WEBVTT

- NOTE duration:"01:06:09.1500000"
- NOTE recognizability:0.815
- NOTE language:en-us
- NOTE Confidence: 0.753344047
- 00:00:00.000 --> 00:00:02.130 Yeah, petrol. It's my pleasure
- NOTE Confidence: 0.753344047
- $00{:}00{:}02{.}130 \dashrightarrow 00{:}00{:}04{.}260$ to introduce Doctor Mark Rubin,
- NOTE Confidence: 0.753344047
- $00{:}00{:}04{.}260 \dashrightarrow 00{:}00{:}05{.}556$ who is a professor and director
- NOTE Confidence: 0.753344047
- 00:00:05.560 --> 00:00:07.168 of Department of Biomedical
- NOTE Confidence: 0.753344047
- $00{:}00{:}07{.}170 \dashrightarrow 00{:}00{:}09{.}190$ Research and Burn Center for
- NOTE Confidence: 0.753344047
- $00{:}00{:}09{.}190 \dashrightarrow 00{:}00{:}10.565$ the Precision Medicine at the
- NOTE Confidence: 0.830919952
- 00:00:10.580 --> 00:00:13.200 University of Bern in Switzerland. Previously
- NOTE Confidence: 0.830048071428571
- 00:00:13.210 --> 00:00:15.464 was moving to Europe. Six years ago,
- NOTE Confidence: 0.830048071428571
- 00:00:15.470 --> 00:00:17.180 Doctor Rubin was a group leader at
- NOTE Confidence: 0.830048071428571
- $00{:}00{:}17.180 \dashrightarrow 00{:}00{:}19.172$ Weill Cornell Medicine Institution that
- NOTE Confidence: 0.830048071428571
- $00{:}00{:}19.172 \dashrightarrow 00{:}00{:}21.638$ remained engaged to the prostate spore
- NOTE Confidence: 0.8936092275
- $00:00:21.710 \longrightarrow 00:00:22.730$ as a project leader.
- NOTE Confidence: 0.845784318571429
- 00:00:23.870 --> 00:00:25.435 Doctor Rubin is a recognized
- NOTE Confidence: 0.845784318571429

 $00:00:25.435 \rightarrow 00:00:27.000$ world renowned leader and prostate

NOTE Confidence: 0.845784318571429

 $00{:}00{:}27.056$ --> $00{:}00{:}28.548$ cancer genomics and pathology.

NOTE Confidence: 0.845784318571429

00:00:28.550 --> 00:00:30.130 And in precision medicine,

NOTE Confidence: 0.845784318571429

 $00:00:30.130 \rightarrow 00:00:32.230$ doctor Rubin's laboratory led a series

NOTE Confidence: 0.845784318571429

 $00:00:32.230 \longrightarrow 00:00:34.100$ of landmark studies defining distinct

NOTE Confidence: 0.845784318571429

 $00:00:34.100 \rightarrow 00:00:36.150$ molecular features of prostate cancer,

NOTE Confidence: 0.845784318571429

 $00:00:36.150 \longrightarrow 00:00:37.555$ revealing pathways that are

NOTE Confidence: 0.845784318571429

 $00:00:37.555 \rightarrow 00:00:39.230$ perturbed and drive different types

NOTE Confidence: 0.845784318571429

 $00:00:39.230 \longrightarrow 00:00:40.814$ of different types of this cancer.

NOTE Confidence: 0.845784318571429

 $00:00:40.814 \dashrightarrow 00:00:42.998$ Furthermore, he has translated many of

NOTE Confidence: 0.845784318571429

 $00{:}00{:}42.998 \dashrightarrow 00{:}00{:}44.790$ the genomic discoveries into clinical

NOTE Confidence: 0.845784318571429

 $00:00:44.790 \longrightarrow 00:00:46.610$ tests that are currently patented

NOTE Confidence: 0.845784318571429

 $00:00:46.610 \rightarrow 00:00:48.680$ and Stanley used in the diagnosis

NOTE Confidence: 0.845784318571429

 $00:00:48.680 \dashrightarrow 00:00:49.993$ and treatment of prostate cancer.

NOTE Confidence: 0.845784318571429

 $00:00:49.993 \dashrightarrow 00:00:52.160$ He founded the Angler Institute for

NOTE Confidence: 0.845784318571429

 $00:00:52.160 \rightarrow 00:00:53.506$ Precision Medicine and most recently,

 $00{:}00{:}53{.}506 \dashrightarrow 00{:}00{:}54{.}102$ the Burn.

NOTE Confidence: 0.845784318571429

 $00{:}00{:}54.102 \dashrightarrow 00{:}00{:}56.808$ Center for Precision Medicine Doctor Rubin

NOTE Confidence: 0.845784318571429

00:00:56.808 --> 00:00:58.778 has published around 300 manuscripts,

NOTE Confidence: 0.845784318571429

 $00:00:58.780 \rightarrow 00:01:00.980$ including those in major top journals.

NOTE Confidence: 0.845784318571429

 $00{:}01{:}00{.}980 \dashrightarrow 00{:}01{:}02{.}884$ Today will tell us about his latest

NOTE Confidence: 0.845784318571429

 $00{:}01{:}02.884 \dashrightarrow 00{:}01{:}05.615$ work in the minor spy summit exploring

NOTE Confidence: 0.845784318571429

 $00:01:05.615 \rightarrow 00:01:07.004$ novel cancer vulnerabilities,

NOTE Confidence: 0.845784318571429

 $00:01:07.070 \longrightarrow 00:01:07.750$ Doctor Rubin.

NOTE Confidence: 0.7229190825

00:01:13.160 --> 00:01:17.210 Well, it's great to. Doctor OK, sure.

NOTE Confidence: 0.74868226

00:01:19.000 --> 00:01:22.580 Her. No, no. I thought Katie

NOTE Confidence: 0.845896133333333

 $00:01:22.590 \rightarrow 00:01:23.886$ would want to say something again.

NOTE Confidence: 0.5709378

 $00{:}01{:}28{.}380 \dashrightarrow 00{:}01{:}30{.}269$ We're OK. So is OK, OK, great.

NOTE Confidence: 0.5709378

00:01:30.269 --> 00:01:32.421 So it's great to be here and I

NOTE Confidence: 0.5709378

00:01:32.421 --> 00:01:34.681 think I last time I was here is

NOTE Confidence: 0.5709378

 $00{:}01{:}34.681 \dashrightarrow 00{:}01{:}36.200$ definitely over 10 years ago.

00:01:36.200 --> 00:01:38.336 So it's it's great to come back and

NOTE Confidence: 0.5709378

 $00:01:38.336 \rightarrow 00:01:40.681$ visit and hopefully I can figure out how

NOTE Confidence: 0.5709378

 $00{:}01{:}40{.}681 \dashrightarrow 00{:}01{:}43{.}320$ to move the slides forward on this. OK.

NOTE Confidence: 0.856139078571429

00:01:45.360 --> 00:01:48.139 There we go. So just the following,

NOTE Confidence: 0.856139078571429

 $00:01:48.140 \rightarrow 00:01:51.328$ mostly non relevant disclosures.

NOTE Confidence: 0.856139078571429

 $00:01:51.328 \longrightarrow 00:01:56.084$ So a lot of people asked in 2017

NOTE Confidence: 0.856139078571429

00:01:56.084 --> 00:01:58.386 when I went to Switzerland, you know,

NOTE Confidence: 0.856139078571429

 $00:01:58.386 \rightarrow 00:02:00.338$ what I was going to do and why I was going.

NOTE Confidence: 0.856139078571429

 $00:02:00.340 \longrightarrow 00:02:02.384$ And so you heard that there were

NOTE Confidence: 0.856139078571429

 $00:02:02.384 \rightarrow 00:02:03.639$ some initiatives that I was,

NOTE Confidence: 0.856139078571429

00:02:03.640 --> 00:02:04.820 I've been involved in,

NOTE Confidence: 0.856139078571429

 $00{:}02{:}04{.}820 \dashrightarrow 00{:}02{:}07{.}042$ so setting up the Burn Center for

NOTE Confidence: 0.856139078571429

00:02:07.042 --> 00:02:08.972 Precision Medicine and running a

NOTE Confidence: 0.856139078571429

 $00{:}02{:}08{.}972 \dashrightarrow 00{:}02{:}11{.}051$ new department and reorganizing a

NOTE Confidence: 0.856139078571429

 $00:02:11.051 \rightarrow 00:02:12.458$ department biomedical research.

NOTE Confidence: 0.856139078571429

 $00{:}02{:}12.460 \dashrightarrow 00{:}02{:}14.371$ But one of the decisions I made

00:02:14.371 --> 00:02:16.230 when I moved was that instead

NOTE Confidence: 0.856139078571429

 $00{:}02{:}16.230 \dashrightarrow 00{:}02{:}18.174$ of taking projects that I had,

NOTE Confidence: 0.856139078571429

 $00{:}02{:}18.180 \dashrightarrow 00{:}02{:}21.480$ I would start from scratch and.

NOTE Confidence: 0.856139078571429

 $00:02:21.480 \rightarrow 00:02:23.328$ Really start new projects and just

NOTE Confidence: 0.856139078571429

00:02:23.328 --> 00:02:26.095 say I know I see we have a lot

NOTE Confidence: 0.856139078571429

 $00{:}02{:}26.095 \dashrightarrow 00{:}02{:}28.138$ of trainees in the audience and I

NOTE Confidence: 0.856139078571429

 $00:02:28.138 \longrightarrow 00:02:30.130$ just think it's a it was a very.

NOTE Confidence: 0.856139078571429

 $00:02:30.130 \longrightarrow 00:02:31.985$ I think it's been an exciting time.

NOTE Confidence: 0.856139078571429

00:02:31.990 --> 00:02:34.348 It didn't count for the pandemic,

NOTE Confidence: 0.856139078571429

 $00:02:34.350 \rightarrow 00:02:35.832$ but it's certainly been an exciting

NOTE Confidence: 0.856139078571429

 $00:02:35.832 \rightarrow 00:02:37.450$ time to think about new projects,

NOTE Confidence: 0.856139078571429

 $00{:}02{:}37{.}450 \dashrightarrow 00{:}02{:}39{.}592$ what you think is important and

NOTE Confidence: 0.856139078571429

 $00{:}02{:}39{.}592 \dashrightarrow 00{:}02{:}42{.}344$ actually going in places that feel a

NOTE Confidence: 0.856139078571429

 $00{:}02{:}42{.}344 \dashrightarrow 00{:}02{:}44{.}024$ bit uncomfortable scientifically just

NOTE Confidence: 0.856139078571429

 $00:02:44.024 \rightarrow 00:02:46.627$ because you need to learn new things.

 $00:02:46.630 \longrightarrow 00:02:48.550$ And so I think I left all the

NOTE Confidence: 0.856139078571429

 $00{:}02{:}48.550 \dashrightarrow 00{:}02{:}49.994$ projects with this prostate spore

NOTE Confidence: 0.856139078571429

 $00:02:49.994 \longrightarrow 00:02:51.812$ and we started a new project.

NOTE Confidence: 0.856139078571429

 $00:02:51.820 \dashrightarrow 00:02:53.980$ So I'll tell you a little bit about

NOTE Confidence: 0.856139078571429

 $00{:}02{:}53{.}980 \dashrightarrow 00{:}02{:}55{.}932$ two things that we worked on more

NOTE Confidence: 0.856139078571429

 $00:02:55.932 \longrightarrow 00:02:57.667$ recently just as way of background NOTE Confidence: 0.856139078571429

 $00:02:57.667 \rightarrow 00:02:59.928$ so many of you are familiar with.

NOTE Confidence: 0.856139078571429

00:02:59.930 --> 00:03:01.960 But you know prostate cancer,

NOTE Confidence: 0.856139078571429

00:03:01.960 --> 00:03:04.291 but I'll just as a
as a means of

NOTE Confidence: 0.856139078571429

 $00:03:04.291 \rightarrow 00:03:06.326$ background just to remind you that

NOTE Confidence: 0.856139078571429

 $00{:}03{:}06{.}326$ --> $00{:}03{:}08{.}041$ the landscape for prostate cancer

NOTE Confidence: 0.856139078571429

 $00:03:08.106 \rightarrow 00:03:09.821$ therapy has really changed dramatically

NOTE Confidence: 0.856139078571429

 $00:03:09.821 \longrightarrow 00:03:13.460$ if we go back ten years ago.

NOTE Confidence: 0.856139078571429

00:03:13.460 - 00:03:16.460 Or 2010, even more than 10 years ago,

NOTE Confidence: 0.856139078571429

 $00:03:16.460 \rightarrow 00:03:19.320$ it was relatively and rogen deprivation

NOTE Confidence: 0.856139078571429

 $00:03:19.320 \longrightarrow 00:03:22.180$ therapy based with the taxanes.

