WEBVTT

NOTE duration:"01:30:00.2560000"

NOTE language:en-us

NOTE Confidence: 0.850683850901468

 $00:00:07.940 \dashrightarrow 00:00:12.567$  everybody. We lcome to our session on behalf

NOTE Confidence: 0.850683850901468

 $00{:}00{:}12.567 \dashrightarrow 00{:}00{:}17.117$  of Yale University and Yale Cancer Center.

NOTE Confidence: 0.850683850901468

 $00:00:17.120 \dashrightarrow 00:00:20.136$  I'm pleased to have you with us as

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 $00:00:20.136 \rightarrow 00:00:23.679$  part of the Yale Engage Cancer series.

NOTE Confidence: 0.850683850901468

 $00:00:23.680 \longrightarrow 00:00:26.450$  This session is entitled defining.

NOTE Confidence: 0.850683850901468

 $00:00:26.450 \longrightarrow 00:00:28.575$  Mechanisms and biomarkers of sensitivity

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 $00{:}00{:}28.575 \dashrightarrow 00{:}00{:}31.430$  and resistance to anti cancer treatments.

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 $00:00:31.430 \longrightarrow 00:00:32.878$  I'll be your moderator.

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

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 $00{:}00{:}34.330 \dashrightarrow 00{:}00{:}37.258$  I'm a medical on cologist and have a interest

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 $00:00:37.258 \rightarrow 00:00:40.390$  in drug development and head neck cancer.

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 $00:00:40.390 \rightarrow 00:00:44.046$  And we have a phenomenal panel of Yale

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 $00:00:44.046 \rightarrow 00:00:46.669$  faculty members and Anna corporate

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

 $00:00:49.370 \rightarrow 00:00:52.555$  And hope to have a very very

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 $00:00:52.555 \rightarrow 00:00:53.465$  interactive session.

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 $00{:}00{:}53.470 \dashrightarrow 00{:}00{:}57.154$  I'd like to start with a

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 $00:00:57.154 \rightarrow 00:00:58.996$  few housekeeping items.

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

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 $00:01:01.570 \longrightarrow 00:01:04.826$  is going to be each of our panel

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 $00:01:04.826 \longrightarrow 00:01:07.977$  members giving a brief about 5 minute

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 $00:01:07.977 \rightarrow 00:01:11.009$  introduction to the work that they do.

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 $00:01:11.010 \dashrightarrow 00:01:14.818$  What they see is as key questions.

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 $00:01:14.820 \rightarrow 00:01:18.061$  Will have all of the panel presentations

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 $00{:}01{:}18.061 \dashrightarrow 00{:}01{:}21.808$  1st and then move on to the discussion.

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 $00{:}01{:}21{.}810 \dashrightarrow 00{:}01{:}23{.}662$  The question and answer.

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 $00{:}01{:}23.662 \dashrightarrow 00{:}01{:}26.440$  We know that to attack cancer

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 $00{:}01{:}26{.}528 \dashrightarrow 00{:}01{:}28{.}328$  we need team science.

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 $00{:}01{:}28.330 \dashrightarrow 00{:}01{:}30.660$  We need collaborations within our

 $00:01:30.660 \rightarrow 00:01:32.990$  organization and across different sectors.

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

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 $00:01:33.419 \rightarrow 00:01:36.422$  public and industry and Yale engage was

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 $00:01:36.422 \rightarrow 00:01:39.048$  designed to build these connections,

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 $00:01:39.050 \longrightarrow 00:01:40.445$  particularly between Yale

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

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 $00:01:42.310 \rightarrow 00:01:45.079$  To keep the discussion lively, we.

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

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 $00{:}01{:}46.396 \dashrightarrow 00{:}01{:}49.030$  Some have been submitted ahead of

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

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 $00{:}01{:}51{.}974 \dashrightarrow 00{:}01{:}54{.}549$  submit them through the Q&A function.

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 $00{:}01{:}54{.}550 \dashrightarrow 00{:}01{:}58{.}126$  On the Web and R we have an

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 $00:01:58.126 \longrightarrow 00:02:00.298$  enormous amount of expertise

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 $00:02:00.298 \rightarrow 00:02:03.808$  among our panelists and will be.

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 $00:02:03.810 \rightarrow 00:02:05.660$  Monitoring those questions as they

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 $00:02:05.660 \rightarrow 00:02:08.705$  come up and and try to get to as

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

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 $00:02:10.992 \rightarrow 00:02:12.854$  want you to know that this web,

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

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 $00:02:14.028 \longrightarrow 00:02:16.177$  so now I'm really pleased to be

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 $00{:}02{:}16.177 \dashrightarrow 00{:}02{:}17.847$  able to introduce Charlie Fuchs.

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 $00:02:17.850 \longrightarrow 00:02:19.390$  He's the secular professor of

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 $00:02:19.390 \longrightarrow 00:02:20.930$  medicine and medical oncology and

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 $00:02:20.987 \longrightarrow 00:02:22.537$  a professor of chronic disease

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

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 $00{:}02{:}23.780 \dashrightarrow 00{:}02{:}25.598$  He's the director of the Yale

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 $00{:}02{:}25{.}598 \dashrightarrow 00{:}02{:}27{.}504$  Cancer Center and Position in chief

NOTE Confidence: 0.850683850901468

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

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 $00{:}02{:}28.770 \dashrightarrow 00{:}02{:}29.080$  Charlie.

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 $00{:}02{:}29{.}710 \dashrightarrow 00{:}02{:}32{.}615$  Forever thank you and thank you for

NOTE Confidence: 0.871820628643036

 $00{:}02{:}32.615 \dashrightarrow 00{:}02{:}35.046$  your leadership on this and welcome

 $00:02:35.046 \longrightarrow 00:02:38.122$  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

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 $00{:}02{:}40.612 \dashrightarrow 00{:}02{:}43.480$  and it's really been an exciting and

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 $00:02:43.480 \rightarrow 00:02:45.505$  incredibly productive series of forms.

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 $00:02:45.510 \longrightarrow 00:02:47.940$  So please it could join us

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 $00{:}02{:}47{.}940 \dashrightarrow 00{:}02{:}49{.}560$  for this third one.

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 $00:02:49.560 \longrightarrow 00:02:51.798$  You know, we we all recognize

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 $00:02:51.798 \longrightarrow 00:02:54.244$  that despite the fact that we're

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 $00:02:54.244 \rightarrow 00:02:56.439$  dealing with a global pandemic,

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 $00:02:56.440 \longrightarrow 00:02:58.088$  the consistent impact of

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 $00:02:58.088 \longrightarrow 00:02:59.736$  cancer on public health.

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 $00{:}02{:}59{.}740 \dashrightarrow 00{:}03{:}01{.}925$  And the morbidity and mortality

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 $00{:}03{:}01{.}925 \dashrightarrow 00{:}03{:}04{.}110$  and costs on our population.

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 $00{:}03{:}04{.}110 \dashrightarrow 00{:}03{:}06{.}666$  Or considerable an it remains one

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 $00:03:06.666 \rightarrow 00:03:09.350$  of the great challenges in medicine.

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 $00:03:09.350 \longrightarrow 00:03:12.409$  And it also is one of the

- NOTE Confidence: 0.871820628643036
- $00:03:12.409 \rightarrow 00:03:13.283$  largest investments.
- NOTE Confidence: 0.871820628643036
- $00{:}03{:}13.290 \dashrightarrow 00{:}03{:}16.216$  I think that goes on and healthcare
- NOTE Confidence: 0.871820628643036
- $00:03:16.216 \rightarrow 00:03:18.321$  research and drug development and
- NOTE Confidence: 0.871820628643036
- $00{:}03{:}18{.}321 \dashrightarrow 00{:}03{:}21{.}023$  our our our efforts at Yale is
- NOTE Confidence: 0.871820628643036
- $00{:}03{:}21.023 \dashrightarrow 00{:}03{:}23.777$  to really tackle this challenge.
- NOTE Confidence: 0.871820628643036
- $00:03:23.780 \longrightarrow 00:03:26.629$  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
- $00{:}03{:}29{.}896 \dashrightarrow 00{:}03{:}31{.}648$  immunology, among other elements.
- NOTE Confidence: 0.871820628643036
- $00:03:31.650 \rightarrow 00:03:35.880$  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
- $00{:}03{:}37{.}664 \dashrightarrow 00{:}03{:}40{.}340$  come out of this University were
- NOTE Confidence: 0.871820628643036
- $00{:}03{:}40{.}414 \dashrightarrow 00{:}03{:}42{.}717$  privileged to work at one of the
- NOTE Confidence: 0.871820628643036
- $00{:}03{:}42{.}717 \dashrightarrow 00{:}03{:}44{.}851$  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,

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 $00{:}03{:}47.765 \dashrightarrow 00{:}03{:}50.810$  and has been a really an area

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 $00{:}03{:}50.892 \dashrightarrow 00{:}03{:}53.503$  that research that is as built a

NOTE Confidence: 0.871820628643036

 $00{:}03{:}53{.}503 \dashrightarrow 00{:}03{:}56{.}179$  legacy of great innovation as well.

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 $00:03:56.180 \longrightarrow 00:03:57.854$  Smilow cancer hospital.

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

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 $00:03:59.530 \rightarrow 00:04:01.805$  Is celebrating its 10th anniversary

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 $00{:}04{:}01{.}805 \dashrightarrow 00{:}04{:}04{.}848$  and is a robust operation that now

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

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 $00:04:07.384 \rightarrow 00:04:10.530$  cancer patient in the state of Connecticut.

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

NOTE Confidence: 0.871820628643036

 $00{:}04{:}11{.}306 \dashrightarrow 00{:}04{:}13{.}634$  we view that through the science

NOTE Confidence: 0.871820628643036

 $00:04:13.634 \rightarrow 00:04:15.833$  and through this robust clinical

NOTE Confidence: 0.871820628643036

 $00:04:15.833 \rightarrow 00:04:18.983$  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

 $00{:}04{:}20{.}259 \dashrightarrow 00{:}04{:}21{.}528$  into the clinic.

- NOTE Confidence: 0.871820628643036
- $00:04:21.530 \longrightarrow 00:04:23.640$  Really pleased with the team
- NOTE Confidence: 0.871820628643036
- $00:04:23.640 \longrightarrow 00:04:25.328$  that's been assembled today,
- NOTE Confidence: 0.871820628643036
- $00:04:25.330 \rightarrow 00:04:28.291$  our first and Yale engage cancer was
- NOTE Confidence: 0.871820628643036
- $00:04:28.291 \rightarrow 00:04:30.350$  focused on immunobiology, our second.
- NOTE Confidence: 0.871820628643036
- $00:04:30.350 \dashrightarrow 00:04:32.325$  Was focused on novel the rapeutics,
- NOTE Confidence: 0.871820628643036
- $00:04:32.330 \longrightarrow 00:04:35.386$  and the third really ties it all together,
- NOTE Confidence: 0.871820628643036
- $00:04:35.390 \longrightarrow 00:04:37.300$  which is to understand now,
- NOTE Confidence: 0.871820628643036
- $00:04:37.300 \rightarrow 00:04:39.988$  given these efforts to develop new drugs,
- NOTE Confidence: 0.871820628643036
- $00:04:39.990 \longrightarrow 00:04:40.754$  new targets,
- NOTE Confidence: 0.871820628643036
- $00:04:40.754 \rightarrow 00:04:42.664$  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
- $00:04:44.580 \dashrightarrow 00:04:47.100$  And how do we further enhance our
- NOTE Confidence: 0.871820628643036
- $00:04:47.100 \longrightarrow 00:04:48.790$  approaches to cancer therapy?
- NOTE Confidence: 0.871820628643036
- $00{:}04{:}48.790 \dashrightarrow 00{:}04{:}51.088$  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

 $00{:}04{:}52{.}240 \dashrightarrow 00{:}04{:}55{.}026$  and we're so pleased to have Doctor

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

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 $00:04:57.360 \longrightarrow 00:04:59.135$  industry partner on the panel,

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 $00:04:59.140 \longrightarrow 00:05:00.376$  and we realize that.

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

NOTE Confidence: 0.871820628643036

 $00:05:02.748 \dashrightarrow 00:05:05.394$  come from the biotech and pharma.

NOTE Confidence: 0.871820628643036

 $00:05:05.400 \longrightarrow 00:05:07.566$  An really part of this effort.

NOTE Confidence: 0.871820628643036

 $00:05:07.570 \longrightarrow 00:05:09.250$  Beyond hearing from these experts

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 $00{:}05{:}09{.}250 \dashrightarrow 00{:}05{:}11{.}401$  in their insights is to really

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

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 $00{:}05{:}12.640 \dashrightarrow 00{:}05{:}14.674$  Because one thing we really welcome

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 $00:05:14.674 \rightarrow 00:05:17.698$  here at Yale is to collaborate with you.

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 $00{:}05{:}17.700 \dashrightarrow 00{:}05{:}19.935$  We want to build strategic

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 $00:05:19.935 \dashrightarrow 00:05:22.170$  partnerships with all of you.

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 $00:05:22.170 \rightarrow 00:05:24.060$  Because ultimately this fight against cancer.

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 $00:05:24.060 \rightarrow 00:05:24.375$  Yes,

- NOTE Confidence: 0.871820628643036
- $00:05:24.375 \longrightarrow 00:05:25.950$  it requires each of these
- NOTE Confidence: 0.871820628643036
- $00:05:25.950 \longrightarrow 00:05:27.210$  domains on the slide,
- NOTE Confidence: 0.871820628643036
- $00:05:27.210 \longrightarrow 00:05:28.785$  but it requires a community
- NOTE Confidence: 0.871820628643036
- $00:05:28.785 \longrightarrow 00:05:30.045$  focused on every aspect,
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}30{.}050 \dashrightarrow 00{:}05{:}31{.}310$  and that includes a cademia
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}31{.}310 \dashrightarrow 00{:}05{:}32{.}570$  and industry in biotech.
- NOTE Confidence: 0.871820628643036
- $00:05:32.570 \longrightarrow 00:05:34.572$  So one thing I want to invite
- NOTE Confidence: 0.871820628643036
- $00:05:34.572 \longrightarrow 00:05:36.659$  you today is to ask questions,
- NOTE Confidence: 0.871820628643036
- $00:05:36.660 \longrightarrow 00:05:37.920$  but after this form,
- NOTE Confidence: 0.871820628643036
- $00:05:37.920 \longrightarrow 00:05:39.495$  please reach out to us,
- NOTE Confidence: 0.871820628643036
- $00:05:39.500 \longrightarrow 00:05:41.070$  will reach out to you.
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}41.070 \dashrightarrow 00{:}05{:}42.960$  And let's think about ways we
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}42{.}960 \dashrightarrow 00{:}05{:}43{.}905$  can work together.
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}43{.}910 \dashrightarrow 00{:}05{:}46{.}054$  I think we have a lot of resources
- NOTE Confidence: 0.871820628643036
- $00{:}05{:}46.054 \dashrightarrow 00{:}05{:}48.227$  we can bring here at Yale to
- NOTE Confidence: 0.871820628643036

 $00:05:48.227 \longrightarrow 00:05:49.797$  partner with all the great

NOTE Confidence: 0.889435529708862

 $00:05:49.862 \rightarrow 00:05:52.734$  things you're all doing and we look forward.

NOTE Confidence: 0.889435529708862

 $00:05:52.740 \dashrightarrow 00:05:53.992$  To continuing this conversation

NOTE Confidence: 0.889435529708862

 $00:05:53.992 \rightarrow 00:05:55.852$  long after this form, so again,

NOTE Confidence: 0.889435529708862

 $00:05:55.852 \longrightarrow 00:05:57.357$  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

 $00:06:04.970 \longrightarrow 00:06:07.510$  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

 $00{:}06{:}10.513 \dashrightarrow 00{:}06{:}13.739$  I just had a brief opportunity to

NOTE Confidence: 0.85655349890391

 $00{:}06{:}13.739 \dashrightarrow 00{:}06{:}17.022$  to scroll through the list of 100

NOTE Confidence: 0.85655349890391

 $00{:}06{:}17.022 \dashrightarrow 00{:}06{:}19.638$  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

 $00{:}06{:}23.050 \dashrightarrow 00{:}06{:}25.920$  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
- $00:06:28.272 \rightarrow 00:06:30.978$  questions from that group. So we've.
- NOTE Confidence: 0.85655349890391
- $00{:}06{:}30{.}978 \dashrightarrow 00{:}06{:}34{.}490$  We've tried to arrange these talks so that.
- NOTE Confidence: 0.85655349890391
- $00:06:34.490 \longrightarrow 00:06:36.314$  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
- $00:06:38.131 \longrightarrow 00:06:40.247$  in the scientific questions,
- NOTE Confidence: 0.85655349890391
- $00{:}06{:}40.250 \dashrightarrow 00{:}06{:}42.693$  and Dan the approaches that are are
- NOTE Confidence: 0.85655349890391
- $00:06:42.693 \rightarrow 00:06:44.470$  taken to understanding resistance.
- NOTE Confidence: 0.85655349890391
- 00:06:44.470 --> 00:06:45.577 As I said,
- NOTE Confidence: 0.85655349890391
- $00:06:45.577 \rightarrow 00:06:47.791$  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
- $00:06:51.000 \rightarrow 00:06:52.215$  his core expertise.
- NOTE Confidence: 0.85655349890391
- $00{:}06{:}52{.}215 \dashrightarrow 00{:}06{:}53{.}835$  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
- $00:06:55.990 \dashrightarrow 00:06:59.758$  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

 $00:07:03.212 \longrightarrow 00:07:04.938$  treatment resistance.

NOTE Confidence: 0.85655349890391

 $00{:}07{:}04{.}940 \dashrightarrow 00{:}07{:}06{.}974$  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

 $00:07:09.390 \longrightarrow 00:07:11.679$  So each of those speakers has been

NOTE Confidence: 0.85655349890391

 $00:07:11.679 \longrightarrow 00:07:14.519$  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

 $00:07:16.970 \longrightarrow 00:07:18.968$  ruthless and and cut you off.

NOTE Confidence: 0.85655349890391

 $00:07:18.970 \longrightarrow 00:07:21.539$  If you go over and that

NOTE Confidence: 0.85655349890391

 $00{:}07{:}21.539 \dashrightarrow 00{:}07{:}23.289$  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

 $00:07:25.090 \longrightarrow 00:07:26.890$  are going to be great,

NOTE Confidence: 0.85655349890391

 $00:07:26.890 \dashrightarrow 00:07:29.050$  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

 $00:07:32.290 \dashrightarrow 00:07:34.809$  and Medicine leader in our Cancer Center.

NOTE Confidence: 0.85655349890391

 $00:07:34.810 \rightarrow 00:07:36.250$  Through those answering signaling

- NOTE Confidence: 0.85655349890391
- 00:07:36.250 --> 00:07:37.690 cancer signaling networks program,
- NOTE Confidence: 0.85655349890391
- $00{:}07{:}37.690 \dashrightarrow 00{:}07{:}40.497$  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
- $00{:}07{:}42.680 \dashrightarrow 00{:}07{:}43.868$  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
- $00:07:48.326 \longrightarrow 00:07:50.735$  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
- $00{:}07{:}53.157 \dashrightarrow 00{:}07{:}55.377$  things that we're interested in.
- NOTE Confidence: 0.877268970012665
- $00:07:55.380 \longrightarrow 00:07:57.851$  I have a cancer biology lab here
- NOTE Confidence: 0.877268970012665
- $00:07:57.851 \rightarrow 00:08:00.756$  really with a focus on lung cancer and
- NOTE Confidence: 0.877268970012665
- $00{:}08{:}00{.}756 \dashrightarrow 00{:}08{:}04{.}007$  one of the areas that we are really
- NOTE Confidence: 0.877268970012665
- $00{:}08{:}04{.}007 \dashrightarrow 00{:}08{:}06{.}815$  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
- $00{:}08{:}08{.}934 \dashrightarrow 00{:}08{:}10.578$  cancer the rapies including targeted
- NOTE Confidence: 0.877268970012665

 $00:08:10.578 \rightarrow 00:08:12.887$  therapies and also immuno therapies and.

NOTE Confidence: 0.877268970012665

 $00{:}08{:}12.890 \dashrightarrow 00{:}08{:}15.664$  Some of the things that we think

NOTE Confidence: 0.877268970012665

 $00{:}08{:}15.664 \dashrightarrow 00{:}08{:}18.040$  about a lot and work on.

NOTE Confidence: 0.877268970012665

 $00:08:18.040 \rightarrow 00:08:20.164$  I'm really approaches to discover new

NOTE Confidence: 0.877268970012665

 $00{:}08{:}20{.}164 \dashrightarrow 00{:}08{:}22{.}041$  mechanisms of resistance were interested

NOTE Confidence: 0.877268970012665

 $00:08:22.041 \rightarrow 00:08:23.649$  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

 $00:08:26.350 \rightarrow 00:08:28.646$  We study the influence of the tumor

NOTE Confidence: 0.877268970012665

 $00{:}08{:}28.646 \dashrightarrow 00{:}08{:}30.123$  micro environment on sensitivity

NOTE Confidence: 0.877268970012665

 $00:08:30.123 \longrightarrow 00:08:32.288$  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

 $00:08:37.246 \rightarrow 00:08:39.610$  apply a therapy and instead other

NOTE Confidence: 0.877268970012665

 $00{:}08{:}39{.}610 \dashrightarrow 00{:}08{:}42{.}584$  cells do not die and stick around

NOTE Confidence: 0.877268970012665

 $00:08:42.584 \rightarrow 00:08:45.664$  and serve as the fertile ground for

NOTE Confidence: 0.877268970012665

 $00:08:45.664 \rightarrow 00:08:47.951$  the emergence of drug resistance?

 $00{:}08{:}47{.}951 \dashrightarrow 00{:}08{:}50{.}753$  And then we also investigate new

NOTE Confidence: 0.877268970012665

 $00{:}08{:}50.753 \dashrightarrow 00{:}08{:}53.254$  approaches based on the science that

NOTE Confidence: 0.877268970012665

 $00{:}08{:}53.254 \dashrightarrow 00{:}08{:}56.166$  we discover to overcome and or to

NOTE Confidence: 0.877268970012665

 $00:08:56.166 \rightarrow 00:08:58.776$  prevent the emergence of drug resistance.

NOTE Confidence: 0.877268970012665

 $00:08:58.780 \rightarrow 00:09:02.303$  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

 $00:09:04.510 \rightarrow 00:09:06.715$  various different models and using

NOTE Confidence: 0.877268970012665

 $00:09:06.715 \longrightarrow 00:09:08.920$  a variety of different technologies.

NOTE Confidence: 0.877268970012665

 $00{:}09{:}08{.}920 \dashrightarrow 00{:}09{:}12{.}007$  We use specimens and data from patients,

NOTE Confidence: 0.877268970012665

 $00:09:12.010 \rightarrow 00:09:15.530$  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

 $00:09:15.971 \dashrightarrow 00:09:19.500$  within the context of the Lung Cancer Group.

NOTE Confidence: 0.877268970012665

 $00:09:19.500 \dashrightarrow 00:09:20.905$  Where we.

NOTE Confidence: 0.877268970012665

 $00:09:20.905 \dashrightarrow 00:09:25.730$  Can obtain biopsies from patients.

NOTE Confidence: 0.877268970012665

 $00{:}09{:}25.730 \dashrightarrow 00{:}09{:}28.238$  Long sort of the spectrum of

 $00:09:28.238 \rightarrow 00:09:29.910$  their treatment with therapies,

NOTE Confidence: 0.877268970012665

 $00{:}09{:}29{.}910 \dashrightarrow 00{:}09{:}32{.}418$  and we can generate patient derived

NOTE Confidence: 0.877268970012665

 $00:09:32.418 \longrightarrow 00:09:34.090$  models from these biopsies,

NOTE Confidence: 0.877268970012665

 $00:09:34.090 \longrightarrow 00:09:35.890$  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

 $00{:}09{:}37.754 \dashrightarrow 00{:}09{:}39.938$  understand resistance in patients.

NOTE Confidence: 0.877268970012665

 $00{:}09{:}39{.}940 \dashrightarrow 00{:}09{:}42{.}268$  We use these models to generate

NOTE Confidence: 0.877268970012665

 $00:09:42.268 \rightarrow 00:09:44.348$  or these specimens to generate

NOTE Confidence: 0.877268970012665

 $00{:}09{:}44.348 \dashrightarrow 00{:}09{:}47.048$  patient drive Zeno graphs as well,

NOTE Confidence: 0.877268970012665

 $00{:}09{:}47.050 \dashrightarrow 00{:}09{:}49.552$  and also 2D or 3D cultures

NOTE Confidence: 0.877268970012665

 $00:09:49.552 \rightarrow 00:09:50.803$  from patient specimens,

NOTE Confidence: 0.877268970012665

 $00:09:50.810 \rightarrow 00:09:53.210$  and we also extensively work

NOTE Confidence: 0.877268970012665

 $00:09:53.210 \rightarrow 00:09:55.130$  with genetically engineered mouse

NOTE Confidence: 0.877268970012665

 $00:09:55.130 \rightarrow 00:09:57.559$  models of lung cancer that we can.

NOTE Confidence: 0.877268970012665

 $00:09:57.560 \dashrightarrow 00:10:00.059$  I used to study resistance and in

NOTE Confidence: 0.877268970012665

 $00:10:00.059 \rightarrow 00:10:02.879$  that regard I'd like to tell you today

- NOTE Confidence: 0.877268970012665
- $00{:}10{:}02{.}879 \dashrightarrow 00{:}10{:}05{.}358$  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
- $00:10:07.910 \longrightarrow 00:10:10.234$  mutant lung cancer. Next slide, please.
- NOTE Confidence: 0.877268970012665
- $00:10:10.234 \rightarrow 00:10:13.972$  To really use models to study resistance
- NOTE Confidence: 0.877268970012665
- $00:10:13.972 \rightarrow 00:10:18.147$  to the EGFR tyrosine kinase inhibitor,
- NOTE Confidence: 0.877268970012665
- $00:10:18.150 \longrightarrow 00:10:19.054$  also Merton.
- NOTE Confidence: 0.877268970012665
- $00:10:19.054 \rightarrow 00:10:22.670$  If and this is a work that really
- NOTE Confidence: 0.877268970012665
- $00{:}10{:}22.775 \dashrightarrow 00{:}10{:}26.119$  illustrates a partnership between.
- NOTE Confidence: 0.877268970012665
- $00{:}10{:}26.120 \dashrightarrow 00{:}10{:}28.090$  Academia and investigators in academia
- NOTE Confidence: 0.877268970012665
- $00:10:28.090 \rightarrow 00:10:30.540$  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
- $00{:}10{:}33.018 \dashrightarrow 00{:}10{:}35.315$  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

 $00:10:42.645 \rightarrow 00:10:44.580$  be targeted with tyrosine kinase

NOTE Confidence: 0.877268970012665

 $00{:}10{:}44{.}649 \dashrightarrow 00{:}10{:}47{.}617$  inhibitors and one of the most recent ones.

NOTE Confidence: 0.877268970012665

 $00:10:47.620 \longrightarrow 00:10:49.545$  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

 $00:10:52.968 \rightarrow 00:10:54.943$  engineered mouse models and ask

NOTE Confidence: 0.877268970012665

 $00:10:54.943 \longrightarrow 00:10:56.507$  the question what happens?

NOTE Confidence: 0.877268970012665

 $00:10:56.510 \rightarrow 00:10:59.526$  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

 $00:11:00.661 \rightarrow 00:11:03.300$  and you treat them with a we some Merton,

NOTE Confidence: 0.877268970012665

 $00:11:03.300 \longrightarrow 00:11:05.939$  if and so we took my sweet,

NOTE Confidence: 0.877268970012665

 $00{:}11{:}05{.}940 \dashrightarrow 00{:}11{:}07{.}815$  treated them till the emergence

NOTE Confidence: 0.877268970012665

 $00{:}11{:}07.815 \dashrightarrow 00{:}11{:}08.565$  of resistance.

NOTE Confidence: 0.877268970012665

 $00{:}11{:}08{.}570 \dashrightarrow 00{:}11{:}10{.}658$  And when we looked at resistant

NOTE Confidence: 0.877268970012665

 $00:11:10.658 \rightarrow 00:11:13.100$  tumors to see what was happening,

NOTE Confidence: 0.838195204734802

 $00:11:13.100 \longrightarrow 00:11:16.054$  we found that almost 50% of the tumors

 $00:11:16.054 \rightarrow 00:11:17.844$  that emerged had secondary mutations

NOTE Confidence: 0.838195204734802

 $00:11:17.844 \longrightarrow 00:11:20.180$  in EGF receptor that confer resistance

NOTE Confidence: 0.838195204734802

 $00{:}11{:}20{.}180 \dashrightarrow 00{:}11{:}22{.}514$  to a we some American if and so.

NOTE Confidence: 0.838195204734802

 $00:11:22.520 \rightarrow 00:11:24.698$  With that information we can actually

NOTE Confidence: 0.838195204734802

 $00:11:24.698 \rightarrow 00:11:27.049$  then go ahead using these models.

NOTE Confidence: 0.838195204734802

 $00:11:27.050 \rightarrow 00:11:28.960$  So we've discovered new mechanisms.

NOTE Confidence: 0.838195204734802

 $00:11:28.960 \rightarrow 00:11:31.744$  We can now use these models for preclinical

NOTE Confidence: 0.838195204734802

 $00:11:31.744 \rightarrow 00:11:33.710$  testing and test new therapies.

NOTE Confidence: 0.838195204734802

 $00{:}11{:}33.710 \dashrightarrow 00{:}11{:}35.756$  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

 $00:11:37.935 \longrightarrow 00:11:40.197$  and analyze the relevance of the

NOTE Confidence: 0.838195204734802

 $00:11:40.197 \dashrightarrow 00:11:41.994$  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

 $00:11:46.700 \dashrightarrow 00:11:49.040$  were particularly relevant to the L.

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

NOTE Confidence: 0.838195204734802

 $00{:}11{:}51{.}960 \dashrightarrow 00{:}11{:}54{.}144$  so there was an allele specificity

NOTE Confidence: 0.838195204734802

 $00:11:54.144 \rightarrow 00:11:56.397$  that was revealed through our studies

NOTE Confidence: 0.838195204734802

 $00:11:56.397 \rightarrow 00:11:58.581$  in mouse models and then working

NOTE Confidence: 0.838195204734802

 $00:11:58.581 \dashrightarrow 00:12:00.349$  with colleagues like Mark Lemon.

NOTE Confidence: 0.838195204734802

 $00:12:00.350 \rightarrow 00:12:03.010$  Here, you're going to hear from next.

NOTE Confidence: 0.838195204734802

 $00:12:03.010 \rightarrow 00:12:06.195$  We can really then study the biochemical

NOTE Confidence: 0.838195204734802

 $00:12:06.195 \rightarrow 00:12:08.909$  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

 $00:12:11.330 \rightarrow 00:12:13.636$  So we also are working extensively

NOTE Confidence: 0.838195204734802

 $00:12:13.636 \longrightarrow 00:12:16.338$  to take these models that we have

NOTE Confidence: 0.838195204734802

 $00{:}12{:}16.338 \dashrightarrow 00{:}12{:}19.067$  and sort of take them to the next

NOTE Confidence: 0.838195204734802

 $00:12:19.067 \longrightarrow 00:12:21.779$  level to study some of the more

NOTE Confidence: 0.838195204734802

 $00:12:21.779 \rightarrow 00:12:23.615$  complex mechanisms of resistance,

NOTE Confidence: 0.838195204734802

 $00:12:23.620 \longrightarrow 00:12:26.308$  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
- $00:12:28.610 \rightarrow 00:12:30.530$  mutant lung cancer to incorporate
- NOTE Confidence: 0.838195204734802
- $00:12:30.530 \longrightarrow 00:12:32.066$  additional genetic alterations that
- NOTE Confidence: 0.838195204734802
- $00{:}12{:}32.070 \dashrightarrow 00{:}12{:}34.756$  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
- $00{:}12{:}36{.}360 \dashrightarrow 00{:}12{:}37{.}260$  for example,
- NOTE Confidence: 0.838195204734802
- $00{:}12{:}37.260 \dashrightarrow 00{:}12{:}39.960$  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
- $00:12:42.820 \longrightarrow 00:12:45.142$  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
- $00:12:47.470 \rightarrow 00:12:48.739$  sensitivity to therapies,
- NOTE Confidence: 0.838195204734802
- $00:12:48.739 \rightarrow 00:12:50.854$  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
- $00:12:53.820 \longrightarrow 00:12:56.669$  we also have a robust program to
- NOTE Confidence: 0.838195204734802
- $00{:}12{:}56.669 \dashrightarrow 00{:}12{:}58.470$  generate patient derived models,
- NOTE Confidence: 0.838195204734802
- $00{:}12{:}58{.}470 \dashrightarrow 00{:}13{:}00{.}744$  and here is really an illustration
- NOTE Confidence: 0.838195204734802

 $00:13:00.744 \longrightarrow 00:13:03.120$  of sort of the different.

NOTE Confidence: 0.838195204734802

 $00{:}13{:}03{.}120 \dashrightarrow 00{:}13{:}05{.}610$  PDX is that we've generated across

NOTE Confidence: 0.838195204734802

 $00:13:05.610 \longrightarrow 00:13:07.270$  various different oncogenic subgroups

NOTE Confidence: 0.838195204734802

 $00:13:07.334 \rightarrow 00:13:09.459$  of lung cancer with different

NOTE Confidence: 0.838195204734802

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

NOTE Confidence: 0.838195204734802

 $00:13:10.740 \rightarrow 00:13:13.326$  and so we're using these models.

NOTE Confidence: 0.838195204734802

 $00{:}13{:}13{.}330 \dashrightarrow 00{:}13{:}15{.}880$  To really study resistance in human

NOTE Confidence: 0.838195204734802

 $00:13:15.880 \longrightarrow 00:13:18.550$  specimens and really use them to

NOTE Confidence: 0.838195204734802

 $00:13:18.550 \rightarrow 00:13:20.780$  study heterogeneity of human tumors,

NOTE Confidence: 0.838195204734802

 $00:13:20.780 \rightarrow 00:13:22.229$  signaling network alterations,

NOTE Confidence: 0.838195204734802

 $00{:}13{:}22{.}229 \dashrightarrow 00{:}13{:}25{.}127$  and the molecular profiles that you

NOTE Confidence: 0.838195204734802

 $00{:}13{:}25{.}127 \dashrightarrow 00{:}13{:}27{.}798$  can have in these human who tumors

NOTE Confidence: 0.838195204734802

 $00:13:27.798 \rightarrow 00:13:29.970$  with or without drug treatment.

NOTE Confidence: 0.838195204734802

 $00:13:29.970 \longrightarrow 00:13:30.850$  Thank you.

