:17:24.777 --> 00:17:27.277 common Exxon 19 deletion mutation.

NOTE Confidence: 0.867878751764706

00:17:27.280 --> 00:17:29.950 And this along with some laboratory

NOTE Confidence: 0.867878751764706

00:17:29.950 --> 00:17:32.495 studies really piqued our interest in

NOTE Confidence: 0.867878751764706

00:17:32.495 --> 00:17:35.239 studying these differences a little bit more.

NOTE Confidence: 0.867878751764706

00:17:35.240 --> 00:17:38.159 And here you see the cryovile appear.

NOTE Confidence: 0.867878751764706

00:17:38.160 --> 00:17:41.776 This is also work that was Zenta Walther

NOTE Confidence: 0.867878751764706

00:17:41.776 --> 00:17:44.640 was really central to helping us

NOTE Confidence: 0.867878751764706

00:17:44.640 --> 00:17:47.880 identify these patients for this study.

NOTE Confidence: 0.867878751764706

00:17:47.880 --> 00:17:51.672 And so working with lots of different

NOTE Confidence: 0.867878751764706

00:17:51.672 --> 00:17:54.454 groups here we were able to show that

NOTE Confidence: 0.867878751764706

00:17:54.454 --> 00:17:56.698 this proline insertion for example what

NOTE Confidence: 0.867878751764706

00:17:56.698 --> 00:17:59.671 you see in Western blots is when you

NOTE Confidence: 0.867878751764706

00:17:59.671 --> 00:18:01.732 treat with tyrosine kinase inhibitors,

NOTE Confidence: 0.867878751764706

00:18:01.732 --> 00:18:04.792 it's less sensitive to various

NOTE Confidence: 0.867878751764706

00:18:04.792 --> 00:18:07.240 tyrosine kinase inhibitors compared

NOTE Confidence: 0.867878751764706

00:18:07.323 --> 00:18:09.124 to the canonical e.g.

NOTE Confidence: 0.867878751764706

00:18:09.124 --> 00:18:11.316 FRXN 19 deletion mutation.

NOTE Confidence: 0.867878751764706

00:18:11.320 --> 00:18:12.244 Not only that,

NOTE Confidence: 0.867878751764706

00:18:12.244 --> 00:18:14.400 when you actually go and look biochemically,

NOTE Confidence: 0.867878751764706

00:18:14.400 --> 00:18:17.235 and this is work that was spearheaded by a

NOTE Confidence: 0.867878751764706

00:18:17.235 --> 00:18:19.998 former student that Mark Lemon and I shared.

NOTE Confidence: 0.867878751764706

00:18:20.000 --> 00:18:21.656 Eris von Alderweil,

NOTE Confidence: 0.867878751764706

00:18:21.656 --> 00:18:24.347 von Rosenberg showing that this

NOTE Confidence: 0.867878751764706

00:18:24.347 --> 00:18:27.521 proline insertion mutation has AKM for

NOTE Confidence: 0.867878751764706

00:18:27.521 --> 00:18:30.956 ATP that is more more closer to the

NOTE Confidence: 0.867878751764706

00:18:30.956 --> 00:18:33.728 wild type in contrast to some of the

NOTE Confidence: 0.867878751764706

00:18:33.728 --> 00:18:35.952 other variants that instead are more

NOTE Confidence: 0.867878751764706

00:18:35.952 --> 00:18:38.077 sensitive to tyrosine kinase inhibitors.

NOTE Confidence: 0.867878751764706

00:18:38.080 --> 00:18:40.768 So really is that affinity of the

NOTE Confidence: 0.867878751764706

00:18:40.768 --> 00:18:42.940 kinase for ATP that is probably

NOTE Confidence: 0.867878751764706

00:18:42.940 --> 00:18:44.840 rendering it more resistant to

NOTE Confidence: 0.867878751764706

00:18:44.840 --> 00:18:46.360 these tyrosine kinase inhibitors.

NOTE Confidence: 0.867878751764706

00:18:46.360 --> 00:18:49.078 So really from the clinical observations,

NOTE Confidence: 0.867878751764706

00:18:49.080 --> 00:18:50.620 from some of the laboratory

NOTE Confidence: 0.867878751764706

00:18:50.620 --> 00:18:52.160 studies going to the biochemistry,

NOTE Confidence: 0.867878751764706

00:18:52.160 --> 00:18:54.834 we're really able to figure out what

NOTE Confidence: 0.867878751764706

00:18:54.834 --> 00:18:56.960 was happening with this variant.

NOTE Confidence: 0.867878751764706

00:18:56.960 --> 00:18:59.936 And this led to work that we did

NOTE Confidence: 0.867878751764706

00:18:59.936 --> 00:19:02.649 together with Mike Grant and Sarah

NOTE Confidence: 0.867878751764706

00:19:02.649 --> 00:19:05.880 Goldberg really putting together a multi

NOTE Confidence: 0.867878751764706

00:19:05.880 --> 00:19:09.040 institutional cohort of patients with e.g.

NOTE Confidence: 0.867878751764706

00:19:09.040 --> 00:19:10.930 Fr XL19 deletion mutations treated

NOTE Confidence: 0.867878751764706

00:19:10.930 --> 00:19:13.190 with asumertinib because we wanted to

NOTE Confidence: 0.867878751764706

00:19:13.190 --> 00:19:15.032 look at the tyrosine kinase inhibitor

NOTE Confidence: 0.867878751764706

00:19:15.032 --> 00:19:16.679 that was really clinically relevant

NOTE Confidence: 0.867878751764706

00:19:16.679 --> 00:19:19.017 for patients right now and that was

NOTE Confidence: 0.867878751764706

00:19:19.017 --> 00:19:21.130 being used to see what outcomes

NOTE Confidence: 0.867878751764706

00:19:21.130 --> 00:19:23.564 were for patients with this Proline

NOTE Confidence: 0.867878751764706

00:19:23.564 --> 00:19:25.920 insertion mutation with asumertinib.

NOTE Confidence: 0.867878751764706

00:19:25.920 --> 00:19:26.970 It's pretty rare.

NOTE Confidence: 0.867878751764706

00:19:26.970 --> 00:19:30.344 So you have to really work together and put

NOTE Confidence: 0.867878751764706

00:19:30.344 --> 00:19:32.918 together a cohort from various institutions.

NOTE Confidence: 0.867878751764706

00:19:32.920 --> 00:19:37.612 And so Mike and Sarah assembled

NOTE Confidence: 0.867878751764706

00:19:37.612 --> 00:19:40.214 this cohort including data from

NOTE Confidence: 0.867878751764706

00:19:40.214 --> 00:19:42.722 our Yale cohort and actually showed

NOTE Confidence: 0.867878751764706

00:19:42.722 --> 00:19:45.619 that in patients whose tumors have

NOTE Confidence: 0.867878751764706

00:19:45.619 --> 00:19:47.543 this proline insertion mutation

NOTE Confidence: 0.867878751764706

00:19:47.543 --> 00:19:49.279 treated with ossomatinib,

NOTE Confidence: 0.867878751764706

00:19:49.280 --> 00:19:52.640 you have worse progression free survival.

NOTE Confidence: 0.867878751764706

00:19:52.640 --> 00:19:55.200 Then if you look at the common e.g.

NOTE Confidence: 0.867878751764706

00:19:55.200 --> 00:19:57.100 Fr XM19 deletion mutation,

NOTE Confidence: 0.867878751764706

00:19:57.100 --> 00:19:59.475 the overall survival isn't quite

NOTE Confidence: 0.867878751764706

00:19:59.475 --> 00:20:00.800 statistically significant,

NOTE Confidence: 0.867878751764706

00:20:00.800 --> 00:20:04.226 but you can see that there is a trend

NOTE Confidence: 0.867878751764706

00:20:04.226 --> 00:20:07.360 in in in in worse outcomes there as well.

NOTE Confidence: 0.867878751764706

00:20:07.360 --> 00:20:09.076 And So what does this mean?

NOTE Confidence: 0.965352661666667

00:20:09.080 --> 00:20:11.360 What does this make us think?

NOTE Confidence: 0.965352661666667

00:20:11.360 --> 00:20:14.570 I think the message here is that

NOTE Confidence: 0.965352661666667

00:20:14.570 --> 00:20:17.480 not all mutations are the same.

NOTE Confidence: 0.965352661666667

00:20:17.480 --> 00:20:19.604 And now we have the tools and the drugs

NOTE Confidence: 0.965352661666667

00:20:19.604 --> 00:20:22.036 to better match mutations with therapies.

NOTE Confidence: 0.965352661666667

00:20:22.040 --> 00:20:23.840 We aren't the only ones who

NOTE Confidence: 0.965352661666667

00:20:23.840 --> 00:20:25.040 are thinking about this.

NOTE Confidence: 0.965352661666667

00:20:25.040 --> 00:20:28.040 There's some other work from

NOTE Confidence: 0.965352661666667

00:20:28.040 --> 00:20:29.656 Jacqueline Robichaud and John

NOTE Confidence: 0.965352661666667

00:20:29.656 --> 00:20:31.676 Haymack's group at MD Anderson,

NOTE Confidence: 0.965352661666667

00:20:31.680 --> 00:20:35.118 work from Christine Lovely at Vanderbilt,

NOTE Confidence: 0.965352661666667

00:20:35.120 --> 00:20:36.998 all really pointing in this direction.

NOTE Confidence: 0.965352661666667

00:20:37.000 --> 00:20:39.317 We need to know about the biology,

NOTE Confidence: 0.965352661666667

00:20:39.320 --> 00:20:41.160 the biochemistry of the mutations,

NOTE Confidence: 0.965352661666667

00:20:41.160 --> 00:20:43.505 and that can help us think about

NOTE Confidence: 0.965352661666667

00:20:43.505 --> 00:20:45.870 perhaps how to better optimize these

NOTE Confidence: 0.965352661666667

00:20:45.870 --> 00:20:48.438 therapies now that we have them.

NOTE Confidence: 0.965352661666667

00:20:48.440 --> 00:20:49.607 Another point, yeah,

NOTE Confidence: 0.965352661666667

00:20:49.607 --> 00:20:51.163 the structural and biochemical

NOTE Confidence: 0.965352661666667

00:20:51.163 --> 00:20:53.086 understanding of the effects of

NOTE Confidence: 0.965352661666667

00:20:53.086 --> 00:20:54.841 the mutation can guide predictions

NOTE Confidence: 0.965352661666667

00:20:54.841 --> 00:20:56.760 for TKI sensitivity and resistance.

NOTE Confidence: 0.965352661666667

00:20:56.760 --> 00:20:57.624 And of course,

NOTE Confidence: 0.965352661666667

00:20:57.624 --> 00:20:59.352 the other question that comes along

NOTE Confidence: 0.965352661666667

00:20:59.352 --> 00:21:01.172 is how do we translate to the

NOTE Confidence: 0.965352661666667

00:21:01.172 --> 00:21:03.078 clinic this to the clinic now what?

NOTE Confidence: 0.965352661666667

00:21:03.080 --> 00:21:05.159 What are the next steps that we can take?

NOTE Confidence: 0.965352661666667

00:21:05.160 --> 00:21:09.633 So we can test trials of like optimal TKI.

NOTE Confidence: 0.965352661666667

00:21:09.640 --> 00:21:11.957 So now we have all these reagents,

NOTE Confidence: 0.965352661666667

00:21:11.960 --> 00:21:13.878 we can test other agents and other

NOTE Confidence: 0.965352661666667

00:21:13.878 --> 00:21:15.393 drugs on these different variants

NOTE Confidence: 0.965352661666667

00:21:15.393 --> 00:21:17.905 and see if there's some that are more

NOTE Confidence: 0.965352661666667

00:21:17.963 --> 00:21:20.318 effective for specific mutational subsets.

NOTE Confidence: 0.965352661666667

00:21:20.320 --> 00:21:21.796 But then the other question is,

NOTE Confidence: 0.965352661666667

00:21:21.800 --> 00:21:24.464 are there other agents that we

NOTE Confidence: 0.965352661666667

00:21:24.464 --> 00:21:26.896 should be thinking about for certain

NOTE Confidence: 0.965352661666667

00:21:26.896 --> 00:21:28.864 subsets of the disease in combination

NOTE Confidence: 0.965352661666667

00:21:28.864 --> 00:21:30.080 with also Mertinib?

NOTE Confidence: 0.965352661666667

00:21:30.080 --> 00:21:31.816 And I think this will be a

NOTE Confidence: 0.965352661666667

00:21:31.816 --> 00:21:33.259 recurring theme throughout the talk.

NOTE Confidence: 0.965352661666667

00:21:33.259 --> 00:21:34.946 So for example, you know,

NOTE Confidence: 0.965352661666667

00:21:34.946 --> 00:21:37.184 should we be thinking about specific

NOTE Confidence: 0.965352661666667

00:21:37.184 --> 00:21:39.172 antibody drug conjugates or other

NOTE Confidence: 0.965352661666667

00:21:39.172 --> 00:21:41.524 approaches to target tumors with that

NOTE Confidence: 0.965352661666667

00:21:41.524 --> 00:21:43.718 don't do as well with monotherapy?

NOTE Confidence: 0.965352661666667

00:21:43.720 --> 00:21:44.580 Awesome.

NOTE Confidence: 0.965352661666667

00:21:44.580 --> 00:21:47.565 Or so after you know thinking

NOTE Confidence: 0.965352661666667

00:21:47.565 --> 00:21:48.840 about the different.

NOTE Confidence: 0.965352661666667

00:21:48.840 --> 00:21:51.878 So we talked about how different EGF

NOTE Confidence: 0.965352661666667

00:21:51.878 --> 00:21:53.550 receptor mutations themselves can

NOTE Confidence: 0.965352661666667

00:21:53.550 --> 00:21:55.772 have an impact and have distinct properties,

NOTE Confidence: 0.965352661666667

00:21:55.772 --> 00:21:57.437 but what about Co mutations?

NOTE Confidence: 0.965352661666667

00:21:57.440 --> 00:22:01.306 How can Co mutations influence tumor

NOTE Confidence: 0.965352661666667

00:22:01.306 --> 00:22:04.636 progression but also TKI sensitivity.

NOTE Confidence: 0.965352661666667

00:22:04.640 --> 00:22:06.956 And so many years ago now,

NOTE Confidence: 0.965352661666667

00:22:06.960 --> 00:22:09.252 I probably started working on this

NOTE Confidence: 0.965352661666667

00:22:09.252 --> 00:22:11.697 actually almost exactly 20 years ago

NOTE Confidence: 0.965352661666667

00:22:11.697 --> 00:22:14.235 when EGF receptor mutations were discovered.