- NOTE Confidence: 0.856139078571429
- $00:03:22.180 \longrightarrow 00:03:24.268$ But it's a very different than
- NOTE Confidence: 0.856139078571429
- $00:03:24.268 \longrightarrow 00:03:25.312$ the landscape today.
- NOTE Confidence: 0.856139078571429
- 00:03:25.320 --> 00:03:26.640 And I'm not going,
- NOTE Confidence: 0.856139078571429
- $00:03:26.640 \rightarrow 00:03:27.960$ I'm not expert oncologists.
- NOTE Confidence: 0.856139078571429
- 00:03:27.960 --> 00:03:29.760 I'm a pathologist by training.
- NOTE Confidence: 0.856139078571429
- 00:03:29.760 --> 00:03:31.340 And I'm not going to go into all the details,
- NOTE Confidence: 0.856139078571429
- $00:03:31.340 \longrightarrow 00:03:33.284$ but just to point out that
- NOTE Confidence: 0.856139078571429
- $00:03:33.284 \rightarrow 00:03:34.580$ there are many choices.
- NOTE Confidence: 0.856139078571429
- 00:03:34.580 --> 00:03:36.939 And if you go to clinical meetings
- NOTE Confidence: 0.856139078571429
- 00:03:36.939 --> 00:03:38.436 and listen about, you know,
- NOTE Confidence: 0.856139078571429
- $00:03:38.436 \rightarrow 00:03:40.137$ what's going on just all the time,
- NOTE Confidence: 0.856139078571429
- $00:03:40.140 \longrightarrow 00:03:41.400$ they're new opportunities.
- NOTE Confidence: 0.856139078571429
- $00:03:41.400 \rightarrow 00:03:44.340$ The one thing I would point out
- NOTE Confidence: 0.856139078571429
- $00{:}03{:}44{.}419 \dashrightarrow 00{:}03{:}47{.}125$ is that as patients are being
- NOTE Confidence: 0.856139078571429
- 00:03:47.125 --> 00:03:48.478 treated with antiandrogen,
- NOTE Confidence: 0.856139078571429

 $00:03:48.480 \longrightarrow 00:03:51.300$ various types of more potent

NOTE Confidence: 0.856139078571429

 $00{:}03{:}51{.}300 \dashrightarrow 00{:}03{:}53{.}556$ antiandrogen the rapies such as

NOTE Confidence: 0.856139078571429

 $00{:}03{:}53{.}556 \dashrightarrow 00{:}03{:}55{.}380$ enzalutamide and a biraterone

NOTE Confidence: 0.856139078571429

 $00:03:55.380 \rightarrow 00:03:57.164$ resistances obviously an inevitable.

NOTE Confidence: 0.856139078571429

 $00:03:57.164 \dashrightarrow 00:04:00.737$ So patients can do well that for a short

NOTE Confidence: 0.856139078571429

 $00:04:00.737 \rightarrow 00:04:03.419$ time or they can do well for long time.

NOTE Confidence: 0.856139078571429

 $00:04:03.420 \longrightarrow 00:04:04.596$ Eventually they'll fail,

NOTE Confidence: 0.856139078571429

 $00{:}04{:}04{.}596 \dashrightarrow 00{:}04{:}06{.}556$ but there are other opportunities.

NOTE Confidence: 0.856139078571429

 $00:04:06.560 \longrightarrow 00:04:07.840$ Now there's PARP inhibitors,

NOTE Confidence: 0.856139078571429

 $00:04:07.840 \longrightarrow 00:04:09.120$ so that's quite exciting.

NOTE Confidence: 0.856139078571429

 $00:04:09.120 \dashrightarrow 00:04:10.470$ Obviously there's immunotherapy

NOTE Confidence: 0.856139078571429

 $00{:}04{:}10.470 \dashrightarrow 00{:}04{:}12.720$ for such a small subset.

NOTE Confidence: 0.856139078571429

 $00{:}04{:}12.720 \dashrightarrow 00{:}04{:}15.576$ For patients where it seems to be

NOTE Confidence: 0.856139078571429

 $00{:}04{:}15{.}576$ --> $00{:}04{:}18{.}269$ effective and then there's PSA treatments

NOTE Confidence: 0.856139078571429

 $00:04:18.269 \rightarrow 00:04:21.902$ or imaging and and treatment and

NOTE Confidence: 0.856139078571429

 $00:04:21.902 \rightarrow 00:04:25.589$ these are again really more therapies.

 $00:04:25.590 \rightarrow 00:04:27.828$ There's problems with all of them,

NOTE Confidence: 0.856139078571429

 $00{:}04{:}27.830 \dashrightarrow 00{:}04{:}30.870$ but there is a lot more opportunity now

NOTE Confidence: 0.856139078571429

00:04:30.870 --> 00:04:33.540 for treating advanced prostate cancer.

NOTE Confidence: 0.856139078571429

 $00:04:33.540 \longrightarrow 00:04:36.473$ Resistance remains a major focus of our

NOTE Confidence: 0.856139078571429

 $00{:}04{:}36{.}473 \dashrightarrow 00{:}04{:}39{.}870$ labs work and and other labs now to

NOTE Confidence: 0.856139078571429

 $00:04:39.870 \longrightarrow 00:04:42.960$ try to understand why patients are failing.

NOTE Confidence: 0.856139078571429

00:04:42.960 --> 00:04:44.885 And what I think is very important

NOTE Confidence: 0.856139078571429

 $00{:}04{:}44.885 \dashrightarrow 00{:}04{:}46.872$ is to think about in all of

NOTE Confidence: 0.856139078571429

 $00:04:46.872 \longrightarrow 00:04:48.522$ these settings what is the key

NOTE Confidence: 0.876171274545455

 $00:04:48.583 \rightarrow 00:04:49.659$ clinical question,

NOTE Confidence: 0.876171274545455

00:04:49.660 - 00:04:51.766 at what time should we change

NOTE Confidence: 0.876171274545455

 $00:04:51.766 \rightarrow 00:04:53.860$ therapies or introduce new therapies.

NOTE Confidence: 0.876171274545455

 $00:04:53.860 \longrightarrow 00:04:55.736$ So that's one of the main things

NOTE Confidence: 0.876171274545455

00:04:55.736 --> 00:04:57.500 we're focusing on. So I'm going to

NOTE Confidence: 0.876171274545455

 $00:04:57.500 \dashrightarrow 00:04:58.940$ make a few comments about lineage,

 $00:04:58.940 \longrightarrow 00:05:00.785$ plasticity and the resistance framework

NOTE Confidence: 0.876171274545455

 $00:05:00.785 \dashrightarrow 00:05:03.850$ and I'm going to talk a little bit about.

NOTE Confidence: 0.876171274545455

00:05:03.850 --> 00:05:06.322 Some work that may be relevant to this

NOTE Confidence: 0.876171274545455

 $00{:}05{:}06{.}322 \dashrightarrow 00{:}05{:}09{.}324$ to the lung spore in the context of

NOTE Confidence: 0.876171274545455

 $00:05:09.324 \dashrightarrow 00:05:11.690$ switch sniff and epigenetic modulation.

NOTE Confidence: 0.876171274545455

 $00:05:11.690 \rightarrow 00:05:14.270$ And then I'm going to talk about a new story NOTE Confidence: 0.876171274545455

 $00{:}05{:}14.337 \dashrightarrow 00{:}05{:}16.157$ that's unpublished that has connections

NOTE Confidence: 0.876171274545455

 $00{:}05{:}16.157 \dashrightarrow 00{:}05{:}18.750$ with both Yale and Connecticut.

NOTE Confidence: 0.876171274545455

 $00{:}05{:}18.750 \dashrightarrow 00{:}05{:}21.070$ And it's our minor splicing.

NOTE Confidence: 0.876171274545455

 $00:05:21.070 \dashrightarrow 00:05:23.527$ So I have my main goal today will be

NOTE Confidence: 0.876171274545455

 $00:05:23.527 \rightarrow 00:05:25.612$ hopefully to tell you about something that

NOTE Confidence: 0.876171274545455

 $00:05:25.612 \rightarrow 00:05:28.146$ you may not know a lot about and maybe,

NOTE Confidence: 0.876171274545455

 $00:05:28.150 \dashrightarrow 00:05:30.185$ maybe we'll all learn something

NOTE Confidence: 0.876171274545455

 $00:05:30.185 \longrightarrow 00:05:31.813$ together about minor splicing

NOTE Confidence: 0.876171274545455

 $00:05:31.813 \rightarrow 00:05:33.848$ and maybe also some insights.

NOTE Confidence: 0.876171274545455

 $00:05:33.850 \dashrightarrow 00:05:36.334$ As well and that we can talk about them.

 $00{:}05{:}36{.}340 \dashrightarrow 00{:}05{:}38{.}716$ So just a few comments about

NOTE Confidence: 0.876171274545455

 $00:05:38.716 \rightarrow 00:05:40.300$ resistance and lineage plasticity.

NOTE Confidence: 0.876171274545455

 $00:05:40.300 \rightarrow 00:05:42.197$ I've been showing these slides for a

NOTE Confidence: 0.876171274545455

 $00:05:42.197 \rightarrow 00:05:44.514$ few years and I think it it helps me a

NOTE Confidence: 0.876171274545455

 $00{:}05{:}44{.}514 \dashrightarrow 00{:}05{:}46{.}304$ lot of giving a framework for thinking

NOTE Confidence: 0.876171274545455

 $00{:}05{:}46{.}304 \dashrightarrow 00{:}05{:}48{.}458$ about what we do clinically in the

NOTE Confidence: 0.876171274545455

 $00:05:48.458 \longrightarrow 00:05:51.324$ setting that most in the in the context

NOTE Confidence: 0.876171274545455

 $00:05:51.324 \rightarrow 00:05:53.893$ that most of the types of the rapies

NOTE Confidence: 0.876171274545455

 $00:05:53.893 \rightarrow 00:05:56.899$ are very index oncogenic pathway driven.

NOTE Confidence: 0.876171274545455

 $00:05:56.900 \rightarrow 00:05:58.916$ So if you have estrogen receptor,

NOTE Confidence: 0.876171274545455

 $00:05:58.920 \longrightarrow 00:06:00.040$ if you have her too,

NOTE Confidence: 0.876171274545455

 $00{:}06{:}00{.}040 \dashrightarrow 00{:}06{:}03{.}659$ if you have EGFR as a main

NOTE Confidence: 0.876171274545455

 $00:06:03.659 \rightarrow 00:06:05.210$ pathway that's activated.

NOTE Confidence: 0.876171274545455

00:06:05.210 --> 00:06:06.746 Braf, et cetera,

NOTE Confidence: 0.876171274545455

 $00:06:06.746 \longrightarrow 00:06:07.770$ the main,

 $00:06:07.770 \longrightarrow 00:06:09.620$ the index oncogenic output is

NOTE Confidence: 0.876171274545455

 $00{:}06{:}09{.}620 \dashrightarrow 00{:}06{:}11{.}942$ being targeted and so then you

NOTE Confidence: 0.876171274545455

 $00{:}06{:}11.942 \dashrightarrow 00{:}06{:}13.927$ have resistance related to that.

NOTE Confidence: 0.876171274545455

 $00{:}06{:}13.930 \dashrightarrow 00{:}06{:}15.826$ But there are alternate effectors and

NOTE Confidence: 0.876171274545455

 $00:06:15.826 \longrightarrow 00:06:17.850$ they're also alternate states that can occur.

NOTE Confidence: 0.876171274545455

 $00:06:17.850 \dashrightarrow 00:06:20.930$ So in the context of prostate cancer,

NOTE Confidence: 0.876171274545455

 $00{:}06{:}20{.}930 \dashrightarrow 00{:}06{:}23{.}660$ the Andrew receptor is the main

NOTE Confidence: 0.876171274545455

 $00:06:23.660 \rightarrow 00:06:26.759$ oncogenic target for most of the therapy,

NOTE Confidence: 0.876171274545455

 $00:06:26.760 \rightarrow 00:06:29.736$ whether it's Andrew and deprivation therapy

NOTE Confidence: 0.876171274545455

 $00:06:29.736 \longrightarrow 00:06:32.630$ or targeted ligand targeted therapy or

NOTE Confidence: 0.876171274545455

 $00:06:32.630 \dashrightarrow 00:06:35.594$ therapy based on decreasing synthesis.

NOTE Confidence: 0.876171274545455

 $00:06:35.594 \longrightarrow 00:06:38.138$ With and rogens or hormones.

NOTE Confidence: 0.876171274545455

 $00{:}06{:}38.140 \dashrightarrow 00{:}06{:}40.172$ So you'd expect and and it is the

NOTE Confidence: 0.876171274545455

 $00{:}06{:}40{.}172 \dashrightarrow 00{:}06{:}42{.}433$ case that most of the mutations are

NOTE Confidence: 0.876171274545455

 $00:06:42.433 \dashrightarrow 00:06:44.720$ resistance occur in the ANGIOMA receptor.

NOTE Confidence: 0.876171274545455

 $00:06:44.720 \longrightarrow 00:06:46.865$ So there's amplifications mutations and

 $00:06:46.865 \rightarrow 00:06:50.627$ so this is this is what you expect but

NOTE Confidence: 0.876171274545455

 $00:06:50.627 \rightarrow 00:06:53.469$ what we also are seeing emerging more

NOTE Confidence: 0.876171274545455

 $00:06:53.469 \rightarrow 00:06:56.217$ and more frequently with very potent

NOTE Confidence: 0.876171274545455

 $00:06:56.217 \rightarrow 00:06:58.446$ anti ancient therapy are alternate

NOTE Confidence: 0.876171274545455

 $00:06:58.446 \rightarrow 00:07:00.984$ pathways and this is getting into

NOTE Confidence: 0.876171274545455

 $00:07:00.984 \rightarrow 00:07:03.757$ the theme of of lineage plasticity.

NOTE Confidence: 0.876171274545455

00:07:03.760 --> 00:07:05.460 So if you switch.

