WEBVTT

NOTE duration:"01:30:00.2560000"

NOTE language:en-us

NOTE Confidence: 0.850683850901468

00:00:07.940 --> 00:00:12.567 everybody. Welcome to our session on behalf

NOTE Confidence: 0.850683850901468

00:00:12.567 --> 00:00:17.117 of Yale University and Yale Cancer Center.

NOTE Confidence: 0.850683850901468

00:00:17.120 --> 00:00:20.136 I'm pleased to have you with us as

NOTE Confidence: 0.850683850901468

00:00:20.136 --> 00:00:23.679 part of the Yale Engage Cancer series.

NOTE Confidence: 0.850683850901468

00:00:23.680 --> 00:00:26.450 This session is entitled defining.

NOTE Confidence: 0.850683850901468

00:00:26.450 --> 00:00:28.575 Mechanisms and biomarkers of sensitivity

NOTE Confidence: 0.850683850901468

00:00:28.575 --> 00:00:31.430 and resistance to anti cancer treatments.

NOTE Confidence: 0.850683850901468

00:00:31.430 --> 00:00:32.878 I'll be your moderator.

NOTE Confidence: 0.850683850901468

00:00:32.878 --> 00:00:34.326 I'm I'm Barbara burtness.

NOTE Confidence: 0.850683850901468

00:00:34.330 --> 00:00:37.258 I'm a medical oncologist and have a interest

NOTE Confidence: 0.850683850901468

00:00:37.258 --> 00:00:40.390 in drug development and head neck cancer.

NOTE Confidence: 0.850683850901468

00:00:40.390 --> 00:00:44.046 And we have a phenomenal panel of Yale

NOTE Confidence: 0.850683850901468

00:00:44.046 --> 00:00:46.669 faculty members and Anna corporate

NOTE Confidence: 0.850683850901468

00:00:46.669 --> 00:00:49.369 guest Susan Galbraith from Etsy.

NOTE Confidence: 0.850683850901468

00:00:49.370 --> 00:00:52.555 And hope to have a very very

NOTE Confidence: 0.850683850901468

00:00:52.555 --> 00:00:53.465 interactive session.

NOTE Confidence: 0.850683850901468

00:00:53.470 --> 00:00:57.154 I'd like to start with a

NOTE Confidence: 0.850683850901468

00:00:57.154 --> 00:00:58.996 few housekeeping items.

NOTE Confidence: 0.850683850901468

00:00:59.000 --> 00:01:01.568 The program format as I said,

NOTE Confidence: 0.850683850901468

00:01:01.570 --> 00:01:04.826 is going to be each of our panel

NOTE Confidence: 0.850683850901468

00:01:04.826 --> 00:01:07.977 members giving a brief about 5 minute

NOTE Confidence: 0.850683850901468

00:01:07.977 --> 00:01:11.009 introduction to the work that they do.

NOTE Confidence: 0.850683850901468

00:01:11.010 --> 00:01:14.818 What they see is as key questions.

NOTE Confidence: 0.850683850901468

00:01:14.820 --> 00:01:18.061 Will have all of the panel presentations

NOTE Confidence: 0.850683850901468

00:01:18.061 --> 00:01:21.808 1st and then move on to the discussion.

NOTE Confidence: 0.850683850901468

00:01:21.810 --> 00:01:23.662 The question and answer.

NOTE Confidence: 0.850683850901468

00:01:23.662 --> 00:01:26.440 We know that to attack cancer

NOTE Confidence: 0.850683850901468

00:01:26.528 --> 00:01:28.328 we need team science.

NOTE Confidence: 0.850683850901468

00:01:28.330 --> 00:01:30.660 We need collaborations within our

NOTE Confidence: 0.850683850901468

00:01:30.660 --> 00:01:32.990 organization and across different sectors.

NOTE Confidence: 0.850683850901468

00:01:32.990 --> 00:01:33.419 Academic,

NOTE Confidence: 0.850683850901468

00:01:33.419 --> 00:01:36.422 public and industry and Yale engage was

NOTE Confidence: 0.850683850901468

00:01:36.422 --> 00:01:39.048 designed to build these connections,

NOTE Confidence: 0.850683850901468

00:01:39.050 --> 00:01:40.445 particularly between Yale

NOTE Confidence: 0.850683850901468

00:01:40.445 --> 00:01:42.305 scientists and industry leaders.

NOTE Confidence: 0.850683850901468

00:01:42.310 --> 00:01:45.079 To keep the discussion lively, we.

NOTE Confidence: 0.850683850901468

00:01:45.079 --> 00:01:46.396 We welcome questions.

NOTE Confidence: 0.850683850901468

00:01:46.396 --> 00:01:49.030 Some have been submitted ahead of

NOTE Confidence: 0.850683850901468

00:01:49.111 --> 00:01:51.974 time and you'll have the ability to

NOTE Confidence: 0.850683850901468

00:01:51.974 --> 00:01:54.549 submit them through the Q&A function.

NOTE Confidence: 0.850683850901468

00:01:54.550 --> 00:01:58.126 On the Web and R we have an

NOTE Confidence: 0.850683850901468

00:01:58.126 --> 00:02:00.298 enormous amount of expertise

NOTE Confidence: 0.850683850901468

00:02:00.298 --> 00:02:03.808 among our panelists and will be.

NOTE Confidence: 0.850683850901468

00:02:03.810 --> 00:02:05.660 Monitoring those questions as they

NOTE Confidence: 0.850683850901468

00:02:05.660 --> 00:02:08.705 come up and and try to get to as

NOTE Confidence: 0.850683850901468

00:02:08.705 --> 00:02:10.992 many of them as possible and I I

NOTE Confidence: 0.850683850901468

00:02:10.992 --> 00:02:12.854 want you to know that this web,

NOTE Confidence: 0.850683850901468

00:02:12.860 --> 00:02:14.028 nor is being recorded,

NOTE Confidence: 0.850683850901468

00:02:14.028 --> 00:02:16.177 so now I'm really pleased to be

NOTE Confidence: 0.850683850901468

00:02:16.177 --> 00:02:17.847 able to introduce Charlie Fuchs.

NOTE Confidence: 0.850683850901468

00:02:17.850 --> 00:02:19.390 He's the secular professor of

NOTE Confidence: 0.850683850901468

00:02:19.390 --> 00:02:20.930 medicine and medical oncology and

NOTE Confidence: 0.850683850901468

00:02:20.987 --> 00:02:22.537 a professor of chronic disease

NOTE Confidence: 0.850683850901468

00:02:22.537 --> 00:02:23.777 Epidemiology here at Yale.

NOTE Confidence: 0.850683850901468

00:02:23.780 --> 00:02:25.598 He's the director of the Yale

NOTE Confidence: 0.850683850901468

00:02:25.598 --> 00:02:27.504 Cancer Center and Position in chief

NOTE Confidence: 0.850683850901468

00:02:27.504 --> 00:02:28.768 at Smilow Cancer Hospital,

NOTE Confidence: 0.850683850901468

00:02:28.770 --> 00:02:29.080 Charlie.

NOTE Confidence: 0.871820628643036

00:02:29.710 --> 00:02:32.615 Forever thank you and thank you for

NOTE Confidence: 0.871820628643036

00:02:32.615 --> 00:02:35.046 your leadership on this and welcome

NOTE Confidence: 0.871820628643036

00:02:35.046 --> 00:02:38.122 to all the attendees to what is now

NOTE Confidence: 0.871820628643036

00:02:38.122 --> 00:02:40.612 our third Yale Engage cancer event

NOTE Confidence: 0.871820628643036

00:02:40.612 --> 00:02:43.480 and it's really been an exciting and

NOTE Confidence: 0.871820628643036

00:02:43.480 --> 00:02:45.505 incredibly productive series of forms.

NOTE Confidence: 0.871820628643036

00:02:45.510 --> 00:02:47.940 So please it could join us

NOTE Confidence: 0.871820628643036

00:02:47.940 --> 00:02:49.560 for this third one.

NOTE Confidence: 0.871820628643036

00:02:49.560 --> 00:02:51.798 You know, we we all recognize

NOTE Confidence: 0.871820628643036

00:02:51.798 --> 00:02:54.244 that despite the fact that we're

NOTE Confidence: 0.871820628643036

00:02:54.244 --> 00:02:56.439 dealing with a global pandemic,

NOTE Confidence: 0.871820628643036

00:02:56.440 --> 00:02:58.088 the consistent impact of

NOTE Confidence: 0.871820628643036

00:02:58.088 --> 00:02:59.736 cancer on public health.

NOTE Confidence: 0.871820628643036

00:02:59.740 --> 00:03:01.925 And the morbidity and mortality

NOTE Confidence: 0.871820628643036

00:03:01.925 --> 00:03:04.110 and costs on our population.

NOTE Confidence: 0.871820628643036

00:03:04.110 --> 00:03:06.666 Or considerable an it remains one

NOTE Confidence: 0.871820628643036

00:03:06.666 --> 00:03:09.350 of the great challenges in medicine.

NOTE Confidence: 0.871820628643036

00:03:09.350 --> 00:03:12.409 And it also is one of the

NOTE Confidence: 0.871820628643036

00:03:12.409 --> 00:03:13.283 largest investments.

NOTE Confidence: 0.871820628643036

00:03:13.290 --> 00:03:16.216 I think that goes on and healthcare

NOTE Confidence: 0.871820628643036

00:03:16.216 --> 00:03:18.321 research and drug development and

NOTE Confidence: 0.871820628643036

00:03:18.321 --> 00:03:21.023 our our our efforts at Yale is

NOTE Confidence: 0.871820628643036

00:03:21.023 --> 00:03:23.777 to really tackle this challenge.

NOTE Confidence: 0.871820628643036

00:03:23.780 --> 00:03:26.629 Yeah Liz had a long legacy in

NOTE Confidence: 0.871820628643036

00:03:26.629 --> 00:03:29.019 Cancer Research and cell biology,

NOTE Confidence: 0.871820628643036

00:03:29.020 --> 00:03:29.896 genetics, pharmacology,

NOTE Confidence: 0.871820628643036

00:03:29.896 --> 00:03:31.648 immunology, among other elements.

NOTE Confidence: 0.871820628643036

00:03:31.650 --> 00:03:35.880 And I think a lot of the history of success,

NOTE Confidence: 0.871820628643036

00:03:35.880 --> 00:03:37.664 including four Yntema therapies,

NOTE Confidence: 0.871820628643036

00:03:37.664 --> 00:03:40.340 come out of this University were

NOTE Confidence: 0.871820628643036

00:03:40.414 --> 00:03:42.717 privileged to work at one of the

NOTE Confidence: 0.871820628643036

00:03:42.717 --> 00:03:44.851 national one of the original

NOTE Confidence: 0.871820628643036

00:03:44.851 --> 00:03:46.456 National Cancer Institute,

NOTE Confidence: 0.871820628643036

00:03:46.460 --> 00:03:47.765 designated Cancer centers,

NOTE Confidence: 0.871820628643036

00:03:47.765 --> 00:03:50.810 and has been a really an area

NOTE Confidence: 0.871820628643036

00:03:50.892 --> 00:03:53.503 that research that is as built a

NOTE Confidence: 0.871820628643036

00:03:53.503 --> 00:03:56.179 legacy of great innovation as well.

NOTE Confidence: 0.871820628643036

00:03:56.180 --> 00:03:57.854 Smilow cancer hospital.

NOTE Confidence: 0.871820628643036

00:03:57.854 --> 00:03:59.528 Our clinical center.

NOTE Confidence: 0.871820628643036

00:03:59.530 --> 00:04:01.805 Is celebrating its 10th anniversary

NOTE Confidence: 0.871820628643036

00:04:01.805 --> 00:04:04.848 and is a robust operation that now

NOTE Confidence: 0.871820628643036

00:04:04.848 --> 00:04:07.384 sees about 48% of every newly diagnosed

NOTE Confidence: 0.871820628643036

00:04:07.384 --> 00:04:10.530 cancer patient in the state of Connecticut.

NOTE Confidence: 0.871820628643036

00:04:10.530 --> 00:04:11.306 And really,

NOTE Confidence: 0.871820628643036

00:04:11.306 --> 00:04:13.634 we view that through the science

NOTE Confidence: 0.871820628643036

00:04:13.634 --> 00:04:15.833 and through this robust clinical

NOTE Confidence: 0.871820628643036

00:04:15.833 --> 00:04:18.983 operation we really are committed to moving,

NOTE Confidence: 0.871820628643036

00:04:18.990 --> 00:04:20.259 discovery scientific discovery

NOTE Confidence: 0.871820628643036

00:04:20.259 --> 00:04:21.528 into the clinic.

NOTE Confidence: 0.871820628643036

00:04:21.530 --> 00:04:23.640 Really pleased with the team

NOTE Confidence: 0.871820628643036

00:04:23.640 --> 00:04:25.328 that's been assembled today,

NOTE Confidence: 0.871820628643036

00:04:25.330 --> 00:04:28.291 our first and Yale engage cancer was

NOTE Confidence: 0.871820628643036

00:04:28.291 --> 00:04:30.350 focused on immunobiology, our second.

NOTE Confidence: 0.871820628643036

00:04:30.350 --> 00:04:32.325 Was focused on novel therapeutics,

NOTE Confidence: 0.871820628643036

00:04:32.330 --> 00:04:35.386 and the third really ties it all together,

NOTE Confidence: 0.871820628643036

00:04:35.390 --> 00:04:37.300 which is to understand now,

NOTE Confidence: 0.871820628643036

00:04:37.300 --> 00:04:39.988 given these efforts to develop new drugs,

NOTE Confidence: 0.871820628643036

00:04:39.990 --> 00:04:40.754 new targets,

NOTE Confidence: 0.871820628643036

00:04:40.754 --> 00:04:42.664 how do we understand resistance?

NOTE Confidence: 0.871820628643036

00:04:42.670 --> 00:04:44.580 How do we understand sensitivity?

NOTE Confidence: 0.871820628643036

00:04:44.580 --> 00:04:47.100 And how do we further enhance our

NOTE Confidence: 0.871820628643036

00:04:47.100 --> 00:04:48.790 approaches to cancer therapy?

NOTE Confidence: 0.871820628643036

00:04:48.790 --> 00:04:51.088 Integral to this fight is our

NOTE Confidence: 0.871820628643036

00:04:51.088 --> 00:04:52.237 collaboration with industry,

NOTE Confidence: 0.871820628643036

00:04:52.240 --> 00:04:55.026 and we're so pleased to have Doctor

NOTE Confidence: 0.871820628643036

00:04:55.026 --> 00:04:57.360 Susan Galbraith join us as our

NOTE Confidence: 0.871820628643036

00:04:57.360 --> 00:04:59.135 industry partner on the panel,

NOTE Confidence: 0.871820628643036

00:04:59.140 --> 00:05:00.376 and we realize that.

NOTE Confidence: 0.871820628643036

00:05:00.376 --> 00:05:02.748 So many of you in the audience

NOTE Confidence: 0.871820628643036

00:05:02.748 --> 00:05:05.394 come from the biotech and pharma.

NOTE Confidence: 0.871820628643036

00:05:05.400 --> 00:05:07.566 An really part of this effort.

NOTE Confidence: 0.871820628643036

00:05:07.570 --> 00:05:09.250 Beyond hearing from these experts

NOTE Confidence: 0.871820628643036

00:05:09.250 --> 00:05:11.401 in their insights is to really

NOTE Confidence: 0.871820628643036

00:05:11.401 --> 00:05:12.637 begin a conversation.

NOTE Confidence: 0.871820628643036

00:05:12.640 --> 00:05:14.674 Because one thing we really welcome

NOTE Confidence: 0.871820628643036

00:05:14.674 --> 00:05:17.698 here at Yale is to collaborate with you.

NOTE Confidence: 0.871820628643036

00:05:17.700 --> 00:05:19.935 We want to build strategic

NOTE Confidence: 0.871820628643036

00:05:19.935 --> 00:05:22.170 partnerships with all of you.

NOTE Confidence: 0.871820628643036

00:05:22.170 --> 00:05:24.060 Because ultimately this fight against cancer.

NOTE Confidence: 0.871820628643036

00:05:24.060 --> 00:05:24.375 Yes,

NOTE Confidence: 0.871820628643036

00:05:24.375 --> 00:05:25.950 it requires each of these

NOTE Confidence: 0.871820628643036

00:05:25.950 --> 00:05:27.210 domains on the slide,

NOTE Confidence: 0.871820628643036

00:05:27.210 --> 00:05:28.785 but it requires a community

NOTE Confidence: 0.871820628643036

00:05:28.785 --> 00:05:30.045 focused on every aspect,

NOTE Confidence: 0.871820628643036

00:05:30.050 --> 00:05:31.310 and that includes academia

NOTE Confidence: 0.871820628643036

00:05:31.310 --> 00:05:32.570 and industry in biotech.

NOTE Confidence: 0.871820628643036

00:05:32.570 --> 00:05:34.572 So one thing I want to invite

NOTE Confidence: 0.871820628643036

00:05:34.572 --> 00:05:36.659 you today is to ask questions,

NOTE Confidence: 0.871820628643036

00:05:36.660 --> 00:05:37.920 but after this form,

NOTE Confidence: 0.871820628643036

00:05:37.920 --> 00:05:39.495 please reach out to us,

NOTE Confidence: 0.871820628643036

00:05:39.500 --> 00:05:41.070 will reach out to you.

NOTE Confidence: 0.871820628643036

00:05:41.070 --> 00:05:42.960 And let's think about ways we

NOTE Confidence: 0.871820628643036

00:05:42.960 --> 00:05:43.905 can work together.

NOTE Confidence: 0.871820628643036

00:05:43.910 --> 00:05:46.054 I think we have a lot of resources

NOTE Confidence: 0.871820628643036

00:05:46.054 --> 00:05:48.227 we can bring here at Yale to

NOTE Confidence: 0.871820628643036

00:05:48.227 --> 00:05:49.797 partner with all the great

NOTE Confidence: 0.889435529708862

00:05:49.862 --> 00:05:52.734 things you're all doing and we look forward.

NOTE Confidence: 0.889435529708862

00:05:52.740 --> 00:05:53.992 To continuing this conversation

NOTE Confidence: 0.889435529708862

00:05:53.992 --> 00:05:55.852 long after this form, so again,

NOTE Confidence: 0.889435529708862

00:05:55.852 --> 00:05:57.357 thank you for joining and

NOTE Confidence: 0.889435529708862

00:05:57.357 --> 00:05:59.328 I'll turn it back to Barbara.

NOTE Confidence: 0.861892461776733

00:06:01.670 --> 00:06:04.970 Thank you Charlie. I think that

NOTE Confidence: 0.861892461776733

00:06:04.970 --> 00:06:07.510 that's a great introduction to

NOTE Confidence: 0.85655349890391

00:06:07.609 --> 00:06:10.513 to what we're trying to do here I

NOTE Confidence: 0.85655349890391

00:06:10.513 --> 00:06:13.739 I just had a brief opportunity to

NOTE Confidence: 0.85655349890391

00:06:13.739 --> 00:06:17.022 to scroll through the list of 100

NOTE Confidence: 0.85655349890391

00:06:17.022 --> 00:06:19.638 participants an it's a formidable group,

NOTE Confidence: 0.85655349890391

00:06:19.640 --> 00:06:21.820 including GAIL scientists, industry partners.

NOTE Confidence: 0.85655349890391

00:06:21.820 --> 00:06:23.050 Alumni are supporters,

NOTE Confidence: 0.85655349890391

00:06:23.050 --> 00:06:25.920 so I think that we can anticipate

NOTE Confidence: 0.85655349890391

00:06:25.997 --> 00:06:28.272 some some pretty hard hitting

NOTE Confidence: 0.85655349890391

00:06:28.272 --> 00:06:30.978 questions from that group. So we've.

NOTE Confidence: 0.85655349890391

00:06:30.978 --> 00:06:34.490 We've tried to arrange these talks so that.

NOTE Confidence: 0.85655349890391

00:06:34.490 --> 00:06:36.314 We hope that there's a little

NOTE Confidence: 0.85655349890391

00:06:36.314 --> 00:06:38.131 bit of a natural progression

NOTE Confidence: 0.85655349890391

00:06:38.131 --> 00:06:40.247 in the scientific questions,

NOTE Confidence: 0.85655349890391

00:06:40.250 --> 00:06:42.693 and Dan the approaches that are are

NOTE Confidence: 0.85655349890391

00:06:42.693 --> 00:06:44.470 taken to understanding resistance.

NOTE Confidence: 0.85655349890391

00:06:44.470 --> 00:06:45.577 As I said,

NOTE Confidence: 0.85655349890391

00:06:45.577 --> 00:06:47.791 every speakers been asked to sort

NOTE Confidence: 0.85655349890391

00:06:47.791 --> 00:06:50.997 of reflect a little bit on what's her,

NOTE Confidence: 0.85655349890391

00:06:51.000 --> 00:06:52.215 his core expertise.

NOTE Confidence: 0.85655349890391

00:06:52.215 --> 00:06:53.835 What questions drive the

NOTE Confidence: 0.85655349890391

00:06:53.835 --> 00:06:55.989 research and how they hope to,

NOTE Confidence: 0.85655349890391

00:06:55.990 --> 00:06:59.758 or Yale hopes to work with industry partners.

NOTE Confidence: 0.85655349890391

00:06:59.760 --> 00:07:03.212 To address cancer cancer

NOTE Confidence: 0.85655349890391

00:07:03.212 --> 00:07:04.938 treatment resistance.

NOTE Confidence: 0.85655349890391

00:07:04.940 --> 00:07:06.974 And what kinds of capabilities and

NOTE Confidence: 0.85655349890391

00:07:06.974 --> 00:07:09.388 resources need to be brought to bear?

NOTE Confidence: 0.85655349890391

00:07:09.390 --> 00:07:11.679 So each of those speakers has been

NOTE Confidence: 0.85655349890391

00:07:11.679 --> 00:07:14.519 asked to go only for about 5 minutes?

NOTE Confidence: 0.85655349890391

00:07:14.520 --> 00:07:16.970 I've been told that I should be

NOTE Confidence: 0.85655349890391

00:07:16.970 --> 00:07:18.968 ruthless and and cut you off.

NOTE Confidence: 0.85655349890391

00:07:18.970 --> 00:07:21.539 If you go over and and that

NOTE Confidence: 0.85655349890391

00:07:21.539 --> 00:07:23.289 will be hard to do.

NOTE Confidence: 0.85655349890391

00:07:23.290 --> 00:07:25.090 'cause I know the talks

NOTE Confidence: 0.85655349890391

00:07:25.090 --> 00:07:26.890 are going to be great,

NOTE Confidence: 0.85655349890391

00:07:26.890 --> 00:07:29.050 but let me start by introducing

NOTE Confidence: 0.85655349890391

00:07:29.050 --> 00:07:30.130 Doctor Katie Palitti.

NOTE Confidence: 0.85655349890391

00:07:30.130 --> 00:07:32.290 She's an associate professor of pathology

NOTE Confidence: 0.85655349890391

00:07:32.290 --> 00:07:34.809 and Medicine leader in our Cancer Center.

NOTE Confidence: 0.85655349890391

00:07:34.810 --> 00:07:36.250 Through those answering signaling

NOTE Confidence: 0.85655349890391

00:07:36.250 --> 00:07:37.690 cancer signaling networks program,

NOTE Confidence: 0.85655349890391

00:07:37.690 --> 00:07:40.497 as well as a leader of our

NOTE Confidence: 0.85655349890391

00:07:40.497 --> 00:07:42.679 lung spore program and Katie.

NOTE Confidence: 0.85655349890391

00:07:42.680 --> 00:07:43.868 Think it away.

NOTE Confidence: 0.877268970012665

00:07:43.870 --> 00:07:45.860 Thank you very much, Barbara.

NOTE Confidence: 0.877268970012665

00:07:45.860 --> 00:07:48.326 And I'm really delighted to have

NOTE Confidence: 0.877268970012665

00:07:48.326 --> 00:07:50.735 the opportunity to speak here today

NOTE Confidence: 0.877268970012665

00:07:50.735 --> 00:07:53.157 and tell you about some of the

NOTE Confidence: 0.877268970012665

00:07:53.157 --> 00:07:55.377 things that we're interested in.

NOTE Confidence: 0.877268970012665

00:07:55.380 --> 00:07:57.851 I have a cancer biology lab here

NOTE Confidence: 0.877268970012665

00:07:57.851 --> 00:08:00.756 really with a focus on lung cancer and

NOTE Confidence: 0.877268970012665

00:08:00.756 --> 00:08:04.007 one of the areas that we are really

NOTE Confidence: 0.877268970012665

00:08:04.007 --> 00:08:06.815 interested in studying is working on

NOTE Confidence: 0.877268970012665

00:08:06.815 --> 00:08:08.934 resistance and resistance to various

NOTE Confidence: 0.877268970012665

00:08:08.934 --> 00:08:10.578 cancer therapies including targeted

NOTE Confidence: 0.877268970012665

00:08:10.578 --> 00:08:12.887 therapies and also immuno therapies and.

NOTE Confidence: 0.877268970012665

00:08:12.890 --> 00:08:15.664 Some of the things that we think

NOTE Confidence: 0.877268970012665

00:08:15.664 --> 00:08:18.040 about a lot and work on.

NOTE Confidence: 0.877268970012665

00:08:18.040 --> 00:08:20.164 I'm really approaches to discover new

NOTE Confidence: 0.877268970012665

00:08:20.164 --> 00:08:22.041 mechanisms of resistance were interested

NOTE Confidence: 0.877268970012665

00:08:22.041 --> 00:08:23.649 in understanding the relationship

NOTE Confidence: 0.877268970012665

00:08:23.649 --> 00:08:26.350 between tumor genotype and drug sensitivity.

NOTE Confidence: 0.877268970012665

00:08:26.350 --> 00:08:28.646 We study the influence of the tumor

NOTE Confidence: 0.877268970012665

00:08:28.646 --> 00:08:30.123 micro environment on sensitivity

NOTE Confidence: 0.877268970012665

00:08:30.123 --> 00:08:32.288 to different therapies and also

NOTE Confidence: 0.877268970012665

00:08:32.288 --> 00:08:34.670 investigate mechanisms of drug tolerance.

NOTE Confidence: 0.877268970012665

00:08:34.670 --> 00:08:37.246 So why do some cells die when you

NOTE Confidence: 0.877268970012665

00:08:37.246 --> 00:08:39.610 apply a therapy and instead other

NOTE Confidence: 0.877268970012665

00:08:39.610 --> 00:08:42.584 cells do not die and stick around

NOTE Confidence: 0.877268970012665

00:08:42.584 --> 00:08:45.664 and serve as the fertile ground for

NOTE Confidence: 0.877268970012665

00:08:45.664 --> 00:08:47.951 the emergence of drug resistance?

NOTE Confidence: 0.877268970012665

00:08:47.951 --> 00:08:50.753 And then we also investigate new

NOTE Confidence: 0.877268970012665

00:08:50.753 --> 00:08:53.254 approaches based on the science that

NOTE Confidence: 0.877268970012665

00:08:53.254 --> 00:08:56.166 we discover to overcome and or to

NOTE Confidence: 0.877268970012665

00:08:56.166 --> 00:08:58.776 prevent the emergence of drug resistance.

NOTE Confidence: 0.877268970012665

00:08:58.780 --> 00:09:02.303 And we do these studies by really integrating

NOTE Confidence: 0.877268970012665

00:09:02.303 --> 00:09:04.508 information from various different systems,

NOTE Confidence: 0.877268970012665

00:09:04.510 --> 00:09:06.715 various different models and using

NOTE Confidence: 0.877268970012665

00:09:06.715 --> 00:09:08.920 a variety of different technologies.

NOTE Confidence: 0.877268970012665

00:09:08.920 --> 00:09:12.007 We use specimens and data from patients,

NOTE Confidence: 0.877268970012665

00:09:12.010 --> 00:09:15.530 so we have a very robust biopsy program.

NOTE Confidence: 0.877268970012665

00:09:15.530 --> 00:09:15.971 Here,

NOTE Confidence: 0.877268970012665

00:09:15.971 --> 00:09:19.500 within the context of the Lung Cancer Group.

NOTE Confidence: 0.877268970012665

00:09:19.500 --> 00:09:20.905 Where we.

NOTE Confidence: 0.877268970012665

00:09:20.905 --> 00:09:25.730 Can obtain biopsies from patients.

NOTE Confidence: 0.877268970012665

00:09:25.730 --> 00:09:28.238 Long sort of the spectrum of

NOTE Confidence: 0.877268970012665

00:09:28.238 --> 00:09:29.910 their treatment with therapies,

NOTE Confidence: 0.877268970012665

00:09:29.910 --> 00:09:32.418 and we can generate patient derived

NOTE Confidence: 0.877268970012665

00:09:32.418 --> 00:09:34.090 models from these biopsies,

NOTE Confidence: 0.877268970012665

00:09:34.090 --> 00:09:35.890 but also then analyze the

NOTE Confidence: 0.877268970012665

00:09:35.890 --> 00:09:37.690 data and information to really

NOTE Confidence: 0.877268970012665

00:09:37.754 --> 00:09:39.938 understand resistance in patients.

NOTE Confidence: 0.877268970012665

00:09:39.940 --> 00:09:42.268 We use these models to generate

NOTE Confidence: 0.877268970012665

00:09:42.268 --> 00:09:44.348 or these specimens to generate

NOTE Confidence: 0.877268970012665

00:09:44.348 --> 00:09:47.048 patient drive Zeno graphs as well,

NOTE Confidence: 0.877268970012665

00:09:47.050 --> 00:09:49.552 and also 2D or 3D cultures

NOTE Confidence: 0.877268970012665

00:09:49.552 --> 00:09:50.803 from patient specimens,

NOTE Confidence: 0.877268970012665

00:09:50.810 --> 00:09:53.210 and we also extensively work

NOTE Confidence: 0.877268970012665

00:09:53.210 --> 00:09:55.130 with genetically engineered mouse

NOTE Confidence: 0.877268970012665

00:09:55.130 --> 00:09:57.559 models of lung cancer that we can.

NOTE Confidence: 0.877268970012665

00:09:57.560 --> 00:10:00.059 I used to study resistance and in

NOTE Confidence: 0.877268970012665

00:10:00.059 --> 00:10:02.879 that regard I'd like to tell you today

NOTE Confidence: 0.877268970012665

00:10:02.879 --> 00:10:05.358 about some work that we have been

NOTE Confidence: 0.877268970012665

00:10:05.358 --> 00:10:07.906 doing in the field of EGF receptor,

NOTE Confidence: 0.877268970012665

00:10:07.910 --> 00:10:10.234 mutant lung cancer. Next slide, please.

NOTE Confidence: 0.877268970012665

00:10:10.234 --> 00:10:13.972 To really use models to study resistance

NOTE Confidence: 0.877268970012665

00:10:13.972 --> 00:10:18.147 to the EGFR tyrosine kinase inhibitor,

NOTE Confidence: 0.877268970012665

00:10:18.150 --> 00:10:19.054 also Merton.

NOTE Confidence: 0.877268970012665

00:10:19.054 --> 00:10:22.670 If and this is a work that really

NOTE Confidence: 0.877268970012665

00:10:22.775 --> 00:10:26.119 illustrates a partnership between.

NOTE Confidence: 0.877268970012665

00:10:26.120 --> 00:10:28.090 Academia and investigators in academia

NOTE Confidence: 0.877268970012665

00:10:28.090 --> 00:10:30.540 and work that we've done together

NOTE Confidence: 0.877268970012665

00:10:30.540 --> 00:10:33.018 with Astra Zeneca and also working

NOTE Confidence: 0.877268970012665

00:10:33.018 --> 00:10:35.315 with Garden Technology and work that

NOTE Confidence: 0.877268970012665

00:10:35.315 --> 00:10:37.301 was published recently this year and

NOTE Confidence: 0.877268970012665

00:10:37.301 --> 00:10:39.555 so EGF receptor mutations are found

NOTE Confidence: 0.877268970012665

00:10:39.555 --> 00:10:42.645 in about 15% of lung cancers and can

NOTE Confidence: 0.877268970012665

00:10:42.645 --> 00:10:44.580 be targeted with tyrosine kinase

NOTE Confidence: 0.877268970012665

00:10:44.649 --> 00:10:47.617 inhibitors and one of the most recent ones.

NOTE Confidence: 0.877268970012665

00:10:47.620 --> 00:10:49.545 Is this tyrosine kinase inhibitor

NOTE Confidence: 0.877268970012665

00:10:49.545 --> 00:10:50.700 awesome Merton Eben?

NOTE Confidence: 0.877268970012665

00:10:50.700 --> 00:10:52.968 So we can take our genetically

NOTE Confidence: 0.877268970012665

00:10:52.968 --> 00:10:54.943 engineered mouse models and ask

NOTE Confidence: 0.877268970012665

00:10:54.943 --> 00:10:56.507 the question what happens?

NOTE Confidence: 0.877268970012665

00:10:56.510 --> 00:10:59.526 If you have mouse models of EGF receptor,

NOTE Confidence: 0.877268970012665

00:10:59.530 --> 00:11:00.661 mutant lung cancer,

NOTE Confidence: 0.877268970012665

00:11:00.661 --> 00:11:03.300 and you treat them with awesome Merton,

NOTE Confidence: 0.877268970012665

00:11:03.300 --> 00:11:05.939 if and so we took my sweet,

NOTE Confidence: 0.877268970012665

00:11:05.940 --> 00:11:07.815 treated them till the emergence

NOTE Confidence: 0.877268970012665

00:11:07.815 --> 00:11:08.565 of resistance.

NOTE Confidence: 0.877268970012665

00:11:08.570 --> 00:11:10.658 And when we looked at resistant

NOTE Confidence: 0.877268970012665

00:11:10.658 --> 00:11:13.100 tumors to see what was happening,

NOTE Confidence: 0.838195204734802

00:11:13.100 --> 00:11:16.054 we found that almost 50% of the tumors

NOTE Confidence: 0.838195204734802

00:11:16.054 --> 00:11:17.844 that emerged had secondary mutations

NOTE Confidence: 0.838195204734802

00:11:17.844 --> 00:11:20.180 in EGF receptor that confer resistance

NOTE Confidence: 0.838195204734802

00:11:20.180 --> 00:11:22.514 to awesome American if and so.

NOTE Confidence: 0.838195204734802

00:11:22.520 --> 00:11:24.698 With that information we can actually

NOTE Confidence: 0.838195204734802

00:11:24.698 --> 00:11:27.049 then go ahead using these models.

NOTE Confidence: 0.838195204734802

00:11:27.050 --> 00:11:28.960 So we've discovered new mechanisms.

NOTE Confidence: 0.838195204734802

00:11:28.960 --> 00:11:31.744 We can now use these models for preclinical

NOTE Confidence: 0.838195204734802

00:11:31.744 --> 00:11:33.710 testing and test new therapies.

NOTE Confidence: 0.838195204734802

00:11:33.710 --> 00:11:35.756 We can also with this information

NOTE Confidence: 0.838195204734802

00:11:35.756 --> 00:11:37.935 go into human specimens and data

NOTE Confidence: 0.838195204734802

00:11:37.935 --> 00:11:40.197 and analyze the relevance of the

NOTE Confidence: 0.838195204734802

00:11:40.197 --> 00:11:41.994 resistance mechanisms there, and so.

NOTE Confidence: 0.838195204734802

00:11:41.994 --> 00:11:44.178 For example, in this study we found

NOTE Confidence: 0.838195204734802

00:11:44.178 --> 00:11:46.700 that the mutations that were emerging

NOTE Confidence: 0.838195204734802

00:11:46.700 --> 00:11:49.040 were particularly relevant to the L.

NOTE Confidence: 0.838195204734802

00:11:49.040 --> 00:11:51.960 8:50 at our subset of EGFR mutant tumors,

NOTE Confidence: 0.838195204734802

00:11:51.960 --> 00:11:54.144 so there was an allele specificity

NOTE Confidence: 0.838195204734802

00:11:54.144 --> 00:11:56.397 that was revealed through our studies

NOTE Confidence: 0.838195204734802

00:11:56.397 --> 00:11:58.581 in mouse models and then working

NOTE Confidence: 0.838195204734802

00:11:58.581 --> 00:12:00.349 with colleagues like Mark Lemon.