NOTE Confidence: 0.965352661666667

00:22:14.240 --> 00:22:18.060 I think it was May 2004 that I started

NOTE Confidence: 0.965352661666667

00:22:18.060 --> 00:22:20.120 generating these mouse models.

NOTE Confidence: 0.965352661666667

00:22:20.120 --> 00:22:23.824 We generated genetically engineered

NOTE Confidence: 0.965352661666667

00:22:23.824 --> 00:22:27.008 mouse models of EGF receptor driven

NOTE Confidence: 0.965352661666667

00:22:27.008 --> 00:22:29.520 lung cancer in which we could express

NOTE Confidence: 0.965352661666667

00:22:29.520 --> 00:22:31.650 the EGF receptor mutants inducibly

NOTE Confidence: 0.965352661666667

00:22:31.650 --> 00:22:33.354 in the lung epithelium.

NOTE Confidence: 0.965352661666667

00:22:33.360 --> 00:22:35.320 And this was really these were really

NOTE Confidence: 0.965352661666667

00:22:35.320 --> 00:22:37.419 to be able to study the biology

NOTE Confidence: 0.965352661666667

00:22:37.419 --> 00:22:38.319 of the disease.

NOTE Confidence: 0.965352661666667

00:22:38.320 --> 00:22:40.642 And we've used these mice extensively

NOTE Confidence: 0.965352661666667

00:22:40.642 --> 00:22:43.759 over the years to study signaling by

NOTE Confidence: 0.965352661666667

00:22:43.759 --> 00:22:46.254 mutant EGF receptor discover resistance

NOTE Confidence: 0.965352661666667

00:22:46.254 --> 00:22:49.160 mutations to tarsine kinase inhibitors,

NOTE Confidence: 0.965352661666667

00:22:49.160 --> 00:22:51.176 identify therapeutic strategies to

NOTE Confidence: 0.965352661666667

00:22:51.176 --> 00:22:54.200 overcome or prevent and or prevent

NOTE Confidence: 0.965352661666667

00:22:54.200 --> 00:22:55.975 drug resistance and study the

NOTE Confidence: 0.965352661666667

00:22:55.975 --> 00:22:57.645 effects of targeted therapies on

NOTE Confidence: 0.965352661666667

00:22:57.645 --> 00:22:58.380 the immune microenvironment.

NOTE Confidence: 0.965352661666667

00:22:58.380 --> 00:23:00.200 And here you can see MRI images.

NOTE Confidence: 0.965352661666667

00:23:00.200 --> 00:23:03.637 We use MRI imaging for our mice to

NOTE Confidence: 0.965352661666667

00:23:03.637 --> 00:23:05.410 look at the lungs and see or you can

NOTE Confidence: 0.965352661666667

00:23:05.461 --> 00:23:07.085 see lungs full of tumors you treat

NOTE Confidence: 0.965352661666667

00:23:07.085 --> 00:23:09.198 them with a tyrosine kinase inhibitors,

NOTE Confidence: 0.965352661666667

00:23:09.200 --> 00:23:12.158 the tumors shrink and go away.

NOTE Confidence: 0.965352661666667

00:23:12.160 --> 00:23:14.029 Over time the tumors come back and

NOTE Confidence: 0.965352661666667

00:23:14.029 --> 00:23:16.199 we can study those resistant tumors.

NOTE Confidence: 0.965352661666667

00:23:16.200 --> 00:23:19.560 So a few years ago we decided to

NOTE Confidence: 0.965352661666667

00:23:19.560 --> 00:23:24.960 upgrade our our mouse model and

NOTE Confidence: 0.932822679444444

00:23:24.960 --> 00:23:26.815 use a slightly different system

NOTE Confidence: 0.932822679444444

00:23:26.815 --> 00:23:29.408 that would allow us then also to

NOTE Confidence: 0.932822679444444

00:23:29.408 --> 00:23:31.400 be able to modulate other genes.

NOTE Confidence: 0.932822679444444

00:23:31.400 --> 00:23:33.262 Because we know that EGF receptor mutations

NOTE Confidence: 0.932822679444444

00:23:33.262 --> 00:23:35.199 and lung cancer don't occur in a vacuum.

NOTE Confidence: 0.932822679444444

00:23:35.200 --> 00:23:37.624 There are other mutations in the tumors there

NOTE Confidence: 0.932822679444444

00:23:37.624 --> 00:23:40.155 and we wanted to be able to model that.

NOTE Confidence: 0.932822679444444

00:23:40.160 --> 00:23:44.108 So we decided to take this still

NOTE Confidence: 0.932822679444444

00:23:44.108 --> 00:23:46.280 this tetracycline inducible EGFR

NOTE Confidence: 0.932822679444444

00:23:46.280 --> 00:23:49.838 allele across it to another mouse.

NOTE Confidence: 0.932822679444444

00:23:49.840 --> 00:23:53.646 That in which using Cree recombinase

NOTE Confidence: 0.932822679444444

00:23:53.646 --> 00:23:56.230 you can then turn on expression of the

NOTE Confidence: 0.932822679444444

00:23:56.296 --> 00:23:57.565 reverse tetracycline transactivator

NOTE Confidence: 0.932822679444444

00:23:57.565 --> 00:24:00.103 which can bind the tetromotor in

NOTE Confidence: 0.932822679444444

00:24:00.103 --> 00:24:02.356 the presence of doxycycline and

NOTE Confidence: 0.932822679444444

00:24:02.356 --> 00:24:04.053 induce expression of EGF receptor.

NOTE Confidence: 0.932822679444444

00:24:04.053 --> 00:24:06.097 And we also crossed it to AP

NOTE Confidence: 0.932822679444444

00:24:06.097 --> 00:24:07.348 53 phloxed allele.

NOTE Confidence: 0.932822679444444

00:24:07.348 --> 00:24:09.850 But using this mouse what happens

NOTE Confidence: 0.932822679444444

00:24:09.930 --> 00:24:12.220 is we can deliver Cree recombinase,

NOTE Confidence: 0.932822679444444

00:24:12.220 --> 00:24:15.940 we deliver it with a Lantivirus

NOTE Confidence: 0.932822679444444

00:24:15.940 --> 00:24:18.000 into the lungs of mice,

NOTE Confidence: 0.932822679444444

00:24:18.000 --> 00:24:19.800 turn on mutated EGF receptor.

NOTE Confidence: 0.932822679444444

00:24:19.800 --> 00:24:23.480 Simultaneously we can delete P53.

NOTE Confidence: 0.932822679444444

00:24:23.480 --> 00:24:24.392 And here's some images,

NOTE Confidence: 0.932822679444444

00:24:24.392 --> 00:24:25.760 these are the lungs of mice.

NOTE Confidence: 0.932822679444444

00:24:25.760 --> 00:24:28.760 You can see the by MRI,

NOTE Confidence: 0.932822679444444

00:24:28.760 --> 00:24:32.026 you can see here by Histology and a a

NOTE Confidence: 0.932822679444444

00:24:32.026 --> 00:24:35.233 bigger magnification of the Histology.

NOTE Confidence: 0.932822679444444

00:24:35.233 --> 00:24:37.197 So we said OK,

NOTE Confidence: 0.932822679444444

00:24:37.200 --> 00:24:39.800 so we have this mouse model with now

NOTE Confidence: 0.932822679444444

00:24:39.800 --> 00:24:42.448 EGFR and mutants and P53 deficient tumors.

NOTE Confidence: 0.932822679444444

00:24:42.448 --> 00:24:45.080 The P53 deficient tumors are higher grade,

NOTE Confidence: 0.932822679444444

00:24:45.080 --> 00:24:45.604 they're nastier.

NOTE Confidence: 0.932822679444444

00:24:45.604 --> 00:24:46.914 I see Rob Homer here.

NOTE Confidence: 0.932822679444444

00:24:46.920 --> 00:24:49.356 He has helped us extensively over the

NOTE Confidence: 0.932822679444444

00:24:49.356 --> 00:24:51.559 years characterize and study these tumors.

NOTE Confidence: 0.932822679444444

00:24:51.560 --> 00:24:53.681 And so one of the questions that

NOTE Confidence: 0.932822679444444

00:24:53.681 --> 00:24:56.392 we had is well in addition to P53,

NOTE Confidence: 0.932822679444444

00:24:56.392 --> 00:24:58.504 what role do other mutations in

NOTE Confidence: 0.932822679444444

00:24:58.504 --> 00:25:00.776 EGF receptor play in EGF receptor

NOTE Confidence: 0.932822679444444

00:25:00.776 --> 00:25:01.919 driven lung cancer?

NOTE Confidence: 0.932822679444444

00:25:01.920 --> 00:25:04.200 How do they affect tumor progression?

NOTE Confidence: 0.932822679444444

00:25:04.200 --> 00:25:05.946 How do they affect TKI resistance

NOTE Confidence: 0.932822679444444

00:25:05.946 --> 00:25:08.382 and how do they affect the molecular

NOTE Confidence: 0.932822679444444

00:25:08.382 --> 00:25:10.800 properties and phenotypes of the tumors?

NOTE Confidence: 0.932822679444444

00:25:10.800 --> 00:25:12.582 And So what we did is we worked with

NOTE Confidence: 0.932822679444444

00:25:12.582 --> 00:25:14.557 a colleague at Stanford University,

NOTE Confidence: 0.932822679444444

00:25:14.560 --> 00:25:15.448 Monty Winslow,

NOTE Confidence: 0.932822679444444

00:25:15.448 --> 00:25:18.556 who had developed an approach in and

NOTE Confidence: 0.932822679444444

00:25:18.556 --> 00:25:21.471 used it in K Ras driven tumors to

NOTE Confidence: 0.932822679444444

00:25:21.471 --> 00:25:24.717 really be able to inactivate using CRISPR,

NOTE Confidence: 0.932822679444444

00:25:24.720 --> 00:25:26.487 CAS 9 technology,

NOTE Confidence: 0.932822679444444

00:25:26.487 --> 00:25:28.843 different tumor suppressor genes

NOTE Confidence: 0.932822679444444

00:25:28.843 --> 00:25:31.840 simultaneously in the lungs of mice.

NOTE Confidence: 0.932822679444444

00:25:31.840 --> 00:25:34.072 So not all of them in the same cell,

NOTE Confidence: 0.932822679444444

00:25:34.080 --> 00:25:36.824 but you can deliver this kind of

NOTE Confidence: 0.932822679444444

00:25:36.824 --> 00:25:39.032 pool of lentiviruses and in different

NOTE Confidence: 0.932822679444444

00:25:39.032 --> 00:25:40.752 cells you can then inactivate

NOTE Confidence: 0.932822679444444

00:25:40.752 --> 00:25:42.440 different tumor suppressor genes.

NOTE Confidence: 0.932822679444444

00:25:42.440 --> 00:25:44.932 And then you can use a computational

NOTE Confidence: 0.932822679444444

00:25:44.932 --> 00:25:47.013 approach that he developed called

NOTE Confidence: 0.932822679444444

00:25:47.013 --> 00:25:48.893 tumor barcode sequencing which

NOTE Confidence: 0.932822679444444

00:25:48.893 --> 00:25:51.420 based on various controls that are

NOTE Confidence: 0.932822679444444

00:25:51.420 --> 00:25:54.262 spiked in and based on barcode IDs.

NOTE Confidence: 0.932822679444444

00:25:54.262 --> 00:25:56.848 You can actually look and quantify

NOTE Confidence: 0.932822679444444

00:25:56.848 --> 00:25:59.569 the effect of inactivating that tumor

NOTE Confidence: 0.932822679444444

00:25:59.569 --> 00:26:02.245 suppressor gene on the number and

NOTE Confidence: 0.932822679444444

00:26:02.319 --> 00:26:04.960 size of tumors in in, in a screen.

NOTE Confidence: 0.932822679444444

00:26:04.960 --> 00:26:06.448 It's essentially a way of doing

NOTE Confidence: 0.932822679444444

00:26:06.448 --> 00:26:07.440 an in vivo screen.

NOTE Confidence: 0.932822679444444

00:26:07.440 --> 00:26:09.460 And so we applied,

NOTE Confidence: 0.932822679444444

00:26:09.460 --> 00:26:12.590 we took this pool of lentiviruses

NOTE Confidence: 0.932822679444444

00:26:12.590 --> 00:26:15.365 targeting different tumor suppressor genes

NOTE Confidence: 0.932822679444444

00:26:15.365 --> 00:26:18.719 that were frequently altered in lung cancer,

NOTE Confidence: 0.932822679444444

00:26:18.720 --> 00:26:20.574 not necessarily in EGF receptor driven

NOTE Confidence: 0.932822679444444

00:26:20.574 --> 00:26:22.499 lung cancer but in lung cancer and

NOTE Confidence: 0.932822679444444

00:26:22.499 --> 00:26:24.556 he had used it in the K Ras model

NOTE Confidence: 0.932822679444444

00:26:24.556 --> 00:26:27.160 previously and so we applied it to our e.g.

NOTE Confidence: 0.932822679444444

00:26:27.160 --> 00:26:30.597 FRL 850 at RP53 model and in particular

NOTE Confidence: 0.932822679444444

00:26:30.597 --> 00:26:32.550 we had also crossed the model that

NOTE Confidence: 0.932822679444444

00:26:32.605 --> 00:26:34.180 I just told you about with one

NOTE Confidence: 0.932822679444444

00:26:34.180 --> 00:26:36.037 that has an inducible CAS 9 Ileo.

NOTE Confidence: 0.82526931

00:26:36.040 --> 00:26:38.596 So these are experimental animals here.

NOTE Confidence: 0.82526931

00:26:38.600 --> 00:26:39.612 These are controls because

NOTE Confidence: 0.82526931

00:26:39.612 --> 00:26:40.877 they don't have CAS nine.

NOTE Confidence: 0.82526931

00:26:40.880 --> 00:26:43.896 You can't do CRISPR CAS 9 mediated genome

NOTE Confidence: 0.82526931

00:26:43.896 --> 00:26:46.398 editing when you don't have CAS 9:00.

NOTE Confidence: 0.82526931

00:26:46.400 --> 00:26:50.080 So we transduced the lungs of the mice,

NOTE Confidence: 0.82526931

00:26:50.080 --> 00:26:53.160 waited 11 weeks and then took the lungs

NOTE Confidence: 0.82526931

00:26:53.160 --> 00:26:56.599 of the mice and did tumor barcode

NOTE Confidence: 0.82526931

00:26:56.599 --> 00:26:58.104 sequencing in our control animals.

NOTE Confidence: 0.82526931

00:26:58.104 --> 00:26:59.580 When you look at the relative

NOTE Confidence: 0.82526931

00:26:59.632 --> 00:27:01.117 tumor size compared to controls,

NOTE Confidence: 0.82526931

00:27:01.120 --> 00:27:03.120 you don't really see any.