NOTE Confidence: 0.876171274545455

 $00:07:05.460 \rightarrow 00:07:08.010$ From an adenocarcinoma to something else,

NOTE Confidence: 0.876171274545455

00:07:08.010 --> 00:07:09.422 you're no longer driven,

NOTE Confidence: 0.876171274545455

 $00:07:09.422 \longrightarrow 00:07:11.187$ so you're a RH negative.

NOTE Confidence: 0.876171274545455

 $00{:}07{:}11.190 \dashrightarrow 00{:}07{:}13.206$ And what are the mechanisms then that

NOTE Confidence: 0.876171274545455

 $00{:}07{:}13.206 \dashrightarrow 00{:}07{:}15.469$ lead to this resistance is what we're

NOTE Confidence: 0.876171274545455

 $00{:}07{:}15.469 \dashrightarrow 00{:}07{:}17.839$ trying to understand and a number of

NOTE Confidence: 0.876171274545455

 $00{:}07{:}17.839 \dashrightarrow 00{:}07{:}20.247$ other groups are doing the same in prostate.

NOTE Confidence: 0.876171274545455

 $00{:}07{:}20.250 \dashrightarrow 00{:}07{:}22.086$ Now obviously this is very interesting

00:07:22.086 --> 00:07:23.770 in other cancers like bladder,

NOTE Confidence: 0.876171274545455

 $00:07:23.770 \longrightarrow 00:07:26.089$ lung and breast.

NOTE Confidence: 0.876171274545455

 $00:07:26.090 \longrightarrow 00:07:28.010$ So just to be specific,

NOTE Confidence: 0.876171274545455

 $00:07:28.010 \dashrightarrow 00:07:30.522$ as a pathologist we look under the microscope

NOTE Confidence: 0.876171274545455

 $00{:}07{:}30{.}522 \dashrightarrow 00{:}07{:}33{.}026$ and we see this is an adenocarcinoma,

NOTE Confidence: 0.876171274545455

00:07:33.030 --> 00:07:34.107 it's very pink.

NOTE Confidence: 0.876171274545455

 $00{:}07{:}34{.}107 \dashrightarrow 00{:}07{:}36{.}620$ The cells have a lot of cytoplasm

NOTE Confidence: 0.876171274545455

 $00{:}07{:}36{.}702 \dashrightarrow 00{:}07{:}39{.}122$ and after antiandrogen the rapy a

NOTE Confidence: 0.876171274545455

 $00{:}07{:}39{.}122 \dashrightarrow 00{:}07{:}41{.}542$ certain subset of these patients.

NOTE Confidence: 0.876171274545455

00:07:41.550 --> 00:07:42.894 And what I'm showing here is

NOTE Confidence: 0.876171274545455

 $00:07:42.894 \longrightarrow 00:07:44.513$ just the types of therapies that

NOTE Confidence: 0.876171274545455

 $00:07:44.513 \longrightarrow 00:07:45.845$ that patients may receive,

NOTE Confidence: 0.876171274545455

 $00:07:45.850 \rightarrow 00:07:48.268$ very strong potent anti entrant therapy,

NOTE Confidence: 0.876171274545455

 $00:07:48.270 \longrightarrow 00:07:49.710$ but after these therapies

NOTE Confidence: 0.876171274545455

 $00:07:49.710 \longrightarrow 00:07:50.790$ where most patients,

NOTE Confidence: 0.876171274545455

 $00:07:50.790 \rightarrow 00:07:54.470$ almost all patients respond initially,

- NOTE Confidence: 0.866359873333333
- 00:07:54.470 > 00:07:55.976 many of the patients will have.
- NOTE Confidence: 0.866359873333333
- $00:07:55.980 \rightarrow 00:07:57.460$ Resistance and there are many
- NOTE Confidence: 0.866359873333333
- 00:07:57.460 --> 00:07:58.644 different flavors of resistance,
- NOTE Confidence: 0.866359873333333
- $00:07:58.650 \longrightarrow 00:07:59.268$ the most common,
- NOTE Confidence: 0.866359873333333
- $00:07:59.268 \rightarrow 00:08:00.710$ so I don't want to mislead you.
- NOTE Confidence: 0.866359873333333
- $00{:}08{:}00{.}710 \dashrightarrow 00{:}08{:}02{.}929$ The most common is probably still something
- NOTE Confidence: 0.866359873333333
- $00:08:02.929 \dashrightarrow 00:08:04.909$ that looks like an adenocarcinoma.
- NOTE Confidence: 0.866359873333333
- $00:08:04.910 \dashrightarrow 00:08:07.584$ It still can be responsive to more
- NOTE Confidence: 0.866359873333333
- $00{:}08{:}07{.}584 \dashrightarrow 00{:}08{:}09{.}412$ potent antiandrogens, but a subset,
- NOTE Confidence: 0.866359873333333
- $00:08:09.412 \longrightarrow 00:08:11.378$ maybe 10 to 15% will have
- NOTE Confidence: 0.866359873333333
- $00:08:11.378 \longrightarrow 00:08:12.748$ something that looks like this.
- NOTE Confidence: 0.866359873333333
- $00{:}08{:}12.750 \dashrightarrow 00{:}08{:}14.980$ So it's a neuroendocrine prostate
- NOTE Confidence: 0.866359873333333
- $00:08:14.980 \rightarrow 00:08:17.210$ cancer that's no longer responding
- NOTE Confidence: 0.866359873333333
- $00{:}08{:}17.283 \dashrightarrow 00{:}08{:}19.283$ to AR the rapy and something
- NOTE Confidence: 0.866359873333333
- $00:08:19.283 \rightarrow 00:08:21.283$ usually these patients have very,
- NOTE Confidence: 0.866359873333333

00:08:21.290 --> 00:08:22.514 very aggressive disease.

NOTE Confidence: 0.866359873333333

 $00{:}08{:}22.514 \dashrightarrow 00{:}08{:}24.962$ If you look under the microscope

NOTE Confidence: 0.866359873333333

00:08:24.962 --> 00:08:27.390 and perform immunohistochemistry,

NOTE Confidence: 0.866359873333333

 $00:08:27.390 \longrightarrow 00:08:30.288$ you'll see that you have the adenocarcinomas

NOTE Confidence: 0.866359873333333

 $00:08:30.288 \longrightarrow 00:08:33.008$ are very positive for Antrim receptor

NOTE Confidence: 0.866359873333333

 $00:08:33.008 \rightarrow 00:08:35.816$ expression and are not positive for

NOTE Confidence: 0.866359873333333

00:08:35.816 --> 00:08:38.357 neuroendocrine markers such as synaptophysin.

NOTE Confidence: 0.866359873333333

00:08:38.360 --> 00:08:40.420 And for neuroendocrine cancers,

NOTE Confidence: 0.866359873333333

 $00:08:40.420 \dashrightarrow 00:08:42.995$ you lose AR protein expression.

NOTE Confidence: 0.866359873333333

 $00:08:43.000 \rightarrow 00:08:43.855$ Now that's important,

NOTE Confidence: 0.866359873333333

 $00:08:43.855 \longrightarrow 00:08:45.618$ just one important point, and this is

NOTE Confidence: 0.866359873333333

 $00:08:45.618 \rightarrow 00:08:46.854$ probably true in many other cancers.

NOTE Confidence: 0.866359873333333

00:08:46.860 --> 00:08:48.900 If you block A R and now you

NOTE Confidence: 0.866359873333333

00:08:48.900 - 00:08:51.019 have a neuroendocrine tumor,

NOTE Confidence: 0.866359873333333

 $00:08:51.020 \longrightarrow 00:08:52.132$ the pathways for AR,

NOTE Confidence: 0.866359873333333

 $00:08:52.132 \rightarrow 00:08:54.560$ so you might see at the transcript.

- NOTE Confidence: 0.866359873333333
- $00:08:54.560 \rightarrow 00:08:56.936$ Level an attempts for Andrew receptor
- NOTE Confidence: 0.866359873333333
- $00:08:56.936 \longrightarrow 00:08:59.312$ to produce protein but but protein
- NOTE Confidence: 0.866359873333333
- $00:08:59.312 \longrightarrow 00:09:01.490$ levels are are usually very low.
- NOTE Confidence: 0.866359873333333
- $00:09:01.490 \longrightarrow 00:09:04.415$ So you don't see active
- NOTE Confidence: 0.866359873333333
- 00:09:04.415 --> 00:09:06.170 Andrew receptor protein.
- NOTE Confidence: 0.866359873333333
- $00:09:06.170 \dashrightarrow 00:09:08.648$ These patients have a very poor outcome.
- NOTE Confidence: 0.866359873333333
- $00:09:08.650 \rightarrow 00:09:12.227$ So patients who are now diagnosed with
- NOTE Confidence: 0.866359873333333
- 00:09:12.227 --> 00:09:14.270 neuroendocrine prostate cancer clinically
- NOTE Confidence: 0.866359873333333
- $00{:}09{:}14.270 \dashrightarrow 00{:}09{:}16.732$ or by biopsy usually have anywhere
- NOTE Confidence: 0.866359873333333
- $00:09:16.732 \longrightarrow 00:09:19.490$ from 7 to 12 months median survival.
- NOTE Confidence: 0.866359873333333
- $00:09:19.490 \longrightarrow 00:09:22.178$ So very poor and there are
- NOTE Confidence: 0.866359873333333
- $00:09:22.178 \longrightarrow 00:09:23.970$ very few therapy options.
- NOTE Confidence: 0.866359873333333
- $00:09:23.970 \longrightarrow 00:09:25.354$ In showing this slide,
- NOTE Confidence: 0.866359873333333
- $00{:}09{:}25{.}354 \dashrightarrow 00{:}09{:}27{.}921$ I can show that we have an
- NOTE Confidence: 0.866359873333333
- 00:09:27.921 --> 00:09:29.549 example of a denocarcinoma all
- NOTE Confidence: 0.866359873333333

 $00:09:29.549 \rightarrow 00:09:32.190$ the way to small cell cancer.

NOTE Confidence: 0.866359873333333

00:09:32.190 --> 00:09:34.500 You can see in the adenocarcinoma it's

NOTE Confidence: 0.866359873333333

 $00:09:34.500 \rightarrow 00:09:36.846$ positive for PSA which is a surrogate

NOTE Confidence: 0.866359873333333

 $00:09:36.846 \longrightarrow 00:09:38.790$ for antron singling and that it's

NOTE Confidence: 0.866359873333333

 $00:09:38.850 \rightarrow 00:09:41.310$ negative for neuroendocrine markers here.

NOTE Confidence: 0.866359873333333

 $00:09:41.310 \longrightarrow 00:09:43.676$ And then as the tumor seems to,

NOTE Confidence: 0.866359873333333

 $00{:}09{:}43.680 \dashrightarrow 00{:}09{:}45.252$ as we see different tumors where

NOTE Confidence: 0.866359873333333

 $00:09:45.252 \rightarrow 00:09:46.610$ you have this neuroendocrine tumor,

NOTE Confidence: 0.866359873333333

 $00:09:46.610 \longrightarrow 00:09:48.692$ we see a positivity for the

NOTE Confidence: 0.866359873333333

 $00:09:48.692 \longrightarrow 00:09:49.386$ neuroendocrine markers.

NOTE Confidence: 0.866359873333333

 $00:09:49.390 \longrightarrow 00:09:51.638$ Now I think the important point here is

NOTE Confidence: 0.866359873333333

 $00:09:51.638 \rightarrow 00:09:53.526$ an additional comment is that this is.

NOTE Confidence: 0.866359873333333

 $00:09:53.530 \longrightarrow 00:09:55.240$ All from the same patient.

NOTE Confidence: 0.866359873333333

 $00:09:55.240 \rightarrow 00:09:57.180$ This patient had metastatic prostate

NOTE Confidence: 0.866359873333333

 $00{:}09{:}57.180 \dashrightarrow 00{:}09{:}59.564$ cancer and these are from almost

NOTE Confidence: 0.866359873333333

 $00:09:59.564 \dashrightarrow 00:10:01.820$ the same lesion in different areas.