NOTE Confidence: 0.834687411785126

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

NOTE Confidence: 0.834687411785126

 $00{:}13{:}35{.}796 \dashrightarrow 00{:}13{:}38{.}790$  I think that there's there's so

 $00{:}13{:}38{.}892 \dashrightarrow 00{:}13{:}42{.}796$  much there for the other speakers to riff

NOTE Confidence: 0.811754882335663

 $00:13:42.796 \longrightarrow 00:13:47.136$  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

 $00{:}13{:}51{.}424 \dashrightarrow 00{:}13{:}54{.}899$  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

 $00{:}13{:}56{.}890 \dashrightarrow 00{:}14{:}00{.}874$  There, an mark is unique and bringing a.

NOTE Confidence: 0.811754882335663

 $00{:}14{:}00{.}880 \dashrightarrow 00{:}14{:}03{.}757$  You know a wealth of expertise in

NOTE Confidence: 0.811754882335663

 $00{:}14{:}03.757 \dashrightarrow 00{:}14{:}06.367$  biology and structural biology to the

NOTE Confidence: 0.811754882335663

 $00:14:06.367 \rightarrow 00:14:08.532$  very interface with drug development

NOTE Confidence: 0.811754882335663

 $00:14:08.532 \rightarrow 00:14:11.676$  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

 $00{:}14{:}15{.}080 \dashrightarrow 00{:}14{:}16{.}612$  Thank you very much,

NOTE Confidence: 0.79191118478775

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

NOTE Confidence: 0.79191118478775

 $00{:}14{:}18{.}150 \dashrightarrow 00{:}14{:}20{.}838$  So a great pleasure to be here.

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

NOTE Confidence: 0.79191118478775

 $00{:}14{:}23.144 \dashrightarrow 00{:}14{:}24.680$  hearing discussion later on.

NOTE Confidence: 0.79191118478775

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

NOTE Confidence: 0.79191118478775

 $00:14:26.260 \longrightarrow 00:14:28.235$  I'm really a basic scientist

NOTE Confidence: 0.79191118478775

 $00{:}14{:}28.235 \dashrightarrow 00{:}14{:}30.060$  interested in how molecules work.

NOTE Confidence: 0.79191118478775

 $00{:}14{:}30{.}060 \dashrightarrow 00{:}14{:}32{.}364$  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

 $00:14:33.900 \longrightarrow 00:14:36.537$  The focus of most of our work is is

NOTE Confidence: 0.79191118478775

 $00{:}14{:}36{.}537 \dashrightarrow 00{:}14{:}38{.}709$  detailed understanding 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 on cogenic signaling actually do

NOTE Confidence: 0.79191118478775

 $00{:}14{:}42.690 \dashrightarrow 00{:}14{:}45.084$  work and do not an atomic detail.

NOTE Confidence: 0.79191118478775

 $00:14:45.090 \rightarrow 00:14:47.000$  Where we can and quantitatively

NOTE Confidence: 0.79191118478775

 $00:14:47.000 \rightarrow 00:14:48.528$  understanding how their properties

NOTE Confidence: 0.79191118478775

 $00:14:48.528 \longrightarrow 00:14:50.231$  are changed by oncogenic

NOTE Confidence: 0.79191118478775

 $00:14:50.231 \rightarrow 00:14:51.488$  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
- $00{:}14{:}54{.}709 \dashrightarrow 00{:}14{:}57{.}037$  we can then use that information
- NOTE Confidence: 0.79191118478775
- $00{:}14{:}57.037 \dashrightarrow 00{:}14{:}58.589$  to guide mechanistically driven
- NOTE Confidence: 0.79191118478775
- $00{:}14{:}58.656 \dashrightarrow 00{:}15{:}01.116$  personalized medicine or put the
- NOTE Confidence: 0.79191118478775
- $00{:}15{:}01{.}116 \dashrightarrow 00{:}15{:}03{.}084$  biochemistry into personalized medicine.
- NOTE Confidence: 0.79191118478775
- $00:15:03.090 \rightarrow 00:15:04.598$  Those kinds of thoughts.
- NOTE Confidence: 0.79191118478775
- $00{:}15{:}04.598 \dashrightarrow 00{:}15{:}07.776$  So our main focus in general is the
- NOTE Confidence: 0.79191118478775
- $00{:}15{:}07.776 \dashrightarrow 00{:}15{:}10.284$  class of receptors that Katie discussed.
- NOTE Confidence: 0.79191118478775
- $00{:}15{:}10.290 \dashrightarrow 00{:}15{:}12.365$  The growth factor receptors that
- NOTE Confidence: 0.79191118478775
- $00:15:12.365 \rightarrow 00:15:14.025$  have interested Harrison Chinese
- NOTE Confidence: 0.79191118478775
- 00:15:14.025 --> 00:15:15.520 domains like EGF receptor.
- NOTE Confidence: 0.79191118478775
- $00{:}15{:}15{.}520 \dashrightarrow 00{:}15{:}18.625$  As you know, and as as key to describe,
- NOTE Confidence: 0.79191118478775
- $00:15:18.630 \rightarrow 00:15:21.059$  these are key targets for cancer therapy,
- NOTE Confidence: 0.79191118478775
- $00:15:21.060 \rightarrow 00:15:21.987$  particularly lung cancer,
- NOTE Confidence: 0.79191118478775

 $00:15:21.987 \rightarrow 00:15:24.150$  and is clear in general in advancing

NOTE Confidence: 0.79191118478775

 $00:15:24.204 \rightarrow 00:15:26.249$  approaches to controlling their behavior.

NOTE Confidence: 0.79191118478775

 $00:15:26.250 \longrightarrow 00:15:28.398$  So the behavior with drugs dealing

NOTE Confidence: 0.79191118478775

 $00:15:28.398 \rightarrow 00:15:30.661$  with resistance really requires us to

NOTE Confidence: 0.79191118478775

 $00{:}15{:}30.661 \dashrightarrow 00{:}15{:}32.201$  understand the molecular mechanisms

NOTE Confidence: 0.79191118478775

 $00{:}15{:}32{.}201 \dashrightarrow 00{:}15{:}33{.}741$  and understanding well enough

NOTE Confidence: 0.79191118478775

 $00{:}15{:}33{.}804 \dashrightarrow 00{:}15{:}35{.}778$  that we can manipulate them in a

NOTE Confidence: 0.79191118478775

 $00{:}15{:}35{.}778 \dashrightarrow 00{:}15{:}37{.}320$  predictable way and also manipulate

NOTE Confidence: 0.79191118478775

 $00{:}15{:}37{.}320 \dashrightarrow 00{:}15{:}39{.}045$  their complex so the networks.

NOTE Confidence: 0.79191118478775

 $00{:}15{:}39{.}050 \dashrightarrow 00{:}15{:}41{.}465$  And I'll give a couple of examples

NOTE Confidence: 0.79191118478775

 $00{:}15{:}41{.}470 \dashrightarrow 00{:}15{:}43{.}569$  of things that are driving have

NOTE Confidence: 0.79191118478775

 $00:15:43.569 \rightarrow 00:15:45.687$  been driving research in my lab.

NOTE Confidence: 0.79191118478775

 $00:15:45.690 \longrightarrow 00:15:46.032$  Recently,

NOTE Confidence: 0.79191118478775

 $00{:}15{:}46.032 \dashrightarrow 00{:}15{:}48.768$  and the first relates to what Katie has

NOTE Confidence: 0.79191118478775

 $00:15:48.768 \rightarrow 00:15:51.336$  been discussing at the level of growth,

NOTE Confidence: 0.79191118478775

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

 $00:15:53.100 \rightarrow 00:15:54.960$  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

 $00{:}15{:}56{.}976 \dashrightarrow 00{:}15{:}58{.}756$  details of how secondary mutations

NOTE Confidence: 0.79191118478775

 $00:15:58.756 \rightarrow 00:16:00.520$  in EGFR cause resistance.

NOTE Confidence: 0.79191118478775

 $00{:}16{:}00{.}520 \dashrightarrow 00{:}16{:}01{.}678$  As she mentioned,

NOTE Confidence: 0.79191118478775

 $00:16:01.678 \longrightarrow 00:16:03.222$  with the automotive resistance

NOTE Confidence: 0.79191118478775

 $00{:}16{:}03.222 \dashrightarrow 00{:}16{:}05.493$  mutations and the additional key colon

NOTE Confidence: 0.79191118478775

 $00:16:05.493 \rightarrow 00:16:07.599$  network is to use that understanding

NOTE Confidence: 0.79191118478775

 $00:16:07.599 \longrightarrow 00:16:09.869$  as it develops to decide when to

NOTE Confidence: 0.79191118478775

 $00{:}16{:}09{.}869 \dashrightarrow 00{:}16{:}12{.}049$  use which inhibitor and how to come

NOTE Confidence: 0.79191118478775

 $00{:}16{:}12.049 \dashrightarrow 00{:}16{:}13.927$  up with new and indeed repurposed

NOTE Confidence: 0.79191118478775

 $00{:}16{:}13.927 \dashrightarrow 00{:}16{:}15.699$  inhibitors in resistance situations.

NOTE Confidence: 0.79191118478775

 $00:16:15.700 \longrightarrow 00:16:17.668$  Not going back to two other

NOTE Confidence: 0.79191118478775

 $00{:}16{:}17.668 \dashrightarrow 00{:}16{:}18.980$  working in the lab,

NOTE Confidence: 0.79191118478775

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

 $00:16:20.600 \rightarrow 00:16:22.571$  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

 $00:16:24.230 \longrightarrow 00:16:26.519$  which is one of the most common

NOTE Confidence: 0.79191118478775

 $00:16:26.519 \rightarrow 00:16:27.173$  pediatric cancers.

NOTE Confidence: 0.79191118478775

 $00{:}16{:}27.180 \dashrightarrow 00{:}16{:}29.203$  And this is related work we've been

NOTE Confidence: 0.79191118478775

 $00{:}16{:}29{.}203 \dashrightarrow 00{:}16{:}30{.}486$  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

 $00{:}16{:}33{.}410 \dashrightarrow 00{:}16{:}34{.}630$  a bit like EGFR,

NOTE Confidence: 0.79191118478775

 $00:16:34.630 \rightarrow 00:16:36.155$  and sequencing out consumers from

NOTE Confidence: 0.79191118478775

 $00:16:36.155 \rightarrow 00:16:37.020$  1600 patients.

NOTE Confidence: 0.79191118478775

 $00{:}16{:}37{.}020 \dashrightarrow 00{:}16{:}38{.}847$  That gave us a list with carve

NOTE Confidence: 0.79191118478775

 $00:16:38.847 \rightarrow 00:16:40.649$  out mutations that we analyzed

NOTE Confidence: 0.79191118478775

 $00:16:40.649 \rightarrow 00:16:41.609$  biochemically structure.

NOTE Confidence: 0.79191118478775

 $00:16:41.610 \longrightarrow 00:16:43.948$  Real transformation did a full work up

NOTE Confidence: 0.79191118478775

 $00{:}16{:}43{.}948 \dashrightarrow 00{:}16{:}46{.}617$  on them and show from that that out.

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

NOTE Confidence: 0.79191118478775

 $00:16:48.460 \rightarrow 00:16:50.170$  and we developed a computational

NOTE Confidence: 0.79191118478775

 $00:16:50.170 \longrightarrow 00:16:52.728$  model that you can see in the middle

NOTE Confidence: 0.79191118478775

 $00:16:52.728 \longrightarrow 00:16:54.925$  of the left hand part of the slide

NOTE Confidence: 0.79191118478775

 $00{:}16{:}54{.}925 \dashrightarrow 00{:}16{:}57{.}357$  that we can with which we can predict

NOTE Confidence: 0.79191118478775

 $00{:}16{:}57{.}357 \dashrightarrow 00{:}16{:}58{.}525$  which mutations are actionable.

NOTE Confidence: 0.79191118478775

 $00{:}16{:}58{.}525 \dashrightarrow 00{:}17{:}00{.}898$  Mr Working on that and an in refining

NOTE Confidence: 0.79191118478775

 $00:17:00.898 \longrightarrow 00:17:02.483$  that to identify out dependent

NOTE Confidence: 0.79191118478775

 $00{:}17{:}02{.}483 \dashrightarrow 00{:}17{:}04{.}731$  tumors in the clinic and what but

NOTE Confidence: 0.79191118478775

 $00:17:04.731 \longrightarrow 00:17:06.266$  importantly this quickly let us

NOTE Confidence: 0.79191118478775

 $00{:}17{:}06.266 \dashrightarrow 00{:}17{:}07{.}909$  to understand that some variants

NOTE Confidence: 0.79191118478775

 $00{:}17{:}07{.}909 \dashrightarrow 00{:}17{:}09{.}624$  are resistant to 1st generation

NOTE Confidence: 0.79191118478775

 $00{:}17{:}09{.}624 \dashrightarrow 00{:}17{:}11{.}390$  out computers result and it does

NOTE Confidence: 0.79191118478775

 $00{:}17{:}11.390 \dashrightarrow 00{:}17{:}12.410$  not work in Europe.

NOTE Confidence: 0.773119211196899

 $00{:}17{:}12{.}410 \dashrightarrow 00{:}17{:}14{.}482$  Last over and we also learned that the

 $00:17:14.482 \longrightarrow 00:17:16.788$  stable of 1st generation are contributors.

NOTE Confidence: 0.773119211196899

 $00:17:16.790 \longrightarrow 00:17:18.315$  We're not that different from

NOTE Confidence: 0.773119211196899

 $00:17:18.315 \longrightarrow 00:17:19.840$  one another and and impedes.

NOTE Confidence: 0.773119211196899

 $00:17:19.840 \longrightarrow 00:17:21.370$  In particular, we have one.

NOTE Confidence: 0.773119211196899

 $00:17:21.370 \longrightarrow 00:17:23.421$  We have to be careful to which

NOTE Confidence: 0.773119211196899

 $00:17:23.421 \rightarrow 00:17:25.329$  drug you choose for the trials,

NOTE Confidence: 0.773119211196899

 $00{:}17{:}25{.}330 \dashrightarrow 00{:}17{:}26{.}550$  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

 $00:17:28.080 \longrightarrow 00:17:29.823$  so more monster pick the right one

NOTE Confidence: 0.773119211196899

 $00:17:29.823 \rightarrow 00:17:31.740$  and over all those considerations,

NOTE Confidence: 0.773119211196899

 $00:17:31.740 \longrightarrow 00:17:32.655$  using their biochemistry

NOTE Confidence: 0.773119211196899

 $00:17:32.655 \rightarrow 00:17:34.180$  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

 $00:17:36.310 \rightarrow 00:17:37.840$  overcomes much of the resistance,

NOTE Confidence: 0.773119211196899

 $00:17:37.840 \rightarrow 00:17:39.996$  although of course we are now experiencing

 $00{:}17{:}39{.}996 \dashrightarrow 00{:}17{:}41{.}500$  resistance that we're working on,

NOTE Confidence: 0.773119211196899

 $00{:}17{:}41.500 \dashrightarrow 00{:}17{:}43.318$  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

 $00{:}17{:}47{.}380 \dashrightarrow 00{:}17{:}49{.}424$  But we could use in principle for

NOTE Confidence: 0.773119211196899

 $00:17:49.424 \rightarrow 00:17:50.979$  any receptor types in Chinese.

NOTE Confidence: 0.773119211196899

 $00:17:50.980 \longrightarrow 00:17:54.068$  So next slide please.

NOTE Confidence: 0.773119211196899

 $00{:}17{:}54.070 \dashrightarrow 00{:}17{:}56.219$  We also very interested in a new

NOTE Confidence: 0.773119211196899

 $00{:}17{:}56{.}219 \dashrightarrow 00{:}17{:}58{.}162$  aspect of getting away from inhibiting

NOTE Confidence: 0.773119211196899

 $00:17:58.162 \rightarrow 00:18:00.931$  receptors per say as we tend to do

NOTE Confidence: 0.773119211196899

 $00:18:00.931 \rightarrow 00:18:02.799$  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

 $00{:}18{:}04.672 \dashrightarrow 00{:}18{:}06.979$  agonists for G protein coupled receptors,

NOTE Confidence: 0.773119211196899

 $00{:}18{:}06{.}980 \dashrightarrow 00{:}18{:}09{.}140$  which can promote different responses to

NOTE Confidence: 0.773119211196899

 $00{:}18{:}09{.}140 \dashrightarrow 00{:}18{:}11{.}867$  the same receptors as strength on the left.

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

NOTE Confidence: 0.773119211196899

 $00{:}18{:}13.262 \dashrightarrow 00{:}18{:}14.306$  whether it's orange,

NOTE Confidence: 0.773119211196899

 $00:18:14.310 \longrightarrow 00:18:15.706$  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

 $00:18:19.550 \dashrightarrow 00:18:21.986$  and there's actually a lot of effort,

NOTE Confidence: 0.773119211196899

 $00:18:21.990 \rightarrow 00:18:24.321$  for example to develop biased agonists of

NOTE Confidence: 0.773119211196899

 $00:18:24.321 \rightarrow 00:18:26.259$  opiate receptors retaining analysic effects.

NOTE Confidence: 0.773119211196899

 $00{:}18{:}26.260 \dashrightarrow 00{:}18{:}27.600$  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

 $00:18:29.280 \longrightarrow 00:18:31.296$  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

 $00{:}18{:}31{.}970 \dashrightarrow 00{:}18{:}33{.}794$  In the light there traditionally thought

NOTE Confidence: 0.773119211196899

 $00{:}18{:}33.794 \dashrightarrow 00{:}18{:}36.000$  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

 $00:18:38.690 \longrightarrow 00:18:40.610$  but we recently showed in the

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

NOTE Confidence: 0.773119211196899

 $00:18:43.011 \longrightarrow 00:18:44.756$  continue to work on that.

NOTE Confidence: 0.773119211196899

 $00:18:44.760 \longrightarrow 00:18:46.902$  Prices have color in their signaling

NOTE Confidence: 0.773119211196899

 $00:18:46.902 \rightarrow 00:18:49.179$  two and as illustrated on the right,

NOTE Confidence: 0.773119211196899

 $00:18:49.180 \longrightarrow 00:18:50.880$  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

 $00:18:52.854 \longrightarrow 00:18:54.570$  can promote self liberation or

NOTE Confidence: 0.773119211196899

 $00{:}18{:}54{.}570 \dashrightarrow 00{:}18{:}56{.}190$  differentiation depending in the

NOTE Confidence: 0.773119211196899

 $00{:}18{:}56{.}190 \dashrightarrow 00{:}18{:}58{.}503$  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

 $00:19:00.400 \longrightarrow 00:19:02.100$  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

 $00{:}19{:}04.426 \dashrightarrow 00{:}19{:}06.358$  for the two ligands with altered

NOTE Confidence: 0.773119211196899

 $00{:}19{:}06{.}358 \dashrightarrow 00{:}19{:}07{.}455$  dimerization and signaling

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

NOTE Confidence: 0.773119211196899

 $00{:}19{:}08{.}900 \dashrightarrow 00{:}19{:}11{.}315$  it turns out the mutations in glioblastoma

NOTE Confidence: 0.773119211196899

 $00:19:11.315 \rightarrow 00:19:12.979$  shift signaling to the right,

NOTE Confidence: 0.773119211196899

 $00:19:12.980 \rightarrow 00:19:14.352$  making it more proliferative.

NOTE Confidence: 0.773119211196899

 $00{:}19{:}14.352 \dashrightarrow 00{:}19{:}15.724$  That's one of their.

NOTE Confidence: 0.773119211196899

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

NOTE Confidence: 0.773119211196899

 $00:19:16.654 \rightarrow 00:19:18.194$  even with small structural changes,

NOTE Confidence: 0.773119211196899

 $00:19:18.200 \longrightarrow 00:19:19.580$  now that we understand the

NOTE Confidence: 0.773119211196899

 $00{:}19{:}19{.}580 \dashrightarrow 00{:}19{:}21{.}379$  structural basis for this but through

NOTE Confidence: 0.773119211196899

 $00:19:21.379 \rightarrow 00:19:22.839$  crystallography and so forth,

NOTE Confidence: 0.773119211196899

 $00{:}19{:}22{.}840 \dashrightarrow 00{:}19{:}24{.}712$  we believe that it's possible to

NOTE Confidence: 0.773119211196899

 $00{:}19{:}24.712 \dashrightarrow 00{:}19{:}26.848$  develop biologics that will do the opposite.

NOTE Confidence: 0.773119211196899

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

NOTE Confidence: 0.773119211196899

 $00:19:27.159 \longrightarrow 00:19:27.777$  for example,

NOTE Confidence: 0.773119211196899

 $00{:}19{:}27.777 \dashrightarrow 00{:}19{:}29.631$  an antibody that could shift EGF

NOTE Confidence: 0.773119211196899

 $00{:}19{:}29{.}631 \dashrightarrow 00{:}19{:}31{.}130$  activated in cancer we mutation

 $00:19:31.130 \rightarrow 00:19:32.840$  allele with living shift signaling to

NOTE Confidence: 0.773119211196899

 $00:19:32.889 \dashrightarrow 00:19:34.579$  the left making it differentiative.

NOTE Confidence: 0.773119211196899

 $00:19:34.580 \longrightarrow 00:19:36.428$  This could be a really powerful

NOTE Confidence: 0.773119211196899

 $00:19:36.428 \rightarrow 00:19:37.352$  approach to signaling,

NOTE Confidence: 0.773119211196899

 $00:19:37.360 \rightarrow 00:19:38.592$  switching or correcting signaling

NOTE Confidence: 0.773119211196899

 $00:19:38.592 \rightarrow 00:19:39.208$  from preparations.

NOTE Confidence: 0.773119211196899

 $00{:}19{:}39{.}210 \dashrightarrow 00{:}19{:}40{.}895$  Differentiation is actually 1 proof

NOTE Confidence: 0.773119211196899

 $00:19:40.895 \longrightarrow 00:19:43.192$  of principle in that with kit and

NOTE Confidence: 0.773119211196899

 $00{:}19{:}43.192 \dashrightarrow 00{:}19{:}44.848$  stem cell factor that causes that

NOTE Confidence: 0.773119211196899

 $00:19:44.848 \longrightarrow 00:19:46.069$  was been working on.

NOTE Confidence: 0.773119211196899

 $00{:}19{:}46.070 \dashrightarrow 00{:}19{:}50.126$  At Stanford, so next slide please.

NOTE Confidence: 0.773119211196899

 $00{:}19{:}50{.}130 \dashrightarrow 00{:}19{:}51{.}297$  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

 $00:19:55.840 \longrightarrow 00:19:58.339$  About 10% of the kinases in kind
$00:19:58.339 \longrightarrow 00:20:00.882$  of is inactive and the blue ones

NOTE Confidence: 0.773119211196899

 $00{:}20{:}00{.}882 \dashrightarrow 00{:}20{:}02{.}976$  here on the left in history.

NOTE Confidence: 0.746865034103394

 $00{:}20{:}02{.}980 \dashrightarrow 00{:}20{:}05{.}828$  Many of them don't even buy native P,

NOTE Confidence: 0.746865034103394

 $00:20:05.830 \longrightarrow 00:20:07.258$  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

 $00:20:11.900 \longrightarrow 00:20:13.328$  but have been totally

NOTE Confidence: 0.746865034103394

 $00{:}20{:}13.328 \dashrightarrow 00{:}20{:}14.756$  ignored as drug targets.

NOTE Confidence: 0.746865034103394

 $00{:}20{:}14.760 \dashrightarrow 00{:}20{:}15.892$  For the most part.

NOTE Confidence: 0.746865034103394

 $00{:}20{:}15{.}892 \dashrightarrow 00{:}20{:}17{.}590$  One hypothesis is that they simply

NOTE Confidence: 0.746865034103394

 $00{:}20{:}17.649 \dashrightarrow 00{:}20{:}19.854$  by switching confirmations to bind

NOTE Confidence: 0.746865034103394

 $00:20:19.854 \longrightarrow 00:20:21.177$  downstream signaling molecules.

NOTE Confidence: 0.746865034103394

 $00:20:21.180 \longrightarrow 00:20:23.010$  We recently determined in this.

NOTE Confidence: 0.746865034103394

 $00:20:23.010 \longrightarrow 00:20:23.922$  Paper in 2022,

NOTE Confidence: 0.746865034103394

 $00:20:23.922 \longrightarrow 00:20:25.442$  referenced here a bunch of

 $00{:}20{:}25{.}442 \dashrightarrow 00{:}20{:}27{.}016$  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

 $00:20:28.536 \longrightarrow 00:20:30.371$  if we could bring in principle

NOTE Confidence: 0.746865034103394

 $00:20:30.371 \longrightarrow 00:20:32.433$  drug these in the middle here in

NOTE Confidence: 0.746865034103394

 $00:20:32.433 \rightarrow 00:20:34.554$  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

 $00:20:35.948 \longrightarrow 00:20:38.360$  inhibitor bound to one of these pseudo

NOTE Confidence: 0.746865034103394

 $00{:}20{:}38{.}360 \dashrightarrow 00{:}20{:}40{.}010$  kinases that doesn't even bind  $80\mathrm{P}$ 

NOTE Confidence: 0.746865034103394

 $00{:}20{:}40.010 \dashrightarrow 00{:}20{:}42.158$  and M as shown in the top right.

NOTE Confidence: 0.746865034103394

 $00{:}20{:}42.160 \dashrightarrow 00{:}20{:}43.560$  We've demonstrated using hydrogen

NOTE Confidence: 0.746865034103394

 $00:20:43.560 \longrightarrow 00:20:45.310$  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

 $00{:}20{:}46.594 \dashrightarrow 00{:}20{:}48.659$  changes in role one as it binds

NOTE Confidence: 0.746865034103394

 $00{:}20{:}48.717 \dashrightarrow 00{:}20{:}50.765$  and so the idea is that this might

NOTE Confidence: 0.746865034103394

 $00:20:50.765 \longrightarrow 00:20:51.912$  inhibit signaling interactions that

 $00:20:51.912 \longrightarrow 00:20:53.492$  naturally there's alot enormous amount

NOTE Confidence: 0.746865034103394

 $00:20:53.492 \rightarrow 00:20:55.620$  of work to do with selectivity and.

NOTE Confidence: 0.746865034103394

 $00:20:55.620 \longrightarrow 00:20:56.544$  And so forth.

NOTE Confidence: 0.746865034103394

 $00:20:56.544 \rightarrow 00:20:58.392$  But early studies of signaling effect

NOTE Confidence: 0.746865034103394

 $00{:}20{:}58{.}392 \dashrightarrow 00{:}21{:}00{.}081$  suggests that banana can inhibit

NOTE Confidence: 0.746865034103394

 $00{:}21{:}00{.}081 \dashrightarrow 00{:}21{:}01{.}736$  went dependent rule one signaling,

NOTE Confidence: 0.746865034103394

 $00:21:01.740 \rightarrow 00:21:03.462$  and so the idea of sharing centrally

NOTE Confidence: 0.746865034103394

 $00:21:03.462 \longrightarrow 00:21:04.648$  here is that confirmational

NOTE Confidence: 0.746865034103394

 $00:21:04.648 \longrightarrow 00:21:06.608$  disruptors like this could be

NOTE Confidence: 0.746865034103394

 $00:21:06.608 \rightarrow 00:21:08.176$  valuable tools for understanding.

NOTE Confidence: 0.746865034103394

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

NOTE Confidence: 0.746865034103394

 $00:21:09.158 \rightarrow 00:21:11.440$  but also targeting them where they play

NOTE Confidence: 0.746865034103394

 $00:21:11.494 \rightarrow 00:21:13.650$  known roles in cancer and other diseases,

NOTE Confidence: 0.746865034103394

 $00:21:13.650 \longrightarrow 00:21:15.582$  and so far they're all being

NOTE Confidence: 0.746865034103394

 $00:21:15.582 \rightarrow 00:21:16.870$  hit the articaine ones.

NOTE Confidence: 0.746865034103394

 $00:21:16.870 \longrightarrow 00:21:18.158$  For example, with antibodies.

- NOTE Confidence: 0.746865034103394
- $00{:}21{:}18.158 \dashrightarrow 00{:}21{:}20.090$  So that's about my brief summary.
- NOTE Confidence: 0.746865034103394
- $00:21:20.090 \longrightarrow 00:21:22.016$  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
- $00{:}21{:}24{.}280 \dashrightarrow 00{:}21{:}26{.}244$  and I look forward.
- NOTE Confidence: 0.746865034103394
- $00:21:26.244 \longrightarrow 00:21:27.717$  To your questions.
- NOTE Confidence: 0.746865034103394
- 00:21:27.720 --> 00:21:29.310 Thank you very
- NOTE Confidence: 0.831698834896088
- $00{:}21{:}29{.}310 \dashrightarrow 00{:}21{:}32{.}490$  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
- $00:21:39.380 \rightarrow 00:21:41.432$  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
- $00{:}21{:}44{.}591 \dashrightarrow 00{:}21{:}47{.}272$  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
- $00{:}21{:}50.091 \dashrightarrow 00{:}21{:}52.479$  here at Yale School of Medicine.
- NOTE Confidence: 0.831698834896088

- $00:21:52.480 \longrightarrow 00:21:54.590$  As past president of our
- NOTE Confidence: 0.831698834896088
- 00:21:54.590 --> 00:21:55.856 faculty Senate equivalent,
- NOTE Confidence: 0.831698834896088
- $00:21:55.860 \rightarrow 00:21:58.392$  the Faculty Advisory Council where she
- NOTE Confidence: 0.831698834896088
- $00:21:58.392 \rightarrow 00:22:00.080$  also showed exceptional leadership.
- NOTE Confidence: 0.831698834896088
- $00:22:00.080 \longrightarrow 00:22:02.606$  Sort of in that other realm,
- NOTE Confidence: 0.831698834896088
- $00{:}22{:}02{.}610 \dashrightarrow 00{:}22{:}05{.}194$  and she's going to be talking to us
- NOTE Confidence: 0.831698834896088
- $00{:}22{:}05{.}194 \dashrightarrow 00{:}22{:}07{.}570$  about very impactful work regarding
- NOTE Confidence: 0.831698834896088
- $00{:}22{:}07.570 \dashrightarrow 00{:}22{:}09.778$  resistance to PARP inhibition.
- NOTE Confidence: 0.872240900993347
- $00{:}22{:}12{.}210 \dashrightarrow 00{:}22{:}13.662$  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
- $00:22:15.477 \longrightarrow 00:22:17.377$  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
- $00{:}22{:}21{.}197 \dashrightarrow 00{:}22{:}23{.}141$  the Yale Cancer Center that is
- NOTE Confidence: 0.872240900993347
- $00:22:23.141 \rightarrow 00:22:24.900$  driven my group with expertise
- NOTE Confidence: 0.872240900993347
- $00:22:24.900 \rightarrow 00:22:26.870$  in genome integrity to really

- NOTE Confidence: 0.872240900993347
- $00:22:26.870 \longrightarrow 00:22:29.182$  focus on those aspects that have
- NOTE Confidence: 0.872240900993347
- $00:22:29.182 \longrightarrow 00:22:30.660$  impacts for cancer therapies.
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}33.030 \dashrightarrow 00{:}22{:}35.734$  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
- $00:22:37.830 \rightarrow 00:22:40.188$  and that are is specifically PARP
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}40.188 \dashrightarrow 00{:}22{:}42.630$  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
- $00{:}22{:}46.153 \dashrightarrow 00{:}22{:}47.830$  the rapies have incredible promise.
- NOTE Confidence: 0.846176207065582
- $00:22:47.830 \longrightarrow 00:22:49.655$  It's well established now that
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}49.655 \dashrightarrow 00{:}22{:}51.978$  the acquired resistance is a major
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}51{.}978 \dashrightarrow 00{:}22{:}54{.}113$  bottleneck for the durability and
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}54.113 \dashrightarrow 00{:}22{:}56.472$  efficacy of these treatments, and so,
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}56{.}472 \dashrightarrow 00{:}22{:}59{.}040$  how do we tackle this problem and other
- NOTE Confidence: 0.846176207065582
- $00{:}22{:}59{.}115 \dashrightarrow 00{:}23{:}01{.}610$  opportunities that are presented when
- NOTE Confidence: 0.846176207065582

 $00:23:01.610 \rightarrow 00:23:04.105$  these tumor cells become resistant?

NOTE Confidence: 0.846176207065582

 $00{:}23{:}04{.}110 \dashrightarrow 00{:}23{:}06{.}120$  So the approach that we've been

NOTE Confidence: 0.846176207065582

 $00:23:06.120 \longrightarrow 00:23:08.598$  taking is first to start by really

NOTE Confidence: 0.846176207065582

 $00:23:08.598 \rightarrow 00:23:10.728$  trying to define the genetic basis

NOTE Confidence: 0.846176207065582

 $00{:}23{:}10.728 \dashrightarrow 00{:}23{:}12.970$  of resistance in this context,

NOTE Confidence: 0.846176207065582

 $00{:}23{:}12{.}970 \dashrightarrow 00{:}23{:}15{.}618$  and so we know that there has been

NOTE Confidence: 0.846176207065582

 $00{:}23{:}15.618 \dashrightarrow 00{:}23{:}17.758$  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

 $00{:}23{:}19{.}974 \dashrightarrow 00{:}23{:}21{.}848$  excited about the possibility of

NOTE Confidence: 0.846176207065582

 $00{:}23{:}21{.}848 \dashrightarrow 00{:}23{:}23{.}548$  circulating tumor DNA sequencing as

NOTE Confidence: 0.846176207065582

 $00{:}23{:}23{.}548 \dashrightarrow 00{:}23{:}25{.}879$  well as potential for serial biopsies,

NOTE Confidence: 0.846176207065582

 $00:23:25.880 \longrightarrow 00:23:27.432$  particularly along this axis.