NOTE Confidence: 0.838195204734802

00:12:00.350 --> 00:12:03.010 Here, you're going to hear from next.

NOTE Confidence: 0.838195204734802

00:12:03.010 --> 00:12:06.195 We can really then study the biochemical

NOTE Confidence: 0.838195204734802

00:12:06.195 --> 00:12:08.909 properties in detail of these mutants.

NOTE Confidence: 0.838195204734802

00:12:08.910 --> 00:12:11.328 Next slide, please.

NOTE Confidence: 0.838195204734802

00:12:11.330 --> 00:12:13.636 So we also are working extensively

NOTE Confidence: 0.838195204734802

00:12:13.636 --> 00:12:16.338 to take these models that we have

NOTE Confidence: 0.838195204734802

00:12:16.338 --> 00:12:19.067 and sort of take them to the next

NOTE Confidence: 0.838195204734802

00:12:19.067 --> 00:12:21.779 level to study some of the more

NOTE Confidence: 0.838195204734802

00:12:21.779 --> 00:12:23.615 complex mechanisms of resistance,

NOTE Confidence: 0.838195204734802

00:12:23.620 --> 00:12:26.308 and we have modified for example this

NOTE Confidence: 0.838195204734802

00:12:26.308 --> 00:12:28.608 initial mouse model of EGF receptor,

NOTE Confidence: 0.838195204734802

00:12:28.610 --> 00:12:30.530 mutant lung cancer to incorporate

NOTE Confidence: 0.838195204734802

00:12:30.530 --> 00:12:32.066 additional genetic alterations that

NOTE Confidence: 0.838195204734802

00:12:32.070 --> 00:12:34.756 are also found in humans in EGFR

NOTE Confidence: 0.838195204734802

00:12:34.756 --> 00:12:36.360 mutant lung cancer, including,

NOTE Confidence: 0.838195204734802

00:12:36.360 --> 00:12:37.260 for example,

NOTE Confidence: 0.838195204734802

00:12:37.260 --> 00:12:39.960 tumor suppressor gene alterations using in

NOTE Confidence: 0.838195204734802

00:12:39.960 --> 00:12:42.818 vivo CRISPR CAS 9 gene editing and so now.

NOTE Confidence: 0.838195204734802

00:12:42.820 --> 00:12:45.142 We can study how those additional

NOTE Confidence: 0.838195204734802

00:12:45.142 --> 00:12:47.470 alterations are impacting tumor progression,

NOTE Confidence: 0.838195204734802

00:12:47.470 --> 00:12:48.739 sensitivity to therapies,

NOTE Confidence: 0.838195204734802

00:12:48.739 --> 00:12:50.854 and the phenotypes of tumors.

NOTE Confidence: 0.838195204734802

00:12:50.860 --> 00:12:53.814 As I mentioned in my first slide,

NOTE Confidence: 0.838195204734802

00:12:53.820 --> 00:12:56.669 we also have a robust program to

NOTE Confidence: 0.838195204734802

00:12:56.669 --> 00:12:58.470 generate patient derived models,

NOTE Confidence: 0.838195204734802

00:12:58.470 --> 00:13:00.744 and here is really an illustration

NOTE Confidence: 0.838195204734802

00:13:00.744 --> 00:13:03.120 of sort of the different.

NOTE Confidence: 0.838195204734802

00:13:03.120 --> 00:13:05.610 PDX is that we've generated across

NOTE Confidence: 0.838195204734802

00:13:05.610 --> 00:13:07.270 various different oncogenic subgroups

NOTE Confidence: 0.838195204734802

00:13:07.334 --> 00:13:09.459 of lung cancer with different

NOTE Confidence: 0.838195204734802

00:13:09.459 --> 00:13:10.734 oncogenic driver alterations,

NOTE Confidence: 0.838195204734802

00:13:10.740 --> 00:13:13.326 and so we're using these models.

NOTE Confidence: 0.838195204734802

00:13:13.330 --> 00:13:15.880 To really study resistance in human

NOTE Confidence: 0.838195204734802

00:13:15.880 --> 00:13:18.550 specimens and really use them to

NOTE Confidence: 0.838195204734802

00:13:18.550 --> 00:13:20.780 study heterogeneity of human tumors,

NOTE Confidence: 0.838195204734802

00:13:20.780 --> 00:13:22.229 signaling network alterations,

NOTE Confidence: 0.838195204734802

00:13:22.229 --> 00:13:25.127 and the molecular profiles that you

NOTE Confidence: 0.838195204734802

00:13:25.127 --> 00:13:27.798 can have in these human who tumors

NOTE Confidence: 0.838195204734802

00:13:27.798 --> 00:13:29.970 with or without drug treatment.

NOTE Confidence: 0.838195204734802

00:13:29.970 --> 00:13:30.850 Thank you.

NOTE Confidence: 0.834687411785126

00:13:32.230 --> 00:13:35.796 Thank you so much Katie. I,

NOTE Confidence: 0.834687411785126

00:13:35.796 --> 00:13:38.790 I think that there's there's so

NOTE Confidence: 0.811754882335663

00:13:38.892 --> 00:13:42.796 much there for the other speakers to riff

NOTE Confidence: 0.811754882335663

00:13:42.796 --> 00:13:47.136 off of and and to set up our questions.

NOTE Confidence: 0.811754882335663

00:13:47.140 --> 00:13:49.678 Next, let me introduce Mark Lemon,

NOTE Confidence: 0.811754882335663

00:13:49.680 --> 00:13:51.424 distinguished Professor of pharmacology.

NOTE Confidence: 0.811754882335663

00:13:51.424 --> 00:13:54.899 You see his leadership roles in the Cancer

NOTE Confidence: 0.811754882335663

00:13:54.899 --> 00:13:56.889 Center in Cancer Biology Institute.

NOTE Confidence: 0.811754882335663

00:13:56.890 --> 00:14:00.874 There, an mark is unique and bringing a.

NOTE Confidence: 0.811754882335663

00:14:00.880 --> 00:14:03.757 You know a wealth of expertise in

NOTE Confidence: 0.811754882335663

00:14:03.757 --> 00:14:06.367 biology and structural biology to the

NOTE Confidence: 0.811754882335663

00:14:06.367 --> 00:14:08.532 very interface with drug development

NOTE Confidence: 0.811754882335663

00:14:08.532 --> 00:14:11.676 and and disease based research and so.

NOTE Confidence: 0.811754882335663

00:14:11.680 --> 00:14:14.270 Looking forward to your comments, mark.

NOTE Confidence: 0.79191118478775

00:14:15.080 --> 00:14:16.612 Thank you very much,

NOTE Confidence: 0.79191118478775

00:14:16.612 --> 00:14:18.144 Robert and good afternoon.

NOTE Confidence: 0.79191118478775

00:14:18.150 --> 00:14:20.838 So a great pleasure to be here.

NOTE Confidence: 0.79191118478775

00:14:20.840 --> 00:14:23.144 I look forward very much to

NOTE Confidence: 0.79191118478775

00:14:23.144 --> 00:14:24.680 hearing discussion later on.

NOTE Confidence: 0.79191118478775

00:14:24.680 --> 00:14:26.260 As as Barbara mentioned,

NOTE Confidence: 0.79191118478775

00:14:26.260 --> 00:14:28.235 I'm really a basic scientist

NOTE Confidence: 0.79191118478775

00:14:28.235 --> 00:14:30.060 interested in how molecules work.

NOTE Confidence: 0.79191118478775

00:14:30.060 --> 00:14:32.364 My core expertise really is in

NOTE Confidence: 0.79191118478775

00:14:32.364 --> 00:14:33.900 biochemistry and structural biology.

NOTE Confidence: 0.79191118478775

00:14:33.900 --> 00:14:36.537 The focus of most of our work is is

NOTE Confidence: 0.79191118478775

00:14:36.537 --> 00:14:38.709 detailed understanding of of how

NOTE Confidence: 0.79191118478775

00:14:38.709 --> 00:14:40.974 molecules and networks involved in

NOTE Confidence: 0.79191118478775

00:14:40.974 --> 00:14:42.690 oncogenic signaling actually do

NOTE Confidence: 0.79191118478775

00:14:42.690 --> 00:14:45.084 work and do not anatomic detail.

NOTE Confidence: 0.79191118478775

00:14:45.090 --> 00:14:47.000 Where we can and quantitatively

NOTE Confidence: 0.79191118478775

00:14:47.000 --> 00:14:48.528 understanding how their properties

NOTE Confidence: 0.79191118478775

00:14:48.528 --> 00:14:50.231 are changed by oncogenic

NOTE Confidence: 0.79191118478775

00:14:50.231 --> 00:14:51.488 and resistance mutations.

NOTE Confidence: 0.79191118478775

00:14:51.490 --> 00:14:52.435 As Katy mentioned,

NOTE Confidence: 0.79191118478775

00:14:52.435 --> 00:14:54.640 work we're doing with her and how

NOTE Confidence: 0.79191118478775

00:14:54.709 --> 00:14:57.037 we can then use that information

NOTE Confidence: 0.79191118478775

00:14:57.037 --> 00:14:58.589 to guide mechanistically driven

NOTE Confidence: 0.79191118478775

00:14:58.656 --> 00:15:01.116 personalized medicine or put the

NOTE Confidence: 0.79191118478775

00:15:01.116 --> 00:15:03.084 biochemistry into personalized medicine.

NOTE Confidence: 0.79191118478775

00:15:03.090 --> 00:15:04.598 Those kinds of thoughts.

NOTE Confidence: 0.79191118478775

00:15:04.598 --> 00:15:07.776 So our main focus in general is the

NOTE Confidence: 0.79191118478775

00:15:07.776 --> 00:15:10.284 class of receptors that Katie discussed.

NOTE Confidence: 0.79191118478775

00:15:10.290 --> 00:15:12.365 The growth factor receptors that

NOTE Confidence: 0.79191118478775

00:15:12.365 --> 00:15:14.025 have interested Harrison Chinese

NOTE Confidence: 0.79191118478775

00:15:14.025 --> 00:15:15.520 domains like EGF receptor.

NOTE Confidence: 0.79191118478775

00:15:15.520 --> 00:15:18.625 As you know, and as as key to describe,

NOTE Confidence: 0.79191118478775

00:15:18.630 --> 00:15:21.059 these are key targets for cancer therapy,

NOTE Confidence: 0.79191118478775

00:15:21.060 --> 00:15:21.987 particularly lung cancer,

NOTE Confidence: 0.79191118478775

00:15:21.987 --> 00:15:24.150 and is clear in general in advancing

NOTE Confidence: 0.79191118478775

00:15:24.204 --> 00:15:26.249 approaches to controlling their behavior.

NOTE Confidence: 0.79191118478775

00:15:26.250 --> 00:15:28.398 So the behavior with drugs dealing

NOTE Confidence: 0.79191118478775

00:15:28.398 --> 00:15:30.661 with resistance really requires us to

NOTE Confidence: 0.79191118478775

00:15:30.661 --> 00:15:32.201 understand the molecular mechanisms

NOTE Confidence: 0.79191118478775

00:15:32.201 --> 00:15:33.741 and understanding well enough

NOTE Confidence: 0.79191118478775

00:15:33.804 --> 00:15:35.778 that we can manipulate them in a

NOTE Confidence: 0.79191118478775

00:15:35.778 --> 00:15:37.320 predictable way and also manipulate

NOTE Confidence: 0.79191118478775

00:15:37.320 --> 00:15:39.045 their complex so the networks.

NOTE Confidence: 0.79191118478775

00:15:39.050 --> 00:15:41.465 And I'll give a couple of examples

NOTE Confidence: 0.79191118478775

00:15:41.470 --> 00:15:43.569 of things that are driving have

NOTE Confidence: 0.79191118478775

00:15:43.569 --> 00:15:45.687 been driving research in my lab.

NOTE Confidence: 0.79191118478775

00:15:45.690 --> 00:15:46.032 Recently,

NOTE Confidence: 0.79191118478775

00:15:46.032 --> 00:15:48.768 and the first relates to what Katie has

NOTE Confidence: 0.79191118478775

00:15:48.768 --> 00:15:51.336 been discussing at the level of growth,

NOTE Confidence: 0.79191118478775

00:15:51.340 --> 00:15:53.100 acquired resistance and primary resistance,

NOTE Confidence: 0.79191118478775

00:15:53.100 --> 00:15:54.960 and we've actually been working with

NOTE Confidence: 0.79191118478775

00:15:54.960 --> 00:15:56.976 Katie quite a bit to understand

NOTE Confidence: 0.79191118478775

00:15:56.976 --> 00:15:58.756 details of how secondary mutations

NOTE Confidence: 0.79191118478775

00:15:58.756 --> 00:16:00.520 in EGFR cause resistance.

NOTE Confidence: 0.79191118478775

00:16:00.520 --> 00:16:01.678 As she mentioned,

NOTE Confidence: 0.79191118478775

00:16:01.678 --> 00:16:03.222 with the automotive resistance

NOTE Confidence: 0.79191118478775

00:16:03.222 --> 00:16:05.493 mutations and the additional key colon

NOTE Confidence: 0.79191118478775

00:16:05.493 --> 00:16:07.599 network is to use that understanding

NOTE Confidence: 0.79191118478775

00:16:07.599 --> 00:16:09.869 as it develops to decide when to

NOTE Confidence: 0.79191118478775

00:16:09.869 --> 00:16:12.049 use which inhibitor and how to come

NOTE Confidence: 0.79191118478775

00:16:12.049 --> 00:16:13.927 up with new and indeed repurposed

NOTE Confidence: 0.79191118478775

00:16:13.927 --> 00:16:15.699 inhibitors in resistance situations.

NOTE Confidence: 0.79191118478775

00:16:15.700 --> 00:16:17.668 Not going back to two other

NOTE Confidence: 0.79191118478775

00:16:17.668 --> 00:16:18.980 working in the lab,

NOTE Confidence: 0.79191118478775

00:16:18.980 --> 00:16:20.600 one of our recent first time

NOTE Confidence: 0.79191118478775

00:16:20.600 --> 00:16:22.571 has been to identify and target

NOTE Confidence: 0.79191118478775

00:16:22.571 --> 00:16:24.227 driver mutations in neuroblastoma,

NOTE Confidence: 0.79191118478775

00:16:24.230 --> 00:16:26.519 which is one of the most common

NOTE Confidence: 0.79191118478775

00:16:26.519 --> 00:16:27.173 pediatric cancers.

NOTE Confidence: 0.79191118478775

00:16:27.180 --> 00:16:29.203 And this is related work we've been

NOTE Confidence: 0.79191118478775

00:16:29.203 --> 00:16:30.486 collaborating with the Children

NOTE Confidence: 0.79191118478775

00:16:30.486 --> 00:16:32.311 Psychology Group on out another

NOTE Confidence: 0.79191118478775

00:16:32.311 --> 00:16:33.406 receptor tyrosine kinase,

NOTE Confidence: 0.79191118478775

00:16:33.410 --> 00:16:34.630 a bit like EGFR,

NOTE Confidence: 0.79191118478775

00:16:34.630 --> 00:16:36.155 and sequencing out consumers from

NOTE Confidence: 0.79191118478775

00:16:36.155 --> 00:16:37.020 1600 patients.

NOTE Confidence: 0.79191118478775

00:16:37.020 --> 00:16:38.847 That gave us a list with carve

NOTE Confidence: 0.79191118478775

00:16:38.847 --> 00:16:40.649 out mutations that we analyzed

NOTE Confidence: 0.79191118478775

00:16:40.649 --> 00:16:41.609 biochemically structure.

NOTE Confidence: 0.79191118478775

00:16:41.610 --> 00:16:43.948 Real transformation did a full work up

NOTE Confidence: 0.79191118478775

00:16:43.948 --> 00:16:46.617 on them and show from that that out.

NOTE Confidence: 0.79191118478775

00:16:46.620 --> 00:16:48.456 About 14% of neuroblastoma without dependent,

NOTE Confidence: 0.79191118478775

00:16:48.460 --> 00:16:50.170 and we developed a computational

NOTE Confidence: 0.79191118478775

00:16:50.170 --> 00:16:52.728 model that you can see in the middle

NOTE Confidence: 0.79191118478775

00:16:52.728 --> 00:16:54.925 of the left hand part of the slide

NOTE Confidence: 0.79191118478775

00:16:54.925 --> 00:16:57.357 that we can with which we can predict

NOTE Confidence: 0.79191118478775

00:16:57.357 --> 00:16:58.525 which mutations are actionable.

NOTE Confidence: 0.79191118478775

00:16:58.525 --> 00:17:00.898 Mr Working on that and an in refining

NOTE Confidence: 0.79191118478775

00:17:00.898 --> 00:17:02.483 that to identify out dependent

NOTE Confidence: 0.79191118478775

00:17:02.483 --> 00:17:04.731 tumors in the clinic and what but

NOTE Confidence: 0.79191118478775

00:17:04.731 --> 00:17:06.266 importantly this quickly let us

NOTE Confidence: 0.79191118478775

00:17:06.266 --> 00:17:07.909 to understand that some variants

NOTE Confidence: 0.79191118478775

00:17:07.909 --> 00:17:09.624 are resistant to 1st generation

NOTE Confidence: 0.79191118478775

00:17:09.624 --> 00:17:11.390 out computers result and it does

NOTE Confidence: 0.79191118478775

00:17:11.390 --> 00:17:12.410 not work in Europe.

NOTE Confidence: 0.773119211196899

00:17:12.410 --> 00:17:14.482 Last over and we also learned that the

NOTE Confidence: 0.773119211196899

00:17:14.482 --> 00:17:16.788 stable of 1st generation are contributors.

NOTE Confidence: 0.773119211196899

00:17:16.790 --> 00:17:18.315 We're not that different from

NOTE Confidence: 0.773119211196899

00:17:18.315 --> 00:17:19.840 one another and and impedes.

NOTE Confidence: 0.773119211196899

00:17:19.840 --> 00:17:21.370 In particular, we have one.

NOTE Confidence: 0.773119211196899

00:17:21.370 --> 00:17:23.421 We have to be careful to which

NOTE Confidence: 0.773119211196899

00:17:23.421 --> 00:17:25.329 drug you choose for the trials,

NOTE Confidence: 0.773119211196899

00:17:25.330 --> 00:17:26.550 because there's a limited

NOTE Confidence: 0.773119211196899

00:17:26.550 --> 00:17:28.075 number of patients in pediatric,

NOTE Confidence: 0.773119211196899

00:17:28.080 --> 00:17:29.823 so more monster pick the right one

NOTE Confidence: 0.773119211196899

00:17:29.823 --> 00:17:31.740 and over all those considerations,

NOTE Confidence: 0.773119211196899

00:17:31.740 --> 00:17:32.655 using their biochemistry

NOTE Confidence: 0.773119211196899

00:17:32.655 --> 00:17:34.180 channel distal mat in it,

NOTE Confidence: 0.773119211196899

00:17:34.180 --> 00:17:35.396 which is now looking

NOTE Confidence: 0.773119211196899

00:17:35.396 --> 00:17:36.308 promising in neuroblastoma,

NOTE Confidence: 0.773119211196899

00:17:36.310 --> 00:17:37.840 overcomes much of the resistance,

NOTE Confidence: 0.773119211196899

00:17:37.840 --> 00:17:39.996 although of course we are now experiencing

NOTE Confidence: 0.773119211196899

00:17:39.996 --> 00:17:41.500 resistance that we're working on,

NOTE Confidence: 0.773119211196899

00:17:41.500 --> 00:17:43.318 and I just want to illustrate that as a

NOTE Confidence: 0.773119211196899

00:17:43.318 --> 00:17:45.262 key approach combining biochemistry and

NOTE Confidence: 0.773119211196899

00:17:45.262 --> 00:17:47.377 structural biology and computational aspects.

NOTE Confidence: 0.773119211196899

00:17:47.380 --> 00:17:49.424 But we could use in principle for

NOTE Confidence: 0.773119211196899

00:17:49.424 --> 00:17:50.979 any receptor types in Chinese.

NOTE Confidence: 0.773119211196899

00:17:50.980 --> 00:17:54.068 So next slide please.

NOTE Confidence: 0.773119211196899

00:17:54.070 --> 00:17:56.219 We also very interested in a new

NOTE Confidence: 0.773119211196899

00:17:56.219 --> 00:17:58.162 aspect of getting away from inhibiting

NOTE Confidence: 0.773119211196899

00:17:58.162 --> 00:18:00.931 receptors per say as we tend to do

NOTE Confidence: 0.773119211196899

00:18:00.931 --> 00:18:02.799 instead correcting their signaling.

NOTE Confidence: 0.773119211196899

00:18:02.800 --> 00:18:04.672 So we're all familiar with biased

NOTE Confidence: 0.773119211196899

00:18:04.672 --> 00:18:06.979 agonists for G protein coupled receptors,

NOTE Confidence: 0.773119211196899

00:18:06.980 --> 00:18:09.140 which can promote different responses to

NOTE Confidence: 0.773119211196899

00:18:09.140 --> 00:18:11.867 the same receptors as strength on the left.

NOTE Confidence: 0.773119211196899

00:18:11.870 --> 00:18:13.262 The color of signaling,

NOTE Confidence: 0.773119211196899

00:18:13.262 --> 00:18:14.306 whether it's orange,

NOTE Confidence: 0.773119211196899

00:18:14.310 --> 00:18:15.706 yellow, green or blue.

NOTE Confidence: 0.773119211196899

00:18:15.706 --> 00:18:17.800 Many common drugs that we take,

NOTE Confidence: 0.773119211196899

00:18:17.800 --> 00:18:19.550 her bias GPS are agonists,

NOTE Confidence: 0.773119211196899

00:18:19.550 --> 00:18:21.986 and there's actually a lot of effort,

NOTE Confidence: 0.773119211196899

00:18:21.990 --> 00:18:24.321 for example to develop biased agonists of

NOTE Confidence: 0.773119211196899

00:18:24.321 --> 00:18:26.259 opiate receptors retaining analgesic effects.

NOTE Confidence: 0.773119211196899

00:18:26.260 --> 00:18:27.600 But without the associated

NOTE Confidence: 0.773119211196899

00:18:27.600 --> 00:18:29.275 problem problems of the opiates,

NOTE Confidence: 0.773119211196899

00:18:29.280 --> 00:18:31.296 we don't do that for receptor

NOTE Confidence: 0.773119211196899

00:18:31.296 --> 00:18:31.968 tyrosine kinases.

NOTE Confidence: 0.773119211196899

00:18:31.970 --> 00:18:33.794 In the light there traditionally thought

NOTE Confidence: 0.773119211196899

00:18:33.794 --> 00:18:36.000 of as being binary signaling systems,

NOTE Confidence: 0.773119211196899

00:18:36.000 --> 00:18:38.688 either on or off as an illustrated here,

NOTE Confidence: 0.773119211196899

00:18:38.690 --> 00:18:40.610 but we recently showed in the

NOTE Confidence: 0.773119211196899

00:18:40.610 --> 00:18:43.011 paper a couple of years ago would

NOTE Confidence: 0.773119211196899

00:18:43.011 --> 00:18:44.756 continue to work on that.

NOTE Confidence: 0.773119211196899

00:18:44.760 --> 00:18:46.902 Prices have color in their signaling

NOTE Confidence: 0.773119211196899

00:18:46.902 --> 00:18:49.179 two and as illustrated on the right,

NOTE Confidence: 0.773119211196899

00:18:49.180 --> 00:18:50.880 the same receptor EGF receptor.

NOTE Confidence: 0.773119211196899

00:18:50.880 --> 00:18:52.854 Again in this case can give you

NOTE Confidence: 0.773119211196899

00:18:52.854 --> 00:18:54.570 can promote self liberation or

NOTE Confidence: 0.773119211196899

00:18:54.570 --> 00:18:56.190 differentiation depending in the

NOTE Confidence: 0.773119211196899

00:18:56.190 --> 00:18:58.503 same cell depending on which growth

NOTE Confidence: 0.773119211196899

00:18:58.503 --> 00:19:00.393 factor is used to activate it,

NOTE Confidence: 0.773119211196899

00:19:00.400 --> 00:19:02.100 and this reflects you know

NOTE Confidence: 0.773119211196899

00:19:02.100 --> 00:19:03.460 a different dimer structure,

NOTE Confidence: 0.773119211196899

00:19:03.460 --> 00:19:04.426 asymmetric or symmetric,

NOTE Confidence: 0.773119211196899

00:19:04.426 --> 00:19:06.358 for the two ligands with altered

NOTE Confidence: 0.773119211196899

00:19:06.358 --> 00:19:07.455 dimerization and signaling

NOTE Confidence: 0.773119211196899

00:19:07.455 --> 00:19:08.899 kinetics that define specificity,

NOTE Confidence: 0.773119211196899

00:19:08.900 --> 00:19:11.315 it turns out the mutations in glioblastoma

NOTE Confidence: 0.773119211196899

00:19:11.315 --> 00:19:12.979 shift signaling to the right,

NOTE Confidence: 0.773119211196899

00:19:12.980 --> 00:19:14.352 making it more proliferative.

NOTE Confidence: 0.773119211196899

00:19:14.352 --> 00:19:15.724 That's one of their.

NOTE Confidence: 0.773119211196899

00:19:15.730 --> 00:19:16.654 At key issues,

NOTE Confidence: 0.773119211196899

00:19:16.654 --> 00:19:18.194 even with small structural changes,

NOTE Confidence: 0.773119211196899

00:19:18.200 --> 00:19:19.580 now that we understand the

NOTE Confidence: 0.773119211196899

00:19:19.580 --> 00:19:21.379 structural basis for this but through

NOTE Confidence: 0.773119211196899

00:19:21.379 --> 00:19:22.839 crystallography and so forth,

NOTE Confidence: 0.773119211196899

00:19:22.840 --> 00:19:24.712 we believe that it's possible to

NOTE Confidence: 0.773119211196899

00:19:24.712 --> 00:19:26.848 develop biologics that will do the opposite.

NOTE Confidence: 0.773119211196899

00:19:26.850 --> 00:19:27.159 Imagine,

NOTE Confidence: 0.773119211196899

00:19:27.159 --> 00:19:27.777 for example,

NOTE Confidence: 0.773119211196899

00:19:27.777 --> 00:19:29.631 an antibody that could shift EGF

NOTE Confidence: 0.773119211196899

00:19:29.631 --> 00:19:31.130 activated in cancer we mutation

NOTE Confidence: 0.773119211196899

00:19:31.130 --> 00:19:32.840 allele with living shift signaling to

NOTE Confidence: 0.773119211196899

00:19:32.889 --> 00:19:34.579 the left making it differentiative.

NOTE Confidence: 0.773119211196899

00:19:34.580 --> 00:19:36.428 This could be a really powerful

NOTE Confidence: 0.773119211196899

00:19:36.428 --> 00:19:37.352 approach to signaling,

NOTE Confidence: 0.773119211196899

00:19:37.360 --> 00:19:38.592 switching or correcting signaling

NOTE Confidence: 0.773119211196899

00:19:38.592 --> 00:19:39.208 from preparations.

NOTE Confidence: 0.773119211196899

00:19:39.210 --> 00:19:40.895 Differentiation is actually 1 proof

NOTE Confidence: 0.773119211196899

00:19:40.895 --> 00:19:43.192 of principle in that with kit and

NOTE Confidence: 0.773119211196899

00:19:43.192 --> 00:19:44.848 stem cell factor that causes that

NOTE Confidence: 0.773119211196899

00:19:44.848 --> 00:19:46.069 was been working on.

NOTE Confidence: 0.773119211196899

00:19:46.070 --> 00:19:50.126 At Stanford, so next slide please.

NOTE Confidence: 0.773119211196899

00:19:50.130 --> 00:19:51.297 And so finally.

NOTE Confidence: 0.773119211196899

00:19:51.297 --> 00:19:53.631 We've also been focusing on an

NOTE Confidence: 0.773119211196899

00:19:53.631 --> 00:19:55.837 undruggable target the pseudo kinases.

NOTE Confidence: 0.773119211196899

00:19:55.840 --> 00:19:58.339 About 10% of the kinases in kind

NOTE Confidence: 0.773119211196899

00:19:58.339 --> 00:20:00.882 of is inactive and the blue ones

NOTE Confidence: 0.773119211196899

00:20:00.882 --> 00:20:02.976 here on the left in history.

NOTE Confidence: 0.746865034103394

00:20:02.980 --> 00:20:05.828 Many of them don't even buy native P,

NOTE Confidence: 0.746865034103394

00:20:05.830 --> 00:20:07.258 and these include regions.

NOTE Confidence: 0.746865034103394

00:20:07.258 --> 00:20:08.329 Interceptors like Roswick,

NOTE Confidence: 0.746865034103394

00:20:08.330 --> 00:20:10.115 PK7 involved in wind signaling

NOTE Confidence: 0.746865034103394

00:20:10.115 --> 00:20:11.900 and involved in several councils,

NOTE Confidence: 0.746865034103394

00:20:11.900 --> 00:20:13.328 but have been totally

NOTE Confidence: 0.746865034103394

00:20:13.328 --> 00:20:14.756 ignored as drug targets.

NOTE Confidence: 0.746865034103394

00:20:14.760 --> 00:20:15.892 For the most part.

NOTE Confidence: 0.746865034103394

00:20:15.892 --> 00:20:17.590 One hypothesis is that they simply

NOTE Confidence: 0.746865034103394

00:20:17.649 --> 00:20:19.854 by switching confirmations to bind

NOTE Confidence: 0.746865034103394

00:20:19.854 --> 00:20:21.177 downstream signaling molecules.

NOTE Confidence: 0.746865034103394

00:20:21.180 --> 00:20:23.010 We recently determined in this.

NOTE Confidence: 0.746865034103394

00:20:23.010 --> 00:20:23.922 Paper in 2022,

NOTE Confidence: 0.746865034103394

00:20:23.922 --> 00:20:25.442 referenced here a bunch of

NOTE Confidence: 0.746865034103394

00:20:25.442 --> 00:20:27.016 structures and script screen for

NOTE Confidence: 0.746865034103394

00:20:27.016 --> 00:20:28.536 small molecule inhibitors to see

NOTE Confidence: 0.746865034103394

00:20:28.536 --> 00:20:30.371 if we could bring in principle

NOTE Confidence: 0.746865034103394

00:20:30.371 --> 00:20:32.433 drug these in the middle here in

NOTE Confidence: 0.746865034103394

00:20:32.433 --> 00:20:34.554 the structure you can see a drug.

NOTE Confidence: 0.746865034103394

00:20:34.560 --> 00:20:35.948 It's actually pronounced enable

NOTE Confidence: 0.746865034103394

00:20:35.948 --> 00:20:38.360 inhibitor bound to one of these pseudo

NOTE Confidence: 0.746865034103394

00:20:38.360 --> 00:20:40.010 kinases that doesn't even bind 80P

NOTE Confidence: 0.746865034103394

00:20:40.010 --> 00:20:42.158 and M as shown in the top right.

NOTE Confidence: 0.746865034103394

00:20:42.160 --> 00:20:43.560 We've demonstrated using hydrogen

NOTE Confidence: 0.746865034103394

00:20:43.560 --> 00:20:45.310 determine change studies that put

NOTE Confidence: 0.746865034103394

00:20:45.310 --> 00:20:46.594 out maybe induces conformational

NOTE Confidence: 0.746865034103394

00:20:46.594 --> 00:20:48.659 changes in role one as it binds

NOTE Confidence: 0.746865034103394

00:20:48.717 --> 00:20:50.765 and so the idea is that this might

NOTE Confidence: 0.746865034103394

00:20:50.765 --> 00:20:51.912 inhibit signaling interactions that

NOTE Confidence: 0.746865034103394

00:20:51.912 --> 00:20:53.492 naturally there's alot enormous amount

NOTE Confidence: 0.746865034103394

00:20:53.492 --> 00:20:55.620 of work to do with selectivity and.

NOTE Confidence: 0.746865034103394

00:20:55.620 --> 00:20:56.544 And so forth.

NOTE Confidence: 0.746865034103394

00:20:56.544 --> 00:20:58.392 But early studies of signaling effect

NOTE Confidence: 0.746865034103394

00:20:58.392 --> 00:21:00.081 suggests that banana can inhibit

NOTE Confidence: 0.746865034103394

00:21:00.081 --> 00:21:01.736 went dependent rule one signaling,

NOTE Confidence: 0.746865034103394

00:21:01.740 --> 00:21:03.462 and so the idea of sharing centrally

NOTE Confidence: 0.746865034103394

00:21:03.462 --> 00:21:04.648 here is that confirmational

NOTE Confidence: 0.746865034103394

00:21:04.648 --> 00:21:06.608 disruptors like this could be

NOTE Confidence: 0.746865034103394

00:21:06.608 --> 00:21:08.176 valuable tools for understanding.

NOTE Confidence: 0.746865034103394

00:21:08.180 --> 00:21:09.158 See Tiffany signaling,

NOTE Confidence: 0.746865034103394

00:21:09.158 --> 00:21:11.440 but also targeting them where they play

NOTE Confidence: 0.746865034103394

00:21:11.494 --> 00:21:13.650 known roles in cancer and other diseases,

NOTE Confidence: 0.746865034103394

00:21:13.650 --> 00:21:15.582 and so far they're all being

NOTE Confidence: 0.746865034103394

00:21:15.582 --> 00:21:16.870 hit the articaine ones.

NOTE Confidence: 0.746865034103394

00:21:16.870 --> 00:21:18.158 For example, with antibodies.

NOTE Confidence: 0.746865034103394

00:21:18.158 --> 00:21:20.090 So that's about my brief summary.

NOTE Confidence: 0.746865034103394

00:21:20.090 --> 00:21:22.016 That's all I wanted to say,

NOTE Confidence: 0.746865034103394

00:21:22.020 --> 00:21:24.274 so thank you very much for attention,

NOTE Confidence: 0.746865034103394

00:21:24.280 --> 00:21:26.244 and I look forward.

NOTE Confidence: 0.746865034103394

00:21:26.244 --> 00:21:27.717 To your questions.

NOTE Confidence: 0.746865034103394

00:21:27.720 --> 00:21:29.310 Thank you very

NOTE Confidence: 0.831698834896088

00:21:29.310 --> 00:21:32.490 much Mark for that wonderful discussion.

NOTE Confidence: 0.831698834896088

00:21:32.490 --> 00:21:35.670 Next, I'll be introducing Meghan King,

NOTE Confidence: 0.831698834896088

00:21:35.670 --> 00:21:37.260 associate professor of

NOTE Confidence: 0.831698834896088

00:21:37.260 --> 00:21:39.380 cell biology and molecular,

NOTE Confidence: 0.831698834896088

00:21:39.380 --> 00:21:41.432 cellular and developmental biology.

NOTE Confidence: 0.831698834896088

00:21:41.432 --> 00:21:44.510 Program leader in our Cancer Center

NOTE Confidence: 0.831698834896088

00:21:44.591 --> 00:21:47.272 and I think notable partly for having

NOTE Confidence: 0.831698834896088

00:21:47.272 --> 00:21:50.091 been elected by the her fellow faculty

NOTE Confidence: 0.831698834896088

00:21:50.091 --> 00:21:52.479 here at Yale School of Medicine.

NOTE Confidence: 0.831698834896088

00:21:52.480 --> 00:21:54.590 As past president of our

NOTE Confidence: 0.831698834896088

00:21:54.590 --> 00:21:55.856 faculty Senate equivalent,

NOTE Confidence: 0.831698834896088

00:21:55.860 --> 00:21:58.392 the Faculty Advisory Council where she

NOTE Confidence: 0.831698834896088

00:21:58.392 --> 00:22:00.080 also showed exceptional leadership.

NOTE Confidence: 0.831698834896088

00:22:00.080 --> 00:22:02.606 Sort of in that other realm,

NOTE Confidence: 0.831698834896088

00:22:02.610 --> 00:22:05.194 and she's going to be talking to us

NOTE Confidence: 0.831698834896088

00:22:05.194 --> 00:22:07.570 about very impactful work regarding

NOTE Confidence: 0.831698834896088

00:22:07.570 --> 00:22:09.778 resistance to PARP inhibition.

NOTE Confidence: 0.872240900993347

00:22:12.210 --> 00:22:13.662 Alright, so thank you.

NOTE Confidence: 0.872240900993347

00:22:13.662 --> 00:22:15.477 I'm also a basic scientist

NOTE Confidence: 0.872240900993347

00:22:15.477 --> 00:22:17.377 an over the past decade.