- NOTE Confidence: 0.866359873333333
- $00:10:01.820 \rightarrow 00:10:04.333$ And so it's possible that you not
- NOTE Confidence: 0.866359873333333
- $00:10:04.333 \rightarrow 00:10:06.803$ only have this trans differentiation
- NOTE Confidence: 0.866359873333333
- 00:10:06.803 --> 00:10:08.777 or lineage plasticity,
- NOTE Confidence: 0.866359873333333
- $00:10:08.780 \longrightarrow 00:10:11.188$ but it may be in the context
- NOTE Confidence: 0.866359873333333
- 00:10:11.188 --> 00:10:12.220 of mixed Histology.
- NOTE Confidence: 0.866359873333333
- 00:10:12.220 --> 00:10:15.620 So I think it's important to just remember
- NOTE Confidence: 0.866359873333333
- $00:10:15.620 \rightarrow 00:10:17.936$ that heterogeneities obviously were is
- NOTE Confidence: 0.866359873333333
- $00:10:17.936 \longrightarrow 00:10:20.256$ an important component of resistance.
- NOTE Confidence: 0.866359873333333
- 00:10:20.260 --> 00:10:21.944 A few years ago,
- NOTE Confidence: 0.866359873333333
- $00:10:21.944 \longrightarrow 00:10:23.879$ probably around 2013 we started
- NOTE Confidence: 0.866359873333333
- $00:10:23.879 \longrightarrow 00:10:25.694$ a stand up to cancer.
- NOTE Confidence: 0.866359873333333
- 00:10:25.700 --> 00:10:28.275 PCF funded prostate Cancer Foundation
- NOTE Confidence: 0.866359873333333
- $00{:}10{:}28.275 \dashrightarrow 00{:}10{:}32.235$ funded trial which was one of the first
- NOTE Confidence: 0.866359873333333
- $00{:}10{:}32.235 \dashrightarrow 00{:}10{:}34.839$ precision on cology trials or number of
- NOTE Confidence: 0.866359873333333
- 00:10:34.839 --> 00:10:37.500 of PI's leading this Charles Sawyers,
- NOTE Confidence: 0.866359873333333

00:10:37.500 --> 00:10:38.450 Real Shanian,

NOTE Confidence: 0.866359873333333

00:10:38.450 --> 00:10:41.300 Levi Garraway among others if Phil

NOTE Confidence: 0.866359873333333

00:10:41.300 --> 00:10:44.750 Kantoff and in this study one of the

NOTE Confidence: 0.866359873333333

 $00:10:44.750 \rightarrow 00:10:47.479$ things that as pathologist was great is,

NOTE Confidence: 0.866359873333333

 $00{:}10{:}47{.}480 \dashrightarrow 00{:}10{:}49{.}552$ is that we're able to look at now

NOTE Confidence: 0.866359873333333

 $00:10:49.552 \longrightarrow 00:10:51.784$ over 1000 cases of patients that

NOTE Confidence: 0.866359873333333

 $00:10:51.784 \rightarrow 00:10:53.428$ were prospectively collected who

NOTE Confidence: 0.866359873333333

 $00:10:53.428 \rightarrow 00:10:55.639$ were failing Andrew and decoration.

NOTE Confidence: 0.866359873333333

 $00:10:55.640 \rightarrow 00:10:58.480$ Therapy and one sort or the other from

NOTE Confidence: 0.866359873333333

 $00:10:58.480 \rightarrow 00:11:00.176$ multiple institutions and we could

NOTE Confidence: 0.866359873333333

 $00{:}11{:}00{.}176$ --> $00{:}11{:}02{.}030$ ask the question as a pathologist.

NOTE Confidence: 0.866359873333333

00:11:02.030 --> 00:11:04.074 If we used AR signaling as one

NOTE Confidence: 0.866359873333333

 $00{:}11{:}04.074 \dashrightarrow 00{:}11{:}05.977$ score to look how a denocarcinoma

NOTE Confidence: 0.866359873333333

00:11:05.977 --> 00:11:07.889 tumor was and neuroendocrine

NOTE Confidence: 0.866359873333333

 $00:11:07.889 \rightarrow 00:11:09.801$ signaling because we had

NOTE Confidence: 0.818726499285714

 $00:11:09.874 \longrightarrow 00:11:12.159$ transcriptomic data as to how

- NOTE Confidence: 0.818726499285714
- 00:11:12.159 --> 00:11:13.530 neuroendocrine tumor was,
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}13.530 \dashrightarrow 00{:}11{:}15.756$ we might expect to see 2A division
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}15.756 \dashrightarrow 00{:}11{:}18.376$ into 2 camps and we could expect that
- NOTE Confidence: 0.818726499285714
- $00:11:18.376 \longrightarrow 00:11:20.838$ there might be a third gradient of
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}20.838 \dashrightarrow 00{:}11{:}23.226$ what tumors that are in transition.
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}23{.}230 \dashrightarrow 00{:}11{:}24{.}730$ This is the real data.
- NOTE Confidence: 0.818726499285714
- $00:11:24.730 \longrightarrow 00:11:26.770$ So it looks doesn't look like.
- NOTE Confidence: 0.818726499285714
- 00:11:26.770 --> 00:11:28.714 Seven, I think this was at the time
- NOTE Confidence: 0.818726499285714
- 00:11:28.714 --> 00:11:30.898 we had around 500 cases, but many,
- NOTE Confidence: 0.818726499285714
- $00:11:30.898 \rightarrow 00:11:33.166$ many of the cases are sitting here,
- NOTE Confidence: 0.818726499285714
- $00:11:33.170 \rightarrow 00:11:36.450$ so high anger receptor signaling
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}36{.}450 \dashrightarrow 00{:}11{:}37{.}574$ only some of them.
- NOTE Confidence: 0.818726499285714
- $00:11:37.574 \rightarrow 00:11:39.260$ So I mentioned about 15 percent,
- NOTE Confidence: 0.818726499285714
- $00{:}11{:}39{.}260 \dashrightarrow 00{:}11{:}42{.}095$ 10 to 15% of our cases showed
- NOTE Confidence: 0.818726499285714
- 00:11:42.095 --> 00:11:42.905 neuroendocrine features.
- NOTE Confidence: 0.818726499285714

 $00:11:42.910 \rightarrow 00:11:45.122$ What was surprising and this is really

NOTE Confidence: 0.818726499285714

00:11:45.122 --> 00:11:47.040 the first prospective study that I was

NOTE Confidence: 0.818726499285714

 $00{:}11{:}47.040 \dashrightarrow 00{:}11{:}49.090$ aware of this or have been involved in,

NOTE Confidence: 0.818726499285714

00:11:49.090 - 00:11:50.818 in prostate cancer in this setting

NOTE Confidence: 0.818726499285714

 $00{:}11{:}50{.}818 \dashrightarrow 00{:}11{:}53{.}184$ was that when we looked in the this

NOTE Confidence: 0.818726499285714

00:11:53.184 --> 00:11:55.337 quadrant here where we expect to see

NOTE Confidence: 0.818726499285714

 $00:11:55.337 \rightarrow 00:11:57.515$ these very blue cells and neuroendocrine.

NOTE Confidence: 0.818726499285714

 $00:11:57.520 \longrightarrow 00:11:59.235$ So they showed you we see things

NOTE Confidence: 0.818726499285714

00:11:59.235 --> 00:12:00.847 that don't quite look like

NOTE Confidence: 0.818726499285714

 $00{:}12{:}00{.}847 \dashrightarrow 00{:}12{:}02{.}080$ neuroendocrine prostate cancer,

NOTE Confidence: 0.818726499285714

 $00:12:02.080 \longrightarrow 00:12:03.500$ they look like something else.

NOTE Confidence: 0.818726499285714

00:12:03.500 --> 00:12:06.020 So it has a squamous appearance,

NOTE Confidence: 0.818726499285714

 $00:12:06.020 \longrightarrow 00:12:06.940$ take my word for it,

NOTE Confidence: 0.818726499285714

00:12:06.940 --> 00:12:07.920 if you're not a pathologist,

NOTE Confidence: 0.818726499285714

00:12:07.920 --> 00:12:10.272 but it doesn't look like a

NOTE Confidence: 0.818726499285714

 $00:12:10.272 \rightarrow 00:12:11.448$ typical neuroendocrine tumor.

- NOTE Confidence: 0.818726499285714
- $00:12:11.450 \longrightarrow 00:12:13.991$ And then in area where we see
- NOTE Confidence: 0.818726499285714
- $00:12:13.991 \longrightarrow 00:12:16.038$ very strong expression for the
- NOTE Confidence: 0.818726499285714
- 00:12:16.038 --> 00:12:17.806 answer and receptor signaling,
- NOTE Confidence: 0.818726499285714
- $00:12:17.810 \rightarrow 00:12:20.150$ not just Andrew receptor but signaling,
- NOTE Confidence: 0.818726499285714
- $00{:}12{:}20{.}150 \dashrightarrow 00{:}12{:}21{.}435$ we see something that looks
- NOTE Confidence: 0.818726499285714
- $00{:}12{:}21{.}435 \dashrightarrow 00{:}12{:}22{.}463$ like a neuroendocrine cancer.
- NOTE Confidence: 0.818726499285714
- $00:12:22.470 \longrightarrow 00:12:23.610$ These were not mixed up.
- NOTE Confidence: 0.818726499285714
- $00:12:23.610 \longrightarrow 00:12:24.612$ We confirmed everything.
- NOTE Confidence: 0.818726499285714
- $00:12:24.612 \longrightarrow 00:12:27.190$ So I think what is very important is,
- NOTE Confidence: 0.818726499285714
- $00:12:27.190 \longrightarrow 00:12:28.886$ is that the Histology,
- NOTE Confidence: 0.818726499285714
- $00{:}12{:}28.886 \dashrightarrow 00{:}12{:}31.430$ so the phenotype and the genotype
- NOTE Confidence: 0.818726499285714
- $00:12:31.513 \rightarrow 00:12:33.485$ don't necessarily correlate that
- NOTE Confidence: 0.818726499285714
- $00:12:33.485 \rightarrow 00:12:37.065$ well and this causes obviously a lot
- NOTE Confidence: 0.818726499285714
- $00{:}12{:}37.065 \dashrightarrow 00{:}12{:}39.249$ of confusion for classification,
- NOTE Confidence: 0.818726499285714
- $00:12:39.250 \rightarrow 00:12:41.638$ which is very important for treatment.
- NOTE Confidence: 0.818726499285714

 $00:12:41.640 \longrightarrow 00:12:43.576$ This is a case that's in the middle

NOTE Confidence: 0.818726499285714

 $00{:}12{:}43.576 \dashrightarrow 00{:}12{:}45.917$ and it shows a very unusual Histology.

NOTE Confidence: 0.818726499285714

 $00:12:45.920 \longrightarrow 00:12:47.960$ So for somebody doing prostate

NOTE Confidence: 0.818726499285714

 $00:12:47.960 \rightarrow 00:12:50.000$ pathology for many years now,

NOTE Confidence: 0.818726499285714

 $00{:}12{:}50{.}000 \dashrightarrow 00{:}12{:}52{.}184$ we usually see certain morphologies but

NOTE Confidence: 0.818726499285714

 $00{:}12{:}52{.}184 \dashrightarrow 00{:}12{:}54{.}900$ we don't see these odd looking nuclei.

NOTE Confidence: 0.818726499285714

 $00{:}12{:}54{.}900 \dashrightarrow 00{:}12{:}57{.}042$ And I think this is really related

NOTE Confidence: 0.818726499285714

 $00:12:57.042 \longrightarrow 00:12:58.600$ to a few factors,

NOTE Confidence: 0.818726499285714

 $00{:}12{:}58{.}600 \dashrightarrow 00{:}13{:}01{.}432$ but at least one factor is that patients

NOTE Confidence: 0.818726499285714

 $00:13:01.432 \rightarrow 00:13:04.057$ are getting very potent anti androgens.

NOTE Confidence: 0.818726499285714

 $00:13:04.060 \rightarrow 00:13:06.314$ Another factor is that they're living longer,

NOTE Confidence: 0.818726499285714

 $00:13:06.320 \rightarrow 00:13:08.300$ so they're able to survive longer.

NOTE Confidence: 0.818726499285714

 $00:13:08.300 \longrightarrow 00:13:10.040$ So we're seeing changes that

NOTE Confidence: 0.818726499285714

 $00:13:10.040 \longrightarrow 00:13:11.432$ we previously hadn't seen.

NOTE Confidence: 0.818726499285714

 $00{:}13{:}11{.}440 \dashrightarrow 00{:}13{:}13{.}328$ So I think this is part of the

NOTE Confidence: 0.818726499285714

 $00{:}13{:}13{.}328 \dashrightarrow 00{:}13{:}14{.}538$ natural evolution of the cancer.

 $00:13:14.540 \longrightarrow 00:13:16.556$ It's just that maybe we haven't seen this.

NOTE Confidence: 0.818726499285714

 $00:13:16.560 \longrightarrow 00:13:17.904$ And then in prostate,

NOTE Confidence: 0.818726499285714

00:13:17.904 --> 00:13:19.920 maybe in other cancers as well,

NOTE Confidence: 0.818726499285714

 $00:13:19.920 \rightarrow 00:13:22.380$ metastatic biopsies are not the norm.

NOTE Confidence: 0.818726499285714

 $00{:}13{:}22{.}380 \dashrightarrow 00{:}13{:}24{.}270$ So usually we're not actually seeing

NOTE Confidence: 0.818726499285714

 $00{:}13{:}24{.}270 \dashrightarrow 00{:}13{:}26{.}680$ what's going on as you treat patients.

NOTE Confidence: 0.818726499285714

 $00:13:26.680 \longrightarrow 00:13:29.158$ So this was eye opening for me

NOTE Confidence: 0.818726499285714

 $00:13:29.158 \longrightarrow 00:13:30.220$ as a pathologist.

NOTE Confidence: 0.818726499285714

 $00{:}13{:}30{.}220 \dashrightarrow 00{:}13{:}31{.}822$ When we looked at the molecular

NOTE Confidence: 0.818726499285714

 $00:13:31.822 \rightarrow 00:13:33.539$ alterations in some of these cases,

NOTE Confidence: 0.818726499285714

 $00:13:33.540 \rightarrow 00:13:36.424$ they tended to have P53 and RB

NOTE Confidence: 0.818726499285714

 $00{:}13{:}36{.}424 \dashrightarrow 00{:}13{:}38{.}692$ alterations in these cases as

NOTE Confidence: 0.818726499285714

 $00{:}13{:}38.692 \dashrightarrow 00{:}13{:}40.580$ well as in neuroendocrine.