NOTE Confidence: 0.846176207065582

 $00{:}23{:}27{.}432 \dashrightarrow 00{:}23{:}29{.}760$  As tumors gain resistance to combine

NOTE Confidence: 0.846176207065582

 $00:23:29.823 \rightarrow 00:23:31.977$  with genome sequencing as well as

NOTE Confidence: 0.846176207065582

 $00{:}23{:}31{.}977 \dashrightarrow 00{:}23{:}33{.}913$  gene expression analysis to provide

NOTE Confidence: 0.846176207065582

 $00:23:33.913 \rightarrow 00:23:36.118$  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
- $00{:}23{:}38{.}330 \dashrightarrow 00{:}23{:}40{.}118$  although from model organisms to mouse
- NOTE Confidence: 0.846176207065582
- $00{:}23{:}40.118 \dashrightarrow 00{:}23{:}42.120$  models to really get the mechanisms,
- NOTE Confidence: 0.846176207065582
- $00{:}23{:}42.120 \dashrightarrow 00{:}23{:}43.860$  and of course the ultimate goal
- NOTE Confidence: 0.846176207065582
- $00:23:43.860 \longrightarrow 00:23:46.102$  is always to really be able to
- NOTE Confidence: 0.846176207065582
- $00{:}23{:}46.102 \dashrightarrow 00{:}23{:}47.807$  leverage the mechanism of resistance,
- NOTE Confidence: 0.846176207065582
- $00:23:47.810 \longrightarrow 00:23:49.706$  ideally to come up with new
- NOTE Confidence: 0.846176207065582
- $00:23:49.706 \longrightarrow 00:23:50.970$  therapies and so awhile.
- NOTE Confidence: 0.846176207065582
- $00:23:50.970 \longrightarrow 00:23:53.056$  Of course we'd like these to be
- NOTE Confidence: 0.846176207065582
- $00:23:53.056 \rightarrow 00:23:54.347$  actionable were really particularly
- NOTE Confidence: 0.846176207065582
- $00:23:54.347 \rightarrow 00:23:56.339$  would like to go beyond that,
- NOTE Confidence: 0.846176207065582
- $00{:}23{:}56{.}340 \dashrightarrow 00{:}23{:}58{.}405$  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
- $00{:}23{:}59{.}820 \dashrightarrow 00{:}24{:}01{.}584$  what can we bring to the table
- NOTE Confidence: 0.846176207065582
- $00:24:01.584 \rightarrow 00:24:03.300$  in terms of stratification?
- NOTE Confidence: 0.846176207065582

 $00{:}24{:}03{.}300 \dashrightarrow 00{:}24{:}05{.}274$  And today I'll talk about an example

NOTE Confidence: 0.846176207065582

 $00{:}24{:}05{.}274 \dashrightarrow 00{:}24{:}07{.}477$  where we really think that we have

NOTE Confidence: 0.846176207065582

 $00{:}24{:}07{.}477 \dashrightarrow 00{:}24{:}09{.}102$  to consider Bracco one patient

NOTE Confidence: 0.846176207065582

 $00:24:09.102 \rightarrow 00:24:10.897$  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

 $00{:}24{:}14.768 \dashrightarrow 00{:}24{:}17.168$  that will further help us stratify

NOTE Confidence: 0.846176207065582

 $00{:}24{:}17.168 \dashrightarrow 00{:}24{:}19.487$  patients based on the mechanisms

NOTE Confidence: 0.846176207065582

 $00{:}24{:}19{.}487 \dashrightarrow 00{:}24{:}20{.}415$  underlying resistance,

NOTE Confidence: 0.846176207065582

 $00{:}24{:}20{.}420 \dashrightarrow 00{:}24{:}22{.}616$  and I think one real potential

NOTE Confidence: 0.846176207065582

 $00:24:22.616 \longrightarrow 00:24:24.080$  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

 $00:24:25.915 \longrightarrow 00:24:28.166$  us to identify patients who have

NOTE Confidence: 0.846176207065582

 $00{:}24{:}28.166 \dashrightarrow 00{:}24{:}29.926$  a so called reversion allele.

NOTE Confidence: 0.846176207065582

 $00{:}24{:}29{.}930 \dashrightarrow 00{:}24{:}31{.}835$  That'll now will make them

NOTE Confidence: 0.846176207065582

 $00:24:31.835 \rightarrow 00:24:33.359$  insensitive Department of Therapy

- NOTE Confidence: 0.846176207065582
- $00:24:33.359 \rightarrow 00:24:35.059$  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
- $00:24:37.112 \longrightarrow 00:24:38.944$  where resistance is arising through
- NOTE Confidence: 0.846176207065582
- $00{:}24{:}38{.}944 \dashrightarrow 00{:}24{:}40{.}929$  a secondary mechanism that maybe.
- NOTE Confidence: 0.846176207065582
- $00{:}24{:}40{.}930 \dashrightarrow 00{:}24{:}42{.}314$  The rapeutically actionable and so
- NOTE Confidence: 0.846176207065582
- $00{:}24{:}42{.}314 \dashrightarrow 00{:}24{:}44{.}778$  I just wanted to take you through
- NOTE Confidence: 0.846176207065582
- $00:24:44.778 \rightarrow 00:24:46.740$  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
- $00{:}24{:}48{.}450 \dashrightarrow 00{:}24{:}50{.}641$  but across our team to look at
- NOTE Confidence: 0.846176207065582
- $00{:}24{:}50.641 \dashrightarrow 00{:}24{:}52.559$  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
- $00:24:53.928 \rightarrow 00:24:55.980$  these crisper screens have been published.
- NOTE Confidence: 0.846176207065582
- $00:24:55.980 \longrightarrow 00:24:58.122$  The work that's been going on here
- NOTE Confidence: 0.846176207065582
- 00:24:58.122 $\operatorname{-->}$ 00:25:00.178 at Yale really has taken advantage
- NOTE Confidence: 0.846176207065582
- $00{:}25{:}00{.}178 \dashrightarrow 00{:}25{:}02{.}670$  of a partnership that we already have
- NOTE Confidence: 0.846176207065582

 $00:25:02.741 \rightarrow 00:25:04.865$  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

 $00:25:05.914 \rightarrow 00:25:08.002$  and Ryan has been modeling reversion

NOTE Confidence: 0.846176207065582

 $00:25:08.002 \rightarrow 00:25:09.719$  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

 $00:25:11.040 \longrightarrow 00:25:12.075$  And testing really,

NOTE Confidence: 0.846176207065582

 $00:25:12.075 \rightarrow 00:25:14.490$  is there still an actionable approach that

NOTE Confidence: 0.846176207065582

 $00:25:14.552 \rightarrow 00:25:16.664$  we could use in these contexts or not?

NOTE Confidence: 0.846176207065582

 $00{:}25{:}16.670 \dashrightarrow 00{:}25{:}17.873$  By functionally characterizing

NOTE Confidence: 0.846176207065582

 $00:25:17.873 \longrightarrow 00:25:19.076$  the reversion alleles?

NOTE Confidence: 0.846176207065582

 $00{:}25{:}19.080 \dashrightarrow 00{:}25{:}20.550$  What I'm particularly excited about

NOTE Confidence: 0.846176207065582

 $00{:}25{:}20.550 \dashrightarrow 00{:}25{:}22.853$  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

 $00:25:25.130 \rightarrow 00:25:27.026$  who you'll hear from in a moment where

NOTE Confidence: 0.846176207065582

 $00:25:27.026 \rightarrow 00:25:29.448$  she is and acquiring these serial biopsies.

NOTE Confidence: 0.830411314964294

 $00:25:29.450 \rightarrow 00:25:30.890$  Along this progression to relapse.

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

NOTE Confidence: 0.830411314964294

 $00:25:33.239 \rightarrow 00:25:35.495$  really look not just a genome changes,

NOTE Confidence: 0.830411314964294

 $00:25:35.500 \rightarrow 00:25:36.708$  but gene expression changes.

NOTE Confidence: 0.830411314964294

 $00:25:36.708 \rightarrow 00:25:37.916$  And so these sequencing

NOTE Confidence: 0.830411314964294

 $00:25:37.916 \longrightarrow 00:25:39.238$  is ongoing at the moment,

NOTE Confidence: 0.830411314964294

 $00:25:39.240 \rightarrow 00:25:41.394$  and we're really excited about the

NOTE Confidence: 0.830411314964294

 $00:25:41.394 \rightarrow 00:25:43.630$  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

 $00{:}25{:}45{.}494 \dashrightarrow 00{:}25{:}47{.}423$  vignette of what was really originally

NOTE Confidence: 0.830411314964294

 $00:25:47.423 \rightarrow 00:25:49.523$  motivated by these in vitro screens,

NOTE Confidence: 0.830411314964294

 $00:25:49.530 \longrightarrow 00:25:51.287$  and some work that my group has

NOTE Confidence: 0.830411314964294

 $00{:}25{:}51{.}287 \dashrightarrow 00{:}25{:}53{.}117$  done and the possibilities that we

NOTE Confidence: 0.830411314964294

 $00{:}25{:}53{.}117 \dashrightarrow 00{:}25{:}55{.}139$  can see for this going forward.

NOTE Confidence: 0.830411314964294

 $00{:}25{:}55{.}140 \dashrightarrow 00{:}25{:}56{.}694$  So it's well established that Braca

NOTE Confidence: 0.830411314964294

 $00{:}25{:}56{.}694 \dashrightarrow 00{:}25{:}59{.}333$  1 one of its key roles is to promote

 $00:25:59.333 \longrightarrow 00:26:01.243$  what's called double strand break and

NOTE Confidence: 0.830411314964294

 $00:26:01.243 \rightarrow 00:26:03.097$  resection through the EXO 1 pathway.

NOTE Confidence: 0.830411314964294

 $00:26:03.100 \longrightarrow 00:26:05.151$  And this is a critical step in

NOTE Confidence: 0.830411314964294

 $00:26:05.151 \rightarrow 00:26:07.546$  the HR pathway and so it was came

NOTE Confidence: 0.830411314964294

 $00{:}26{:}07{.}546 \dashrightarrow 00{:}26{:}08{.}702$  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

 $00:26:11.280 \longrightarrow 00:26:13.052$  7 can drive the rapy resistance in

NOTE Confidence: 0.830411314964294

 $00{:}26{:}13.052 \dashrightarrow 00{:}26{:}14.978$  the context of Graco one mutations.

NOTE Confidence: 0.830411314964294

 $00:26:14.980 \longrightarrow 00:26:16.990$  Well, my group discovered is that

NOTE Confidence: 0.830411314964294

 $00:26:16.990 \rightarrow 00:26:18.913$  these are negative regulators of the

NOTE Confidence: 0.830411314964294

 $00{:}26{:}18{.}913 \dashrightarrow 00{:}26{:}20{.}503$  bloom helicase acting with DNA 2,

NOTE Confidence: 0.830411314964294

 $00{:}26{:}20{.}510 \dashrightarrow 00{:}26{:}22{.}045$  which is an alternative and

NOTE Confidence: 0.830411314964294

 $00:26:22.045 \longrightarrow 00:26:22.659$  resection mechanism.

NOTE Confidence: 0.830411314964294

 $00{:}26{:}22.660 \dashrightarrow 00{:}26{:}24.652$  So this is a way where these tumor

NOTE Confidence: 0.830411314964294

 $00:26:24.652 \rightarrow 00:26:26.376$  cells have essentially rewired reception

NOTE Confidence: 0.830411314964294

 $00:26:26.376 \rightarrow 00:26:28.704$  so they're no longer dependent on

 $00{:}26{:}28.704 \dashrightarrow 00{:}26{:}30.777$  bracca one and instead can use this

NOTE Confidence: 0.830411314964294

 $00:26:30.777 \rightarrow 00:26:32.432$  bloom pathway and so as examples

NOTE Confidence: 0.830411314964294

 $00{:}26{:}32{.}432 \dashrightarrow 00{:}26{:}34{.}118$  of what that mechanism has brought

NOTE Confidence: 0.830411314964294

 $00:26:34.118 \longrightarrow 00:26:36.379$  about in terms of the way we're

NOTE Confidence: 0.830411314964294

 $00:26:36.379 \rightarrow 00:26:37.695$  thinking about future therapeutics,

NOTE Confidence: 0.830411314964294

 $00{:}26{:}37.700 \dashrightarrow 00{:}26{:}39.230$  the first is that identifies

NOTE Confidence: 0.830411314964294

 $00:26:39.230 \longrightarrow 00:26:40.148$  the bloom helicases,

NOTE Confidence: 0.830411314964294

 $00:26:40.150 \longrightarrow 00:26:42.376$  a really novel target that we have

NOTE Confidence: 0.830411314964294

 $00{:}26{:}42.376 \dashrightarrow 00{:}26{:}44.713$  already shown in vitro is also synthetic

NOTE Confidence: 0.830411314964294

 $00{:}26{:}44.713 \dashrightarrow 00{:}26{:}47.010$  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

 $00{:}26{:}51{.}178 \dashrightarrow 00{:}26{:}53{.}260$  ways in which this has changed.

NOTE Confidence: 0.830411314964294

 $00{:}26{:}53{.}260 \dashrightarrow 00{:}26{:}55{.}126$  Our thinking is that it highlights

NOTE Confidence: 0.830411314964294

 $00{:}26{:}55{.}126 \dashrightarrow 00{:}26{:}56{.}819$  also the potential for combinations

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

NOTE Confidence: 0.830411314964294

 $00{:}26{:}59{.}160 \dashrightarrow 00{:}27{:}01{.}491$  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

 $00{:}27{:}03.637 \dashrightarrow 00{:}27{:}05.809$  helicase is driving resection at very

NOTE Confidence: 0.830411314964294

 $00{:}27{:}05{.}809 \dashrightarrow 00{:}27{:}08{.}237$  high rates and this leads not just

NOTE Confidence: 0.830411314964294

 $00{:}27{:}08{.}237 \dashrightarrow 00{:}27{:}10{.}262$  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

 $00:27:12.340 \longrightarrow 00:27:14.416$  and ATR is an important negative

NOTE Confidence: 0.830411314964294

 $00:27:14.416 \longrightarrow 00:27:15.454$  regulator of resection,

NOTE Confidence: 0.830411314964294

 $00{:}27{:}15{.}460 \dashrightarrow 00{:}27{:}17{.}938$  and so we think that this combination

NOTE Confidence: 0.830411314964294

 $00{:}27{:}17{.}938 \dashrightarrow 00{:}27{:}19{.}699$  of treatments will push this.

NOTE Confidence: 0.830411314964294

 $00:27:19.700 \longrightarrow 00:27:20.976$  Hyper resection even further,

NOTE Confidence: 0.830411314964294

 $00:27:20.976 \rightarrow 00:27:23.998$  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

 $00{:}27{:}25.700 \dashrightarrow 00{:}27{:}28.076$  mutations may not respond well to a

NOTE Confidence: 0.830411314964294

 $00:27:28.076 \rightarrow 00:27:29.626$  combination with an ATR inhibitor,

 $00{:}27{:}29{.}630 \dashrightarrow 00{:}27{:}31{.}966$  but when there is a mechanism that down

NOTE Confidence: 0.830411314964294

 $00{:}27{:}31.966 \dashrightarrow 00{:}27{:}33.322$  regulates these particular proteins

NOTE Confidence: 0.830411314964294

 $00:27:33.322 \longrightarrow 00:27:35.458$  that that will make these tumors

NOTE Confidence: 0.830411314964294

 $00:27:35.458 \rightarrow 00:27:37.240$  very sensitive to the combination,

NOTE Confidence: 0.830411314964294

 $00:27:37.240 \longrightarrow 00:27:39.472$  and so along those lines we're

NOTE Confidence: 0.830411314964294

 $00{:}27{:}39{.}472 \dashrightarrow 00{:}27{:}41{.}289$  currently just submitting anello I

NOTE Confidence: 0.830411314964294

 $00:27:41.289 \rightarrow 00:27:43.151$  with paleru so where we are proposing

NOTE Confidence: 0.830411314964294

 $00{:}27{:}43.151 \dashrightarrow 00{:}27{:}45.452$  to do a trial specifically in Bracco

NOTE Confidence: 0.830411314964294

 $00:27:45.452 \longrightarrow 00:27:47.832$  in patients because this is not a

NOTE Confidence: 0.830411314964294

 $00:27:47.832 \rightarrow 00:27:49.818$  mechanism that's relevant for the bracket,

NOTE Confidence: 0.830411314964294

 $00:27:49.820 \longrightarrow 00:27:50.450$  two patients.

NOTE Confidence: 0.830411314964294

 $00:27:50.450 \rightarrow 00:27:52.655$  Hoping to really test this idea clinically,

NOTE Confidence: 0.830411314964294

 $00:27:52.660 \rightarrow 00:27:54.536$  so thank you and I look forward

NOTE Confidence: 0.830411314964294

 $00:27:54.536 \longrightarrow 00:27:55.340$  to the questions.

NOTE Confidence: 0.830411314964294

 $00{:}27{:}55{.}340 \dashrightarrow 00{:}27{:}56{.}978$  I also just like to highlight that

 $00{:}27{:}56{.}978 \dashrightarrow 00{:}27{:}58{.}863$  much of this work as I mentioned

NOTE Confidence: 0.830411314964294

 $00{:}27{:}58.863 \dashrightarrow 00{:}28{:}00{.}278$  was a collaboration with Astra

NOTE Confidence: 0.830411314964294

 $00{:}28{:}00{.}278 \dashrightarrow 00{:}28{:}02{.}000$  Zeneca and is also supported very

NOTE Confidence: 0.830411314964294

 $00:28:02.000 \rightarrow 00:28:03.380$  generously by the Great Foundation.

NOTE Confidence: 0.789911925792694

 $00{:}28{:}06{.}740 \dashrightarrow 00{:}28{:}10{.}016$  Thank you Megan. That was terrific.

NOTE Confidence: 0.789911925792694

 $00{:}28{:}10.020 \dashrightarrow 00{:}28{:}14.470$  Next, I'd like to introduce.

NOTE Confidence: 0.789911925792694

 $00:28:14.470 \longrightarrow 00:28:16.990$  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

 $00{:}28{:}19.590 \dashrightarrow 00{:}28{:}21.760$  our Epigenetics program here at

NOTE Confidence: 0.789911925792694

 $00:28:21.760 \longrightarrow 00:28:24.663$  Yale and will be talking about

NOTE Confidence: 0.789911925792694

 $00{:}28{:}24.663 \dashrightarrow 00{:}28{:}27.267$  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

 $00{:}28{:}32{.}552 \dashrightarrow 00{:}28{:}35{.}768$  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

 $00:28:38.094 \longrightarrow 00:28:40.218$  magnet is critical for cancer

NOTE Confidence: 0.693806850910187

 $00:28:40.218 \longrightarrow 00:28:41.796$  initiation and progression.

- NOTE Confidence: 0.693806850910187
- $00:28:41.800 \longrightarrow 00:28:44.212$  Especially my laptop is interested in
- NOTE Confidence: 0.693806850910187
- $00{:}28{:}44{.}212 \dashrightarrow 00{:}28{:}45{.}820$  understanding how epigenetic regulators,
- NOTE Confidence: 0.693806850910187
- $00{:}28{:}45{.}820 \dashrightarrow 00{:}28{:}48{.}284$  also called reader writer and erasers of
- NOTE Confidence: 0.693806850910187
- $00:28:48.284 \rightarrow 00:28:50.640$  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
- $00:28:52.248 \longrightarrow 00:28:53.454$  of cancer progression?
- NOTE Confidence: 0.693806850910187
- 00:28:53.460 --> 00:28:55.470 My number to your interest
- NOTE Confidence: 0.693806850910187
- $00:28:55.470 \longrightarrow 00:28:57.480$  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
- $00:28:59.084 \rightarrow 00:29:00.688$  to anti cancer drugs,
- NOTE Confidence: 0.693806850910187
- $00:29:00.690 \longrightarrow 00:29:03.180$  which is the main topic today.
- NOTE Confidence: 0.693806850910187
- $00{:}29{:}03.180 \dashrightarrow 00{:}29{:}05.370$  Cancer metastasis and tumor in valuation,
- NOTE Confidence: 0.693806850910187
- $00{:}29{:}05{.}370 \dashrightarrow 00{:}29{:}07{.}953$  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
- $00:29:10.378 \longrightarrow 00:29:12.838$  more about later on and next.
- NOTE Confidence: 0.693806850910187

 $00:29:12.840 \longrightarrow 00:29:14.976$  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

 $00:29:16.364 \rightarrow 00:29:19.222$  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

 $00{:}29{:}25{.}429 \dashrightarrow 00{:}29{:}26{.}953$  the NCI Experimental the rapeutics

NOTE Confidence: 0.693806850910187

 $00{:}29{:}26{.}953 \dashrightarrow 00{:}29{:}29{.}350$  program and right now I'm also

NOTE Confidence: 0.693806850910187

 $00{:}29{:}29{.}350 \dashrightarrow 00{:}29{:}31{.}315$  collaborating some about tech and

NOTE Confidence: 0.693806850910187

 $00{:}29{:}31{.}315 \dashrightarrow 00{:}29{:}32{.}745$  pharmaceutical company in this

NOTE Confidence: 0.693806850910187

 $00{:}29{:}32{.}745 \dashrightarrow 00{:}29{:}35{.}933$  area as well and in the next 2

NOTE Confidence: 0.693806850910187

 $00:29:35.933 \rightarrow 00:29:38.348$  slides I'm going to tell you some

NOTE Confidence: 0.693806850910187

 $00{:}29{:}38{.}348 \dashrightarrow 00{:}29{:}40{.}942$  of the examples that we have done

NOTE Confidence: 0.693806850910187

 $00{:}29{:}40.942 \dashrightarrow 00{:}29{:}43.930$  to look at the resistant mechanisms.

NOTE Confidence: 0.693806850910187

 $00:29:43.930 \longrightarrow 00:29:45.470$  Next please.

NOTE Confidence: 0.693806850910187

00:29:45.470 - 00:29:47.180 One which is targeted therapy,

 $00{:}29{:}47.180 \dashrightarrow 00{:}29{:}49.546$  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

 $00{:}29{:}51{.}630 \dashrightarrow 00{:}29{:}53{.}682$  and we can generate those resistant

NOTE Confidence: 0.693806850910187

 $00:29:53.682 \rightarrow 00:29:55.050$  cells in tissue culture.

NOTE Confidence: 0.693806850910187

 $00:29:55.050 \longrightarrow 00:29:57.262$  And we found that those resistant cells

NOTE Confidence: 0.693806850910187

 $00{:}29{:}57{.}262 \dashrightarrow 00{:}29{:}59{.}827$  actually are do not have genetic mutations.

NOTE Confidence: 0.693806850910187

 $00:29:59.830 \rightarrow 00:30:01.362$  They actually resistant mechanism

NOTE Confidence: 0.693806850910187

 $00:30:01.362 \rightarrow 00:30:03.660$  is actually reversible if you take

NOTE Confidence: 0.693806850910187

 $00:30:03.717 \longrightarrow 00:30:05.684$  the drug away from the cells for

NOTE Confidence: 0.693806850910187

 $00:30:05.684 \rightarrow 00:30:07.657$  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

 $00:30:08.730 \longrightarrow 00:30:11.026$  But if you take it away for

NOTE Confidence: 0.693806850910187

 $00:30:11.026 \longrightarrow 00:30:12.490$  a long period time,

NOTE Confidence: 0.693806850910187

 $00{:}30{:}12{.}490 \dashrightarrow 00{:}30{:}14{.}536$  for example about months and those

NOTE Confidence: 0.693806850910187

 $00{:}30{:}14.536 \dashrightarrow 00{:}30{:}16.979$  cells becomes those so called watch out.

 $00{:}30{:}16{.}980 \dashrightarrow 00{:}30{:}20{.}800$  And those cells become sensitive

NOTE Confidence: 0.693806850910187

 $00{:}30{:}20{.}800 \dashrightarrow 00{:}30{:}23{.}856$  to just over again.

NOTE Confidence: 0.693806850910187

 $00:30:23.860 \dashrightarrow 00:30:26.980$  To local internal mechanism next piece.

NOTE Confidence: 0.693806850910187

 $00:30:26.980 \longrightarrow 00:30:29.458$  We profile the expression of the

NOTE Confidence: 0.693806850910187

 $00{:}30{:}29{.}458 \dashrightarrow 00{:}30{:}31{.}642$  expression profile of the reason

NOTE Confidence: 0.693806850910187

 $00:30:31.642 \dashrightarrow 00:30:34.390$  cells compared to the sensitive cells.

NOTE Confidence: 0.693806850910187

 $00{:}30{:}34{.}390 \dashrightarrow 00{:}30{:}37{.}253$  We can see that those resistant cells

NOTE Confidence: 0.693806850910187

 $00:30:37.253 \rightarrow 00:30:39.007$  have increased oxidative phosphorylation

NOTE Confidence: 0.693806850910187

 $00{:}30{:}39{.}007 \dashrightarrow 00{:}30{:}42{.}234$  or called off force and remarkable need.

NOTE Confidence: 0.693806850910187

 $00:30:42.240 \rightarrow 00:30:44.415$  Those cells are very sensitive

NOTE Confidence: 0.693806850910187

 $00{:}30{:}44{.}415 \dashrightarrow 00{:}30{:}46{.}155$  to ox force inhibitor.

NOTE Confidence: 0.693806850910187

00:30:46.160 $\operatorname{-->}$ 00:30:49.016 As you can see the tumor regression if

NOTE Confidence: 0.693806850910187

 $00{:}30{:}49.016 \dashrightarrow 00{:}30{:}51.353$ you combine traditional Antonio Massenet

NOTE Confidence: 0.693806850910187

 $00:30:51.353 \rightarrow 00:30:54.449$  which is 1 nautical force inhibitor.

NOTE Confidence: 0.693806850910187

 $00:30:54.450 \dashrightarrow 00:30:57.108$  You can see regression of those.

NOTE Confidence: 0.693806850910187

 $00{:}30{:}57{.}110 \dashrightarrow 00{:}30{:}59{.}744$  Resistant tumors Next place as I

 $00:30:59.744 \rightarrow 00:31:02.752$  mentioned that this app is genetic

NOTE Confidence: 0.693806850910187

 $00{:}31{:}02.752 \dashrightarrow 00{:}31{:}05.667$  mechanism that contributes to resistance,

NOTE Confidence: 0.693806850910187

 $00{:}31{:}05.670 \dashrightarrow 00{:}31{:}07.990$  so we are one of the mechanism we

NOTE Confidence: 0.693806850910187

 $00:31:07.990 \longrightarrow 00:31:10.498$  found is that Arcadian 5 histone

NOTE Confidence: 0.693806850910187

 $00{:}31{:}10{.}498 \dashrightarrow 00{:}31{:}12{.}813$  demethylase are critical for this

NOTE Confidence: 0.693806850910187

 $00:31:12.813 \rightarrow 00:31:14.873$  formation of those resistant cells

NOTE Confidence: 0.693806850910187

 $00:31:14.873 \longrightarrow 00:31:17.153$  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

 $00:31:19.224 \rightarrow 00:31:21.989$  this is one of the early generation

NOTE Confidence: 0.693806850910187

 $00:31:21.989 \longrightarrow 00:31:24.629$  inhibitor and four to prevent the

NOTE Confidence: 0.693806850910187

 $00:31:24.629 \dashrightarrow 00:31:26.891$  formation of the recent sales for

NOTE Confidence: 0.693806850910187

 $00:31:26.891 \rightarrow 00:31:29.042$  both breast cancer which is beating

NOTE Confidence: 0.693806850910187

 $00:31:29.042 \longrightarrow 00:31:30.610$  for some report cells.

NOTE Confidence: 0.693806850910187

 $00{:}31{:}30.610 \dashrightarrow 00{:}31{:}34.586$  And non cancer cells on PC 9 cells.

NOTE Confidence: 0.693806850910187

 $00{:}31{:}34{.}590 \dashrightarrow 00{:}31{:}36{.}111$  And next race.

00:31:36.111 -> 00:31:39.153 So we are also very interested

NOTE Confidence: 0.693806850910187

 $00:31:39.153 \longrightarrow 00:31:41.670$  in understanding how.

NOTE Confidence: 0.693806850910187

00:31:41.670 --> 00:31:43.970 Resistant happens to our email

NOTE Confidence: 0.693806850910187

 $00:31:43.970 \longrightarrow 00:31:46.270$  checkpoint blockade and this is

NOTE Confidence: 0.693806850910187

 $00{:}31{:}46{.}348 \dashrightarrow 00{:}31{:}48{.}616$  our version of the cancer immunity

NOTE Confidence: 0.693806850910187

 $00{:}31{:}48.616 \dashrightarrow 00{:}31{:}51.100$  cycle and and as you can see,

NOTE Confidence: 0.693806850910187

 $00:31:51.100 \longrightarrow 00:31:53.680$  there's actually 2 steps are the

NOTE Confidence: 0.693806850910187

 $00{:}31{:}53.680 \dashrightarrow 00{:}31{:}55.400$  critical for email checkpoint

NOTE Confidence: 0.81779956817627

 $00{:}31{:}55{.}478 \dashrightarrow 00{:}31{:}57{.}854$  to work is the trafficking and

NOTE Confidence: 0.81779956817627

 $00{:}31{:}57.854 \dashrightarrow 00{:}32{:}00.286$  infiltration of the immune cells to

NOTE Confidence: 0.81779956817627

 $00{:}32{:}00{.}286 \dashrightarrow 00{:}32{:}03{.}009$  the tumor and apparently some of the

NOTE Confidence: 0.81779956817627

 $00:32:03.009 \rightarrow 00:32:05.040$  epigenetic modulators have been shown

NOTE Confidence: 0.81779956817627

 $00:32:05.040 \dashrightarrow 00:32:07.500$  to be critical for those processes,

NOTE Confidence: 0.81779956817627

 $00{:}32{:}07{.}500 \dashrightarrow 00{:}32{:}10{.}251$  and then I will just show example

NOTE Confidence: 0.81779956817627

 $00:32:10.251 \longrightarrow 00:32:12.440$  in our laboratory next please.

NOTE Confidence: 0.81779956817627

 $00:32:12.440 \longrightarrow 00:32:14.990$  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
- $00{:}32{:}17.540 \dashrightarrow 00{:}32{:}21.959$  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
- $00{:}32{:}23{.}598 \dashrightarrow 00{:}32{:}27{.}420$  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
- $00{:}32{:}29{.}400 \dashrightarrow 00{:}32{:}32{.}158$  I I in those Yamaha 1.7 cells,
- NOTE Confidence: 0.81779956817627
- $00:32:32.160 \longrightarrow 00:32:33.740$  which is more smaller,
- NOTE Confidence: 0.81779956817627
- 00:32:33.740 --> 00:32:35.320 generated by Markus Persson.
- NOTE Confidence: 0.81779956817627
- $00{:}32{:}35{.}320 \dashrightarrow 00{:}32{:}38{.}664$  Book idea we can see that if you
- NOTE Confidence: 0.81779956817627
- $00:32:38.664 \longrightarrow 00:32:40.894$  knockout account info be those
- NOTE Confidence: 0.81779956817627
- $00:32:40.894 \longrightarrow 00:32:43.510$  cells are unable to form tumors.
- NOTE Confidence: 0.81779956817627
- $00{:}32{:}43{.}510 \dashrightarrow 00{:}32{:}45{.}540$  And if we re challenge,
- NOTE Confidence: 0.81779956817627
- $00{:}32{:}45{.}540 \dashrightarrow 00{:}32{:}48{.}368$  those are two mice with control sales,
- NOTE Confidence: 0.81779956817627
- $00{:}32{:}48{.}370 \dashrightarrow 00{:}32{:}50{.}400$  which normally grow very well.
- NOTE Confidence: 0.81779956817627
- $00{:}32{:}50{.}400 \dashrightarrow 00{:}32{:}53{.}046$  You can see they cannot grow and
- NOTE Confidence: 0.81779956817627

 $00:32:53.046 \longrightarrow 00:32:55.781$  meaning that those might have gained

NOTE Confidence: 0.81779956817627

 $00:32:55.781 \rightarrow 00:32:58.326$  immunity against those younger cells.

NOTE Confidence: 0.81779956817627

 $00{:}32{:}58{.}330 \dashrightarrow 00{:}33{:}01{.}426$  If you look at the the pony IMO Genic

NOTE Confidence: 0.81779956817627

 $00:33:01.426 \rightarrow 00:33:04.650$  young one point cells down in the policy,

NOTE Confidence: 0.81779956817627

 $00{:}33{:}04.650 \dashrightarrow 00{:}33{:}07.184$  you can see those cells are not

NOTE Confidence: 0.81779956817627

 $00{:}33{:}07{.}184 \dashrightarrow 00{:}33{:}09{.}858$  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

 $00:33:12.092 \rightarrow 00:33:13.580$  file before those cells,

NOTE Confidence: 0.81779956817627

 $00{:}33{:}13{.}580 \dashrightarrow 00{:}33{:}16{.}180$  you can see the slowdown of the growth

NOTE Confidence: 0.81779956817627

 $00{:}33{:}16.180 \dashrightarrow 00{:}33{:}18.857$  of cells and if you combine with PD

NOTE Confidence: 0.81779956817627

 $00{:}33{:}18.857 \dashrightarrow 00{:}33{:}20.719$  one blockade you can significantly

NOTE Confidence: 0.81779956817627

 $00:33:20.719 \dashrightarrow 00:33:23.629$  extend the lifespan of those miles.

NOTE Confidence: 0.81779956817627

 $00{:}33{:}23.630 \dashrightarrow 00{:}33{:}25.522$  To my very mice.

NOTE Confidence: 0.81779956817627

 $00{:}33{:}25{.}522 \dashrightarrow 00{:}33{:}27{.}946$  So this suggests that can you

NOTE Confidence: 0.81779956817627

 $00{:}33{:}27{.}946 \dashrightarrow 00{:}33{:}30{.}312$  invite me is that very good target

NOTE Confidence: 0.81779956817627

 $00:33:30.312 \rightarrow 00:33:32.909$  to overcome resistance to email,

 $00{:}33{:}32{.}910 \dashrightarrow 00{:}33{:}35{.}535$  check one blockade and I would just

NOTE Confidence: 0.81779956817627

 $00{:}33{:}35{.}535 \dashrightarrow 00{:}33{:}38{.}835$  want to mention that this is done in

NOTE Confidence: 0.81779956817627

 $00:33:38.835 \rightarrow 00:33:41.380$  collaboration with multiple laps and yell,

NOTE Confidence: 0.81779956817627

00:33:41.380 --> 00:33:42.184 including archical,

NOTE Confidence: 0.81779956817627

 $00{:}33{:}42.184 \dashrightarrow 00{:}33{:}44.596$  even sucking and much boesenberg snap.

NOTE Confidence: 0.81779956817627

 $00{:}33{:}44.600 \dashrightarrow 00{:}33{:}48.227$  So team science is one of the same idea.

NOTE Confidence: 0.81779956817627

 $00:33:48.230 \longrightarrow 00:33:50.870$  We workout together or not.

NOTE Confidence: 0.81779956817627

00:33:50.870 --> 00:33:51.590 Thank you.

NOTE Confidence: 0.769105613231659

 $00:33:53.980 \longrightarrow 00:33:57.164$  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

 $00:33:59.970 \longrightarrow 00:34:01.562$  He's an assistant professor

NOTE Confidence: 0.769105613231659

 $00:34:01.562 \rightarrow 00:34:03.154$  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

 $00{:}34{:}05{.}040 \dashrightarrow 00{:}34{:}07{.}550$  end of an NCI Merit Award.