NOTE Confidence: 0.872240900993347

00:22:17.380 --> 00:22:19.255 It's really been my interactions

NOTE Confidence: 0.872240900993347

00:22:19.255 --> 00:22:21.130 with my colleagues here in

NOTE Confidence: 0.872240900993347

00:22:21.197 --> 00:22:23.141 the Yale Cancer Center that is

NOTE Confidence: 0.872240900993347

00:22:23.141 --> 00:22:24.900 driven my group with expertise

NOTE Confidence: 0.872240900993347

00:22:24.900 --> 00:22:26.870 in genome integrity to really

NOTE Confidence: 0.872240900993347

00:22:26.870 --> 00:22:29.182 focus on those aspects that have

NOTE Confidence: 0.872240900993347

00:22:29.182 --> 00:22:30.660 impacts for cancer therapies.

NOTE Confidence: 0.846176207065582

00:22:33.030 --> 00:22:35.734 So I'm going to start with this classic

NOTE Confidence: 0.846176207065582

00:22:35.734 --> 00:22:37.830 example of synthetic lethality,

NOTE Confidence: 0.846176207065582

00:22:37.830 --> 00:22:40.188 and that are is specifically PARP

NOTE Confidence: 0.846176207065582

00:22:40.188 --> 00:22:42.630 inhibitors in the context of Bracco

NOTE Confidence: 0.846176207065582

00:22:42.630 --> 00:22:44.208 Wanan bracket, two mutations,

NOTE Confidence: 0.846176207065582

00:22:44.208 --> 00:22:46.153 an, although of course these

NOTE Confidence: 0.846176207065582

00:22:46.153 --> 00:22:47.830 therapies have incredible promise.

NOTE Confidence: 0.846176207065582

00:22:47.830 --> 00:22:49.655 It's well established now that

NOTE Confidence: 0.846176207065582

00:22:49.655 --> 00:22:51.978 the acquired resistance is a major

NOTE Confidence: 0.846176207065582

00:22:51.978 --> 00:22:54.113 bottleneck for the durability and

NOTE Confidence: 0.846176207065582

00:22:54.113 --> 00:22:56.472 efficacy of these treatments, and so,

NOTE Confidence: 0.846176207065582

00:22:56.472 --> 00:22:59.040 how do we tackle this problem and other

NOTE Confidence: 0.846176207065582

00:22:59.115 --> 00:23:01.610 opportunities that are presented when

NOTE Confidence: 0.846176207065582

00:23:01.610 --> 00:23:04.105 these tumor cells become resistant?

NOTE Confidence: 0.846176207065582

00:23:04.110 --> 00:23:06.120 So the approach that we've been

NOTE Confidence: 0.846176207065582

00:23:06.120 --> 00:23:08.598 taking is first to start by really

NOTE Confidence: 0.846176207065582

00:23:08.598 --> 00:23:10.728 trying to define the genetic basis

NOTE Confidence: 0.846176207065582

00:23:10.728 --> 00:23:12.970 of resistance in this context,

NOTE Confidence: 0.846176207065582

00:23:12.970 --> 00:23:15.618 and so we know that there has been

NOTE Confidence: 0.846176207065582

00:23:15.618 --> 00:23:17.758 real value in crisper screens.

NOTE Confidence: 0.846176207065582

00:23:17.760 --> 00:23:19.974 But I think increasingly we're very

NOTE Confidence: 0.846176207065582

00:23:19.974 --> 00:23:21.848 excited about the possibility of

NOTE Confidence: 0.846176207065582

00:23:21.848 --> 00:23:23.548 circulating tumor DNA sequencing as

NOTE Confidence: 0.846176207065582

00:23:23.548 --> 00:23:25.879 well as potential for serial biopsies,

NOTE Confidence: 0.846176207065582

00:23:25.880 --> 00:23:27.432 particularly along this axis.

NOTE Confidence: 0.846176207065582

00:23:27.432 --> 00:23:29.760 As tumors gain resistance to combine

NOTE Confidence: 0.846176207065582

00:23:29.823 --> 00:23:31.977 with genome sequencing as well as

NOTE Confidence: 0.846176207065582

00:23:31.977 --> 00:23:33.913 gene expression analysis to provide

NOTE Confidence: 0.846176207065582

00:23:33.913 --> 00:23:36.118 new insights into therapy resistance.

NOTE Confidence: 0.846176207065582

00:23:36.120 --> 00:23:38.325 And we use a range of models,

NOTE Confidence: 0.846176207065582

00:23:38.330 --> 00:23:40.118 although from model organisms to mouse

NOTE Confidence: 0.846176207065582

00:23:40.118 --> 00:23:42.120 models to really get the mechanisms,

NOTE Confidence: 0.846176207065582

00:23:42.120 --> 00:23:43.860 and of course the ultimate goal

NOTE Confidence: 0.846176207065582

00:23:43.860 --> 00:23:46.102 is always to really be able to

NOTE Confidence: 0.846176207065582

00:23:46.102 --> 00:23:47.807 leverage the mechanism of resistance,

NOTE Confidence: 0.846176207065582

00:23:47.810 --> 00:23:49.706 ideally to come up with new

NOTE Confidence: 0.846176207065582

00:23:49.706 --> 00:23:50.970 therapies and so awhile.

NOTE Confidence: 0.846176207065582

00:23:50.970 --> 00:23:53.056 Of course we'd like these to be

NOTE Confidence: 0.846176207065582

00:23:53.056 --> 00:23:54.347 actionable were really particularly

NOTE Confidence: 0.846176207065582

00:23:54.347 --> 00:23:56.339 would like to go beyond that,

NOTE Confidence: 0.846176207065582

00:23:56.340 --> 00:23:58.405 and to be sure to consider based

NOTE Confidence: 0.846176207065582

00:23:58.405 --> 00:23:59.820 on our mechanistic studies,

NOTE Confidence: 0.846176207065582

00:23:59.820 --> 00:24:01.584 what can we bring to the table

NOTE Confidence: 0.846176207065582

00:24:01.584 --> 00:24:03.300 in terms of stratification?

NOTE Confidence: 0.846176207065582

00:24:03.300 --> 00:24:05.274 And today I'll talk about an example

NOTE Confidence: 0.846176207065582

00:24:05.274 --> 00:24:07.477 where we really think that we have

NOTE Confidence: 0.846176207065582

00:24:07.477 --> 00:24:09.102 to consider Bracco one patient

NOTE Confidence: 0.846176207065582

00:24:09.102 --> 00:24:10.897 separately from bracket two patients.

NOTE Confidence: 0.846176207065582

00:24:10.900 --> 00:24:12.720 Of course it would be best really

NOTE Confidence: 0.846176207065582

00:24:12.720 --> 00:24:14.768 if we can develop new biomarkers

NOTE Confidence: 0.846176207065582

00:24:14.768 --> 00:24:17.168 that will further help us stratify

NOTE Confidence: 0.846176207065582

00:24:17.168 --> 00:24:19.487 patients based on the mechanisms

NOTE Confidence: 0.846176207065582

00:24:19.487 --> 00:24:20.415 underlying resistance,

NOTE Confidence: 0.846176207065582

00:24:20.420 --> 00:24:22.616 and I think one real potential

NOTE Confidence: 0.846176207065582

00:24:22.616 --> 00:24:24.080 there is for example,

NOTE Confidence: 0.846176207065582

00:24:24.080 --> 00:24:25.915 circulating tumor DNA may allow

NOTE Confidence: 0.846176207065582

00:24:25.915 --> 00:24:28.166 us to identify patients who have

NOTE Confidence: 0.846176207065582

00:24:28.166 --> 00:24:29.926 a so called reversion allele.

NOTE Confidence: 0.846176207065582

00:24:29.930 --> 00:24:31.835 That'll now will make them

NOTE Confidence: 0.846176207065582

00:24:31.835 --> 00:24:33.359 insensitive Department of Therapy

NOTE Confidence: 0.846176207065582

00:24:33.359 --> 00:24:35.059 and that baby one cohort,

NOTE Confidence: 0.846176207065582

00:24:35.060 --> 00:24:37.112 but there may be other patients

NOTE Confidence: 0.846176207065582

00:24:37.112 --> 00:24:38.944 where resistance is arising through

NOTE Confidence: 0.846176207065582

00:24:38.944 --> 00:24:40.929 a secondary mechanism that maybe.

NOTE Confidence: 0.846176207065582

00:24:40.930 --> 00:24:42.314 Therapeutically actionable and so

NOTE Confidence: 0.846176207065582

00:24:42.314 --> 00:24:44.778 I just wanted to take you through

NOTE Confidence: 0.846176207065582

00:24:44.778 --> 00:24:46.740 the work that we've been doing,

NOTE Confidence: 0.846176207065582

00:24:46.740 --> 00:24:48.450 just not just my lab,

NOTE Confidence: 0.846176207065582

00:24:48.450 --> 00:24:50.641 but across our team to look at

NOTE Confidence: 0.846176207065582

00:24:50.641 --> 00:24:52.559 the genetic basis of resistance.

NOTE Confidence: 0.846176207065582

00:24:52.560 --> 00:24:53.928 So much of again,

NOTE Confidence: 0.846176207065582

00:24:53.928 --> 00:24:55.980 these crisper screens have been published.

NOTE Confidence: 0.846176207065582

00:24:55.980 --> 00:24:58.122 The work that's been going on here

NOTE Confidence: 0.846176207065582

00:24:58.122 --> 00:25:00.178 at Yale really has taken advantage

NOTE Confidence: 0.846176207065582

00:25:00.178 --> 00:25:02.670 of a partnership that we already have

NOTE Confidence: 0.846176207065582

00:25:02.741 --> 00:25:04.865 between Astra Zeneca and our team,

NOTE Confidence: 0.846176207065582

00:25:04.870 --> 00:25:05.914 particularly Ryan Jensen,

NOTE Confidence: 0.846176207065582

00:25:05.914 --> 00:25:08.002 and Ryan has been modeling reversion

NOTE Confidence: 0.846176207065582

00:25:08.002 --> 00:25:09.719 alleles that are arising from

NOTE Confidence: 0.846176207065582

00:25:09.719 --> 00:25:11.035 patient derived DNA sequencing.

NOTE Confidence: 0.846176207065582

00:25:11.040 --> 00:25:12.075 And testing really,

NOTE Confidence: 0.846176207065582

00:25:12.075 --> 00:25:14.490 is there still an actionable approach that

NOTE Confidence: 0.846176207065582

00:25:14.552 --> 00:25:16.664 we could use in these contexts or not?

NOTE Confidence: 0.846176207065582

00:25:16.670 --> 00:25:17.873 By functionally characterizing

NOTE Confidence: 0.846176207065582

00:25:17.873 --> 00:25:19.076 the reversion alleles?

NOTE Confidence: 0.846176207065582

00:25:19.080 --> 00:25:20.550 What I'm particularly excited about

NOTE Confidence: 0.846176207065582

00:25:20.550 --> 00:25:22.853 at the moment is that paleru so has

NOTE Confidence: 0.846176207065582

00:25:22.853 --> 00:25:25.130 been leading a trial along with Kurt Shopper,

NOTE Confidence: 0.846176207065582

00:25:25.130 --> 00:25:27.026 who you'll hear from in a moment where

NOTE Confidence: 0.846176207065582

00:25:27.026 --> 00:25:29.448 she is and acquiring these serial biopsies.

NOTE Confidence: 0.830411314964294

00:25:29.450 --> 00:25:30.890 Along this progression to relapse.

NOTE Confidence: 0.830411314964294

00:25:30.890 --> 00:25:33.239 And this allows us now to go in and

NOTE Confidence: 0.830411314964294

00:25:33.239 --> 00:25:35.495 really look not just a genome changes,

NOTE Confidence: 0.830411314964294

00:25:35.500 --> 00:25:36.708 but gene expression changes.

NOTE Confidence: 0.830411314964294

00:25:36.708 --> 00:25:37.916 And so these sequencing

NOTE Confidence: 0.830411314964294

00:25:37.916 --> 00:25:39.238 is ongoing at the moment,

NOTE Confidence: 0.830411314964294

00:25:39.240 --> 00:25:41.394 and we're really excited about the

NOTE Confidence: 0.830411314964294

00:25:41.394 --> 00:25:43.630 new targets that it may reveal.

NOTE Confidence: 0.830411314964294

00:25:43.630 --> 00:25:45.494 So I just want to give you one

NOTE Confidence: 0.830411314964294

00:25:45.494 --> 00:25:47.423 vignette of what was really originally

NOTE Confidence: 0.830411314964294

00:25:47.423 --> 00:25:49.523 motivated by these in vitro screens,

NOTE Confidence: 0.830411314964294

00:25:49.530 --> 00:25:51.287 and some work that my group has

NOTE Confidence: 0.830411314964294

00:25:51.287 --> 00:25:53.117 done and the possibilities that we

NOTE Confidence: 0.830411314964294

00:25:53.117 --> 00:25:55.139 can see for this going forward.

NOTE Confidence: 0.830411314964294

00:25:55.140 --> 00:25:56.694 So it's well established that Braca

NOTE Confidence: 0.830411314964294

00:25:56.694 --> 00:25:59.333 1 one of its key roles is to promote

NOTE Confidence: 0.830411314964294

00:25:59.333 --> 00:26:01.243 what's called double strand break and

NOTE Confidence: 0.830411314964294

00:26:01.243 --> 00:26:03.097 resection through the EXO 1 pathway.

NOTE Confidence: 0.830411314964294

00:26:03.100 --> 00:26:05.151 And this is a critical step in

NOTE Confidence: 0.830411314964294

00:26:05.151 --> 00:26:07.546 the HR pathway and so it was came

NOTE Confidence: 0.830411314964294

00:26:07.546 --> 00:26:08.702 out of these screens.

NOTE Confidence: 0.830411314964294

00:26:08.710 --> 00:26:11.280 That loss of either 50 BP one or Rev

NOTE Confidence: 0.830411314964294

00:26:11.280 --> 00:26:13.052 7 can drive therapy resistance in

NOTE Confidence: 0.830411314964294

00:26:13.052 --> 00:26:14.978 the context of Graco one mutations.

NOTE Confidence: 0.830411314964294

00:26:14.980 --> 00:26:16.990 Well, my group discovered is that

NOTE Confidence: 0.830411314964294

00:26:16.990 --> 00:26:18.913 these are negative regulators of the

NOTE Confidence: 0.830411314964294

00:26:18.913 --> 00:26:20.503 bloom helicase acting with DNA 2,

NOTE Confidence: 0.830411314964294

00:26:20.510 --> 00:26:22.045 which is an alternative and

NOTE Confidence: 0.830411314964294

00:26:22.045 --> 00:26:22.659 resection mechanism.

NOTE Confidence: 0.830411314964294

00:26:22.660 --> 00:26:24.652 So this is a way where these tumor

NOTE Confidence: 0.830411314964294

00:26:24.652 --> 00:26:26.376 cells have essentially rewired reception

NOTE Confidence: 0.830411314964294

00:26:26.376 --> 00:26:28.704 so they're no longer dependent on

NOTE Confidence: 0.830411314964294

00:26:28.704 --> 00:26:30.777 bracca one and instead can use this

NOTE Confidence: 0.830411314964294

00:26:30.777 --> 00:26:32.432 bloom pathway and so as examples

NOTE Confidence: 0.830411314964294

00:26:32.432 --> 00:26:34.118 of what that mechanism has brought

NOTE Confidence: 0.830411314964294

00:26:34.118 --> 00:26:36.379 about in terms of the way we're

NOTE Confidence: 0.830411314964294

00:26:36.379 --> 00:26:37.695 thinking about future therapeutics,

NOTE Confidence: 0.830411314964294

00:26:37.700 --> 00:26:39.230 the first is that identifies

NOTE Confidence: 0.830411314964294

00:26:39.230 --> 00:26:40.148 the bloom helicases,

NOTE Confidence: 0.830411314964294

00:26:40.150 --> 00:26:42.376 a really novel target that we have

NOTE Confidence: 0.830411314964294

00:26:42.376 --> 00:26:44.713 already shown in vitro is also synthetic

NOTE Confidence: 0.830411314964294

00:26:44.713 --> 00:26:47.010 lethal with Bracco one on its own.

NOTE Confidence: 0.830411314964294

00:26:47.010 --> 00:26:49.786 Particularly if we think in the short term,

NOTE Confidence: 0.830411314964294

00:26:49.790 --> 00:26:51.178 maybe more actionable input

NOTE Confidence: 0.830411314964294

00:26:51.178 --> 00:26:53.260 ways in which this has changed.

NOTE Confidence: 0.830411314964294

00:26:53.260 --> 00:26:55.126 Our thinking is that it highlights

NOTE Confidence: 0.830411314964294

00:26:55.126 --> 00:26:56.819 also the potential for combinations

NOTE Confidence: 0.830411314964294

00:26:56.819 --> 00:26:59.159 of PARP inhibitors in ATR inhibitors,

NOTE Confidence: 0.830411314964294

00:26:59.160 --> 00:27:01.491 and that's because the other thing we

NOTE Confidence: 0.830411314964294

00:27:01.491 --> 00:27:03.637 discovered is that this blue mediated

NOTE Confidence: 0.830411314964294

00:27:03.637 --> 00:27:05.809 helicase is driving resection at very

NOTE Confidence: 0.830411314964294

00:27:05.809 --> 00:27:08.237 high rates and this leads not just

NOTE Confidence: 0.830411314964294

00:27:08.237 --> 00:27:10.262 to functional reception to do repair.

NOTE Confidence: 0.830411314964294

00:27:10.262 --> 00:27:12.338 It actually leads to hyper resection,

NOTE Confidence: 0.830411314964294

00:27:12.340 --> 00:27:14.416 and ATR is an important negative

NOTE Confidence: 0.830411314964294

00:27:14.416 --> 00:27:15.454 regulator of resection,

NOTE Confidence: 0.830411314964294

00:27:15.460 --> 00:27:17.938 and so we think that this combination

NOTE Confidence: 0.830411314964294

00:27:17.938 --> 00:27:19.699 of treatments will push this.

NOTE Confidence: 0.830411314964294

00:27:19.700 --> 00:27:20.976 Hyper resection even further,

NOTE Confidence: 0.830411314964294

00:27:20.976 --> 00:27:23.998 and this is a really good rationale for why.

NOTE Confidence: 0.830411314964294

00:27:24.000 --> 00:27:25.700 Initially patients with RK one

NOTE Confidence: 0.830411314964294

00:27:25.700 --> 00:27:28.076 mutations may not respond well to a

NOTE Confidence: 0.830411314964294

00:27:28.076 --> 00:27:29.626 combination with an ATR inhibitor,

NOTE Confidence: 0.830411314964294

00:27:29.630 --> 00:27:31.966 but when there is a mechanism that down

NOTE Confidence: 0.830411314964294

00:27:31.966 --> 00:27:33.322 regulates these particular proteins

NOTE Confidence: 0.830411314964294

00:27:33.322 --> 00:27:35.458 that that will make these tumors

NOTE Confidence: 0.830411314964294

00:27:35.458 --> 00:27:37.240 very sensitive to the combination,

NOTE Confidence: 0.830411314964294

00:27:37.240 --> 00:27:39.472 and so along those lines we're

NOTE Confidence: 0.830411314964294

00:27:39.472 --> 00:27:41.289 currently just submitting anello I

NOTE Confidence: 0.830411314964294

00:27:41.289 --> 00:27:43.151 with paleru so where we are proposing

NOTE Confidence: 0.830411314964294

00:27:43.151 --> 00:27:45.452 to do a trial specifically in Bracco

NOTE Confidence: 0.830411314964294

00:27:45.452 --> 00:27:47.832 in patients because this is not a

NOTE Confidence: 0.830411314964294

00:27:47.832 --> 00:27:49.818 mechanism that's relevant for the bracket,

NOTE Confidence: 0.830411314964294

00:27:49.820 --> 00:27:50.450 two patients.

NOTE Confidence: 0.830411314964294

00:27:50.450 --> 00:27:52.655 Hoping to really test this idea clinically,

NOTE Confidence: 0.830411314964294

00:27:52.660 --> 00:27:54.536 so thank you and I look forward

NOTE Confidence: 0.830411314964294

00:27:54.536 --> 00:27:55.340 to the questions.

NOTE Confidence: 0.830411314964294

00:27:55.340 --> 00:27:56.978 I also just like to highlight that

NOTE Confidence: 0.830411314964294

00:27:56.978 --> 00:27:58.863 much of this work as I mentioned

NOTE Confidence: 0.830411314964294

00:27:58.863 --> 00:28:00.278 was a collaboration with Astra

NOTE Confidence: 0.830411314964294

00:28:00.278 --> 00:28:02.000 Zeneca and is also supported very

NOTE Confidence: 0.830411314964294

00:28:02.000 --> 00:28:03.380 generously by the Great Foundation.

NOTE Confidence: 0.789911925792694

00:28:06.740 --> 00:28:10.016 Thank you Megan. That was terrific.

NOTE Confidence: 0.789911925792694

00:28:10.020 --> 00:28:14.470 Next, I'd like to introduce.

NOTE Confidence: 0.789911925792694

00:28:14.470 --> 00:28:16.990 Jinyoung he's an associate professor

NOTE Confidence: 0.789911925792694

00:28:16.990 --> 00:28:19.510 of pathology and director of

NOTE Confidence: 0.789911925792694

00:28:19.590 --> 00:28:21.760 our Epigenetics program here at

NOTE Confidence: 0.789911925792694

00:28:21.760 --> 00:28:24.663 Yale and will be talking about

NOTE Confidence: 0.789911925792694

00:28:24.663 --> 00:28:27.267 epigenetic mechanisms of resistance.

NOTE Confidence: 0.693806850910187

00:28:28.420 --> 00:28:32.552 Thank you, Barbara. On So, uh,

NOTE Confidence: 0.693806850910187

00:28:32.552 --> 00:28:35.768 my expertise in the menu on cancer genetics,

NOTE Confidence: 0.693806850910187

00:28:35.770 --> 00:28:38.094 and as you all know I project

NOTE Confidence: 0.693806850910187

00:28:38.094 --> 00:28:40.218 magnet is critical for cancer

NOTE Confidence: 0.693806850910187

00:28:40.218 --> 00:28:41.796 initiation and progression.

NOTE Confidence: 0.693806850910187

00:28:41.800 --> 00:28:44.212 Especially my laptop is interested in

NOTE Confidence: 0.693806850910187

00:28:44.212 --> 00:28:45.820 understanding how epigenetic regulators,

NOTE Confidence: 0.693806850910187

00:28:45.820 --> 00:28:48.284 also called reader writer and erasers of

NOTE Confidence: 0.693806850910187

00:28:48.284 --> 00:28:50.640 being an maceration histone modification.

NOTE Confidence: 0.693806850910187

00:28:50.640 --> 00:28:52.248 How regulate different steps

NOTE Confidence: 0.693806850910187

00:28:52.248 --> 00:28:53.454 of cancer progression?

NOTE Confidence: 0.693806850910187

00:28:53.460 --> 00:28:55.470 My number to your interest

NOTE Confidence: 0.693806850910187

00:28:55.470 --> 00:28:57.480 in a couple different areas?

NOTE Confidence: 0.693806850910187

00:28:57.480 --> 00:28:59.084 One is resistant mechanism

NOTE Confidence: 0.693806850910187

00:28:59.084 --> 00:29:00.688 to anti cancer drugs,

NOTE Confidence: 0.693806850910187

00:29:00.690 --> 00:29:03.180 which is the main topic today.

NOTE Confidence: 0.693806850910187

00:29:03.180 --> 00:29:05.370 Cancer metastasis and tumor in valuation,

NOTE Confidence: 0.693806850910187

00:29:05.370 --> 00:29:07.953 which is one of the areas that

NOTE Confidence: 0.693806850910187

00:29:07.953 --> 00:29:10.378 I could show but will talk

NOTE Confidence: 0.693806850910187

00:29:10.378 --> 00:29:12.838 more about later on and next.

NOTE Confidence: 0.693806850910187

00:29:12.840 --> 00:29:14.976 My #2 is also very interesting,

NOTE Confidence: 0.693806850910187

00:29:14.980 --> 00:29:16.364 developing different epigenetic drugs

NOTE Confidence: 0.693806850910187

00:29:16.364 --> 00:29:19.222 and and we have done some work with

NOTE Confidence: 0.693806850910187

00:29:19.222 --> 00:29:21.027 your Center for molecular discovery,

NOTE Confidence: 0.693806850910187

00:29:21.030 --> 00:29:22.997 which is our in house training center

NOTE Confidence: 0.693806850910187

00:29:22.997 --> 00:29:25.429 and I have done some work with

NOTE Confidence: 0.693806850910187

00:29:25.429 --> 00:29:26.953 the NCI Experimental therapeutics

NOTE Confidence: 0.693806850910187

00:29:26.953 --> 00:29:29.350 program and right now I'm also

NOTE Confidence: 0.693806850910187

00:29:29.350 --> 00:29:31.315 collaborating some about tech and

NOTE Confidence: 0.693806850910187

00:29:31.315 --> 00:29:32.745 pharmaceutical company in this

NOTE Confidence: 0.693806850910187

00:29:32.745 --> 00:29:35.933 area as well and and in the next 2

NOTE Confidence: 0.693806850910187

00:29:35.933 --> 00:29:38.348 slides I'm going to tell you some

NOTE Confidence: 0.693806850910187

00:29:38.348 --> 00:29:40.942 of the examples that we have done

NOTE Confidence: 0.693806850910187

00:29:40.942 --> 00:29:43.930 to look at the resistant mechanisms.

NOTE Confidence: 0.693806850910187

00:29:43.930 --> 00:29:45.470 Next please.

NOTE Confidence: 0.693806850910187

00:29:45.470 --> 00:29:47.180 One which is targeted therapy,

NOTE Confidence: 0.693806850910187

00:29:47.180 --> 00:29:49.546 and in this case the transaction number

NOTE Confidence: 0.693806850910187

00:29:49.546 --> 00:29:51.630 one called Herceptin for breast cancer,

NOTE Confidence: 0.693806850910187

00:29:51.630 --> 00:29:53.682 and we can generate those resistant

NOTE Confidence: 0.693806850910187

00:29:53.682 --> 00:29:55.050 cells in tissue culture.

NOTE Confidence: 0.693806850910187

00:29:55.050 --> 00:29:57.262 And we found that those resistant cells

NOTE Confidence: 0.693806850910187

00:29:57.262 --> 00:29:59.827 actually are do not have genetic mutations.

NOTE Confidence: 0.693806850910187

00:29:59.830 --> 00:30:01.362 They actually resistant mechanism

NOTE Confidence: 0.693806850910187

00:30:01.362 --> 00:30:03.660 is actually reversible if you take

NOTE Confidence: 0.693806850910187

00:30:03.717 --> 00:30:05.684 the drug away from the cells for

NOTE Confidence: 0.693806850910187

00:30:05.684 --> 00:30:07.657 short period time and they are

NOTE Confidence: 0.693806850910187

00:30:07.657 --> 00:30:08.725 still maintain resistant.

NOTE Confidence: 0.693806850910187

00:30:08.730 --> 00:30:11.026 But if you take it away for

NOTE Confidence: 0.693806850910187

00:30:11.026 --> 00:30:12.490 a long period time,

NOTE Confidence: 0.693806850910187

00:30:12.490 --> 00:30:14.536 for example about months and those

NOTE Confidence: 0.693806850910187

00:30:14.536 --> 00:30:16.979 cells becomes those so called watch out.

NOTE Confidence: 0.693806850910187

00:30:16.980 --> 00:30:20.800 And those cells become sensitive

NOTE Confidence: 0.693806850910187

00:30:20.800 --> 00:30:23.856 to just over again.

NOTE Confidence: 0.693806850910187

00:30:23.860 --> 00:30:26.980 To local internal mechanism next piece.

NOTE Confidence: 0.693806850910187

00:30:26.980 --> 00:30:29.458 We profile the expression of the

NOTE Confidence: 0.693806850910187

00:30:29.458 --> 00:30:31.642 expression profile of the reason

NOTE Confidence: 0.693806850910187

00:30:31.642 --> 00:30:34.390 cells compared to the sensitive cells.

NOTE Confidence: 0.693806850910187

00:30:34.390 --> 00:30:37.253 We can see that those resistant cells

NOTE Confidence: 0.693806850910187

00:30:37.253 --> 00:30:39.007 have increased oxidative phosphorylation

NOTE Confidence: 0.693806850910187

00:30:39.007 --> 00:30:42.234 or called off force and remarkable need.

NOTE Confidence: 0.693806850910187

00:30:42.240 --> 00:30:44.415 Those cells are very sensitive

NOTE Confidence: 0.693806850910187

00:30:44.415 --> 00:30:46.155 to ox force inhibitor.

NOTE Confidence: 0.693806850910187

00:30:46.160 --> 00:30:49.016 As you can see the tumor regression if

NOTE Confidence: 0.693806850910187

00:30:49.016 --> 00:30:51.353 you combine traditional Antonio Massenet

NOTE Confidence: 0.693806850910187

00:30:51.353 --> 00:30:54.449 which is 1 nautical force inhibitor.

NOTE Confidence: 0.693806850910187

00:30:54.450 --> 00:30:57.108 You can see regression of those.

NOTE Confidence: 0.693806850910187

00:30:57.110 --> 00:30:59.744 Resistant tumors Next place as I

NOTE Confidence: 0.693806850910187

00:30:59.744 --> 00:31:02.752 mentioned that this app is genetic

NOTE Confidence: 0.693806850910187

00:31:02.752 --> 00:31:05.667 mechanism that contributes to resistance,

NOTE Confidence: 0.693806850910187

00:31:05.670 --> 00:31:07.990 so we are one of the mechanism we

NOTE Confidence: 0.693806850910187

00:31:07.990 --> 00:31:10.498 found is that Arcadian 5 histone

NOTE Confidence: 0.693806850910187

00:31:10.498 --> 00:31:12.813 demethylase are critical for this

NOTE Confidence: 0.693806850910187

00:31:12.813 --> 00:31:14.873 formation of those resistant cells

NOTE Confidence: 0.693806850910187

00:31:14.873 --> 00:31:17.153 we can combine with the target

NOTE Confidence: 0.693806850910187

00:31:17.160 --> 00:31:19.224 therapy and Kaden 5 inhibitor which

NOTE Confidence: 0.693806850910187

00:31:19.224 --> 00:31:21.989 this is one of the early generation

NOTE Confidence: 0.693806850910187

00:31:21.989 --> 00:31:24.629 inhibitor and four to prevent the

NOTE Confidence: 0.693806850910187

00:31:24.629 --> 00:31:26.891 formation of the recent sales for

NOTE Confidence: 0.693806850910187

00:31:26.891 --> 00:31:29.042 both breast cancer which is beating

NOTE Confidence: 0.693806850910187

00:31:29.042 --> 00:31:30.610 for some report cells.

NOTE Confidence: 0.693806850910187

00:31:30.610 --> 00:31:34.586 And non cancer cells on PC 9 cells.

NOTE Confidence: 0.693806850910187

00:31:34.590 --> 00:31:36.111 And next race.

NOTE Confidence: 0.693806850910187

00:31:36.111 --> 00:31:39.153 So we are also very interested

NOTE Confidence: 0.693806850910187

00:31:39.153 --> 00:31:41.670 in understanding how.

NOTE Confidence: 0.693806850910187

00:31:41.670 --> 00:31:43.970 Resistant happens to our email

NOTE Confidence: 0.693806850910187

00:31:43.970 --> 00:31:46.270 checkpoint blockade and this is

NOTE Confidence: 0.693806850910187

00:31:46.348 --> 00:31:48.616 our version of the cancer immunity

NOTE Confidence: 0.693806850910187

00:31:48.616 --> 00:31:51.100 cycle and and as you can see,

NOTE Confidence: 0.693806850910187

00:31:51.100 --> 00:31:53.680 there's actually 2 steps are the

NOTE Confidence: 0.693806850910187

00:31:53.680 --> 00:31:55.400 critical for email checkpoint

NOTE Confidence: 0.81779956817627

00:31:55.478 --> 00:31:57.854 to work is the trafficking and

NOTE Confidence: 0.81779956817627

00:31:57.854 --> 00:32:00.286 infiltration of the immune cells to

NOTE Confidence: 0.81779956817627

00:32:00.286 --> 00:32:03.009 the tumor and apparently some of the

NOTE Confidence: 0.81779956817627

00:32:03.009 --> 00:32:05.040 epigenetic modulators have been shown

NOTE Confidence: 0.81779956817627

00:32:05.040 --> 00:32:07.500 to be critical for those processes,

NOTE Confidence: 0.81779956817627

00:32:07.500 --> 00:32:10.251 and then I will just show example

NOTE Confidence: 0.81779956817627

00:32:10.251 --> 00:32:12.440 in our laboratory next please.

NOTE Confidence: 0.81779956817627

00:32:12.440 --> 00:32:14.990 Where we found the Canadian

NOTE Confidence: 0.81779956817627

00:32:14.990 --> 00:32:17.540 Fire B or history history.

NOTE Confidence: 0.81779956817627

00:32:17.540 --> 00:32:21.959 You must nice file B is critical off for.

NOTE Confidence: 0.81779956817627

00:32:21.960 --> 00:32:23.598 Infiltration and trafficking

NOTE Confidence: 0.81779956817627

00:32:23.598 --> 00:32:27.420 of the T cells to the tumors.

NOTE Confidence: 0.81779956817627

00:32:27.420 --> 00:32:29.400 And if not colocating 5B,

NOTE Confidence: 0.81779956817627

00:32:29.400 --> 00:32:32.158 I I in those Yamaha 1.7 cells,

NOTE Confidence: 0.81779956817627

00:32:32.160 --> 00:32:33.740 which is more smaller,

NOTE Confidence: 0.81779956817627

00:32:33.740 --> 00:32:35.320 generated by Markus Persson.

NOTE Confidence: 0.81779956817627

00:32:35.320 --> 00:32:38.664 Book idea we can see that if you

NOTE Confidence: 0.81779956817627

00:32:38.664 --> 00:32:40.894 knockout account info be those

NOTE Confidence: 0.81779956817627

00:32:40.894 --> 00:32:43.510 cells are unable to form tumors.

NOTE Confidence: 0.81779956817627

00:32:43.510 --> 00:32:45.540 And if we re challenge,

NOTE Confidence: 0.81779956817627

00:32:45.540 --> 00:32:48.368 those are two mice with control sales,

NOTE Confidence: 0.81779956817627

00:32:48.370 --> 00:32:50.400 which normally grow very well.

NOTE Confidence: 0.81779956817627

00:32:50.400 --> 00:32:53.046 You can see they cannot grow and

NOTE Confidence: 0.81779956817627

00:32:53.046 --> 00:32:55.781 meaning that those might have gained

NOTE Confidence: 0.81779956817627

00:32:55.781 --> 00:32:58.326 immunity against those younger cells.

NOTE Confidence: 0.81779956817627

00:32:58.330 --> 00:33:01.426 If you look at the the pony IMO Genic

NOTE Confidence: 0.81779956817627

00:33:01.426 --> 00:33:04.650 young one point cells down in the policy,

NOTE Confidence: 0.81779956817627

00:33:04.650 --> 00:33:07.184 you can see those cells are not

NOTE Confidence: 0.81779956817627

00:33:07.184 --> 00:33:09.858 responsive to PD one blockade at all.

NOTE Confidence: 0.81779956817627

00:33:09.860 --> 00:33:12.092 And if we do need killing

NOTE Confidence: 0.81779956817627

00:33:12.092 --> 00:33:13.580 file before those cells,

NOTE Confidence: 0.81779956817627

00:33:13.580 --> 00:33:16.180 you can see the slowdown of the growth

NOTE Confidence: 0.81779956817627

00:33:16.180 --> 00:33:18.857 of cells and if you combine with PD

NOTE Confidence: 0.81779956817627

00:33:18.857 --> 00:33:20.719 one blockade you can significantly

NOTE Confidence: 0.81779956817627

00:33:20.719 --> 00:33:23.629 extend the lifespan of those miles.

NOTE Confidence: 0.81779956817627

00:33:23.630 --> 00:33:25.522 To my very mice.