NOTE Confidence: 0.818726499285714

00:13:40.580 --> 00:13:41.600 I'll talk a little bit more.

NOTE Confidence: 0.818726499285714

 $00:13:41.600 \longrightarrow 00:13:42.274$ About that.

 $00:13:42.274 \rightarrow 00:13:44.633$ But this leaves us with a picture

NOTE Confidence: 0.818726499285714

 $00{:}13{:}44{.}633 \dashrightarrow 00{:}13{:}47{.}029$ where we have a spectrum of disease.

NOTE Confidence: 0.818726499285714

00:13:47.030 --> 00:13:48.845 It's very difficult just looking

NOTE Confidence: 0.818726499285714

 $00:13:48.845 \rightarrow 00:13:50.890$ under the microscope to classify it.

NOTE Confidence: 0.818726499285714

 $00:13:50.890 \longrightarrow 00:13:52.416$ So it really suggested to us that

NOTE Confidence: 0.818726499285714

 $00:13:52.416 \longrightarrow 00:13:54.164$ we need to come up with other

NOTE Confidence: 0.818726499285714

 $00:13:54.164 \longrightarrow 00:13:55.204$ ways of classifying it.

NOTE Confidence: 0.818726499285714

00:13:55.210 --> 00:13:57.950 And I would say right now we don't have that.

NOTE Confidence: 0.818726499285714

00:13:57.950 --> 00:13:59.306 I mean, we're moving towards that,

NOTE Confidence: 0.876687335555556

 $00:13:59.310 \longrightarrow 00:14:01.165$ but we don't really have

NOTE Confidence: 0.876687335555556

 $00{:}14{:}01{.}165 \dashrightarrow 00{:}14{:}02{.}649$ that established to date.

NOTE Confidence: 0.876687335555556

00:14:02.650 --> 00:14:05.760 So as I just mentioned,

NOTE Confidence: 0.876687335555556

 $00:14:05.760 \longrightarrow 00:14:07.824$ the phenotype and the scores or

NOTE Confidence: 0.876687335555556

 $00:14:07.824 \rightarrow 00:14:10.115$ the signaling scores that you have

NOTE Confidence: 0.876687335555556

 $00:14:10.115 \rightarrow 00:14:11.807$ from transcriptomics don't match.

NOTE Confidence: 0.876687335555556

 $00:14:11.810 \rightarrow 00:14:14.276$ Perfectly so. And we also recognize

 $00:14:14.276 \rightarrow 00:14:15.920$ they're probably intermediate states.

NOTE Confidence: 0.876687335555556

 $00{:}14{:}15{.}920 \dashrightarrow 00{:}14{:}18{.}174$ So I think those are important observations.

NOTE Confidence: 0.876687335555556

 $00{:}14{:}18{.}180 \dashrightarrow 00{:}14{:}21{.}042$ So we start out with a model where we

NOTE Confidence: 0.876687335555556

 $00:14:21.042 \rightarrow 00:14:24.116$ wanted to look at very discrete differences,

NOTE Confidence: 0.876687335555556

 $00:14:24.120 \rightarrow 00:14:26.524$ adenocarcinoma and neuroendocrine tumors.

NOTE Confidence: 0.876687335555556

 $00:14:26.524 \rightarrow 00:14:28.940$ In fact, when we look more carefully,

NOTE Confidence: 0.876687335555556

 $00{:}14{:}28{.}940 \dashrightarrow 00{:}14{:}32{.}034$ what we see is a whole collection

NOTE Confidence: 0.876687335555556

00:14:32.034 --> 00:14:33.360 of intermediate morphologies,

NOTE Confidence: 0.876687335555556

 $00{:}14{:}33{.}360 \dashrightarrow 00{:}14{:}35{.}888$ genotype and also transcriptomic

NOTE Confidence: 0.876687335555556

 $00:14:35.888 \rightarrow 00:14:38.416$ and probably epigenetic alterations

NOTE Confidence: 0.876687335555556

 $00:14:38.416 \dashrightarrow 00:14:41.869$ about the same time we wanted to do.

NOTE Confidence: 0.876687335555556

 $00:14:41.870 \longrightarrow 00:14:43.802$ A very focused study at looking

NOTE Confidence: 0.876687335555556

 $00{:}14{:}43.802 \dashrightarrow 00{:}14{:}45.784$ at these extremes to ask the

NOTE Confidence: 0.876687335555556

 $00{:}14{:}45{.}784 \dashrightarrow 00{:}14{:}47{.}989$ question what are some of the other

NOTE Confidence: 0.876687335555556

 $00:14:47.989 \longrightarrow 00:14:49.800$ factors that might play a role.

 $00:14:49.800 \rightarrow 00:14:54.264$ So genomics but also epigenetics and

NOTE Confidence: 0.876687335555556

 $00:14:54.264 \rightarrow 00:14:57.670$ transcriptomics were applied then to.

NOTE Confidence: 0.876687335555556

 $00:14:57.670 \longrightarrow 00:14:58.381$ A set of,

NOTE Confidence: 0.876687335555556

 $00:14:58.381 \longrightarrow 00:15:01.002$ I think at the time 50 or 60 cases

NOTE Confidence: 0.876687335555556

 $00{:}15{:}01.002 \dashrightarrow 00{:}15{:}03.237$ where we had bonafide neuroendocrine

NOTE Confidence: 0.876687335555556

 $00:15:03.237 \rightarrow 00:15:05.632$ cancers diagnosed by pathology and

NOTE Confidence: 0.876687335555556

 $00{:}15{:}05{.}632 \dashrightarrow 00{:}15{:}08{.}097$ a denocarcinomas and we compared them.

NOTE Confidence: 0.876687335555556

00:15:08.100 --> 00:15:09.472 And I'm not going to go through

NOTE Confidence: 0.876687335555556

 $00:15:09.472 \longrightarrow 00:15:10.060$ these published studies,

NOTE Confidence: 0.876687335555556

00:15:10.060 --> 00:15:11.116 but I just want to highlight,

NOTE Confidence: 0.876687335555556

 $00:15:11.120 \longrightarrow 00:15:14.130$ I think the important finding for us

NOTE Confidence: 0.876687335555556

 $00:15:14.130 \longrightarrow 00:15:17.757$ was that we expected to see some some

NOTE Confidence: 0.876687335555556

 $00:15:17.760 \rightarrow 00:15:19.935$ really exciting genomic alteration that

NOTE Confidence: 0.876687335555556

 $00:15:19.935 \rightarrow 00:15:21.675$ would characterize the difference,

NOTE Confidence: 0.876687335555556

 $00{:}15{:}21.680 \dashrightarrow 00{:}15{:}22.640$ but we didn't.

NOTE Confidence: 0.876687335555556

 $00:15:22.640 \rightarrow 00:15:24.880$ What we really see is a commonality

00:15:24.944 --> 00:15:27.960 that RB1 and P53 are very commonly.

NOTE Confidence: 0.876687335555556

 $00:15:27.960 \rightarrow 00:15:30.246$ Altered in the small cell phenotype,

NOTE Confidence: 0.876687335555556

00:15:30.250 --> 00:15:33.826 less commonly altered in the adenocarcinoma,

NOTE Confidence: 0.876687335555556

 $00:15:33.830 \rightarrow 00:15:36.152$ but we do see it and that in general

NOTE Confidence: 0.876687335555556

 $00:15:36.152 \rightarrow 00:15:38.488$ the overlap in genomic alterations,

NOTE Confidence: 0.876687335555556

 $00:15:38.490 \rightarrow 00:15:40.518$ copy number alterations is very similar

NOTE Confidence: 0.876687335555556

 $00:15:40.518 \rightarrow 00:15:42.618$ except for let's say the Andrew

NOTE Confidence: 0.876687335555556

 $00:15:42.618 \rightarrow 00:15:44.682$ receptor where that would be something

NOTE Confidence: 0.876687335555556

 $00:15:44.682 \rightarrow 00:15:46.778$ that's very different and altered in

NOTE Confidence: 0.876687335555556

 $00{:}15{:}46.778 \dashrightarrow 00{:}15{:}50.470$ a denocarcinoma but not in the small cell.

NOTE Confidence: 0.876687335555556

 $00:15:50.470 \longrightarrow 00:15:52.886$ When we looked at the data in combination,

NOTE Confidence: 0.876687335555556

 $00:15:52.890 \longrightarrow 00:15:54.474$ so looking at DNA,

NOTE Confidence: 0.876687335555556

 $00{:}15{:}54{.}474 \dashrightarrow 00{:}15{:}56{.}850$ RNA and epigenetics and then asking

NOTE Confidence: 0.876687335555556

 $00{:}15{:}56{.}926 \dashrightarrow 00{:}15{:}59{.}491$ the question what which element

NOTE Confidence: 0.876687335555556

 $00{:}15{:}59{.}491 \dashrightarrow 00{:}16{:}01{.}543$ best explained the differences

 $00:16:01.543 \rightarrow 00:16:03.528$ between the two phenotypes.

NOTE Confidence: 0.876687335555556

00:16:03.530 --> 00:16:05.095 I think importantly the numbers

NOTE Confidence: 0.876687335555556

00:16:05.095 --> 00:16:06.660 may differ depending on the

NOTE Confidence: 0.876687335555556

 $00:16:06.718 \rightarrow 00:16:08.788$ configuration of the of the population.

NOTE Confidence: 0.876687335555556

 $00:16:08.790 \longrightarrow 00:16:11.470$ But certainly epigenetics or methylation

NOTE Confidence: 0.876687335555556

 $00:16:11.470 \rightarrow 00:16:14.150$ helped explain the difference quite,

NOTE Confidence: 0.876687335555556

 $00:16:14.150 \longrightarrow 00:16:16.430$ quite well in this population.

NOTE Confidence: 0.876687335555556

00:16:16.430 --> 00:16:17.522 And I'm not going to say too

NOTE Confidence: 0.876687335555556

 $00:16:17.522 \rightarrow 00:16:18.210$ much more about that,

NOTE Confidence: 0.876687335555556

 $00:16:18.210 \rightarrow 00:16:20.250$ but we think methylation or epigenetic.

NOTE Confidence: 0.876687335555556

 $00:16:20.250 \rightarrow 00:16:22.250$ Alterations are very important.

NOTE Confidence: 0.876687335555556

 $00:16:22.250 \longrightarrow 00:16:25.733$ So here's a figure that we made

NOTE Confidence: 0.876687335555556

00:16:25.733 --> 00:16:28.449 for a review and the concept was

NOTE Confidence: 0.876687335555556

 $00:16:28.449 \longrightarrow 00:16:31.649$ that at some point adenocarcinomas,

NOTE Confidence: 0.876687335555556

00:16:31.650 --> 00:16:32.356 there's a,

NOTE Confidence: 0.876687335555556

 $00:16:32.356 \longrightarrow 00:16:34.121$ there's an inflection point where

- NOTE Confidence: 0.876687335555556
- $00:16:34.121 \rightarrow 00:16:35.509$ adenocarcinomas maybe go through

 $00{:}16{:}35{.}509 \dashrightarrow 00{:}16{:}37{.}406$ some sort of stem like state and

NOTE Confidence: 0.876687335555556

00:16:37.406 --> 00:16:38.980 then undergo lineage plasticity.

NOTE Confidence: 0.876687335555556

 $00:16:38.980 \longrightarrow 00:16:40.898$ Now I think for people in the

NOTE Confidence: 0.876687335555556

 $00:16:40.898 \longrightarrow 00:16:41.720$ lung cancer field,

NOTE Confidence: 0.876687335555556

 $00{:}16{:}41.720 \dashrightarrow 00{:}16{:}44.180$ this was something not unexpected,

NOTE Confidence: 0.876687335555556

 $00{:}16{:}44{.}180 \dashrightarrow 00{:}16{:}46{.}623$ but this is something we wanted to

NOTE Confidence: 0.876687335555556

 $00:16:46.623 \rightarrow 00:16:48.671$ explore in prostate as well because

NOTE Confidence: 0.876687335555556

 $00{:}16{:}48.671 \dashrightarrow 00{:}16{:}50.841$ we think that at some point he's

NOTE Confidence: 0.876687335555556

 $00:16:50.914 \longrightarrow 00:16:53.159$ around 10 to 15% of the cases.

NOTE Confidence: 0.876687335555556

 $00:16:53.159 \rightarrow 00:16:55.980$ Are no longer responding to AR driven

NOTE Confidence: 0.876687335555556

 $00{:}16{:}56.065 \dashrightarrow 00{:}16{:}58.435$ the rapies and become a RH negative

NOTE Confidence: 0.876687335555556

 $00{:}16{:}58{.}435 \dashrightarrow 00{:}17{:}01{.}998$ in a sense that then they will then

NOTE Confidence: 0.876687335555556

 $00{:}17{:}01{.}998 \dashrightarrow 00{:}17{:}04{.}368$ either trans differentiate to small

NOTE Confidence: 0.876687335555556

 $00{:}17{:}04.368 \dashrightarrow 00{:}17{:}08.170$ cell or AR negative neuroendocrine negative.

 $00:17:08.170 \longrightarrow 00:17:10.384$ So another type of air negative

NOTE Confidence: 0.876687335555556

 $00:17:10.384 \rightarrow 00:17:12.687$ phenotype and that's I think that

NOTE Confidence: 0.876687335555556

 $00:17:12.687 \rightarrow 00:17:14.943$ was supported by some of the

NOTE Confidence: 0.876687335555556

 $00:17:14.943 \rightarrow 00:17:17.069$ morphologies we saw from the trial.