NOTE Confidence: 0.769105613231659

 $00{:}34{:}07{.}550 \dashrightarrow 00{:}34{:}09{.}660$  He conducts really cutting edge

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

 $00{:}34{:}18{.}370 \dashrightarrow 00{:}34{:}20{.}584$  So I I trained clinical molecular

NOTE Confidence: 0.825054228305817

 $00{:}34{:}20{.}584 \dashrightarrow 00{:}34{:}22{.}832$  diagnostics that I've been working in

NOTE Confidence: 0.825054228305817

 $00:34:22.832 \rightarrow 00:34:25.317$  cancer immunology for about 10 years now,

NOTE Confidence: 0.825054228305817

 $00{:}34{:}25{.}320 \dashrightarrow 00{:}34{:}27{.}170$  and it's unquestionable that immuno

NOTE Confidence: 0.825054228305817

 $00:34:27.170 \longrightarrow 00:34:28.650$  on cology has really revolutionized

NOTE Confidence: 0.825054228305817

 $00:34:28.650 \longrightarrow 00:34:30.080$  the treatment of cancer.

NOTE Confidence: 0.825054228305817

 $00:34:30.080 \dashrightarrow 00:34:31.910$  But there are major challenges

NOTE Confidence: 0.825054228305817

 $00:34:31.910 \longrightarrow 00:34:33.008$  still to overcome,

NOTE Confidence: 0.825054228305817

 $00{:}34{:}33.010 \dashrightarrow 00{:}34{:}35.450$  so I'll cover a few of the challenges

NOTE Confidence: 0.825054228305817

 $00{:}34{:}35{.}450 \dashrightarrow 00{:}34{:}37{.}834$  that I think are critical to

NOTE Confidence: 0.825054228305817

 $00:34:37.834 \dashrightarrow 00:34:39.954$  potentially move the few forward,

NOTE Confidence: 0.825054228305817

 $00:34:39.960 \longrightarrow 00:34:42.112$  one of which is that I think there

NOTE Confidence: 0.825054228305817

 $00{:}34{:}42.112 \dashrightarrow 00{:}34{:}43.595$  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
- $00{:}34{:}46{.}235 \dashrightarrow 00{:}34{:}48{.}039$  and identification of biomarkers.
- NOTE Confidence: 0.825054228305817
- 00:34:48.040 --> 00:34:49.340 Relative to drug development,
- NOTE Confidence: 0.825054228305817
- $00{:}34{:}49{.}340 \dashrightarrow 00{:}34{:}52{.}192$  I think the focus of many people developing
- NOTE Confidence: 0.825054228305817
- $00:34:52.192 \rightarrow 00:34:54.718$  targets has been on immuno stimulation,
- NOTE Confidence: 0.825054228305817
- $00{:}34{:}54{.}720 \dashrightarrow 00{:}34{:}57{.}015$  but that doesn't necessarily consider
- NOTE Confidence: 0.825054228305817
- $00:34:57.015 \dashrightarrow 00:34:59.310$  correcting alterations in the tumor
- NOTE Confidence: 0.825054228305817
- $00:34:59.373 \dashrightarrow 00:35:01.837$  and this is critical because if we're
- NOTE Confidence: 0.825054228305817
- $00{:}35{:}01{.}837 \dashrightarrow 00{:}35{:}04{.}113$  only stimulating T cells we are and
- NOTE Confidence: 0.825054228305817
- $00{:}35{:}04{.}113 \dashrightarrow 00{:}35{:}06{.}221$  there is not a clear gradient towards
- NOTE Confidence: 0.825054228305817
- $00:35:06.221 \longrightarrow 00:35:08.447$  activating it more in the tumor.
- NOTE Confidence: 0.825054228305817
- $00{:}35{:}08{.}450 \dashrightarrow 00{:}35{:}10{.}406$  It's likely that the the rapeutic index
- NOTE Confidence: 0.825054228305817
- $00:35:10.406 \dashrightarrow 00:35:12.622$  is smaller and the potential benefit
- NOTE Confidence: 0.825054228305817
- $00{:}35{:}12.622 \dashrightarrow 00{:}35{:}14.747$  and toxicity balances is affected.
- NOTE Confidence: 0.825054228305817
- $00:35:14.750 \rightarrow 00:35:17.693$  So I think the concept is that we shouldn't
- NOTE Confidence: 0.825054228305817

 $00:35:17.693 \rightarrow 00:35:20.685$  focus only on stimulating T cells everywhere.

NOTE Confidence: 0.825054228305817

 $00{:}35{:}20.690 \dashrightarrow 00{:}35{:}22.560$  We should probably look for.

NOTE Confidence: 0.825054228305817

 $00:35:22.560 \rightarrow 00:35:24.540$  Signals that have a gradient favoring

NOTE Confidence: 0.825054228305817

 $00:35:24.540 \longrightarrow 00:35:27.073$  the tumor in relative to the development

NOTE Confidence: 0.825054228305817

 $00{:}35{:}27.073 \dashrightarrow 00{:}35{:}28.609$  of biomarkers for resistance.

NOTE Confidence: 0.825054228305817

 $00{:}35{:}28.610 \dashrightarrow 00{:}35{:}31.306$  I think there have been a little bit

NOTE Confidence: 0.825054228305817

 $00{:}35{:}31{.}306 \dashrightarrow 00{:}35{:}33{.}670$  of confusion in the field because it

NOTE Confidence: 0.825054228305817

 $00:35:33.670 \rightarrow 00:35:36.539$  mean a therapy has been used so widely

NOTE Confidence: 0.825054228305817

 $00{:}35{:}36{.}539 \dashrightarrow 00{:}35{:}38{.}891$  that people are calling every patient

NOTE Confidence: 0.825054228305817

 $00:35:38.891 \rightarrow 00:35:41.070$  that don't respond as a resistance.

NOTE Confidence: 0.825054228305817

 $00{:}35{:}41.070 \dashrightarrow 00{:}35{:}43.182$  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

 $00:35:45.354 \rightarrow 00:35:47.114$  L1 expression tumor mutational burden,

NOTE Confidence: 0.825054228305817

 $00:35:47.120 \longrightarrow 00:35:49.968$  any biology should not respond to start with,

NOTE Confidence: 0.825054228305817

 $00{:}35{:}49{.}970 \dashrightarrow 00{:}35{:}52{.}850$  so I think there is a confusion between.

NOTE Confidence: 0.825054228305817

 $00:35:52.850 \longrightarrow 00:35:54.675$  Any patient that Blacks benefit

- NOTE Confidence: 0.825054228305817
- 00:35:54.675 --> 00:35:55.770 versus true resistance,
- NOTE Confidence: 0.825054228305817
- $00:35:55.770 \longrightarrow 00:35:58.115$  which in my opinion are the patients
- NOTE Confidence: 0.825054228305817
- $00:35:58.115 \dashrightarrow 00:36:00.519$  that should have responded but didn't.
- NOTE Confidence: 0.825054228305817
- $00:36:00.520 \rightarrow 00:36:03.019$  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
- $00{:}36{:}04{.}530 \dashrightarrow 00{:}36{:}06{.}280$  The second important concept that
- NOTE Confidence: 0.825054228305817
- $00:36:06.280 \dashrightarrow 00:36:08.030$  it's connected with the previous
- NOTE Confidence: 0.825054228305817
- $00:36:08.086 \rightarrow 00:36:10.282$  one is that it's probably necessary
- NOTE Confidence: 0.825054228305817
- $00:36:10.282 \longrightarrow 00:36:11.746$  to identify dominant immunization
- NOTE Confidence: 0.825054228305817
- $00:36:11.802 \rightarrow 00:36:13.657$  pathways that are well represented.
- NOTE Confidence: 0.825054228305817
- $00:36:13.660 \longrightarrow 00:36:16.628$  The tumor and this is for the same
- NOTE Confidence: 0.825054228305817
- $00{:}36{:}16.628 \dashrightarrow 00{:}36{:}18.998$  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
- $00{:}36{:}20{.}928 \dashrightarrow 00{:}36{:}23{.}217$  in the tumor to be able to.
- NOTE Confidence: 0.825054228305817
- $00{:}36{:}23.220 \dashrightarrow 00{:}36{:}25.608$  Achieve a meaningful anti cancer response
- NOTE Confidence: 0.825054228305817

 $00{:}36{:}25.608 \dashrightarrow 00{:}36{:}28.324$  and then another major need in the

NOTE Confidence: 0.825054228305817

 $00:36:28.324 \rightarrow 00:36:30.448$  field is trying to identify potential

NOTE Confidence: 0.825054228305817

 $00{:}36{:}30{.}448 \dashrightarrow 00{:}36{:}32{.}609$  targets that are beyond the T cells.

NOTE Confidence: 0.825054228305817

 $00:36:32.610 \rightarrow 00:36:34.584$  So to have complementary effort and

NOTE Confidence: 0.825054228305817

 $00:36:34.584 \rightarrow 00:36:36.580$  not have only redundant mechanisms,

NOTE Confidence: 0.825054228305817

 $00{:}36{:}36{.}580 \dashrightarrow 00{:}36{:}38{.}400$  another important observation is that

NOTE Confidence: 0.825054228305817

 $00{:}36{:}38{.}400 \dashrightarrow 00{:}36{:}41{.}782$  we as I follow you know when we look at

NOTE Confidence: 0.825054228305817

 $00:36:41.782 \rightarrow 00:36:44.165$  the tumors we realize how difficult and

NOTE Confidence: 0.825054228305817

 $00:36:44.165 \rightarrow 00:36:47.042$  how complex is the tumor micro environment.

NOTE Confidence: 0.825054228305817

 $00{:}36{:}47.050 \dashrightarrow 00{:}36{:}49.213$  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

 $00:36:51.380 \longrightarrow 00:36:53.230$  And I think the suffering.

NOTE Confidence: 0.825054228305817

 $00{:}36{:}53{.}230 \dashrightarrow 00{:}36{:}55{.}687$  The tumor micro environment and how different

NOTE Confidence: 0.825054228305817

 $00:36:55.687 \dashrightarrow 00:36:57.939$  is across tumors and across patients.

NOTE Confidence: 0.825054228305817

 $00{:}36{:}57{.}940 \dashrightarrow 00{:}37{:}00{.}756$  It's a major need to really drive better

NOTE Confidence: 0.825054228305817

 $00:37:00.756 \dashrightarrow 00:37:02.879$  biomarkers and better immunotherapy.

 $00:37:02.880 \dashrightarrow 00:37:05.260$  Then also I think we need to do a better

NOTE Confidence: 0.825054228305817

 $00{:}37{:}05{.}323 \dashrightarrow 00{:}37{:}07{.}673$  work at understanding the interactions

NOTE Confidence: 0.825054228305817

 $00{:}37{:}07{.}673 \dashrightarrow 00{:}37{:}09{.}553$  between major dominant on cogenic

NOTE Confidence: 0.825054228305817

 $00:37:09.553 \rightarrow 00:37:11.759$  signals and immune evasion pathways.

NOTE Confidence: 0.825054228305817

 $00:37:11.760 \longrightarrow 00:37:13.926$  This has been somehow being revealed

NOTE Confidence: 0.825054228305817

 $00{:}37{:}13.926 \dashrightarrow 00{:}37{:}16.180$  in EGFR mutant tumors that are

NOTE Confidence: 0.825054228305817

 $00:37:16.180 \longrightarrow 00:37:18.045$  less sensitive and less inflamed,

NOTE Confidence: 0.825054228305817

 $00:37:18.050 \longrightarrow 00:37:20.640$  but they I think there's a whole

NOTE Confidence: 0.825054228305817

 $00:37:20.640 \longrightarrow 00:37:21.750$  world to discover.

NOTE Confidence: 0.826502799987793

00:37:21.750 --> 00:37:23.600 What alterations in the tumor,

NOTE Confidence: 0.826502799987793

 $00:37:23.600 \rightarrow 00:37:25.820$  somatic alterations are able to manipulate.

NOTE Confidence: 0.826502799987793

 $00{:}37{:}25{.}820 \dashrightarrow 00{:}37{:}28{.}400$  It means an immune response.

NOTE Confidence: 0.826502799987793

 $00:37:28.400 \longrightarrow 00:37:29.459$  And then finally,

NOTE Confidence: 0.826502799987793

 $00{:}37{:}29{.}459 \dashrightarrow 00{:}37{:}31{.}930$  I think there are limitations of traditional

NOTE Confidence: 0.826502799987793

 $00:37:31.987 \dashrightarrow 00:37:33.975$  studies as we just solve from Jane.

 $00:37:33.980 \rightarrow 00:37:36.269$  Many alterations are not the genomic level.

NOTE Confidence: 0.826502799987793

 $00{:}37{:}36{.}270 \dashrightarrow 00{:}37{:}38{.}654$  Which is the favorite way we used to

NOTE Confidence: 0.826502799987793

 $00{:}37{:}38.654 \dashrightarrow 00{:}37{:}41.187$  analyze the tumor site of the interaction.

NOTE Confidence: 0.826502799987793

 $00:37:41.190 \rightarrow 00:37:43.814$  So I think by just doing genomic analysis,

NOTE Confidence: 0.826502799987793

 $00:37:43.820 \dashrightarrow 00:37:45.824$  we're missing a lot of alterations

NOTE Confidence: 0.826502799987793

 $00:37:45.824 \rightarrow 00:37:47.750$  that the immune system and this.

NOTE Confidence: 0.826502799987793

 $00{:}37{:}47.750 \dashrightarrow 00{:}37{:}50.123$  I think it's it's something we can

NOTE Confidence: 0.826502799987793

 $00{:}37{:}50{.}123 \dashrightarrow 00{:}37{:}52{.}468$  overcome and finally think that most of

NOTE Confidence: 0.826502799987793

 $00{:}37{:}52.468 \dashrightarrow 00{:}37{:}55.049$  the studies are focusing on both ends on

NOTE Confidence: 0.826502799987793

 $00:37:55.049 \rightarrow 00:37:57.254$  the very early discovery type of work,

NOTE Confidence: 0.826502799987793

 $00:37:57.260 \rightarrow 00:37:59.288$  with crisper screens and other strategies.

NOTE Confidence: 0.826502799987793

 $00{:}37{:}59{.}290 \dashrightarrow 00{:}38{:}01{.}327$  And then there is a huge effort

NOTE Confidence: 0.826502799987793

 $00:38:01.327 \longrightarrow 00:38:03.010$  on the clinical development,

NOTE Confidence: 0.826502799987793

 $00{:}38{:}03{.}010 \dashrightarrow 00{:}38{:}06{.}295$  but I think there is room to improve some

NOTE Confidence: 0.826502799987793

 $00:38:06.295 \dashrightarrow 00:38:09.350$  studies in more sort of human real context.

NOTE Confidence: 0.826502799987793

 $00:38:09.350 \longrightarrow 00:38:11.780$  Next slide, please.

 $00{:}38{:}11.780 \dashrightarrow 00{:}38{:}14.084$  So this is an example of the approach

NOTE Confidence: 0.826502799987793

 $00:38:14.084 \rightarrow 00:38:16.920$  that we have taken in my group where

NOTE Confidence: 0.826502799987793

 $00:38:16.920 \rightarrow 00:38:18.854$  we generate hypothesis using discovery

NOTE Confidence: 0.826502799987793

 $00:38:18.854 \rightarrow 00:38:21.682$  in biology and then we actually have

NOTE Confidence: 0.826502799987793

 $00:38:21.682 \rightarrow 00:38:24.002$  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

 $00:38:26.336 \longrightarrow 00:38:27.488$  in the same issue.

NOTE Confidence: 0.826502799987793

 $00:38:27.490 \rightarrow 00:38:29.779$  So we can actually do both genomic

NOTE Confidence: 0.826502799987793

 $00:38:29.779 \longrightarrow 00:38:31.229$  analysis to understand the

NOTE Confidence: 0.826502799987793

00:38:31.229 --> 00:38:32.837 genomic context during drivers,

NOTE Confidence: 0.826502799987793

 $00:38:32.840 \longrightarrow 00:38:35.216$  but then we can also look at the

NOTE Confidence: 0.826502799987793

 $00{:}38{:}35{.}216 \dashrightarrow 00{:}38{:}36{.}771$  immune contexture and pathways

NOTE Confidence: 0.826502799987793

 $00:38:36.771 \longrightarrow 00:38:38.555$  that are potentially actionable.

NOTE Confidence: 0.826502799987793

 $00{:}38{:}38{.}560 \dashrightarrow 00{:}38{:}40{.}365$  We have become pretty good

NOTE Confidence: 0.826502799987793

 $00{:}38{:}40{.}365 \dashrightarrow 00{:}38{:}41{.}809$  at looking at multiple.

 $00:38:41.810 \longrightarrow 00:38:43.210$  High throughput methods to

NOTE Confidence: 0.826502799987793

 $00{:}38{:}43{.}210 \dashrightarrow 00{:}38{:}45{.}310$  detect protein level and then we

NOTE Confidence: 0.826502799987793

 $00:38:45.369 \rightarrow 00:38:47.029$  can do single cell analysis,

NOTE Confidence: 0.826502799987793

 $00:38:47.030 \rightarrow 00:38:48.630$  spatial analysis and really try

NOTE Confidence: 0.826502799987793

 $00{:}38{:}48{.}630 \dashrightarrow 00{:}38{:}50{.}230$  to understand the tumor micro

NOTE Confidence: 0.826502799987793

 $00{:}38{:}50{.}283 \dashrightarrow 00{:}38{:}51{.}775$  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

 $00:38:53.640 \rightarrow 00:38:55.602$  we usually use aggressive analysis using

NOTE Confidence: 0.826502799987793

 $00{:}38{:}55{.}602 \dashrightarrow 00{:}38{:}57{.}470$  outcomes and response to treatment.

NOTE Confidence: 0.826502799987793

 $00:38:57.470 \longrightarrow 00:39:00.221$  So that way we can identify which

NOTE Confidence: 0.826502799987793

 $00{:}39{:}00{.}221 \dashrightarrow 00{:}39{:}02{.}572$  signals are relevant from the ones

NOTE Confidence: 0.826502799987793

 $00:39:02.572 \longrightarrow 00:39:04.756$  that are not next slide please.

NOTE Confidence: 0.826502799987793

 $00:39:04.760 \rightarrow 00:39:06.390$  This is important because ultimately

NOTE Confidence: 0.826502799987793

 $00:39:06.390 \dashrightarrow 00:39:08.340$  those signals are the ones with.

NOTE Confidence: 0.826502799987793

 $00:39:08.340 \longrightarrow 00:39:10.321$  Then we can validate in vitro to

NOTE Confidence: 0.826502799987793

 $00:39:10.321 \rightarrow 00:39:12.381$  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
- $00:39:13.540 \rightarrow 00:39:15.375$  but they are mechanistically relevant
- NOTE Confidence: 0.826502799987793
- $00:39:15.375 \rightarrow 00:39:17.757$  and then ultimately we can go back
- NOTE Confidence: 0.826502799987793
- $00{:}39{:}17.757 \dashrightarrow 00{:}39{:}19.444$  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
- $00:39:22.960 \longrightarrow 00:39:25.600$  of that next slide, please.
- NOTE Confidence: 0.826502799987793
- $00:39:25.600 \dashrightarrow 00:39:28.379$  So just for to illustrate how this
- NOTE Confidence: 0.826502799987793
- $00:39:28.379 \rightarrow 00:39:31.568$  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
- $00{:}39{:}37{.}723 \dashrightarrow 00{:}39{:}39{.}425$  environment as dominant immunization
- NOTE Confidence: 0.826502799987793
- $00:39:39.425 \dashrightarrow 00:39:41.517$  pathway and resistant mechanism.
- NOTE Confidence: 0.826502799987793
$00:39:41.520 \longrightarrow 00:39:43.872$  So the story started a few years

NOTE Confidence: 0.826502799987793

 $00:39:43.872 \longrightarrow 00:39:46.791$  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

 $00:39:49.080 \rightarrow 00:39:51.278$  and we found that it was producing

NOTE Confidence: 0.826502799987793

 $00{:}39{:}51{.}278 \dashrightarrow 00{:}39{:}53{.}800$  tumor cells and highly associated with

NOTE Confidence: 0.826502799987793

 $00:39:53.800 \dashrightarrow 00:39:56.315$  resistance to immune checkpoint blockers.

NOTE Confidence: 0.826502799987793

 $00{:}39{:}56{.}320 \dashrightarrow 00{:}39{:}58{.}130$  So to advance this further,

NOTE Confidence: 0.826502799987793

 $00:39:58.130 \rightarrow 00:40:00.560$  we look at the relationship between

NOTE Confidence: 0.826502799987793

 $00{:}40{:}00{.}560 \dashrightarrow 00{:}40{:}02.872$  Interleukin 8 and neutral fields as

NOTE Confidence: 0.826502799987793

 $00:40:02.872 \longrightarrow 00:40:05.368$  shown in the upper side of the slide,

NOTE Confidence: 0.826502799987793

 $00{:}40{:}05{.}370 \dashrightarrow 00{:}40{:}07{.}904$  and then we found a fraction of

NOTE Confidence: 0.826502799987793

 $00:40:07.904 \longrightarrow 00:40:10.184$  tumors that had up regulation of

NOTE Confidence: 0.826502799987793

 $00{:}40{:}10.184 \dashrightarrow 00{:}40{:}12.269$  Interleukin 8 and an unfavorable

NOTE Confidence: 0.826502799987793

 $00:40:12.269 \rightarrow 00:40:13.857$  micro environment characterized by

NOTE Confidence: 0.826502799987793

 $00{:}40{:}13.857 \dashrightarrow 00{:}40{:}15.507$  increased deals in fewer T cells.

NOTE Confidence: 0.826502799987793

 $00:40:15.510 \longrightarrow 00:40:17.310$  We also did genomic analysis to

 $00:40:17.310 \longrightarrow 00:40:18.992$  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

 $00:40:22.380 \longrightarrow 00:40:24.414$  and then we finally were able

NOTE Confidence: 0.826502799987793

 $00{:}40{:}24{.}414 \dashrightarrow 00{:}40{:}25{.}770$  to demonstrate that the

NOTE Confidence: 0.8223637342453

 $00{:}40{:}25.834 \dashrightarrow 00{:}40{:}28.198$  production of Interlake in the tumor.

NOTE Confidence: 0.8223637342453

 $00:40:28.200 \longrightarrow 00:40:29.960$  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

 $00{:}40{:}32.160 \dashrightarrow 00{:}40{:}34.918$  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

 $00:40:40.960 \rightarrow 00:40:43.462$  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

 $00{:}40{:}46{.}240 \dashrightarrow 00{:}40{:}48{.}880$  have up regulation of interleukin Aiden.

NOTE Confidence: 0.8223637342453

 $00:40:48.880 \longrightarrow 00:40:51.440$  They have low sensitivity to

 $00:40:51.440 \longrightarrow 00:40:52.976$  immune checkpoint blockers.

NOTE Confidence: 0.8223637342453

00:40:52.980 --> 00:40:55.788 Next slide, please.

NOTE Confidence: 0.8223637342453

 $00:40:55.790 \rightarrow 00:40:57.520$  Then to further demonstrate this,

NOTE Confidence: 0.8223637342453

 $00:40:57.520 \longrightarrow 00:40:59.956$  we need another study in which we

NOTE Confidence: 0.8223637342453

 $00{:}40{:}59{.}956 \dashrightarrow 00{:}41{:}02{.}122$  cultured neutrophils and my Lord arise

NOTE Confidence: 0.8223637342453

 $00{:}41{:}02{.}122 \dashrightarrow 00{:}41{:}04{.}246$  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

 $00:41:06.604 \rightarrow 00:41:08.592$  that formation of Nets was involved

NOTE Confidence: 0.8223637342453

 $00{:}41{:}08.592 \dashrightarrow 00{:}41{:}09.976$  in affective response suppression,

NOTE Confidence: 0.8223637342453

 $00{:}41{:}09{.}980 \dashrightarrow 00{:}41{:}11{.}660$  and then ultimately we're working

NOTE Confidence: 0.8223637342453

 $00{:}41{:}11{.}660 \dashrightarrow 00{:}41{:}13{.}340$  with the clinical trial where

NOTE Confidence: 0.8223637342453

 $00{:}41{:}13.396 \dashrightarrow 00{:}41{:}15.604$  patients are being treated with an

NOTE Confidence: 0.8223637342453

 $00:41:15.604 \rightarrow 00:41:17.240$  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

 $00:41:19.620 \rightarrow 00:41:21.738$  actually be action in real patients,

NOTE Confidence: 0.8223637342453

 $00:41:21.740 \rightarrow 00:41:24.218$  and hopefully we can use the biology

 $00:41:24.218 \longrightarrow 00:41:26.259$  that we figure out to drive.

NOTE Confidence: 0.8223637342453

 $00{:}41{:}26.260 \dashrightarrow 00{:}41{:}29.596$  The biomarker plant next slide please.

NOTE Confidence: 0.8223637342453

 $00:41:29.600 \rightarrow 00:41:32.688$  So finally we have gotten a little bit

NOTE Confidence: 0.8223637342453

 $00:41:32.688 \rightarrow 00:41:34.665$  more sophisticated now and generated

NOTE Confidence: 0.8223637342453

 $00{:}41{:}34.665 \dashrightarrow 00{:}41{:}37.318$  models or in in vitro tumor treatment.

NOTE Confidence: 0.8223637342453

 $00:41:37.320 \longrightarrow 00:41:40.425$  And this is just an example of what we're

NOTE Confidence: 0.8223637342453

 $00:41:40.425 \rightarrow 00:41:43.497$  doing where we can culture primary tumors,

NOTE Confidence: 0.8223637342453

 $00:41:43.500 \longrightarrow 00:41:45.828$  treat them in vitro but intact so that

NOTE Confidence: 0.8223637342453

 $00{:}41{:}45.828 \dashrightarrow 00{:}41{:}48.412$  we can then generate preparations and

NOTE Confidence: 0.8223637342453

 $00:41:48.412 \rightarrow 00:41:50.822$  analyze the tumor micro environment.

NOTE Confidence: 0.8223637342453

 $00:41:50.830 \rightarrow 00:41:52.765$  Change now perturbing these tumors

NOTE Confidence: 0.8223637342453

 $00:41:52.765 \longrightarrow 00:41:54.313$  with immunostimulatory or other

NOTE Confidence: 0.8223637342453

 $00{:}41{:}54{.}313 \dashrightarrow 00{:}41{:}56{.}470$  anti cancer agents and we are

NOTE Confidence: 0.8223637342453

 $00:41:56.470 \longrightarrow 00:41:57.842$  incorporating new technologies such

NOTE Confidence: 0.8223637342453

 $00{:}41{:}57.842 \dashrightarrow 00{:}41{:}59.768$  as single cell transcriptomics.

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

 $00:42:07.938 \rightarrow 00:42:10.209$  everybody can see the incredible

NOTE Confidence: 0.853574156761169

 $00:42:10.209 \longrightarrow 00:42:12.885$  power of that of that approach.

NOTE Confidence: 0.853574156761169

 $00:42:12.890 \longrightarrow 00:42:15.317$  Well, we said at the outset,

NOTE Confidence: 0.853574156761169

 $00{:}42{:}15{.}317 \dashrightarrow 00{:}42{:}17{.}816$  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

 $00:42:20.320 \longrightarrow 00:42:22.798$  and in each of these seminars,

NOTE Confidence: 0.853574156761169

 $00:42:22.800 \longrightarrow 00:42:24.452$  we've invited an industry

NOTE Confidence: 0.853574156761169

 $00{:}42{:}24{.}452 \dashrightarrow 00{:}42{:}26{.}517$  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

 $00{:}42{:}29{.}000 \dashrightarrow 00{:}42{:}31{.}508$ it's Susan Galbreath she's a senior

NOTE Confidence: 0.853574156761169

 $00{:}42{:}31{.}508 \dashrightarrow 00{:}42{:}34{.}045$  Vice president and head of early

NOTE Confidence: 0.853574156761169

 $00{:}42{:}34.045 \dashrightarrow 00{:}42{:}36.020$  on cology R&D and Astra Zeneca.

NOTE Confidence: 0.853574156761169

 $00:42:36.020 \longrightarrow 00:42:38.946$  She's been there about 10 years and.

00:42:38.950 - 00:42:42.480 In the early development program,

NOTE Confidence: 0.853574156761169

 $00{:}42{:}42{.}480 \dashrightarrow 00{:}42{:}47{.}408$  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

 $00:42:51.160 \rightarrow 00:42:53.620$  the third generation EGFR inhibitor.

NOTE Confidence: 0.853574156761169

 $00:42:53.620 \rightarrow 00:42:56.578$  Awesome Merton if that our colleague,

NOTE Confidence: 0.853574156761169

 $00{:}42{:}56{.}580 \dashrightarrow 00{:}42{:}59{.}616$  Roy Herbst, was involved in presenting

NOTE Confidence: 0.853574156761169

 $00:42:59.616 \rightarrow 00:43:02.480$  very impactful angemon trial this year.

NOTE Confidence: 0.853574156761169

 $00{:}43{:}02{.}480 \dashrightarrow 00{:}43{:}04{.}448$  Megan met inhibitors selective

NOTE Confidence: 0.853574156761169

 $00{:}43{:}04{.}448 \dashrightarrow 00{:}43{:}06{.}416$  estrogen receptor directed agents.

NOTE Confidence: 0.853574156761169

 $00{:}43{:}06{.}420 \dashrightarrow 00{:}43{:}08{.}880$  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

 $00:43:12.322 \rightarrow 00:43:15.759$  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

 $00{:}43{:}18.616 \dashrightarrow 00{:}43{:}21.102$  It's a it's a pleasure to be here

 $00:43:21.102 \rightarrow 00:43:22.950$  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

 $00{:}43{:}28{.}276 \dashrightarrow 00{:}43{:}30{.}529$  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

 $00:43:32.198 \longrightarrow 00:43:34.088$  in the early Development Group and

NOTE Confidence: 0.825893580913544

 $00:43:34.088 \rightarrow 00:43:36.148$  and stayed there for about 9 years.

NOTE Confidence: 0.825893580913544

 $00:43:36.148 \longrightarrow 00:43:38.290$  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

 $00:43:40.893 \rightarrow 00:43:43.294$  some of the thoughts we've got about,

NOTE Confidence: 0.825893580913544

 $00:43:43.300 \rightarrow 00:43:44.464$  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

 $00:43:48.056 \rightarrow 00:43:49.840$  really having access to the samples.

NOTE Confidence: 0.825893580913544

 $00{:}43{:}49{.}840 \dashrightarrow 00{:}43{:}51{.}496$  That would enable us to understand

- NOTE Confidence: 0.825893580913544
- $00:43:51.496 \longrightarrow 00:43:52.324$  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
- $00{:}43{:}54{.}426 \dashrightarrow 00{:}43{:}56{.}494$  about some of the models that we can
- NOTE Confidence: 0.825893580913544
- $00:43:56.494 \rightarrow 00:43:58.430$  use pre clinically to model resistance.
- NOTE Confidence: 0.825893580913544
- $00:43:58.430 \longrightarrow 00:44:00.092$  One of the challenges we've got
- NOTE Confidence: 0.825893580913544
- $00:44:00.092 \rightarrow 00:44:01.200$  with those techniques though,
- NOTE Confidence: 0.825893580913544
- $00:44:01.200 \longrightarrow 00:44:02.904$  is that it doesn't always predict
- NOTE Confidence: 0.825893580913544
- $00:44:02.904 \longrightarrow 00:44:04.571$  what the true prevalence of the
- NOTE Confidence: 0.825893580913544
- $00:44:04.571 \longrightarrow 00:44:05.771$  resistance mechanisms is going to
- NOTE Confidence: 0.825893580913544
- $00:44:05.771 \longrightarrow 00:44:07.570$  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
- $00{:}44{:}09{.}469 \dashrightarrow 00{:}44{:}11{.}765$  so when you look at the mechanisms
- NOTE Confidence: 0.825893580913544
- $00{:}44{:}11.765 \dashrightarrow 00{:}44{:}13.109$  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
- $00:44:14.342 \rightarrow 00:44:16.513$  what the true prevalence of all the
- NOTE Confidence: 0.825893580913544

 $00:44:16.513 \rightarrow 00:44:18.157$  things are when patients are starting

NOTE Confidence: 0.825893580913544

 $00:44:18.157 \longrightarrow 00:44:19.848$  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

 $00:44:22.200 \rightarrow 00:44:23.610$  mutant lung cancer.

NOTE Confidence: 0.825893580913544

 $00{:}44{:}23.610 \dashrightarrow 00{:}44{:}25.724$  The other challenge that you've got is

NOTE Confidence: 0.825893580913544

 $00{:}44{:}25{.}724 \dashrightarrow 00{:}44{:}27{.}856$  tried for number of years to actually

NOTE Confidence: 0.825893580913544

 $00:44:27.856 \rightarrow 00:44:30.002$  get biopsies from patients on at the

NOTE Confidence: 0.825893580913544

 $00:44:30.002 \rightarrow 00:44:32.030$  time of progression in clinical trials,

NOTE Confidence: 0.825893580913544

 $00{:}44{:}32.030 \dashrightarrow 00{:}44{:}34.452$  or must we concluded that you know

NOTE Confidence: 0.825893580913544

 $00:44:34.452 \rightarrow 00:44:37.257$  typically has to be as an optional biopsy.

NOTE Confidence: 0.825893580913544

 $00:44:37.260 \longrightarrow 00:44:38.790$  At that time of progression,

NOTE Confidence: 0.825893580913544

 $00:44:38.790 \longrightarrow 00:44:40.010$  we've actually heard across

NOTE Confidence: 0.825893580913544

 $00:44:40.010 \rightarrow 00:44:41.535$  the range of clinical trials.

NOTE Confidence: 0.825893580913544

 $00:44:41.540 \longrightarrow 00:44:42.764$  Relatively few of those

NOTE Confidence: 0.825893580913544

 $00:44:42.764 \longrightarrow 00:44:43.376$  actually materialized,

NOTE Confidence: 0.825893580913544

 $00{:}44{:}43{.}380 \dashrightarrow 00{:}44{:}45{.}543$  and so that means that our mechanisms

- NOTE Confidence: 0.825893580913544
- $00:44:45.543 \rightarrow 00:44:46.813$  of understanding resistance during
- NOTE Confidence: 0.825893580913544
- $00:44:46.813 \rightarrow 00:44:48.278$  the development of certain IP,
- NOTE Confidence: 0.825893580913544
- $00{:}44{:}48{.}280 \dashrightarrow 00{:}44{:}50{.}110$  you know, have been somewhat limited.
- NOTE Confidence: 0.825893580913544
- $00:44:50.110 \longrightarrow 00:44:51.976$  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
- $00:44:53.480 \longrightarrow 00:44:55.316$  it right from the phase one
- NOTE Confidence: 0.825893580913544
- $00:44:55.316 \longrightarrow 00:44:56.540$  trials with awesome antonym,
- NOTE Confidence: 0.825893580913544
- $00:44:56.540 \rightarrow 00:44:58.484$  and we have some understanding of
- NOTE Confidence: 0.825893580913544
- $00:44:58.484 \longrightarrow 00:45:00.109$  actually published some of the
- NOTE Confidence: 0.825893580913544
- $00:45:00.109 \rightarrow 00:45:01.729$  data from the first line study
- NOTE Confidence: 0.825893580913544
- $00:45:01.729 \longrightarrow 00:45:03.534$  with a semantic that flora trial
- NOTE Confidence: 0.825893580913544
- $00:45:03.534 \rightarrow 00:45:05.406$  looking at those CT DNA mechanisms,
- NOTE Confidence: 0.825893580913544
- $00{:}45{:}05{.}410 \dashrightarrow 00{:}45{:}07{.}348$  but really actually one of the
- NOTE Confidence: 0.825893580913544
- $00{:}45{:}07{.}348 \dashrightarrow 00{:}45{:}09{.}390$  things that comes out of that is,
- NOTE Confidence: 0.825893580913544
- $00:45:09.390 \longrightarrow 00:45:10.502$  we could only explain.
- NOTE Confidence: 0.825893580913544

 $00:45:10.502 \rightarrow 00:45:13.068$  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

 $00{:}45{:}14.736 \dashrightarrow 00{:}45{:}17.360$  at city DNA and the patterns that

NOTE Confidence: 0.825893580913544

 $00:45:17.360 \longrightarrow 00:45:19.714$  we saw there was we saw their city.