NOTE Confidence: 0.81779956817627

00:33:25.522 --> 00:33:27.946 So this suggests that can you

NOTE Confidence: 0.81779956817627

00:33:27.946 --> 00:33:30.312 invite me is that very good target

NOTE Confidence: 0.81779956817627

00:33:30.312 --> 00:33:32.909 to overcome resistance to email,

NOTE Confidence: 0.81779956817627

00:33:32.910 --> 00:33:35.535 check one blockade and I would just

NOTE Confidence: 0.81779956817627

00:33:35.535 --> 00:33:38.835 want to mention that this is done in

NOTE Confidence: 0.81779956817627

00:33:38.835 --> 00:33:41.380 collaboration with multiple laps and yell,

NOTE Confidence: 0.81779956817627

00:33:41.380 --> 00:33:42.184 including archical,

NOTE Confidence: 0.81779956817627

00:33:42.184 --> 00:33:44.596 even sucking and much boesenberg snap.

NOTE Confidence: 0.81779956817627

00:33:44.600 --> 00:33:48.227 So team science is one of the same idea.

NOTE Confidence: 0.81779956817627

00:33:48.230 --> 00:33:50.870 We workout together or not.

NOTE Confidence: 0.81779956817627

00:33:50.870 --> 00:33:51.590 Thank you.

NOTE Confidence: 0.769105613231659

00:33:53.980 --> 00:33:57.164 Thank you that is such a terrific story.

NOTE Confidence: 0.769105613231659

00:33:57.170 --> 00:33:59.970 Now I'm pleased to introduce Curt Shopper.

NOTE Confidence: 0.769105613231659

00:33:59.970 --> 00:34:01.562 He's an assistant professor

NOTE Confidence: 0.769105613231659

00:34:01.562 --> 00:34:03.154 of pathology and medicine.

NOTE Confidence: 0.769105613231659

00:34:03.160 --> 00:34:05.040 An recent rooms at the

NOTE Confidence: 0.769105613231659

00:34:05.040 --> 00:34:07.550 end of an NCI Merit Award.

NOTE Confidence: 0.769105613231659

00:34:07.550 --> 00:34:09.660 He conducts really cutting edge

NOTE Confidence: 0.769105613231659

00:34:09.660 --> 00:34:11.348 immuno profiling studies and

NOTE Confidence: 0.769105613231659

00:34:11.348 --> 00:34:13.530 look forward to your talk Kurt.

NOTE Confidence: 0.648846089839935

00:34:14.930 --> 00:34:18.370 Thank you, Barbara. Next slide please.

NOTE Confidence: 0.825054228305817

00:34:18.370 --> 00:34:20.584 So I I trained clinical molecular

NOTE Confidence: 0.825054228305817

00:34:20.584 --> 00:34:22.832 diagnostics that I've been working in

NOTE Confidence: 0.825054228305817

00:34:22.832 --> 00:34:25.317 cancer immunology for about 10 years now,

NOTE Confidence: 0.825054228305817

00:34:25.320 --> 00:34:27.170 and it's unquestionable that immuno

NOTE Confidence: 0.825054228305817

00:34:27.170 --> 00:34:28.650 oncology has really revolutionized

NOTE Confidence: 0.825054228305817

00:34:28.650 --> 00:34:30.080 the treatment of cancer.

NOTE Confidence: 0.825054228305817

00:34:30.080 --> 00:34:31.910 But there are major challenges

NOTE Confidence: 0.825054228305817

00:34:31.910 --> 00:34:33.008 still to overcome,

NOTE Confidence: 0.825054228305817

00:34:33.010 --> 00:34:35.450 so I'll cover a few of the challenges

NOTE Confidence: 0.825054228305817

00:34:35.450 --> 00:34:37.834 that I think are critical to

NOTE Confidence: 0.825054228305817

00:34:37.834 --> 00:34:39.954 potentially move the few forward,

NOTE Confidence: 0.825054228305817

00:34:39.960 --> 00:34:42.112 one of which is that I think there

NOTE Confidence: 0.825054228305817

00:34:42.112 --> 00:34:43.595 have been conceptual limitations

NOTE Confidence: 0.825054228305817

00:34:43.595 --> 00:34:46.235 of in both in drug development

NOTE Confidence: 0.825054228305817

00:34:46.235 --> 00:34:48.039 and identification of biomarkers.

NOTE Confidence: 0.825054228305817

00:34:48.040 --> 00:34:49.340 Relative to drug development,

NOTE Confidence: 0.825054228305817

00:34:49.340 --> 00:34:52.192 I think the focus of many people developing

NOTE Confidence: 0.825054228305817

00:34:52.192 --> 00:34:54.718 targets has been on immuno stimulation,

NOTE Confidence: 0.825054228305817

00:34:54.720 --> 00:34:57.015 but that doesn't necessarily consider

NOTE Confidence: 0.825054228305817

00:34:57.015 --> 00:34:59.310 correcting alterations in the tumor

NOTE Confidence: 0.825054228305817

00:34:59.373 --> 00:35:01.837 and this is critical because if we're

NOTE Confidence: 0.825054228305817

00:35:01.837 --> 00:35:04.113 only stimulating T cells we are and

NOTE Confidence: 0.825054228305817

00:35:04.113 --> 00:35:06.221 there is not a clear gradient towards

NOTE Confidence: 0.825054228305817

00:35:06.221 --> 00:35:08.447 activating it more in the tumor.

NOTE Confidence: 0.825054228305817

00:35:08.450 --> 00:35:10.406 It's likely that the therapeutic index

NOTE Confidence: 0.825054228305817

00:35:10.406 --> 00:35:12.622 is smaller and the potential benefit

NOTE Confidence: 0.825054228305817

00:35:12.622 --> 00:35:14.747 and toxicity balances is affected.

NOTE Confidence: 0.825054228305817

00:35:14.750 --> 00:35:17.693 So I think the concept is that we shouldn't

NOTE Confidence: 0.825054228305817

00:35:17.693 --> 00:35:20.685 focus only on stimulating T cells everywhere.

NOTE Confidence: 0.825054228305817

00:35:20.690 --> 00:35:22.560 We should probably look for.

NOTE Confidence: 0.825054228305817

00:35:22.560 --> 00:35:24.540 Signals that have a gradient favoring

NOTE Confidence: 0.825054228305817

00:35:24.540 --> 00:35:27.073 the tumor in relative to the development

NOTE Confidence: 0.825054228305817

00:35:27.073 --> 00:35:28.609 of biomarkers for resistance.

NOTE Confidence: 0.825054228305817

00:35:28.610 --> 00:35:31.306 I think there have been a little bit

NOTE Confidence: 0.825054228305817

00:35:31.306 --> 00:35:33.670 of confusion in the field because it

NOTE Confidence: 0.825054228305817

00:35:33.670 --> 00:35:36.539 mean a therapy has been used so widely

NOTE Confidence: 0.825054228305817

00:35:36.539 --> 00:35:38.891 that people are calling every patient

NOTE Confidence: 0.825054228305817

00:35:38.891 --> 00:35:41.070 that don't respond as a resistance.

NOTE Confidence: 0.825054228305817

00:35:41.070 --> 00:35:43.182 And conceptually I think that's probably

NOTE Confidence: 0.825054228305817

00:35:43.182 --> 00:35:45.354 not accurate because patients without PD

NOTE Confidence: 0.825054228305817

00:35:45.354 --> 00:35:47.114 L1 expression tumor mutational burden,

NOTE Confidence: 0.825054228305817

00:35:47.120 --> 00:35:49.968 any biology should not respond to start with,

NOTE Confidence: 0.825054228305817

00:35:49.970 --> 00:35:52.850 so I think there is a confusion between.

NOTE Confidence: 0.825054228305817

00:35:52.850 --> 00:35:54.675 Any patient that Blacks benefit

NOTE Confidence: 0.825054228305817

00:35:54.675 --> 00:35:55.770 versus true resistance,

NOTE Confidence: 0.825054228305817

00:35:55.770 --> 00:35:58.115 which in my opinion are the patients

NOTE Confidence: 0.825054228305817

00:35:58.115 --> 00:36:00.519 that should have responded but didn't.

NOTE Confidence: 0.825054228305817

00:36:00.520 --> 00:36:03.019 I think this is critical to design

NOTE Confidence: 0.825054228305817

00:36:03.019 --> 00:36:04.530 programs and biomarker plans.

NOTE Confidence: 0.825054228305817

00:36:04.530 --> 00:36:06.280 The second important concept that

NOTE Confidence: 0.825054228305817

00:36:06.280 --> 00:36:08.030 it's connected with the previous

NOTE Confidence: 0.825054228305817

00:36:08.086 --> 00:36:10.282 one is that it's probably necessary

NOTE Confidence: 0.825054228305817

00:36:10.282 --> 00:36:11.746 to identify dominant immunization

NOTE Confidence: 0.825054228305817

00:36:11.802 --> 00:36:13.657 pathways that are well represented.

NOTE Confidence: 0.825054228305817

00:36:13.660 --> 00:36:16.628 The tumor and this is for the same

NOTE Confidence: 0.825054228305817

00:36:16.628 --> 00:36:18.998 reason because we need to have

NOTE Confidence: 0.825054228305817

00:36:18.998 --> 00:36:20.928 this gradient and strong biology

NOTE Confidence: 0.825054228305817

00:36:20.928 --> 00:36:23.217 in the tumor to be able to.

NOTE Confidence: 0.825054228305817

00:36:23.220 --> 00:36:25.608 Achieve a meaningful anti cancer response

NOTE Confidence: 0.825054228305817

00:36:25.608 --> 00:36:28.324 and then another major need in the

NOTE Confidence: 0.825054228305817

00:36:28.324 --> 00:36:30.448 field is trying to identify potential

NOTE Confidence: 0.825054228305817

00:36:30.448 --> 00:36:32.609 targets that are beyond the T cells.

NOTE Confidence: 0.825054228305817

00:36:32.610 --> 00:36:34.584 So to have complementary effort and

NOTE Confidence: 0.825054228305817

00:36:34.584 --> 00:36:36.580 not have only redundant mechanisms,

NOTE Confidence: 0.825054228305817

00:36:36.580 --> 00:36:38.400 another important observation is that

NOTE Confidence: 0.825054228305817

00:36:38.400 --> 00:36:41.782 we as I follow you know when we look at

NOTE Confidence: 0.825054228305817

00:36:41.782 --> 00:36:44.165 the tumors we realize how difficult and

NOTE Confidence: 0.825054228305817

00:36:44.165 --> 00:36:47.042 how complex is the tumor micro environment.

NOTE Confidence: 0.825054228305817

00:36:47.050 --> 00:36:49.213 Where where is most interactions between

NOTE Confidence: 0.825054228305817

00:36:49.213 --> 00:36:51.379 tumor and immune cells are happening.

NOTE Confidence: 0.825054228305817

00:36:51.380 --> 00:36:53.230 And I think the suffering.

NOTE Confidence: 0.825054228305817

00:36:53.230 --> 00:36:55.687 The tumor micro environment and how different

NOTE Confidence: 0.825054228305817

00:36:55.687 --> 00:36:57.939 is across tumors and across patients.

NOTE Confidence: 0.825054228305817

00:36:57.940 --> 00:37:00.756 It's a major need to really drive better

NOTE Confidence: 0.825054228305817

00:37:00.756 --> 00:37:02.879 biomarkers and better immunotherapy.

NOTE Confidence: 0.825054228305817

00:37:02.880 --> 00:37:05.260 Then also I think we need to do a better

NOTE Confidence: 0.825054228305817

00:37:05.323 --> 00:37:07.673 work at understanding the interactions

NOTE Confidence: 0.825054228305817

00:37:07.673 --> 00:37:09.553 between major dominant oncogenic

NOTE Confidence: 0.825054228305817

00:37:09.553 --> 00:37:11.759 signals and immune evasion pathways.

NOTE Confidence: 0.825054228305817

00:37:11.760 --> 00:37:13.926 This has been somehow being revealed

NOTE Confidence: 0.825054228305817

00:37:13.926 --> 00:37:16.180 in EGFR mutant tumors that are

NOTE Confidence: 0.825054228305817

00:37:16.180 --> 00:37:18.045 less sensitive and less inflamed,

NOTE Confidence: 0.825054228305817

00:37:18.050 --> 00:37:20.640 but they I think there's a whole

NOTE Confidence: 0.825054228305817

00:37:20.640 --> 00:37:21.750 world to discover.

NOTE Confidence: 0.826502799987793

00:37:21.750 --> 00:37:23.600 What alterations in the tumor,

NOTE Confidence: 0.826502799987793

00:37:23.600 --> 00:37:25.820 somatic alterations are able to manipulate.

NOTE Confidence: 0.826502799987793

00:37:25.820 --> 00:37:28.400 It means an immune response.

NOTE Confidence: 0.826502799987793

00:37:28.400 --> 00:37:29.459 And then finally,

NOTE Confidence: 0.826502799987793

00:37:29.459 --> 00:37:31.930 I think there are limitations of traditional

NOTE Confidence: 0.826502799987793

00:37:31.987 --> 00:37:33.975 studies as we just solve from Jane.

NOTE Confidence: 0.826502799987793

00:37:33.980 --> 00:37:36.269 Many alterations are not the genomic level.

NOTE Confidence: 0.826502799987793

00:37:36.270 --> 00:37:38.654 Which is the favorite way we used to

NOTE Confidence: 0.826502799987793

00:37:38.654 --> 00:37:41.187 analyze the tumor site of the interaction.

NOTE Confidence: 0.826502799987793

00:37:41.190 --> 00:37:43.814 So I think by just doing genomic analysis,

NOTE Confidence: 0.826502799987793

00:37:43.820 --> 00:37:45.824 we're missing a lot of alterations

NOTE Confidence: 0.826502799987793

00:37:45.824 --> 00:37:47.750 that the immune system and this.

NOTE Confidence: 0.826502799987793

00:37:47.750 --> 00:37:50.123 I think it's it's something we can

NOTE Confidence: 0.826502799987793

00:37:50.123 --> 00:37:52.468 overcome and finally think that most of

NOTE Confidence: 0.826502799987793

00:37:52.468 --> 00:37:55.049 the studies are focusing on both ends on

NOTE Confidence: 0.826502799987793

00:37:55.049 --> 00:37:57.254 the very early discovery type of work,

NOTE Confidence: 0.826502799987793

00:37:57.260 --> 00:37:59.288 with crisper screens and other strategies.

NOTE Confidence: 0.826502799987793

00:37:59.290 --> 00:38:01.327 And then there is a huge effort

NOTE Confidence: 0.826502799987793

00:38:01.327 --> 00:38:03.010 on the clinical development,

NOTE Confidence: 0.826502799987793

00:38:03.010 --> 00:38:06.295 but I think there is room to improve some

NOTE Confidence: 0.826502799987793

00:38:06.295 --> 00:38:09.350 studies in more sort of human real context.

NOTE Confidence: 0.826502799987793

00:38:09.350 --> 00:38:11.780 Next slide, please.

NOTE Confidence: 0.826502799987793

00:38:11.780 --> 00:38:14.084 So this is an example of the approach

NOTE Confidence: 0.826502799987793

00:38:14.084 --> 00:38:16.920 that we have taken in my group where

NOTE Confidence: 0.826502799987793

00:38:16.920 --> 00:38:18.854 we generate hypothesis using discovery

NOTE Confidence: 0.826502799987793

00:38:18.854 --> 00:38:21.682 in biology and then we actually have

NOTE Confidence: 0.826502799987793

00:38:21.682 --> 00:38:24.002 generated assays to screen for pathways,

NOTE Confidence: 0.826502799987793

00:38:24.002 --> 00:38:26.270 cell types in tumor cell indicators

NOTE Confidence: 0.826502799987793

00:38:26.336 --> 00:38:27.488 in the same issue.

NOTE Confidence: 0.826502799987793

00:38:27.490 --> 00:38:29.779 So we can actually do both genomic

NOTE Confidence: 0.826502799987793

00:38:29.779 --> 00:38:31.229 analysis to understand the

NOTE Confidence: 0.826502799987793

00:38:31.229 --> 00:38:32.837 genomic context during drivers,

NOTE Confidence: 0.826502799987793

00:38:32.840 --> 00:38:35.216 but then we can also look at the

NOTE Confidence: 0.826502799987793

00:38:35.216 --> 00:38:36.771 immune contexture and pathways

NOTE Confidence: 0.826502799987793

00:38:36.771 --> 00:38:38.555 that are potentially actionable.

NOTE Confidence: 0.826502799987793

00:38:38.560 --> 00:38:40.365 We have become pretty good

NOTE Confidence: 0.826502799987793

00:38:40.365 --> 00:38:41.809 at looking at multiple.

NOTE Confidence: 0.826502799987793

00:38:41.810 --> 00:38:43.210 High throughput methods to

NOTE Confidence: 0.826502799987793

00:38:43.210 --> 00:38:45.310 detect protein level and then we

NOTE Confidence: 0.826502799987793

00:38:45.369 --> 00:38:47.029 can do single cell analysis,

NOTE Confidence: 0.826502799987793

00:38:47.030 --> 00:38:48.630 spatial analysis and really try

NOTE Confidence: 0.826502799987793

00:38:48.630 --> 00:38:50.230 to understand the tumor micro

NOTE Confidence: 0.826502799987793

00:38:50.283 --> 00:38:51.775 environment to prioritize what

NOTE Confidence: 0.826502799987793

00:38:51.775 --> 00:38:53.640 signals are dominant or relevant,

NOTE Confidence: 0.826502799987793

00:38:53.640 --> 00:38:55.602 we usually use aggressive analysis using

NOTE Confidence: 0.826502799987793

00:38:55.602 --> 00:38:57.470 outcomes and response to treatment.

NOTE Confidence: 0.826502799987793

00:38:57.470 --> 00:39:00.221 So that way we can identify which

NOTE Confidence: 0.826502799987793

00:39:00.221 --> 00:39:02.572 signals are relevant from the ones

NOTE Confidence: 0.826502799987793

00:39:02.572 --> 00:39:04.756 that are not next slide please.

NOTE Confidence: 0.826502799987793

00:39:04.760 --> 00:39:06.390 This is important because ultimately

NOTE Confidence: 0.826502799987793

00:39:06.390 --> 00:39:08.340 those signals are the ones with.

NOTE Confidence: 0.826502799987793

00:39:08.340 --> 00:39:10.321 Then we can validate in vitro to

NOTE Confidence: 0.826502799987793

00:39:10.321 --> 00:39:12.381 demonstrate that these are not just

NOTE Confidence: 0.826502799987793

00:39:12.381 --> 00:39:13.539 epiphenomenon's or correlations,

NOTE Confidence: 0.826502799987793

00:39:13.540 --> 00:39:15.375 but they are mechanistically relevant

NOTE Confidence: 0.826502799987793

00:39:15.375 --> 00:39:17.757 and then ultimately we can go back

NOTE Confidence: 0.826502799987793

00:39:17.757 --> 00:39:19.444 and look at this in the context

NOTE Confidence: 0.826502799987793

00:39:19.444 --> 00:39:21.009 of human clinical trials,

NOTE Confidence: 0.826502799987793

00:39:21.010 --> 00:39:22.960 and I'll show you an example

NOTE Confidence: 0.826502799987793

00:39:22.960 --> 00:39:25.600 of that next slide, please.

NOTE Confidence: 0.826502799987793

00:39:25.600 --> 00:39:28.379 So just for to illustrate how this

NOTE Confidence: 0.826502799987793

00:39:28.379 --> 00:39:31.568 cycle works, this is a story that it's,

NOTE Confidence: 0.826502799987793

00:39:31.570 --> 00:39:31.919 uh,

NOTE Confidence: 0.826502799987793

00:39:31.919 --> 00:39:34.013 have published this year where we

NOTE Confidence: 0.826502799987793

00:39:34.013 --> 00:39:35.863 identify Interleukin 8 and local

NOTE Confidence: 0.826502799987793

00:39:35.863 --> 00:39:37.723 neutrophils in the tumor micro

NOTE Confidence: 0.826502799987793

00:39:37.723 --> 00:39:39.425 environment as dominant immunization

NOTE Confidence: 0.826502799987793

00:39:39.425 --> 00:39:41.517 pathway and resistant mechanism.

NOTE Confidence: 0.826502799987793

00:39:41.520 --> 00:39:43.872 So the story started a few years

NOTE Confidence: 0.826502799987793

00:39:43.872 --> 00:39:46.791 ago where we look at inside too

NOTE Confidence: 0.826502799987793

00:39:46.791 --> 00:39:49.076 aren't expression for Interleukin 8,

NOTE Confidence: 0.826502799987793

00:39:49.080 --> 00:39:51.278 and we found that it was producing

NOTE Confidence: 0.826502799987793

00:39:51.278 --> 00:39:53.800 tumor cells and highly associated with

NOTE Confidence: 0.826502799987793

00:39:53.800 --> 00:39:56.315 resistance to immune checkpoint blockers.

NOTE Confidence: 0.826502799987793

00:39:56.320 --> 00:39:58.130 So to advance this further,

NOTE Confidence: 0.826502799987793

00:39:58.130 --> 00:40:00.560 we look at the relationship between

NOTE Confidence: 0.826502799987793

00:40:00.560 --> 00:40:02.872 Interleukin 8 and neutral fields as

NOTE Confidence: 0.826502799987793

00:40:02.872 --> 00:40:05.368 shown in the upper side of the slide,

NOTE Confidence: 0.826502799987793

00:40:05.370 --> 00:40:07.904 and then we found a fraction of

NOTE Confidence: 0.826502799987793

00:40:07.904 --> 00:40:10.184 tumors that had up regulation of

NOTE Confidence: 0.826502799987793

00:40:10.184 --> 00:40:12.269 Interleukin 8 and an unfavorable

NOTE Confidence: 0.826502799987793

00:40:12.269 --> 00:40:13.857 micro environment characterized by

NOTE Confidence: 0.826502799987793

00:40:13.857 --> 00:40:15.507 increased deals in fewer T cells.

NOTE Confidence: 0.826502799987793

00:40:15.510 --> 00:40:17.310 We also did genomic analysis to

NOTE Confidence: 0.826502799987793

00:40:17.310 --> 00:40:18.992 understand that this was independent

NOTE Confidence: 0.826502799987793

00:40:18.992 --> 00:40:20.684 from tumor mutational burden

NOTE Confidence: 0.826502799987793

00:40:20.684 --> 00:40:22.376 and major genomic alterations,

NOTE Confidence: 0.826502799987793

00:40:22.380 --> 00:40:24.414 and then we finally were able

NOTE Confidence: 0.826502799987793

00:40:24.414 --> 00:40:25.770 to demonstrate that the

NOTE Confidence: 0.8223637342453

00:40:25.834 --> 00:40:28.198 production of Interlake in the tumor.

NOTE Confidence: 0.8223637342453

00:40:28.200 --> 00:40:29.960 Was actually associated with

NOTE Confidence: 0.8223637342453

00:40:29.960 --> 00:40:32.160 interleukin 8IN serum in circulation,

NOTE Confidence: 0.8223637342453

00:40:32.160 --> 00:40:34.918 so we that we conducted an studying

NOTE Confidence: 0.8223637342453

00:40:34.918 --> 00:40:37.774 over 1200 cancer patients from three

NOTE Confidence: 0.8223637342453

00:40:37.774 --> 00:40:40.960 phase three pivotal trials using immune

NOTE Confidence: 0.8223637342453

00:40:40.960 --> 00:40:43.462 checkpoint blockers and we found that

NOTE Confidence: 0.8223637342453

00:40:43.462 --> 00:40:46.240 about 1/3 of a patients across tumors

NOTE Confidence: 0.8223637342453

00:40:46.240 --> 00:40:48.880 have up regulation of interleukin Aiden.

NOTE Confidence: 0.8223637342453

00:40:48.880 --> 00:40:51.440 They have low sensitivity to

NOTE Confidence: 0.8223637342453

00:40:51.440 --> 00:40:52.976 immune checkpoint blockers.

NOTE Confidence: 0.8223637342453

00:40:52.980 --> 00:40:55.788 Next slide, please.

NOTE Confidence: 0.8223637342453

00:40:55.790 --> 00:40:57.520 Then to further demonstrate this,

NOTE Confidence: 0.8223637342453

00:40:57.520 --> 00:40:59.956 we need another study in which we

NOTE Confidence: 0.8223637342453

00:40:59.956 --> 00:41:02.122 cultured neutrophils and my Lord arise

NOTE Confidence: 0.8223637342453

00:41:02.122 --> 00:41:04.246 suppressor cells to show the mechanism

NOTE Confidence: 0.8223637342453

00:41:04.246 --> 00:41:06.604 behind and we were able to demonstrate

NOTE Confidence: 0.8223637342453

00:41:06.604 --> 00:41:08.592 that formation of Nets was involved

NOTE Confidence: 0.8223637342453

00:41:08.592 --> 00:41:09.976 in affective response suppression,

NOTE Confidence: 0.8223637342453

00:41:09.980 --> 00:41:11.660 and then ultimately we're working

NOTE Confidence: 0.8223637342453

00:41:11.660 --> 00:41:13.340 with the clinical trial where

NOTE Confidence: 0.8223637342453

00:41:13.396 --> 00:41:15.604 patients are being treated with an

NOTE Confidence: 0.8223637342453

00:41:15.604 --> 00:41:17.240 antibody and targeting Interleukin 8,

NOTE Confidence: 0.8223637342453

00:41:17.240 --> 00:41:19.620 and to understand if this pathway can

NOTE Confidence: 0.8223637342453

00:41:19.620 --> 00:41:21.738 actually be action in real patients,

NOTE Confidence: 0.8223637342453

00:41:21.740 --> 00:41:24.218 and hopefully we can use the biology

NOTE Confidence: 0.8223637342453

00:41:24.218 --> 00:41:26.259 that we figure out to drive.

NOTE Confidence: 0.8223637342453

00:41:26.260 --> 00:41:29.596 The biomarker plant next slide please.

NOTE Confidence: 0.8223637342453

00:41:29.600 --> 00:41:32.688 So finally we have gotten a little bit

NOTE Confidence: 0.8223637342453

00:41:32.688 --> 00:41:34.665 more sophisticated now and generated

NOTE Confidence: 0.8223637342453

00:41:34.665 --> 00:41:37.318 models or in in vitro tumor treatment.

NOTE Confidence: 0.8223637342453

00:41:37.320 --> 00:41:40.425 And this is just an example of what we're

NOTE Confidence: 0.8223637342453

00:41:40.425 --> 00:41:43.497 doing where we can culture primary tumors,

NOTE Confidence: 0.8223637342453

00:41:43.500 --> 00:41:45.828 treat them in vitro but intact so that

NOTE Confidence: 0.8223637342453

00:41:45.828 --> 00:41:48.412 we can then generate preparations and

NOTE Confidence: 0.8223637342453

00:41:48.412 --> 00:41:50.822 analyze the tumor micro environment.

NOTE Confidence: 0.8223637342453

00:41:50.830 --> 00:41:52.765 Change now perturbing these tumors

NOTE Confidence: 0.8223637342453

00:41:52.765 --> 00:41:54.313 with immunostimulatory or other

NOTE Confidence: 0.8223637342453

00:41:54.313 --> 00:41:56.470 anti cancer agents and we are

NOTE Confidence: 0.8223637342453

00:41:56.470 --> 00:41:57.842 incorporating new technologies such

NOTE Confidence: 0.8223637342453

00:41:57.842 --> 00:41:59.768 as single cell transcriptomics.

NOTE Confidence: 0.8223637342453

00:41:59.770 --> 00:42:03.200 Another analysis to do more unbiased studies.

NOTE Confidence: 0.8223637342453

00:42:03.200 --> 00:42:03.760 Thank you.

NOTE Confidence: 0.853574156761169

00:42:04.530 --> 00:42:07.938 Thank you Kurt. I mean I think probably

NOTE Confidence: 0.853574156761169

00:42:07.938 --> 00:42:10.209 everybody can see the incredible

NOTE Confidence: 0.853574156761169

00:42:10.209 --> 00:42:12.885 power of that of that approach.

NOTE Confidence: 0.853574156761169

00:42:12.890 --> 00:42:15.317 Well, we said at the outset,

NOTE Confidence: 0.853574156761169

00:42:15.317 --> 00:42:17.816 Yale engage is focused on building bridges

NOTE Confidence: 0.853574156761169

00:42:17.816 --> 00:42:20.320 and and collaboration with industry,

NOTE Confidence: 0.853574156761169

00:42:20.320 --> 00:42:22.798 and in each of these seminars,

NOTE Confidence: 0.853574156761169

00:42:22.800 --> 00:42:24.452 we've invited an industry

NOTE Confidence: 0.853574156761169

00:42:24.452 --> 00:42:26.517 partner to speak to us,

NOTE Confidence: 0.853574156761169

00:42:26.520 --> 00:42:28.998 and I'm really thrilled that today,

NOTE Confidence: 0.853574156761169

00:42:29.000 --> 00:42:31.508 it's Susan Galbreath she's a senior

NOTE Confidence: 0.853574156761169

00:42:31.508 --> 00:42:34.045 Vice president and head of early

NOTE Confidence: 0.853574156761169

00:42:34.045 --> 00:42:36.020 oncology R&D and Astra Zeneca.

NOTE Confidence: 0.853574156761169

00:42:36.020 --> 00:42:38.946 She's been there about 10 years and.

NOTE Confidence: 0.853574156761169

00:42:38.950 --> 00:42:42.480 In the early development program,

NOTE Confidence: 0.853574156761169

00:42:42.480 --> 00:42:47.408 there brought 7 compounds into phase three.

NOTE Confidence: 0.853574156761169

00:42:47.410 --> 00:42:51.160 The story with. PARP inhibition,

NOTE Confidence: 0.853574156761169

00:42:51.160 --> 00:42:53.620 the third generation EGFR inhibitor.

NOTE Confidence: 0.853574156761169

00:42:53.620 --> 00:42:56.578 Awesome Merton if that our colleague,

NOTE Confidence: 0.853574156761169

00:42:56.580 --> 00:42:59.616 Roy Herbst, was involved in presenting

NOTE Confidence: 0.853574156761169

00:42:59.616 --> 00:43:02.480 very impactful angemon trial this year.

NOTE Confidence: 0.853574156761169

00:43:02.480 --> 00:43:04.448 Megan met inhibitors selective

NOTE Confidence: 0.853574156761169

00:43:04.448 --> 00:43:06.416 estrogen receptor directed agents.

NOTE Confidence: 0.853574156761169

00:43:06.420 --> 00:43:08.880 Really phenomenal portfolio and a

NOTE Confidence: 0.853574156761169

00:43:08.880 --> 00:43:11.340 phenomenal track record of success.

NOTE Confidence: 0.853574156761169

00:43:11.340 --> 00:43:12.322 So Suzan,

NOTE Confidence: 0.853574156761169

00:43:12.322 --> 00:43:15.759 we look forward to hearing your thoughts.

NOTE Confidence: 0.825893580913544

00:43:17.340 --> 00:43:18.616 Thank you, Barbara Ann.

NOTE Confidence: 0.825893580913544

00:43:18.616 --> 00:43:21.102 It's a it's a pleasure to be here

NOTE Confidence: 0.825893580913544

00:43:21.102 --> 00:43:22.950 with you and just a bit introduction.

NOTE Confidence: 0.825893580913544

00:43:22.950 --> 00:43:24.422 I'm a clinical psychologist by

NOTE Confidence: 0.825893580913544

00:43:24.422 --> 00:43:26.186 training MD PhD and I've been,

NOTE Confidence: 0.825893580913544

00:43:26.190 --> 00:43:28.276 as Barbara said, Astra Zeneca for 10

NOTE Confidence: 0.825893580913544

00:43:28.276 --> 00:43:30.529 years and before that I was in the

NOTE Confidence: 0.825893580913544

00:43:30.529 --> 00:43:32.198 US with Bristol Myers Squibb also

NOTE Confidence: 0.825893580913544

00:43:32.198 --> 00:43:34.088 in the early Development Group and

NOTE Confidence: 0.825893580913544

00:43:34.088 --> 00:43:36.148 and stayed there for about 9 years.

NOTE Confidence: 0.825893580913544

00:43:36.148 --> 00:43:38.290 Just go on to the next slide.

NOTE Confidence: 0.825893580913544

00:43:38.290 --> 00:43:40.820 I want to talk a little bit to build on

NOTE Confidence: 0.825893580913544

00:43:40.893 --> 00:43:43.294 some of the thoughts we've got about,

NOTE Confidence: 0.825893580913544

00:43:43.300 --> 00:43:44.464 you know, understanding resistance

NOTE Confidence: 0.825893580913544

00:43:44.464 --> 00:43:46.556 and one of the challenges that we've

NOTE Confidence: 0.825893580913544

00:43:46.556 --> 00:43:48.056 got about understanding resistance is

NOTE Confidence: 0.825893580913544

00:43:48.056 --> 00:43:49.840 really having access to the samples.

NOTE Confidence: 0.825893580913544

00:43:49.840 --> 00:43:51.496 That would enable us to understand

NOTE Confidence: 0.825893580913544

00:43:51.496 --> 00:43:52.324 the clinical resistance.

NOTE Confidence: 0.825893580913544

00:43:52.330 --> 00:43:54.426 So Katie Elite is already talked to you

NOTE Confidence: 0.825893580913544

00:43:54.426 --> 00:43:56.494 about some of the models that we can

NOTE Confidence: 0.825893580913544

00:43:56.494 --> 00:43:58.430 use pre clinically to model resistance.

NOTE Confidence: 0.825893580913544

00:43:58.430 --> 00:44:00.092 One of the challenges we've got

NOTE Confidence: 0.825893580913544

00:44:00.092 --> 00:44:01.200 with those techniques though,

NOTE Confidence: 0.825893580913544

00:44:01.200 --> 00:44:02.904 is that it doesn't always predict

NOTE Confidence: 0.825893580913544

00:44:02.904 --> 00:44:04.571 what the true prevalence of the

NOTE Confidence: 0.825893580913544

00:44:04.571 --> 00:44:05.771 resistance mechanisms is going to

NOTE Confidence: 0.825893580913544

00:44:05.771 --> 00:44:07.570 be in in the clinical setting.

NOTE Confidence: 0.825893580913544

00:44:07.570 --> 00:44:09.469 So if you start off with a PC 9

NOTE Confidence: 0.825893580913544

00:44:09.469 --> 00:44:11.765 so when you look at the mechanisms

NOTE Confidence: 0.825893580913544

00:44:11.765 --> 00:44:13.109 of resistance to that,

NOTE Confidence: 0.825893580913544

00:44:13.110 --> 00:44:14.342 you don't necessarily understand

NOTE Confidence: 0.825893580913544

00:44:14.342 --> 00:44:16.513 what the true prevalence of all the

NOTE Confidence: 0.825893580913544

00:44:16.513 --> 00:44:18.157 things are when patients are starting

NOTE Confidence: 0.825893580913544

00:44:18.157 --> 00:44:19.848 with their with their own set of.

NOTE Confidence: 0.825893580913544

00:44:19.850 --> 00:44:22.200 Wiring diagrams in their EGFR

NOTE Confidence: 0.825893580913544

00:44:22.200 --> 00:44:23.610 mutant lung cancer.

NOTE Confidence: 0.825893580913544

00:44:23.610 --> 00:44:25.724 The other challenge that you've got is

NOTE Confidence: 0.825893580913544

00:44:25.724 --> 00:44:27.856 tried for number of years to actually

NOTE Confidence: 0.825893580913544

00:44:27.856 --> 00:44:30.002 get biopsies from patients on at the

NOTE Confidence: 0.825893580913544

00:44:30.002 --> 00:44:32.030 time of progression in clinical trials,

NOTE Confidence: 0.825893580913544

00:44:32.030 --> 00:44:34.452 or must we concluded that you know

NOTE Confidence: 0.825893580913544

00:44:34.452 --> 00:44:37.257 typically has to be as an optional biopsy.

NOTE Confidence: 0.825893580913544

00:44:37.260 --> 00:44:38.790 At that time of progression,

NOTE Confidence: 0.825893580913544

00:44:38.790 --> 00:44:40.010 we've actually heard across

NOTE Confidence: 0.825893580913544

00:44:40.010 --> 00:44:41.535 the range of clinical trials.