NOTE Confidence: 0.876687335555556

00:17:17.070 --> 00:17:18.390 I list a number of studies,

NOTE Confidence: 0.8355068866666667

 $00:17:18.390 \longrightarrow 00:17:20.315$ I'll just very briefly make a few

NOTE Confidence: 0.8355068866666667

00:17:20.315 --> 00:17:21.879 comments about the Polycom gene,

NOTE Confidence: 0.8355068866666667

 $00:17:21.880 \longrightarrow 00:17:24.218$ so easy H2. And also the switch

NOTE Confidence: 0.8355068866666667

 $00:17:24.218 \longrightarrow 00:17:26.079$ sniff work that we've done,

NOTE Confidence: 0.8355068866666667

 $00{:}17{:}26.080 \dashrightarrow 00{:}17{:}28.744$ but I I think others are are quite

NOTE Confidence: 0.8355068866666667

 $00{:}17{:}28.744 \dashrightarrow 00{:}17{:}30.977$ interested also for the lung cancer spore.

NOTE Confidence: 0.8355068866666667

 $00:17:30.980 \longrightarrow 00:17:32.916$ It's probably quite interesting

NOTE Confidence: 0.8355068866666667

 $00:17:32.916 \longrightarrow 00:17:34.852$ thinking about epigenetic regulation

NOTE Confidence: 0.8355068866666667

 $00:17:34.852 \longrightarrow 00:17:36.818$ and where we stand today.

NOTE Confidence: 0.835506886666667

 $00:17:36.820 \rightarrow 00:17:39.367$ So I think this is a very nice review.

NOTE Confidence: 0.8355068866666667

 $00:17:39.370 \rightarrow 00:17:42.156$ They came out after two papers were

- NOTE Confidence: 0.8355068866666667
- $00:17:42.156 \rightarrow 00:17:44.276$ published in science suggesting that
- NOTE Confidence: 0.8355068866666667
- $00{:}17{:}44.276 \dashrightarrow 00{:}17{:}47.258$ there's a stem like state that occurs
- NOTE Confidence: 0.8355068866666667
- 00:17:47.258 --> 00:17:49.211 before you go to neuroendocrine
- NOTE Confidence: 0.8355068866666667
- $00:17:49.211 \longrightarrow 00:17:51.716$ or to a negative state and that
- NOTE Confidence: 0.8355068866666667
- $00:17:51.716 \longrightarrow 00:17:53.346$ one of the key players.
- NOTE Confidence: 0.835506886666667
- $00:17:53.350 \longrightarrow 00:17:56.738$ It's probably easy H2 so a Polycom
- NOTE Confidence: 0.8355068866666667
- $00:17:56.738 \longrightarrow 00:17:59.058$ gene that's responsible for repression
- NOTE Confidence: 0.835506886666667
- 00:17:59.058 --> 00:18:02.194 of of a large number of of genes
- NOTE Confidence: 0.8355068866666667
- $00{:}18{:}02.280 \dashrightarrow 00{:}18{:}04.700$ associated with AR signaling.
- NOTE Confidence: 0.8355068866666667
- 00:18:04.700 00:18:06.541 And this is just one key experiment
- NOTE Confidence: 0.8355068866666667
- $00:18:06.541 \longrightarrow 00:18:08.274$ from one of the papers from
- NOTE Confidence: 0.835506886666667
- 00:18:08.274 --> 00:18:10.454 David Goodrich's group where they
- NOTE Confidence: 0.835506886666667
- 00:18:10.454 --> 00:18:13.280 demonstrate that if you knock out
- NOTE Confidence: 0.8355068866666667
- 00:18:13.363 --> 00:18:16.040 in a mouse model P53 and RB and
- NOTE Confidence: 0.8355068866666667
- $00:18:16.040 \longrightarrow 00:18:18.200$ that's what's shown here the the
- NOTE Confidence: 0.8355068866666667

 $00:18:18.279 \longrightarrow 00:18:21.543$ tumors are no longer sensitive to

NOTE Confidence: 0.8355068866666667

 $00:18:21.543 \rightarrow 00:18:23.719$ the potent antiandrogen enzalutamide.

NOTE Confidence: 0.8355068866666667

 $00{:}18{:}23{.}720 \dashrightarrow 00{:}18{:}25{.}752$ And so you could see that the tumors

NOTE Confidence: 0.8355068866666667

 $00:18:25.752 \rightarrow 00:18:27.754$ are now continuing to grow even

NOTE Confidence: 0.835506886666667

 $00{:}18{:}27.754 \dashrightarrow 00{:}18{:}29.549$ in the presence of enzalutamide.

NOTE Confidence: 0.8355068866666667

00:18:29.550 --> 00:18:31.558 If you use EH2,

NOTE Confidence: 0.8355068866666667

 $00{:}18{:}31{.}558 \dashrightarrow 00{:}18{:}34{.}068$ you can reactivate or resensitize

NOTE Confidence: 0.8355068866666667

 $00:18:34.068 \rightarrow 00:18:37.353$ these tumors to the epigenetic drugs

NOTE Confidence: 0.835506886666667

 $00:18:37.353 \longrightarrow 00:18:40.616$ that are used now clinically for

NOTE Confidence: 0.8355068866666667

 $00{:}18{:}40.616 \dashrightarrow 00{:}18{:}43.934$ as easy as two inhibitors and you

NOTE Confidence: 0.8355068866666667

 $00:18:43.934 \rightarrow 00:18:45.570$ can reactivate air sensitivity.

NOTE Confidence: 0.8355068866666667

 $00:18:45.570 \longrightarrow 00:18:48.724$ So this is just a concept that this is

NOTE Confidence: 0.8355068866666667

 $00:18:48.724 \rightarrow 00:18:50.920$ a stem like state that's potentially

NOTE Confidence: 0.8355068866666667

 $00:18:50.920 \rightarrow 00:18:53.920$ reversible and I think that's an interesting.

NOTE Confidence: 0.835506886666667

 $00:18:53.920 \longrightarrow 00:18:54.628$ Concept there.

NOTE Confidence: 0.8355068866666667

 $00:18:54.628 \rightarrow 00:18:57.106$ I'm happy to discuss more about those.

- NOTE Confidence: 0.8355068866666667
- $00:18:57.110 \longrightarrow 00:18:58.850$ There's some controversy a little
- NOTE Confidence: 0.8355068866666667
- $00:18:58.850 \longrightarrow 00:18:59.894$ bit about that,
- NOTE Confidence: 0.8355068866666667
- $00:18:59.900 \rightarrow 00:19:02.528$ but I'll just leave it at that for now.
- NOTE Confidence: 0.8355068866666667
- $00:19:02.530 \longrightarrow 00:19:04.030$ We were interested in the other,
- NOTE Confidence: 0.8355068866666667
- $00:19:04.030 \rightarrow 00:19:06.564$ the flip side of the Polycom complex,
- NOTE Confidence: 0.835506886666667
- 00:19:06.570 --> 00:19:08.175 which is a repressive complex
- NOTE Confidence: 0.8355068866666667
- $00:19:08.175 \rightarrow 00:19:10.190$ looking at the switch sniff complex
- NOTE Confidence: 0.835506886666667
- $00:19:10.190 \longrightarrow 00:19:12.633$ and the things that really were of
- NOTE Confidence: 0.8355068866666667
- 00:19:12.633 --> 00:19:14.238 particular interest to us were one,
- NOTE Confidence: 0.8355068866666667
- $00:19:14.240 \longrightarrow 00:19:16.270$ that there's an embryonic switch
- NOTE Confidence: 0.8355068866666667
- $00:19:16.270 \longrightarrow 00:19:18.799$ sniff complex that goes to other
- NOTE Confidence: 0.8355068866666667
- $00:19:18.799 \longrightarrow 00:19:20.089$ types of complexes.
- NOTE Confidence: 0.8355068866666667
- 00:19:20.090 --> 00:19:22.835 So you can have this a stem like complex,
- NOTE Confidence: 0.8355068866666667
- $00{:}19{:}22.840 \dashrightarrow 00{:}19{:}23.818$ but it also.
- NOTE Confidence: 0.8355068866666667
- $00{:}19{:}23.818 \dashrightarrow 00{:}19{:}25.774$ A neuronal complex and the idea
- NOTE Confidence: 0.8355068866666667

 $00:19:25.774 \rightarrow 00:19:28.177$ was that in development it's very

NOTE Confidence: 0.8355068866666667

00:19:28.177 --> 00:19:30.700 important that you're able to have

NOTE Confidence: 0.8355068866666667

00:19:30.700 --> 00:19:32.940 neural development and switch sniff NOTE Confidence: 0.8355068866666667

 $00:19:32.940 \longrightarrow 00:19:35.326$ complex activates and can facilitate

NOTE Confidence: 0.8355068866666667

 $00:19:35.326 \rightarrow 00:19:38.256$ a neural development and playing

NOTE Confidence: 0.8355068866666667

 $00:19:38.256 \rightarrow 00:19:42.394$ an important role that H3K27 marks

NOTE Confidence: 0.8355068866666667

 $00:19:42.394 \longrightarrow 00:19:44.188$ of escalation.

NOTE Confidence: 0.8355068866666667

 $00:19:44.190 \rightarrow 00:19:46.278$ So this is important in development,

NOTE Confidence: 0.835506886666667

00:19:46.280 --> 00:19:49.088 but in cancer it's also known

NOTE Confidence: 0.8355068866666667

 $00:19:49.088 \rightarrow 00:19:51.620$ that that the switch sniff,

NOTE Confidence: 0.8355068866666667

 $00:19:51.620 \rightarrow 00:19:52.583$ particularly the ATP,

NOTE Confidence: 0.8355068866666667

 $00{:}19{:}52{.}583 \dashrightarrow 00{:}19{:}55{.}222$ As us market two and Smart K for are

NOTE Confidence: 0.8355068866666667

 $00{:}19{:}55{.}222 \dashrightarrow 00{:}19{:}57{.}184$ often altered and a particular interest

NOTE Confidence: 0.8355068866666667

 $00:19:57.184 \rightarrow 00:19:59.987$ in many of the synthetic lethal screens.

NOTE Confidence: 0.8355068866666667

 $00:19:59.990 \longrightarrow 00:20:02.286$ So Mark four and smart K2 come

NOTE Confidence: 0.8355068866666667

 $00:20:02.286 \longrightarrow 00:20:05.433$ up as sort of key findings and so
- NOTE Confidence: 0.8355068866666667
- $00{:}20{:}05{.}433 \dashrightarrow 00{:}20{:}08{.}216$ there's been a great interest in
- NOTE Confidence: 0.8355068866666667
- $00:20:08.216 \longrightarrow 00:20:10.696$ translationally developing drugs that
- NOTE Confidence: 0.8355068866666667
- 00:20:10.696 --> 00:20:13.726 would knockout smarca 2 specifically.
- NOTE Confidence: 0.8355068866666667
- $00:20:13.726 \longrightarrow 00:20:17.807$ In smart key for ultra tumors and
- NOTE Confidence: 0.8355068866666667
- $00{:}20{:}17.807 \dashrightarrow 00{:}20{:}20.896$ unfortunately as many of us are
- NOTE Confidence: 0.835506886666667
- 00:20:20.896 --> 00:20:23.301 aware and knowing what's happened,
- NOTE Confidence: 0.8355068866666667
- $00:20:23.310 \longrightarrow 00:20:25.128$ it's very difficult to actually have
- NOTE Confidence: 0.835506886666667
- 00:20:25.128 --> 00:20:27.029 a specific smart gate 2 inhibitor.
- NOTE Confidence: 0.8355068866666667
- $00{:}20{:}27.030 \dashrightarrow 00{:}20{:}29.858$ So most of whether it's an ATP
- NOTE Confidence: 0.8355068866666667
- 00:20:29.858 --> 00:20:31.930 ACE inhibitor or a protac,
- NOTE Confidence: 0.8355068866666667
- $00:20:31.930 \longrightarrow 00:20:33.080$ this has been a difficult,
- NOTE Confidence: 0.8355068866666667
- $00{:}20{:}33.080 \dashrightarrow 00{:}20{:}33.884$ it's been challenging.
- NOTE Confidence: 0.8355068866666667
- $00:20:33.884 \longrightarrow 00:20:35.760$ So most of the work is is
- NOTE Confidence: 0.88847246047619
- $00{:}20{:}35{.}824 \dashrightarrow 00{:}20{:}37{.}840$ really focused on knocking out both
- NOTE Confidence: 0.88847246047619
- $00:20:37.840 \longrightarrow 00:20:39.800$ and creating a synthetic lethality.
- NOTE Confidence: 0.811509029285714

 $00:20:41.930 \longrightarrow 00:20:44.562$ What we found in a sort of as

NOTE Confidence: 0.811509029285714

 $00:20:44.562 \rightarrow 00:20:47.570$ as is very common in prostate,

NOTE Confidence: 0.811509029285714

 $00:20:47.570 \rightarrow 00:20:49.880$ so prostate tends to prostate cancer.

NOTE Confidence: 0.811509029285714

 $00:20:49.880 \rightarrow 00:20:51.710$ Research tends to look at things

NOTE Confidence: 0.811509029285714

 $00:20:51.710 \longrightarrow 00:20:52.930$ differently because for whatever

NOTE Confidence: 0.811509029285714

 $00{:}20{:}52{.}983 \dashrightarrow 00{:}20{:}54{.}699$ reason prostate is a little bit

NOTE Confidence: 0.811509029285714

 $00{:}20{:}54.699 \dashrightarrow 00{:}20{:}55.843$ different than other cancers.