NOTE Confidence: 0.82526931

00:27:03.120 --> 00:27:04.488 The tumor suppressor gene

NOTE Confidence: 0.82526931

00:27:04.488 --> 00:27:06.198 inactivation doesn't have any effect,

NOTE Confidence: 0.82526931

00:27:06.200 --> 00:27:08.120 but that's because you don't have CAS 9,

NOTE Confidence: 0.82526931

00:27:08.120 --> 00:27:09.680 so you shouldn't see anything.

NOTE Confidence: 0.82526931

00:27:09.680 --> 00:27:10.736 So that was reassuring.

NOTE Confidence: 0.82526931

00:27:10.736 --> 00:27:13.317 What do we see in the mice with CAS 9?

NOTE Confidence: 0.82526931

00:27:13.320 --> 00:27:15.480 So one of the things that we saw is

NOTE Confidence: 0.82526931

00:27:15.480 --> 00:27:18.885 that when you inactivate APC from the

NOTE Confidence: 0.82526931

00:27:18.885 --> 00:27:23.206 wind signaling pathway RBM 10 and RB1,

NOTE Confidence: 0.82526931

00:27:23.206 --> 00:27:25.298 these three tumor suppressor

NOTE Confidence: 0.82526931

00:27:25.298 --> 00:27:27.910 genes when inactivated had the

NOTE Confidence: 0.82526931

00:27:27.910 --> 00:27:29.828 biggest effect on tumor growth.

NOTE Confidence: 0.82526931

00:27:29.828 --> 00:27:31.712 So the tumors grew faster when

NOTE Confidence: 0.82526931

00:27:31.712 --> 00:27:33.864 you were inactivating these tumor

NOTE Confidence: 0.82526931

00:27:33.864 --> 00:27:36.913 suppressor genes compared to controls.

NOTE Confidence: 0.82526931

00:27:36.913 --> 00:27:39.677 We also noticed interestingly

NOTE Confidence: 0.82526931

00:27:39.677 --> 00:27:42.958 that SET D2 and LKB 1,

NOTE Confidence: 0.82526931

00:27:42.960 --> 00:27:44.615 both of these putative tumor

NOTE Confidence: 0.82526931

00:27:44.615 --> 00:27:46.618 suppressor genes I'd say actually had

NOTE Confidence: 0.82526931

00:27:46.618 --> 00:27:48.358 a negative effect on tumor growth,

NOTE Confidence: 0.82526931

00:27:48.360 --> 00:27:49.512 which was quite interesting

NOTE Confidence: 0.82526931

00:27:49.512 --> 00:27:50.952 and is and I'll go,

NOTE Confidence: 0.82526931

00:27:50.960 --> 00:27:51.956 I'll tell you a little bit

NOTE Confidence: 0.82526931

00:27:51.956 --> 00:27:53.000 more about that in a minute,

NOTE Confidence: 0.82526931

00:27:53.000 --> 00:27:55.280 but it's a topic of interest,

NOTE Confidence: 0.82526931

00:27:55.280 --> 00:27:56.480 interesting work that we're doing.

NOTE Confidence: 0.82526931

00:27:56.480 --> 00:27:58.475 And then there were a number of

NOTE Confidence: 0.82526931

00:27:58.475 --> 00:27:59.937 tumor suppressor genes that really

NOTE Confidence: 0.82526931

00:27:59.937 --> 00:28:01.599 had no effect on tumor growth.

NOTE Confidence: 0.82526931

00:28:01.600 --> 00:28:04.426 We went ahead and we validated

NOTE Confidence: 0.82526931

00:28:04.426 --> 00:28:06.180 these using single SGRNAS.

NOTE Confidence: 0.82526931

00:28:06.180 --> 00:28:08.560 This is towards APC and this is

NOTE Confidence: 0.82526931

00:28:08.560 --> 00:28:11.728 to RBM 10 which is an RNA binding

NOTE Confidence: 0.82526931

00:28:11.728 --> 00:28:14.198 protein and a splicing factor.

NOTE Confidence: 0.82526931

00:28:14.200 --> 00:28:16.440 And you can see that when you

NOTE Confidence: 0.82526931

00:28:16.440 --> 00:28:18.532 inactivate them you see these bigger

NOTE Confidence: 0.82526931

00:28:18.532 --> 00:28:20.935 tumors and tumors progress faster

NOTE Confidence: 0.82526931

00:28:20.935 --> 00:28:24.376 than in the EGF receptor P53 model.

NOTE Confidence: 0.82526931

00:28:24.376 --> 00:28:26.224 So what does this mean though

NOTE Confidence: 0.82526931

00:28:26.224 --> 00:28:28.479 in the context of human cancer?

NOTE Confidence: 0.82526931

00:28:28.480 --> 00:28:31.040 And so if we,

NOTE Confidence: 0.82526931

00:28:31.040 --> 00:28:33.848 what we did at that time is we

NOTE Confidence: 0.82526931

00:28:33.848 --> 00:28:35.462 actually interrogated the ACR

NOTE Confidence: 0.82526931

00:28:35.462 --> 00:28:36.719 Project Genie database,

NOTE Confidence: 0.82526931

00:28:36.720 --> 00:28:39.015 which is a large data set that has a

NOTE Confidence: 0.82526931

00:28:39.015 --> 00:28:41.200 lot of mutational information that

NOTE Confidence: 0.82526931

00:28:41.200 --> 00:28:44.028 has been contributed to this data

NOTE Confidence: 0.82526931

00:28:44.028 --> 00:28:46.408 set from various institutions that

NOTE Confidence: 0.82526931

00:28:46.408 --> 00:28:49.318 are from their tumor sequencing

NOTE Confidence: 0.82526931

00:28:49.320 --> 00:28:51.752 efforts at their institutions.

NOTE Confidence: 0.82526931

00:28:51.752 --> 00:28:55.312 And when we look in this data set at e.g.

NOTE Confidence: 0.82526931

00:28:55.320 --> 00:28:57.736 F RP53 driven tumors and we look at

NOTE Confidence: 0.82526931

00:28:57.736 --> 00:28:59.863 the frequency with which there are

NOTE Confidence: 0.82526931

00:28:59.863 --> 00:29:01.683 alterations in this Co occurring

NOTE Confidence: 0.82526931

00:29:01.683 --> 00:29:03.159 tumor suppressor genes,

NOTE Confidence: 0.82526931

00:29:03.160 --> 00:29:05.869 you actually see that the top hits

NOTE Confidence: 0.82526931

00:29:05.869 --> 00:29:09.292 RBM 10 RB one and APC are where the

NOTE Confidence: 0.82526931

00:29:09.292 --> 00:29:13.120 top hits in our functional screen in mice.

NOTE Confidence: 0.82526931

00:29:13.120 --> 00:29:15.432 So we think that our screen in mice

NOTE Confidence: 0.82526931

00:29:15.432 --> 00:29:17.412 is actually telling us something

NOTE Confidence: 0.82526931

00:29:17.412 --> 00:29:19.632 about the functional relevance of

NOTE Confidence: 0.82526931

00:29:19.632 --> 00:29:21.449 these alterations in the human

NOTE Confidence: 0.82526931

00:29:21.449 --> 00:29:23.472 tumors and arid 1A didn't come out

NOTE Confidence: 0.82526931

00:29:23.480 --> 00:29:25.598 in our screen at 11 weeks,

NOTE Confidence: 0.82526931

00:29:25.600 --> 00:29:27.166 but we actually did another time

NOTE Confidence: 0.82526931

00:29:27.166 --> 00:29:29.158 point at 19 weeks and it popped up.

NOTE Confidence: 0.82526931

00:29:29.160 --> 00:29:32.190 So perhaps it's more important later

NOTE Confidence: 0.82526931

00:29:32.190 --> 00:29:34.210 in tumorigenesis And interestingly

NOTE Confidence: 0.82526931

00:29:34.290 --> 00:29:36.000 Genes SDK 11 is LKB one,

NOTE Confidence: 0.82526931

00:29:36.000 --> 00:29:37.840 it's really not frequently altered

NOTE Confidence: 0.82526931

00:29:37.840 --> 00:29:40.753 and that was the one that I showed

NOTE Confidence: 0.82526931

00:29:40.753 --> 00:29:43.091 you seemed to have a negative effect

NOTE Confidence: 0.922542002

00:29:43.167 --> 00:29:44.637 in our in vivo screen.

NOTE Confidence: 0.922542002

00:29:44.640 --> 00:29:46.059 So we've actually,

NOTE Confidence: 0.922542002

00:29:46.059 --> 00:29:48.897 this has been a really powerful

NOTE Confidence: 0.922542002

00:29:48.897 --> 00:29:51.607 system and we've actually been able

NOTE Confidence: 0.922542002

00:29:51.607 --> 00:29:54.140 to do broader screens with more

NOTE Confidence: 0.922542002

00:29:54.140 --> 00:29:57.485 genes and try to learn a little bit

NOTE Confidence: 0.922542002

00:29:57.485 --> 00:29:59.744 more about what genes are important

NOTE Confidence: 0.922542002

00:29:59.744 --> 00:30:01.952 for the progression of these tumors.

NOTE Confidence: 0.922542002

00:30:01.960 --> 00:30:04.000 And I'd just like to highlight

NOTE Confidence: 0.922542002

00:30:04.000 --> 00:30:07.906 an example of work that we

NOTE Confidence: 0.922542002

00:30:07.906 --> 00:30:11.038 did continuing this continuing

NOTE Confidence: 0.922542002

00:30:11.038 --> 00:30:14.206 this effort with D2G Oncology,

NOTE Confidence: 0.922542002

00:30:14.206 --> 00:30:16.264 a company that was founded Co

NOTE Confidence: 0.922542002

00:30:16.264 --> 00:30:17.927 founded by our collaborators

NOTE Confidence: 0.922542002

00:30:17.927 --> 00:30:20.197 Monty Winslow and Dmitry Petrov.

NOTE Confidence: 0.922542002

00:30:20.200 --> 00:30:22.840 And we work together on doing

NOTE Confidence: 0.922542002

00:30:22.840 --> 00:30:25.266 this screen of additional tumor

NOTE Confidence: 0.922542002

00:30:25.266 --> 00:30:27.636 suppressor genes in the context of

NOTE Confidence: 0.922542002

00:30:27.636 --> 00:30:29.857 EGFR tumors but also in the context

NOTE Confidence: 0.922542002

00:30:29.857 --> 00:30:32.356 of K Ras driven tumors for example.

NOTE Confidence: 0.922542002

00:30:32.360 --> 00:30:35.470 And you know I just like to go back to

NOTE Confidence: 0.922542002

00:30:35.561 --> 00:30:38.203 LKB one for example showing how this

NOTE Confidence: 0.922542002

00:30:38.203 --> 00:30:41.280 has a negative effect on EGFR driven tumors.

NOTE Confidence: 0.922542002

00:30:41.280 --> 00:30:44.720 It's not really a contributing,

NOTE Confidence: 0.922542002

00:30:44.720 --> 00:30:47.200 it doesn't really Co occur

NOTE Confidence: 0.922542002

00:30:47.200 --> 00:30:49.680 mutationally with EGFR driven tumors.

NOTE Confidence: 0.922542002

00:30:49.680 --> 00:30:52.064 So it seems to be like a synthetic

NOTE Confidence: 0.922542002

00:30:52.064 --> 00:30:53.520 lethality with these tumors.

NOTE Confidence: 0.922542002

00:30:53.520 --> 00:30:55.578 But it's an amazing contrast with what

NOTE Confidence: 0.922542002

00:30:55.578 --> 00:30:57.994 we see in Keras driven tumors where it

NOTE Confidence: 0.922542002

00:30:57.994 --> 00:31:00.997 is one of the major drivers of tumor growth.

NOTE Confidence: 0.922542002

00:31:01.000 --> 00:31:02.757 And so this is I think telling

NOTE Confidence: 0.922542002

00:31:02.757 --> 00:31:04.354 us and it's frequently mutated

NOTE Confidence: 0.922542002

00:31:04.354 --> 00:31:06.314 with Keras in human tumors.

NOTE Confidence: 0.922542002

00:31:06.320 --> 00:31:08.528 So we're really,

NOTE Confidence: 0.922542002

00:31:08.528 --> 00:31:11.420 we're really think that this is a

NOTE Confidence: 0.922542002

00:31:11.420 --> 00:31:13.830 cool system to be able to understand

NOTE Confidence: 0.922542002

00:31:13.830 --> 00:31:15.678 how Co occurring alterations

NOTE Confidence: 0.922542002

00:31:15.680 --> 00:31:18.160 impact the fitness of tumors.

NOTE Confidence: 0.922542002

00:31:18.160 --> 00:31:20.519 And Fran Exposito in the lab is

NOTE Confidence: 0.922542002

00:31:20.519 --> 00:31:23.020 really working a lot to understand

NOTE Confidence: 0.922542002

00:31:23.020 --> 00:31:25.375 this synthetic lethality and is

NOTE Confidence: 0.922542002

00:31:25.375 --> 00:31:28.831 doing experiments to knock it LKB

NOTE Confidence: 0.922542002

00:31:28.831 --> 00:31:30.973 one out and established EGF receptor

NOTE Confidence: 0.922542002

00:31:30.973 --> 00:31:33.439 tumors and see what happens and

NOTE Confidence: 0.922542002

00:31:33.439 --> 00:31:35.071 also to understand mechanistically

NOTE Confidence: 0.922542002

00:31:35.071 --> 00:31:37.399 what is happening in these tumors.

NOTE Confidence: 0.922542002

00:31:37.400 --> 00:31:39.703 So stay tuned for for data on

NOTE Confidence: 0.922542002

00:31:39.703 --> 00:31:41.960 these studies that I think will

NOTE Confidence: 0.922542002

00:31:41.960 --> 00:31:43.160 be really fascinating.

NOTE Confidence: 0.922542002

00:31:43.160 --> 00:31:45.246 And there are some other targets that

NOTE Confidence: 0.922542002

00:31:45.246 --> 00:31:47.524 we're studying along these lines as well.

NOTE Confidence: 0.922542002

00:31:47.524 --> 00:31:50.198 So I think a very powerful system.

NOTE Confidence: 0.922542002

00:31:50.200 --> 00:31:53.567 We've also used this approach not just

NOTE Confidence: 0.922542002

00:31:53.567 --> 00:31:56.840 to study mechanisms of tumor progression,

NOTE Confidence: 0.922542002

00:31:56.840 --> 00:31:59.451 but also use this type of approach

NOTE Confidence: 0.922542002

00:31:59.451 --> 00:32:01.379 to really understand what genes

NOTE Confidence: 0.922542002

00:32:01.379 --> 00:32:03.424 can modulate the sensitivity to

NOTE Confidence: 0.922542002

00:32:03.424 --> 00:32:04.840 tyrosine kinase inhibitors.