NOTE Confidence: 0.825893580913544

 $00{:}45{:}19{.}714 \dashrightarrow 00{:}45{:}21{.}084$  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

 $00:45:24.510 \longrightarrow 00:45:26.388$  An activation fee 10 losses and

NOTE Confidence: 0.825893580913544

 $00:45:26.388 \rightarrow 00:45:28.430$  in some cases and MEK pathway

NOTE Confidence: 0.825893580913544

 $00:45:28.430 \longrightarrow 00:45:30.590$  activation as well in some cases.

NOTE Confidence: 0.825893580913544

 $00:45:30.590 \longrightarrow 00:45:32.690$  But the really the majority of patients

NOTE Confidence: 0.825893580913544

 $00{:}45{:}32.690 \dashrightarrow 00{:}45{:}35.143$  we still had a question mark over

NOTE Confidence: 0.825893580913544

 $00{:}45{:}35{.}143 \dashrightarrow 00{:}45{:}37{.}003$  what the resistance mechanisms worth.

NOTE Confidence: 0.825893580913544

 $00:45:37.010 \rightarrow 00:45:39.271$  So that led us to design that

NOTE Confidence: 0.825893580913544

 $00{:}45{:}39{.}271 \dashrightarrow 00{:}45{:}40{.}780$  this kind of study.

NOTE Confidence: 0.825893580913544

 $00{:}45{:}40{.}780 \dashrightarrow 00{:}45{:}43{.}195$  It's called the Orchard and platform study.

- NOTE Confidence: 0.825893580913544
- $00:45:43.200 \longrightarrow 00:45:44.580$  This takes patients that
- NOTE Confidence: 0.825893580913544
- $00:45:44.580 \longrightarrow 00:45:45.615$  we're progressing on.
- NOTE Confidence: 0.825893580913544
- $00:45:45.620 \rightarrow 00:45:46.601$  First line automotive,
- NOTE Confidence: 0.825893580913544
- $00:45:46.601 \longrightarrow 00:45:48.563$  and it offers them something that
- NOTE Confidence: 0.825893580913544
- $00:45:48.563 \longrightarrow 00:45:50.049$  is potentially of potentially
- NOTE Confidence: 0.825893580913544
- $00:45:50.049 \longrightarrow 00:45:51.509$  of benefit to them,
- NOTE Confidence: 0.825893580913544
- $00:45:51.510 \longrightarrow 00:45:53.470$  which is to take a biopsy to
- NOTE Confidence: 0.825893580913544
- $00:45:53.470 \longrightarrow 00:45:54.310$  look at what
- NOTE Confidence: 0.818565964698792
- $00{:}45{:}54{.}382 \dashrightarrow 00{:}45{:}57{.}385$  the data says on next generation sequencing.
- NOTE Confidence: 0.818565964698792
- $00:45:57.390 \longrightarrow 00:45:59.406$  From that biopsy and then to allocate
- NOTE Confidence: 0.818565964698792
- $00:45:59.406 \rightarrow 00:46:01.934$  them to a range of different potential
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}01{.}934 \dashrightarrow 00{:}46{:}04{.}328$  arms and this biomarker matched arms
- NOTE Confidence: 0.818565964698792
- $00:46:04.392 \rightarrow 00:46:07.088$  which you can see above depending on the
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}07.088 \dashrightarrow 00{:}46{:}09.500$  mechanism that that is seen with resistance.
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}09{.}500 \dashrightarrow 00{:}46{:}12{.}268$  And then there's also non biomarker match on.
- NOTE Confidence: 0.818565964698792

 $00:46:12.270 \longrightarrow 00:46:14.790$  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

 $00:46:19.415 \longrightarrow 00:46:21.533$  given a consent to have a biopsy

NOTE Confidence: 0.818565964698792

 $00:46:21.533 \longrightarrow 00:46:23.008$  gets the offer of something.

NOTE Confidence: 0.818565964698792

 $00{:}46{:}23.008 \dashrightarrow 00{:}46{:}25.514$  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

 $00:46:27.840 \longrightarrow 00:46:29.570$  but it gives them that,

NOTE Confidence: 0.818565964698792

 $00:46:29.570 \longrightarrow 00:46:31.170$  and that has driven really

NOTE Confidence: 0.818565964698792

 $00:46:31.170 \longrightarrow 00:46:33.583$  quite a good uptake in terms of

NOTE Confidence: 0.818565964698792

 $00:46:33.583 \longrightarrow 00:46:35.448$  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

 $00:46:37.886 \longrightarrow 00:46:39.950$  that we've already learned now is,

NOTE Confidence: 0.818565964698792

 $00:46:39.950 \rightarrow 00:46:41.680$  we've now got, you know,

NOTE Confidence: 0.818565964698792

 $00:46:41.680 \longrightarrow 00:46:43.440$  data and over 60 patients.

NOTE Confidence: 0.818565964698792

00:46:43.440 --> 00:46:44.106 You know,

- NOTE Confidence: 0.818565964698792
- $00{:}46{:}44.106 \dashrightarrow 00{:}46{:}46.770$  with with tissue available at the time of
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}46{.}839 \dashrightarrow 00{:}46{:}49{.}647$  progression in the in the Orchard study,
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}49{.}650 \dashrightarrow 00{:}46{:}52{.}242$  and now that we can we have an
- NOTE Confidence: 0.818565964698792
- $00:46:52.242 \rightarrow 00:46:53.790$  identifiable resistance mechanism now,
- NOTE Confidence: 0.818565964698792
- $00:46:53.790 \longrightarrow 00:46:56.205$  in the in nearly 2/3 of patients,
- NOTE Confidence: 0.818565964698792
- $00:46:56.210 \longrightarrow 00:46:58.280$  as opposed to just a third.
- NOTE Confidence: 0.818565964698792
- $00{:}46{:}58{.}280 \dashrightarrow 00{:}47{:}00{.}210$  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
- $00{:}47{:}02.199 \dashrightarrow 00{:}47{:}04.053$  which can be under estimated using
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}04.053 \dashrightarrow 00{:}47{:}05.994$  CT DNA would increase the detection
- NOTE Confidence: 0.818565964698792
- $00:47:05.994 \rightarrow 00:47:07.938$  of some of the Fusion mechanisms,
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}07{.}940 \dashrightarrow 00{:}47{:}09{.}818$  which can also be difficult to
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}09{.}818 \dashrightarrow 00{:}47{:}12{.}079$  detect using the CT DNA techniques.
- NOTE Confidence: 0.818565964698792
- $00:47:12.080 \longrightarrow 00:47:14.216$  And we've got a better sense.
- NOTE Confidence: 0.818565964698792
- $00:47:14.220 \longrightarrow 00:47:15.099$  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

 $00{:}47{:}17{.}470 \dashrightarrow 00{:}47{:}19{.}351$  and I still think we need to look at

NOTE Confidence: 0.818565964698792

 $00:47:19.351 \longrightarrow 00:47:21.148$  the epigenetic mechanisms that are

NOTE Confidence: 0.818565964698792

 $00:47:21.148 \rightarrow 00:47:23.063$  driving resistance in this setting,

NOTE Confidence: 0.818565964698792

 $00{:}47{:}23.070 \dashrightarrow 00{:}47{:}25.009$  but I just wanted to illustrate this

NOTE Confidence: 0.818565964698792

 $00{:}47{:}25{.}009 \dashrightarrow 00{:}47{:}27{.}763$  as a sa an example of one way that we

NOTE Confidence: 0.818565964698792

 $00:47:27.763 \rightarrow 00:47:30.446$  need to look at in terms of understanding,

NOTE Confidence: 0.818565964698792

 $00:47:30.450 \rightarrow 00:47:32.020$  documenting resistance and moving on

NOTE Confidence: 0.818565964698792

 $00:47:32.020 \longrightarrow 00:47:34.869$  from it so we can go to the next slide.

NOTE Confidence: 0.818565964698792

 $00:47:34.870 \longrightarrow 00:47:36.370$  The similar approach has been

NOTE Confidence: 0.818565964698792

 $00:47:36.370 \longrightarrow 00:47:37.570$  taken in the understanding.

NOTE Confidence: 0.818565964698792

 $00{:}47{:}37{.}570 \dashrightarrow 00{:}47{:}39{.}242$  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

 $00:47:44.205 \longrightarrow 00:47:46.140$  is on a checkpoint inhibitor

NOTE Confidence: 0.818565964698792

 $00:47:46.213 \rightarrow 00:47:48.249$  is necessarily truly resistant,

- NOTE Confidence: 0.818565964698792
- $00{:}47{:}48.250 \dashrightarrow 00{:}47{:}50.861$  but I think we need to understand
- NOTE Confidence: 0.818565964698792
- $00:47:50.861 \rightarrow 00:47:53.690$  some of those mechanisms, and again,
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}53.690 \dashrightarrow 00{:}47{:}56.690$  this is a mechanism where you can get
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}56.770 \dashrightarrow 00{:}47{:}59.350$  the biopsies from these patients.
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}59{.}350 \dashrightarrow 00{:}47{:}59{.}761$  Also,
- NOTE Confidence: 0.818565964698792
- $00{:}47{:}59.761 \dashrightarrow 00{:}48{:}01.405$  some peripheral blood sampling
- NOTE Confidence: 0.818565964698792
- $00:48:01.405 \longrightarrow 00:48:04.416$  and look at ways in which we
- NOTE Confidence: 0.818565964698792
- $00:48:04.416 \longrightarrow 00:48:06.176$  can potentially offer them.
- NOTE Confidence: 0.818565964698792
- $00:48:06.180 \longrightarrow 00:48:08.244$  Treatments that may have the opportunity
- NOTE Confidence: 0.818565964698792
- $00{:}48{:}08{.}244 \dashrightarrow 00{:}48{:}10{.}829$  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
- $00{:}48{:}11{.}406 \dashrightarrow 00{:}48{:}13{.}710$  I just want to share with you a
- NOTE Confidence: 0.818565964698792
- $00{:}48{:}13.781 \dashrightarrow 00{:}48{:}16.096$  couple of observations from this.
- NOTE Confidence: 0.818565964698792
- $00{:}48{:}16.100 \dashrightarrow 00{:}48{:}18.938$  We're going to the next slide.
- NOTE Confidence: 0.818565964698792
- $00:48:18.940 \longrightarrow 00:48:20.320$  So first of all,
- NOTE Confidence: 0.818565964698792

 $00{:}48{:}20{.}320 \dashrightarrow 00{:}48{:}22{.}390$  there are some mechanisms that we

NOTE Confidence: 0.818565964698792

 $00{:}48{:}22.467 \dashrightarrow 00{:}48{:}24.747$  might anticipate seeing based on,

NOTE Confidence: 0.818565964698792

00:48:24.750 --> 00:48:25.522 you know,

NOTE Confidence: 0.818565964698792

 $00:48:25.522 \rightarrow 00:48:27.838$  really good data that's already emerged,

NOTE Confidence: 0.818565964698792

 $00{:}48{:}27{.}840 \dashrightarrow 00{:}48{:}30{.}514$  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

 $00:48:33.281 \longrightarrow 00:48:35.573$  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

 $00:48:37.515 \longrightarrow 00:48:38.676$  of these checkpoints,

NOTE Confidence: 0.818565964698792

 $00:48:38.680 \longrightarrow 00:48:39.841$  inhibitors and increased

NOTE Confidence: 0.818565964698792

 $00{:}48{:}39{.}841 \dashrightarrow 00{:}48{:}42{.}550$  prevalence of loss of HLA or MHC.

NOTE Confidence: 0.818565964698792

 $00:48:42.550 \longrightarrow 00:48:45.790$  In the inability of the of the tumors

NOTE Confidence: 0.818565964698792

 $00:48:45.790 \longrightarrow 00:48:49.268$  to be seen by an an an effective

NOTE Confidence: 0.818565964698792

 $00{:}48{:}49{.}268 \dashrightarrow 00{:}48{:}52{.}252$  by at the adaptive immune mechanisms

NOTE Confidence: 0.818565964698792

 $00{:}48{:}52{.}252 \dashrightarrow 00{:}48{:}56{.}410$  of if the antigen can't be presented

NOTE Confidence: 0.850832909345627

 $00:48:56.410 \rightarrow 00:48:57.769$  effectively, it's like.

- NOTE Confidence: 0.850832909345627
- $00:48:57.769 \longrightarrow 00:49:00.034$  Other things that we're doing.
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}00{.}040 \dashrightarrow 00{:}49{:}02{.}122$  We've seen a range of different
- NOTE Confidence: 0.850832909345627
- $00:49:02.122 \longrightarrow 00:49:03.510$  mechanisms that we have.
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}03{.}510 \dashrightarrow 00{:}49{:}05{.}946$  We have looked at in this setting.
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}05{.}950 \dashrightarrow 00{:}49{:}07{.}535$  Wilson mentioned the fact that
- NOTE Confidence: 0.850832909345627
- $00:49:07.535 \longrightarrow 00:49:09.120$  obviously we're looking at the
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}09{.}172 \dashrightarrow 00{:}49{:}10.666$  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
- $00:49:12.290 \longrightarrow 00:49:14.201$  but in fact actually one of the
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}14.201 \dashrightarrow 00{:}49{:}16.062$  observations that we made earlier phase
- NOTE Confidence: 0.850832909345627
- $00:49:16.062 \rightarrow 00:49:18.024$  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
- $00{:}49{:}19{.}540 \dashrightarrow 00{:}49{:}21{.}563$  is that we were seeing some unusual
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}21.563 \dashrightarrow 00{:}49{:}23.422$  responses in patients that had a
- NOTE Confidence: 0.850832909345627
- $00{:}49{:}23{.}422 \dashrightarrow 00{:}49{:}24{.}670$  prior checkpoints in innovation.
- NOTE Confidence: 0.850832909345627

 $00:49:24.670 \longrightarrow 00:49:25.754$  In some other trials,

NOTE Confidence: 0.850832909345627

 $00:49:25.754 \longrightarrow 00:49:27.834$  and so that led to some further

NOTE Confidence: 0.850832909345627

 $00:49:27.834 \rightarrow 00:49:30.150$  investigation and so so there are

NOTE Confidence: 0.850832909345627

 $00:49:30.150 \rightarrow 00:49:32.314$  certain underbelly map is one of the

NOTE Confidence: 0.850832909345627

 $00{:}49{:}32{.}314 \dashrightarrow 00{:}49{:}34{.}262$  arms in the in the Hudson study and

NOTE Confidence: 0.850832909345627

 $00{:}49{:}34{.}262 \dashrightarrow 00{:}49{:}36{.}124$  some of the data that we're seeing

NOTE Confidence: 0.850832909345627

 $00:49:36.124 \rightarrow 00:49:38.320$  is quite interesting in seeing that.

NOTE Confidence: 0.850832909345627

 $00:49:38.320 \rightarrow 00:49:40.735$  Getting a decrease in exhausted T cells,

NOTE Confidence: 0.850832909345627

 $00{:}49{:}40{.}740 \dashrightarrow 00{:}49{:}42{.}882$  exhausted NK cells and an increase in

NOTE Confidence: 0.850832909345627

 $00{:}49{:}42{.}882 \dashrightarrow 00{:}49{:}44{.}567$  antigen presentation in patients that

NOTE Confidence: 0.850832909345627

 $00{:}49{:}44{.}567 \dashrightarrow 00{:}49{:}46{.}703$  have both got primary resistance to

NOTE Confidence: 0.850832909345627

 $00:49:46.703 \rightarrow 00:49:48.195$  checkpoint inhibition and subsequently

NOTE Confidence: 0.850832909345627

 $00{:}49{:}48.195 \dashrightarrow 00{:}49{:}50.361$  had some degree of response and

NOTE Confidence: 0.850832909345627

 $00:49:50.361 \rightarrow 00:49:51.688$  subsequently progressed as well.

NOTE Confidence: 0.850832909345627

 $00{:}49{:}51{.}688 \dashrightarrow 00{:}49{:}54{.}552$  And we're also seeing it not just in the

NOTE Confidence: 0.850832909345627

 $00:49:54.552 \rightarrow 00:49:56.946$  ATM mutant patients that are selected,

- NOTE Confidence: 0.850832909345627
- $00:49:56.950 \longrightarrow 00:49:59.024$  but also more more broadly, so.
- NOTE Confidence: 0.850832909345627
- $00:49:59.024 \rightarrow 00:50:01.088$  This is just an interesting observation.
- NOTE Confidence: 0.850832909345627
- $00{:}50{:}01{.}090 \dashrightarrow 00{:}50{:}03{.}519$  There's a lot more mechanistic data that
- NOTE Confidence: 0.850832909345627
- $00:50:03.519 \rightarrow 00:50:05.915$  is required and that will be followed
- NOTE Confidence: 0.850832909345627
- $00:50:05.915 \rightarrow 00:50:08.350$  up in order to understand this better.
- NOTE Confidence: 0.850832909345627
- $00{:}50{:}08{.}350 \dashrightarrow 00{:}50{:}10{.}240$  But I do think that these kinds of trials
- NOTE Confidence: 0.850832909345627
- $00:50:10.240 \rightarrow 00:50:12.318$  are really helpful in trying to understand
- NOTE Confidence: 0.850832909345627
- $00:50:12.318 \rightarrow 00:50:14.100$  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
- $00:50:15.470 \longrightarrow 00:50:16.566$  data that can feedback,
- NOTE Confidence: 0.850832909345627
- 00:50:16.570 --> 00:50:17.431 and you know,
- NOTE Confidence: 0.850832909345627
- $00{:}50{:}17{.}431 \dashrightarrow 00{:}50{:}18{.}866$  back with the preclinical work
- NOTE Confidence: 0.850832909345627
- $00:50:18.866 \longrightarrow 00:50:21.062$  that we can do to them to then
- NOTE Confidence: 0.850832909345627
- $00{:}50{:}21.062 \dashrightarrow 00{:}50{:}22.599$  understand what we might do next.
- NOTE Confidence: 0.850832909345627
- $00:50:22.600 \rightarrow 00:50:24.287$  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

 $00:50:25.975 \rightarrow 00:50:27.793$  questions that you might might have.

NOTE Confidence: 0.850832909345627

00:50:27.800 --> 00:50:29.390 Thank you.

NOTE Confidence: 0.850832909345627

 $00{:}50{:}29{.}390 \dashrightarrow 00{:}50{:}30{.}460$  That was

NOTE Confidence: 0.864805579185486

 $00:50:30.460 \longrightarrow 00:50:33.140$  fabulous. Thank you very much.

NOTE Confidence: 0.864805579185486

 $00{:}50{:}33.140 \dashrightarrow 00{:}50{:}37.290$  I am now going to ask that all of the

NOTE Confidence: 0.864805579185486

 $00{:}50{:}37{.}402 \dashrightarrow 00{:}50{:}41{.}637$  panelists turned on their audio and video

NOTE Confidence: 0.864805579185486

 $00:50:41.637 \rightarrow 00:50:47.159$  and will now go into the full discussion.

NOTE Confidence: 0.864805579185486

 $00{:}50{:}47.160 \dashrightarrow 00{:}50{:}51.696$  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

 $00:50:56.274 \rightarrow 00:51:00.840$  monitoring these and the first one, I think.

NOTE Confidence: 0.864805579185486

 $00:51:00.840 \longrightarrow 00:51:03.740$  Basically immediately follows that the

NOTE Confidence: 0.864805579185486

 $00{:}51{:}03.740 \dashrightarrow 00{:}51{:}07.955$  last slide that we saw and so maybe I'll

NOTE Confidence: 0.864805579185486

 $00{:}51{:}07{.}955 \dashrightarrow 00{:}51{:}11{.}570$  ask Susan and Kurt both to address this.

NOTE Confidence: 0.864805579185486

 $00{:}51{:}11{.}570 \dashrightarrow 00{:}51{:}14.867$  How critical is it to overcome the

NOTE Confidence: 0.864805579185486

 $00:51:14.867 \longrightarrow 00:51:17.399$  mechanical functional barriers to immune

 $00:51:17.399 \longrightarrow 00:51:20.009$  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

 $00:51:22.300 \longrightarrow 00:51:25.186$  although I can think of other

NOTE Confidence: 0.864805579185486

 $00:51:25.186 \rightarrow 00:51:27.677$  mechanisms related to hypoxemia and

NOTE Confidence: 0.864805579185486

 $00{:}51{:}27.677 \dashrightarrow 00{:}51{:}30.107$  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

 $00:51:33.080 \rightarrow 00:51:35.072$  Potential pathways and targets to overcome

NOTE Confidence: 0.864805579185486

 $00{:}51{:}35{.}072 \dashrightarrow 00{:}51{:}36{.}749$  mechanical and functional barriers to

NOTE Confidence: 0.864805579185486

 $00{:}51{:}36{.}749 \dashrightarrow 00{:}51{:}38{.}259$  immune checkpoint inhibitors and Susan.

NOTE Confidence: 0.864805579185486

 $00:51:38.260 \rightarrow 00:51:40.852$  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

 $00{:}51{:}43{.}150 \dashrightarrow 00{:}51{:}45{.}292$  Yeah well, the the the Council

NOTE Confidence: 0.83586585521698

 $00{:}51{:}45{.}292 \dashrightarrow 00{:}51{:}48{.}459$  you think of when I think of 1st when

NOTE Confidence: 0.83586585521698

 $00{:}51{:}48.459 \dashrightarrow 00{:}51{:}50.431$  you're talking about mechanical barriers

NOTE Confidence: 0.83586585521698

 $00{:}51{:}50{.}431 \dashrightarrow 00{:}51{:}53{.}107$  potentially is is of pancreatic cancer.

00:51:53.110 --> 00:51:55.806 Cause at the high level of you know

NOTE Confidence: 0.83586585521698

 $00:51:55.806 \rightarrow 00:51:58.203$  Disney plastic streamer that you see that

NOTE Confidence: 0.83586585521698

 $00{:}51{:}58{.}203 \dashrightarrow 00{:}52{:}00{.}778$  you see there that has been discussed

NOTE Confidence: 0.83586585521698

 $00:52:00.778 \rightarrow 00:52:03.753$  as not just having actually a physical

NOTE Confidence: 0.83586585521698

 $00{:}52{:}03.753 \dashrightarrow 00{:}52{:}06.110$  potential barrier to treatment but also

NOTE Confidence: 0.83586585521698

 $00:52:06.110 \longrightarrow 00:52:08.609$  the presence of the constituents of that.

NOTE Confidence: 0.83586585521698

 $00:52:08.610 \longrightarrow 00:52:09.346$  Desmond plastics.

NOTE Confidence: 0.83586585521698

 $00:52:09.346 \rightarrow 00:52:11.922$  German may also have a you know,

NOTE Confidence: 0.83586585521698

 $00{:}52{:}11{.}930 \dashrightarrow 00{:}52{:}13{.}418$  biochemical effects that reduce

NOTE Confidence: 0.83586585521698

 $00:52:13.418 \longrightarrow 00:52:15.278$  the likelihood of sensitivity to.

NOTE Confidence: 0.83586585521698

 $00{:}52{:}15{.}280 \dashrightarrow 00{:}52{:}17{.}458$  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

 $00{:}52{:}18{.}910 \dashrightarrow 00{:}52{:}21{.}457$  and I think there are a lot of data

NOTE Confidence: 0.83586585521698

 $00:52:21.457 \rightarrow 00:52:23.167$  suggesting that understanding the

NOTE Confidence: 0.83586585521698

 $00:52:23.167 \rightarrow 00:52:25.437$  components of the micro environment,

NOTE Confidence: 0.83586585521698

 $00:52:25.440 \longrightarrow 00:52:27.618$  the distribution and types of you

- NOTE Confidence: 0.83586585521698
- 00:52:27.618 --> 00:52:29.070 know cancer associated fibroblasts,

 $00:52:29.070 \longrightarrow 00:52:29.798$  for example,

NOTE Confidence: 0.83586585521698

 $00:52:29.798 \longrightarrow 00:52:31.618$  and not in that disease,

NOTE Confidence: 0.83586585521698

 $00:52:31.620 \longrightarrow 00:52:33.906$  and their feelings that might be

NOTE Confidence: 0.83586585521698

 $00:52:33.906 \rightarrow 00:52:35.430$  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

 $00{:}52{:}37.760 \dashrightarrow 00{:}52{:}41.158$  I think in the context of loss of HLA.

NOTE Confidence: 0.83586585521698

 $00:52:41.160 \longrightarrow 00:52:43.552$  It it's you know that you know lots

NOTE Confidence: 0.83586585521698

 $00{:}52{:}43{.}552 \dashrightarrow 00{:}52{:}46{.}333$  of HLA may increase the sensitivity

NOTE Confidence: 0.83586585521698

 $00{:}52{:}46{.}333 \dashrightarrow 00{:}52{:}48{.}968$  potentially to other mechanisms like

NOTE Confidence: 0.83586585521698

 $00{:}52{:}48{.}968 \dashrightarrow 00{:}52{:}51{.}366$  inducing the innate immune system

NOTE Confidence: 0.83586585521698

 $00{:}52{:}51{.}366 \dashrightarrow 00{:}52{:}54{.}060$  rather than the adaptive immune system

NOTE Confidence: 0.83586585521698

 $00:52:54.060 \dashrightarrow 00:52:56.210$  to NK cell enhancement potentially.

NOTE Confidence: 0.83586585521698

 $00{:}52{:}56{.}210 \dashrightarrow 00{:}52{:}57{.}722$  Then you know so.

NOTE Confidence: 0.83586585521698

 $00:52:57.722 \longrightarrow 00:52:59.990$  So there are things that then

00:53:00.080 --> 00:53:02.660 creates a formability I suppose.

NOTE Confidence: 0.83586585521698

 $00{:}53{:}02.660 \dashrightarrow 00{:}53{:}05.724$  I think the issue from my perspective is

NOTE Confidence: 0.83586585521698

 $00:53:05.724 \rightarrow 00:53:09.109$  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

 $00{:}53{:}10.975 \dashrightarrow 00{:}53{:}12.840$  response to something that requires

NOTE Confidence: 0.83586585521698

00:53:12.898 --> 00:53:14.269 HLA antigen presentation.

NOTE Confidence: 0.83586585521698

 $00:53:14.270 \longrightarrow 00:53:17.042$  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

 $00:53:17.840 \longrightarrow 00:53:20.563$  so we should be segmenting patients by

NOTE Confidence: 0.83586585521698

 $00{:}53{:}20{.}563 \dashrightarrow 00{:}53{:}22{.}661$  an understanding of these mechanisms

NOTE Confidence: 0.83586585521698

 $00{:}53{:}22.661 \dashrightarrow 00{:}53{:}25.235$  in order to identify the populations

NOTE Confidence: 0.83586585521698

 $00{:}53{:}25{.}235 \dashrightarrow 00{:}53{:}28{.}049$  that might best be subsequently treated

NOTE Confidence: 0.83586585521698

 $00{:}53{:}28.049 \dashrightarrow 00{:}53{:}30.399$  with different kinds of the rapies.

NOTE Confidence: 0.83586585521698

 $00:53:30.400 \rightarrow 00:53:31.930$  Cut any thoughts from you.

NOTE Confidence: 0.820202529430389

 $00:53:32.680 \dashrightarrow 00:53:34.969$  Yes, I agree with all the comments.

NOTE Confidence: 0.820202529430389

 $00:53:34.970 \rightarrow 00:53:37.140$  I think there is more biology emerging

 $00:53:37.140 \longrightarrow 00:53:38.467$  suggesting that the mechanical

NOTE Confidence: 0.820202529430389

 $00:53:38.467 \dashrightarrow 00:53:40.525$  barriers may not be so mechanical.

NOTE Confidence: 0.820202529430389

 $00{:}53{:}40{.}530 \dashrightarrow 00{:}53{:}43{.}155$  You know some of these fibroblast basic

NOTE Confidence: 0.820202529430389

 $00:53:43.155 \rightarrow 00:53:45.607$  read inhibitory molecule so it may be

NOTE Confidence: 0.820202529430389

 $00:53:45.607 \rightarrow 00:53:47.503$  also an active immunity victory component

NOTE Confidence: 0.820202529430389

 $00:53:47.568 \dashrightarrow 00:53:49.680$  to that and that I think is driving.

NOTE Confidence: 0.820202529430389

 $00:53:49.680 \rightarrow 00:53:52.210$  I think they were going to see a lot of

NOTE Confidence: 0.820202529430389

 $00{:}53{:}52{.}279 \dashrightarrow 00{:}53{:}54{.}811$  new studies showing active mechanism of

NOTE Confidence: 0.820202529430389

 $00{:}53{:}54{.}811 \dashrightarrow 00{:}53{:}57{.}734$  rejection of immune cells in the tumor bed

NOTE Confidence: 0.820202529430389

 $00:53:57.734 \rightarrow 00:53:59.844$  and relative to the empty in presentation.

NOTE Confidence: 0.820202529430389

 $00:53:59.844 \rightarrow 00:54:02.322$  We have actually a study under review

NOTE Confidence: 0.820202529430389

 $00:54:02.322 \longrightarrow 00:54:04.159$  that should see the light soon.

NOTE Confidence: 0.820202529430389

 $00{:}54{:}04{.}160 \dashrightarrow 00{:}54{:}06{.}060$  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

 $00{:}54{:}07{.}580 \dashrightarrow 00{:}54{:}10{.}022$  different parts of the antigen presentation

 $00:54:10.022 \rightarrow 00:54:13.104$  pathway in a Long story short where we've

NOTE Confidence: 0.820202529430389

 $00:54:13.104 \rightarrow 00:54:16.318$  learned is that when we look at the genomics,

NOTE Confidence: 0.820202529430389

 $00:54:16.320 \longrightarrow 00:54:17.676$  we don't see that.

NOTE Confidence: 0.820202529430389

 $00:54:17.676 \rightarrow 00:54:20.213$  So the majority of alterations are non

NOTE Confidence: 0.820202529430389

 $00:54:20.213 \rightarrow 00:54:22.398$  genomic meaning non mutation related.

NOTE Confidence: 0.820202529430389

 $00{:}54{:}22{.}400 \dashrightarrow 00{:}54{:}24{.}680$  In the second interesting lesson is

NOTE Confidence: 0.820202529430389

 $00{:}54{:}24{.}680 \dashrightarrow 00{:}54{:}27{.}015$  that depending on what molecule is

NOTE Confidence: 0.820202529430389

 $00:54:27.015 \rightarrow 00:54:29.612$  lost in the tumor cell meaning HAHABCV,

NOTE Confidence: 0.820202529430389

 $00{:}54{:}29.620 \dashrightarrow 00{:}54{:}31.140$  A2M or other proteins,

NOTE Confidence: 0.820202529430389

 $00:54:31.140 \dashrightarrow 00:54:32.660$  the immune contexture changes.

NOTE Confidence: 0.820202529430389

 $00{:}54{:}32{.}660 \dashrightarrow 00{:}54{:}33{.}964$  So so I think.

NOTE Confidence: 0.820202529430389

 $00:54:33.964 \rightarrow 00:54:35.920$  Understanding that part will be critical

NOTE Confidence: 0.820202529430389

 $00:54:35.986 \rightarrow 00:54:38.478$  to understand how to treat those patients,

NOTE Confidence: 0.820202529430389

 $00:54:38.480 \longrightarrow 00:54:40.334$  we do see upregulation of natural

NOTE Confidence: 0.820202529430389

 $00{:}54{:}40{.}334 \dashrightarrow 00{:}54{:}42{.}380$  killer service in in certain loss.

NOTE Confidence: 0.820202529430389

 $00:54:42.380 \longrightarrow 00:54:43.030$  Eventually molecules,

 $00:54:43.030 \longrightarrow 00:54:44.330$  but not in everyone,

NOTE Confidence: 0.820202529430389

 $00{:}54{:}44{.}330 \dashrightarrow 00{:}54{:}47{.}021$  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

 $00:54:48.880 \rightarrow 00:54:50.500$  NK cells, and other cells.

NOTE Confidence: 0.820202529430389

 $00{:}54{:}50{.}500 \dashrightarrow 00{:}54{:}52{.}714$  So I think it will be critical to do

NOTE Confidence: 0.820202529430389

 $00{:}54{:}52{.}714 \dashrightarrow 00{:}54{:}54{.}665$  those studies to understand how granular

NOTE Confidence: 0.820202529430389

 $00{:}54{:}54{.}665 \dashrightarrow 00{:}54{:}57{.}580$  disease and if we can lump the antigen

NOTE Confidence: 0.820202529430389

 $00:54:57.580 \rightarrow 00:54:59.595$  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

 $00:55:02.200 \longrightarrow 00:55:04.475$  I think that's to be figured out.

NOTE Confidence: 0.809990227222443

 $00:55:05.380 \rightarrow 00:55:07.900$  So just continuing on with this theme

NOTE Confidence: 0.809990227222443

 $00{:}55{:}07{.}900 \dashrightarrow 00{:}55{:}11{.}762$  in in a question for Chin can HLA loss

NOTE Confidence: 0.809990227222443

 $00:55:11.762 \rightarrow 00:55:14.680$  be overcome by epigenetic modification?

NOTE Confidence: 0.809990227222443

 $00{:}55{:}14.680 \dashrightarrow 00{:}55{:}18.224$  Or what is epigenetic role in HLA loss?

NOTE Confidence: 0.84406441450119

 $00{:}55{:}18{.}960 \dashrightarrow 00{:}55{:}22{.}551$  So this is not an area I have been

 $00:55:22.551 \rightarrow 00:55:25.230$  working on very well having it,

NOTE Confidence: 0.84406441450119

 $00{:}55{:}25{.}230 \dashrightarrow 00{:}55{:}27.636$  but I could just mention another

NOTE Confidence: 0.84406441450119

 $00{:}55{:}27.636 \dashrightarrow 00{:}55{:}30.151$  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

 $00{:}55{:}32{.}231 \dashrightarrow 00{:}55{:}34{.}430$  tools to execute those jeans.