NOTE Confidence: 0.825893580913544

00:44:41.540 --> 00:44:42.764 Relatively few of those

NOTE Confidence: 0.825893580913544

00:44:42.764 --> 00:44:43.376 actually materialized,

NOTE Confidence: 0.825893580913544

00:44:43.380 --> 00:44:45.543 and so that means that our mechanisms

NOTE Confidence: 0.825893580913544

00:44:45.543 --> 00:44:46.813 of understanding resistance during

NOTE Confidence: 0.825893580913544

00:44:46.813 --> 00:44:48.278 the development of certain IP,

NOTE Confidence: 0.825893580913544

00:44:48.280 --> 00:44:50.110 you know, have been somewhat limited.

NOTE Confidence: 0.825893580913544

00:44:50.110 --> 00:44:51.976 We started right the beginning by

NOTE Confidence: 0.825893580913544

00:44:51.976 --> 00:44:53.480 looking at circulating tumor DNA,

NOTE Confidence: 0.825893580913544

00:44:53.480 --> 00:44:55.316 it right from the phase one

NOTE Confidence: 0.825893580913544

00:44:55.316 --> 00:44:56.540 trials with awesome antonym,

NOTE Confidence: 0.825893580913544

00:44:56.540 --> 00:44:58.484 and we have some understanding of

NOTE Confidence: 0.825893580913544

00:44:58.484 --> 00:45:00.109 actually published some of the

NOTE Confidence: 0.825893580913544

00:45:00.109 --> 00:45:01.729 data from the first line study

NOTE Confidence: 0.825893580913544

00:45:01.729 --> 00:45:03.534 with a semantic that flora trial

NOTE Confidence: 0.825893580913544

00:45:03.534 --> 00:45:05.406 looking at those CT DNA mechanisms,

NOTE Confidence: 0.825893580913544

00:45:05.410 --> 00:45:07.348 but really actually one of the

NOTE Confidence: 0.825893580913544

00:45:07.348 --> 00:45:09.390 things that comes out of that is,

NOTE Confidence: 0.825893580913544

00:45:09.390 --> 00:45:10.502 we could only explain.

NOTE Confidence: 0.825893580913544

00:45:10.502 --> 00:45:13.068 I am just over 1/3 of the patients

NOTE Confidence: 0.825893580913544

00:45:13.068 --> 00:45:14.736 resistance mechanisms through looking

NOTE Confidence: 0.825893580913544

00:45:14.736 --> 00:45:17.360 at city DNA and the patterns that

NOTE Confidence: 0.825893580913544

00:45:17.360 --> 00:45:19.714 we saw there was we saw their city.

NOTE Confidence: 0.825893580913544

00:45:19.714 --> 00:45:21.084 The emergence of the Sistine

NOTE Confidence: 0.825893580913544

00:45:21.084 --> 00:45:22.689 797 S mutation met amplification

NOTE Confidence: 0.825893580913544

00:45:22.689 --> 00:45:24.509 PSP KEARNEYS pathway mutation.

NOTE Confidence: 0.825893580913544

00:45:24.510 --> 00:45:26.388 An activation fee 10 losses and

NOTE Confidence: 0.825893580913544

00:45:26.388 --> 00:45:28.430 in some cases and MEK pathway

NOTE Confidence: 0.825893580913544

00:45:28.430 --> 00:45:30.590 activation as well in some cases.

NOTE Confidence: 0.825893580913544

00:45:30.590 --> 00:45:32.690 But the really the majority of patients

NOTE Confidence: 0.825893580913544

00:45:32.690 --> 00:45:35.143 we still had a question mark over

NOTE Confidence: 0.825893580913544

00:45:35.143 --> 00:45:37.003 what the resistance mechanisms worth.

NOTE Confidence: 0.825893580913544

00:45:37.010 --> 00:45:39.271 So that led us to design that

NOTE Confidence: 0.825893580913544

00:45:39.271 --> 00:45:40.780 this kind of study.

NOTE Confidence: 0.825893580913544

00:45:40.780 --> 00:45:43.195 It's called the Orchard and platform study.

NOTE Confidence: 0.825893580913544

00:45:43.200 --> 00:45:44.580 This takes patients that

NOTE Confidence: 0.825893580913544

00:45:44.580 --> 00:45:45.615 we're progressing on.

NOTE Confidence: 0.825893580913544

00:45:45.620 --> 00:45:46.601 First line automotive,

NOTE Confidence: 0.825893580913544

00:45:46.601 --> 00:45:48.563 and it offers them something that

NOTE Confidence: 0.825893580913544

00:45:48.563 --> 00:45:50.049 is potentially of potentially

NOTE Confidence: 0.825893580913544

00:45:50.049 --> 00:45:51.509 of benefit to them,

NOTE Confidence: 0.825893580913544

00:45:51.510 --> 00:45:53.470 which is to take a biopsy to

NOTE Confidence: 0.825893580913544

00:45:53.470 --> 00:45:54.310 look at what

NOTE Confidence: 0.818565964698792

00:45:54.382 --> 00:45:57.385 the data says on next generation sequencing.

NOTE Confidence: 0.818565964698792

00:45:57.390 --> 00:45:59.406 From that biopsy and then to allocate

NOTE Confidence: 0.818565964698792

00:45:59.406 --> 00:46:01.934 them to a range of different potential

NOTE Confidence: 0.818565964698792

00:46:01.934 --> 00:46:04.328 arms and this biomarker matched arms

NOTE Confidence: 0.818565964698792

00:46:04.392 --> 00:46:07.088 which you can see above depending on the

NOTE Confidence: 0.818565964698792

00:46:07.088 --> 00:46:09.500 mechanism that that is seen with resistance.

NOTE Confidence: 0.818565964698792

00:46:09.500 --> 00:46:12.268 And then there's also non biomarker match on.

NOTE Confidence: 0.818565964698792

00:46:12.270 --> 00:46:14.790 And this has been an important component

NOTE Confidence: 0.818565964698792

00:46:14.790 --> 00:46:17.099 of many platform trial designs because

NOTE Confidence: 0.818565964698792

00:46:17.099 --> 00:46:19.415 it means that every patient whose

NOTE Confidence: 0.818565964698792

00:46:19.415 --> 00:46:21.533 given a consent to have a biopsy

NOTE Confidence: 0.818565964698792

00:46:21.533 --> 00:46:23.008 gets the offer of something.

NOTE Confidence: 0.818565964698792

00:46:23.008 --> 00:46:25.514 I can't guarantee that than what they're

NOTE Confidence: 0.818565964698792

00:46:25.514 --> 00:46:27.838 getting offered is necessarily going to work,

NOTE Confidence: 0.818565964698792

00:46:27.840 --> 00:46:29.570 but it gives them that,

NOTE Confidence: 0.818565964698792

00:46:29.570 --> 00:46:31.170 and that has driven really

NOTE Confidence: 0.818565964698792

00:46:31.170 --> 00:46:33.583 quite a good uptake in terms of

NOTE Confidence: 0.818565964698792

00:46:33.583 --> 00:46:35.448 enrollment and accrual in this.

NOTE Confidence: 0.818565964698792

00:46:35.450 --> 00:46:37.886 And actually, what one of the things

NOTE Confidence: 0.818565964698792

00:46:37.886 --> 00:46:39.950 that we've already learned now is,

NOTE Confidence: 0.818565964698792

00:46:39.950 --> 00:46:41.680 we've now got, you know,

NOTE Confidence: 0.818565964698792

00:46:41.680 --> 00:46:43.440 data and over 60 patients.

NOTE Confidence: 0.818565964698792

00:46:43.440 --> 00:46:44.106 You know,

NOTE Confidence: 0.818565964698792

00:46:44.106 --> 00:46:46.770 with with tissue available at the time of

NOTE Confidence: 0.818565964698792

00:46:46.839 --> 00:46:49.647 progression in in the in the Orchard study,

NOTE Confidence: 0.818565964698792

00:46:49.650 --> 00:46:52.242 and now that we can we have an

NOTE Confidence: 0.818565964698792

00:46:52.242 --> 00:46:53.790 identifiable resistance mechanism now,

NOTE Confidence: 0.818565964698792

00:46:53.790 --> 00:46:56.205 in the in nearly 2/3 of patients,

NOTE Confidence: 0.818565964698792

00:46:56.210 --> 00:46:58.280 as opposed to just a third.

NOTE Confidence: 0.818565964698792

00:46:58.280 --> 00:47:00.210 We've increased the detection and

NOTE Confidence: 0.818565964698792

00:47:00.210 --> 00:47:02.140 some of the amplification mechanisms

NOTE Confidence: 0.818565964698792

00:47:02.199 --> 00:47:04.053 which can be under estimated using

NOTE Confidence: 0.818565964698792

00:47:04.053 --> 00:47:05.994 CT DNA would increase the detection

NOTE Confidence: 0.818565964698792

00:47:05.994 --> 00:47:07.938 of some of the Fusion mechanisms,

NOTE Confidence: 0.818565964698792

00:47:07.940 --> 00:47:09.818 which can also be difficult to

NOTE Confidence: 0.818565964698792

00:47:09.818 --> 00:47:12.079 detect using the CT DNA techniques.

NOTE Confidence: 0.818565964698792

00:47:12.080 --> 00:47:14.216 And we've got a better sense.

NOTE Confidence: 0.818565964698792

00:47:14.220 --> 00:47:15.099 With the prevalence,

NOTE Confidence: 0.818565964698792

00:47:15.099 --> 00:47:17.470 there's still some work to be done here,

NOTE Confidence: 0.818565964698792

00:47:17.470 --> 00:47:19.351 and I still think we need to look at

NOTE Confidence: 0.818565964698792

00:47:19.351 --> 00:47:21.148 the epigenetic mechanisms that are

NOTE Confidence: 0.818565964698792

00:47:21.148 --> 00:47:23.063 driving resistance in this setting,

NOTE Confidence: 0.818565964698792

00:47:23.070 --> 00:47:25.009 but I just wanted to illustrate this

NOTE Confidence: 0.818565964698792

00:47:25.009 --> 00:47:27.763 as a as an example of one way that we

NOTE Confidence: 0.818565964698792

00:47:27.763 --> 00:47:30.446 need to look at in terms of understanding,

NOTE Confidence: 0.818565964698792

00:47:30.450 --> 00:47:32.020 documenting resistance and moving on

NOTE Confidence: 0.818565964698792

00:47:32.020 --> 00:47:34.869 from it so we can go to the next slide.

NOTE Confidence: 0.818565964698792

00:47:34.870 --> 00:47:36.370 The similar approach has been

NOTE Confidence: 0.818565964698792

00:47:36.370 --> 00:47:37.570 taken in the understanding.

NOTE Confidence: 0.818565964698792

00:47:37.570 --> 00:47:39.242 Resistance to checkpoint inhibition,

NOTE Confidence: 0.818565964698792

00:47:39.242 --> 00:47:42.270 and I completely agree with shoppers comment,

NOTE Confidence: 0.818565964698792

00:47:42.270 --> 00:47:44.205 but not everybody who progress

NOTE Confidence: 0.818565964698792

00:47:44.205 --> 00:47:46.140 is on a checkpoint inhibitor

NOTE Confidence: 0.818565964698792

00:47:46.213 --> 00:47:48.249 is necessarily truly resistant,

NOTE Confidence: 0.818565964698792

00:47:48.250 --> 00:47:50.861 but I think we need to understand

NOTE Confidence: 0.818565964698792

00:47:50.861 --> 00:47:53.690 some of those mechanisms, and again,

NOTE Confidence: 0.818565964698792

00:47:53.690 --> 00:47:56.690 this is a mechanism where you can get

NOTE Confidence: 0.818565964698792

00:47:56.770 --> 00:47:59.350 the biopsies from these patients.

NOTE Confidence: 0.818565964698792

00:47:59.350 --> 00:47:59.761 Also,

NOTE Confidence: 0.818565964698792

00:47:59.761 --> 00:48:01.405 some peripheral blood sampling

NOTE Confidence: 0.818565964698792

00:48:01.405 --> 00:48:04.416 and look at ways in which we

NOTE Confidence: 0.818565964698792

00:48:04.416 --> 00:48:06.176 can potentially offer them.

NOTE Confidence: 0.818565964698792

00:48:06.180 --> 00:48:08.244 Treatments that may have the opportunity

NOTE Confidence: 0.818565964698792

00:48:08.244 --> 00:48:10.829 to to make it make a difference.

NOTE Confidence: 0.818565964698792

00:48:10.830 --> 00:48:11.406 So again,

NOTE Confidence: 0.818565964698792

00:48:11.406 --> 00:48:13.710 I just want to share with you a

NOTE Confidence: 0.818565964698792

00:48:13.781 --> 00:48:16.096 couple of observations from this.

NOTE Confidence: 0.818565964698792

00:48:16.100 --> 00:48:18.938 We're going to the next slide.

NOTE Confidence: 0.818565964698792

00:48:18.940 --> 00:48:20.320 So first of all,

NOTE Confidence: 0.818565964698792

00:48:20.320 --> 00:48:22.390 there are some mechanisms that we

NOTE Confidence: 0.818565964698792

00:48:22.467 --> 00:48:24.747 might anticipate seeing based on,

NOTE Confidence: 0.818565964698792

00:48:24.750 --> 00:48:25.522 you know,

NOTE Confidence: 0.818565964698792

00:48:25.522 --> 00:48:27.838 really good data that's already emerged,

NOTE Confidence: 0.818565964698792

00:48:27.840 --> 00:48:30.514 and this is about the loss of

NOTE Confidence: 0.818565964698792

00:48:30.514 --> 00:48:33.281 her Psycho City for HLA or MHC

NOTE Confidence: 0.818565964698792

00:48:33.281 --> 00:48:35.573 and we are seeing as expected.

NOTE Confidence: 0.818565964698792

00:48:35.580 --> 00:48:37.515 But after treatment or one

NOTE Confidence: 0.818565964698792

00:48:37.515 --> 00:48:38.676 of these checkpoints,

NOTE Confidence: 0.818565964698792

00:48:38.680 --> 00:48:39.841 inhibitors and increased

NOTE Confidence: 0.818565964698792

00:48:39.841 --> 00:48:42.550 prevalence of loss of HLA or MHC.

NOTE Confidence: 0.818565964698792

00:48:42.550 --> 00:48:45.790 In the inability of the of the tumors

NOTE Confidence: 0.818565964698792

00:48:45.790 --> 00:48:49.268 to be seen by an an an an effective

NOTE Confidence: 0.818565964698792

00:48:49.268 --> 00:48:52.252 by at the adaptive immune mechanisms

NOTE Confidence: 0.818565964698792

00:48:52.252 --> 00:48:56.410 of if the antigen can't be presented

NOTE Confidence: 0.850832909345627

00:48:56.410 --> 00:48:57.769 effectively, it's like.

NOTE Confidence: 0.850832909345627

00:48:57.769 --> 00:49:00.034 Other things that we're doing.

NOTE Confidence: 0.850832909345627

00:49:00.040 --> 00:49:02.122 We've seen a range of different

NOTE Confidence: 0.850832909345627

00:49:02.122 --> 00:49:03.510 mechanisms that we have.

NOTE Confidence: 0.850832909345627

00:49:03.510 --> 00:49:05.946 We have looked at in this setting.

NOTE Confidence: 0.850832909345627

00:49:05.950 --> 00:49:07.535 Wilson mentioned the fact that

NOTE Confidence: 0.850832909345627

00:49:07.535 --> 00:49:09.120 obviously we're looking at the

NOTE Confidence: 0.850832909345627

00:49:09.172 --> 00:49:10.666 ATR combination with a lap robe

NOTE Confidence: 0.850832909345627

00:49:10.666 --> 00:49:12.290 in terms of part resistance,

NOTE Confidence: 0.850832909345627

00:49:12.290 --> 00:49:14.201 but in fact actually one of the

NOTE Confidence: 0.850832909345627

00:49:14.201 --> 00:49:16.062 observations that we made earlier phase

NOTE Confidence: 0.850832909345627

00:49:16.062 --> 00:49:18.024 one with our selected slot assertive,

NOTE Confidence: 0.850832909345627

00:49:18.030 --> 00:49:19.540 which is, uh, ATI inhibitor,

NOTE Confidence: 0.850832909345627

00:49:19.540 --> 00:49:21.563 is that we were seeing some unusual

NOTE Confidence: 0.850832909345627

00:49:21.563 --> 00:49:23.422 responses in patients that had a

NOTE Confidence: 0.850832909345627

00:49:23.422 --> 00:49:24.670 prior checkpoints in innovation.

NOTE Confidence: 0.850832909345627

00:49:24.670 --> 00:49:25.754 In some other trials,

NOTE Confidence: 0.850832909345627

00:49:25.754 --> 00:49:27.834 and so that led to some further

NOTE Confidence: 0.850832909345627

00:49:27.834 --> 00:49:30.150 investigation and so so there are

NOTE Confidence: 0.850832909345627

00:49:30.150 --> 00:49:32.314 certain underbelly map is one of the

NOTE Confidence: 0.850832909345627

00:49:32.314 --> 00:49:34.262 arms in the in the Hudson study and

NOTE Confidence: 0.850832909345627

00:49:34.262 --> 00:49:36.124 some of the data that we're seeing

NOTE Confidence: 0.850832909345627

00:49:36.124 --> 00:49:38.320 is quite interesting in seeing that.

NOTE Confidence: 0.850832909345627

00:49:38.320 --> 00:49:40.735 Getting a decrease in exhausted T cells,

NOTE Confidence: 0.850832909345627

00:49:40.740 --> 00:49:42.882 exhausted NK cells and an increase in

NOTE Confidence: 0.850832909345627

00:49:42.882 --> 00:49:44.567 antigen presentation in patients that

NOTE Confidence: 0.850832909345627

00:49:44.567 --> 00:49:46.703 have both got primary resistance to

NOTE Confidence: 0.850832909345627

00:49:46.703 --> 00:49:48.195 checkpoint inhibition and subsequently

NOTE Confidence: 0.850832909345627

00:49:48.195 --> 00:49:50.361 had some degree of response and

NOTE Confidence: 0.850832909345627

00:49:50.361 --> 00:49:51.688 subsequently progressed as well.

NOTE Confidence: 0.850832909345627

00:49:51.688 --> 00:49:54.552 And we're also seeing it not just in the

NOTE Confidence: 0.850832909345627

00:49:54.552 --> 00:49:56.946 ATM mutant patients that are selected,

NOTE Confidence: 0.850832909345627

00:49:56.950 --> 00:49:59.024 but also more more broadly, so.

NOTE Confidence: 0.850832909345627

00:49:59.024 --> 00:50:01.088 This is just an interesting observation.

NOTE Confidence: 0.850832909345627

00:50:01.090 --> 00:50:03.519 There's a lot more mechanistic data that

NOTE Confidence: 0.850832909345627

00:50:03.519 --> 00:50:05.915 is required and that will be followed

NOTE Confidence: 0.850832909345627

00:50:05.915 --> 00:50:08.350 up in order to understand this better.

NOTE Confidence: 0.850832909345627

00:50:08.350 --> 00:50:10.240 But I do think that these kinds of trials

NOTE Confidence: 0.850832909345627

00:50:10.240 --> 00:50:12.318 are really helpful in trying to understand

NOTE Confidence: 0.850832909345627

00:50:12.318 --> 00:50:14.100 the clinical prevalence of resistance.

NOTE Confidence: 0.850832909345627

00:50:14.100 --> 00:50:15.470 Mechanisms get a lot more

NOTE Confidence: 0.850832909345627

00:50:15.470 --> 00:50:16.566 data that can feedback,

NOTE Confidence: 0.850832909345627

00:50:16.570 --> 00:50:17.431 and you know,

NOTE Confidence: 0.850832909345627

00:50:17.431 --> 00:50:18.866 back with the preclinical work

NOTE Confidence: 0.850832909345627

00:50:18.866 --> 00:50:21.062 that we can do to them to then

NOTE Confidence: 0.850832909345627

00:50:21.062 --> 00:50:22.599 understand what we might do next.

NOTE Confidence: 0.850832909345627

00:50:22.600 --> 00:50:24.287 So I'm going to stop there and

NOTE Confidence: 0.850832909345627

00:50:24.287 --> 00:50:25.975 I'm very happy to address any

NOTE Confidence: 0.850832909345627

00:50:25.975 --> 00:50:27.793 questions that you might might have.

NOTE Confidence: 0.850832909345627

00:50:27.800 --> 00:50:29.390 Thank you.

NOTE Confidence: 0.850832909345627

00:50:29.390 --> 00:50:30.460 That was

NOTE Confidence: 0.864805579185486

00:50:30.460 --> 00:50:33.140 fabulous. Thank you very much.

NOTE Confidence: 0.864805579185486

00:50:33.140 --> 00:50:37.290 I am now going to ask that all of the

NOTE Confidence: 0.864805579185486

00:50:37.402 --> 00:50:41.637 panelists turned on their audio and video

NOTE Confidence: 0.864805579185486

00:50:41.637 --> 00:50:47.159 and will now go into the the full discussion.

NOTE Confidence: 0.864805579185486

00:50:47.160 --> 00:50:51.696 And I'm going to ask the attendees to

NOTE Confidence: 0.864805579185486

00:50:51.696 --> 00:50:56.274 please continue to post questions we we are

NOTE Confidence: 0.864805579185486

00:50:56.274 --> 00:51:00.840 monitoring these and the first one, I think.

NOTE Confidence: 0.864805579185486

00:51:00.840 --> 00:51:03.740 Basically immediately follows that the

NOTE Confidence: 0.864805579185486

00:51:03.740 --> 00:51:07.955 last slide that we saw and so maybe I'll

NOTE Confidence: 0.864805579185486

00:51:07.955 --> 00:51:11.570 ask Susan and Kurt both to address this.

NOTE Confidence: 0.864805579185486

00:51:11.570 --> 00:51:14.867 How critical is it to overcome the

NOTE Confidence: 0.864805579185486

00:51:14.867 --> 00:51:17.399 mechanical functional barriers to immune

NOTE Confidence: 0.864805579185486

00:51:17.399 --> 00:51:20.009 checkpoint inhibitors and the question

NOTE Confidence: 0.864805579185486

00:51:20.009 --> 00:51:22.300 relates specifically to HLA loss,

NOTE Confidence: 0.864805579185486

00:51:22.300 --> 00:51:25.186 although I can think of other

NOTE Confidence: 0.864805579185486

00:51:25.186 --> 00:51:27.677 mechanisms related to hypoxemia and

NOTE Confidence: 0.864805579185486

00:51:27.677 --> 00:51:30.107 and vascular alterations as well,

NOTE Confidence: 0.864805579185486

00:51:30.110 --> 00:51:33.080 but can you please comment on?

NOTE Confidence: 0.864805579185486

00:51:33.080 --> 00:51:35.072 Potential pathways and targets to overcome

NOTE Confidence: 0.864805579185486

00:51:35.072 --> 00:51:36.749 mechanical and functional barriers to

NOTE Confidence: 0.864805579185486

00:51:36.749 --> 00:51:38.259 immune checkpoint inhibitors and Susan.

NOTE Confidence: 0.864805579185486

00:51:38.260 --> 00:51:40.852 Do you want to go first and then

NOTE Confidence: 0.864805579185486

00:51:40.852 --> 00:51:42.478 kick it to to Kurt?

NOTE Confidence: 0.83586585521698

00:51:43.150 --> 00:51:45.292 Yeah well, the the the the Council

NOTE Confidence: 0.83586585521698

00:51:45.292 --> 00:51:48.459 you think of when I think of 1st when

NOTE Confidence: 0.83586585521698

00:51:48.459 --> 00:51:50.431 you're talking about mechanical barriers

NOTE Confidence: 0.83586585521698

00:51:50.431 --> 00:51:53.107 potentially is is of pancreatic cancer.

NOTE Confidence: 0.83586585521698

00:51:53.110 --> 00:51:55.806 Cause at the high level of you know

NOTE Confidence: 0.83586585521698

00:51:55.806 --> 00:51:58.203 Disney plastic streamer that you see that

NOTE Confidence: 0.83586585521698

00:51:58.203 --> 00:52:00.778 you see there that has been discussed

NOTE Confidence: 0.83586585521698

00:52:00.778 --> 00:52:03.753 as not just having actually a physical

NOTE Confidence: 0.83586585521698

00:52:03.753 --> 00:52:06.110 potential barrier to treatment but also

NOTE Confidence: 0.83586585521698

00:52:06.110 --> 00:52:08.609 the presence of the constituents of that.

NOTE Confidence: 0.83586585521698

00:52:08.610 --> 00:52:09.346 Desmond plastics.

NOTE Confidence: 0.83586585521698

00:52:09.346 --> 00:52:11.922 German may also have a you know,

NOTE Confidence: 0.83586585521698

00:52:11.930 --> 00:52:13.418 biochemical effects that reduce

NOTE Confidence: 0.83586585521698

00:52:13.418 --> 00:52:15.278 the likelihood of sensitivity to.

NOTE Confidence: 0.83586585521698

00:52:15.280 --> 00:52:17.458 Of the tumor cells that are

NOTE Confidence: 0.83586585521698

00:52:17.458 --> 00:52:18.910 adjacent about two treatment,

NOTE Confidence: 0.83586585521698

00:52:18.910 --> 00:52:21.457 and I think there are a lot of data

NOTE Confidence: 0.83586585521698

00:52:21.457 --> 00:52:23.167 suggesting that understanding the

NOTE Confidence: 0.83586585521698

00:52:23.167 --> 00:52:25.437 components of the micro environment,

NOTE Confidence: 0.83586585521698

00:52:25.440 --> 00:52:27.618 the distribution and types of you

NOTE Confidence: 0.83586585521698

00:52:27.618 --> 00:52:29.070 know cancer associated fibroblasts,

NOTE Confidence: 0.83586585521698

00:52:29.070 --> 00:52:29.798 for example,

NOTE Confidence: 0.83586585521698

00:52:29.798 --> 00:52:31.618 and not in that disease,

NOTE Confidence: 0.83586585521698

00:52:31.620 --> 00:52:33.906 and their feelings that might be

NOTE Confidence: 0.83586585521698

00:52:33.906 --> 00:52:35.430 absolutely critical to understanding

NOTE Confidence: 0.83586585521698

00:52:35.492 --> 00:52:37.757 mechanisms of resistance and sensitivity.

NOTE Confidence: 0.83586585521698

00:52:37.760 --> 00:52:41.158 I think in the context of loss of HLA.

NOTE Confidence: 0.83586585521698

00:52:41.160 --> 00:52:43.552 It it's you know that you know lots

NOTE Confidence: 0.83586585521698

00:52:43.552 --> 00:52:46.333 of HLA may increase the sensitivity

NOTE Confidence: 0.83586585521698

00:52:46.333 --> 00:52:48.968 potentially to other mechanisms like

NOTE Confidence: 0.83586585521698

00:52:48.968 --> 00:52:51.366 inducing the innate immune system

NOTE Confidence: 0.83586585521698

00:52:51.366 --> 00:52:54.060 rather than the adaptive immune system

NOTE Confidence: 0.83586585521698

00:52:54.060 --> 00:52:56.210 to NK cell enhancement potentially.

NOTE Confidence: 0.83586585521698

00:52:56.210 --> 00:52:57.722 Then you know so.

NOTE Confidence: 0.83586585521698

00:52:57.722 --> 00:52:59.990 So there are things that then

NOTE Confidence: 0.83586585521698

00:53:00.080 --> 00:53:02.660 creates a formability I suppose.

NOTE Confidence: 0.83586585521698

00:53:02.660 --> 00:53:05.724 I think the issue from my perspective is

NOTE Confidence: 0.83586585521698

00:53:05.724 --> 00:53:09.109 it you know you wouldn't be expecting.

NOTE Confidence: 0.83586585521698

00:53:09.110 --> 00:53:10.975 No high likelihood of subsequent

NOTE Confidence: 0.83586585521698

00:53:10.975 --> 00:53:12.840 response to something that requires

NOTE Confidence: 0.83586585521698

00:53:12.898 --> 00:53:14.269 HLA antigen presentation.

NOTE Confidence: 0.83586585521698

00:53:14.270 --> 00:53:17.042 If you've got lots of HP laser

NOTE Confidence: 0.83586585521698

00:53:17.042 --> 00:53:17.834 fundamental mechanism,

NOTE Confidence: 0.83586585521698

00:53:17.840 --> 00:53:20.563 so we should be segmenting patients by

NOTE Confidence: 0.83586585521698

00:53:20.563 --> 00:53:22.661 an understanding of these mechanisms

NOTE Confidence: 0.83586585521698

00:53:22.661 --> 00:53:25.235 in order to identify the populations

NOTE Confidence: 0.83586585521698

00:53:25.235 --> 00:53:28.049 that might best be subsequently treated

NOTE Confidence: 0.83586585521698

00:53:28.049 --> 00:53:30.399 with different kinds of therapies.

NOTE Confidence: 0.83586585521698

00:53:30.400 --> 00:53:31.930 Cut any thoughts from you.

NOTE Confidence: 0.820202529430389

00:53:32.680 --> 00:53:34.969 Yes, I agree with all the comments.

NOTE Confidence: 0.820202529430389

00:53:34.970 --> 00:53:37.140 I think there is more biology emerging

NOTE Confidence: 0.820202529430389

00:53:37.140 --> 00:53:38.467 suggesting that the mechanical

NOTE Confidence: 0.820202529430389

00:53:38.467 --> 00:53:40.525 barriers may not be so mechanical.

NOTE Confidence: 0.820202529430389

00:53:40.530 --> 00:53:43.155 You know some of these fibroblast basic

NOTE Confidence: 0.820202529430389

00:53:43.155 --> 00:53:45.607 read inhibitory molecule so it may be

NOTE Confidence: 0.820202529430389

00:53:45.607 --> 00:53:47.503 also an active immunity victory component

NOTE Confidence: 0.820202529430389

00:53:47.568 --> 00:53:49.680 to that and that I think is driving.

NOTE Confidence: 0.820202529430389

00:53:49.680 --> 00:53:52.210 I think they were going to see a lot of

NOTE Confidence: 0.820202529430389

00:53:52.279 --> 00:53:54.811 new studies showing active mechanism of

NOTE Confidence: 0.820202529430389

00:53:54.811 --> 00:53:57.734 rejection of immune cells in the tumor bed

NOTE Confidence: 0.820202529430389

00:53:57.734 --> 00:53:59.844 and relative to the empty in presentation.

NOTE Confidence: 0.820202529430389

00:53:59.844 --> 00:54:02.322 We have actually a study under review

NOTE Confidence: 0.820202529430389

00:54:02.322 --> 00:54:04.159 that should see the light soon.

NOTE Confidence: 0.820202529430389

00:54:04.160 --> 00:54:06.060 When we look at large

NOTE Confidence: 0.820202529430389

00:54:06.060 --> 00:54:07.580 cohorts of tumor mapping,

NOTE Confidence: 0.820202529430389

00:54:07.580 --> 00:54:10.022 different parts of the antigen presentation

NOTE Confidence: 0.820202529430389

00:54:10.022 --> 00:54:13.104 pathway in a Long story short where we've

NOTE Confidence: 0.820202529430389

00:54:13.104 --> 00:54:16.318 learned is that when we look at the genomics,

NOTE Confidence: 0.820202529430389

00:54:16.320 --> 00:54:17.676 we don't see that.

NOTE Confidence: 0.820202529430389

00:54:17.676 --> 00:54:20.213 So the majority of alterations are non

NOTE Confidence: 0.820202529430389

00:54:20.213 --> 00:54:22.398 genomic meaning non mutation related.

NOTE Confidence: 0.820202529430389

00:54:22.400 --> 00:54:24.680 In the second interesting lesson is

NOTE Confidence: 0.820202529430389

00:54:24.680 --> 00:54:27.015 that depending on what molecule is

NOTE Confidence: 0.820202529430389

00:54:27.015 --> 00:54:29.612 lost in the tumor cell meaning HAHABCV,

NOTE Confidence: 0.820202529430389

00:54:29.620 --> 00:54:31.140 A2M or other proteins,

NOTE Confidence: 0.820202529430389

00:54:31.140 --> 00:54:32.660 the immune contexture changes.

NOTE Confidence: 0.820202529430389

00:54:32.660 --> 00:54:33.964 So so I think.

NOTE Confidence: 0.820202529430389

00:54:33.964 --> 00:54:35.920 Understanding that part will be critical

NOTE Confidence: 0.820202529430389

00:54:35.986 --> 00:54:38.478 to understand how to treat those patients,

NOTE Confidence: 0.820202529430389

00:54:38.480 --> 00:54:40.334 we do see upregulation of natural

NOTE Confidence: 0.820202529430389

00:54:40.334 --> 00:54:42.380 killer service in in certain loss.

NOTE Confidence: 0.820202529430389

00:54:42.380 --> 00:54:43.030 Eventually molecules,

NOTE Confidence: 0.820202529430389

00:54:43.030 --> 00:54:44.330 but not in everyone,

NOTE Confidence: 0.820202529430389

00:54:44.330 --> 00:54:47.021 and each of them has sort of a certain

NOTE Confidence: 0.820202529430389

00:54:47.021 --> 00:54:48.880 different balance between T cells,

NOTE Confidence: 0.820202529430389

00:54:48.880 --> 00:54:50.500 NK cells, and other cells.

NOTE Confidence: 0.820202529430389

00:54:50.500 --> 00:54:52.714 So I think it will be critical to do

NOTE Confidence: 0.820202529430389

00:54:52.714 --> 00:54:54.665 those studies to understand how granular

NOTE Confidence: 0.820202529430389

00:54:54.665 --> 00:54:57.580 disease and if we can lump the antigen

NOTE Confidence: 0.820202529430389

00:54:57.580 --> 00:54:59.595 presentation defect into one category.

NOTE Confidence: 0.820202529430389

00:54:59.600 --> 00:55:02.200 Or maybe it will be more than that.

NOTE Confidence: 0.820202529430389

00:55:02.200 --> 00:55:04.475 I think that's to be figured out.

NOTE Confidence: 0.809990227222443

00:55:05.380 --> 00:55:07.900 So just continuing on with this theme

NOTE Confidence: 0.809990227222443

00:55:07.900 --> 00:55:11.762 in in a question for Chin can HLA loss

NOTE Confidence: 0.809990227222443

00:55:11.762 --> 00:55:14.680 be overcome by epigenetic modification?

NOTE Confidence: 0.809990227222443

00:55:14.680 --> 00:55:18.224 Or what is epigenetic role in HLA loss?

NOTE Confidence: 0.84406441450119

00:55:18.960 --> 00:55:22.551 So this is not an area I have been

NOTE Confidence: 0.84406441450119

00:55:22.551 --> 00:55:25.230 working on very well having it,

NOTE Confidence: 0.84406441450119

00:55:25.230 --> 00:55:27.636 but I could just mention another

NOTE Confidence: 0.84406441450119

00:55:27.636 --> 00:55:30.151 with those changes are non genetic

NOTE Confidence: 0.84406441450119

00:55:30.151 --> 00:55:32.231 changes so we have different

NOTE Confidence: 0.84406441450119

00:55:32.231 --> 00:55:34.430 tools to execute those jeans.

NOTE Confidence: 0.84406441450119

00:55:34.430 --> 00:55:36.114 Reactivate those jeans and

NOTE Confidence: 0.84406441450119

00:55:36.114 --> 00:55:38.219 to make them successful too.

NOTE Confidence: 0.84406441450119

00:55:38.220 --> 00:55:41.460 Make make them to be sensitive

NOTE Confidence: 0.84406441450119

00:55:41.460 --> 00:55:43.080 to our treatment.

NOTE Confidence: 0.84406441450119

00:55:43.080 --> 00:55:45.735 So email checkpoint blockade will

NOTE Confidence: 0.84406441450119

00:55:45.735 --> 00:55:49.020 work if you re reactivate those.

NOTE Confidence: 0.834680736064911

00:55:50.670 --> 00:55:54.270 Terrific terrific, I have a question

NOTE Confidence: 0.834680736064911

00:55:54.270 --> 00:55:59.640 that was submitted earlier, but I think.

NOTE Confidence: 0.834680736064911

00:55:59.640 --> 00:56:01.926 Could probably be answered extensively or

NOTE Confidence: 0.834680736064911

00:56:01.926 --> 00:56:04.500 exhaustively by each one of the panelists,

NOTE Confidence: 0.834680736064911

00:56:04.500 --> 00:56:06.702 but maybe I'll ask Katie and

NOTE Confidence: 0.834680736064911

00:56:06.702 --> 00:56:08.989 Mark to start on this one.