NOTE Confidence: 0.922542002

00:32:04.840 --> 00:32:08.546 So we did the same experiment and instead

NOTE Confidence: 0.922542002

00:32:08.546 --> 00:32:11.997 of just waiting and collecting the tumors,

NOTE Confidence: 0.922542002

00:32:12.000 --> 00:32:13.908 what we did is we also had an arm

NOTE Confidence: 0.922542002

00:32:13.908 --> 00:32:16.352 where we treated for two weeks with a

NOTE Confidence: 0.922542002

00:32:16.352 --> 00:32:18.000 tyrosine kinase inhibitor osumertinib.

NOTE Confidence: 0.922542002

00:32:18.000 --> 00:32:19.911 You see here the tumors go away

NOTE Confidence: 0.922542002

00:32:19.911 --> 00:32:21.160 or they're shrinking mostly.

NOTE Confidence: 0.922542002

00:32:21.160 --> 00:32:22.690 They're not completely going away at

NOTE Confidence: 0.922542002

00:32:22.690 --> 00:32:24.676 two weeks, but you do see a response.

NOTE Confidence: 0.922542002

00:32:24.680 --> 00:32:26.984 And so we did the same tumor bar

NOTE Confidence: 0.922542002

00:32:26.984 --> 00:32:28.652 code sequencing and what we found

NOTE Confidence: 0.922542002

00:32:28.652 --> 00:32:30.356 here is so this is the,

NOTE Confidence: 0.922542002

00:32:30.360 --> 00:32:33.402 this is the plot that I showed you earlier

NOTE Confidence: 0.922542002

00:32:33.402 --> 00:32:36.120 looking at what is affecting tumor growth.

NOTE Confidence: 0.922542002

00:32:36.120 --> 00:32:36.400 Well,

NOTE Confidence: 0.922542002

00:32:36.400 --> 00:32:37.520 when we add Asamertinib,

NOTE Confidence: 0.922542002

00:32:37.520 --> 00:32:40.643 one of the things that we saw is that

NOTE Confidence: 0.922542002

00:32:40.643 --> 00:32:42.680 keep 1 the tumor suppressor gene,

NOTE Confidence: 0.922542002

00:32:42.680 --> 00:32:45.321 keep one that really didn't have much

NOTE Confidence: 0.922542002

00:32:45.321 --> 00:32:47.641 of an effect on the growth of the

NOTE Confidence: 0.922542002

00:32:47.641 --> 00:32:50.105 tumors in the absence of drug now

NOTE Confidence: 0.922542002

00:32:50.105 --> 00:32:52.120 limits the sensitivity to Asamertinib.

NOTE Confidence: 0.922542002

00:32:52.120 --> 00:32:53.560 In other words,

NOTE Confidence: 0.922542002

00:32:53.560 --> 00:32:55.765 the tumors aren't shrinking as

NOTE Confidence: 0.922542002

00:32:55.765 --> 00:32:57.970 much as wild wild type

NOTE Confidence: 0.749463982631579

00:32:58.053 --> 00:32:59.753 or control tumors do

NOTE Confidence: 0.749463982631579

00:32:59.753 --> 00:33:01.878 when keep one is present.

NOTE Confidence: 0.749463982631579

00:33:01.880 --> 00:33:03.476 What do we think is happening here?

NOTE Confidence: 0.749463982631579

00:33:03.480 --> 00:33:07.288 Well, we know that keep one is important

NOTE Confidence: 0.749463982631579

00:33:07.288 --> 00:33:10.398 to sequester NRF 2 in the cytoplasm.

NOTE Confidence: 0.749463982631579

00:33:10.400 --> 00:33:12.116 When you knock out KEEP 1,

NOTE Confidence: 0.749463982631579

00:33:12.120 --> 00:33:15.873 NRF 2 can then go into the nucleus and

NOTE Confidence: 0.749463982631579

00:33:15.880 --> 00:33:18.485 activate antioxidant response elements and

NOTE Confidence: 0.749463982631579

00:33:18.485 --> 00:33:21.631 those gene expression programs that allow

NOTE Confidence: 0.749463982631579

00:33:21.631 --> 00:33:24.439 cells to really withstand oxidative stress.

NOTE Confidence: 0.749463982631579

00:33:24.440 --> 00:33:27.460 And when we take our mice and we just use

NOTE Confidence: 0.749463982631579

00:33:27.543 --> 00:33:30.719 an individual SGR and a targeting keep one,

NOTE Confidence: 0.749463982631579

00:33:30.720 --> 00:33:32.180 these are the control mice

NOTE Confidence: 0.749463982631579

00:33:32.180 --> 00:33:33.640 that don't have CAS nine,

NOTE Confidence: 0.749463982631579

00:33:33.640 --> 00:33:36.678 you use Asamertinib, the tumors go away,

NOTE Confidence: 0.749463982631579

00:33:36.680 --> 00:33:38.080 you don't really see anything

NOTE Confidence: 0.749463982631579

00:33:38.080 --> 00:33:39.200 left in the lungs.

NOTE Confidence: 0.749463982631579

00:33:39.200 --> 00:33:41.272 But if you have the experimental mice

NOTE Confidence: 0.749463982631579

00:33:41.272 --> 00:33:44.162 that have CAS 9 and you use the SGR and a

NOTE Confidence: 0.749463982631579

00:33:44.162 --> 00:33:46.277 targeting keep one treat with Asamertinib,

NOTE Confidence: 0.749463982631579

00:33:46.280 --> 00:33:49.080 you see tumors are still left over.

NOTE Confidence: 0.749463982631579

00:33:49.080 --> 00:33:50.211 And so again,

NOTE Confidence: 0.749463982631579

00:33:50.211 --> 00:33:52.473 what does that mean for patients?

NOTE Confidence: 0.749463982631579

00:33:52.480 --> 00:33:55.072 So at the time what we did is we

NOTE Confidence: 0.749463982631579

00:33:55.072 --> 00:33:57.904 worked with Jessica Hellier and Heather

NOTE Confidence: 0.749463982631579

00:33:57.904 --> 00:34:01.241 Wakeley at Stanford University who had a

NOTE Confidence: 0.749463982631579

00:34:01.241 --> 00:34:03.992 collection of data from patients with e.g.

NOTE Confidence: 0.749463982631579

00:34:04.000 --> 00:34:06.720 F RP53 driven lung cancer and looked at

NOTE Confidence: 0.749463982631579

00:34:06.720 --> 00:34:08.727 whether there were mutations in genes

NOTE Confidence: 0.749463982631579

00:34:08.727 --> 00:34:11.520 in the keep one access in these tumors.

NOTE Confidence: 0.749463982631579

00:34:11.520 --> 00:34:14.238 And you can see here in this blue line,

NOTE Confidence: 0.749463982631579

00:34:14.240 --> 00:34:16.753 the patients who had mutations in the

NOTE Confidence: 0.749463982631579

00:34:16.753 --> 00:34:19.384 keep One access in their tumors had

NOTE Confidence: 0.749463982631579

00:34:19.384 --> 00:34:22.168 a shorter time to treatment failure

NOTE Confidence: 0.749463982631579

00:34:22.168 --> 00:34:25.552 compared to controls suggesting that if

NOTE Confidence: 0.749463982631579

00:34:25.552 --> 00:34:30.450 you have alterations in this this program,

NOTE Confidence: 0.749463982631579

00:34:30.450 --> 00:34:33.600 this antioxidant response response program,

NOTE Confidence: 0.749463982631579

00:34:33.600 --> 00:34:37.066 you're going to have limited sensitivity

NOTE Confidence: 0.749463982631579

00:34:37.066 --> 00:34:40.158 to tyrosine kinase inhibitors.

NOTE Confidence: 0.749463982631579

00:34:40.160 --> 00:34:43.229 And so I think one of the things that

NOTE Confidence: 0.749463982631579

00:34:43.229 --> 00:34:46.108 we're really seeing emerging from this

NOTE Confidence: 0.749463982631579

00:34:46.108 --> 00:34:48.965 work looking at the tumor suppressor

NOTE Confidence: 0.749463982631579

00:34:48.965 --> 00:34:52.457 genes is that when you do have mutations

NOTE Confidence: 0.749463982631579

00:34:52.457 --> 00:34:55.376 or you have alterations that Co occur

NOTE Confidence: 0.749463982631579

00:34:55.376 --> 00:34:58.516 with EGF receptor and with EGF receptor

NOTE Confidence: 0.749463982631579

00:34:58.520 --> 00:35:00.998 P53 these can modulate both the growth

NOTE Confidence: 0.749463982631579

00:35:01.000 --> 00:35:04.000 and sensitivity to these agents.

NOTE Confidence: 0.749463982631579

00:35:04.000 --> 00:35:06.190 We we were interested in looking

NOTE Confidence: 0.749463982631579

00:35:06.190 --> 00:35:09.100 further and in work that Paul

NOTE Confidence: 0.749463982631579

00:35:09.100 --> 00:35:12.206 Stockhammer who was a resident is

NOTE Confidence: 0.749463982631579

00:35:12.206 --> 00:35:15.426 now a hospitalist here and is an

NOTE Confidence: 0.749463982631579

00:35:15.426 --> 00:35:18.780 incoming he monk fellow did recently.

NOTE Confidence: 0.749463982631579

00:35:18.780 --> 00:35:23.820 He looked at both our Yale internal data

NOTE Confidence: 0.749463982631579

00:35:23.945 --> 00:35:26.260 from our tissue collection program.

NOTE Confidence: 0.749463982631579

00:35:26.260 --> 00:35:28.560 You see the cryovial here,

NOTE Confidence: 0.749463982631579

00:35:28.560 --> 00:35:32.322 but also at the ACR project gene data set

NOTE Confidence: 0.749463982631579

00:35:32.322 --> 00:35:37.525 and looked at outcomes for patients on

NOTE Confidence: 0.749463982631579

00:35:37.525 --> 00:35:41.234 tyrosine kinase inhibitors whose tumors

NOTE Confidence: 0.749463982631579

00:35:41.234 --> 00:35:44.319 had different combinations of mutations.

NOTE Confidence: 0.749463982631579

00:35:44.320 --> 00:35:46.588 And I think the take away here is he

NOTE Confidence: 0.749463982631579

00:35:46.588 --> 00:35:48.938 was able to look at tumors that had

NOTE Confidence: 0.749463982631579

00:35:48.938 --> 00:35:51.555 mutations in a subset of tumor suppressor

NOTE Confidence: 0.749463982631579

00:35:51.555 --> 00:35:54.084 genes because tumors had been analyzed

NOTE Confidence: 0.749463982631579

00:35:54.084 --> 00:35:57.400 across a wide variety of different platforms.

NOTE Confidence: 0.749463982631579

00:35:57.400 --> 00:36:00.800 So we had to sort of focus in on the the,

NOTE Confidence: 0.749463982631579

00:36:00.800 --> 00:36:02.804 the common subset of tumor suppressor

NOTE Confidence: 0.749463982631579

00:36:02.804 --> 00:36:05.320 genes that were looked at across platforms.

NOTE Confidence: 0.749463982631579

00:36:05.320 --> 00:36:10.036 But essentially if tumors had both

NOTE Confidence: 0.749463982631579

00:36:10.040 --> 00:36:11.800 P53 mutations and a mutation,

NOTE Confidence: 0.749463982631579

00:36:11.800 --> 00:36:13.462 at least one of these tumor

NOTE Confidence: 0.749463982631579

00:36:13.462 --> 00:36:15.159 suppressor genes that he looked at,

NOTE Confidence: 0.749463982631579

00:36:15.160 --> 00:36:16.836 they had worse outcomes.

NOTE Confidence: 0.749463982631579

00:36:16.836 --> 00:36:19.350 These are EGFR mutant tumors even

NOTE Confidence: 0.749463982631579

00:36:19.428 --> 00:36:21.960 compared to mutations that just had

NOTE Confidence: 0.749463982631579

00:36:21.960 --> 00:36:25.128 TPF 3 mutations and were wild type for

NOTE Confidence: 0.749463982631579

00:36:25.128 --> 00:36:27.679 those different tumor suppressor genes.

NOTE Confidence: 0.749463982631579

00:36:27.680 --> 00:36:28.676 And So what does that mean?

NOTE Confidence: 0.954063358

00:36:28.680 --> 00:36:32.434 Again, I think we're identifying a subset

NOTE Confidence: 0.954063358

00:36:32.434 --> 00:36:35.130 of tumors where there may be a benefit

NOTE Confidence: 0.954063358

00:36:35.211 --> 00:36:37.724 from adding a different therapy or it

NOTE Confidence: 0.954063358

00:36:37.724 --> 00:36:40.430 should be at least be investigated from

NOTE Confidence: 0.954063358

00:36:40.430 --> 00:36:43.668 the get go because they are likely to

NOTE Confidence: 0.954063358

00:36:43.668 --> 00:36:45.938 have worse outcomes with monotherapy

NOTE Confidence: 0.954063358

00:36:45.938 --> 00:36:48.000 tyrosine kinase inhibitor treatment.

NOTE Confidence: 0.954063358

00:36:48.000 --> 00:36:49.848 And this is very relevant right now

NOTE Confidence: 0.954063358

00:36:49.848 --> 00:36:52.334 at least in the field of EGF receptor

NOTE Confidence: 0.954063358

00:36:52.334 --> 00:36:54.376 driven lung cancer because there are

NOTE Confidence: 0.954063358

00:36:54.376 --> 00:36:56.121 studies of chemotherapy plus asamartinib

NOTE Confidence: 0.954063358

00:36:56.121 --> 00:36:58.591 in the first line that are positive.

NOTE Confidence: 0.954063358

00:36:58.591 --> 00:37:00.733 But people are very reluctant to

NOTE Confidence: 0.954063358

00:37:00.733 --> 00:37:03.079 give that combination to everybody.

NOTE Confidence: 0.954063358

00:37:03.080 --> 00:37:05.229 If we can identify people who might

NOTE Confidence: 0.954063358

00:37:05.229 --> 00:37:07.778 benefit more or might need it more than

NOTE Confidence: 0.954063358

00:37:07.778 --> 00:37:10.234 that could be really helpful for deploying

NOTE Confidence: 0.954063358

00:37:10.234 --> 00:37:12.718 these different strategies in the clinic.

NOTE Confidence: 0.954063358

00:37:12.720 --> 00:37:16.000 And then I think another point is that

NOTE Confidence: 0.954063358

00:37:16.000 --> 00:37:18.919 we're really learning the Co mutations

NOTE Confidence: 0.954063358

00:37:18.920 --> 00:37:20.348 can affect therapeutic sensitivity

NOTE Confidence: 0.954063358

00:37:20.348 --> 00:37:22.989 and it isn't only in the context

NOTE Confidence: 0.954063358

00:37:22.989 --> 00:37:25.159 of EGFR tyrosine kinase inhibitors.