NOTE Confidence: 0.84406441450119

 $00{:}55{:}34{.}430 \dashrightarrow 00{:}55{:}36{.}114$  Reactivate those jeans and

NOTE Confidence: 0.84406441450119

 $00{:}55{:}36{.}114 \dashrightarrow 00{:}55{:}38{.}219$  to make them successful too.

NOTE Confidence: 0.84406441450119

 $00:55:38.220 \rightarrow 00:55:41.460$  Make make them to be sensitive

NOTE Confidence: 0.84406441450119

 $00{:}55{:}41{.}460 \dashrightarrow 00{:}55{:}43{.}080$  to our treatment.

NOTE Confidence: 0.84406441450119

 $00:55:43.080 \dashrightarrow 00:55:45.735$  So email checkpoint blockade will

NOTE Confidence: 0.84406441450119

 $00:55:45.735 \dashrightarrow 00:55:49.020$  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

 $00{:}55{:}54{.}270 \dashrightarrow 00{:}55{:}59{.}640$  that was submitted earlier, but I think.

NOTE Confidence: 0.834680736064911

 $00:55:59.640 \rightarrow 00:56:01.926$  Could probably be answered extensively or

NOTE Confidence: 0.834680736064911

 $00:56:01.926 \rightarrow 00:56:04.500$  exhaustively by each one of the panelists,

NOTE Confidence: 0.834680736064911

 $00:56:04.500 \rightarrow 00:56:06.702$  but maybe I'll ask Katie and

- NOTE Confidence: 0.834680736064911
- $00{:}56{:}06{.}702 \dashrightarrow 00{:}56{:}08{.}989$  Mark to start on this one.
- NOTE Confidence: 0.834680736064911
- $00{:}56{:}08{.}990 \dashrightarrow 00{:}56{:}11{.}454$  How does the mutational landscape of a
- NOTE Confidence: 0.834680736064911
- $00:56:11.454 \rightarrow 00:56:13.479$  tumor affect resistance and sensitivity?
- NOTE Confidence: 0.834680736064911
- $00:56:13.480 \longrightarrow 00:56:15.916$  And I'm interpreting that the questioner
- NOTE Confidence: 0.834680736064911
- $00:56:15.916 \rightarrow 00:56:17.919$  means the other mutations besides
- NOTE Confidence: 0.834680736064911
- $00:56:17.919 \rightarrow 00:56:19.840$  the one in your target molecule.
- NOTE Confidence: 0.884686589241028
- $00:56:22.170 \longrightarrow 00:56:24.350$  Thank you sure I can.
- NOTE Confidence: 0.884686589241028
- $00:56:24.350 \longrightarrow 00:56:26.960$  I can get started with that.
- NOTE Confidence: 0.884686589241028
- $00:56:26.960 \longrightarrow 00:56:29.696$  I think this is really an area that
- NOTE Confidence: 0.884686589241028
- $00:56:29.696 \rightarrow 00:56:32.587$  we are starting to learn more about
- NOTE Confidence: 0.884686589241028
- $00:56:32.587 \longrightarrow 00:56:35.834$  as we have learned more about the
- NOTE Confidence: 0.884686589241028
- $00:56:35.834 \rightarrow 00:56:38.966$  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
- $00:56:41.348 \longrightarrow 00:56:44.470$  So now one of the things that
- NOTE Confidence: 0.884686589241028
- $00:56:44.561 \rightarrow 00:56:46.967$  we've been able to look at,
- NOTE Confidence: 0.884686589241028

 $00:56:46.970 \longrightarrow 00:56:49.819$  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

 $00:56:53.318 \rightarrow 00:56:57.058$  We can look at the pattern of Co occurring

NOTE Confidence: 0.884686589241028

 $00:56:57.058 \rightarrow 00:56:59.126$  genetic alterations that happened,

NOTE Confidence: 0.884686589241028

 $00:56:59.130 \rightarrow 00:57:01.740$  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

 $00{:}57{:}03{.}910 \dashrightarrow 00{:}57{:}06{.}948$  these can Co occur with P53 mutations.

NOTE Confidence: 0.884686589241028

 $00:57:06.950 \longrightarrow 00:57:09.602$  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

 $00:57:11.720 \longrightarrow 00:57:13.890$  also known as Elchibey one.

NOTE Confidence: 0.884686589241028

 $00:57:13.890 \longrightarrow 00:57:15.626$  And we're really beginning

NOTE Confidence: 0.884686589241028

 $00:57:15.626 \longrightarrow 00:57:18.230$  to learn about what it means.

NOTE Confidence: 0.884686589241028

 $00{:}57{:}18{.}230 \dashrightarrow 00{:}57{:}20{.}939$  If the tumor has Akira's mutation and

NOTE Confidence: 0.884686589241028

 $00{:}57{:}20{.}939 \dashrightarrow 00{:}57{:}23{.}900$  a P53 mutation versus ACARAS mutation.

NOTE Confidence: 0.884686589241028

 $00:57:23.900 \rightarrow 00:57:27.456$  And then Elchibey one mutation for example.

 $00:57:27.460 \rightarrow 00:57:30.772$  And what and that the LKB one meeting

NOTE Confidence: 0.884686589241028

 $00{:}57{:}30{.}772 \dashrightarrow 00{:}57{:}34{.}653$  tumors seem to have a different or

NOTE Confidence: 0.884686589241028

 $00:57:34.653 \rightarrow 00:57:37.021$  reduced sensitivity to immunotherapy

NOTE Confidence: 0.884686589241028

 $00:57:37.021 \rightarrow 00:57:39.432$  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 the rapies,

NOTE Confidence: 0.884686589241028

 $00:57:43.380 \longrightarrow 00:57:45.555$  we're really starting to scratch

NOTE Confidence: 0.884686589241028

 $00{:}57{:}45{.}555 \dashrightarrow 00{:}57{:}48{.}241$  the surface and really beginning to

NOTE Confidence: 0.884686589241028

 $00{:}57{:}48.241 \dashrightarrow 00{:}57{:}50.893$  start to understand how different Co

NOTE Confidence: 0.884686589241028

 $00:57:50.893 \rightarrow 00:57:52.794$  occurring alterations also impact

NOTE Confidence: 0.884686589241028

 $00:57:52.794 \rightarrow 00:57:54.826$  response to targeted therapies.

NOTE Confidence: 0.884686589241028

 $00{:}57{:}54{.}830 \dashrightarrow 00{:}57{:}55{.}928$  So for example,

NOTE Confidence: 0.884686589241028

 $00{:}57{:}55{.}928 \dashrightarrow 00{:}57{:}58{.}490$  some of the work that we've been

NOTE Confidence: 0.884686589241028

 $00:57:58.570 \rightarrow 00:58:01.315$  doing recently looking at different

NOTE Confidence: 0.884686589241028

 $00{:}58{:}01{.}315 \dashrightarrow 00{:}58{:}03{.}511$  tumor suppressor gene alterations

00:58:03.511 --> 00:58:06.353 in EGFR mutant lung cancer and

NOTE Confidence: 0.884686589241028

 $00:58:06.353 \rightarrow 00:58:08.563$  how they affect sensitivity to

NOTE Confidence: 0.884686589241028

00:58:08.570 --> 00:58:09.800 tyrosine kinase inhibitors.

NOTE Confidence: 0.884686589241028

 $00:58:09.800 \rightarrow 00:58:12.670$  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

 $00:58:14.990 \rightarrow 00:58:18.078$  an also is emerging from studies of patients.

NOTE Confidence: 0.884686589241028

 $00:58:18.080 \rightarrow 00:58:20.810$  Patient specimens is that if you have

NOTE Confidence: 0.884686589241028

 $00{:}58{:}20{.}810 \dashrightarrow 00{:}58{:}23{.}175$  EGFR mutant tumors that also have

NOTE Confidence: 0.884686589241028

 $00{:}58{:}23.175 \dashrightarrow 00{:}58{:}25.407$  mutations in the keep one access,

NOTE Confidence: 0.884686589241028

 $00:58:25.410 \longrightarrow 00:58:28.122$  so the keep 1 NRF 2 access that

NOTE Confidence: 0.884686589241028

 $00{:}58{:}28{.}122 \dashrightarrow 00{:}58{:}30{.}187$  is important for the antioxidant

NOTE Confidence: 0.884686589241028

 $00:58:30.187 \longrightarrow 00:58:32.357$  response of a tumor cell.

NOTE Confidence: 0.884686589241028

 $00{:}58{:}32{.}360 \dashrightarrow 00{:}58{:}34{.}872$  If you have mutations that Co occur in

NOTE Confidence: 0.884686589241028

 $00:58:34.872 \rightarrow 00:58:37.821$  that path where you have a decreased

NOTE Confidence: 0.884686589241028

 $00:58:37.821 \rightarrow 00:58:40.076$  sensitivity to tyrosine kinase inhibitors,

NOTE Confidence: 0.884686589241028

 $00:58:40.080 \longrightarrow 00:58:42.035$  so the tumors will shrink

- NOTE Confidence: 0.884686589241028
- $00{:}58{:}42.035 \dashrightarrow 00{:}58{:}43.599$  less on treatment with.
- NOTE Confidence: 0.884686589241028
- 00:58:43.600 -> 00:58:44.884 These targeted therapies,
- NOTE Confidence: 0.884686589241028
- $00:58:44.884 \rightarrow 00:58:47.452$  and so that begs the question,
- NOTE Confidence: 0.884686589241028
- $00:58:47.460 \rightarrow 00:58:51.312$  is that a subset of patients who you could,
- NOTE Confidence: 0.884686589241028
- $00{:}58{:}51{.}320 \dashrightarrow 00{:}58{:}52{.}176$  for example,
- NOTE Confidence: 0.884686589241028
- $00:58:52.176 \longrightarrow 00:58:53.888$  select initially for treatment
- NOTE Confidence: 0.884686589241028
- $00:58:53.888 \rightarrow 00:58:55.172$  with different therapies,
- NOTE Confidence: 0.884686589241028
- $00:58:55.180 \longrightarrow 00:58:57.080$  or for combination the rapies
- NOTE Confidence: 0.884686589241028
- $00{:}58{:}57{.}080 \dashrightarrow 00{:}58{:}59{.}455$  together with a tyrosine kinase
- NOTE Confidence: 0.884686589241028
- $00:58:59.455 \longrightarrow 00:59:01.218$  inhibitor so that you could.
- NOTE Confidence: 0.884686589241028
- $00:59:01.220 \rightarrow 00:59:02.760$  Improve outcomes in patients
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}02{.}760 \dashrightarrow 00{:}59{:}03{.}915$  with that disease.
- NOTE Confidence: 0.884686589241028
- 00:59:03.920 --> 00:59:05.212 I think of course,
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}05{.}212 \dashrightarrow 00{:}59{:}06{.}827$  this these types of landscapes
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}06{.}827 \dashrightarrow 00{:}59{:}08{.}815$  also this studying these landscapes
- NOTE Confidence: 0.884686589241028

 $00:59:08.815 \rightarrow 00:59:11.221$  really requires a lot of mechanistic

NOTE Confidence: 0.884686589241028

 $00:59:11.281 \rightarrow 00:59:12.953$  investigation to understand exactly

NOTE Confidence: 0.884686589241028

 $00:59:12.953 \rightarrow 00:59:15.461$  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

 $00{:}59{:}21{.}322 \dashrightarrow 00{:}59{:}24{.}121$  landscape also has to do with the

NOTE Confidence: 0.884686589241028

 $00{:}59{:}24{.}121 \dashrightarrow 00{:}59{:}26{.}191$  overall mutation burden and the

NOTE Confidence: 0.884686589241028

 $00:59:26.191 \rightarrow 00:59:28.031$  overall tumor mutation burden, which.

NOTE Confidence: 0.884686589241028

 $00{:}59{:}28{.}031 \dashrightarrow 00{:}59{:}30{.}791$  You know we talk a lot about it

NOTE Confidence: 0.884686589241028

 $00{:}59{:}30{.}791 \dashrightarrow 00{:}59{:}32{.}777$  in the context of immuno the rapies

NOTE Confidence: 0.884686589241028

 $00:59:32.777 \rightarrow 00:59:34.550$  and where you know we've.

NOTE Confidence: 0.884686589241028

 $00{:}59{:}34{.}550 \dashrightarrow 00{:}59{:}36{.}776$  We've heard about a lot about it

NOTE Confidence: 0.884686589241028

 $00:59:36.776 \longrightarrow 00:59:38.230$  in in recent years.

NOTE Confidence: 0.884686589241028

 $00:59:38.230 \longrightarrow 00:59:40.365$  I'd say also there's some evidence that

NOTE Confidence: 0.884686589241028

 $00:59:40.365 \rightarrow 00:59:42.589$  in the context of targeted therapies,

- NOTE Confidence: 0.884686589241028
- $00{:}59{:}42{.}590 \dashrightarrow 00{:}59{:}44{.}660$  the overall genetic landscape or the
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}44.660 \dashrightarrow 00{:}59{:}46.737$  tumor mutation burden can have an
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}46{.}737 \dashrightarrow 00{:}59{:}48{.}949$  effect on the response to targeted the rapy.
- NOTE Confidence: 0.884686589241028
- 00:59:48.950 --> 00:59:50.864 So again in EGFR mutant lung
- NOTE Confidence: 0.884686589241028
- $00{:}59{:}50{.}864 \dashrightarrow 00{:}59{:}52{.}140$  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
- $00:59:56.320 \longrightarrow 00:59:57.668$  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
- $00:59:59.360 \longrightarrow 01:00:01.034$  But in that highest circle seemed
- NOTE Confidence: 0.842104613780975
- $01:00:01.034 \rightarrow 01:00:03.066$  to do worse on treatment with
- NOTE Confidence: 0.842104613780975
- $01:00:03.066 \rightarrow 01:00:04.766$  targeted therapies with tyrosine
- NOTE Confidence: 0.842104613780975
- $01{:}00{:}04.766 \dashrightarrow 01{:}00{:}07.195$  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
- $01{:}00{:}08.860 \dashrightarrow 01{:}00{:}10.972$  So there are lots of different
- NOTE Confidence: 0.842104613780975
- $01:00:10.972 \longrightarrow 01:00:12.028$  aspects to consider.
- NOTE Confidence: 0.842104613780975
- $01:00:12.030 \longrightarrow 01:00:13.338$  The specific mutation.
- NOTE Confidence: 0.842104613780975
- $01:00:13.338 \rightarrow 01:00:15.518$  So qualitatively but also quantitatively.
- NOTE Confidence: 0.842104613780975
- $01:00:15.520 \longrightarrow 01:00:16.090$  Yep,
- NOTE Confidence: 0.625242710113525
- $01{:}00{:}16.090 \dashrightarrow 01{:}00{:}22.390$  I was just at the office or at a kind of.
- NOTE Confidence: 0.625242710113525
- $01{:}00{:}22.390 \dashrightarrow 01{:}00{:}24.178$  Broad conceptual thought to
- NOTE Confidence: 0.625242710113525
- $01:00:24.178 \longrightarrow 01:00:25.966$  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
- $01:00:28.660 \longrightarrow 01:00:30.900$  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
- $01:00:33.306 \rightarrow 01:00:36.279$  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
- $01:00:38.068 \rightarrow 01:00:40.303$  whether its intracellular intra tissue,
- NOTE Confidence: 0.625242710113525
- $01:00:40.310 \longrightarrow 01:00:41.645$  Inter intra Organism.
- NOTE Confidence: 0.625242710113525
- $01{:}00{:}41.645 \dashrightarrow 01{:}00{:}44.760$  Once regular network and in a sense
- NOTE Confidence: 0.625242710113525
- $01:00:44.842 \longrightarrow 01:00:47.628$  if you think about the fact that

 $01:00:47.628 \longrightarrow 01:00:50.357$  cancers are really caused by the

NOTE Confidence: 0.625242710113525

 $01{:}00{:}50{.}357 \dashrightarrow 01{:}00{:}52{.}293$  networks losing robustness and

NOTE Confidence: 0.625242710113525

 $01:00:52.293 \rightarrow 01:00:55.598$  kind of careering out of control to

NOTE Confidence: 0.625242710113525

 $01:00:55.598 \rightarrow 01:00:57.446$  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

 $01:01:02.221 \longrightarrow 01:01:04.423$  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

 $01:01:06.020 \rightarrow 01:01:08.055$  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

 $01{:}01{:}10.914 \dashrightarrow 01{:}01{:}13.770$  But that's not enough to cause cancer,

NOTE Confidence: 0.625242710113525

 $01:01:13.770 \longrightarrow 01:01:15.810$  so the context is key,

NOTE Confidence: 0.625242710113525

 $01:01:15.810 \longrightarrow 01:01:17.217$  and the targeted,

 $01:01:17.217 \rightarrow 01:01:20.830$  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

 $01:01:22.714 \longrightarrow 01:01:25.085$  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 $\operatorname{-->}$ 01:01:29.620 so I think I think that the answer

NOTE Confidence: 0.625242710113525

 $01{:}01{:}29.620 \dashrightarrow 01{:}01{:}32.175$  the answer to the question is that we

NOTE Confidence: 0.625242710113525

 $01:01:32.175 \rightarrow 01:01:35.189$  need to think about these things as networks.

NOTE Confidence: 0.625242710113525

 $01:01:35.190 \rightarrow 01:01:37.176$  We need to get into considering

NOTE Confidence: 0.625242710113525

 $01{:}01{:}37{.}176 \dashrightarrow 01{:}01{:}38{.}870$  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

 $01:01:40.868 \longrightarrow 01:01:42.540$  of thinking about that one,

NOTE Confidence: 0.625242710113525

 $01:01:42.540 \longrightarrow 01:01:44.964$  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

 $01:01:47.220 \longrightarrow 01:01:48.544$  AI types of approaches,

NOTE Confidence: 0.625242710113525

 $01{:}01{:}48.544 \dashrightarrow 01{:}01{:}50.890$  whereas we collect more and more data.

NOTE Confidence: 0.625242710113525

 $01{:}01{:}50.890 \dashrightarrow 01{:}01{:}52.440$  For the mutational landscape to

 $01:01:52.440 \longrightarrow 01:01:54.456$  try to understand their with with

NOTE Confidence: 0.625242710113525

 $01:01:54.456 \rightarrow 01:01:56.108$  various their principle components,

NOTE Confidence: 0.625242710113525

 $01:01:56.110 \rightarrow 01:01:58.254$  analysis and what have you, what.

NOTE Confidence: 0.625242710113525

 $01:01:58.254 \rightarrow 01:02:00.274$  How we can correlate combinations

NOTE Confidence: 0.625242710113525

 $01{:}02{:}00{.}274 \dashrightarrow 01{:}02{:}01{.}890$  of mutations with sensitivity

NOTE Confidence: 0.625242710113525

 $01{:}02{:}01{.}956 \dashrightarrow 01{:}02{:}03.066$  and so on so forth.

NOTE Confidence: 0.625242710113525

 $01{:}02{:}03.070 \dashrightarrow 01{:}02{:}05.074$  But there's another element I think

NOTE Confidence: 0.625242710113525

 $01:02:05.074 \rightarrow 01:02:07.544$  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

 $01:02:09.330 \longrightarrow 01:02:11.766$  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

 $01:02:13.822 \rightarrow 01:02:15.600$  resistance illustrates this very nicely.

NOTE Confidence: 0.625242710113525

 $01{:}02{:}15{.}600 \dashrightarrow 01{:}02{:}18{.}345$  Is that we we can actually learn an awful

NOTE Confidence: 0.625242710113525

 $01{:}02{:}18.345 \dashrightarrow 01{:}02{:}20.818$  lot about how the networks operate,

NOTE Confidence: 0.625242710113525

01:02:20.820 --> 01:02:21.410 you know?

 $01:02:21.410 \longrightarrow 01:02:23.180$  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

 $01:02:24.420 \longrightarrow 01:02:25.692$  then the graph inhibited

NOTE Confidence: 0.625242710113525

 $01:02:25.692 \rightarrow 01:02:26.964$  does the wrong thing,

NOTE Confidence: 0.625242710113525

01:02:26.970 --> 01:02:27.534 you know,

NOTE Confidence: 0.625242710113525

 $01:02:27.534 \rightarrow 01:02:29.790$  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

 $01{:}02{:}32{.}223 \dashrightarrow 01{:}02{:}34{.}269$  beyond the targets to the networks

NOTE Confidence: 0.625242710113525

 $01:02:34.269 \longrightarrow 01:02:36.509$  and what the effect of the targeted NOTE Confidence: 0.625242710113525

 $01:02:36.510 \longrightarrow 01:02:38.424$  the rapeutics is on the networks and NOTE Confidence: 0.625242710113525

 $01:02:38.424 \rightarrow 01:02:40.928$  that that of course is going to hold NOTE Confidence: 0.625242710113525

 $01:02:40.928 \longrightarrow 01:02:42.668$  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

 $01{:}02{:}46.684 \dashrightarrow 01{:}02{:}48.269$  what you're actually dealing with,

NOTE Confidence: 0.625242710113525

 $01{:}02{:}48.270 \dashrightarrow 01{:}02{:}48.802$  that is,

- NOTE Confidence: 0.625242710113525
- $01{:}02{:}48.802 \dashrightarrow 01{:}02{:}50.930$  is trying to restore balance in an incredibly
- NOTE Confidence: 0.625242710113525
- $01:02:50.984 \rightarrow 01:02:52.808$  complicated interstellar the network.
- NOTE Confidence: 0.625242710113525
- $01:02:52.810 \longrightarrow 01:02:55.022$  So I think there's a couple of
- NOTE Confidence: 0.625242710113525
- $01:02:55.022 \rightarrow 01:02:56.530$  perspectives I would like to.
- NOTE Confidence: 0.717755913734436
- $01{:}02{:}57{.}060 \dashrightarrow 01{:}02{:}59{.}286$  Could you could you just answer
- NOTE Confidence: 0.717755913734436
- $01:02:59.286 \longrightarrow 01:03:01.132$  that by introducing people a
- NOTE Confidence: 0.717755913734436
- $01:03:01.132 \longrightarrow 01:03:03.190$  little bit to what's going on at
- NOTE Confidence: 0.717755913734436
- $01:03:03.190 \longrightarrow 01:03:04.999$  the Systems Biology Institute.
- NOTE Confidence: 0.717755913734436
- $01{:}03{:}05{.}000 \dashrightarrow 01{:}03{:}06{.}810$  Not all of the audience
- NOTE Confidence: 0.717755913734436
- $01:03:06.810 \longrightarrow 01:03:10.059$  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
- $01{:}03{:}12{.}300 \dashrightarrow 01{:}03{:}14{.}524$  have a system colleges too that's
- NOTE Confidence: 0.717755913734436
- $01{:}03{:}14.524 \dashrightarrow 01{:}03{:}16.918$  actually headed up by Andra Chanco,
- NOTE Confidence: 0.717755913734436
- $01{:}03{:}16{.}920 \dashrightarrow 01{:}03{:}18{.}720$  who's the Director of Vietnam.
- NOTE Confidence: 0.717755913734436
- $01{:}03{:}18.720 \dashrightarrow 01{:}03{:}21.087$  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

 $01:03:23.770 \longrightarrow 01:03:25.936$  There's a NCI has a physical

NOTE Confidence: 0.717755913734436

 $01:03:25.936 \rightarrow 01:03:27.770$  Sciences long college center that.

NOTE Confidence: 0.717755913734436

 $01:03:27.770 \rightarrow 01:03:29.595$  Actually, that initiative that you're

NOTE Confidence: 0.717755913734436

 $01{:}03{:}29{.}595 \dashrightarrow 01{:}03{:}32{.}742$  involved with one of those at Penn and and

NOTE Confidence: 0.717755913734436

 $01:03:32.742 \rightarrow 01:03:34.626$  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

 $01:03:35.998 \longrightarrow 01:03:37.366$  that 100 grand sent,

NOTE Confidence: 0.717755913734436

 $01:03:37.370 \longrightarrow 01:03:39.266$  and so the Systems Biology Institute

NOTE Confidence: 0.717755913734436

 $01:03:39.266 \rightarrow 01:03:41.489$  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

 $01:03:43.536 \rightarrow 01:03:45.305$  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

 $01:03:47.660 \longrightarrow 01:03:49.718$  and Andre is an integral part

NOTE Confidence: 0.717755913734436

 $01:03:49.718 \longrightarrow 01:03:51.090$  of the Cancer Center.

NOTE Confidence: 0.717755913734436

 $01:03:51.090 \rightarrow 01:03:53.498$  Of course, the Council biologist is too,

- NOTE Confidence: 0.717755913734436
- $01:03:53.500 \rightarrow 01:03:56.380$  and so are most members of the Systems
- NOTE Confidence: 0.717755913734436
- $01:03:56.380 \rightarrow 01:03:58.718$  Biology Institute and the kinds of things.
- NOTE Confidence: 0.717755913734436
- $01:03:58.720 \longrightarrow 01:04:00.032$  Being looked at there,
- NOTE Confidence: 0.717755913734436
- $01:04:00.032 \rightarrow 01:04:02.000$  which is actually related to this,
- NOTE Confidence: 0.717755913734436
- $01{:}04{:}02{.}000 \dashrightarrow 01{:}04{:}04{.}352$  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
- $01:04:06.579 \rightarrow 01:04:08.107$  interested in looking at.
- NOTE Confidence: 0.717755913734436
- $01:04:08.110 \longrightarrow 01:04:12.130$  But it sells from brain tumors
- NOTE Confidence: 0.717755913734436
- $01:04:12.130 \longrightarrow 01:04:14.810$  in particular and asking.
- NOTE Confidence: 0.717755913734436
- $01{:}04{:}14{.}810 \dashrightarrow 01{:}04{:}17{.}813$  Adam and looking at at migration versus
- NOTE Confidence: 0.717755913734436
- $01:04:17.813 \rightarrow 01:04:20.210$  proliferation in those in those cells,
- NOTE Confidence: 0.717755913734436
- $01:04:20.210 \longrightarrow 01:04:22.200$  and the epigenetic difference between
- NOTE Confidence: 0.717755913734436
- $01{:}04{:}22.200 \dashrightarrow 01{:}04{:}24.644$  between those in terms of what's
- NOTE Confidence: 0.717755913734436
- $01{:}04{:}24.644 \dashrightarrow 01{:}04{:}26.599$  defining the signaling networks that
- NOTE Confidence: 0.717755913734436
- $01:04:26.599 \rightarrow 01:04:29.749$  cause the cells to behave very differently.
- NOTE Confidence: 0.717755913734436

 $01:04:29.750 \longrightarrow 01:04:32.851$  And he can do that with some

NOTE Confidence: 0.717755913734436

 $01:04:32.851 \rightarrow 01:04:35.050$  microfabricated devices where you can

NOTE Confidence: 0.717755913734436

 $01:04:35.050 \rightarrow 01:04:37.432$  separate cells based on how rapidly

NOTE Confidence: 0.717755913734436

 $01:04:37.432 \rightarrow 01:04:40.639$  they can migrate and then go in and

NOTE Confidence: 0.717755913734436

 $01{:}04{:}40.639 \dashrightarrow 01{:}04{:}43.030$  look with various single cell and

NOTE Confidence: 0.717755913734436

 $01{:}04{:}43.030 \dashrightarrow 01{:}04{:}45.520$  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

 $01{:}04{:}46.621 \dashrightarrow 01{:}04{:}48.456$  gentleman and epic transcriptome etc.

NOTE Confidence: 0.717755913734436

 $01:04:48.460 \longrightarrow 01:04:50.290$  So that's really very exciting.

NOTE Confidence: 0.717755913734436

 $01{:}04{:}50{.}290 \dashrightarrow 01{:}04{:}52{.}420$  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

 $01:04:54.922 \longrightarrow 01:04:56.994$  that is one of city channel that

NOTE Confidence: 0.717755913734436

 $01{:}04{:}56{.}994 \dashrightarrow 01{:}04{:}59{.}099$  many of you will come across.

NOTE Confidence: 0.717755913734436

 $01{:}04{:}59{.}100 \dashrightarrow 01{:}05{:}02{.}151$  City is doing an awful lot of work in

NOTE Confidence: 0.717755913734436

 $01:05:02.151 \rightarrow 01:05:05.340$  terms of it in the system bars Institute.

NOTE Confidence: 0.717755913734436

 $01:05:05.340 \rightarrow 01:05:07.545$  Two in terms of trying to understand

01:05:07.545 --> 01:05:10.109 using using in vivo CRISPR technologies.

NOTE Confidence: 0.717755913734436

 $01:05:10.110 \longrightarrow 01:05:11.945$  Origins of resistance to terminate

NOTE Confidence: 0.717755913734436

 $01:05:11.945 \rightarrow 01:05:13.780$  therapies and another therapeutic approaches.

NOTE Confidence: 0.717755913734436

 $01:05:13.780 \longrightarrow 01:05:16.426$  And so that's really very exciting again.

NOTE Confidence: 0.717755913734436

 $01:05:16.430 \longrightarrow 01:05:18.674$  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

 $01:05:20.420 \rightarrow 01:05:22.240$  and then one other aspect,

NOTE Confidence: 0.717755913734436

 $01:05:22.240 \longrightarrow 01:05:25.136$  which I which I think is really cool.

NOTE Confidence: 0.717755913734436

 $01{:}05{:}25{.}140 \dashrightarrow 01{:}05{:}27{.}813$  Actually as a project in our in EU 54

NOTE Confidence: 0.717755913734436

 $01{:}05{:}27.813 \dashrightarrow 01{:}05{:}30.589$  that Andre Valances that Gunter Wagner,

NOTE Confidence: 0.717755913734436

 $01:05:30.590 \rightarrow 01:05:32.545$  who's an evolutionary biologist is

NOTE Confidence: 0.717755913734436

 $01:05:32.545 \rightarrow 01:05:35.090$  is very interested in why certain.

NOTE Confidence: 0.717755913734436

 $01{:}05{:}35{.}090 \dashrightarrow 01{:}05{:}36{.}920$  Mammals don't tend to get meta

NOTE Confidence: 0.717755913734436

 $01{:}05{:}36{.}920 \dashrightarrow 01{:}05{:}38{.}850$  static cancer cows in particular.

NOTE Confidence: 0.717755913734436

 $01{:}05{:}38.850 \dashrightarrow 01{:}05{:}40.752$  As an example that caused him

 $01:05:40.752 \rightarrow 01:05:42.610$  not to die of cancer,

NOTE Confidence: 0.717755913734436

 $01:05:42.610 \longrightarrow 01:05:44.320$  they just they carry them

NOTE Confidence: 0.717755913734436

 $01:05:44.320 \longrightarrow 01:05:45.688$  around with the carry.

NOTE Confidence: 0.717755913734436

 $01:05:45.690 \longrightarrow 01:05:47.400$  The tumors around with him

NOTE Confidence: 0.717755913734436

01:05:47.400 --> 01:05:48.426 without metastasize Ng,

NOTE Confidence: 0.717755913734436

 $01{:}05{:}48{.}430 \dashrightarrow 01{:}05{:}51{.}122$  and pretty much we don't see them here

NOTE Confidence: 0.717755913734436

 $01:05:51.122 \longrightarrow 01:05:53.048$  because they all killed before they

NOTE Confidence: 0.717755913734436

 $01:05:53.048 \dashrightarrow 01:05:55.606$  get to that stage for other purposes.

NOTE Confidence: 0.717755913734436

 $01{:}05{:}55{.}610 \dashrightarrow 01{:}05{:}57{.}656$  But but and so that's fascinating.

NOTE Confidence: 0.717755913734436

 $01:05:57.660 \longrightarrow 01:05:58.686$  And so again,

NOTE Confidence: 0.717755913734436

 $01{:}05{:}58.686 \dashrightarrow 01{:}06{:}00.738$  it's looking at the network context.

NOTE Confidence: 0.717755913734436

 $01{:}06{:}00.740 \dashrightarrow 01{:}06{:}02.325$  The network differences between the

NOTE Confidence: 0.717755913734436

 $01{:}06{:}02.325 \dashrightarrow 01{:}06{:}04.748$  mammals that do and don't suffer from

NOTE Confidence: 0.717755913734436

 $01:06:04.748 \dashrightarrow 01:06:06.192$  metastatic cancer, and actually.

NOTE Confidence: 0.717755913734436

 $01:06:06.192 \rightarrow 01:06:08.509$  It's kind of related in some senses

NOTE Confidence: 0.717755913734436

 $01{:}06{:}08{.}509 \dashrightarrow 01{:}06{:}10{.}888$  to placental invasiveness in some.