NOTE Confidence: 0.834680736064911

00:56:08.990 --> 00:56:11.454 How does the mutational landscape of a

NOTE Confidence: 0.834680736064911

00:56:11.454 --> 00:56:13.479 tumor affect resistance and sensitivity?

NOTE Confidence: 0.834680736064911

00:56:13.480 --> 00:56:15.916 And I'm interpreting that the questioner

NOTE Confidence: 0.834680736064911

00:56:15.916 --> 00:56:17.919 means the other mutations besides

NOTE Confidence: 0.834680736064911

00:56:17.919 --> 00:56:19.840 the one in your target molecule.

NOTE Confidence: 0.884686589241028

00:56:22.170 --> 00:56:24.350 Thank you sure I can.

NOTE Confidence: 0.884686589241028

00:56:24.350 --> 00:56:26.960 I can get started with that.

NOTE Confidence: 0.884686589241028

00:56:26.960 --> 00:56:29.696 I think this is really an area that

NOTE Confidence: 0.884686589241028

00:56:29.696 --> 00:56:32.587 we are starting to learn more about

NOTE Confidence: 0.884686589241028

00:56:32.587 --> 00:56:35.834 as we have learned more about the

NOTE Confidence: 0.884686589241028

00:56:35.834 --> 00:56:38.966 mutational profiles of tumors and of

NOTE Confidence: 0.884686589241028

00:56:38.966 --> 00:56:41.348 different genetic subgroups of tumors.

NOTE Confidence: 0.884686589241028

00:56:41.348 --> 00:56:44.470 So now one of the things that

NOTE Confidence: 0.884686589241028

00:56:44.561 --> 00:56:46.967 we've been able to look at,

NOTE Confidence: 0.884686589241028

00:56:46.970 --> 00:56:49.819 for example, are in if we think

NOTE Confidence: 0.884686589241028

00:56:49.819 --> 00:56:52.190 about lung cancers in different.

NOTE Confidence: 0.884686589241028

00:56:52.190 --> 00:56:53.318 Oncogenic driver subgroups.

NOTE Confidence: 0.884686589241028

00:56:53.318 --> 00:56:57.058 We can look at the pattern of Co occurring

NOTE Confidence: 0.884686589241028

00:56:57.058 --> 00:56:59.126 genetic alterations that happened,

NOTE Confidence: 0.884686589241028

00:56:59.130 --> 00:57:01.740 so I'm thinking about for example,

NOTE Confidence: 0.884686589241028

00:57:01.740 --> 00:57:03.910 in K Rasputin lung cancers,

NOTE Confidence: 0.884686589241028

00:57:03.910 --> 00:57:06.948 these can Co occur with P53 mutations.

NOTE Confidence: 0.884686589241028

00:57:06.950 --> 00:57:09.602 They can Co occur for example

NOTE Confidence: 0.884686589241028

00:57:09.602 --> 00:57:11.720 with mutations in STK 11,

NOTE Confidence: 0.884686589241028

00:57:11.720 --> 00:57:13.890 also known as Elchibey one.

NOTE Confidence: 0.884686589241028

00:57:13.890 --> 00:57:15.626 And we're really beginning

NOTE Confidence: 0.884686589241028

00:57:15.626 --> 00:57:18.230 to learn about what it means.

NOTE Confidence: 0.884686589241028

00:57:18.230 --> 00:57:20.939 If the tumor has Akira's mutation and

NOTE Confidence: 0.884686589241028

00:57:20.939 --> 00:57:23.900 a P53 mutation versus ACARAS mutation.

NOTE Confidence: 0.884686589241028

00:57:23.900 --> 00:57:27.456 And then Elchibey one mutation for example.

NOTE Confidence: 0.884686589241028

00:57:27.460 --> 00:57:30.772 And what and that the LKB one meeting

NOTE Confidence: 0.884686589241028

00:57:30.772 --> 00:57:34.653 tumors seem to have a different or

NOTE Confidence: 0.884686589241028

00:57:34.653 --> 00:57:37.021 reduced sensitivity to immunotherapy

NOTE Confidence: 0.884686589241028

00:57:37.021 --> 00:57:39.432 treatment, for example, and.

NOTE Confidence: 0.884686589241028

00:57:39.432 --> 00:57:40.640 In parallel,

NOTE Confidence: 0.884686589241028

00:57:40.640 --> 00:57:43.376 I think similarly with targeted therapies,

NOTE Confidence: 0.884686589241028

00:57:43.380 --> 00:57:45.555 we're really starting to scratch

NOTE Confidence: 0.884686589241028

00:57:45.555 --> 00:57:48.241 the surface and really beginning to

NOTE Confidence: 0.884686589241028

00:57:48.241 --> 00:57:50.893 start to understand how different Co

NOTE Confidence: 0.884686589241028

00:57:50.893 --> 00:57:52.794 occurring alterations also impact

NOTE Confidence: 0.884686589241028

00:57:52.794 --> 00:57:54.826 response to targeted therapies.

NOTE Confidence: 0.884686589241028

00:57:54.830 --> 00:57:55.928 So for example,

NOTE Confidence: 0.884686589241028

00:57:55.928 --> 00:57:58.490 some of the work that we've been

NOTE Confidence: 0.884686589241028

00:57:58.570 --> 00:58:01.315 doing recently looking at different

NOTE Confidence: 0.884686589241028

00:58:01.315 --> 00:58:03.511 tumor suppressor gene alterations

NOTE Confidence: 0.884686589241028

00:58:03.511 --> 00:58:06.353 in EGFR mutant lung cancer and

NOTE Confidence: 0.884686589241028

00:58:06.353 --> 00:58:08.563 how they affect sensitivity to

NOTE Confidence: 0.884686589241028

00:58:08.570 --> 00:58:09.800 tyrosine kinase inhibitors.

NOTE Confidence: 0.884686589241028

00:58:09.800 --> 00:58:12.670 One of the things that has emerged

NOTE Confidence: 0.884686589241028

00:58:12.740 --> 00:58:14.990 from our studies in animal models,

NOTE Confidence: 0.884686589241028

00:58:14.990 --> 00:58:18.078 an also is emerging from studies of patients.

NOTE Confidence: 0.884686589241028

00:58:18.080 --> 00:58:20.810 Patient specimens is that if you have

NOTE Confidence: 0.884686589241028

00:58:20.810 --> 00:58:23.175 EGFR mutant tumors that also have

NOTE Confidence: 0.884686589241028

00:58:23.175 --> 00:58:25.407 mutations in the keep one access,

NOTE Confidence: 0.884686589241028

00:58:25.410 --> 00:58:28.122 so the keep 1 NRF 2 access that

NOTE Confidence: 0.884686589241028

00:58:28.122 --> 00:58:30.187 is important for the antioxidant

NOTE Confidence: 0.884686589241028

00:58:30.187 --> 00:58:32.357 response of a tumor cell.

NOTE Confidence: 0.884686589241028

00:58:32.360 --> 00:58:34.872 If you have mutations that Co occur in

NOTE Confidence: 0.884686589241028

00:58:34.872 --> 00:58:37.821 that path where you have a decreased

NOTE Confidence: 0.884686589241028

00:58:37.821 --> 00:58:40.076 sensitivity to tyrosine kinase inhibitors,

NOTE Confidence: 0.884686589241028

00:58:40.080 --> 00:58:42.035 so the tumors will shrink

NOTE Confidence: 0.884686589241028

00:58:42.035 --> 00:58:43.599 less on treatment with.

NOTE Confidence: 0.884686589241028

00:58:43.600 --> 00:58:44.884 These targeted therapies,

NOTE Confidence: 0.884686589241028

00:58:44.884 --> 00:58:47.452 and so that begs the question,

NOTE Confidence: 0.884686589241028

00:58:47.460 --> 00:58:51.312 is that a subset of patients who you could,

NOTE Confidence: 0.884686589241028

00:58:51.320 --> 00:58:52.176 for example,

NOTE Confidence: 0.884686589241028

00:58:52.176 --> 00:58:53.888 select initially for treatment

NOTE Confidence: 0.884686589241028

00:58:53.888 --> 00:58:55.172 with different therapies,

NOTE Confidence: 0.884686589241028

00:58:55.180 --> 00:58:57.080 or for combination therapies

NOTE Confidence: 0.884686589241028

00:58:57.080 --> 00:58:59.455 together with a tyrosine kinase

NOTE Confidence: 0.884686589241028

00:58:59.455 --> 00:59:01.218 inhibitor so that you could.

NOTE Confidence: 0.884686589241028

00:59:01.220 --> 00:59:02.760 Improve outcomes in patients

NOTE Confidence: 0.884686589241028

00:59:02.760 --> 00:59:03.915 with that disease.

NOTE Confidence: 0.884686589241028

00:59:03.920 --> 00:59:05.212 I think of course,

NOTE Confidence: 0.884686589241028

00:59:05.212 --> 00:59:06.827 this these types of landscapes

NOTE Confidence: 0.884686589241028

00:59:06.827 --> 00:59:08.815 also this studying these landscapes

NOTE Confidence: 0.884686589241028

00:59:08.815 --> 00:59:11.221 really requires a lot of mechanistic

NOTE Confidence: 0.884686589241028

00:59:11.281 --> 00:59:12.953 investigation to understand exactly

NOTE Confidence: 0.884686589241028

00:59:12.953 --> 00:59:15.461 what is happening in those tumors.

NOTE Confidence: 0.884686589241028

00:59:15.470 --> 00:59:15.825 Finally,

NOTE Confidence: 0.884686589241028

00:59:15.825 --> 00:59:18.665 I think one of the other things to

NOTE Confidence: 0.884686589241028

00:59:18.665 --> 00:59:21.322 think about in terms of the genetic

NOTE Confidence: 0.884686589241028

00:59:21.322 --> 00:59:24.121 landscape also has to do with the

NOTE Confidence: 0.884686589241028

00:59:24.121 --> 00:59:26.191 overall mutation burden and the

NOTE Confidence: 0.884686589241028

00:59:26.191 --> 00:59:28.031 overall tumor mutation burden, which.

NOTE Confidence: 0.884686589241028

00:59:28.031 --> 00:59:30.791 You know we talk a lot about it

NOTE Confidence: 0.884686589241028

00:59:30.791 --> 00:59:32.777 in the context of immuno therapies

NOTE Confidence: 0.884686589241028

00:59:32.777 --> 00:59:34.550 and where you know we've.

NOTE Confidence: 0.884686589241028

00:59:34.550 --> 00:59:36.776 We've heard about a lot about it

NOTE Confidence: 0.884686589241028

00:59:36.776 --> 00:59:38.230 in in recent years.

NOTE Confidence: 0.884686589241028

00:59:38.230 --> 00:59:40.365 I'd say also there's some evidence that

NOTE Confidence: 0.884686589241028

00:59:40.365 --> 00:59:42.589 in the context of targeted therapies,

NOTE Confidence: 0.884686589241028

00:59:42.590 --> 00:59:44.660 the overall genetic landscape or the

NOTE Confidence: 0.884686589241028

00:59:44.660 --> 00:59:46.737 tumor mutation burden can have an

NOTE Confidence: 0.884686589241028

00:59:46.737 --> 00:59:48.949 effect on the response to targeted therapy.

NOTE Confidence: 0.884686589241028

00:59:48.950 --> 00:59:50.864 So again in EGFR mutant lung

NOTE Confidence: 0.884686589241028

00:59:50.864 --> 00:59:52.140 cancer tumors that seem

NOTE Confidence: 0.842104613780975

00:59:52.205 --> 00:59:54.354 that have that are in the highest

NOTE Confidence: 0.842104613780975

00:59:54.354 --> 00:59:56.319 tertile of tumor mutation burden,

NOTE Confidence: 0.842104613780975

00:59:56.320 --> 00:59:57.668 which is generally lower

NOTE Confidence: 0.842104613780975

00:59:57.668 --> 00:59:59.353 than most other lung cancers.

NOTE Confidence: 0.842104613780975

00:59:59.360 --> 01:00:01.034 But in that highest circle seemed

NOTE Confidence: 0.842104613780975

01:00:01.034 --> 01:00:03.066 to do worse on treatment with

NOTE Confidence: 0.842104613780975

01:00:03.066 --> 01:00:04.766 targeted therapies with tyrosine

NOTE Confidence: 0.842104613780975

01:00:04.766 --> 01:00:07.195 kinase inhibitors and the ones with

NOTE Confidence: 0.842104613780975

01:00:07.195 --> 01:00:08.860 the lower two mutation burden.

NOTE Confidence: 0.842104613780975

01:00:08.860 --> 01:00:10.972 So there are lots of different

NOTE Confidence: 0.842104613780975

01:00:10.972 --> 01:00:12.028 aspects to consider.

NOTE Confidence: 0.842104613780975

01:00:12.030 --> 01:00:13.338 The specific mutation.

NOTE Confidence: 0.842104613780975

01:00:13.338 --> 01:00:15.518 So qualitatively but also quantitatively.

NOTE Confidence: 0.842104613780975

01:00:15.520 --> 01:00:16.090 Yep,

NOTE Confidence: 0.625242710113525

01:00:16.090 --> 01:00:22.390 I was just at the office or at a kind of.

NOTE Confidence: 0.625242710113525

01:00:22.390 --> 01:00:24.178 Broad conceptual thought to

NOTE Confidence: 0.625242710113525

01:00:24.178 --> 01:00:25.966 that which is ultimately,

NOTE Confidence: 0.625242710113525

01:00:25.970 --> 01:00:28.658 I think, with all of these,

NOTE Confidence: 0.625242710113525

01:00:28.660 --> 01:00:30.900 with all of the therapies.

NOTE Confidence: 0.625242710113525

01:00:30.900 --> 01:00:33.306 We're talking about, one is really

NOTE Confidence: 0.625242710113525

01:00:33.306 --> 01:00:36.279 trying to correct the signaling network.

NOTE Confidence: 0.625242710113525

01:00:36.280 --> 01:00:38.068 However you define network,

NOTE Confidence: 0.625242710113525

01:00:38.068 --> 01:00:40.303 whether its intracellular intra tissue,

NOTE Confidence: 0.625242710113525

01:00:40.310 --> 01:00:41.645 Inter intra Organism.

NOTE Confidence: 0.625242710113525

01:00:41.645 --> 01:00:44.760 Once regular network and in a sense

NOTE Confidence: 0.625242710113525

01:00:44.842 --> 01:00:47.628 if you think about the fact that

NOTE Confidence: 0.625242710113525

01:00:47.628 --> 01:00:50.357 cancers are really caused by the

NOTE Confidence: 0.625242710113525

01:00:50.357 --> 01:00:52.293 networks losing robustness and

NOTE Confidence: 0.625242710113525

01:00:52.293 --> 01:00:55.598 kind of careering out of control to

NOTE Confidence: 0.625242710113525

01:00:55.598 --> 01:00:57.446 uncontrolled proliferation so far.

NOTE Confidence: 0.625242710113525

01:00:57.450 --> 01:00:59.078 It's almost surprising actually.

NOTE Confidence: 0.625242710113525

01:00:59.078 --> 01:01:01.113 The targeted therapy can work,

NOTE Confidence: 0.625242710113525

01:01:01.120 --> 01:01:02.221 and indeed, actually,

NOTE Confidence: 0.625242710113525

01:01:02.221 --> 01:01:04.423 if you create models where you

NOTE Confidence: 0.625242710113525

01:01:04.423 --> 01:01:06.019 just mutated something,

NOTE Confidence: 0.625242710113525

01:01:06.020 --> 01:01:08.055 we're hitting with a targeted

NOTE Confidence: 0.625242710113525

01:01:08.055 --> 01:01:09.683 therapeutic and nothing else.

NOTE Confidence: 0.625242710113525

01:01:09.690 --> 01:01:10.914 You don't actually.

NOTE Confidence: 0.625242710113525

01:01:10.914 --> 01:01:13.770 But that's not enough to cause cancer,

NOTE Confidence: 0.625242710113525

01:01:13.770 --> 01:01:15.810 so the context is key,

NOTE Confidence: 0.625242710113525

01:01:15.810 --> 01:01:17.217 and the targeted,

NOTE Confidence: 0.625242710113525

01:01:17.217 --> 01:01:20.830 the target that we're trying to correct is.

NOTE Confidence: 0.625242710113525

01:01:20.830 --> 01:01:22.714 It's really just kind of an

NOTE Confidence: 0.625242710113525

01:01:22.714 --> 01:01:25.085 Achilles heel in the sense for the

NOTE Confidence: 0.625242710113525

01:01:25.085 --> 01:01:27.179 rather plastic tour in some sense,

NOTE Confidence: 0.625242710113525

01:01:27.180 --> 01:01:29.620 so I think I think that the answer

NOTE Confidence: 0.625242710113525

01:01:29.620 --> 01:01:32.175 the answer to the question is that we

NOTE Confidence: 0.625242710113525

01:01:32.175 --> 01:01:35.189 need to think about these things as networks.

NOTE Confidence: 0.625242710113525

01:01:35.190 --> 01:01:37.176 We need to get into considering

NOTE Confidence: 0.625242710113525

01:01:37.176 --> 01:01:38.870 the systems biology of this.

NOTE Confidence: 0.625242710113525

01:01:38.870 --> 01:01:40.868 I think there are two ways

NOTE Confidence: 0.625242710113525

01:01:40.868 --> 01:01:42.540 of thinking about that one,

NOTE Confidence: 0.625242710113525

01:01:42.540 --> 01:01:44.964 and you'll be aware of this as the

NOTE Confidence: 0.625242710113525

01:01:44.964 --> 01:01:47.220 enormous effort put into machine learning,

NOTE Confidence: 0.625242710113525

01:01:47.220 --> 01:01:48.544 AI types of approaches,

NOTE Confidence: 0.625242710113525

01:01:48.544 --> 01:01:50.890 whereas we collect more and more data.

NOTE Confidence: 0.625242710113525

01:01:50.890 --> 01:01:52.440 For the mutational landscape to

NOTE Confidence: 0.625242710113525

01:01:52.440 --> 01:01:54.456 try to understand their with with

NOTE Confidence: 0.625242710113525

01:01:54.456 --> 01:01:56.108 various their principle components,

NOTE Confidence: 0.625242710113525

01:01:56.110 --> 01:01:58.254 analysis and what have you, what.

NOTE Confidence: 0.625242710113525

01:01:58.254 --> 01:02:00.274 How we can correlate combinations

NOTE Confidence: 0.625242710113525

01:02:00.274 --> 01:02:01.890 of mutations with sensitivity

NOTE Confidence: 0.625242710113525

01:02:01.956 --> 01:02:03.066 and so on so forth.

NOTE Confidence: 0.625242710113525

01:02:03.070 --> 01:02:05.074 But there's another element I think

NOTE Confidence: 0.625242710113525

01:02:05.074 --> 01:02:07.544 we have to consider the a variety

NOTE Confidence: 0.625242710113525

01:02:07.544 --> 01:02:09.329 of systems biologists are taking,

NOTE Confidence: 0.625242710113525

01:02:09.330 --> 01:02:11.766 which I think is is really key.

NOTE Confidence: 0.625242710113525

01:02:11.770 --> 01:02:13.822 And actually I think RAF inhibitor

NOTE Confidence: 0.625242710113525

01:02:13.822 --> 01:02:15.600 resistance illustrates this very nicely.

NOTE Confidence: 0.625242710113525

01:02:15.600 --> 01:02:18.345 Is that we we can actually learn an awful

NOTE Confidence: 0.625242710113525

01:02:18.345 --> 01:02:20.818 lot about how the networks operate,

NOTE Confidence: 0.625242710113525

01:02:20.820 --> 01:02:21.410 you know?

NOTE Confidence: 0.625242710113525

01:02:21.410 --> 01:02:23.180 A classic example is if you

NOTE Confidence: 0.625242710113525

01:02:23.180 --> 01:02:24.420 ever ask mutation,

NOTE Confidence: 0.625242710113525

01:02:24.420 --> 01:02:25.692 then the graph inhibited

NOTE Confidence: 0.625242710113525

01:02:25.692 --> 01:02:26.964 does the wrong thing,

NOTE Confidence: 0.625242710113525

01:02:26.970 --> 01:02:27.534 you know,

NOTE Confidence: 0.625242710113525

01:02:27.534 --> 01:02:29.790 but the bottom line is I think that

NOTE Confidence: 0.625242710113525

01:02:29.857 --> 01:02:32.223 we really we need to start thinking

NOTE Confidence: 0.625242710113525

01:02:32.223 --> 01:02:34.269 beyond the targets to the networks

NOTE Confidence: 0.625242710113525

01:02:34.269 --> 01:02:36.509 and what the effect of the targeted

NOTE Confidence: 0.625242710113525

01:02:36.510 --> 01:02:38.424 therapeutics is on the networks and

NOTE Confidence: 0.625242710113525

01:02:38.424 --> 01:02:40.928 that that of course is going to hold

NOTE Confidence: 0.625242710113525

01:02:40.928 --> 01:02:42.668 in the immune context too because

NOTE Confidence: 0.625242710113525

01:02:42.734 --> 01:02:44.389 again what you actually correcting

NOTE Confidence: 0.625242710113525

01:02:44.389 --> 01:02:46.684 as as as curtain Susan pointed out

NOTE Confidence: 0.625242710113525

01:02:46.684 --> 01:02:48.269 what you're actually dealing with,

NOTE Confidence: 0.625242710113525

01:02:48.270 --> 01:02:48.802 that is,

NOTE Confidence: 0.625242710113525

01:02:48.802 --> 01:02:50.930 is trying to restore balance in an incredibly

NOTE Confidence: 0.625242710113525

01:02:50.984 --> 01:02:52.808 complicated interstellar the network.

NOTE Confidence: 0.625242710113525

01:02:52.810 --> 01:02:55.022 So I think there's a couple of

NOTE Confidence: 0.625242710113525

01:02:55.022 --> 01:02:56.530 perspectives I would like to.

NOTE Confidence: 0.717755913734436

01:02:57.060 --> 01:02:59.286 Could you could you just answer

NOTE Confidence: 0.717755913734436

01:02:59.286 --> 01:03:01.132 that by introducing people a

NOTE Confidence: 0.717755913734436

01:03:01.132 --> 01:03:03.190 little bit to what's going on at

NOTE Confidence: 0.717755913734436

01:03:03.190 --> 01:03:04.999 the Systems Biology Institute.

NOTE Confidence: 0.717755913734436

01:03:05.000 --> 01:03:06.810 Not all of the audience

NOTE Confidence: 0.717755913734436

01:03:06.810 --> 01:03:10.059 may may know about the scale of the effort.

NOTE Confidence: 0.717755913734436

01:03:10.060 --> 01:03:12.300 Yeah indeed. So actually at yeah we

NOTE Confidence: 0.717755913734436

01:03:12.300 --> 01:03:14.524 have a system colleges too that's

NOTE Confidence: 0.717755913734436

01:03:14.524 --> 01:03:16.918 actually headed up by Andra Chanco,

NOTE Confidence: 0.717755913734436

01:03:16.920 --> 01:03:18.720 who's the Director of Vietnam.

NOTE Confidence: 0.717755913734436

01:03:18.720 --> 01:03:21.087 Very is also a Pi on one of the

NOTE Confidence: 0.717755913734436

01:03:21.087 --> 01:03:23.769 NCI cancer Systems biology centers.

NOTE Confidence: 0.717755913734436

01:03:23.770 --> 01:03:25.936 There's a NCI has a physical

NOTE Confidence: 0.717755913734436

01:03:25.936 --> 01:03:27.770 Sciences long college center that.

NOTE Confidence: 0.717755913734436

01:03:27.770 --> 01:03:29.595 Actually, that initiative that you're

NOTE Confidence: 0.717755913734436

01:03:29.595 --> 01:03:32.742 involved with one of those at Penn and and

NOTE Confidence: 0.717755913734436

01:03:32.742 --> 01:03:34.626 also the system cancer systems biology,

NOTE Confidence: 0.717755913734436

01:03:34.630 --> 01:03:35.998 can sort centers consortia

NOTE Confidence: 0.717755913734436

01:03:35.998 --> 01:03:37.366 that 100 grand sent,

NOTE Confidence: 0.717755913734436

01:03:37.370 --> 01:03:39.266 and so the Systems Biology Institute

NOTE Confidence: 0.717755913734436

01:03:39.266 --> 01:03:41.489 here is really very council focused.

NOTE Confidence: 0.717755913734436

01:03:41.490 --> 01:03:43.536 It has a lot of interactions

NOTE Confidence: 0.717755913734436

01:03:43.536 --> 01:03:45.305 with the Cancer Biology Institute

NOTE Confidence: 0.717755913734436

01:03:45.305 --> 01:03:47.657 on also on West Campus at Yale,

NOTE Confidence: 0.717755913734436

01:03:47.660 --> 01:03:49.718 and Andre is an integral part

NOTE Confidence: 0.717755913734436

01:03:49.718 --> 01:03:51.090 of the Cancer Center.

NOTE Confidence: 0.717755913734436

01:03:51.090 --> 01:03:53.498 Of course, the Council biologist is too,

NOTE Confidence: 0.717755913734436

01:03:53.500 --> 01:03:56.380 and so are most members of the Systems

NOTE Confidence: 0.717755913734436

01:03:56.380 --> 01:03:58.718 Biology Institute and the kinds of things.

NOTE Confidence: 0.717755913734436

01:03:58.720 --> 01:04:00.032 Being looked at there,

NOTE Confidence: 0.717755913734436

01:04:00.032 --> 01:04:02.000 which is actually related to this,

NOTE Confidence: 0.717755913734436

01:04:02.000 --> 01:04:04.352 so that Barbara it's a good point

NOTE Confidence: 0.717755913734436

01:04:04.352 --> 01:04:06.579 are for example Andre is very

NOTE Confidence: 0.717755913734436

01:04:06.579 --> 01:04:08.107 interested in looking at.

NOTE Confidence: 0.717755913734436

01:04:08.110 --> 01:04:12.130 But it sells from brain tumors

NOTE Confidence: 0.717755913734436

01:04:12.130 --> 01:04:14.810 in particular and asking.

NOTE Confidence: 0.717755913734436

01:04:14.810 --> 01:04:17.813 Adam and looking at at migration versus

NOTE Confidence: 0.717755913734436

01:04:17.813 --> 01:04:20.210 proliferation in those in those cells,

NOTE Confidence: 0.717755913734436

01:04:20.210 --> 01:04:22.200 and the epigenetic difference between

NOTE Confidence: 0.717755913734436

01:04:22.200 --> 01:04:24.644 between those in terms of what's

NOTE Confidence: 0.717755913734436

01:04:24.644 --> 01:04:26.599 defining the signaling networks that

NOTE Confidence: 0.717755913734436

01:04:26.599 --> 01:04:29.749 cause the cells to behave very differently.

NOTE Confidence: 0.717755913734436

01:04:29.750 --> 01:04:32.851 And he can do that with some

NOTE Confidence: 0.717755913734436

01:04:32.851 --> 01:04:35.050 microfabricated devices where you can

NOTE Confidence: 0.717755913734436

01:04:35.050 --> 01:04:37.432 separate cells based on how rapidly

NOTE Confidence: 0.717755913734436

01:04:37.432 --> 01:04:40.639 they can migrate and then go in and

NOTE Confidence: 0.717755913734436

01:04:40.639 --> 01:04:43.030 look with various single cell and

NOTE Confidence: 0.717755913734436

01:04:43.030 --> 01:04:45.520 other technologies to look at their.

NOTE Confidence: 0.717755913734436

01:04:45.520 --> 01:04:46.621 Transcriptome and obviously

NOTE Confidence: 0.717755913734436

01:04:46.621 --> 01:04:48.456 gentleman and epic transcriptome etc.

NOTE Confidence: 0.717755913734436

01:04:48.460 --> 01:04:50.290 So that's really very exciting.

NOTE Confidence: 0.717755913734436

01:04:50.290 --> 01:04:52.420 There's another element which is

NOTE Confidence: 0.717755913734436

01:04:52.420 --> 01:04:54.922 really at another #2 elements of

NOTE Confidence: 0.717755913734436

01:04:54.922 --> 01:04:56.994 that is one of city channel that

NOTE Confidence: 0.717755913734436

01:04:56.994 --> 01:04:59.099 many of you will come across.

NOTE Confidence: 0.717755913734436

01:04:59.100 --> 01:05:02.151 City is doing an awful lot of work in

NOTE Confidence: 0.717755913734436

01:05:02.151 --> 01:05:05.340 terms of it in the system bars Institute.

NOTE Confidence: 0.717755913734436

01:05:05.340 --> 01:05:07.545 Two in terms of trying to understand

NOTE Confidence: 0.717755913734436

01:05:07.545 --> 01:05:10.109 using using in vivo CRISPR technologies.

NOTE Confidence: 0.717755913734436

01:05:10.110 --> 01:05:11.945 Origins of resistance to terminate

NOTE Confidence: 0.717755913734436

01:05:11.945 --> 01:05:13.780 therapies and another therapeutic approaches.

NOTE Confidence: 0.717755913734436

01:05:13.780 --> 01:05:16.426 And so that's really very exciting again.

NOTE Confidence: 0.717755913734436

01:05:16.430 --> 01:05:18.674 Is is plugged into the network

NOTE Confidence: 0.717755913734436

01:05:18.674 --> 01:05:20.420 consideration of what's going on,

NOTE Confidence: 0.717755913734436

01:05:20.420 --> 01:05:22.240 and then one other aspect,

NOTE Confidence: 0.717755913734436

01:05:22.240 --> 01:05:25.136 which I which I think is really cool.

NOTE Confidence: 0.717755913734436

01:05:25.140 --> 01:05:27.813 Actually as a project in our in EU 54

NOTE Confidence: 0.717755913734436

01:05:27.813 --> 01:05:30.589 that Andre Valances that Gunter Wagner,

NOTE Confidence: 0.717755913734436

01:05:30.590 --> 01:05:32.545 who's an evolutionary biologist is

NOTE Confidence: 0.717755913734436

01:05:32.545 --> 01:05:35.090 is very interested in why certain.

NOTE Confidence: 0.717755913734436

01:05:35.090 --> 01:05:36.920 Mammals don't tend to get meta

NOTE Confidence: 0.717755913734436

01:05:36.920 --> 01:05:38.850 static cancer cows in particular.

NOTE Confidence: 0.717755913734436

01:05:38.850 --> 01:05:40.752 As an example that caused him

NOTE Confidence: 0.717755913734436

01:05:40.752 --> 01:05:42.610 not to die of cancer,

NOTE Confidence: 0.717755913734436

01:05:42.610 --> 01:05:44.320 they just they carry them

NOTE Confidence: 0.717755913734436

01:05:44.320 --> 01:05:45.688 around with the carry.

NOTE Confidence: 0.717755913734436

01:05:45.690 --> 01:05:47.400 The tumors around with him

NOTE Confidence: 0.717755913734436

01:05:47.400 --> 01:05:48.426 without metastasize Ng,

NOTE Confidence: 0.717755913734436

01:05:48.430 --> 01:05:51.122 and pretty much we don't see them here

NOTE Confidence: 0.717755913734436

01:05:51.122 --> 01:05:53.048 because they all killed before they

NOTE Confidence: 0.717755913734436

01:05:53.048 --> 01:05:55.606 get to that stage for other purposes.

NOTE Confidence: 0.717755913734436

01:05:55.610 --> 01:05:57.656 But but and so that's fascinating.

NOTE Confidence: 0.717755913734436

01:05:57.660 --> 01:05:58.686 And so again,

NOTE Confidence: 0.717755913734436

01:05:58.686 --> 01:06:00.738 it's looking at the network context.

NOTE Confidence: 0.717755913734436

01:06:00.740 --> 01:06:02.325 The network differences between the

NOTE Confidence: 0.717755913734436

01:06:02.325 --> 01:06:04.748 mammals that do and don't suffer from

NOTE Confidence: 0.717755913734436

01:06:04.748 --> 01:06:06.192 metastatic cancer, and actually.

NOTE Confidence: 0.717755913734436

01:06:06.192 --> 01:06:08.509 It's kind of related in some senses

NOTE Confidence: 0.717755913734436

01:06:08.509 --> 01:06:10.888 to placental invasiveness in some.

NOTE Confidence: 0.717755913734436

01:06:10.890 --> 01:06:12.810 In these of these organisms,

NOTE Confidence: 0.760184228420258

01:06:12.810 --> 01:06:15.874 which kind of makes sense in some ways.

NOTE Confidence: 0.760184228420258

01:06:15.880 --> 01:06:18.772 And so. So there's a cost, if any.

NOTE Confidence: 0.760184228420258

01:06:18.772 --> 01:06:22.218 There was a cost in some ways of of having

NOTE Confidence: 0.760184228420258

01:06:22.218 --> 01:06:24.708 placenta that more interdigitate ihd,

NOTE Confidence: 0.760184228420258

01:06:24.710 --> 01:06:27.377 which is that you more susceptible to

NOTE Confidence: 0.760184228420258

01:06:27.377 --> 01:06:29.320 metastatic metastasis in your cancer.

NOTE Confidence: 0.760184228420258

01:06:29.320 --> 01:06:31.618 So so so these different perspectives,

NOTE Confidence: 0.760184228420258

01:06:31.620 --> 01:06:32.784 whether it's immune.

NOTE Confidence: 0.760184228420258

01:06:32.784 --> 01:06:34.336 Immunology approaches targeted therapeutics.

NOTE Confidence: 0.760184228420258

01:06:34.340 --> 01:06:36.620 I think there's a a burgeoning

NOTE Confidence: 0.760184228420258

01:06:36.620 --> 01:06:38.450 and is very strong at.

NOTE Confidence: 0.760184228420258

01:06:38.450 --> 01:06:40.320 Yeah, I'm really very exciting.

NOTE Confidence: 0.760184228420258

01:06:40.320 --> 01:06:42.090 I think a burgeoning effort

NOTE Confidence: 0.760184228420258

01:06:42.090 --> 01:06:44.330 and understanding of how to put

NOTE Confidence: 0.760184228420258

01:06:44.330 --> 01:06:45.926 this into the quantitative,

NOTE Confidence: 0.760184228420258

01:06:45.930 --> 01:06:48.290 and I think it needs to be quantitative

NOTE Confidence: 0.760184228420258

01:06:48.290 --> 01:06:50.380 in the sense of biochemical

NOTE Confidence: 0.760184228420258

01:06:50.380 --> 01:06:52.288 networks and pathways contexts.

NOTE Confidence: 0.822815236837968

01:06:53.940 --> 01:06:55.952 Wonderful. Oh, it's perfect.

NOTE Confidence: 0.822815236837968

01:06:55.952 --> 01:06:58.970 I have a question here asking

NOTE Confidence: 0.822815236837968

01:06:59.059 --> 01:07:02.090 the panel to comment on the role

NOTE Confidence: 0.822815236837968

01:07:02.090 --> 01:07:04.988 of proteomics and studying tumor

NOTE Confidence: 0.822815236837968

01:07:04.988 --> 01:07:07.084 resistance, and maybe you'll

NOTE Confidence: 0.822815236837968

01:07:07.084 --> 01:07:09.780 you'll take that first mark in

NOTE Confidence: 0.796327888965607

01:07:09.780 --> 01:07:11.336 the market. Only relates

NOTE Confidence: 0.796327888965607

01:07:11.336 --> 01:07:13.670 exactly to what I was saying.

NOTE Confidence: 0.796327888965607

01:07:13.670 --> 01:07:16.358 I mean, you know you as a biochemist.

NOTE Confidence: 0.796327888965607

01:07:16.360 --> 01:07:18.790 My view is that. Biochemist,

NOTE Confidence: 0.796327888965607

01:07:18.790 --> 01:07:21.296 but my chemistry is defined by the

NOTE Confidence: 0.796327888965607

01:07:21.296 --> 01:07:23.182 component by the combination of

NOTE Confidence: 0.796327888965607

01:07:23.182 --> 01:07:25.378 components that you have and so

NOTE Confidence: 0.796327888965607

01:07:25.378 --> 01:07:28.010 and a lot of those are proteins.