NOTE Confidence: 0.954063358

00:37:25.160 --> 00:37:27.830 This is happening in multiple contexts

NOTE Confidence: 0.954063358

00:37:27.830 --> 00:37:29.731 and with with multiple agents.

NOTE Confidence: 0.954063358

00:37:29.731 --> 00:37:31.079 So here an example,

NOTE Confidence: 0.954063358

00:37:31.080 --> 00:37:32.880 I'm just just giving you a few examples.

NOTE Confidence: 0.954063358

00:37:32.880 --> 00:37:35.358 There are many more in the literature.

NOTE Confidence: 0.954063358

00:37:35.360 --> 00:37:36.599 But if we look at keep one,

NOTE Confidence: 0.954063358

00:37:36.600 --> 00:37:39.320 going back to keep one, keep one,

NOTE Confidence: 0.954063358

00:37:39.320 --> 00:37:43.412 alterations seem to have been negative

NOTE Confidence: 0.954063358

00:37:43.412 --> 00:37:45.842 for response rates to Sotirasip

NOTE Confidence: 0.954063358

00:37:45.842 --> 00:37:49.520 in K Rash G12C driven lung cancer.

NOTE Confidence: 0.954063358

00:37:49.520 --> 00:37:51.480 Worse,

NOTE Confidence: 0.954063358

00:37:51.480 --> 00:37:54.155 you know higher local recurrence

NOTE Confidence: 0.954063358

00:37:54.155 --> 00:37:57.599 with chemo radiation in the context

NOTE Confidence: 0.954063358

00:37:57.599 --> 00:38:00.664 of immunotherapy LKB 1 mutations

NOTE Confidence: 0.954063358

00:38:00.664 --> 00:38:03.600 actually seem to be worse confer,

NOTE Confidence: 0.954063358

00:38:03.600 --> 00:38:06.478 you know be worse for or describe,

NOTE Confidence: 0.954063358

00:38:06.478 --> 00:38:08.512 define a word a subset that

NOTE Confidence: 0.954063358

00:38:08.512 --> 00:38:10.519 does worse with immunotherapy.

NOTE Confidence: 0.954063358

00:38:10.520 --> 00:38:14.432 And so in conclusion for this

NOTE Confidence: 0.954063358

00:38:14.432 --> 00:38:16.000 part of the talk,

NOTE Confidence: 0.954063358

00:38:16.000 --> 00:38:18.443 the nature of the oncogenic mutation and

NOTE Confidence: 0.954063358

00:38:18.443 --> 00:38:20.344 Co occurring mutations effects sensitivity

NOTE Confidence: 0.954063358

00:38:20.344 --> 00:38:22.714 to Tkis and mechanisms of resistance.

NOTE Confidence: 0.954063358

00:38:22.720 --> 00:38:25.606 We've developed a new generation of

NOTE Confidence: 0.954063358

00:38:25.606 --> 00:38:27.928 genetically engineered mouse models that

NOTE Confidence: 0.954063358

00:38:27.928 --> 00:38:30.559 can be used to study these complex genotypes.

NOTE Confidence: 0.954063358

00:38:30.559 --> 00:38:32.792 And I'd like to point out that

NOTE Confidence: 0.954063358

00:38:32.792 --> 00:38:35.164 really we have a lot of work that

NOTE Confidence: 0.954063358

00:38:35.164 --> 00:38:37.264 is happening now studying these

NOTE Confidence: 0.954063358

00:38:37.264 --> 00:38:39.160 individual different components.

NOTE Confidence: 0.954063358

00:38:39.160 --> 00:38:40.288 Mariana Do Carmos,

NOTE Confidence: 0.954063358

00:38:40.288 --> 00:38:41.040 an MD,

NOTE Confidence: 0.954063358

00:38:41.040 --> 00:38:42.360 PhD student in the lab.

NOTE Confidence: 0.954063358

00:38:42.360 --> 00:38:46.399 She's studying the role of RBM 10

NOTE Confidence: 0.954063358

00:38:46.400 --> 00:38:49.088 in EGF receptor driven lung cancer

NOTE Confidence: 0.954063358

00:38:49.088 --> 00:38:51.240 working with Luisa escobarahoyos lab.

NOTE Confidence: 0.954063358

00:38:51.240 --> 00:38:52.680 Because we really can

NOTE Confidence: 0.822266775

00:38:54.720 --> 00:38:56.862 join forces and Luisa is an

NOTE Confidence: 0.822266775

00:38:56.862 --> 00:38:59.221 expert in splicing and this is

NOTE Confidence: 0.822266775

00:38:59.221 --> 00:39:00.830 really important gene protein

NOTE Confidence: 0.822266775

00:39:00.830 --> 00:39:03.080 that is involved in in splicing.

NOTE Confidence: 0.822266775

00:39:03.080 --> 00:39:04.296 So we're doing that.

NOTE Confidence: 0.822266775

00:39:04.296 --> 00:39:06.120 I told you about Fran's work.

NOTE Confidence: 0.822266775

00:39:06.120 --> 00:39:09.910 We have Kita who's working on KMT 2D,

NOTE Confidence: 0.822266775

00:39:09.910 --> 00:39:11.800 which I didn't tell you about

NOTE Confidence: 0.822266775

00:39:11.800 --> 00:39:12.840 another potential target

NOTE Confidence: 0.822266775

00:39:12.840 --> 00:39:14.160 that came out of this screen.

NOTE Confidence: 0.822266775

00:39:14.160 --> 00:39:16.380 So really we can really study

NOTE Confidence: 0.822266775

00:39:16.380 --> 00:39:17.860 these different genotypes and

NOTE Confidence: 0.822266775

00:39:17.931 --> 00:39:20.112 understand the biology of these

NOTE Confidence: 0.822266775

00:39:20.112 --> 00:39:21.276 different complex genotypes,

NOTE Confidence: 0.822266775

00:39:21.280 --> 00:39:23.560 which is really exciting.

NOTE Confidence: 0.822266775

00:39:23.560 --> 00:39:27.280 We have found out that an activation of

NOTE Confidence: 0.822266775

00:39:27.280 --> 00:39:28.792 these different tumor suppressor genes

NOTE Confidence: 0.822266775

00:39:28.792 --> 00:39:30.646 can have different effects on both

NOTE Confidence: 0.822266775

00:39:30.646 --> 00:39:32.362 tumor growth including positive and

NOTE Confidence: 0.822266775

00:39:32.362 --> 00:39:34.102 negative effects and TKI sensitivity

NOTE Confidence: 0.822266775

00:39:34.102 --> 00:39:37.479 depending on the oncogenic context.

NOTE Confidence: 0.822266775

00:39:37.480 --> 00:39:40.336 We showed that keep one loss limits

NOTE Confidence: 0.822266775

00:39:40.336 --> 00:39:42.302 sensitivity to osmertinib in mice

NOTE Confidence: 0.822266775

00:39:42.302 --> 00:39:44.528 and in patients and think that

NOTE Confidence: 0.822266775

00:39:44.528 --> 00:39:47.298 this is really potentially a bad

NOTE Confidence: 0.822266775

00:39:47.298 --> 00:39:49.534 actor if there's Q1 alterations

NOTE Confidence: 0.822266775

00:39:49.534 --> 00:39:51.856 either at the genetic level or

NOTE Confidence: 0.822266775

00:39:51.856 --> 00:39:53.638 also alterations in the pathway.

NOTE Confidence: 0.822266775

00:39:53.640 --> 00:39:55.640 The pathway can be modulated

NOTE Confidence: 0.822266775

00:39:55.640 --> 00:39:57.240 in many different ways,

NOTE Confidence: 0.822266775

00:39:57.240 --> 00:39:59.430 and tumor suppressant gene mutations

NOTE Confidence: 0.822266775

00:39:59.430 --> 00:40:02.360 can be used to identify patients,

NOTE Confidence: 0.822266775

00:40:02.360 --> 00:40:04.850 subsets of patients who are likely

NOTE Confidence: 0.822266775

00:40:04.850 --> 00:40:07.767 to have worse outcomes and could

NOTE Confidence: 0.822266775

00:40:07.767 --> 00:40:10.131 be considered for additional

NOTE Confidence: 0.822266775

00:40:10.131 --> 00:40:11.313 therapeutic interventions.

NOTE Confidence: 0.822266775

00:40:11.320 --> 00:40:14.640 So in the last part of the talk,

NOTE Confidence: 0.822266775

00:40:14.640 --> 00:40:17.706 I'd like to tell you about some

NOTE Confidence: 0.822266775

00:40:17.706 --> 00:40:20.680 other work that we've been doing

NOTE Confidence: 0.822266775

00:40:20.680 --> 00:40:23.598 more recently to study non mutational

NOTE Confidence: 0.822266775

00:40:23.598 --> 00:40:25.693 mechanisms of resistance and I'd

NOTE Confidence: 0.822266775

00:40:25.693 --> 00:40:27.880 say also of persistence.

NOTE Confidence: 0.822266775

00:40:27.880 --> 00:40:30.400 So on tyrosine kinase inhibitors.

NOTE Confidence: 0.822266775

00:40:30.400 --> 00:40:34.186 And So what are some of the things

NOTE Confidence: 0.822266775

00:40:34.186 --> 00:40:35.897 that we're thinking about broadly

NOTE Confidence: 0.822266775

00:40:35.897 --> 00:40:38.449 in the lab when we think about this

NOTE Confidence: 0.822266775

00:40:38.449 --> 00:40:40.429 problem of this 50% of tumors that

NOTE Confidence: 0.822266775

00:40:40.429 --> 00:40:42.550 we don't what for which we don't

NOTE Confidence: 0.822266775

00:40:42.622 --> 00:40:44.557 know why a resistance emerges.

NOTE Confidence: 0.822266775

00:40:44.560 --> 00:40:47.059 So some of the things that we're

NOTE Confidence: 0.822266775

00:40:47.059 --> 00:40:49.161 really interested in in understanding

NOTE Confidence: 0.822266775

00:40:49.161 --> 00:40:52.035 and studying are how the tumor

NOTE Confidence: 0.822266775

00:40:52.035 --> 00:40:53.222 microenvironment effects resistance

NOTE Confidence: 0.822266775

00:40:53.222 --> 00:40:53.924 and persistence.

NOTE Confidence: 0.822266775

00:40:53.924 --> 00:40:56.706 And this is work that we're doing

NOTE Confidence: 0.822266775

00:40:56.706 --> 00:40:57.320 collaboratively,

NOTE Confidence: 0.822266775

00:40:57.320 --> 00:41:00.128 Jake Schillo in the lab doing

NOTE Confidence: 0.822266775

00:41:00.128 --> 00:41:02.136 collaboratively working with Don

NOTE Confidence: 0.822266775

00:41:02.136 --> 00:41:03.160 Nguyen's lab.

NOTE Confidence: 0.822266775

00:41:03.160 --> 00:41:06.310 We are studying lineage plasticity

NOTE Confidence: 0.822266775

00:41:06.310 --> 00:41:08.200 and tumor heterogeneity.

NOTE Confidence: 0.822266775

00:41:08.200 --> 00:41:10.832 And I'll tell you about an example

NOTE Confidence: 0.822266775

00:41:10.832 --> 00:41:13.408 of this that was just recently

NOTE Confidence: 0.822266775

00:41:13.408 --> 00:41:16.144 published this month and that comes

NOTE Confidence: 0.822266775

00:41:16.144 --> 00:41:18.580 out of work studying mechanisms

NOTE Confidence: 0.822266775

00:41:18.580 --> 00:41:20.320 of tumor persistence.

NOTE Confidence: 0.822266775

00:41:20.320 --> 00:41:22.006 And of course another area that

NOTE Confidence: 0.822266775

00:41:22.006 --> 00:41:23.575 we're really interested in is while

NOTE Confidence: 0.822266775

00:41:23.575 --> 00:41:25.640 we've we're talked a lot about genes

NOTE Confidence: 0.822266775

00:41:25.640 --> 00:41:27.238 and mutations and genetics here,

NOTE Confidence: 0.822266775

00:41:27.240 --> 00:41:29.872 but are there ways of reading out

NOTE Confidence: 0.822266775

00:41:29.872 --> 00:41:31.875 pathways and learning about how

NOTE Confidence: 0.822266775

00:41:31.875 --> 00:41:33.880 pathways are altered in tumours

NOTE Confidence: 0.822266775

00:41:33.880 --> 00:41:36.706 which might be an important way

NOTE Confidence: 0.822266775

00:41:36.706 --> 00:41:38.119 of understanding resistance

NOTE Confidence: 0.822266775

00:41:38.119 --> 00:41:40.159 and persistence as well.

NOTE Confidence: 0.822266775

00:41:40.160 --> 00:41:42.435 And so one of the non mutational

NOTE Confidence: 0.822266775

00:41:42.435 --> 00:41:43.951 mechanisms that we recently

NOTE Confidence: 0.822266775

00:41:43.951 --> 00:41:45.839 discovered and published on,

NOTE Confidence: 0.822266775

00:41:45.840 --> 00:41:48.240 I'm not going to tell you about that

NOTE Confidence: 0.822266775

00:41:48.240 --> 00:41:50.052 today because I don't really have

NOTE Confidence: 0.822266775

00:41:50.052 --> 00:41:52.080 time is that we identified a role

NOTE Confidence: 0.822266775

00:41:52.080 --> 00:41:55.024 for the ATP as of the SLY sniff

NOTE Confidence: 0.822266775

00:41:55.024 --> 00:41:57.315 complex in mediating resistance

NOTE Confidence: 0.822266775

00:41:57.315 --> 00:42:00.760 to tyrosine kinase inhibitors and

NOTE Confidence: 0.822266775

00:42:00.760 --> 00:42:03.880 SMARCA 4 is actually usually lost,

NOTE Confidence: 0.822266775

00:42:03.880 --> 00:42:05.560 you have loss of function mutations

NOTE Confidence: 0.822266775

00:42:05.560 --> 00:42:06.120 in tumors.