NOTE Confidence: 0.811509029285714

 $00:20:55.850 \rightarrow 00:20:58.643$ And we were interested in looking at

NOTE Confidence: 0.811509029285714

 $00:20:58.643 \rightarrow 00:21:00.739$ the overexpression of smart Guy 4,

NOTE Confidence: 0.811509029285714

 $00:21:00.740 \longrightarrow 00:21:02.721$ which is not usually the case in

NOTE Confidence: 0.811509029285714

 $00:21:02.721 \longrightarrow 00:21:05.165$ in many of the tumors that have

NOTE Confidence: 0.811509029285714

 $00{:}21{:}05{.}165 \dashrightarrow 00{:}21{:}07{.}070$ lost smart gave for expression.

NOTE Confidence: 0.811509029285714

 $00{:}21{:}07{.}070 \dashrightarrow 00{:}21{:}09{.}435$ So these are complicated complexes

NOTE Confidence: 0.811509029285714

 $00:21:09.435 \longrightarrow 00:21:11.327$ and I'll simplify it.

NOTE Confidence: 0.811509029285714

 $00:21:11.330 \longrightarrow 00:21:13.448$ By just saying that there's a

NOTE Confidence: 0.811509029285714

 $00:21:13.448 \longrightarrow 00:21:15.224$ working component which is a

 $00:21:15.224 \rightarrow 00:21:17.006$ TPA and there are two paralogs,

NOTE Confidence: 0.811509029285714

00:21:17.010 --> 00:21:18.746 mark four and smart K2 and fortunately

NOTE Confidence: 0.811509029285714

 $00:21:18.746 \longrightarrow 00:21:20.290$ they also have different names.

NOTE Confidence: 0.811509029285714

00:21:20.290 --> 00:21:22.747 So there's Brahma and Berg one,

NOTE Confidence: 0.811509029285714

00:21:22.750 --> 00:21:26.130 but I'll just call it smart K4 and smart K2.

NOTE Confidence: 0.811509029285714

 $00{:}21{:}26{.}130 \dashrightarrow 00{:}21{:}27{.}975$ And the idea is that most of the work

NOTE Confidence: 0.811509029285714

 $00:21:27.975 \rightarrow 00:21:29.927$ is going and targeting these and we

NOTE Confidence: 0.811509029285714

 $00:21:29.927 \rightarrow 00:21:31.863$ were interested to see what happens

NOTE Confidence: 0.811509029285714

 $00{:}21{:}31{.}863 \dashrightarrow 00{:}21{:}33{.}367$ in prostate cancer progression,

NOTE Confidence: 0.811509029285714

 $00{:}21{:}33{.}370 \dashrightarrow 00{:}21{:}35{.}680$ whether there were mutations or

NOTE Confidence: 0.811509029285714

 $00{:}21{:}35{.}680 \dashrightarrow 00{:}21{:}38{.}510$ alterations in these in the ATP Aces.

NOTE Confidence: 0.811509029285714

 $00{:}21{:}38{.}510 \dashrightarrow 00{:}21{:}39{.}950$ What we found is,

NOTE Confidence: 0.811509029285714

 $00{:}21{:}39{.}950 \dashrightarrow 00{:}21{:}41{.}774$ is that when we look there's as you

NOTE Confidence: 0.811509029285714

 $00{:}21{:}41.774 \dashrightarrow 00{:}21{:}43.769$ look in prostate cancer progression,

NOTE Confidence: 0.811509029285714

 $00{:}21{:}43.770 \dashrightarrow 00{:}21{:}46.458$ we sent to see an increase in smart

 $00:21:46.458 \longrightarrow 00:21:49.050$ K4 and a decrease in smart K2.

NOTE Confidence: 0.811509029285714

 $00{:}21{:}49{.}050 \dashrightarrow 00{:}21{:}51{.}444$ So that's a little bit different than

NOTE Confidence: 0.811509029285714

 $00:21:51.444 \rightarrow 00:21:53.790$ what's seen in some other cancers,

NOTE Confidence: 0.811509029285714

 $00:21:53.790 \longrightarrow 00:21:55.150$ but the other important.

NOTE Confidence: 0.811509029285714

00:21:55.150 --> 00:21:57.739 Features as you see as you look

NOTE Confidence: 0.811509029285714

00:21:57.739 --> 00:21:59.659 at prostate cancer progression,

NOTE Confidence: 0.811509029285714

 $00{:}21{:}59.660 \dashrightarrow 00{:}22{:}02.768$ we also see an increase in some

NOTE Confidence: 0.811509029285714

 $00{:}22{:}02{.}768 \dashrightarrow 00{:}22{:}05{.}285$ of the neural components of the

NOTE Confidence: 0.811509029285714

 $00{:}22{:}05{.}285 \dashrightarrow 00{:}22{:}07{.}655$ switch sniff complex that are there

NOTE Confidence: 0.811509029285714

 $00{:}22{:}07.655 \dashrightarrow 00{:}22{:}09.431$ associated with the the neural

NOTE Confidence: 0.811509029285714

 $00{:}22{:}09{.}431 \dashrightarrow 00{:}22{:}11{.}574$ complex which is called back 53B as

NOTE Confidence: 0.811509029285714

 $00:22:11.574 \rightarrow 00:22:13.550$ one of the as one of the proteins.

NOTE Confidence: 0.811509029285714

 $00{:}22{:}13.550 \dashrightarrow 00{:}22{:}16.350$ So just to visualize this as a pathologist

NOTE Confidence: 0.811509029285714

 $00:22:16.350 \rightarrow 00:22:18.638$ their core complexes don't change.

NOTE Confidence: 0.811509029285714

 $00:22:18.640 \longrightarrow 00:22:21.226$ So going from localized disease or

NOTE Confidence: 0.811509029285714

 $00:22:21.226 \rightarrow 00:22:23.638$ benign tissue to advanced disease

 $00:22:23.638 \rightarrow 00:22:26.106$ that's neuroendocrine positive you.

NOTE Confidence: 0.811509029285714

 $00{:}22{:}26.110 \dashrightarrow 00{:}22{:}27.972$ You don't see any differences but what

NOTE Confidence: 0.811509029285714

00:22:27.972 --> 00:22:30.226 you do see is the neural marker shown

NOTE Confidence: 0.811509029285714

 $00:22:30.226 \rightarrow 00:22:32.385$ here back 53B is only expressed in

NOTE Confidence: 0.811509029285714

 $00:22:32.385 \rightarrow 00:22:34.450$ their endocrine tumor as you'd expect.

NOTE Confidence: 0.811509029285714

 $00{:}22{:}34{.}450 \dashrightarrow 00{:}22{:}37{.}042$ And what we see here is that smart K4,

NOTE Confidence: 0.811509029285714

00:22:37.050 --> 00:22:39.516 so one of the two ATP A says a

NOTE Confidence: 0.811509029285714

 $00:22:39.516 \rightarrow 00:22:41.613$ paralogs is very highly expressed

NOTE Confidence: 0.811509029285714

 $00{:}22{:}41.613 \dashrightarrow 00{:}22{:}43.793$ in the neuroendocrine tumors or

NOTE Confidence: 0.811509029285714

 $00:22:43.793 \rightarrow 00:22:46.252$ maybe the stem like type tumors that

NOTE Confidence: 0.811509029285714

 $00{:}22{:}46{.}252 \dashrightarrow 00{:}22{:}48{.}399$ we see smart K2 is not expressed.

NOTE Confidence: 0.811509029285714

 $00{:}22{:}48{.}399 \dashrightarrow 00{:}22{:}50{.}097$ So we were originally thinking that

NOTE Confidence: 0.811509029285714

 $00:22:50.097 \rightarrow 00:22:51.870$ for us would be very interesting,

NOTE Confidence: 0.811509029285714

 $00{:}22{:}51{.}870 \dashrightarrow 00{:}22{:}53{.}850$ interesting to modulate smart K4

NOTE Confidence: 0.811509029285714

 $00{:}22{:}53.850 \dashrightarrow 00{:}22{:}56.370$ in the contest of prostate cancer.

 $00:22:56.370 \longrightarrow 00:22:57.510$ And just as an aside,

NOTE Confidence: 0.811509029285714

 $00{:}22{:}57{.}510 \dashrightarrow 00{:}23{:}00{.}330$ we don't see any mutations that are

NOTE Confidence: 0.811509029285714

 $00{:}23{:}00{.}330 \dashrightarrow 00{:}23{:}02{.}780$ seen in other cancers in either of

NOTE Confidence: 0.811509029285714

 $00:23:02.780 \longrightarrow 00:23:05.541$ the of the paralogs or in any of the

NOTE Confidence: 0.811509029285714

 $00{:}23{:}05{.}541 \dashrightarrow 00{:}23{:}08{.}288$ of the Swiss sniff complex members.

NOTE Confidence: 0.811509029285714

 $00:23:08.290 \rightarrow 00:23:10.250$ When we look at pathology,

NOTE Confidence: 0.811509029285714

 $00:23:10.250 \longrightarrow 00:23:13.036$ again if you look at cases where

NOTE Confidence: 0.811509029285714

 $00:23:13.036 \rightarrow 00:23:14.948$ you have a denocarcinoma here and

NOTE Confidence: 0.811509029285714

 $00{:}23{:}14.948 \dashrightarrow 00{:}23{:}16.604$ then you have some neuroendocrine

NOTE Confidence: 0.811509029285714

 $00:23:16.604 \rightarrow 00:23:18.848$ cancer in the exact same tumor,

NOTE Confidence: 0.811509029285714

 $00{:}23{:}18{.}850 \dashrightarrow 00{:}23{:}20{.}313$ you can very nicely see some of

NOTE Confidence: 0.811509029285714

 $00:23:20.313 \rightarrow 00:23:21.809$ the things I'm telling you about.

NOTE Confidence: 0.811509029285714

 $00{:}23{:}21{.}810 \dashrightarrow 00{:}23{:}24{.}642$ So the small cell expression of

NOTE Confidence: 0.811509029285714

 $00:23:24.642 \rightarrow 00:23:26.530$ synaptophysin the scene here.

NOTE Confidence: 0.811509029285714

 $00:23:26.530 \longrightarrow 00:23:27.616$ The BAT 53B,

NOTE Confidence: 0.811509029285714

 $00:23:27.616 \rightarrow 00:23:29.788$ which again is a neural component,

00:23:29.790 --> 00:23:33.120 neural protein component of the Swiss

NOTE Confidence: 0.811509029285714

 $00:23:33.120 \longrightarrow 00:23:35.950$ sniff complex is expressed there,

NOTE Confidence: 0.811509029285714

 $00{:}23{:}35{.}950 \dashrightarrow 00{:}23{:}37{.}710$ but not in the adenocarcinoma.

NOTE Confidence: 0.811509029285714

 $00:23:37.710 \longrightarrow 00:23:38.760$ So that's important.

NOTE Confidence: 0.811509029285714

 $00{:}23{:}38{.}760 \dashrightarrow 00{:}23{:}41{.}210$ And then here is I think a

NOTE Confidence: 0.830189032666667

 $00{:}23{:}41{.}286 \dashrightarrow 00{:}23{:}44{.}408$ very important finding at least in the

NOTE Confidence: 0.830189032666667

 $00:23:44.408 \rightarrow 00:23:47.558$ published paper where we took an organoid

NOTE Confidence: 0.830189032666667

 $00{:}23{:}47{.}558 \dashrightarrow 00{:}23{:}49{.}718$ that was a neuroendocrine organoid

NOTE Confidence: 0.830189032666667

 $00{:}23{:}49{.}718$ --> $00{:}23{:}52{.}061$ and from a patient and looked at it

NOTE Confidence: 0.830189032666667

 $00:23:52.061 \rightarrow 00:23:54.190$ now this we're seeing heterogeneity.

NOTE Confidence: 0.830189032666667

 $00:23:54.190 \longrightarrow 00:23:55.335$ So that's one thing that's

NOTE Confidence: 0.830189032666667

 $00:23:55.335 \longrightarrow 00:23:56.910$ important is even in a patient.

NOTE Confidence: 0.830189032666667

 $00{:}23{:}56{.}910 \dashrightarrow 00{:}23{:}58{.}502$ Private organoid this passage

NOTE Confidence: 0.830189032666667

 $00{:}23{:}58{.}502 \dashrightarrow 00{:}24{:}00{.}492$ many times we see heterogeneity.

NOTE Confidence: 0.830189032666667

 $00{:}24{:}00{.}500 \dashrightarrow 00{:}24{:}02{.}348$ And what's interesting here is smart

 $00:24:02.348 \rightarrow 00:24:04.738$ guy four is expressed here, socks two.

NOTE Confidence: 0.830189032666667

00:24:04.738 --> 00:24:06.833 So transcription factor that's very

NOTE Confidence: 0.830189032666667

 $00{:}24{:}06{.}833 \dashrightarrow 00{:}24{:}09{.}618$ much involved in stemness is expressed.