NOTE Confidence: 0.796327888965607

01:07:28.010 --> 01:07:30.593 Of course, it's not just proteins and

NOTE Confidence: 0.796327888965607

01:07:30.593 --> 01:07:33.549 that there are lots of other things too,

NOTE Confidence: 0.796327888965607

01:07:33.550 --> 01:07:35.926 but oh mix of various sorts are crucial

NOTE Confidence: 0.796327888965607

01:07:35.926 --> 01:07:38.348 for really getting a quantitative handle

NOTE Confidence: 0.796327888965607

01:07:38.348 --> 01:07:40.558 on an understanding signaling itself.

NOTE Confidence: 0.796327888965607

01:07:40.560 --> 01:07:42.032 Response to therapeutic have

NOTE Confidence: 0.796327888965607

01:07:42.032 --> 01:07:43.136 course therefore resistance,

NOTE Confidence: 0.796327888965607

01:07:43.140 --> 01:07:47.028 and I think there are two components of it.

NOTE Confidence: 0.796327888965607

01:07:47.030 --> 01:07:49.352 What is just at and I would just want

NOTE Confidence: 0.796327888965607

01:07:49.352 --> 01:07:52.730 to stress this one is just the I guess

NOTE Confidence: 0.796327888965607

01:07:52.730 --> 01:07:54.246 fingerprinting approach that one

NOTE Confidence: 0.796327888965607

01:07:54.246 --> 01:07:56.640 often sees with pretty and say what

NOTE Confidence: 0.796327888965607

01:07:56.640 --> 01:07:58.650 proteins are there in the snapshot?

NOTE Confidence: 0.796327888965607

01:07:58.650 --> 01:08:00.195 What metabolites are there in

NOTE Confidence: 0.796327888965607

01:08:00.195 --> 01:08:02.300 Tableau makes sense in the snapshot.

NOTE Confidence: 0.796327888965607

01:08:02.300 --> 01:08:04.564 That's one aspect and that can give you

NOTE Confidence: 0.796327888965607

01:08:04.564 --> 01:08:06.995 a lot of information but but looking

NOTE Confidence: 0.796327888965607

01:08:06.995 --> 01:08:09.536 at changes in the proteome changes in

NOTE Confidence: 0.796327888965607

01:08:09.536 --> 01:08:11.916 the metabolon with time is really a

NOTE Confidence: 0.796327888965607

01:08:11.916 --> 01:08:14.246 crucial aspect is really that's what what?

NOTE Confidence: 0.796327888965607

01:08:14.250 --> 01:08:16.786 What gives us a picture of the networks

NOTE Confidence: 0.796327888965607

01:08:16.786 --> 01:08:19.329 that we're trying to correct and corral.

NOTE Confidence: 0.796327888965607

01:08:19.330 --> 01:08:21.885 When we're targeting them in with all

NOTE Confidence: 0.796327888965607

01:08:21.885 --> 01:08:23.880 of therapeutics that that we discuss

NOTE Confidence: 0.796327888965607

01:08:23.880 --> 01:08:26.440 it and I just point out that there's a

NOTE Confidence: 0.796327888965607

01:08:26.440 --> 01:08:28.934 quite a lot of activity on this at Yale,

NOTE Confidence: 0.796327888965607

01:08:28.934 --> 01:08:30.578 and one of the people recruited

NOTE Confidence: 0.796327888965607

01:08:30.578 --> 01:08:32.390 into the Cancer Biology Institute,

NOTE Confidence: 0.796327888965607

01:08:32.390 --> 01:08:34.256 for example, is yeah, Shane Lou,

NOTE Confidence: 0.796327888965607

01:08:34.260 --> 01:08:37.370 who has been doing a lot of work looking at,

NOTE Confidence: 0.796327888965607

01:08:37.370 --> 01:08:38.158 for example.

NOTE Confidence: 0.796327888965607

01:08:38.158 --> 01:08:38.946 Proteomic Lee,

NOTE Confidence: 0.796327888965607

01:08:38.946 --> 01:08:40.916 both snapshots and time evolution

NOTE Confidence: 0.796327888965607

01:08:40.916 --> 01:08:42.419 of protein contents.

NOTE Confidence: 0.796327888965607

01:08:42.420 --> 01:08:44.310 It is considered an employee,

NOTE Confidence: 0.796327888965607

01:08:44.310 --> 01:08:46.949 and you know it's kind of interesting

NOTE Confidence: 0.796327888965607

01:08:46.949 --> 01:08:47.703 you really.

NOTE Confidence: 0.796327888965607

01:08:47.710 --> 01:08:49.978 If you look at any point,

NOTE Confidence: 0.796327888965607

01:08:49.980 --> 01:08:52.332 sells the effects on the protein

NOTE Confidence: 0.796327888965607

01:08:52.332 --> 01:08:55.151 were really not what you would have

NOTE Confidence: 0.796327888965607

01:08:55.151 --> 01:08:57.895 predicted based on on what you've lost

NOTE Confidence: 0.796327888965607

01:08:57.970 --> 01:09:00.554 in terms of of gene copies or gain.

NOTE Confidence: 0.796327888965607

01:09:00.560 --> 01:09:01.262 And Moreover,

NOTE Confidence: 0.796327888965607

01:09:01.262 --> 01:09:03.017 it's important to note that

NOTE Confidence: 0.796327888965607

01:09:03.017 --> 01:09:04.720 reaction is really pioneered.

NOTE Confidence: 0.796327888965607

01:09:04.720 --> 01:09:07.088 This too that RNA seek data and proteomic

NOTE Confidence: 0.796327888965607

01:09:07.088 --> 01:09:09.259 data have substantial discrepancies,

NOTE Confidence: 0.796327888965607

01:09:09.260 --> 01:09:11.927 and so and so that means also

NOTE Confidence: 0.796327888965607

01:09:11.927 --> 01:09:13.070 appreciate the proteomics.

NOTE Confidence: 0.796327888965607

01:09:13.070 --> 01:09:15.300 Is really an important thing

NOTE Confidence: 0.796327888965607

01:09:15.300 --> 01:09:18.619 to add to all of this code.

NOTE Confidence: 0.796327888965607

01:09:18.620 --> 01:09:18.970 Yes,

NOTE Confidence: 0.823916912078857

01:09:18.970 --> 01:09:22.075 so stay think I would like just to comment

NOTE Confidence: 0.823916912078857

01:09:22.075 --> 01:09:24.145 about the frustration of analyzing tissue

NOTE Confidence: 0.823916912078857

01:09:24.145 --> 01:09:25.870 level data without spatial resolution.

NOTE Confidence: 0.823916912078857

01:09:25.870 --> 01:09:28.630 This is critical because as a smart pointed,

NOTE Confidence: 0.823916912078857

01:09:28.630 --> 01:09:30.718 we see a striking difference between

NOTE Confidence: 0.823916912078857

01:09:30.718 --> 01:09:32.843 our name protein which is becoming

NOTE Confidence: 0.823916912078857

01:09:32.843 --> 01:09:34.835 the rule more than the exception.

NOTE Confidence: 0.823916912078857

01:09:34.840 --> 01:09:36.820 But second, the protein measurements and

NOTE Confidence: 0.823916912078857

01:09:36.820 --> 01:09:39.319 any other like really is context dependent.

NOTE Confidence: 0.823916912078857

01:09:39.320 --> 01:09:41.588 So for example, just to give you

NOTE Confidence: 0.823916912078857

01:09:41.588 --> 01:09:43.714 a rough example measurement of K

NOTE Confidence: 0.823916912078857

01:09:43.714 --> 01:09:45.874 67 protein in any given sample,

NOTE Confidence: 0.823916912078857

01:09:45.880 --> 01:09:47.950 if it's in the tumor cell,

NOTE Confidence: 0.823916912078857

01:09:47.950 --> 01:09:49.690 it means that you know.

NOTE Confidence: 0.823916912078857

01:09:49.690 --> 01:09:51.220 Tumors are proliferating if it's

NOTE Confidence: 0.823916912078857

01:09:51.220 --> 01:09:53.097 in the immune cells means good

NOTE Confidence: 0.823916912078857

01:09:53.097 --> 01:09:54.237 T cells are expanding,

NOTE Confidence: 0.823916912078857

01:09:54.240 --> 01:09:56.284 so really I think having the possibility

NOTE Confidence: 0.823916912078857

01:09:56.284 --> 01:09:58.776 of looking at the proteins in the in

NOTE Confidence: 0.823916912078857

01:09:58.776 --> 01:10:00.348 the context of tissue organization,

NOTE Confidence: 0.823916912078857

01:10:00.348 --> 01:10:01.616 it's critical for understanding

NOTE Confidence: 0.823916912078857

01:10:01.616 --> 01:10:02.420 what's going on,

NOTE Confidence: 0.823916912078857

01:10:02.420 --> 01:10:04.814 and I think that's a little bit when I

NOTE Confidence: 0.823916912078857

01:10:04.814 --> 01:10:06.959 tried to reflect in my presentation,

NOTE Confidence: 0.823916912078857

01:10:06.960 --> 01:10:07.869 we're still early.

NOTE Confidence: 0.823916912078857

01:10:07.869 --> 01:10:09.081 We're getting more quantitative

NOTE Confidence: 0.823916912078857

01:10:09.081 --> 01:10:09.687 than throughput.

NOTE Confidence: 0.823916912078857

01:10:09.690 --> 01:10:11.200 It's coming up to speed,

NOTE Confidence: 0.823916912078857

01:10:11.200 --> 01:10:13.018 but but I think it's a.

NOTE Confidence: 0.823916912078857

01:10:13.020 --> 01:10:14.232 It's an important dimension

NOTE Confidence: 0.823916912078857

01:10:14.232 --> 01:10:15.747 of the protein and any

NOTE Confidence: 0.842197835445404

01:10:15.750 --> 01:10:17.260 other light data. Absolutely perfect

NOTE Confidence: 0.842197835445404

01:10:17.260 --> 01:10:19.692 and Megan. Do you want to just jump

NOTE Confidence: 0.842197835445404

01:10:19.692 --> 01:10:22.512 in on this one as well? I just wanted

NOTE Confidence: 0.842197835445404

01:10:22.512 --> 01:10:25.200 to add just also OK, great. You

NOTE Confidence: 0.855397522449493

01:10:25.200 --> 01:10:26.964 know, as a first, just to say

NOTE Confidence: 0.855397522449493

01:10:26.964 --> 01:10:28.810 I think this is exactly right.

NOTE Confidence: 0.855397522449493

01:10:28.810 --> 01:10:30.200 When we asked us why,

NOTE Confidence: 0.855397522449493

01:10:30.200 --> 01:10:32.062 we know that just doing the genome

NOTE Confidence: 0.855397522449493

01:10:32.062 --> 01:10:34.089 sequencing is not going to be sufficient.

NOTE Confidence: 0.855397522449493

01:10:34.090 --> 01:10:35.650 We can start with the gene

NOTE Confidence: 0.855397522449493

01:10:35.650 --> 01:10:36.690 expression analysis because there

NOTE Confidence: 0.855397522449493

01:10:36.733 --> 01:10:37.989 are these epigenetic changes,

NOTE Confidence: 0.855397522449493

01:10:37.990 --> 01:10:39.380 but it's very clear that

NOTE Confidence: 0.855397522449493

01:10:39.380 --> 01:10:40.770 that's also in not sufficient.

NOTE Confidence: 0.855397522449493

01:10:40.770 --> 01:10:42.842 And one thing I just wanted to point

NOTE Confidence: 0.855397522449493

01:10:42.842 --> 01:10:44.939 out is that as a cell biologist,

NOTE Confidence: 0.855397522449493

01:10:44.940 --> 01:10:46.488 I think we we know understand

NOTE Confidence: 0.855397522449493

01:10:46.488 --> 01:10:47.990 really well that for example,

NOTE Confidence: 0.855397522449493

01:10:47.990 --> 01:10:49.102 translational capacity is something

NOTE Confidence: 0.855397522449493

01:10:49.102 --> 01:10:50.492 that's highly affected by stress,

NOTE Confidence: 0.855397522449493

01:10:50.500 --> 01:10:52.316 and so when we think about what's going

NOTE Confidence: 0.855397522449493

01:10:52.316 --> 01:10:54.388 on in a particular tumor environment,

NOTE Confidence: 0.855397522449493

01:10:54.390 --> 01:10:56.058 how that might be affecting the.

NOTE Confidence: 0.855397522449493

01:10:56.060 --> 01:10:57.288 Relative efficiencies of translation,

NOTE Confidence: 0.855397522449493

01:10:57.288 --> 01:10:58.823 which will never be fully

NOTE Confidence: 0.855397522449493

01:10:58.823 --> 01:11:00.187 reflected in an RNA seek data set,

NOTE Confidence: 0.855397522449493

01:11:00.190 --> 01:11:01.738 is going to be really important.

NOTE Confidence: 0.855397522449493

01:11:01.740 --> 01:11:02.511 And you know,

NOTE Confidence: 0.855397522449493

01:11:02.511 --> 01:11:04.060 one of the things, for example,

NOTE Confidence: 0.855397522449493

01:11:04.060 --> 01:11:05.880 that we think about a lot because

NOTE Confidence: 0.855397522449493

01:11:05.880 --> 01:11:07.491 appeared lasers work is thinking about

NOTE Confidence: 0.855397522449493

01:11:07.491 --> 01:11:09.219 hypoxia as a good example of this,

NOTE Confidence: 0.855397522449493

01:11:09.220 --> 01:11:10.768 and then the protein turnover aspects,

NOTE Confidence: 0.855397522449493

01:11:10.770 --> 01:11:11.021 right?

NOTE Confidence: 0.855397522449493

01:11:11.021 --> 01:11:13.280 And so these are all the factors that are

NOTE Confidence: 0.855397522449493

01:11:13.335 --> 01:11:15.344 that are contributing to what we might

NOTE Confidence: 0.855397522449493

01:11:15.344 --> 01:11:17.466 see different in a in a podium data set.

NOTE Confidence: 0.855397522449493

01:11:17.470 --> 01:11:19.018 And I was going to exactly

NOTE Confidence: 0.855397522449493

01:11:19.018 --> 01:11:20.050 the same point about,

NOTE Confidence: 0.855397522449493

01:11:20.050 --> 01:11:20.824 you know, aneuploidy,

NOTE Confidence: 0.855397522449493

01:11:20.824 --> 01:11:21.598 because you know,

NOTE Confidence: 0.855397522449493

01:11:21.600 --> 01:11:22.108 we know,

NOTE Confidence: 0.855397522449493

01:11:22.108 --> 01:11:23.378 and this is particularly relevant

NOTE Confidence: 0.855397522449493

01:11:23.378 --> 01:11:25.187 also for DNA repair factors that one

NOTE Confidence: 0.855397522449493

01:11:25.187 --> 01:11:27.013 of the ideas of why aneuploidy causes

NOTE Confidence: 0.855397522449493

01:11:27.013 --> 01:11:28.675 such changes in the proteomes that.

NOTE Confidence: 0.855397522449493

01:11:28.680 --> 01:11:30.310 We have these large protein

NOTE Confidence: 0.855397522449493

01:11:30.310 --> 01:11:31.940 complexes which are very codependent

NOTE Confidence: 0.855397522449493

01:11:31.996 --> 01:11:33.851 and they become kind of out of

NOTE Confidence: 0.855397522449493

01:11:33.851 --> 01:11:35.209 titration with regard to the

NOTE Confidence: 0.855397522449493

01:11:35.209 --> 01:11:36.739 components and that can you know,

NOTE Confidence: 0.855397522449493

01:11:36.740 --> 01:11:38.522 most of us are working on

NOTE Confidence: 0.855397522449493

01:11:38.522 --> 01:11:39.710 complex molecular machines where

NOTE Confidence: 0.855397522449493

01:11:39.762 --> 01:11:41.346 that's going to have an impact,

NOTE Confidence: 0.855397522449493

01:11:41.350 --> 01:11:42.790 and so that's going to

NOTE Confidence: 0.855397522449493

01:11:42.790 --> 01:11:43.654 really require detailed,

NOTE Confidence: 0.855397522449493

01:11:43.660 --> 01:11:45.100 the kind of mechanistic analysis.

NOTE Confidence: 0.855397522449493

01:11:45.100 --> 01:11:46.934 But we might get pointed to the

NOTE Confidence: 0.855397522449493

01:11:46.934 --> 01:11:49.067 fact that we need to do that work

NOTE Confidence: 0.855397522449493

01:11:49.067 --> 01:11:51.100 only if we go actually looking for

NOTE Confidence: 0.855397522449493

01:11:51.100 --> 01:11:53.158 proteome wide data instead of just

NOTE Confidence: 0.828034579753876

01:11:53.160 --> 01:11:54.600 the genomics. Thanks great Katie.

NOTE Confidence: 0.879784941673279

01:11:55.150 --> 01:11:58.426 Yes, so I just wanted to add to the

NOTE Confidence: 0.879784941673279

01:11:58.426 --> 01:12:00.635 conversation that because of the

NOTE Confidence: 0.879784941673279

01:12:00.635 --> 01:12:02.835 challenges of studying the pathways

NOTE Confidence: 0.879784941673279

01:12:02.835 --> 01:12:05.640 in in patient specimens directly,

NOTE Confidence: 0.879784941673279

01:12:05.640 --> 01:12:08.082 all of the things that were

NOTE Confidence: 0.879784941673279

01:12:08.082 --> 01:12:10.450 brought up the patient arrived.

NOTE Confidence: 0.879784941673279

01:12:10.450 --> 01:12:12.420 Models actually represent a really

NOTE Confidence: 0.879784941673279

01:12:12.420 --> 01:12:15.435 useful system to look at signaling and

NOTE Confidence: 0.879784941673279

01:12:15.435 --> 01:12:17.870 how signaling changes with treatment.

NOTE Confidence: 0.879784941673279

01:12:17.870 --> 01:12:20.677 And it's one of the reasons for

NOTE Confidence: 0.879784941673279

01:12:20.677 --> 01:12:23.988 which we did engage in this effort.

NOTE Confidence: 0.879784941673279

01:12:23.990 --> 01:12:26.636 In developing these models and also.

NOTE Confidence: 0.879784941673279

01:12:26.640 --> 01:12:28.932 Allows us to really explore how

NOTE Confidence: 0.879784941673279

01:12:28.932 --> 01:12:30.460 heterogeneous these samples are

NOTE Confidence: 0.879784941673279

01:12:30.522 --> 01:12:32.277 across different patient tumors so

NOTE Confidence: 0.879784941673279

01:12:32.277 --> 01:12:34.815 we can take tumors with a specific

NOTE Confidence: 0.879784941673279

01:12:34.815 --> 01:12:36.600 alterations or just across the

NOTE Confidence: 0.879784941673279

01:12:36.600 --> 01:12:38.466 wear resistant to specific therapy,

NOTE Confidence: 0.879784941673279

01:12:38.466 --> 01:12:41.217 and we can look at specific things

NOTE Confidence: 0.879784941673279

01:12:41.217 --> 01:12:43.611 in terms of at the protein level

NOTE Confidence: 0.879784941673279

01:12:43.611 --> 01:12:46.486 in those and we can look if we

NOTE Confidence: 0.879784941673279

01:12:46.486 --> 01:12:47.620 apply other therapies,

NOTE Confidence: 0.879784941673279

01:12:47.620 --> 01:12:49.816 what changes and so that really,

NOTE Confidence: 0.879784941673279

01:12:49.820 --> 01:12:50.432 I think,

NOTE Confidence: 0.879784941673279

01:12:50.432 --> 01:12:52.268 is a very valuable system in

NOTE Confidence: 0.879784941673279

01:12:52.268 --> 01:12:54.669 which to study what's happening at

NOTE Confidence: 0.879784941673279

01:12:54.669 --> 01:12:56.814 the protein level and signaling.

NOTE Confidence: 0.802920758724213

01:12:57.920 --> 01:13:00.587 Susan, could I just ask you to

NOTE Confidence: 0.802920758724213

01:13:00.587 --> 01:13:03.743 comment on how the the the different

NOTE Confidence: 0.802920758724213

01:13:03.743 --> 01:13:06.153 omics are approached from within

NOTE Confidence: 0.802920758724213

01:13:06.153 --> 01:13:09.476 an organization like yours and and

NOTE Confidence: 0.802920758724213

01:13:09.476 --> 01:13:12.226 to what extent leveraging systems

NOTE Confidence: 0.802920758724213

01:13:12.230 --> 01:13:14.970 biology approaches is is practical

NOTE Confidence: 0.802920758724213

01:13:14.970 --> 01:13:17.390 within your organization? Yeah, sure,

NOTE Confidence: 0.838525116443634

01:13:17.390 --> 01:13:20.326 and so I mean, I agree with the

NOTE Confidence: 0.838525116443634

01:13:20.326 --> 01:13:22.369 comments that have been made.

NOTE Confidence: 0.838525116443634

01:13:22.370 --> 01:13:24.834 First of all that we do need to

NOTE Confidence: 0.838525116443634

01:13:24.834 --> 01:13:26.879 look at these different mechanisms

NOTE Confidence: 0.838525116443634

01:13:26.879 --> 01:13:30.029 and it is possible to do that.

NOTE Confidence: 0.838525116443634

01:13:30.030 --> 01:13:32.052 Increasingly, you know where we are

NOTE Confidence: 0.838525116443634

01:13:32.052 --> 01:13:33.888 looking with things like Multiplex

NOTE Confidence: 0.838525116443634

01:13:33.888 --> 01:13:35.576 immediate fluorescence at the

NOTE Confidence: 0.838525116443634

01:13:35.576 --> 01:13:37.686 spatial organization of the tumors,

NOTE Confidence: 0.838525116443634

01:13:37.690 --> 01:13:41.128 and in doing that in in patient samples now.

NOTE Confidence: 0.838525116443634

01:13:41.130 --> 01:13:44.146 So I think the technologies are advancing to

NOTE Confidence: 0.838525116443634

01:13:44.146 --> 01:13:47.309 enable you to do that single cell sequencing.

NOTE Confidence: 0.838525116443634

01:13:47.310 --> 01:13:48.222 Is also helping.

NOTE Confidence: 0.838525116443634

01:13:48.222 --> 01:13:51.667 I think you know what I would say is that you

NOTE Confidence: 0.838525116443634

01:13:51.667 --> 01:13:54.330 can't do that intensively on on many child,

NOTE Confidence: 0.838525116443634

01:13:54.330 --> 01:13:56.430 so you have to choose the trial

NOTE Confidence: 0.838525116443634

01:13:56.430 --> 01:13:58.478 setting and the context for that.

NOTE Confidence: 0.838525116443634

01:13:58.480 --> 01:14:00.622 And it does have to be complemented

NOTE Confidence: 0.838525116443634

01:14:00.622 --> 01:14:02.584 by the kinds of things that

NOTE Confidence: 0.838525116443634

01:14:02.584 --> 01:14:04.540 Katie was talked about as well,

NOTE Confidence: 0.838525116443634

01:14:04.540 --> 01:14:06.766 so I think you know you can.

NOTE Confidence: 0.838525116443634

01:14:06.770 --> 01:14:09.202 You can see some sense of the overall

NOTE Confidence: 0.838525116443634

01:14:09.202 --> 01:14:11.036 picture emerging from some of the

NOTE Confidence: 0.838525116443634

01:14:11.036 --> 01:14:12.496 clinical trial data you really

NOTE Confidence: 0.838525116443634

01:14:12.496 --> 01:14:14.429 need to understand the mechanism,

NOTE Confidence: 0.838525116443634

01:14:14.430 --> 01:14:16.368 and for that you need a

NOTE Confidence: 0.838525116443634

01:14:16.368 --> 01:14:17.337 different setting and.

NOTE Confidence: 0.838525116443634

01:14:17.340 --> 01:14:19.548 Environment to do that in the

NOTE Confidence: 0.838525116443634

01:14:19.548 --> 01:14:21.379 different techniques and then you

NOTE Confidence: 0.838525116443634

01:14:21.379 --> 01:14:23.388 know the the PDX models have the

NOTE Confidence: 0.838525116443634

01:14:23.388 --> 01:14:25.503 have some challenges the Gen models

NOTE Confidence: 0.838525116443634

01:14:25.503 --> 01:14:27.711 have their own set of challenges.

NOTE Confidence: 0.838525116443634

01:14:27.720 --> 01:14:29.796 The humanized models for IO have

NOTE Confidence: 0.838525116443634

01:14:29.796 --> 01:14:32.212 their own set of challenges and I

NOTE Confidence: 0.838525116443634

01:14:32.212 --> 01:14:34.876 think what we can try and do is

NOTE Confidence: 0.838525116443634

01:14:34.876 --> 01:14:37.054 by looking collectively at at at,

NOTE Confidence: 0.838525116443634

01:14:37.060 --> 01:14:39.090 you know the clinical sample data and

NOTE Confidence: 0.838525116443634

01:14:39.090 --> 01:14:41.221 these range of preclinical models and

NOTE Confidence: 0.838525116443634

01:14:41.221 --> 01:14:43.633 backwards and forwards across that divide,

NOTE Confidence: 0.838525116443634

01:14:43.640 --> 01:14:45.782 that that's how you build up the

NOTE Confidence: 0.838525116443634

01:14:45.782 --> 01:14:47.809 bigger picture of of understanding.

NOTE Confidence: 0.838525116443634

01:14:47.810 --> 01:14:48.869 But you know,

NOTE Confidence: 0.838525116443634

01:14:48.870 --> 01:14:51.694 I think it's like it is like trying to

NOTE Confidence: 0.838525116443634

01:14:51.694 --> 01:14:54.381 sort of workout the overall picture from

NOTE Confidence: 0.838525116443634

01:14:54.381 --> 01:14:57.018 having several pieces of the jigsaw together,

NOTE Confidence: 0.838525116443634

01:14:57.018 --> 01:14:58.080 which is great,

NOTE Confidence: 0.838525116443634

01:14:58.080 --> 01:14:59.396 but you know nothing,

NOTE Confidence: 0.838525116443634

01:14:59.396 --> 01:15:01.041 that holistic view is absolutely

NOTE Confidence: 0.838525116443634

01:15:01.041 --> 01:15:02.320 critical to understanding,

NOTE Confidence: 0.838525116443634

01:15:02.320 --> 01:15:04.776 so I you know my comment would be

NOTE Confidence: 0.838525116443634

01:15:04.776 --> 01:15:07.135 that I think that the technology

NOTE Confidence: 0.838525116443634

01:15:07.135 --> 01:15:10.031 advances are now in place to enable

NOTE Confidence: 0.838525116443634

01:15:10.031 --> 01:15:12.615 us to see so much more than we

NOTE Confidence: 0.838525116443634

01:15:12.615 --> 01:15:15.070 were able to see 510 years ago.

NOTE Confidence: 0.838525116443634

01:15:15.070 --> 01:15:17.188 We need to bring that together,

NOTE Confidence: 0.838525116443634

01:15:17.190 --> 01:15:18.960 but have an integrated plan

NOTE Confidence: 0.838525116443634

01:15:18.960 --> 01:15:20.376 that goes across preclinical.

NOTE Confidence: 0.838525116443634

01:15:20.380 --> 01:15:22.480 Translational and clinical trial environment.

NOTE Confidence: 0.838525116443634

01:15:22.480 --> 01:15:24.580 Then I think that's critical,

NOTE Confidence: 0.838525116443634

01:15:24.580 --> 01:15:27.037 so we spend a lot of time in what

NOTE Confidence: 0.838525116443634

01:15:27.037 --> 01:15:29.632 is called early stage oncology

NOTE Confidence: 0.838525116443634

01:15:29.632 --> 01:15:31.876 without translation of medicine

NOTE Confidence: 0.838525116443634

01:15:31.876 --> 01:15:34.308 group actually working with drugs

NOTE Confidence: 0.838525116443634

01:15:34.308 --> 01:15:37.171 and programs that are in late phase

NOTE Confidence: 0.838525116443634

01:15:37.180 --> 01:15:39.285 development already on the market

NOTE Confidence: 0.838525116443634

01:15:39.285 --> 01:15:41.800 like awesome Internet and you know.

NOTE Confidence: 0.838525116443634

01:15:41.800 --> 01:15:42.952 And if I'm out.

NOTE Confidence: 0.838525116443634

01:15:42.952 --> 01:15:45.074 The other drugs that we have there

NOTE Confidence: 0.838525116443634

01:15:45.074 --> 01:15:47.000 because the two reasons one is

NOTE Confidence: 0.838525116443634

01:15:47.000 --> 01:15:48.912 that I think that's absolutely

NOTE Confidence: 0.838525116443634

01:15:48.912 --> 01:15:51.107 critical to understanding how to

NOTE Confidence: 0.838525116443634

01:15:51.107 --> 01:15:53.393 develop those in and continue that.

NOTE Confidence: 0.838525116443634

01:15:53.393 --> 01:15:54.677 But Secondly that understanding

NOTE Confidence: 0.838525116443634

01:15:54.677 --> 01:15:56.440 their feedback into the discovery

NOTE Confidence: 0.838525116443634

01:15:56.440 --> 01:15:57.940 organization for new opportunities.

NOTE Confidence: 0.838525116443634

01:15:57.940 --> 01:16:00.775 And I think the final piece I would say

NOTE Confidence: 0.838525116443634

01:16:00.775 --> 01:16:03.790 is that we can't do it all internally.

NOTE Confidence: 0.838525116443634

01:16:03.790 --> 01:16:04.819 Collaborations with organizations

NOTE Confidence: 0.838525116443634

01:16:04.819 --> 01:16:06.534 like Yale is absolutely critical.

NOTE Confidence: 0.838525116443634

01:16:06.540 --> 01:16:08.864 You've already heard a number of examples

NOTE Confidence: 0.838525116443634

01:16:08.864 --> 01:16:11.018 of the kinds of collaborations that

NOTE Confidence: 0.838525116443634

01:16:11.018 --> 01:16:13.810 that that we have that really helped to.

NOTE Confidence: 0.838525116443634

01:16:13.810 --> 01:16:15.080 And to feed and stimulate

NOTE Confidence: 0.838525116443634

01:16:15.080 --> 01:16:16.350 the work that we're doing

NOTE Confidence: 0.772767424583435

01:16:16.402 --> 01:16:18.090 internally. So you know really

NOTE Confidence: 0.772767424583435

01:16:18.090 --> 01:16:19.800 appreciate the work that that Megan,

NOTE Confidence: 0.772767424583435

01:16:19.800 --> 01:16:21.669 a team of doing that Katie Ability

NOTE Confidence: 0.772767424583435

01:16:21.669 --> 01:16:23.557 and her team are doing because

NOTE Confidence: 0.772767424583435

01:16:23.557 --> 01:16:25.603 that that sees what we're doing

NOTE Confidence: 0.772767424583435

01:16:25.603 --> 01:16:27.486 internally and we can't do all of it.

NOTE Confidence: 0.840360403060913

01:16:28.580 --> 01:16:30.746 Great good, there's a question here

NOTE Confidence: 0.840360403060913

01:16:30.746 --> 01:16:33.090 asking can we share examples of

NOTE Confidence: 0.840360403060913

01:16:33.090 --> 01:16:35.160 partnership with other academic centers

NOTE Confidence: 0.840360403060913

01:16:35.160 --> 01:16:38.390 that we may have for precision medicine

NOTE Confidence: 0.840360403060913

01:16:38.390 --> 01:16:40.310 efforts and adaptive combination

NOTE Confidence: 0.840360403060913

01:16:40.310 --> 01:16:42.527 treatment to overcome resistance and?

NOTE Confidence: 0.840360403060913

01:16:42.527 --> 01:16:45.460 And I'll talk about that maybe a

NOTE Confidence: 0.840360403060913

01:16:45.538 --> 01:16:48.040 little bit from the medicine side.

NOTE Confidence: 0.840360403060913

01:16:48.040 --> 01:16:50.610 Pet Larusso here leads experimental

NOTE Confidence: 0.840360403060913

01:16:50.610 --> 01:16:52.152 therapeutics clinical trials

NOTE Confidence: 0.840360403060913

01:16:52.152 --> 01:16:54.510 network U M1 grant that has.

NOTE Confidence: 0.840360403060913

01:16:54.510 --> 01:16:57.762 Many consortium members and she and

NOTE Confidence: 0.840360403060913

01:16:57.762 --> 01:17:01.455 her colleagues are leaders in taking

NOTE Confidence: 0.840360403060913

01:17:01.455 --> 01:17:04.323 molecularly driven questions and

NOTE Confidence: 0.840360403060913

01:17:04.323 --> 01:17:07.191 actually molecular selection strategies

NOTE Confidence: 0.840360403060913

01:17:07.281 --> 01:17:10.777 forward in the Umm in the ETCTN network.

NOTE Confidence: 0.840360403060913

01:17:10.780 --> 01:17:15.365 Jeff Sklar, here, runs one of the.

NOTE Confidence: 0.840360403060913

01:17:15.370 --> 01:17:19.150 Lamps that did the precision medicine

NOTE Confidence: 0.840360403060913

01:17:19.150 --> 01:17:22.390 sequencing for the match trial.

NOTE Confidence: 0.840360403060913

01:17:22.390 --> 01:17:24.942 We have investigators here

NOTE Confidence: 0.840360403060913

01:17:24.942 --> 01:17:27.494 leading match sub trials.

NOTE Confidence: 0.840360403060913

01:17:27.500 --> 01:17:30.867 We have, I think within our spores,

NOTE Confidence: 0.840360403060913

01:17:30.870 --> 01:17:32.774 collaborations across other cancer

NOTE Confidence: 0.840360403060913

01:17:32.774 --> 01:17:34.678 centers that are molecularly

NOTE Confidence: 0.840360403060913

01:17:34.678 --> 01:17:36.659 driven clinical trial questions.

NOTE Confidence: 0.840360403060913

01:17:36.660 --> 01:17:40.988 So I think from the disease based and

NOTE Confidence: 0.840360403060913

01:17:40.988 --> 01:17:44.051 clinical arena Ann from the Phase

NOTE Confidence: 0.840360403060913

01:17:44.051 --> 01:17:47.490 one arena there is quite a rich.

NOTE Confidence: 0.840360403060913

01:17:47.490 --> 01:17:50.610 A network of of these types of interactions,

NOTE Confidence: 0.840360403060913

01:17:50.610 --> 01:17:53.368 I don't know if anybody wants to

NOTE Confidence: 0.840360403060913

01:17:53.368 --> 01:17:55.889 address more from the preclinical.

NOTE Confidence: 0.840360403060913

01:17:55.890 --> 01:17:56.530 Level.

NOTE Confidence: 0.786874294281006

01:17:59.390 --> 01:18:02.042 I could just just comment that the

NOTE Confidence: 0.786874294281006

01:18:02.042 --> 01:18:03.570 anaplastic lymphoma kinase work

NOTE Confidence: 0.786874294281006

01:18:03.636 --> 01:18:05.126 that I mentioned at work.

NOTE Confidence: 0.786874294281006

01:18:05.130 --> 01:18:07.140 That's all guns are long term

NOTE Confidence: 0.786874294281006

01:18:07.140 --> 01:18:08.892 collaboration with people at Children's

NOTE Confidence: 0.786874294281006

01:18:08.892 --> 01:18:10.974 Hospital in Philadelphia and a new

NOTE Confidence: 0.786874294281006

01:18:10.974 --> 01:18:13.232 pen where much of the computational

NOTE Confidence: 0.786874294281006

01:18:13.232 --> 01:18:15.542 modeling is done actually through that.

NOTE Confidence: 0.786874294281006

01:18:15.550 --> 01:18:17.400 And then another approach that

NOTE Confidence: 0.786874294281006

01:18:17.400 --> 01:18:19.490 another aspect that we're working on,

NOTE Confidence: 0.786874294281006

01:18:19.490 --> 01:18:22.370 which is a collaboration of many.

NOTE Confidence: 0.786874294281006

01:18:22.370 --> 01:18:24.884 Out of many academic medical centers

NOTE Confidence: 0.786874294281006

01:18:24.884 --> 01:18:27.479 actually in the US and abroad,

NOTE Confidence: 0.786874294281006

01:18:27.480 --> 01:18:29.508 we actually have through the Alex

NOTE Confidence: 0.786874294281006

01:18:29.508 --> 01:18:32.517 is now in H Town Foundation and

NOTE Confidence: 0.786874294281006

01:18:32.517 --> 01:18:35.147 approach to targeting Myc signaling.