NOTE Confidence: 0.822266775

00:42:06.120 --> 00:42:08.374 One of the things that we found

NOTE Confidence: 0.822266775

00:42:08.374 --> 00:42:10.562 which was really interesting is that

NOTE Confidence: 0.822266775

00:42:10.562 --> 00:42:12.860 actually it seems to be important

NOTE Confidence: 0.822266775

00:42:12.860 --> 00:42:15.138 for the resistance phenotype because

NOTE Confidence: 0.822266775

00:42:15.138 --> 00:42:17.880 in resistant tumors it actually can

NOTE Confidence: 0.822266775

00:42:17.880 --> 00:42:19.936 promote accessibility of chromatin

NOTE Confidence: 0.822266775

00:42:19.936 --> 00:42:23.020 at both cell proliferation genes but

NOTE Confidence: 0.858663129230769

00:42:23.098 --> 00:42:27.100 also at genes it are NRF 2 low size

NOTE Confidence: 0.858663129230769

00:42:27.100 --> 00:42:29.782 so that allow activation of genes

NOTE Confidence: 0.858663129230769

00:42:29.782 --> 00:42:31.594 that are antioxidant genes with that.

NOTE Confidence: 0.858663129230769

00:42:31.600 --> 00:42:34.995 So it links to that keep one,

NOTE Confidence: 0.858663129230769

00:42:35.000 --> 00:42:37.037 keep one finding that we had in

NOTE Confidence: 0.858663129230769

00:42:37.037 --> 00:42:38.640 our tumor suppressor gene screen.

NOTE Confidence: 0.858663129230769

00:42:38.640 --> 00:42:40.800 So I'm not going to tell you about this,

NOTE Confidence: 0.858663129230769

00:42:40.800 --> 00:42:43.278 but I did want to highlight it

NOTE Confidence: 0.858663129230769

00:42:43.278 --> 00:42:46.024 as as one of the some of the work

NOTE Confidence: 0.858663129230769

00:42:46.024 --> 00:42:48.146 that we have done recently on non

NOTE Confidence: 0.858663129230769

00:42:48.146 --> 00:42:49.998 mutational mechanisms of resistance.

NOTE Confidence: 0.858663129230769

00:42:50.000 --> 00:42:52.544 What I really wanted to focus the last

NOTE Confidence: 0.858663129230769

00:42:52.544 --> 00:42:54.962 few minutes of the talk on is telling

NOTE Confidence: 0.858663129230769

00:42:54.962 --> 00:42:57.263 you about some work that we've been

NOTE Confidence: 0.858663129230769

00:42:57.263 --> 00:42:59.812 doing to study tolerance and persistence

NOTE Confidence: 0.858663129230769

00:42:59.812 --> 00:43:01.996 to tyrosine kinase inhibitors.

NOTE Confidence: 0.858663129230769

00:43:02.000 --> 00:43:05.720 And you saw this waterfall plot earlier.

NOTE Confidence: 0.858663129230769

00:43:05.720 --> 00:43:07.752 But one of the and one of the

NOTE Confidence: 0.858663129230769

00:43:07.752 --> 00:43:09.653 questions that that we've had and I

NOTE Confidence: 0.858663129230769

00:43:09.653 --> 00:43:11.364 think that is a prominent question

NOTE Confidence: 0.858663129230769

00:43:11.364 --> 00:43:13.948 in the field is why aren't all cells

NOTE Confidence: 0.858663129230769

00:43:13.948 --> 00:43:15.099 eradicated upon TKI treatment,

NOTE Confidence: 0.858663129230769

00:43:15.099 --> 00:43:17.010 right, Because if we could get rid

NOTE Confidence: 0.858663129230769

00:43:17.060 --> 00:43:18.878 of all of the cells from the get go,

NOTE Confidence: 0.858663129230769

00:43:18.880 --> 00:43:21.330 we wouldn't have the problem of acquired

NOTE Confidence: 0.858663129230769

00:43:21.330 --> 00:43:22.696 resistance. And here's some scans.

NOTE Confidence: 0.858663129230769

00:43:22.696 --> 00:43:24.849 You see the tumor and you see several

NOTE Confidence: 0.858663129230769

00:43:24.849 --> 00:43:26.990 months later the tumor is still there,

NOTE Confidence: 0.858663129230769

00:43:26.990 --> 00:43:30.000 there still is some residual tumor leftover.

NOTE Confidence: 0.858663129230769

00:43:30.000 --> 00:43:32.840 So what is the biology of residual disease?

NOTE Confidence: 0.858663129230769

00:43:32.840 --> 00:43:35.288 Well, we decided and this is work from

NOTE Confidence: 0.858663129230769

00:43:35.288 --> 00:43:37.798 a former graduate student in the lab,

NOTE Confidence: 0.858663129230769

00:43:37.800 --> 00:43:38.510 Boom Yao,

NOTE Confidence: 0.858663129230769

00:43:38.510 --> 00:43:41.066 who who is now in Arno Osher's lab

NOTE Confidence: 0.858663129230769

00:43:41.066 --> 00:43:41.918 as a post doc.

NOTE Confidence: 0.858663129230769

00:43:41.920 --> 00:43:43.117 And I think Boom Yao is here.

NOTE Confidence: 0.858663129230769

00:43:43.120 --> 00:43:44.880 I thought I saw him.

NOTE Confidence: 0.858663129230769

00:43:44.880 --> 00:43:47.814 And So what Bom Yao did is he took

NOTE Confidence: 0.858663129230769

00:43:47.814 --> 00:43:50.106 advantage again of our collection

NOTE Confidence: 0.858663129230769

00:43:50.106 --> 00:43:51.994 of specimens from patients.

NOTE Confidence: 0.858663129230769

00:43:52.000 --> 00:43:53.444 And he said, well,

NOTE Confidence: 0.858663129230769

00:43:53.444 --> 00:43:55.610 what happens if I implant these

NOTE Confidence: 0.858663129230769

00:43:55.683 --> 00:43:57.559 PDXS that we've generated,

NOTE Confidence: 0.858663129230769

00:43:57.560 --> 00:44:00.479 treat them with a tyrosine kinase inhibitor

NOTE Confidence: 0.858663129230769

00:44:00.480 --> 00:44:02.640 and then look at residual disease?

NOTE Confidence: 0.858663129230769

00:44:02.640 --> 00:44:04.264 We can harvest that.

NOTE Confidence: 0.858663129230769

00:44:04.264 --> 00:44:06.708 You know, we take it at a plateau, right?

NOTE Confidence: 0.858663129230769

00:44:06.708 --> 00:44:08.556 Once the tumors aren't shrinking anymore,

NOTE Confidence: 0.858663129230769

00:44:08.560 --> 00:44:09.632 that's what's left over.

NOTE Confidence: 0.858663129230769

00:44:09.632 --> 00:44:11.952 And can we we it's really hard to

NOTE Confidence: 0.858663129230769

00:44:11.952 --> 00:44:13.597 study residual disease in patients.

NOTE Confidence: 0.858663129230769

00:44:13.600 --> 00:44:15.730 We can't really easily do biopsies

NOTE Confidence: 0.858663129230769

00:44:15.730 --> 00:44:16.440 on treatment,

NOTE Confidence: 0.858663129230769

00:44:16.440 --> 00:44:19.280 but this is as a surrogate of that.

NOTE Confidence: 0.858663129230769

00:44:19.280 --> 00:44:22.276 And so here are some examples of

NOTE Confidence: 0.858663129230769

00:44:22.276 --> 00:44:25.238 the PDXS that Boom Yao studied.

NOTE Confidence: 0.858663129230769

00:44:25.240 --> 00:44:26.640 So he took these PDXS,

NOTE Confidence: 0.858663129230769

00:44:26.640 --> 00:44:29.111 treated them and then took what was

NOTE Confidence: 0.858663129230769

00:44:29.111 --> 00:44:31.349 leftover after four to six weeks

NOTE Confidence: 0.858663129230769

00:44:31.349 --> 00:44:33.194 of treatment when they plateaued.

NOTE Confidence: 0.858663129230769

00:44:33.200 --> 00:44:35.513 And you can see in all of the cases

NOTE Confidence: 0.858663129230769

00:44:35.520 --> 00:44:37.836 there was tumor leftover after treatment,

NOTE Confidence: 0.858663129230769

00:44:37.840 --> 00:44:39.892 varying amounts of tumor and in

NOTE Confidence: 0.858663129230769

00:44:39.892 --> 00:44:40.918 some very little,

NOTE Confidence: 0.858663129230769

00:44:40.920 --> 00:44:42.600 very small islands of tumor,

NOTE Confidence: 0.858663129230769

00:44:42.600 --> 00:44:44.480 but there was tumor leftover.

NOTE Confidence: 0.858663129230769

00:44:44.480 --> 00:44:46.167 And I'd like to highlight an example

NOTE Confidence: 0.858663129230769

00:44:46.167 --> 00:44:48.175 of one of the things that we found

NOTE Confidence: 0.858663129230769

00:44:48.175 --> 00:44:49.986 from one of these PDXS that we

NOTE Confidence: 0.858663129230769

00:44:49.986 --> 00:44:51.558 studied in a little more detail.

NOTE Confidence: 0.858663129230769

00:44:51.560 --> 00:44:54.245 We found that in one of them we

NOTE Confidence: 0.858663129230769

00:44:54.245 --> 00:44:57.155 saw up regulation of Ascl 1.

NOTE Confidence: 0.858663129230769

00:44:57.160 --> 00:45:00.632 ASCL one is a basic Helix loop

NOTE Confidence: 0.858663129230769

00:45:00.632 --> 00:45:02.120 Helix transcription factor.

NOTE Confidence: 0.858663129230769

00:45:02.120 --> 00:45:04.451 It has a role in neuronal differentiation

NOTE Confidence: 0.858663129230769

00:45:04.451 --> 00:45:06.185 and its expression actually identifies

NOTE Confidence: 0.858663129230769

00:45:06.185 --> 00:45:08.558 a subset of small cell lung cancer.

NOTE Confidence: 0.858663129230769

00:45:08.560 --> 00:45:11.500 So it was really up in the residual

NOTE Confidence: 0.858663129230769

00:45:11.500 --> 00:45:14.160 disease in this tumor and not only

NOTE Confidence: 0.951652336666667

00:45:14.238 --> 00:45:16.788 was it up at the transcriptional

NOTE Confidence: 0.951652336666667

00:45:16.788 --> 00:45:19.380 level and the signature was was

NOTE Confidence: 0.951652336666667

00:45:19.380 --> 00:45:22.280 enriched in the residual disease,

NOTE Confidence: 0.951652336666667

00:45:22.280 --> 00:45:25.255 but it's downstream targets rat BCL two

NOTE Confidence: 0.951652336666667

00:45:25.255 --> 00:45:29.024 and DLL three were also all turned on in

NOTE Confidence: 0.951652336666667

00:45:29.024 --> 00:45:31.840 the residual disease in in that tumor.

NOTE Confidence: 0.951652336666667

00:45:31.840 --> 00:45:33.560 Ossumertinib was working really well.

NOTE Confidence: 0.951652336666667

00:45:33.560 --> 00:45:36.840 You can see phospho EGFR is gone here.

NOTE Confidence: 0.951652336666667

00:45:36.840 --> 00:45:39.199 And so this was really interesting to

NOTE Confidence: 0.951652336666667

00:45:39.199 --> 00:45:42.030 us because we know that a subset of

NOTE Confidence: 0.951652336666667

00:45:42.030 --> 00:45:44.480 EGFR driven tumors when they're treated

NOTE Confidence: 0.951652336666667

00:45:44.480 --> 00:45:47.620 with osumertinib can actually undergo

NOTE Confidence: 0.951652336666667

00:45:47.620 --> 00:45:49.457 neuroendocrine differentiation and

NOTE Confidence: 0.951652336666667

00:45:49.457 --> 00:45:52.919 transformed to small cell lung cancer,

NOTE Confidence: 0.951652336666667

00:45:52.920 --> 00:45:56.200 a subset of which are ASCL 1 positive.

NOTE Confidence: 0.951652336666667

00:45:56.200 --> 00:45:59.160 And so this kind of piqued our interest.

NOTE Confidence: 0.951652336666667

00:45:59.160 --> 00:46:01.744 And so one of the first questions that

NOTE Confidence: 0.951652336666667

00:46:01.744 --> 00:46:04.980 we had was are these ASCL one cells

NOTE Confidence: 0.951652336666667

00:46:04.980 --> 00:46:07.280 present in the tumor pretreatment.

NOTE Confidence: 0.951652336666667

00:46:07.280 --> 00:46:09.200 And so when we looked and we did

NOTE Confidence: 0.951652336666667

00:46:09.200 --> 00:46:10.560 single cell RNA sequencing,

NOTE Confidence: 0.951652336666667

00:46:10.560 --> 00:46:14.824 we actually saw that the if you look at

NOTE Confidence: 0.951652336666667

00:46:14.824 --> 00:46:17.320 the pretreatment specimen here in blue,

NOTE Confidence: 0.951652336666667

00:46:17.320 --> 00:46:19.840 there is a subset of these cells that

NOTE Confidence: 0.951652336666667

00:46:19.840 --> 00:46:22.117 is present that is ASCL 1 positive.

NOTE Confidence: 0.951652336666667

00:46:22.120 --> 00:46:24.622 So we think that those cells

NOTE Confidence: 0.951652336666667

00:46:24.622 --> 00:46:25.873 were present beforehand.

NOTE Confidence: 0.951652336666667

00:46:25.880 --> 00:46:28.757 Whether other cells then turned it on,

NOTE Confidence: 0.951652336666667

00:46:28.760 --> 00:46:30.266 we can't really tell from the

NOTE Confidence: 0.951652336666667

00:46:30.266 --> 00:46:31.640 types of experiments that we did.

NOTE Confidence: 0.951652336666667

00:46:31.640 --> 00:46:33.864 But we do know that there was a

NOTE Confidence: 0.951652336666667

00:46:33.864 --> 00:46:35.838 population that was there pretreatment.

NOTE Confidence: 0.951652336666667

00:46:35.840 --> 00:46:38.856 And so our next question after that was

NOTE Confidence: 0.951652336666667

00:46:38.856 --> 00:46:42.438 well how is ASCL 1 conferring TKI tolerance,

NOTE Confidence: 0.951652336666667

00:46:42.440 --> 00:46:44.048 what is happening.

NOTE Confidence: 0.951652336666667

00:46:44.048 --> 00:46:46.023 And so we said OK,

NOTE Confidence: 0.951652336666667

00:46:46.023 --> 00:46:47.829 let's turn to our human EGF

NOTE Confidence: 0.951652336666667

00:46:47.829 --> 00:46:49.855 receptor driven cell lines and let's

NOTE Confidence: 0.951652336666667

00:46:49.855 --> 00:46:51.960 express ASCL one in these cells.