- NOTE Confidence: 0.717755913734436
- $01:06:10.890 \longrightarrow 01:06:12.810$  In these of these organisms,
- NOTE Confidence: 0.760184228420258
- $01:06:12.810 \rightarrow 01:06:15.874$  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
- $01{:}06{:}18.772 \dashrightarrow 01{:}06{:}22.218$  There was a cost in some ways of of having
- NOTE Confidence: 0.760184228420258
- $01{:}06{:}22.218 \dashrightarrow 01{:}06{:}24.708$  placenta that more interdigitate ihd,
- NOTE Confidence: 0.760184228420258
- $01{:}06{:}24.710 \dashrightarrow 01{:}06{:}27.377$  which is that you more susceptible to
- NOTE Confidence: 0.760184228420258
- $01:06:27.377 \longrightarrow 01:06:29.320$  metastatic metastasis in your cancer.
- NOTE Confidence: 0.760184228420258
- $01:06:29.320 \longrightarrow 01:06:31.618$  So so so these different perspectives,
- NOTE Confidence: 0.760184228420258
- $01:06:31.620 \longrightarrow 01:06:32.784$  whether it's immune.
- NOTE Confidence: 0.760184228420258
- 01:06:32.784 --> 01:06:34.336 Immunology approaches targeted therapeutics.
- NOTE Confidence: 0.760184228420258
- $01:06:34.340 \longrightarrow 01:06:36.620$  I think there's a burgeoning
- NOTE Confidence: 0.760184228420258
- $01:06:36.620 \longrightarrow 01:06:38.450$  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
- $01:06:42.090 \rightarrow 01:06:44.330$  and understanding of how to put
- NOTE Confidence: 0.760184228420258

- $01:06:44.330 \longrightarrow 01:06:45.926$  this into the quantitative,
- NOTE Confidence: 0.760184228420258
- $01{:}06{:}45{.}930 \dashrightarrow 01{:}06{:}48{.}290$  and I think it needs to be quantitative
- NOTE Confidence: 0.760184228420258
- $01:06:48.290 \longrightarrow 01:06:50.380$  in the sense of biochemical
- NOTE Confidence: 0.760184228420258
- $01:06:50.380 \rightarrow 01:06:52.288$  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
- $01{:}06{:}55{.}952 \dashrightarrow 01{:}06{:}58{.}970$  I have a question here asking
- NOTE Confidence: 0.822815236837968
- $01:06:59.059 \longrightarrow 01:07:02.090$  the panel to comment on the role
- NOTE Confidence: 0.822815236837968
- $01:07:02.090 \rightarrow 01:07:04.988$  of proteomics and studying tumor
- NOTE Confidence: 0.822815236837968
- $01{:}07{:}04.988 \dashrightarrow 01{:}07{:}07{.}084$  resistance, and maybe you'll
- NOTE Confidence: 0.822815236837968
- $01:07:07.084 \longrightarrow 01:07:09.780$  you'll take that first mark in
- NOTE Confidence: 0.796327888965607
- $01:07:09.780 \longrightarrow 01:07:11.336$  the market. Only relates
- NOTE Confidence: 0.796327888965607
- $01:07:11.336 \longrightarrow 01:07:13.670$  exactly to what I was saying.
- NOTE Confidence: 0.796327888965607
- $01{:}07{:}13.670 \dashrightarrow 01{:}07{:}16.358$  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
- $01:07:18.790 \rightarrow 01:07:21.296$  but my chemistry is defined by the
- NOTE Confidence: 0.796327888965607
- $01:07:21.296 \rightarrow 01:07:23.182$  component by the combination of

- NOTE Confidence: 0.796327888965607
- $01{:}07{:}23.182 \dashrightarrow 01{:}07{:}25.378$  components that you have and so
- NOTE Confidence: 0.796327888965607
- $01:07:25.378 \longrightarrow 01:07:28.010$  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
- $01:07:30.593 \rightarrow 01:07:33.549$  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
- $01:07:38.348 \longrightarrow 01:07:40.558$  on an understanding signaling itself.
- NOTE Confidence: 0.796327888965607
- $01:07:40.560 \longrightarrow 01:07:42.032$  Response to the rapeutic have
- NOTE Confidence: 0.796327888965607
- $01{:}07{:}42.032 \dashrightarrow 01{:}07{:}43.136$  course therefore resistance,
- NOTE Confidence: 0.796327888965607
- $01{:}07{:}43.140 \dashrightarrow 01{:}07{:}47.028$  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
- $01{:}07{:}49{.}352 \dashrightarrow 01{:}07{:}52{.}730$  to stress this one is just the I guess
- NOTE Confidence: 0.796327888965607
- $01{:}07{:}52{.}730 \dashrightarrow 01{:}07{:}54{.}246$  fingerprinting approach that one
- NOTE Confidence: 0.796327888965607
- $01{:}07{:}54.246 \dashrightarrow 01{:}07{:}56.640$  often sees with pretty and say what
- NOTE Confidence: 0.796327888965607
- $01:07:56.640 \rightarrow 01:07:58.650$  proteins are there in the snapshot?
- NOTE Confidence: 0.796327888965607

 $01{:}07{:}58.650 \dashrightarrow 01{:}08{:}00.195$  What metabolites are there in

NOTE Confidence: 0.796327888965607

 $01:08:00.195 \rightarrow 01:08:02.300$  Tableau makes sense in the snapshot.

NOTE Confidence: 0.796327888965607

 $01:08:02.300 \longrightarrow 01:08:04.564$  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

 $01{:}08{:}14.250 \dashrightarrow 01{:}08{:}16.786$  What gives us a picture of the networks

NOTE Confidence: 0.796327888965607

 $01{:}08{:}16.786 \dashrightarrow 01{:}08{:}19.329$  that we're trying to correct and corral.

NOTE Confidence: 0.796327888965607

 $01:08:19.330 \longrightarrow 01:08:21.885$  When we're targeting them in with all NOTE Confidence: 0.796327888965607

 $01{:}08{:}21.885 \dashrightarrow 01{:}08{:}23.880$  of the rapeutics that that we discuss

NOTE Confidence: 0.796327888965607

 $01{:}08{:}23{.}880 \dashrightarrow 01{:}08{:}26{.}440$  it and I just point out that there's a

NOTE Confidence: 0.796327888965607

 $01{:}08{:}26{.}440 \dashrightarrow 01{:}08{:}28{.}934$  quite a lot of activity on this at Yale,

NOTE Confidence: 0.796327888965607

 $01{:}08{:}28{.}934 \dashrightarrow 01{:}08{:}30{.}578$  and one of the people recruited

NOTE Confidence: 0.796327888965607

 $01{:}08{:}30{.}578 \dashrightarrow 01{:}08{:}32{.}390$  into the Cancer Biology Institute,

NOTE Confidence: 0.796327888965607

01:08:32.390 --> 01:08:34.256 for example, is yeah, Shane Lou,

01:08:34.260 --> 01:08:37.370 who has been doing a lot of work looking at,

NOTE Confidence: 0.796327888965607

 $01:08:37.370 \longrightarrow 01:08:38.158$  for example.

NOTE Confidence: 0.796327888965607

01:08:38.158 --> 01:08:38.946 Proteomic Lee,

NOTE Confidence: 0.796327888965607

 $01:08:38.946 \rightarrow 01:08:40.916$  both snapshots and time evolution

NOTE Confidence: 0.796327888965607

 $01:08:40.916 \longrightarrow 01:08:42.419$  of protein contents.

NOTE Confidence: 0.796327888965607

 $01:08:42.420 \longrightarrow 01:08:44.310$  It is considered an employee,

NOTE Confidence: 0.796327888965607

 $01{:}08{:}44{.}310 \dashrightarrow 01{:}08{:}46{.}949$  and you know it's kind of interesting

NOTE Confidence: 0.796327888965607

 $01:08:46.949 \longrightarrow 01:08:47.703$  you really.

NOTE Confidence: 0.796327888965607

 $01:08:47.710 \longrightarrow 01:08:49.978$  If you look at any point,

NOTE Confidence: 0.796327888965607

 $01{:}08{:}49{.}980 \dashrightarrow 01{:}08{:}52{.}332$  sells the effects on the protein

NOTE Confidence: 0.796327888965607

 $01:08:52.332 \longrightarrow 01:08:55.151$  were really not what you would have

NOTE Confidence: 0.796327888965607

 $01{:}08{:}55{.}151 \dashrightarrow 01{:}08{:}57{.}895$  predicted based on on what you've lost

NOTE Confidence: 0.796327888965607

 $01:08:57.970 \longrightarrow 01:09:00.554$  in terms of of gene copies or gain.

NOTE Confidence: 0.796327888965607

 $01{:}09{:}00.560 \dashrightarrow 01{:}09{:}01.262$  And Moreover,

NOTE Confidence: 0.796327888965607

 $01:09:01.262 \longrightarrow 01:09:03.017$  it's important to note that

 $01:09:03.017 \longrightarrow 01:09:04.720$  reaction is really pioneered.

NOTE Confidence: 0.796327888965607

 $01:09:04.720 \longrightarrow 01:09:07.088$  This too that RNA seek data and proteomic

NOTE Confidence: 0.796327888965607

 $01:09:07.088 \longrightarrow 01:09:09.259$  data have substantial discrepancies,

NOTE Confidence: 0.796327888965607

 $01:09:09.260 \longrightarrow 01:09:11.927$  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

 $01{:}09{:}13.070 \dashrightarrow 01{:}09{:}15.300$  Is really an important thing

NOTE Confidence: 0.796327888965607

 $01:09:15.300 \longrightarrow 01:09:18.619$  to add to all of this code.

NOTE Confidence: 0.796327888965607

01:09:18.620 --> 01:09:18.970 Yes,

NOTE Confidence: 0.823916912078857

 $01{:}09{:}18{.}970 \dashrightarrow 01{:}09{:}22{.}075$  so stay think I would like just to comment

NOTE Confidence: 0.823916912078857

 $01{:}09{:}22.075 \dashrightarrow 01{:}09{:}24.145$  about the frustration of analyzing tissue

NOTE Confidence: 0.823916912078857

 $01{:}09{:}24.145 \dashrightarrow 01{:}09{:}25.870$  level data without spatial resolution.

NOTE Confidence: 0.823916912078857

 $01:09:25.870 \rightarrow 01:09:28.630$  This is critical because as a smart pointed,

NOTE Confidence: 0.823916912078857

 $01:09:28.630 \rightarrow 01:09:30.718$  we see a striking difference between

NOTE Confidence: 0.823916912078857

 $01{:}09{:}30{.}718 \dashrightarrow 01{:}09{:}32{.}843$  our name protein which is becoming

NOTE Confidence: 0.823916912078857

 $01{:}09{:}32.843 \dashrightarrow 01{:}09{:}34.835$  the rule more than the exception.

NOTE Confidence: 0.823916912078857

 $01:09:34.840 \rightarrow 01:09:36.820$  But second, the protein measurements and

- NOTE Confidence: 0.823916912078857
- $01:09:36.820 \rightarrow 01:09:39.319$  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
- $01:09:45.880 \longrightarrow 01:09:47.950$  if it's in the tumor cell,
- NOTE Confidence: 0.823916912078857
- $01:09:47.950 \longrightarrow 01:09:49.690$  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
- $01:09:51.220 \longrightarrow 01:09:53.097$  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
- $01:09:54.240 \rightarrow 01:09:56.284$  so really I think having the possibility
- NOTE Confidence: 0.823916912078857
- $01:09:56.284 \longrightarrow 01:09:58.776$  of looking at the proteins in the in
- NOTE Confidence: 0.823916912078857
- $01{:}09{:}58.776 \dashrightarrow 01{:}10{:}00.348$  the context of tissue organization,
- NOTE Confidence: 0.823916912078857
- $01:10:00.348 \longrightarrow 01:10:01.616$  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
- $01{:}10{:}02{.}420 \dashrightarrow 01{:}10{:}04{.}814$  and I think that's a little bit when I
- NOTE Confidence: 0.823916912078857

- $01:10:04.814 \rightarrow 01:10:06.959$  tried to reflect in my presentation,
- NOTE Confidence: 0.823916912078857
- $01:10:06.960 \longrightarrow 01:10:07.869$  we're still early.
- NOTE Confidence: 0.823916912078857
- $01:10:07.869 \rightarrow 01:10:09.081$  We're getting more quantitative
- NOTE Confidence: 0.823916912078857
- $01:10:09.081 \longrightarrow 01:10:09.687$  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
- $01:10:13.020 \longrightarrow 01:10:14.232$  It's an important dimension
- NOTE Confidence: 0.823916912078857
- $01:10:14.232 \longrightarrow 01:10:15.747$  of the protein and any
- NOTE Confidence: 0.842197835445404
- $01{:}10{:}15.750 \dashrightarrow 01{:}10{:}17.260$  other light data. Absolutely perfect
- NOTE Confidence: 0.842197835445404
- $01{:}10{:}17{.}260 \dashrightarrow 01{:}10{:}19{.}692$  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
- $01:10:28.810 \rightarrow 01:10:30.200$  When we asked us why,
- NOTE Confidence: 0.855397522449493
- $01:10:30.200 \rightarrow 01:10:32.062$  we know that just doing the genome

 $01:10:32.062 \rightarrow 01:10:34.089$  sequencing is not going to be sufficient.

NOTE Confidence: 0.855397522449493

 $01:10:34.090 \longrightarrow 01:10:35.650$  We can start with the gene

NOTE Confidence: 0.855397522449493

 $01:10:35.650 \rightarrow 01:10:36.690$  expression analysis because there

NOTE Confidence: 0.855397522449493

 $01:10:36.733 \rightarrow 01:10:37.989$  are these epigenetic changes,

NOTE Confidence: 0.855397522449493

 $01:10:37.990 \longrightarrow 01:10:39.380$  but it's very clear that

NOTE Confidence: 0.855397522449493

 $01:10:39.380 \longrightarrow 01:10:40.770$  that's also in not sufficient.

NOTE Confidence: 0.855397522449493

 $01:10:40.770 \longrightarrow 01:10:42.842$  And one thing I just wanted to point

NOTE Confidence: 0.855397522449493

 $01:10:42.842 \rightarrow 01:10:44.939$  out is that as a cell biologist,

NOTE Confidence: 0.855397522449493

 $01:10:44.940 \longrightarrow 01:10:46.488$  I think we we know understand

NOTE Confidence: 0.855397522449493

 $01:10:46.488 \longrightarrow 01:10:47.990$  really well that for example,

NOTE Confidence: 0.855397522449493

 $01:10:47.990 \longrightarrow 01:10:49.102$  translational capacity is something

NOTE Confidence: 0.855397522449493

 $01{:}10{:}49{.}102 \dashrightarrow 01{:}10{:}50{.}492$  that's highly affected by stress,

NOTE Confidence: 0.855397522449493

 $01:10:50.500 \rightarrow 01:10:52.316$  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

 $01{:}10{:}54.390 \dashrightarrow 01{:}10{:}56.058$  how that might be affecting the.

01:10:56.060 --> 01:10:57.288 Relative efficiencies of translation,

NOTE Confidence: 0.855397522449493

 $01:10:57.288 \rightarrow 01:10:58.823$  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

 $01:11:00.190 \rightarrow 01:11:01.738$  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

 $01:11:02.511 \rightarrow 01:11:04.060$  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

 $01{:}11{:}05{.}880 \dashrightarrow 01{:}11{:}07{.}491$  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

 $01:11:09.220 \rightarrow 01:11:10.768$  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 $\operatorname{-->}$ 01:11:13.280 And so these are all the factors that are

NOTE Confidence: 0.855397522449493

 $01:11:13.335 \rightarrow 01:11:15.344$  that are contributing to what we might

NOTE Confidence: 0.855397522449493

 $01{:}11{:}15{.}344 \dashrightarrow 01{:}11{:}17{.}466$  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

 $01:11:19.018 \longrightarrow 01:11:20.050$  the same point about,

- NOTE Confidence: 0.855397522449493
- 01:11:20.050 --> 01:11:20.824 you know, an euploidy,
- NOTE Confidence: 0.855397522449493
- 01:11:20.824 --> 01:11:21.598 because you know,
- NOTE Confidence: 0.855397522449493
- $01:11:21.600 \longrightarrow 01:11:22.108$  we know,
- NOTE Confidence: 0.855397522449493
- $01{:}11{:}22.108 \dashrightarrow 01{:}11{:}23.378$  and this is particularly relevant
- NOTE Confidence: 0.855397522449493
- $01{:}11{:}23.378 \dashrightarrow 01{:}11{:}25.187$  also for DNA repair factors that one
- NOTE Confidence: 0.855397522449493
- $01{:}11{:}25{.}187 \dashrightarrow 01{:}11{:}27{.}013$  of the ideas of why an euploidy causes
- NOTE Confidence: 0.855397522449493
- $01:11:27.013 \rightarrow 01:11:28.675$  such changes in the proteomes that.
- NOTE Confidence: 0.855397522449493
- $01:11:28.680 \longrightarrow 01:11:30.310$  We have these large protein
- NOTE Confidence: 0.855397522449493
- $01:11:30.310 \longrightarrow 01:11:31.940$  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
- $01:11:33.851 \rightarrow 01:11:35.209$  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
- $01:11:36.740 \longrightarrow 01:11:38.522 \text{ most of us are working on}$
- NOTE Confidence: 0.855397522449493
- $01:11:38.522 \rightarrow 01:11:39.710$  complex molecular machines where
- NOTE Confidence: 0.855397522449493
- $01:11:39.762 \longrightarrow 01:11:41.346$  that's going to have an impact,
- NOTE Confidence: 0.855397522449493

 $01:11:41.350 \longrightarrow 01:11:42.790$  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

 $01:11:43.660 \rightarrow 01:11:45.100$  the kind of mechanistic analysis.

NOTE Confidence: 0.855397522449493

 $01:11:45.100 \rightarrow 01:11:46.934$  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

 $01:11:49.067 \rightarrow 01:11:51.100$  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

 $01{:}11{:}53{.}160 \dashrightarrow 01{:}11{:}54{.}600$  the genomics. Thanks great Katie.

NOTE Confidence: 0.879784941673279

 $01:11:55.150 \rightarrow 01:11:58.426$  Yes, so I just wanted to add to the NOTE Confidence: 0.879784941673279

 $01{:}11{:}58{.}426 \dashrightarrow 01{:}12{:}00{.}635$  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

 $01{:}12{:}02.835 \dashrightarrow 01{:}12{:}05.640$  in in patient specimens directly,

NOTE Confidence: 0.879784941673279

 $01:12:05.640 \longrightarrow 01:12:08.082$  all of the things that were

NOTE Confidence: 0.879784941673279

 $01:12:08.082 \rightarrow 01:12:10.450$  brought up the patient arrived.

NOTE Confidence: 0.879784941673279

 $01:12:10.450 \rightarrow 01:12:12.420$  Models actually represent a really

NOTE Confidence: 0.879784941673279

 $01:12:12.420 \longrightarrow 01:12:15.435$  useful system to look at signaling and

 $01:12:15.435 \rightarrow 01:12:17.870$  how signaling changes with treatment.

NOTE Confidence: 0.879784941673279

 $01:12:17.870 \longrightarrow 01:12:20.677$  And it's one of the reasons for

NOTE Confidence: 0.879784941673279

 $01:12:20.677 \longrightarrow 01:12:23.988$  which we did engage in this effort.

NOTE Confidence: 0.879784941673279

 $01:12:23.990 \rightarrow 01:12:26.636$  In developing these models and also.

NOTE Confidence: 0.879784941673279

 $01{:}12{:}26.640 \dashrightarrow 01{:}12{:}28.932$  Allows us to really explore how

NOTE Confidence: 0.879784941673279

 $01:12:28.932 \rightarrow 01:12:30.460$  heterogeneous these samples are

NOTE Confidence: 0.879784941673279

 $01{:}12{:}30{.}522 \dashrightarrow 01{:}12{:}32{.}277$  across different patient tumors so

NOTE Confidence: 0.879784941673279

 $01:12:32.277 \rightarrow 01:12:34.815$  we can take tumors with a specific

NOTE Confidence: 0.879784941673279

 $01:12:34.815 \longrightarrow 01:12:36.600$  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

 $01:12:38.466 \longrightarrow 01:12:41.217$  and we can look at specific things

NOTE Confidence: 0.879784941673279

 $01:12:41.217 \longrightarrow 01:12:43.611$  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

 $01:12:46.486 \longrightarrow 01:12:47.620$  apply other the rapies,

NOTE Confidence: 0.879784941673279

 $01:12:47.620 \longrightarrow 01:12:49.816$  what changes and so that really,

- 01:12:49.820 --> 01:12:50.432 I think,
- NOTE Confidence: 0.879784941673279
- $01:12:50.432 \longrightarrow 01:12:52.268$  is a very valuable system in
- NOTE Confidence: 0.879784941673279
- $01:12:52.268 \rightarrow 01:12:54.669$  which to study what's happening at
- NOTE Confidence: 0.879784941673279
- $01:12:54.669 \rightarrow 01:12:56.814$  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 different
- NOTE Confidence: 0.802920758724213
- $01{:}13{:}03{.}743 \dashrightarrow 01{:}13{:}06{.}153$  omics are approached from within
- NOTE Confidence: 0.802920758724213
- $01:13:06.153 \rightarrow 01:13:09.476$  an organization like yours and and
- NOTE Confidence: 0.802920758724213
- $01{:}13{:}09{.}476 \dashrightarrow 01{:}13{:}12{.}226$  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
- $01:13:20.326 \longrightarrow 01:13:22.369$  comments that have been made.
- NOTE Confidence: 0.838525116443634
- $01:13:22.370 \longrightarrow 01:13:24.834$  First of all that we do need to
- NOTE Confidence: 0.838525116443634
- $01:13:24.834 \rightarrow 01:13:26.879$  look at these different mechanisms
- NOTE Confidence: 0.838525116443634
- $01:13:26.879 \rightarrow 01:13:30.029$  and it is possible to do that.

01:13:30.030 --> 01:13:32.052 Increasingly, you know where we are

NOTE Confidence: 0.838525116443634

 $01{:}13{:}32.052 \dashrightarrow 01{:}13{:}33.888$  looking with things like Multiplex

NOTE Confidence: 0.838525116443634

 $01:13:33.888 \longrightarrow 01:13:35.576$  immediate fluorescence at the

NOTE Confidence: 0.838525116443634

 $01:13:35.576 \rightarrow 01:13:37.686$  spatial organization of the tumors,

NOTE Confidence: 0.838525116443634

 $01:13:37.690 \rightarrow 01:13:41.128$  and in doing that in in patient samples now.

NOTE Confidence: 0.838525116443634

 $01{:}13{:}41{.}130 \dashrightarrow 01{:}13{:}44{.}146$  So I think the technologies are advancing to

NOTE Confidence: 0.838525116443634

 $01:13:44.146 \rightarrow 01:13:47.309$  enable you to do that single cell sequencing.

NOTE Confidence: 0.838525116443634

 $01:13:47.310 \longrightarrow 01:13:48.222$  Is also helping.

NOTE Confidence: 0.838525116443634

 $01:13:48.222 \rightarrow 01:13:51.667$  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

 $01:13:54.330 \longrightarrow 01:13:56.430$  so you have to choose the trial

NOTE Confidence: 0.838525116443634

 $01{:}13{:}56{.}430 \dashrightarrow 01{:}13{:}58{.}478$  setting and the context for that.

NOTE Confidence: 0.838525116443634

 $01{:}13{:}58{.}480 \dashrightarrow 01{:}14{:}00{.}622$  And it does have to be complemented

NOTE Confidence: 0.838525116443634

 $01{:}14{:}00{.}622 \dashrightarrow 01{:}14{:}02{.}584$  by the kinds of things that

NOTE Confidence: 0.838525116443634

 $01:14:02.584 \rightarrow 01:14:04.540$  Katie was talked about as well,

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

 $01:14:09.202 \rightarrow 01:14:11.036$  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

 $01:14:12.496 \longrightarrow 01:14:14.429$  need to understand the mechanism,

NOTE Confidence: 0.838525116443634

 $01{:}14{:}14{.}430 \dashrightarrow 01{:}14{:}16{.}368$  and for that you need a

NOTE Confidence: 0.838525116443634

 $01:14:16.368 \longrightarrow 01:14:17.337$  different setting and.

NOTE Confidence: 0.838525116443634

 $01:14:17.340 \longrightarrow 01:14:19.548$  Environment to do that in the

NOTE Confidence: 0.838525116443634

 $01{:}14{:}19{.}548 \dashrightarrow 01{:}14{:}21{.}379$  different techniques and then you

NOTE Confidence: 0.838525116443634

 $01:14:21.379 \rightarrow 01:14:23.388$  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

 $01{:}14{:}25{.}503 \dashrightarrow 01{:}14{:}27{.}711$  have their own set of challenges.

NOTE Confidence: 0.838525116443634

 $01{:}14{:}27.720 \dashrightarrow 01{:}14{:}29.796$  The humanized models for IO have

NOTE Confidence: 0.838525116443634

 $01{:}14{:}29.796 \dashrightarrow 01{:}14{:}32.212$  their own set of challenges and I

NOTE Confidence: 0.838525116443634

 $01:14:32.212 \longrightarrow 01:14:34.876$  think what we can try and do is

NOTE Confidence: 0.838525116443634

 $01:14:34.876 \longrightarrow 01:14:37.054$  by looking collectively at at at,

 $01:14:37.060 \longrightarrow 01:14:39.090$  you know the clinical sample data and

NOTE Confidence: 0.838525116443634

 $01:14:39.090 \longrightarrow 01:14:41.221$  these range of preclinical models and

NOTE Confidence: 0.838525116443634

 $01{:}14{:}41{.}221 \dashrightarrow 01{:}14{:}43{.}633$  backwards and forwards across that divide,

NOTE Confidence: 0.838525116443634

 $01:14:43.640 \rightarrow 01:14:45.782$  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

 $01:14:48.870 \longrightarrow 01:14:51.694$  I think it's like it is like trying to

NOTE Confidence: 0.838525116443634

 $01:14:51.694 \rightarrow 01:14:54.381$  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

 $01:14:57.018 \rightarrow 01:14:58.080$  which is great,

NOTE Confidence: 0.838525116443634

01:14:58.080 --> 01:14:59.396 but you know nothing,

NOTE Confidence: 0.838525116443634

 $01:14:59.396 \rightarrow 01:15:01.041$  that holistic view is absolutely

NOTE Confidence: 0.838525116443634

 $01:15:01.041 \dashrightarrow 01:15:02.320$  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

 $01:15:07.135 \rightarrow 01:15:10.031$  advances are now in place to enable

NOTE Confidence: 0.838525116443634

 $01:15:10.031 \longrightarrow 01:15:12.615$  us to see so much more than we

NOTE Confidence: 0.838525116443634

 $01:15:12.615 \rightarrow 01:15:15.070$  were able to see 510 years ago.

NOTE Confidence: 0.838525116443634

 $01:15:15.070 \rightarrow 01:15:17.188$  We need to bring that together,

NOTE Confidence: 0.838525116443634

01:15:17.190 $\operatorname{-->}$ 01:15:18.960 but have an integrated plan

NOTE Confidence: 0.838525116443634

 $01{:}15{:}18.960 \dashrightarrow 01{:}15{:}20.376$  that goes across preclinical.

NOTE Confidence: 0.838525116443634

 $01{:}15{:}20{.}380 \dashrightarrow 01{:}15{:}22{.}480$  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

 $01{:}15{:}24.580 \dashrightarrow 01{:}15{:}27.037$  so we spend a lot of time in what

NOTE Confidence: 0.838525116443634

 $01:15:27.037 \rightarrow 01:15:29.632$  is called early stage oncology

NOTE Confidence: 0.838525116443634

 $01{:}15{:}29{.}632 \dashrightarrow 01{:}15{:}31{.}876$  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

 $01:15:34.308 \longrightarrow 01:15:37.171$  and programs that are in late phase

NOTE Confidence: 0.838525116443634

 $01{:}15{:}37{.}180 \dashrightarrow 01{:}15{:}39{.}285$  development already on the market

NOTE Confidence: 0.838525116443634

 $01{:}15{:}39{.}285 \dashrightarrow 01{:}15{:}41{.}800$  like a we some Internet and you know.

NOTE Confidence: 0.838525116443634

 $01:15:41.800 \longrightarrow 01:15:42.952$  And if I'm out.

 $01:15:42.952 \longrightarrow 01:15:45.074$  The other drugs that we have there

NOTE Confidence: 0.838525116443634

 $01:15:45.074 \longrightarrow 01:15:47.000$  because the two reasons one is

NOTE Confidence: 0.838525116443634

 $01:15:47.000 \longrightarrow 01:15:48.912$  that I think that's absolutely

NOTE Confidence: 0.838525116443634

 $01:15:48.912 \longrightarrow 01:15:51.107$  critical to understanding how to

NOTE Confidence: 0.838525116443634

 $01:15:51.107 \rightarrow 01:15:53.393$  develop those in and continue that.

NOTE Confidence: 0.838525116443634

 $01:15:53.393 \rightarrow 01:15:54.677$  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

 $01:15:56.440 \rightarrow 01:15:57.940$  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

 $01:16:03.790 \longrightarrow 01:16:04.819$  Collaborations with organizations

NOTE Confidence: 0.838525116443634

 $01{:}16{:}04{.}819 \dashrightarrow 01{:}16{:}06{.}534$  like Yale is absolutely critical.

NOTE Confidence: 0.838525116443634

 $01{:}16{:}06{.}540 \dashrightarrow 01{:}16{:}08{.}864$  You've already heard a number of examples

NOTE Confidence: 0.838525116443634

01:16:08.864 $\operatorname{-->}$ 01:16:11.018 of the kinds of collaborations that

NOTE Confidence: 0.838525116443634

 $01{:}16{:}11.018 \dashrightarrow 01{:}16{:}13.810$  that that we have that really helped to.

 $01:16:13.810 \longrightarrow 01:16:15.080$  And to feed and stimulate

NOTE Confidence: 0.838525116443634

 $01:16:15.080 \rightarrow 01:16:16.350$  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

 $01:16:18.090 \rightarrow 01:16:19.800$  appreciate the work that Megan,

NOTE Confidence: 0.772767424583435

 $01:16:19.800 \longrightarrow 01:16:21.669$  a team of doing that Katie Ability

NOTE Confidence: 0.772767424583435

 $01{:}16{:}21.669 \dashrightarrow 01{:}16{:}23.557$  and her team are doing because

NOTE Confidence: 0.772767424583435

 $01:16:23.557 \longrightarrow 01:16:25.603$  that that sees what we're doing

NOTE Confidence: 0.772767424583435

 $01{:}16{:}25{.}603 \dashrightarrow 01{:}16{:}27{.}486$  internally and we can't do all of it.

NOTE Confidence: 0.840360403060913

 $01{:}16{:}28.580 \dashrightarrow 01{:}16{:}30.746$  Great good, there's a question here

NOTE Confidence: 0.840360403060913

 $01{:}16{:}30.746 \dashrightarrow 01{:}16{:}33.090$  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

 $01:16:35.160 \rightarrow 01:16:38.390$  that we may have for precision medicine

NOTE Confidence: 0.840360403060913

 $01:16:38.390 \longrightarrow 01:16:40.310$  efforts and adaptive combination

NOTE Confidence: 0.840360403060913

 $01:16:40.310 \rightarrow 01:16:42.527$  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

 $01{:}16{:}45{.}538 \dashrightarrow 01{:}16{:}48{.}040$  little bit from the medicine side.

- NOTE Confidence: 0.840360403060913
- $01:16:48.040 \rightarrow 01:16:50.610$  Pet Larusso here leads experimental
- NOTE Confidence: 0.840360403060913
- $01:16:50.610 \longrightarrow 01:16:52.152$  the rapeutics clinical trials
- NOTE Confidence: 0.840360403060913
- $01{:}16{:}52{.}152 \dashrightarrow 01{:}16{:}54{.}510$  network U M1 grant that has.
- NOTE Confidence: 0.840360403060913
- $01{:}16{:}54{.}510 \dashrightarrow 01{:}16{:}57{.}762$  Many consortium members and she and
- NOTE Confidence: 0.840360403060913
- $01:16:57.762 \rightarrow 01:17:01.455$  her colleagues are leaders in taking
- NOTE Confidence: 0.840360403060913
- $01{:}17{:}01{.}455 \dashrightarrow 01{:}17{:}04{.}323$  molecularly driven questions and
- NOTE Confidence: 0.840360403060913
- $01:17:04.323 \longrightarrow 01:17:07.191$  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
- $01:17:15.370 \longrightarrow 01:17:19.150$  Lamps that did the precision medicine
- NOTE Confidence: 0.840360403060913
- $01:17:19.150 \longrightarrow 01:17:22.390$  sequencing for the match trial.
- NOTE Confidence: 0.840360403060913
- $01:17:22.390 \longrightarrow 01:17:24.942$  We have investigators here
- NOTE Confidence: 0.840360403060913
- $01:17:24.942 \longrightarrow 01:17:27.494$  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
- $01{:}17{:}30.870 \dashrightarrow 01{:}17{:}32.774$  collaborations across other cancer
- NOTE Confidence: 0.840360403060913

 $01:17:32.774 \longrightarrow 01:17:34.678$  centers that are molecularly

NOTE Confidence: 0.840360403060913

 $01{:}17{:}34.678 \dashrightarrow 01{:}17{:}36.659$  driven clinical trial questions.

NOTE Confidence: 0.840360403060913

 $01{:}17{:}36.660 \dashrightarrow 01{:}17{:}40.988$  So I think from the disease based and

NOTE Confidence: 0.840360403060913

 $01{:}17{:}40.988 \dashrightarrow 01{:}17{:}44.051$ clinical arena Ann from the Phase

NOTE Confidence: 0.840360403060913

 $01:17:44.051 \rightarrow 01:17:47.490$  one arena there is quite a rich.

NOTE Confidence: 0.840360403060913

 $01:17:47.490 \rightarrow 01:17:50.610$  A network of these types of interactions,

NOTE Confidence: 0.840360403060913

01:17:50.610 --> 01:17:53.368 I don't know if any<br/>body wants to

NOTE Confidence: 0.840360403060913

 $01{:}17{:}53.368 \dashrightarrow 01{:}17{:}55.889$  address more from the preclinical.

NOTE Confidence: 0.840360403060913

 $01{:}17{:}55.890 \dashrightarrow 01{:}17{:}56.530$  Level.

NOTE Confidence: 0.786874294281006

 $01{:}17{:}59{.}390 \dashrightarrow 01{:}18{:}02{.}042$  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

 $01{:}18{:}03.636 \dashrightarrow 01{:}18{:}05.126$  that I mentioned at work.

NOTE Confidence: 0.786874294281006

 $01:18:05.130 \longrightarrow 01:18:07.140$  That's all guns are long term

NOTE Confidence: 0.786874294281006

 $01{:}18{:}07{.}140 \dashrightarrow 01{:}18{:}08{.}892$  collaboration with people at Children's

NOTE Confidence: 0.786874294281006

 $01:18:08.892 \rightarrow 01:18:10.974$  Hospital in Philadelphia and a new

NOTE Confidence: 0.786874294281006

 $01:18:10.974 \rightarrow 01:18:13.232$  pen where much of the computational

 $01:18:13.232 \rightarrow 01:18:15.542$  modeling is done actually through that.

NOTE Confidence: 0.786874294281006

 $01:18:15.550 \rightarrow 01:18:17.400$  And then another approach that

NOTE Confidence: 0.786874294281006

 $01:18:17.400 \rightarrow 01:18:19.490$  another aspect that we're working on,

NOTE Confidence: 0.786874294281006

 $01:18:19.490 \longrightarrow 01:18:22.370$  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

 $01:18:24.884 \rightarrow 01:18:27.479$  actually in the US and abroad,

NOTE Confidence: 0.786874294281006

 $01{:}18{:}27{.}480 \dashrightarrow 01{:}18{:}29{.}508$  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

 $01:18:32.517 \rightarrow 01:18:35.147$  approach to targeting Myc signaling.

NOTE Confidence: 0.786874294281006

 $01:18:35.150 \rightarrow 01:18:37.388$  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

 $01{:}18{:}39{.}937 \dashrightarrow 01{:}18{:}42{.}387$  combination the rapies and so forth,

NOTE Confidence: 0.786874294281006

 $01{:}18{:}42{.}390 \dashrightarrow 01{:}18{:}44{.}976$  the idea being that multigroup approach.