NOTE Confidence: 0.786874294281006

01:18:35.150 --> 01:18:37.388 Let me say it's not targeting

NOTE Confidence: 0.786874294281006

01:18:37.388 --> 01:18:39.937 Nick Per saver comes relates to

NOTE Confidence: 0.786874294281006

01:18:39.937 --> 01:18:42.387 combination therapies and so forth,

NOTE Confidence: 0.786874294281006

01:18:42.390 --> 01:18:44.976 the idea being that multigroup approach.

NOTE Confidence: 0.786874294281006

01:18:44.980 --> 01:18:47.647 With the idea that that make aberrations,

NOTE Confidence: 0.786874294281006

01:18:47.650 --> 01:18:48.799 particularly making neuroblastoma

NOTE Confidence: 0.786874294281006

01:18:48.799 --> 01:18:49.948 affect the network,

NOTE Confidence: 0.786874294281006

01:18:49.950 --> 01:18:52.344 and in principle one could rescue the

NOTE Confidence: 0.786874294281006

01:18:52.344 --> 01:18:54.150 network with appropriate combinations,

NOTE Confidence: 0.786874294281006

01:18:54.150 --> 01:18:56.436 and I think with the technologies,

NOTE Confidence: 0.786874294281006

01:18:56.440 --> 01:18:57.968 as Susan pointed out,

NOTE Confidence: 0.786874294281006

01:18:57.968 --> 01:18:58.350 advancing,

NOTE Confidence: 0.786874294281006

01:18:58.350 --> 01:19:01.455 I think the time is is is is is

NOTE Confidence: 0.786874294281006

01:19:01.455 --> 01:19:04.300 right to get to ask that question

NOTE Confidence: 0.786874294281006

01:19:04.300 --> 01:19:06.370 in that type of way.

NOTE Confidence: 0.819485902786255

01:19:09.450 --> 01:19:10.866 Anybody else wanna OK?

NOTE Confidence: 0.819485902786255

01:19:10.866 --> 01:19:12.990 There's a question here in the

NOTE Confidence: 0.819485902786255

01:19:13.062 --> 01:19:15.270 context of overcoming resistance.

NOTE Confidence: 0.819485902786255

01:19:15.270 --> 01:19:17.115 Can panelists share with their

NOTE Confidence: 0.819485902786255

01:19:17.115 --> 01:19:18.960 most excited about in terms

NOTE Confidence: 0.819485902786255

01:19:19.025 --> 01:19:20.678 of combination modalities?

NOTE Confidence: 0.819485902786255

01:19:20.680 --> 01:19:24.424 And maybe I'll just ask him to go first?

NOTE Confidence: 0.819485902786255

01:19:24.430 --> 01:19:28.294 'cause I love the KTM Ivy story.

NOTE Confidence: 0.819485902786255

01:19:28.300 --> 01:19:30.604 But I think everybody probably has

NOTE Confidence: 0.819485902786255

01:19:30.604 --> 01:19:32.440 their own favorite combination too,

NOTE Confidence: 0.819485902786255

01:19:32.440 --> 01:19:33.559 and you just

NOTE Confidence: 0.773967266082764

01:19:33.560 --> 01:19:36.192 want to, yeah, so of course I

NOTE Confidence: 0.773967266082764

01:19:36.192 --> 01:19:38.452 think because I work samples next,

NOTE Confidence: 0.773967266082764

01:19:38.452 --> 01:19:40.708 my my opinion might be any

NOTE Confidence: 0.76289176940918

01:19:40.710 --> 01:19:41.910 bias. Modulation is

NOTE Confidence: 0.757354021072388

01:19:41.910 --> 01:19:43.119 critical for that

NOTE Confidence: 0.757354021072388

01:19:43.120 --> 01:19:45.140 and not only the case.

NOTE Confidence: 0.757354021072388

01:19:45.140 --> 01:19:47.972 So one of the example I have showed

NOTE Confidence: 0.757354021072388

01:19:47.972 --> 01:19:51.330 this Acadian 5B where we can show pretty

NOTE Confidence: 0.757354021072388

01:19:51.330 --> 01:19:53.954 synergistic effect that you're going to

NOTE Confidence: 0.757354021072388

01:19:53.954 --> 01:19:56.444 check my blanket in multiple models.

NOTE Confidence: 0.757354021072388

01:19:56.450 --> 01:19:59.278 I only showed one in breast cancer.

NOTE Confidence: 0.757354021072388

01:19:59.280 --> 01:20:02.238 Will also see that as well.

NOTE Confidence: 0.757354021072388

01:20:02.240 --> 01:20:04.082 In addition, an and there's other

NOTE Confidence: 0.757354021072388

01:20:04.082 --> 01:20:06.141 modalities that you can actually modulate

NOTE Confidence: 0.757354021072388

01:20:06.141 --> 01:20:08.066 the tumor micro environment and,

NOTE Confidence: 0.757354021072388

01:20:08.070 --> 01:20:10.134 for example, someone that can recognize

NOTE Confidence: 0.757354021072388

01:20:10.134 --> 01:20:12.528 this as we are working on one,

NOTE Confidence: 0.757354021072388

01:20:12.530 --> 01:20:14.588 then it's called the CCR two,

NOTE Confidence: 0.757354021072388

01:20:14.590 --> 01:20:17.246 we can by inhibiting that we can change

NOTE Confidence: 0.757354021072388

01:20:17.246 --> 01:20:19.387 the macrophage population and by that,

NOTE Confidence: 0.757354021072388

01:20:19.390 --> 01:20:21.448 by doing that we can change

NOTE Confidence: 0.757354021072388

01:20:21.448 --> 01:20:22.820 the T cell activity.

NOTE Confidence: 0.757354021072388

01:20:22.820 --> 01:20:24.800 So, but basically it's just moderating

NOTE Confidence: 0.757354021072388

01:20:24.800 --> 01:20:26.546 the whole tumor micro environment

NOTE Confidence: 0.757354021072388

01:20:26.546 --> 01:20:28.648 and make it sensitive for email,

NOTE Confidence: 0.757354021072388

01:20:28.650 --> 01:20:30.370 checkpoint blockade and and this.

NOTE Confidence: 0.757354021072388

01:20:30.370 --> 01:20:32.446 This works well an intimate asks.

NOTE Confidence: 0.757354021072388

01:20:32.450 --> 01:20:34.598 Setting so I'm quite excited about

NOTE Confidence: 0.757354021072388

01:20:34.598 --> 01:20:37.339 that and that many of you probably

NOTE Confidence: 0.757354021072388

01:20:37.339 --> 01:20:39.399 know in other other institutions

NOTE Confidence: 0.757354021072388

01:20:39.399 --> 01:20:41.650 have studied with DMT inhibitors,

NOTE Confidence: 0.757354021072388

01:20:41.650 --> 01:20:42.450 HVAC inhibitors,

NOTE Confidence: 0.757354021072388

01:20:42.450 --> 01:20:44.450 and is it still inhibitors

NOTE Confidence: 0.757354021072388

01:20:44.450 --> 01:20:45.650 and those actually,

NOTE Confidence: 0.757354021072388

01:20:45.650 --> 01:20:48.198 I showed him assuming have showed strong

NOTE Confidence: 0.757354021072388

01:20:48.198 --> 01:20:50.450 efficacy in many different models,

NOTE Confidence: 0.757354021072388

01:20:50.450 --> 01:20:52.850 so I'm quite excited about this.

NOTE Confidence: 0.757354021072388

01:20:52.850 --> 01:20:54.450 This kind of combination.

NOTE Confidence: 0.792126417160034

01:20:55.580 --> 01:20:58.202 Yeah, I I think in Karen

NOTE Confidence: 0.792126417160034

01:20:58.202 --> 01:21:00.730 Anderson and Eli are broken.

NOTE Confidence: 0.792126417160034

01:21:00.730 --> 01:21:02.486 Working on demethylating therapy

NOTE Confidence: 0.792126417160034

01:21:02.486 --> 01:21:04.242 to uncover immune silencing

NOTE Confidence: 0.792126417160034

01:21:04.242 --> 01:21:06.339 and virally associated cancers.

NOTE Confidence: 0.792126417160034

01:21:06.340 --> 01:21:10.400 And I think there are a lot of examples.

NOTE Confidence: 0.792126417160034

01:21:10.400 --> 01:21:12.089 Coming on that so so

NOTE Confidence: 0.845456838607788

01:21:12.090 --> 01:21:14.816 I I just wanted to come and I think

NOTE Confidence: 0.845456838607788

01:21:14.816 --> 01:21:16.926 that's a very hard question, you know,

NOTE Confidence: 0.845456838607788

01:21:16.930 --> 01:21:18.680 because I think ultimately there the

NOTE Confidence: 0.845456838607788

01:21:18.680 --> 01:21:20.270 best combination is not going to

NOTE Confidence: 0.845456838607788

01:21:20.270 --> 01:21:21.935 be one combination that works every

NOTE Confidence: 0.845456838607788

01:21:21.935 --> 01:21:24.701 time I think it is so clear now that

NOTE Confidence: 0.845456838607788

01:21:24.701 --> 01:21:26.511 the tumors evade immunity through

NOTE Confidence: 0.845456838607788

01:21:26.511 --> 01:21:28.173 different dominant pathways and and

NOTE Confidence: 0.845456838607788

01:21:28.173 --> 01:21:30.039 more advanced tumors tend to have

NOTE Confidence: 0.845456838607788

01:21:30.039 --> 01:21:31.706 multiple pathways that I think the

NOTE Confidence: 0.845456838607788

01:21:31.706 --> 01:21:34.034 question has to do with where in an

NOTE Confidence: 0.845456838607788

01:21:34.034 --> 01:21:35.342 immunization pathways dominant and

NOTE Confidence: 0.845456838607788

01:21:35.342 --> 01:21:37.134 where more than one is dominant.

NOTE Confidence: 0.845456838607788

01:21:37.134 --> 01:21:39.010 And I think that should drive the

NOTE Confidence: 0.845456838607788

01:21:39.070 --> 01:21:40.950 combination not think the opposite.

NOTE Confidence: 0.845456838607788

01:21:40.950 --> 01:21:43.456 Wait and think that one combination will

NOTE Confidence: 0.845456838607788

01:21:43.456 --> 01:21:45.820 fix tumors with different problems.

NOTE Confidence: 0.883789777755737

01:21:46.750 --> 01:21:49.102 Yeah, so I think it's very interesting

NOTE Confidence: 0.883789777755737

01:21:49.102 --> 01:21:51.881 that you heard that question as an

NOTE Confidence: 0.883789777755737

01:21:51.881 --> 01:21:53.912 immune resistance question. It was.

NOTE Confidence: 0.883789777755737

01:21:53.912 --> 01:21:56.544 It was a very broad resistance question,

NOTE Confidence: 0.883789777755737

01:21:56.550 --> 01:21:58.440 but that's an interesting perspective.

NOTE Confidence: 0.883789777755737

01:21:58.440 --> 01:22:00.708 I think one of the things that

NOTE Confidence: 0.883789777755737

01:22:00.708 --> 01:22:03.446 that I think about sometimes is how

NOTE Confidence: 0.883789777755737

01:22:03.446 --> 01:22:05.978 some of the same mechanisms that.

NOTE Confidence: 0.883789777755737

01:22:05.980 --> 01:22:08.055 Have generated resistance to conventional

NOTE Confidence: 0.883789777755737

01:22:08.055 --> 01:22:10.130 therapies are now also generating

NOTE Confidence: 0.883789777755737

01:22:10.193 --> 01:22:11.633 resistance to immunotherapy and

NOTE Confidence: 0.883789777755737

01:22:11.633 --> 01:22:13.793 how you know our relentless focus

NOTE Confidence: 0.883789777755737

01:22:13.851 --> 01:22:15.676 on target instead of environment,

NOTE Confidence: 0.883789777755737

01:22:15.680 --> 01:22:16.841 which you know?

NOTE Confidence: 0.883789777755737

01:22:16.841 --> 01:22:19.163 I think it's something I've heard.

NOTE Confidence: 0.883789777755737

01:22:19.170 --> 01:22:20.722 You speak about alot.

NOTE Confidence: 0.883789777755737

01:22:20.722 --> 01:22:23.396 Kurt, you know we may have the

NOTE Confidence: 0.883789777755737

01:22:23.396 --> 01:22:25.776 same Achilles heel over and over

NOTE Confidence: 0.883789777755737

01:22:25.776 --> 01:22:28.098 again and in head neck cancer.

NOTE Confidence: 0.883789777755737

01:22:28.100 --> 01:22:30.809 A clear example of this is hypoxia,

NOTE Confidence: 0.883789777755737

01:22:30.810 --> 01:22:32.362 which leads to resistance

NOTE Confidence: 0.883789777755737

01:22:32.362 --> 01:22:33.914 to DNA damaging agents.

NOTE Confidence: 0.883789777755737

01:22:33.920 --> 01:22:36.530 It leads to resistance to.

NOTE Confidence: 0.883789777755737

01:22:36.530 --> 01:22:37.540 Radiation therapy.

NOTE Confidence: 0.883789777755737

01:22:37.540 --> 01:22:38.550 Prime example,

NOTE Confidence: 0.883789777755737

01:22:38.550 --> 01:22:42.490 but is now increasingly linked to resistance,

NOTE Confidence: 0.883789777755737

01:22:42.490 --> 01:22:43.180 demeanor,

NOTE Confidence: 0.883789777755737

01:22:43.180 --> 01:22:45.250 therapy as well.

NOTE Confidence: 0.883789777755737

01:22:45.250 --> 01:22:45.710 Yeah,

NOTE Confidence: 0.769990742206573

01:22:45.710 --> 01:22:49.560 and I say even taking it down to the simplest

NOTE Confidence: 0.769990742206573

01:22:49.653 --> 01:22:52.581 level of talking therapeutics it the

NOTE Confidence: 0.769990742206573

01:22:52.581 --> 01:22:56.338 answer is it depends because for example,

NOTE Confidence: 0.769990742206573

01:22:56.340 --> 01:22:59.106 just thinking about RAF inhibitor resistance.

NOTE Confidence: 0.769990742206573

01:22:59.110 --> 01:23:02.014 Actually David Stern and Marcus Bosenberg

NOTE Confidence: 0.769990742206573

01:23:02.014 --> 01:23:05.672 and others did a nice study that they

NOTE Confidence: 0.769990742206573

01:23:05.672 --> 01:23:09.161 published it a few years ago of combination

NOTE Confidence: 0.769990742206573

01:23:09.161 --> 01:23:12.486 combinations of drugs in a variety of

NOTE Confidence: 0.769990742206573

01:23:12.486 --> 01:23:15.340 cell lines for Melanoma and elsewhere.

NOTE Confidence: 0.769990742206573

01:23:15.340 --> 01:23:17.728 And showed that the combination which

NOTE Confidence: 0.769990742206573

01:23:17.728 --> 01:23:20.043 combinations work in which cells is

NOTE Confidence: 0.769990742206573

01:23:20.043 --> 01:23:22.017 very valuable and actually one of

NOTE Confidence: 0.769990742206573

01:23:22.017 --> 01:23:24.238 the things I'm quite excited about.

NOTE Confidence: 0.769990742206573

01:23:24.240 --> 01:23:27.184 The moment we're working as a group with

NOTE Confidence: 0.769990742206573

01:23:27.184 --> 01:23:29.080 systems biology island and equipment

NOTE Confidence: 0.769990742206573

01:23:29.080 --> 01:23:32.050 Los Alamos in the group and trying to

NOTE Confidence: 0.769990742206573

01:23:32.050 --> 01:23:34.626 understand that in terms of of the

NOTE Confidence: 0.769990742206573

01:23:34.626 --> 01:23:36.794 signaling networks around RAF and MEK

NOTE Confidence: 0.769990742206573

01:23:36.794 --> 01:23:39.460 and and and rest in different cells,

NOTE Confidence: 0.769990742206573

01:23:39.460 --> 01:23:41.310 some cells from different cancers,

NOTE Confidence: 0.769990742206573

01:23:41.310 --> 01:23:42.148 and innocence.

NOTE Confidence: 0.769990742206573

01:23:42.148 --> 01:23:43.824 Which combinations work depends

NOTE Confidence: 0.769990742206573

01:23:43.824 --> 01:23:46.168 say on the level of KSR 1.

NOTE Confidence: 0.769990742206573

01:23:46.170 --> 01:23:47.800 And that's a key determinant,

NOTE Confidence: 0.769990742206573

01:23:47.800 --> 01:23:50.152 and so it just depends on so much

NOTE Confidence: 0.769990742206573

01:23:50.152 --> 01:23:52.359 on how the network is wired,

NOTE Confidence: 0.769990742206573

01:23:52.360 --> 01:23:54.316 which of course goes back to

NOTE Confidence: 0.769990742206573

01:23:54.316 --> 01:23:55.620 the question about proteomics,

NOTE Confidence: 0.769990742206573

01:23:55.620 --> 01:23:57.525 because ultimately that you you're

NOTE Confidence: 0.769990742206573

01:23:57.525 --> 01:24:00.172 trying to control the system and the way

NOTE Confidence: 0.769990742206573

01:24:00.172 --> 01:24:02.470 the system is set up by a chemically,

NOTE Confidence: 0.769990742206573

01:24:02.470 --> 01:24:04.622 it defines on how it will define how

NOTE Confidence: 0.769990742206573

01:24:04.622 --> 01:24:06.708 we respond to different combinations.

NOTE Confidence: 0.769990742206573

01:24:06.710 --> 01:24:08.798 And so I think we're going to want

NOTE Confidence: 0.769990742206573

01:24:08.798 --> 01:24:11.406 to get into things at that kind of

NOTE Confidence: 0.769990742206573

01:24:11.406 --> 01:24:13.637 level to understand where we should

NOTE Confidence: 0.769990742206573

01:24:13.637 --> 01:24:14.858 use which combination,

NOTE Confidence: 0.769990742206573

01:24:14.860 --> 01:24:16.810 and I think it occurs .2.

NOTE Confidence: 0.769990742206573

01:24:16.810 --> 01:24:17.641 That's that's exactly.

NOTE Confidence: 0.769990742206573

01:24:17.641 --> 01:24:20.118 Got it that the case is going to be

NOTE Confidence: 0.769990742206573

01:24:20.118 --> 01:24:21.798 the case in the more complex systems

NOTE Confidence: 0.769990742206573

01:24:21.798 --> 01:24:23.800 of intercellular communication too.

NOTE Confidence: 0.837461471557617

01:24:25.130 --> 01:24:26.420 And can I just add?

NOTE Confidence: 0.837461471557617

01:24:26.420 --> 01:24:27.976 There's also the kinetic component, right?

NOTE Confidence: 0.837461471557617

01:24:27.976 --> 01:24:29.838 So I think when things were still

NOTE Confidence: 0.837461471557617

01:24:29.838 --> 01:24:31.817 not clear on is are you better

NOTE Confidence: 0.837461471557617

01:24:31.817 --> 01:24:33.202 off with this combination early

NOTE Confidence: 0.837461471557617

01:24:33.261 --> 01:24:35.005 on or is this going to be better

NOTE Confidence: 0.837461471557617

01:24:35.005 --> 01:24:36.221 once you get initial resistance?

NOTE Confidence: 0.837461471557617

01:24:36.221 --> 01:24:37.763 And actually that's may seem trivial,

NOTE Confidence: 0.837461471557617

01:24:37.770 --> 01:24:39.810 but I really don't think it is and

NOTE Confidence: 0.837461471557617

01:24:39.810 --> 01:24:41.140 requires modeling to think about

NOTE Confidence: 0.837461471557617

01:24:41.140 --> 01:24:42.925 just how the kinetics is playing out.

NOTE Confidence: 0.844868659973145

01:24:44.450 --> 01:24:46.290 Great, related, related to that,

NOTE Confidence: 0.844868659973145

01:24:46.290 --> 01:24:49.640 one of the things that I was going to say

NOTE Confidence: 0.844868659973145

01:24:49.723 --> 01:24:52.907 is one of the things I'm excited about.

NOTE Confidence: 0.844868659973145

01:24:52.910 --> 01:24:55.682 Sort of going forward and looking at

NOTE Confidence: 0.844868659973145

01:24:55.682 --> 01:24:58.623 the field over the next few years is

NOTE Confidence: 0.844868659973145

01:24:58.623 --> 01:25:01.445 is really what we can learn about the

NOTE Confidence: 0.844868659973145

01:25:01.445 --> 01:25:04.510 tumor from the get go that can tell us

NOTE Confidence: 0.844868659973145

01:25:04.510 --> 01:25:07.327 how we would want to treat it to stave

NOTE Confidence: 0.844868659973145

01:25:07.327 --> 01:25:09.837 off certain mechanisms of resistance.

NOTE Confidence: 0.844868659973145

01:25:09.840 --> 01:25:12.164 I think we're starting to see some

NOTE Confidence: 0.844868659973145

01:25:12.164 --> 01:25:14.049 examples also of clinical trials

NOTE Confidence: 0.844868659973145

01:25:14.049 --> 01:25:16.094 that are starting to subset.

NOTE Confidence: 0.844868659973145

01:25:16.100 --> 01:25:17.955 Patients with certain tumor Gina

NOTE Confidence: 0.844868659973145

01:25:17.955 --> 01:25:20.179 types or whether tumors have certain

NOTE Confidence: 0.844868659973145

01:25:20.179 --> 01:25:22.611 features and sort of put them and and

NOTE Confidence: 0.844868659973145

01:25:22.611 --> 01:25:25.048 into trials with specific combinations,

NOTE Confidence: 0.844868659973145

01:25:25.050 --> 01:25:28.258 and I think that's going to be really

NOTE Confidence: 0.844868659973145

01:25:28.258 --> 01:25:30.649 interesting approach in the next few years.

NOTE Confidence: 0.84442663192749

01:25:32.070 --> 01:25:33.198 Terrific, thanks, just

NOTE Confidence: 0.84442663192749

01:25:33.200 --> 01:25:35.090 a couple comments on this,

NOTE Confidence: 0.84442663192749

01:25:35.090 --> 01:25:37.502 so there's a few things that

NOTE Confidence: 0.84442663192749

01:25:37.502 --> 01:25:39.532 you that you've heard there

NOTE Confidence: 0.84442663192749

01:25:39.532 --> 01:25:42.244 that I just like to to build on.

NOTE Confidence: 0.84442663192749

01:25:42.250 --> 01:25:44.386 A completely agree that we need

NOTE Confidence: 0.84442663192749

01:25:44.386 --> 01:25:46.265 to understand what's the right

NOTE Confidence: 0.84442663192749

01:25:46.265 --> 01:25:48.593 combination for the set of what

NOTE Confidence: 0.84442663192749

01:25:48.593 --> 01:25:50.194 the adaptive mechanisms have

NOTE Confidence: 0.84442663192749

01:25:50.194 --> 01:25:52.049 been in that particular tumor,

NOTE Confidence: 0.84442663192749

01:25:52.050 --> 01:25:54.306 and I think to that end,

NOTE Confidence: 0.84442663192749

01:25:54.310 --> 01:25:56.632 looking at the adaptation at an

NOTE Confidence: 0.84442663192749

01:25:56.632 --> 01:25:58.618 earlier point than we typically

NOTE Confidence: 0.84442663192749

01:25:58.618 --> 01:26:01.474 do is a key part of this strategy,

NOTE Confidence: 0.84442663192749

01:26:01.480 --> 01:26:03.400 so there's some really interesting.

NOTE Confidence: 0.84442663192749

01:26:03.400 --> 01:26:05.578 Concepts here that you will be

NOTE Confidence: 0.84442663192749

01:26:05.578 --> 01:26:07.453 working with Gordon Mills from

NOTE Confidence: 0.84442663192749

01:26:07.453 --> 01:26:09.903 OHSU on and looking at the adaptive

NOTE Confidence: 0.84442663192749

01:26:09.903 --> 01:26:12.272 rewiring that goes on which really

NOTE Confidence: 0.84442663192749

01:26:12.272 --> 01:26:13.469 happens quite quickly.

NOTE Confidence: 0.84442663192749

01:26:13.470 --> 01:26:15.282 And of course one element of

NOTE Confidence: 0.84442663192749

01:26:15.282 --> 01:26:17.463 that that we need to understand

NOTE Confidence: 0.84442663192749

01:26:17.463 --> 01:26:19.275 is undoubtedly the epigenetic

NOTE Confidence: 0.84442663192749

01:26:19.275 --> 01:26:21.679 mechanisms that that that come in,

NOTE Confidence: 0.84442663192749

01:26:21.680 --> 01:26:23.405 'cause they're quite commonly involved

NOTE Confidence: 0.84442663192749

01:26:23.405 --> 01:26:25.780 in some of the resistance mechanisms,

NOTE Confidence: 0.84442663192749

01:26:25.780 --> 01:26:27.650 and as I pointed out,

NOTE Confidence: 0.84442663192749

01:26:27.650 --> 01:26:30.478 we don't really have good techniques for

NOTE Confidence: 0.84442663192749

01:26:30.478 --> 01:26:33.650 looking for those if we haven't got a biopsy.

NOTE Confidence: 0.84442663192749

01:26:33.650 --> 01:26:34.326 Early on,

NOTE Confidence: 0.84442663192749

01:26:34.326 --> 01:26:36.692 so I think that's that's absolutely key,

NOTE Confidence: 0.84442663192749

01:26:36.700 --> 01:26:39.066 and then I think that also informs,

NOTE Confidence: 0.84442663192749

01:26:39.070 --> 01:26:41.268 but the potential for how we do

NOTE Confidence: 0.84442663192749

01:26:41.268 --> 01:26:43.252 combinations 'cause one of the limiting

NOTE Confidence: 0.84442663192749

01:26:43.252 --> 01:26:44.882 factors of actually getting these

NOTE Confidence: 0.84442663192749

01:26:44.882 --> 01:26:47.432 to work has been the Taler ability

NOTE Confidence: 0.84442663192749

01:26:47.432 --> 01:26:48.904 of the combinations clinically.

NOTE Confidence: 0.84442663192749

01:26:48.910 --> 01:26:51.798 And for that I think there's a couple

NOTE Confidence: 0.84442663192749

01:26:51.798 --> 01:26:54.668 of chinks of light of what we can do.

NOTE Confidence: 0.84442663192749

01:26:54.670 --> 01:26:55.567 First of all,

NOTE Confidence: 0.84442663192749

01:26:55.567 --> 01:26:57.361 we're starting to develop some better

NOTE Confidence: 0.84442663192749

01:26:57.361 --> 01:26:58.740 tolerated therapies inherently,

NOTE Confidence: 0.84442663192749

01:26:58.740 --> 01:27:01.332 so I think that gives us a bit

NOTE Confidence: 0.84442663192749

01:27:01.332 --> 01:27:03.475 more headroom for some of the

NOTE Confidence: 0.84442663192749

01:27:03.475 --> 01:27:05.599 combinations that we need to do.

NOTE Confidence: 0.84442663192749

01:27:05.600 --> 01:27:06.440 Things like Adcs,

NOTE Confidence: 0.84442663192749

01:27:06.440 --> 01:27:07.840 better ways of you know,

NOTE Confidence: 0.84442663192749

01:27:07.840 --> 01:27:09.328 delivering some of the mechanisms of

NOTE Confidence: 0.84442663192749

01:27:09.328 --> 01:27:11.295 killing give you a bit more headroom

NOTE Confidence: 0.84442663192749

01:27:11.295 --> 01:27:13.155 and understanding what drives total ability,

NOTE Confidence: 0.84442663192749

01:27:13.160 --> 01:27:14.942 and then looking at the sequencing

NOTE Confidence: 0.84442663192749

01:27:14.942 --> 01:27:16.970 rather than trying to do it does

NOTE Confidence: 0.84442663192749

01:27:16.970 --> 01:27:18.530 everything at the same time is

NOTE Confidence: 0.84442663192749

01:27:18.530 --> 01:27:20.204 another innovation that I think will

NOTE Confidence: 0.84442663192749

01:27:20.204 --> 01:27:22.391 come in that will help us with that.

NOTE Confidence: 0.84442663192749

01:27:22.391 --> 01:27:24.666 And but again I think we're going to

NOTE Confidence: 0.84442663192749

01:27:24.666 --> 01:27:26.834 need to apply all of these tools that

NOTE Confidence: 0.84442663192749

01:27:26.834 --> 01:27:29.117 we've got and the modeling of that too,

NOTE Confidence: 0.84442663192749

01:27:29.120 --> 01:27:31.024 to reduce down the number of options

NOTE Confidence: 0.84442663192749

01:27:31.024 --> 01:27:32.770 that we actually bring into the

NOTE Confidence: 0.84442663192749

01:27:32.770 --> 01:27:34.230 clinic and increase the likelihood

NOTE Confidence: 0.84442663192749

01:27:34.230 --> 01:27:35.850 of each one of those being.

NOTE Confidence: 0.84442663192749

01:27:35.850 --> 01:27:37.525 Being successful with in combination

NOTE Confidence: 0.84442663192749

01:27:37.525 --> 01:27:39.535 therapy is going to keep us

NOTE Confidence: 0.84442663192749

01:27:39.535 --> 01:27:41.185 occupied for a little while yet

NOTE Confidence: 0.84442663192749

01:27:41.185 --> 01:27:42.779 before we solve that problem.

NOTE Confidence: 0.8606778383255

01:27:44.110 --> 01:27:45.980 Terrific great well this I,

NOTE Confidence: 0.8606778383255

01:27:45.980 --> 01:27:48.410 I hope the attendees have enjoyed

NOTE Confidence: 0.8606778383255

01:27:48.410 --> 01:27:50.423 this exchange of opinion and

NOTE Confidence: 0.8606778383255

01:27:50.423 --> 01:27:52.337 knowledge as much as I have.

NOTE Confidence: 0.8606778383255

01:27:52.340 --> 01:27:55.084 I'd like to turn it back now to

NOTE Confidence: 0.8606778383255

01:27:55.084 --> 01:27:57.671 Charlie Fuchs and just ask him to

NOTE Confidence: 0.8606778383255

01:27:57.671 --> 01:28:00.190 share a couple of concluding remarks.

NOTE Confidence: 0.8606778383255

01:28:00.190 --> 01:28:00.936 Well, Barbara,

NOTE Confidence: 0.8606778383255

01:28:00.936 --> 01:28:03.174 thank you and all the panelists.

NOTE Confidence: 0.8606778383255

01:28:03.180 --> 01:28:05.556 It was a fantastic discussion and

NOTE Confidence: 0.8606778383255

01:28:05.556 --> 01:28:07.560 really provided so much insight

NOTE Confidence: 0.8606778383255

01:28:07.560 --> 01:28:09.947 in terms of how we continue to

NOTE Confidence: 0.8606778383255

01:28:09.947 --> 01:28:12.204 move grade science into the clinic

NOTE Confidence: 0.8606778383255

01:28:12.204 --> 01:28:14.460 and frankly how we learn more.

NOTE Confidence: 0.8606778383255

01:28:14.460 --> 01:28:16.260 About the tests in clinical

NOTE Confidence: 0.8606778383255

01:28:16.260 --> 01:28:18.060 trials that were actively doing

NOTE Confidence: 0.8606778383255

01:28:18.121 --> 01:28:19.886 as part of our investigation,

NOTE Confidence: 0.8606778383255

01:28:19.890 --> 01:28:22.067 this is I mentioned is the third

NOTE Confidence: 0.8606778383255

01:28:22.067 --> 01:28:24.281 of our Yale engage cancer forms

NOTE Confidence: 0.8606778383255

01:28:24.281 --> 01:28:26.699 and I hope that our attendees

NOTE Confidence: 0.8606778383255

01:28:26.699 --> 01:28:28.937 enjoyed it and benefited from it.

NOTE Confidence: 0.8606778383255

01:28:28.940 --> 01:28:30.332 And as I mentioned,

NOTE Confidence: 0.8606778383255

01:28:30.332 --> 01:28:32.866 the work continues and we very much

NOTE Confidence: 0.8606778383255

01:28:32.866 --> 01:28:35.498 want this to be the beginning of

NOTE Confidence: 0.8606778383255

01:28:35.498 --> 01:28:37.363 the conversation and so hopefully

NOTE Confidence: 0.8606778383255

01:28:37.363 --> 01:28:39.799 what will what you'll do and what

NOTE Confidence: 0.8606778383255

01:28:39.800 --> 01:28:42.271 we'll do is engage each other in

NOTE Confidence: 0.8606778383255

01:28:42.271 --> 01:28:44.140 thinking through how we partner,

NOTE Confidence: 0.8606778383255

01:28:44.140 --> 01:28:46.010 how we work strategically together.

NOTE Confidence: 0.8606778383255

01:28:46.010 --> 01:28:47.194 To think of these,

NOTE Confidence: 0.8606778383255

01:28:47.194 --> 01:28:49.431 the ideas that are panels are brought

NOTE Confidence: 0.8606778383255

01:28:49.431 --> 01:28:51.386 up an develop new initiatives,

NOTE Confidence: 0.8606778383255

01:28:51.390 --> 01:28:53.304 so people should feel free to

NOTE Confidence: 0.8606778383255

01:28:53.304 --> 01:28:56.043 reach out to me or any of the

NOTE Confidence: 0.8606778383255

01:28:56.043 --> 01:28:57.427 panelists to think about.

NOTE Confidence: 0.8606778383255

01:28:57.430 --> 01:28:59.560 These collaborations will be contacting you

NOTE Confidence: 0.8606778383255

01:28:59.560 --> 01:29:01.470 really appreciate your taking the time.

NOTE Confidence: 0.8606778383255

01:29:01.470 --> 01:29:03.480 You know when I listen to

NOTE Confidence: 0.8606778383255

01:29:03.480 --> 01:29:04.485 discussions like this,

NOTE Confidence: 0.8606778383255

01:29:04.490 --> 01:29:06.802 I think it gives all of us hope

NOTE Confidence: 0.8606778383255

01:29:06.802 --> 01:29:08.610 and excitement about the years

NOTE Confidence: 0.8606778383255

01:29:08.610 --> 01:29:10.540 ahead of of cancer investigation.

NOTE Confidence: 0.8606778383255

01:29:10.540 --> 01:29:12.885 So let me just turn it back,

NOTE Confidence: 0.8606778383255

01:29:12.890 --> 01:29:14.900 turn it back to Barbara for

NOTE Confidence: 0.8606778383255

01:29:14.900 --> 01:29:15.905 some final thoughts.

NOTE Confidence: 0.88388192653656

01:29:17.630 --> 01:29:21.626 You know, so I've been at Yale about 6

NOTE Confidence: 0.88388192653656

01:29:21.626 --> 01:29:25.669 1/2 years and the conversation today.

NOTE Confidence: 0.88388192653656

01:29:25.670 --> 01:29:27.756 Sort of reminds me of of the

NOTE Confidence: 0.88388192653656

01:29:27.756 --> 01:29:30.158 excitement that I felt when I started

NOTE Confidence: 0.88388192653656

01:29:30.158 --> 01:29:31.958 going to seminars around here.

NOTE Confidence: 0.88388192653656

01:29:31.960 --> 01:29:33.525 I mean, there's just unbelievable

NOTE Confidence: 0.88388192653656

01:29:33.525 --> 01:29:35.502 scale of work of this quality

NOTE Confidence: 0.88388192653656

01:29:35.502 --> 01:29:37.257 going on at this institution,

NOTE Confidence: 0.88388192653656

01:29:37.260 --> 01:29:39.542 and a lot of people thinking about

NOTE Confidence: 0.88388192653656

01:29:39.542 --> 01:29:42.300 how to make cancer treatment better.

NOTE Confidence: 0.88388192653656

01:29:42.300 --> 01:29:45.476 So thank you all for joining us today.

NOTE Confidence: 0.88388192653656

01:29:45.480 --> 01:29:48.084 Please stay in touch and I want

NOTE Confidence: 0.88388192653656

01:29:48.084 --> 01:29:50.260 to thank Susan and curtain,

NOTE Confidence: 0.88388192653656

01:29:50.260 --> 01:29:52.804 Katie and Mark and Megan Inch in for

NOTE Confidence: 0.88388192653656

01:29:52.804 --> 01:29:55.039 their their wonderful presentation.

NOTE Confidence: 0.88388192653656

01:29:55.040 --> 01:29:56.628 Thank you very much.

NOTE Confidence: 0.533962070941925

01:29:58.850 --> 01:30:00.256 Keyboard.