NOTE Confidence: 0.951652336666667

00:46:51.960 --> 00:46:53.600 And so one of the first things that we did,

NOTE Confidence: 0.951652336666667

00:46:53.600 --> 00:46:56.669 we expressed ASCL one in the cells and you

NOTE Confidence: 0.951652336666667

00:46:56.669 --> 00:46:59.677 can see here in this HCCA 27 cell line,

NOTE Confidence: 0.951652336666667

00:46:59.680 --> 00:47:01.968 we expressed it and we saw more colonies

NOTE Confidence: 0.951652336666667

00:47:01.968 --> 00:47:04.655 and you can see this quantified here

NOTE Confidence: 0.951652336666667

00:47:04.655 --> 00:47:06.299 after treatment with osmertinib

NOTE Confidence: 0.951652336666667

00:47:06.299 --> 00:47:08.436 compared to the empty vector control,

NOTE Confidence: 0.951652336666667

00:47:08.440 --> 00:47:11.328 we did this across in another cell line

NOTE Confidence: 0.951652336666667

00:47:11.328 --> 00:47:14.432 and we saw no effect of ASCL one expression.

NOTE Confidence: 0.951652336666667

00:47:14.432 --> 00:47:17.079 And so this was also interesting and we said,

NOTE Confidence: 0.951652336666667

00:47:17.080 --> 00:47:17.426 OK,

NOTE Confidence: 0.951652336666667

00:47:17.426 --> 00:47:19.848 so why does ASCL one having a

NOTE Confidence: 0.951652336666667

00:47:19.848 --> 00:47:22.001 phenotype has a phenotype in one

NOTE Confidence: 0.951652336666667

00:47:22.001 --> 00:47:24.077 cell line but not the other.

NOTE Confidence: 0.951652336666667

00:47:24.080 --> 00:47:26.460 We did gene expression profiling and what

NOTE Confidence: 0.951652336666667

00:47:26.460 --> 00:47:29.477 we saw is that in the permissive cells,

NOTE Confidence: 0.951652336666667

00:47:29.480 --> 00:47:31.552 these HCC 827 cells,

NOTE Confidence: 0.951652336666667

00:47:31.552 --> 00:47:35.280 you actually saw that ASCL one could

NOTE Confidence: 0.951652336666667

00:47:35.280 --> 00:47:37.968 lead to an EMT gene expression

NOTE Confidence: 0.951652336666667

00:47:37.968 --> 00:47:40.905 program was it had no effect at

NOTE Confidence: 0.951652336666667

00:47:40.905 --> 00:47:43.256 all in the PC-9 cell line.

NOTE Confidence: 0.951652336666667

00:47:43.256 --> 00:47:47.336 And we went on and we looked with ataxiq

NOTE Confidence: 0.951652336666667

00:47:47.336 --> 00:47:50.504 at chromatin accessibility at EMT genes

NOTE Confidence: 0.951652336666667

00:47:50.504 --> 00:47:54.361 and we see that upon ESAS CL1 expression,

NOTE Confidence: 0.951652336666667

00:47:54.361 --> 00:47:57.403 you do see changes in chromatin

NOTE Confidence: 0.951652336666667

00:47:57.403 --> 00:47:59.348 accessibility at both epithelial

NOTE Confidence: 0.951652336666667

00:47:59.348 --> 00:48:01.613 genes and mesenchymal genes when

NOTE Confidence: 0.951652336666667

00:48:01.613 --> 00:48:05.680 you put Ascl one into these HCC

NOTE Confidence: 0.951652336666667

00:48:05.680 --> 00:48:07.680 827 cells that are permissive,

NOTE Confidence: 0.951652336666667

00:48:07.680 --> 00:48:09.330 but you don't see any changes

NOTE Confidence: 0.951652336666667

00:48:09.330 --> 00:48:10.800 in the PC-9 cells.

NOTE Confidence: 0.951652336666667

00:48:10.800 --> 00:48:14.480 And So what do we think is happening?

NOTE Confidence: 0.951652336666667

00:48:14.480 --> 00:48:17.812 So we think that when you have,

NOTE Confidence: 0.951652336666667

00:48:17.812 --> 00:48:19.756 when you don't have ASCL 1,

NOTE Confidence: 0.951652336666667

00:48:19.760 --> 00:48:22.360 the TKI can work and you see death

NOTE Confidence: 0.951652336666667

00:48:22.360 --> 00:48:25.159 of the EGF receptor driven cells.

NOTE Confidence: 0.951652336666667

00:48:25.160 --> 00:48:28.046 If you have a permissive cellular

NOTE Confidence: 0.951652336666667

00:48:28.046 --> 00:48:30.400 context what happens is that

NOTE Confidence: 0.901540450357143

00:48:30.400 --> 00:48:32.672 you can have ASCL one can turn on

NOTE Confidence: 0.901540450357143

00:48:32.672 --> 00:48:35.512 or can lead to an EMT program and we

NOTE Confidence: 0.901540450357143

00:48:35.512 --> 00:48:38.128 know that that is associated with

NOTE Confidence: 0.901540450357143

00:48:38.128 --> 00:48:40.798 resistance to tyrosine kinase inhibitors.

NOTE Confidence: 0.901540450357143

00:48:40.800 --> 00:48:43.200 In a non permissive cellular

NOTE Confidence: 0.901540450357143

00:48:43.200 --> 00:48:45.597 context though that you don't have,

NOTE Confidence: 0.901540450357143

00:48:45.597 --> 00:48:47.830 you don't turn on this program so

NOTE Confidence: 0.901540450357143

00:48:47.900 --> 00:48:50.764 you don't have a difference in ASCL 1

NOTE Confidence: 0.901540450357143

00:48:50.764 --> 00:48:52.919 expressing versus non expressing cells.

NOTE Confidence: 0.901540450357143

00:48:52.920 --> 00:48:55.240 We also found that pre-existing

NOTE Confidence: 0.901540450357143

00:48:55.240 --> 00:48:57.096 cells with transcriptional features

NOTE Confidence: 0.901540450357143

00:48:57.096 --> 00:48:59.501 of drug tolerant cells are present

NOTE Confidence: 0.901540450357143

00:48:59.501 --> 00:49:00.783 in the untreated tumors.

NOTE Confidence: 0.901540450357143

00:49:00.783 --> 00:49:03.243 And I think one of the questions that

NOTE Confidence: 0.901540450357143

00:49:03.243 --> 00:49:05.308 we've we're really interested in is you

NOTE Confidence: 0.901540450357143

00:49:05.308 --> 00:49:07.795 know why are some cells permissive or not.

NOTE Confidence: 0.901540450357143

00:49:07.800 --> 00:49:09.760 I think this is sort of one of

NOTE Confidence: 0.901540450357143

00:49:09.760 --> 00:49:11.479 the major problems in cancer,

NOTE Confidence: 0.901540450357143

00:49:11.480 --> 00:49:12.888 one of the things that has been a

NOTE Confidence: 0.901540450357143

00:49:12.888 --> 00:49:14.438 mystery in cancer over all of the years.

NOTE Confidence: 0.901540450357143

00:49:14.440 --> 00:49:16.344 Why do you see certain phenotypes when

NOTE Confidence: 0.901540450357143

00:49:16.344 --> 00:49:18.400 you have certain settings and not others?

NOTE Confidence: 0.901540450357143

00:49:18.400 --> 00:49:20.199 And in the case of ASCL one,

NOTE Confidence: 0.901540450357143

00:49:20.200 --> 00:49:22.440 this is very reminiscent of

NOTE Confidence: 0.901540450357143

00:49:22.440 --> 00:49:24.232 reprogramming because it's known,

NOTE Confidence: 0.901540450357143

00:49:24.240 --> 00:49:25.280 for example,

NOTE Confidence: 0.901540450357143

00:49:25.280 --> 00:49:28.824 that you can put ASCL one into

NOTE Confidence: 0.901540450357143

00:49:28.824 --> 00:49:31.800 fibroblasts and reprogram them to neurons,

NOTE Confidence: 0.901540450357143

00:49:31.800 --> 00:49:33.592 but you put them when you put them

NOTE Confidence: 0.901540450357143

00:49:33.592 --> 00:49:34.040 in keratinocytes.

NOTE Confidence: 0.901540450357143

00:49:34.040 --> 00:49:36.119 You can't and this has been shown

NOTE Confidence: 0.901540450357143

00:49:36.119 --> 00:49:38.816 to be due to actually the chromatin

NOTE Confidence: 0.901540450357143

00:49:38.816 --> 00:49:40.118 landscape at Ascl,

NOTE Confidence: 0.901540450357143

00:49:40.120 --> 00:49:41.800 one target genes in the different cells.

NOTE Confidence: 0.901540450357143

00:49:41.800 --> 00:49:43.738 So could something like that be

NOTE Confidence: 0.901540450357143

00:49:43.738 --> 00:49:45.918 happening in the cancer cells as well?

NOTE Confidence: 0.901540450357143

00:49:45.920 --> 00:49:47.782 And one of the other questions of

NOTE Confidence: 0.901540450357143

00:49:47.782 --> 00:49:50.080 course that we have is since Ascl

NOTE Confidence: 0.901540450357143

00:49:50.080 --> 00:49:54.070 one is important for and neuronal

NOTE Confidence: 0.901540450357143

00:49:54.070 --> 00:49:54.625 differentiation,

NOTE Confidence: 0.901540450357143

00:49:54.625 --> 00:49:56.845 it's associated with neuroendocrine

NOTE Confidence: 0.901540450357143

00:49:56.845 --> 00:49:59.000 differentiation, Is it poising these cells?

NOTE Confidence: 0.901540450357143

00:49:59.000 --> 00:50:01.744 We didn't see any other, you know,

NOTE Confidence: 0.901540450357143

00:50:01.744 --> 00:50:03.400 neuroendocrine markers on,

NOTE Confidence: 0.901540450357143

00:50:03.400 --> 00:50:05.808 but is it poising the cells to

NOTE Confidence: 0.901540450357143

00:50:05.808 --> 00:50:07.639 undergo that type of change?

NOTE Confidence: 0.901540450357143

00:50:07.640 --> 00:50:09.840 And so,

NOTE Confidence: 0.901540450357143

00:50:09.840 --> 00:50:12.152 so some of the things that we're thinking

NOTE Confidence: 0.901540450357143

00:50:12.152 --> 00:50:14.597 about now and we have experiments ongoing,

NOTE Confidence: 0.901540450357143

00:50:14.600 --> 00:50:17.344 we have Mark Wiesehofer in the lab

NOTE Confidence: 0.901540450357143

00:50:17.344 --> 00:50:19.705 who's been thinking about this and

NOTE Confidence: 0.901540450357143

00:50:19.705 --> 00:50:22.295 working about on this in the context

NOTE Confidence: 0.901540450357143

00:50:22.372 --> 00:50:24.672 of both prostate cancer where very

NOTE Confidence: 0.901540450357143

00:50:24.672 --> 00:50:27.360 similar things happen and lung cancer.

NOTE Confidence: 0.901540450357143

00:50:27.360 --> 00:50:29.208 We're asking how does a chromatin

NOTE Confidence: 0.901540450357143

00:50:29.208 --> 00:50:31.426 state of a cancer cell affect

NOTE Confidence: 0.901540450357143

00:50:31.426 --> 00:50:33.716 responsiveness to therapy and plasticity.

NOTE Confidence: 0.901540450357143

00:50:33.720 --> 00:50:35.360 And so you can have these different cells,

NOTE Confidence: 0.901540450357143

00:50:35.360 --> 00:50:37.012 you add ASCL one and you can

NOTE Confidence: 0.901540450357143

00:50:37.012 --> 00:50:38.393 see different things happen in

NOTE Confidence: 0.901540450357143

00:50:38.393 --> 00:50:39.320 these different cells.

NOTE Confidence: 0.901540450357143

00:50:39.320 --> 00:50:41.000 And why is that happening?

NOTE Confidence: 0.901540450357143

00:50:41.000 --> 00:50:42.694 And is there something that we can

NOTE Confidence: 0.901540450357143

00:50:42.694 --> 00:50:44.161 learn from these cells that then

NOTE Confidence: 0.901540450357143

00:50:44.161 --> 00:50:45.757 we can apply to human tumors and

NOTE Confidence: 0.901540450357143

00:50:45.811 --> 00:50:47.236 could we use this information?

NOTE Confidence: 0.901540450357143

00:50:47.240 --> 00:50:49.560 I'm thinking far a little bit far ahead,

NOTE Confidence: 0.901540450357143

00:50:49.560 --> 00:50:51.072 but it's something that's in the back of the,

NOTE Confidence: 0.901540450357143

00:50:51.080 --> 00:50:54.212 my mind is can we predict how a tumor

NOTE Confidence: 0.901540450357143

00:50:54.212 --> 00:50:57.956 will evolve on treatment with this knowledge.

NOTE Confidence: 0.901540450357143

00:50:57.960 --> 00:51:02.200 So finally a couple of final thoughts.

NOTE Confidence: 0.901540450357143

00:51:02.200 --> 00:51:03.957 So what have I told you today,

NOTE Confidence: 0.901540450357143

00:51:03.960 --> 00:51:06.135 baseline mutations and Co mutations

NOTE Confidence: 0.901540450357143

00:51:06.135 --> 00:51:07.875 can affect disease progression,

NOTE Confidence: 0.901540450357143

00:51:07.880 --> 00:51:09.320 drug sensitivity and mechanisms

NOTE Confidence: 0.901540450357143

00:51:09.320 --> 00:51:12.006 of drug resistance and how can we

NOTE Confidence: 0.901540450357143

00:51:12.006 --> 00:51:13.842 incorporate this knowledge into

NOTE Confidence: 0.901540450357143

00:51:13.842 --> 00:51:15.678 clinical investigation and practice.

NOTE Confidence: 0.901540450357143

00:51:15.680 --> 00:51:18.677 This is something that we think about a lot.

NOTE Confidence: 0.901540450357143

00:51:18.680 --> 00:51:21.090 There's a vast heterogeneity and

NOTE Confidence: 0.901540450357143

00:51:21.090 --> 00:51:23.500 complexity of non mutational resistance

NOTE Confidence: 0.901540450357143

00:51:23.568 --> 00:51:25.412 and persistence mechanisms and

NOTE Confidence: 0.901540450357143

00:51:25.412 --> 00:51:27.717 we're working to identify them,

NOTE Confidence: 0.901540450357143

00:51:27.720 --> 00:51:29.370 establish when they are relevant

NOTE Confidence: 0.901540450357143

00:51:29.370 --> 00:51:31.020 for specific tumors and find

NOTE Confidence: 0.8897641448

00:51:31.075 --> 00:51:32.590 vulnerabilities of these and be

NOTE Confidence: 0.8897641448

00:51:32.590 --> 00:51:34.528 happy to talk more about these

NOTE Confidence: 0.8897641448

00:51:34.528 --> 00:51:36.000 thoughts throughout the day.