NOTE Confidence: 0.786874294281006

 $01{:}18{:}44{.}980 \dashrightarrow 01{:}18{:}47{.}647$  With the idea that that make aberrations,

NOTE Confidence: 0.786874294281006

 $01{:}18{:}47.650 \dashrightarrow 01{:}18{:}48.799$  particularly making neuroblastoma

- 01:18:48.799 --> 01:18:49.948 affect the network,
- NOTE Confidence: 0.786874294281006
- $01:18:49.950 \rightarrow 01:18:52.344$  and in principle one could rescue the
- NOTE Confidence: 0.786874294281006
- $01:18:52.344 \rightarrow 01:18:54.150$  network with appropriate combinations,
- NOTE Confidence: 0.786874294281006
- $01:18:54.150 \rightarrow 01:18:56.436$  and I think with the technologies,
- NOTE Confidence: 0.786874294281006
- $01{:}18{:}56{.}440 \dashrightarrow 01{:}18{:}57{.}968$  as Susan pointed out,
- NOTE Confidence: 0.786874294281006
- $01:18:57.968 \longrightarrow 01:18:58.350$  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
- $01:19:04.300 \longrightarrow 01:19:06.370$  in that type of way.
- NOTE Confidence: 0.819485902786255
- $01:19:09.450 \rightarrow 01:19:10.866$  Anybody else wanna OK?
- NOTE Confidence: 0.819485902786255
- $01:19:10.866 \longrightarrow 01:19:12.990$  There's a question here in the
- NOTE Confidence: 0.819485902786255
- $01:19:13.062 \rightarrow 01:19:15.270$  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
- $01:19:17.115 \longrightarrow 01:19:18.960$  most excited about in terms
- NOTE Confidence: 0.819485902786255
- $01:19:19.025 \longrightarrow 01:19:20.678$  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
- $01:19:28.300 \longrightarrow 01:19:30.604$  But I think everybody probably has
- NOTE Confidence: 0.819485902786255
- $01{:}19{:}30.604 \dashrightarrow 01{:}19{:}32.440$  their own favorite combination too,
- NOTE Confidence: 0.819485902786255
- $01:19:32.440 \longrightarrow 01:19:33.559$  and you just
- NOTE Confidence: 0.773967266082764
- $01:19:33.560 \longrightarrow 01:19:36.192$  want to, yeah, so of course I
- NOTE Confidence: 0.773967266082764
- $01{:}19{:}36{.}192 \dashrightarrow 01{:}19{:}38{.}452$  think because I work samples next,
- NOTE Confidence: 0.773967266082764
- $01:19:38.452 \longrightarrow 01:19:40.708$  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
- $01:19:41.910 \longrightarrow 01:19:43.119$  critical for that
- NOTE Confidence: 0.757354021072388
- $01:19:43.120 \longrightarrow 01:19:45.140$  and not only the case.
- NOTE Confidence: 0.757354021072388
- $01:19:45.140 \longrightarrow 01:19:47.972$  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
- $01{:}19{:}51{.}330 \dashrightarrow 01{:}19{:}53{.}954$  synergistic effect that you're going to
- NOTE Confidence: 0.757354021072388
- $01{:}19{:}53.954 \dashrightarrow 01{:}19{:}56.444$  check my blanket in multiple models.
- NOTE Confidence: 0.757354021072388
- $01{:}19{:}56{.}450 \dashrightarrow 01{:}19{:}59{.}278$  I only showed one in breast cancer.
- NOTE Confidence: 0.757354021072388
$01:19:59.280 \longrightarrow 01:20:02.238$  Will also see that as well.

NOTE Confidence: 0.757354021072388

 $01{:}20{:}02.240 \dashrightarrow 01{:}20{:}04.082$  In addition, an and there's other

NOTE Confidence: 0.757354021072388

 $01{:}20{:}04.082 \dashrightarrow 01{:}20{:}06.141$  modalities that you can actually modulate

NOTE Confidence: 0.757354021072388

 $01:20:06.141 \rightarrow 01:20:08.066$  the tumor micro environment and,

NOTE Confidence: 0.757354021072388

 $01{:}20{:}08.070 \dashrightarrow 01{:}20{:}10.134$  for example, someone that can recognize

NOTE Confidence: 0.757354021072388

 $01:20:10.134 \rightarrow 01:20:12.528$  this as we are working on one,

NOTE Confidence: 0.757354021072388

 $01{:}20{:}12{.}530 \dashrightarrow 01{:}20{:}14{.}588$  then it's called the CCR two,

NOTE Confidence: 0.757354021072388

 $01:20:14.590 \rightarrow 01:20:17.246$  we can by inhibiting that we can change

NOTE Confidence: 0.757354021072388

 $01:20:17.246 \rightarrow 01:20:19.387$  the macrophage population and by that,

NOTE Confidence: 0.757354021072388

 $01:20:19.390 \longrightarrow 01:20:21.448$  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

 $01{:}20{:}24.800 \dashrightarrow 01{:}20{:}26.546$  the whole tumor micro environment

NOTE Confidence: 0.757354021072388

 $01:20:26.546 \rightarrow 01:20:28.648$  and make it sensitive for email,

NOTE Confidence: 0.757354021072388

 $01:20:28.650 \longrightarrow 01:20:30.370$  checkpoint blockade and this.

NOTE Confidence: 0.757354021072388

 $01{:}20{:}30{.}370 \dashrightarrow 01{:}20{:}32{.}446$  This works well an intimate asks.

- NOTE Confidence: 0.757354021072388
- $01{:}20{:}32{.}450 \dashrightarrow 01{:}20{:}34{.}598$  Setting so I'm quite excited about
- NOTE Confidence: 0.757354021072388
- $01:20:34.598 \longrightarrow 01:20:37.339$  that and that many of you probably
- NOTE Confidence: 0.757354021072388
- $01{:}20{:}37{.}339 \dashrightarrow 01{:}20{:}39{.}399$  know in other other institutions
- NOTE Confidence: 0.757354021072388
- $01{:}20{:}39{.}399 \dashrightarrow 01{:}20{:}41{.}650$  have studied with DMT inhibitors,
- NOTE Confidence: 0.757354021072388
- 01:20:41.650 --> 01:20:42.450 HVAC inhibitors,
- NOTE Confidence: 0.757354021072388
- $01:20:42.450 \longrightarrow 01:20:44.450$  and is it still inhibitors
- NOTE Confidence: 0.757354021072388
- $01:20:44.450 \longrightarrow 01:20:45.650$  and those actually,
- NOTE Confidence: 0.757354021072388
- $01:20:45.650 \rightarrow 01:20:48.198$  I showed him assuming have showed strong
- NOTE Confidence: 0.757354021072388
- $01{:}20{:}48.198 \dashrightarrow 01{:}20{:}50.450$  efficacy in many different models,
- NOTE Confidence: 0.757354021072388
- $01:20:50.450 \rightarrow 01:20:52.850$  so I'm quite excited about this.
- NOTE Confidence: 0.757354021072388
- $01:20:52.850 \longrightarrow 01:20:54.450$  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
- $01{:}20{:}58{.}202 \dashrightarrow 01{:}21{:}00{.}730$  Anderson and Eli are broken.
- NOTE Confidence: 0.792126417160034
- $01{:}21{:}00.730 \dashrightarrow 01{:}21{:}02.486$  Working on demethylating the rapy
- NOTE Confidence: 0.792126417160034
- 01:21:02.486 --> 01:21:04.242 to uncover immune silencing
- NOTE Confidence: 0.792126417160034

 $01:21:04.242 \rightarrow 01:21:06.339$  and virally associated cancers.

NOTE Confidence: 0.792126417160034

 $01:21:06.340 \longrightarrow 01:21:10.400$  And I think there are a lot of examples.

NOTE Confidence: 0.792126417160034

 $01:21:10.400 \longrightarrow 01:21:12.089$  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

 $01{:}21{:}14.816 \dashrightarrow 01{:}21{:}16.926$  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

 $01:21:18.680 \longrightarrow 01:21:20.270$  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

 $01:21:30.039 \rightarrow 01:21:31.706$  multiple pathways that I think the

NOTE Confidence: 0.845456838607788

 $01{:}21{:}31{.}706 \dashrightarrow 01{:}21{:}34{.}034$  question has to do with where in an

NOTE Confidence: 0.845456838607788

 $01:21:34.034 \rightarrow 01:21:35.342$  immunization pathways dominant and

NOTE Confidence: 0.845456838607788

 $01{:}21{:}35{.}342 \dashrightarrow 01{:}21{:}37{.}134$  where more than one is dominant.

 $01:21:37.134 \longrightarrow 01:21:39.010$  And I think that should drive the

NOTE Confidence: 0.845456838607788

 $01:21:39.070 \longrightarrow 01:21:40.950$  combination not think the opposite.

NOTE Confidence: 0.845456838607788

 $01{:}21{:}40.950 \dashrightarrow 01{:}21{:}43.456$  Wait and think that one combination will

NOTE Confidence: 0.845456838607788

 $01:21:43.456 \rightarrow 01:21:45.820$  fix tumors with different problems.

NOTE Confidence: 0.88378977755737

01:21:46.750 --> 01:21:49.102 Yeah, so I think it's very interesting

NOTE Confidence: 0.88378977755737

 $01{:}21{:}49{.}102 \dashrightarrow 01{:}21{:}51{.}881$  that you heard that question as an

NOTE Confidence: 0.883789777755737

 $01:21:51.881 \rightarrow 01:21:53.912$  immune resistance question. It was.

NOTE Confidence: 0.883789777755737

 $01:21:53.912 \rightarrow 01:21:56.544$  It was a very broad resistance question,

NOTE Confidence: 0.88378977755737

 $01:21:56.550 \rightarrow 01:21:58.440$  but that's an interesting perspective.

NOTE Confidence: 0.88378977755737

 $01:21:58.440 \longrightarrow 01:22:00.708$  I think one of the things that

NOTE Confidence: 0.883789777755737

 $01:22:00.708 \longrightarrow 01:22:03.446$  that I think about sometimes is how

NOTE Confidence: 0.88378977755737

 $01{:}22{:}03.446 \dashrightarrow 01{:}22{:}05.978$  some of the same mechanisms that.

NOTE Confidence: 0.88378977755737

 $01:22:05.980 \rightarrow 01:22:08.055$  Have generated resistance to conventional

NOTE Confidence: 0.88378977755737

 $01{:}22{:}08.055 \dashrightarrow 01{:}22{:}10.130$  the rapies are now also generating

NOTE Confidence: 0.883789777755737

 $01{:}22{:}10.193 \dashrightarrow 01{:}22{:}11.633$  resistance to immunotherapy and

 $01:22:11.633 \rightarrow 01:22:13.793$  how you know our relentless focus

NOTE Confidence: 0.88378977755737

01:22:13.851 --> 01:22:15.676 on target instead of environment,

NOTE Confidence: 0.88378977755737

01:22:15.680 --> 01:22:16.841 which you know?

NOTE Confidence: 0.883789777755737

 $01:22:16.841 \rightarrow 01:22:19.163$  I think it's something I've heard.

NOTE Confidence: 0.88378977755737

01:22:19.170 --> 01:22:20.722 You speak about alot.

NOTE Confidence: 0.88378977755737

01:22:20.722 --> 01:22:23.396 Kurt, you know we may have the

NOTE Confidence: 0.88378977755737

 $01:22:23.396 \longrightarrow 01:22:25.776$  same Achilles heel over and over

NOTE Confidence: 0.88378977755737

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: 0.88378977755737

01:22:30.810 --> 01:22:32.362 which leads to resistance

NOTE Confidence: 0.883789777755737

 $01:22:32.362 \longrightarrow 01:22:33.914$  to DNA damaging agents.

NOTE Confidence: 0.88378977755737

 $01{:}22{:}33{.}920 \dashrightarrow 01{:}22{:}36{.}530$  It leads to resistance to.

NOTE Confidence: 0.88378977755737

01:22:36.530 --> 01:22:37.540 Radiation therapy.

NOTE Confidence: 0.88378977755737

01:22:37.540 --> 01:22:38.550 Prime example,

NOTE Confidence: 0.883789777755737

 $01:22:38.550 \rightarrow 01:22:42.490$  but is now increasingly linked to resistance,

NOTE Confidence: 0.88378977755737

01:22:42.490 --> 01:22:43.180 demean<br/>or,

- NOTE Confidence: 0.88378977755737
- $01:22:43.180 \longrightarrow 01:22:45.250$  therapy as well.
- NOTE Confidence: 0.883789777755737
- 01:22:45.250 --> 01:22:45.710 Yeah,
- NOTE Confidence: 0.769990742206573
- $01:22:45.710 \rightarrow 01:22:49.560$  and I say even taking it down to the simplest
- NOTE Confidence: 0.769990742206573
- $01:22:49.653 \rightarrow 01:22:52.581$  level of talking the rapeutics it the
- NOTE Confidence: 0.769990742206573
- $01:22:52.581 \rightarrow 01:22:56.338$  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
- $01:23:02.014 \rightarrow 01:23:05.672$  and others did a nice study that they
- NOTE Confidence: 0.769990742206573
- $01{:}23{:}05{.}672 \dashrightarrow 01{:}23{:}09{.}161$  published it a few years ago of combination
- NOTE Confidence: 0.769990742206573
- $01{:}23{:}09{.}161 \dashrightarrow 01{:}23{:}12{.}486$  combinations of drugs in a variety of
- NOTE Confidence: 0.769990742206573
- $01:23:12.486 \rightarrow 01:23:15.340$  cell lines for Melanoma and elsewhere.
- NOTE Confidence: 0.769990742206573
- $01{:}23{:}15{.}340 \dashrightarrow 01{:}23{:}17{.}728$  And showed that the combination which
- NOTE Confidence: 0.769990742206573
- $01{:}23{:}17.728 \dashrightarrow 01{:}23{:}20.043$  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
- $01{:}23{:}22.017 \dashrightarrow 01{:}23{:}24.238$  the things I'm quite excited about.
- NOTE Confidence: 0.769990742206573

 $01:23:24.240 \rightarrow 01:23:27.184$  The moment we're working as a group with

NOTE Confidence: 0.769990742206573

 $01:23:27.184 \rightarrow 01:23:29.080$  systems biology island and equipment

NOTE Confidence: 0.769990742206573

 $01{:}23{:}29{.}080 \dashrightarrow 01{:}23{:}32{.}050$  Los Alamos in the group and trying to

NOTE Confidence: 0.769990742206573

 $01{:}23{:}32.050 \dashrightarrow 01{:}23{:}34.626$  understand that in terms of of the

NOTE Confidence: 0.769990742206573

 $01{:}23{:}34.626 \dashrightarrow 01{:}23{:}36.794$  signaling networks around RAF and MEK

NOTE Confidence: 0.769990742206573

01:23:36.794 --> 01:23:39.460 and and rest in different cells,

NOTE Confidence: 0.769990742206573

 $01:23:39.460 \longrightarrow 01:23:41.310$  some cells from different cancers,

NOTE Confidence: 0.769990742206573

 $01:23:41.310 \longrightarrow 01:23:42.148$  and innocence.

NOTE Confidence: 0.769990742206573

 $01:23:42.148 \rightarrow 01:23:43.824$  Which combinations work depends

NOTE Confidence: 0.769990742206573

 $01:23:43.824 \rightarrow 01:23:46.168$  say on the level of KSR 1.

NOTE Confidence: 0.769990742206573

 $01:23:46.170 \longrightarrow 01:23:47.800$  And that's a key determinant,

NOTE Confidence: 0.769990742206573

 $01{:}23{:}47.800 \dashrightarrow 01{:}23{:}50.152$  and so it just depends on so much

NOTE Confidence: 0.769990742206573

 $01:23:50.152 \rightarrow 01:23:52.359$  on how the network is wired,

NOTE Confidence: 0.769990742206573

 $01:23:52.360 \longrightarrow 01:23:54.316$  which of course goes back to

NOTE Confidence: 0.769990742206573

 $01:23:54.316 \longrightarrow 01:23:55.620$  the question about proteomics,

NOTE Confidence: 0.769990742206573

 $01:23:55.620 \rightarrow 01:23:57.525$  because ultimately that you you're

 $01:23:57.525 \rightarrow 01:24:00.172$  trying to control the system and the way

NOTE Confidence: 0.769990742206573

 $01{:}24{:}00.172 \dashrightarrow 01{:}24{:}02.470$  the system is set up by a chemically,

NOTE Confidence: 0.769990742206573

 $01:24:02.470 \longrightarrow 01:24:04.622$  it defines on how it will define how

NOTE Confidence: 0.769990742206573

 $01:24:04.622 \rightarrow 01:24:06.708$  we respond to different combinations.

NOTE Confidence: 0.769990742206573

 $01:24:06.710 \longrightarrow 01:24:08.798$  And so I think we're going to want

NOTE Confidence: 0.769990742206573

 $01:24:08.798 \longrightarrow 01:24:11.406$  to get into things at that kind of

NOTE Confidence: 0.769990742206573

 $01{:}24{:}11{.}406 \dashrightarrow 01{:}24{:}13{.}637$  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

 $01:24:14.860 \longrightarrow 01:24:16.810$  and I think it occurs .2.

NOTE Confidence: 0.769990742206573

 $01:24:16.810 \rightarrow 01:24:17.641$  That's that's exactly.

NOTE Confidence: 0.769990742206573

 $01:24:17.641 \longrightarrow 01:24:20.118$  Got it that the case is going to be

NOTE Confidence: 0.769990742206573

 $01{:}24{:}20.118 \dashrightarrow 01{:}24{:}21.798$  the case in the more complex systems

NOTE Confidence: 0.769990742206573

 $01:24:21.798 \longrightarrow 01:24:23.800$  of intercellular communication too.

NOTE Confidence: 0.837461471557617

 $01{:}24{:}25{.}130 \dashrightarrow 01{:}24{:}26{.}420$  And can I just add?

NOTE Confidence: 0.837461471557617

 $01:24:26.420 \rightarrow 01:24:27.976$  There's also the kinetic component, right?

01:24:27.976 --> 01:24:29.838 So I think when things were still

NOTE Confidence: 0.837461471557617

 $01:24:29.838 \longrightarrow 01:24:31.817$  not clear on is are you better

NOTE Confidence: 0.837461471557617

 $01:24:31.817 \rightarrow 01:24:33.202$  off with this combination early

NOTE Confidence: 0.837461471557617

 $01:24:33.261 \longrightarrow 01:24:35.005$  on or is this going to be better

NOTE Confidence: 0.837461471557617

 $01{:}24{:}35.005 \dashrightarrow 01{:}24{:}36.221$  once you get initial resistance?

NOTE Confidence: 0.837461471557617

 $01:24:36.221 \rightarrow 01:24:37.763$  And actually that's may seem trivial,

NOTE Confidence: 0.837461471557617

 $01{:}24{:}37{.}770 \dashrightarrow 01{:}24{:}39{.}810$  but I really don't think it is and

NOTE Confidence: 0.837461471557617

 $01:24:39.810 \longrightarrow 01:24:41.140$  requires modeling to think about

NOTE Confidence: 0.837461471557617

 $01:24:41.140 \longrightarrow 01:24:42.925$  just how the kinetics is playing out.

NOTE Confidence: 0.844868659973145

 $01:24:44.450 \longrightarrow 01:24:46.290$  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

 $01:24:49.723 \rightarrow 01:24:52.907$  is one of the things I'm excited about.

NOTE Confidence: 0.844868659973145

 $01{:}24{:}52{.}910 \dashrightarrow 01{:}24{:}55{.}682$  Sort of going forward and looking at

NOTE Confidence: 0.844868659973145

 $01:24:55.682 \rightarrow 01:24:58.623$  the field over the next few years is

NOTE Confidence: 0.844868659973145

 $01{:}24{:}58.623 \dashrightarrow 01{:}25{:}01.445$  is really what we can learn about the

NOTE Confidence: 0.844868659973145

 $01:25:01.445 \longrightarrow 01:25:04.510$  tumor from the get go that can tell us

 $01:25:04.510 \longrightarrow 01:25:07.327$  how we would want to treat it to stave

NOTE Confidence: 0.844868659973145

 $01{:}25{:}07{.}327 \dashrightarrow 01{:}25{:}09{.}837$  off certain mechanisms of resistance.

NOTE Confidence: 0.844868659973145

 $01:25:09.840 \longrightarrow 01:25:12.164$  I think we're starting to see some

NOTE Confidence: 0.844868659973145

 $01:25:12.164 \longrightarrow 01:25:14.049$  examples also of clinical trials

NOTE Confidence: 0.844868659973145

 $01:25:14.049 \longrightarrow 01:25:16.094$  that are starting to subset.

NOTE Confidence: 0.844868659973145

 $01{:}25{:}16{.}100 \dashrightarrow 01{:}25{:}17{.}955$  Patients with certain tumor Gina

NOTE Confidence: 0.844868659973145

 $01{:}25{:}17.955 \dashrightarrow 01{:}25{:}20.179$  types or whether tumors have certain

NOTE Confidence: 0.844868659973145

 $01:25:20.179 \longrightarrow 01:25:22.611$  features and sort of put them and and

NOTE Confidence: 0.844868659973145

 $01{:}25{:}22.611 \dashrightarrow 01{:}25{:}25.048$  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

 $01:25:28.258 \rightarrow 01:25:30.649$  interesting approach in the next few years.

NOTE Confidence: 0.84442663192749

 $01:25:32.070 \longrightarrow 01:25:33.198$  Terrific, thanks, just

NOTE Confidence: 0.84442663192749

 $01:25:33.200 \longrightarrow 01:25:35.090$  a couple comments on this,

NOTE Confidence: 0.84442663192749

 $01{:}25{:}35{.}090 \dashrightarrow 01{:}25{:}37{.}502$  so there's a few things that

NOTE Confidence: 0.84442663192749

 $01:25:37.502 \longrightarrow 01:25:39.532$  you that you've heard there

 $01:25:39.532 \longrightarrow 01:25:42.244$  that I just like to build on.

NOTE Confidence: 0.84442663192749

 $01{:}25{:}42.250 \dashrightarrow 01{:}25{:}44.386$  A completely agree that we need

NOTE Confidence: 0.84442663192749

 $01:25:44.386 \longrightarrow 01:25:46.265$  to understand what's the right

NOTE Confidence: 0.84442663192749

 $01:25:46.265 \longrightarrow 01:25:48.593$  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

 $01{:}25{:}50{.}194 \dashrightarrow 01{:}25{:}52{.}049$  been in that particular tumor,

NOTE Confidence: 0.84442663192749

 $01{:}25{:}52.050 \dashrightarrow 01{:}25{:}54.306$  and I think to that end,

NOTE Confidence: 0.84442663192749

 $01{:}25{:}54{.}310 \dashrightarrow 01{:}25{:}56{.}632$  looking at the adaptation at an

NOTE Confidence: 0.84442663192749

 $01{:}25{:}56{.}632 \dashrightarrow 01{:}25{:}58{.}618$  earlier point than we typically

NOTE Confidence: 0.84442663192749

 $01:25:58.618 \rightarrow 01:26:01.474$  do is a key part of this strategy,

NOTE Confidence: 0.84442663192749

 $01{:}26{:}01{.}480 \dashrightarrow 01{:}26{:}03{.}400$  so there's some really interesting.

NOTE Confidence: 0.84442663192749

 $01:26:03.400 \longrightarrow 01:26:05.578$  Concepts here that you will be

NOTE Confidence: 0.84442663192749

 $01{:}26{:}05{.}578 \dashrightarrow 01{:}26{:}07{.}453$  working with Gordon Mills from

NOTE Confidence: 0.84442663192749

 $01{:}26{:}07{.}453 \dashrightarrow 01{:}26{:}09{.}903$  OHSU on and looking at the adaptive

NOTE Confidence: 0.84442663192749

 $01:26:09.903 \rightarrow 01:26:12.272$  rewiring that goes on which really

NOTE Confidence: 0.84442663192749

 $01:26:12.272 \rightarrow 01:26:13.469$  happens quite quickly.

- NOTE Confidence: 0.84442663192749
- $01:26:13.470 \longrightarrow 01:26:15.282$  And of course one element of
- NOTE Confidence: 0.84442663192749
- $01:26:15.282 \longrightarrow 01:26:17.463$  that that we need to understand
- NOTE Confidence: 0.84442663192749
- $01:26:17.463 \rightarrow 01:26:19.275$  is undoubtedly the epigenetic
- NOTE Confidence: 0.84442663192749
- $01:26:19.275 \rightarrow 01:26:21.679$  mechanisms that that come in,
- NOTE Confidence: 0.84442663192749
- $01:26:21.680 \rightarrow 01:26:23.405$  'cause they're quite commonly involved
- NOTE Confidence: 0.84442663192749
- $01:26:23.405 \rightarrow 01:26:25.780$  in some of the resistance mechanisms,
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}25.780 \dashrightarrow 01{:}26{:}27.650$  and as I pointed out,
- NOTE Confidence: 0.84442663192749
- $01:26:27.650 \rightarrow 01:26:30.478$  we don't really have good techniques for
- NOTE Confidence: 0.84442663192749
- $01:26:30.478 \rightarrow 01:26:33.650$  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
- $01:26:34.326 \rightarrow 01:26:36.692$  so I think that's that's absolutely key,
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}36.700 \dashrightarrow 01{:}26{:}39.066$  and then I think that also informs,
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}39{.}070 \dashrightarrow 01{:}26{:}41{.}268$  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
- $01{:}26{:}43.252 \dashrightarrow 01{:}26{:}44.882$  factors of actually getting these
- NOTE Confidence: 0.84442663192749

- $01:26:44.882 \rightarrow 01:26:47.432$  to work has been the Taler ability
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}47{.}432 \dashrightarrow 01{:}26{:}48{.}904$  of the combinations clinically.
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}48.910 \dashrightarrow 01{:}26{:}51.798$  And for that I think there's a couple
- NOTE Confidence: 0.84442663192749
- $01{:}26{:}51.798 \dashrightarrow 01{:}26{:}54.668$  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
- $01{:}26{:}55{.}567 \dashrightarrow 01{:}26{:}57{.}361$  we're starting to develop some better
- NOTE Confidence: 0.84442663192749
- $01:26:57.361 \rightarrow 01:26:58.740$  tolerated therapies inherently,
- NOTE Confidence: 0.84442663192749
- $01:26:58.740 \longrightarrow 01:27:01.332$  so I think that gives us a bit
- NOTE Confidence: 0.84442663192749
- $01{:}27{:}01{.}332 \dashrightarrow 01{:}27{:}03{.}475$  more headroom for some of the
- NOTE Confidence: 0.84442663192749
- $01{:}27{:}03.475 \dashrightarrow 01{:}27{:}05.599$  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
- $01:27:06.440 \longrightarrow 01:27:07.840$  better ways of you know,
- NOTE Confidence: 0.84442663192749
- $01{:}27{:}07{.}840 \dashrightarrow 01{:}27{:}09{.}328$  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
- $01:27:11.295 \rightarrow 01:27:13.155$  and understanding what drives total ability,
- NOTE Confidence: 0.84442663192749
- $01:27:13.160 \rightarrow 01:27:14.942$  and then looking at the sequencing

01:27:14.942 --> 01:27:16.970 rather than trying to do it does

NOTE Confidence: 0.84442663192749

 $01:27:16.970 \longrightarrow 01:27:18.530$  everything at the same time is

NOTE Confidence: 0.84442663192749

 $01{:}27{:}18.530 \dashrightarrow 01{:}27{:}20.204$  another innovation that I think will

NOTE Confidence: 0.84442663192749

 $01:27:20.204 \rightarrow 01:27:22.391$  come in that will help us with that.

NOTE Confidence: 0.84442663192749

 $01{:}27{:}22{.}391 \dashrightarrow 01{:}27{:}24{.}666$  And but again I think we're going to

NOTE Confidence: 0.84442663192749

 $01:27:24.666 \longrightarrow 01:27:26.834$  need to apply all of these tools that

NOTE Confidence: 0.84442663192749

 $01{:}27{:}26.834 \dashrightarrow 01{:}27{:}29.117$  we've got and the modeling of that too,

NOTE Confidence: 0.84442663192749

 $01:27:29.120 \longrightarrow 01:27:31.024$  to reduce down the number of options

NOTE Confidence: 0.84442663192749

 $01:27:31.024 \rightarrow 01:27:32.770$  that we actually bring into the

NOTE Confidence: 0.84442663192749

 $01{:}27{:}32{.}770 \dashrightarrow 01{:}27{:}34{.}230$  clinic and increase the likelihood

NOTE Confidence: 0.84442663192749

 $01:27:34.230 \longrightarrow 01:27:35.850$  of each one of those being.

NOTE Confidence: 0.84442663192749

 $01:27:35.850 \longrightarrow 01:27:37.525$  Being successful with in combination

NOTE Confidence: 0.84442663192749

 $01:27:37.525 \longrightarrow 01:27:39.535$  therapy is going to keep us

NOTE Confidence: 0.84442663192749

 $01:27:39.535 \dashrightarrow 01:27:41.185$  occupied for a little while yet

NOTE Confidence: 0.84442663192749

 $01:27:41.185 \longrightarrow 01:27:42.779$  before we solve that problem.

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

 $01:27:48.410 \longrightarrow 01:27:50.423$  this exchange of opinion and

NOTE Confidence: 0.8606778383255

 $01:27:50.423 \longrightarrow 01:27:52.337$  knowledge as much as I have.

NOTE Confidence: 0.8606778383255

 $01{:}27{:}52{.}340 \dashrightarrow 01{:}27{:}55{.}084$  I'd like to turn it back now to

NOTE Confidence: 0.8606778383255

 $01:27:55.084 \rightarrow 01:27:57.671$  Charlie Fuchs and just ask him to

NOTE Confidence: 0.8606778383255

 $01:27:57.671 \rightarrow 01:28:00.190$  share a couple of concluding remarks.

NOTE Confidence: 0.8606778383255

01:28:00.190 --> 01:28:00.936 Well, Barbara,

NOTE Confidence: 0.8606778383255

 $01:28:00.936 \longrightarrow 01:28:03.174$  thank you and all the panelists.

NOTE Confidence: 0.8606778383255

 $01{:}28{:}03{.}180 \dashrightarrow 01{:}28{:}05{.}556$  It was a fantastic discussion and

NOTE Confidence: 0.8606778383255

 $01{:}28{:}05{.}556 \dashrightarrow 01{:}28{:}07{.}560$  really provided so much insight

NOTE Confidence: 0.8606778383255

 $01:28:07.560 \longrightarrow 01:28:09.947$  in terms of how we continue to

NOTE Confidence: 0.8606778383255

 $01{:}28{:}09{.}947 \dashrightarrow 01{:}28{:}12{.}204$  move grade science into the clinic

NOTE Confidence: 0.8606778383255

 $01:28:12.204 \rightarrow 01:28:14.460$  and frankly how we learn more.

NOTE Confidence: 0.8606778383255

 $01{:}28{:}14.460 \dashrightarrow 01{:}28{:}16.260$  About the tests in clinical

NOTE Confidence: 0.8606778383255

 $01:28:16.260 \rightarrow 01:28:18.060$  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
- $01{:}28{:}19.890 \dashrightarrow 01{:}28{:}22.067$  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
- $01{:}28{:}24{.}281 \dashrightarrow 01{:}28{:}26{.}699$  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
- $01:28:28.940 \longrightarrow 01:28:30.332$  And as I mentioned,
- NOTE Confidence: 0.8606778383255
- $01:28:30.332 \rightarrow 01:28:32.866$  the work continues and we very much
- NOTE Confidence: 0.8606778383255
- $01:28:32.866 \rightarrow 01:28:35.498$  want this to be the beginning of
- NOTE Confidence: 0.8606778383255
- $01{:}28{:}35{.}498 \dashrightarrow 01{:}28{:}37{.}363$  the conversation and so hopefully
- NOTE Confidence: 0.8606778383255
- $01:28:37.363 \longrightarrow 01:28:39.799$  what will what you'll do and what
- NOTE Confidence: 0.8606778383255
- $01:28:39.800 \longrightarrow 01:28:42.271$  we'll do is engage each other in
- NOTE Confidence: 0.8606778383255
- $01:28:42.271 \longrightarrow 01:28:44.140$  thinking through how we partner,
- NOTE Confidence: 0.8606778383255
- $01:28:44.140 \longrightarrow 01:28:46.010$  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
- $01{:}28{:}47{.}194 \dashrightarrow 01{:}28{:}49{.}431$  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

 $01{:}28{:}51{.}390 \dashrightarrow 01{:}28{:}53{.}304$  so people should feel free to

NOTE Confidence: 0.8606778383255

 $01:28:53.304 \longrightarrow 01:28:56.043$  reach out to me or any of the

NOTE Confidence: 0.8606778383255

 $01:28:56.043 \rightarrow 01:28:57.427$  panelists to think about.

NOTE Confidence: 0.8606778383255

 $01{:}28{:}57{.}430 \dashrightarrow 01{:}28{:}59{.}560$  These collaborations will be contacting you

NOTE Confidence: 0.8606778383255

 $01:28:59.560 \rightarrow 01:29:01.470$  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

 $01{:}29{:}06.802 \dashrightarrow 01{:}29{:}08.610$  and excitement about the years

NOTE Confidence: 0.8606778383255

 $01{:}29{:}08.610 \dashrightarrow 01{:}29{:}10.540$  ahead of of cancer investigation.

NOTE Confidence: 0.8606778383255

 $01:29:10.540 \longrightarrow 01:29:12.885$  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

 $01:29:14.900 \rightarrow 01:29:15.905$  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

 $01:29:21.626 \rightarrow 01:29:25.669 1/2$  years and the conversation today.

- NOTE Confidence: 0.88388192653656
- $01:29:25.670 \longrightarrow 01:29:27.756$  Sort of reminds me of the
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}27.756 \dashrightarrow 01{:}29{:}30.158$  excitement that I felt when I started
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}30{.}158 \dashrightarrow 01{:}29{:}31{.}958$  going to seminars around here.
- NOTE Confidence: 0.88388192653656
- $01:29:31.960 \longrightarrow 01:29:33.525$  I mean, there's just unbelievable
- NOTE Confidence: 0.88388192653656
- $01:29:33.525 \longrightarrow 01:29:35.502$  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
- $01{:}29{:}37{.}260 \dashrightarrow 01{:}29{:}39{.}542$  and a lot of people thinking about
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}39{.}542 \dashrightarrow 01{:}29{:}42{.}300$  how to make cancer treatment better.
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}42{.}300 \dashrightarrow 01{:}29{:}45{.}476$  So thank you all for joining us today.
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}45{.}480 \dashrightarrow 01{:}29{:}48{.}084$  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
- $01{:}29{:}50{.}260 \dashrightarrow 01{:}29{:}52{.}804$  Katie and Mark and Megan Inch in for
- NOTE Confidence: 0.88388192653656
- $01{:}29{:}52{.}804 \dashrightarrow 01{:}29{:}55{.}039$  their their wonderful presentation.
- NOTE Confidence: 0.88388192653656
- 01:29:55.040 --> 01:29:56.628 Thank you very much.
- NOTE Confidence: 0.533962070941925
- $01:29:58.850 \longrightarrow 01:30:00.256$  Keyboard.