NOTE Confidence: 0.8897641448

00:51:36.000 --> 00:51:39.400 Today I there are a lot

NOTE Confidence: 0.8897641448

00:51:39.400 --> 00:51:40.872 of people to acknowledge.

NOTE Confidence: 0.8897641448

00:51:40.880 --> 00:51:43.816 Here are some pictures of lab

NOTE Confidence: 0.8897641448

00:51:43.816 --> 00:51:46.440 members throughout the years.

NOTE Confidence: 0.8897641448

00:51:46.440 --> 00:51:49.560 Here's a particularly fun one.

NOTE Confidence: 0.8897641448

00:51:49.560 --> 00:51:51.945 This was a fundraising picture

NOTE Confidence: 0.8897641448

00:51:51.945 --> 00:51:55.250 for a closer to free team that so

NOTE Confidence: 0.8897641448

00:51:55.250 --> 00:51:56.600 I thought that was pretty cool.

NOTE Confidence: 0.8897641448

00:51:56.600 --> 00:51:59.360 These are Halloween,

NOTE Confidence: 0.8897641448

00:51:59.360 --> 00:52:01.868 one of our Halloween parties and

NOTE Confidence: 0.8897641448

00:52:01.868 --> 00:52:04.520 other pictures from the we have the.

NOTE Confidence: 0.8897641448

00:52:04.520 --> 00:52:06.320 All of the lab has contributed

NOTE Confidence: 0.8897641448

00:52:06.320 --> 00:52:07.920 tremendously to all of these

NOTE Confidence: 0.8897641448

00:52:07.920 --> 00:52:09.200 efforts over the years,

NOTE Confidence: 0.8897641448

00:52:09.200 --> 00:52:11.516 and I'm so grateful to have

NOTE Confidence: 0.8897641448

00:52:11.516 --> 00:52:13.440 the opportunity to work with

NOTE Confidence: 0.8897641448

00:52:13.440 --> 00:52:14.952 so many talented people.

NOTE Confidence: 0.8897641448

00:52:14.952 --> 00:52:17.733 There are lots of people to acknowledge

NOTE Confidence: 0.8897641448

00:52:17.733 --> 00:52:20.349 who have contributed to this work

NOTE Confidence: 0.8897641448

00:52:20.349 --> 00:52:23.117 in addition to members of the lab,

NOTE Confidence: 0.8897641448

00:52:23.120 --> 00:52:26.720 so many collaborators outside of Yale,

NOTE Confidence: 0.8897641448

00:52:26.720 --> 00:52:29.198 but in particular everybody here at Yale,

NOTE Confidence: 0.8897641448

00:52:29.200 --> 00:52:31.320 which I, I, I really,

NOTE Confidence: 0.8897641448

00:52:31.320 --> 00:52:34.519 I hope everybody is on this slide.

NOTE Confidence: 0.8897641448

00:52:34.520 --> 00:52:36.760 It's one of the things that I was

NOTE Confidence: 0.8897641448

00:52:36.760 --> 00:52:38.553 worried about but want to make

NOTE Confidence: 0.8897641448

00:52:38.553 --> 00:52:40.129 sure that everybody is acknowledged

NOTE Confidence: 0.8897641448

00:52:40.129 --> 00:52:42.174 here because of the tremendous

NOTE Confidence: 0.8897641448

00:52:42.174 --> 00:52:44.172 contributions that makes it such

NOTE Confidence: 0.8897641448

00:52:44.172 --> 00:52:47.480 an amazing place to work together.

NOTE Confidence: 0.8897641448

00:52:47.480 --> 00:52:49.235 A couple of things that I'd like to say,

NOTE Confidence: 0.8897641448

00:52:49.240 --> 00:52:51.880 we have a retreat too on thoracic cancers.

NOTE Confidence: 0.8897641448

00:52:51.880 --> 00:52:54.720 On Monday, it's retreat season.

NOTE Confidence: 0.8897641448

00:52:54.720 --> 00:52:56.800 It is at West Campus,

NOTE Confidence: 0.8897641448

00:52:56.800 --> 00:53:00.797 so you're all invited to join us.

NOTE Confidence: 0.8897641448

00:53:00.800 --> 00:53:03.720 We have a team that has been working.

NOTE Confidence: 0.8897641448

00:53:03.720 --> 00:53:04.800 Sarah's in here, I think.

NOTE Confidence: 0.8897641448

00:53:04.800 --> 00:53:06.880 Sarah Goldberg, Justin Blasberg.

NOTE Confidence: 0.8897641448

00:53:06.880 --> 00:53:09.900 We have Glynis Arnold and Melody

NOTE Confidence: 0.8897641448

00:53:09.900 --> 00:53:12.328 Noga MENA who's been working

NOTE Confidence: 0.8897641448

00:53:12.328 --> 00:53:14.120 to organize this retreat.

NOTE Confidence: 0.8897641448

00:53:14.120 --> 00:53:17.513 So we hope you can join us and then

NOTE Confidence: 0.8897641448

00:53:17.520 --> 00:53:20.124 save the date for our annual lung

NOTE Confidence: 0.8897641448

00:53:20.124 --> 00:53:22.678 cancer workshop on June 12th and 13th.

NOTE Confidence: 0.8897641448

00:53:22.680 --> 00:53:25.240 It is also going to be at West

NOTE Confidence: 0.8897641448

00:53:25.240 --> 00:53:27.500 Campus here and it's particularly

NOTE Confidence: 0.8897641448

00:53:27.500 --> 00:53:30.542 special this year because we are

NOTE Confidence: 0.8897641448

00:53:30.542 --> 00:53:33.088 going to be recognizing the 20th

NOTE Confidence: 0.8897641448

00:53:33.088 --> 00:53:35.032 anniversary of the discovery of EGF

NOTE Confidence: 0.8897641448

00:53:35.032 --> 00:53:36.558 receptor mutations and lung cancer,

NOTE Confidence: 0.8897641448

00:53:36.560 --> 00:53:38.240 which has really transformed the field.

NOTE Confidence: 0.8897641448

00:53:38.240 --> 00:53:40.576 It's near and dear front to my heart

NOTE Confidence: 0.8897641448

00:53:40.576 --> 00:53:42.560 as you can imagine from the talk,

NOTE Confidence: 0.8897641448

00:53:42.560 --> 00:53:45.773 but it's really going to be I think a

NOTE Confidence: 0.8897641448

00:53:45.773 --> 00:53:47.986 spectacular event with lots of people

NOTE Confidence: 0.8897641448

00:53:47.986 --> 00:53:51.066 coming from all over to mark this,

NOTE Confidence: 0.8897641448

00:53:51.066 --> 00:53:51.812 this moment.

NOTE Confidence: 0.8897641448

00:53:51.812 --> 00:53:54.580 And so we hope that you can

NOTE Confidence: 0.8897641448

00:53:54.580 --> 00:53:56.360 participate in that too.

NOTE Confidence: 0.8897641448

00:53:56.360 --> 00:53:57.572 Thank you very much and I'll

NOTE Confidence: 0.8897641448

00:53:57.572 --> 00:53:58.880 be happy to take questions.

NOTE Confidence: 0.89088666

00:54:09.880 --> 00:54:10.800 Thank you so much, Katie.

NOTE Confidence: 0.89088666

00:54:10.800 --> 00:54:11.811 That was wonderful.

NOTE Confidence: 0.89088666

00:54:11.811 --> 00:54:13.833 Are there questions in the room?

NOTE Confidence: 0.893251607333333

00:54:16.000 --> 00:54:18.149 Maybe I'll start as a person who

NOTE Confidence: 0.893251607333333

00:54:18.149 --> 00:54:20.220 knows more about squamous cell

NOTE Confidence: 0.893251607333333

00:54:20.220 --> 00:54:21.840 cancers than adenocarcinomas.

NOTE Confidence: 0.893251607333333

00:54:21.840 --> 00:54:24.720 When you talk about P53 mutations,

NOTE Confidence: 0.893251607333333

00:54:24.720 --> 00:54:26.970 are they always the same

NOTE Confidence: 0.893251607333333

00:54:26.970 --> 00:54:28.320 in adenocarcinoma patients?

NOTE Confidence: 0.893251607333333

00:54:28.320 --> 00:54:29.811 And we spend a lot of time

NOTE Confidence: 0.893251607333333

00:54:29.811 --> 00:54:31.140 in the squamous world talking

NOTE Confidence: 0.893251607333333

00:54:31.140 --> 00:54:32.280 about disruptive mutations,

NOTE Confidence: 0.893251607333333

00:54:32.280 --> 00:54:36.120 gain of function mutations. Yeah,

NOTE Confidence: 0.918960678888889

00:54:36.120 --> 00:54:40.314 we have, I think there's a wide variety of

NOTE Confidence: 0.918960678888889

00:54:40.320 --> 00:54:44.000 P53 mutations that you see in lung cancer.

NOTE Confidence: 0.918960678888889

00:54:44.000 --> 00:54:46.760 So they're like different types and

NOTE Confidence: 0.923658161111111

00:54:46.760 --> 00:54:48.704 have you dissected out if they

NOTE Confidence: 0.923658161111111

00:54:48.704 --> 00:54:49.676 have different implications.

NOTE Confidence: 0.923658161111111

00:54:49.680 --> 00:54:51.534 We think the gain of function

NOTE Confidence: 0.923658161111111

00:54:51.534 --> 00:54:53.239 mutations don't lead to as much

NOTE Confidence: 0.923658161111111

00:54:53.240 --> 00:54:55.160 genomic instability for example. Yeah,

NOTE Confidence: 0.882860934444444

00:54:55.160 --> 00:54:56.980 those are things that we

NOTE Confidence: 0.882860934444444

00:54:56.980 --> 00:54:58.436 haven't studied that much.

NOTE Confidence: 0.882860934444444

00:54:58.440 --> 00:55:00.645 I think Paul had looked at the

NOTE Confidence: 0.882860934444444

00:55:00.645 --> 00:55:01.980 different mutations a little

NOTE Confidence: 0.882860934444444

00:55:01.980 --> 00:55:03.595 bit in terms of outcomes,

NOTE Confidence: 0.882860934444444

00:55:03.600 --> 00:55:05.300 Paul Stockhammer and I don't

NOTE Confidence: 0.882860934444444

00:55:05.300 --> 00:55:07.396 think he had found differences in

NOTE Confidence: 0.882860934444444

00:55:07.396 --> 00:55:09.370 terms of outcomes with Tkis with

NOTE Confidence: 0.882860934444444

00:55:09.370 --> 00:55:11.520 the different classes mutations.

NOTE Confidence: 0.882860934444444

00:55:11.520 --> 00:55:16.440 So is the polycommers suppressor

NOTE Confidence: 0.882860934444444

00:55:16.440 --> 00:55:18.600 name screen that your

NOTE Confidence: 0.906045539230769

00:55:18.600 --> 00:55:21.060 biggest hit at least in one

NOTE Confidence: 0.906045539230769

00:55:21.060 --> 00:55:23.798 of the assays was loss of RB,

NOTE Confidence: 0.906045539230769

00:55:23.800 --> 00:55:26.635 but it looks like in the in the cancers

NOTE Confidence: 0.906045539230769

00:55:26.635 --> 00:55:29.359 RB loss was relatively infrequent.

NOTE Confidence: 0.906045539230769

00:55:29.360 --> 00:55:31.222 Does it does that suggest or have

NOTE Confidence: 0.906045539230769

00:55:31.222 --> 00:55:33.045 you looked at whether there's other

NOTE Confidence: 0.906045539230769

00:55:33.045 --> 00:55:35.007 dysregulators of the RB pathway that

NOTE Confidence: 0.906045539230769

00:55:35.007 --> 00:55:37.217 are more common in lung cancer like

NOTE Confidence: 0.906045539230769

00:55:37.217 --> 00:55:39.180 the Cyclone CDK pathway and that's

NOTE Confidence: 0.906045539230769

00:55:39.180 --> 00:55:41.000 a potentially targetable approach?

NOTE Confidence: 0.965819242

00:55:41.880 --> 00:55:43.280 Yeah, that's a great question.

NOTE Confidence: 0.965819242

00:55:43.280 --> 00:55:47.151 So it's interesting because RB as you

NOTE Confidence: 0.965819242

00:55:47.151 --> 00:55:51.410 said RB one loss is one of the biggest

NOTE Confidence: 0.965819242

00:55:51.410 --> 00:55:54.560 drivers of tumor growth in our screen.

NOTE Confidence: 0.965819242

00:55:54.560 --> 00:55:59.080 It is also if you look at how frequently

NOTE Confidence: 0.965819242

00:55:59.080 --> 00:56:02.464 it Co occurs with EGFR and P53 mutations,

NOTE Confidence: 0.965819242

00:56:02.464 --> 00:56:04.228 it's one of the tumor suppressor genes

NOTE Confidence: 0.965819242

00:56:04.228 --> 00:56:05.837 that is most frequently Co altered.

NOTE Confidence: 0.965819242

00:56:05.840 --> 00:56:07.640 So none of them go really

NOTE Confidence: 0.965819242

00:56:07.640 --> 00:56:09.600 above the like 10% threshold.

NOTE Confidence: 0.926580323333333

00:56:12.160 --> 00:56:14.512 We do know, we haven't really looked at

NOTE Confidence: 0.926580323333333

00:56:14.512 --> 00:56:17.050 other ways in which the P50 in which the

NOTE Confidence: 0.926580323333333

00:56:17.050 --> 00:56:19.157 RB pathway could be altered in tumors.

NOTE Confidence: 0.926580323333333

00:56:19.160 --> 00:56:20.876 We haven't really looked at that.

NOTE Confidence: 0.926580323333333

00:56:20.880 --> 00:56:24.806 What we do know is that if

NOTE Confidence: 0.926580323333333

00:56:24.806 --> 00:56:27.036 you have tumors with e.g.

NOTE Confidence: 0.926580323333333

00:56:27.040 --> 00:56:30.680 F, RP53 and RB alterations,

NOTE Confidence: 0.926580323333333

00:56:30.680 --> 00:56:32.871 those are the ones that have the

NOTE Confidence: 0.926580323333333

00:56:32.871 --> 00:56:34.554 highest likelihood of undergoing

NOTE Confidence: 0.926580323333333

00:56:34.554 --> 00:56:36.600 that neuroendocrine differentiation.

NOTE Confidence: 0.926580323333333

00:56:36.600 --> 00:56:39.000 And so like 1/4 of those will undergo

NOTE Confidence: 0.926580323333333

00:56:39.000 --> 00:56:40.520 the neuroendocrine differentiation.

NOTE Confidence: 0.9359382

00:56:44.600 --> 00:56:47.399 Any other questions from.

NOTE Confidence: 0.947424084285714

00:56:47.400 --> 00:56:51.080 OK, Thank you again so very much. Thank you.