NOTE Confidence: 0.830189032666667

 $00:24:09.620 \rightarrow 00:24:12.532$ But the neural markers that I mentioned

NOTE Confidence: 0.830189032666667

00:24:12.532 --> 00:24:14.460 back 53B are not expressed here,

NOTE Confidence: 0.830189032666667

 $00:24:14.460 \longrightarrow 00:24:16.520$ but they are expressed in

NOTE Confidence: 0.830189032666667

 $00{:}24{:}16{.}520 \dashrightarrow 00{:}24{:}18{.}580$ the Smart Gate 2 area.

NOTE Confidence: 0.830189032666667

 $00{:}24{:}18{.}580 \dashrightarrow 00{:}24{:}21{.}044$ So it looks like the paralogs play a

NOTE Confidence: 0.830189032666667

 $00:24:21.044 \rightarrow 00:24:22.878$ different role in modulating them.

NOTE Confidence: 0.830189032666667

 $00:24:22.880 \rightarrow 00:24:24.760$ May do something very different.

NOTE Confidence: 0.830189032666667

 $00{:}24{:}24{.}760 \dashrightarrow 00{:}24{:}27{.}704$ And so we think that there's a dynamic.

NOTE Confidence: 0.830189032666667

00:24:27.710 --> 00:24:28.718 Activity going on,

NOTE Confidence: 0.830189032666667

 $00{:}24{:}28.718 \dashrightarrow 00{:}24{:}31.070$ you have some cells that are more

NOTE Confidence: 0.830189032666667

 $00:24:31.136 \rightarrow 00:24:33.251$ poised to be neuroendocrine and

NOTE Confidence: 0.830189032666667

 $00{:}24{:}33{.}251 \dashrightarrow 00{:}24{:}35{.}425$ others that are potentially that

NOTE Confidence: 0.830189032666667

 $00:24:35.425 \rightarrow 00:24:37.800$ are potentially still very stem

- NOTE Confidence: 0.830189032666667
- $00:24:37.800 \rightarrow 00:24:39.700$ like and potentially reversible.

00:24:44.880 --> 00:24:47.860 David Goodrich, who and collaborations,

NOTE Confidence: 0.746438354

 $00:24:47.860 \rightarrow 00:24:50.121$ has shared some of the organizers he's

NOTE Confidence: 0.746438354

 $00:24:50.121 \rightarrow 00:24:52.320$ developed through some of these mouse models.

NOTE Confidence: 0.746438354

 $00{:}24{:}52{.}320 \dashrightarrow 00{:}24{:}54{.}070$ So I mentioned that he's

NOTE Confidence: 0.746438354

 $00:24:54.070 \longrightarrow 00:24:55.470$ developed mouse models where

NOTE Confidence: 0.746438354

 $00:24:55.470 \longrightarrow 00:24:58.029$ he's done knockout of P53 and RB.

NOTE Confidence: 0.746438354

 $00:24:58.029 \rightarrow 00:24:59.994$ They've also knocked out P-10.

NOTE Confidence: 0.746438354

 $00{:}25{:}00{.}000 \dashrightarrow 00{:}25{:}02{.}928$ And so in black we have P-10 knocked

NOTE Confidence: 0.746438354

 $00{:}25{:}02{.}928 \dashrightarrow 00{:}25{:}06{.}106$ out in blue we have both RB and P-10.

NOTE Confidence: 0.746438354

00:25:06.106 --> 00:25:08.220 And in red we had we include,

NOTE Confidence: 0.746438354

00:25:08.220 --> 00:25:10.020 he included P53 knock
out in

NOTE Confidence: 0.746438354

 $00:25:10.020 \longrightarrow 00:25:11.460$ these various mouse models.

NOTE Confidence: 0.746438354

 $00{:}25{:}11.460 \dashrightarrow 00{:}25{:}13.440$ And you can see that in the mouse models.

NOTE Confidence: 0.746438354

 $00{:}25{:}13.440 \dashrightarrow 00{:}25{:}16.359$ You also have the same observation that

00:25:16.359 --> 00:25:19.765 smart K4 goes up when you knock out a RB1.

NOTE Confidence: 0.746438354

 $00{:}25{:}19.765 \dashrightarrow 00{:}25{:}21.885$ And a little bit of the controversy is

NOTE Confidence: 0.746438354

 $00{:}25{:}21.885 \dashrightarrow 00{:}25{:}23.905$ whether you need P53 or not because we

NOTE Confidence: 0.746438354

00:25:23.905 --> 00:25:26.043 don't see much change when you add P53,

NOTE Confidence: 0.746438354

 $00{:}25{:}26{.}043 \dashrightarrow 00{:}25{:}28{.}581$ but that's a sort of another

NOTE Confidence: 0.746438354

 $00{:}25{:}28{.}581 \dashrightarrow 00{:}25{:}30{.}410$ discussion and then smart.

NOTE Confidence: 0.746438354

 $00{:}25{:}30{.}410 \dashrightarrow 00{:}25{:}31{.}890$ The two goes down dramatically

NOTE Confidence: 0.746438354

 $00:25:31.890 \longrightarrow 00:25:33.370$ when you knock out either

NOTE Confidence: 0.820125292

 $00:25:35.400 \longrightarrow 00:25:37.960$ P53RB alone or with P53.

NOTE Confidence: 0.820125292

 $00:25:37.960 \rightarrow 00:25:40.600$ There's some other interesting findings.

NOTE Confidence: 0.820125292

 $00:25:40.600 \longrightarrow 00:25:42.235$ The methyl transferases

NOTE Confidence: 0.820125292

 $00:25:42.235 \rightarrow 00:25:44.960$ increase when you do this,

NOTE Confidence: 0.820125292

00:25:44.960 --> 00:25:46.535 and I'm not going to talk about it today,

NOTE Confidence: 0.820125292

 $00{:}25{:}46{.}540 \dashrightarrow 00{:}25{:}48{.}754$ but there's I think an interesting

NOTE Confidence: 0.820125292

 $00:25:48.754 \rightarrow 00:25:51.588$ story related to the epigenetic side of

NOTE Confidence: 0.820125292

 $00:25:51.588 \rightarrow 00:25:54.591$ methylation that also occurs in this setting.

- NOTE Confidence: 0.820125292
- 00:25:54.600 --> 00:25:56.000 One other, I think important
- NOTE Confidence: 0.820125292
- $00:25:56.000 \rightarrow 00:25:57.790$ point is in this mouse model,
- NOTE Confidence: 0.820125292
- $00:25:57.790 \longrightarrow 00:26:00.709$ we then did proteomics on the patient
- NOTE Confidence: 0.820125292
- $00:26:00.709 \rightarrow 00:26:02.799$ derived organoids from this model.
- NOTE Confidence: 0.820125292
- $00{:}26{:}02{.}800 \dashrightarrow 00{:}26{:}04{.}475$ And what's interesting and what
- NOTE Confidence: 0.820125292
- $00:26:04.475 \longrightarrow 00:26:06.851$ you'd expect is if you have these
- NOTE Confidence: 0.820125292
- 00:26:06.851 --> 00:26:08.759 models where you knock it out,
- NOTE Confidence: 0.820125292
- $00:26:08.760 \rightarrow 00:26:10.790$ that we see overexpression of socks too,
- NOTE Confidence: 0.820125292
- $00{:}26{:}10.790 \dashrightarrow 00{:}26{:}12.488$ which I showed you in the
- NOTE Confidence: 0.820125292
- $00:26:12.488 \longrightarrow 00:26:13.620$ in the human samples.
- NOTE Confidence: 0.820125292
- $00:26:13.620 \rightarrow 00:26:16.245$ We also have smart K fours overexpressed.
- NOTE Confidence: 0.820125292
- $00{:}26{:}16.250 \dashrightarrow 00{:}26{:}17.660$ But what's quite interesting is,
- NOTE Confidence: 0.820125292
- $00:26:17.660 \longrightarrow 00:26:20.210$ is that if you take this model out of the
- NOTE Confidence: 0.820125292
- $00{:}26{:}20{.}281 \dashrightarrow 00{:}26{:}22{.}831$ mouse and now put it and just grow it in,
- NOTE Confidence: 0.820125292
- $00:26:22.840 \rightarrow 00:26:24.163$ in, in, in.
- NOTE Confidence: 0.820125292

00:26:24.163 --> 00:26:26.809 In vitro should say in vitro,

NOTE Confidence: 0.820125292

 $00:26:26.810 \longrightarrow 00:26:27.599$ not in vivo.

NOTE Confidence: 0.820125292

 $00:26:27.599 \rightarrow 00:26:29.177$ What ends up happening is you

NOTE Confidence: 0.820125292

 $00:26:29.177 \rightarrow 00:26:30.930$ don't see these changes anymore.

NOTE Confidence: 0.820125292

 $00:26:30.930 \longrightarrow 00:26:32.988$ So just one other comment that environment

NOTE Confidence: 0.820125292

 $00{:}26{:}32.988 \dashrightarrow 00{:}26{:}34.865$ we think is very important and I

NOTE Confidence: 0.820125292

 $00:26:34.865 \longrightarrow 00:26:37.330$ think when do a lot of us when we're

NOTE Confidence: 0.820125292

 $00:26:37.330 \rightarrow 00:26:39.000$ doing the our organoid experiments,

NOTE Confidence: 0.820125292

 $00{:}26{:}39{.}000 \dashrightarrow 00{:}26{:}40{.}645$ we have to be mindful that the

NOTE Confidence: 0.820125292

 $00:26:40.645 \rightarrow 00:26:42.150$ results could be very different.

NOTE Confidence: 0.820125292

 $00{:}26{:}42.150 \dashrightarrow 00{:}26{:}44.589$ And there's I think more to come about this.

NOTE Confidence: 0.820125292

 $00{:}26{:}44.590 \dashrightarrow 00{:}26{:}46.912$ I think Walter Carter who's was

NOTE Confidence: 0.820125292

 $00{:}26{:}46{.}912 \dashrightarrow 00{:}26{:}49{.}747$ at memorial now is in Lisanne and

NOTE Confidence: 0.820125292

00:26:49.747 - 00:26:52.561 others are working very much in this,

NOTE Confidence: 0.820125292

 $00{:}26{:}52{.}570 \dashrightarrow 00{:}26{:}54{.}019$ in this area.

NOTE Confidence: 0.820125292

 $00:26:54.019 \rightarrow 00:26:58.160$ So just a final comments about switch sniffs.

- NOTE Confidence: 0.820125292
- $00{:}26{:}58{.}160 \dashrightarrow 00{:}27{:}01{.}220$ So we were sort of surprised
- NOTE Confidence: 0.820125292
- $00:27:01.220 \longrightarrow 00:27:04.240$ at the end of 21,
- NOTE Confidence: 0.820125292
- $00:27:04.240 \longrightarrow 00:27:06.352$ so beginning of 22 to see a paper
- NOTE Confidence: 0.820125292
- $00{:}27{:}06{.}352 \dashrightarrow 00{:}27{:}08{.}386$ from rural Shanes group because we
- NOTE Confidence: 0.820125292
- $00:27:08.386 \longrightarrow 00:27:10.546$ were we've been following this field
- NOTE Confidence: 0.820125292
- 00:27:10.613 --> 00:27:12.839 for a
while and we've known about the
- NOTE Confidence: 0.820125292
- $00:27:12.839 \rightarrow 00:27:15.192$ toxicity for the Protex if you try
- NOTE Confidence: 0.820125292
- $00:27:15.192 \longrightarrow 00:27:17.777$ to target switch net and they have
- NOTE Confidence: 0.820125292
- 00:27:17.777 --> 00:27:20.267 very nice paper where they developed
- NOTE Confidence: 0.820125292
- $00{:}27{:}20.267 \dashrightarrow 00{:}27{:}22.777$ a protech that was not a toxic.
- NOTE Confidence: 0.820125292
- $00:27:22.780 \longrightarrow 00:27:24.355$ So they showed not a lot of.
- NOTE Confidence: 0.820125292
- 00:27:24.360 --> 00:27:26.898 Very nice toxicology data from their
- NOTE Confidence: 0.820125292
- $00:27:26.898 \longrightarrow 00:27:29.383$ in their paper that's not toxic
- NOTE Confidence: 0.820125292
- 00:27:29.383 --> 00:27:31.882 and at least the mouse models that
- NOTE Confidence: 0.820125292
- $00{:}27{:}31.882 \dashrightarrow 00{:}27{:}35.145$ they show and that the switch sniff
- NOTE Confidence: 0.820125292

 $00{:}27{:}35.145 \dashrightarrow 00{:}27{:}38.895$ protect for a combined smart A4

NOTE Confidence: 0.820125292

 $00{:}27{:}38.895 \dashrightarrow 00{:}27{:}42.455$ and smart K2 are exquisitely potent

NOTE Confidence: 0.820125292

 $00{:}27{:}42.455 \dashrightarrow 00{:}27{:}45.530$ against AR sensitive prostate cancer.

NOTE Confidence: 0.820125292

 $00:27:45.530 \rightarrow 00:27:47.910$ And so we found that quite interesting.

NOTE Confidence: 0.820125292

 $00:27:47.910 \longrightarrow 00:27:50.381$ We we have been following up we

NOTE Confidence: 0.820125292

 $00{:}27{:}50{.}381 \dashrightarrow 00{:}27{:}52{.}385$ had actually been working on

NOTE Confidence: 0.820125292

 $00:27:52.385 \rightarrow 00:27:54.550$ something similar and have.

NOTE Confidence: 0.820125292

 $00:27:54.550 \rightarrow 00:27:55.940$ Come to a similar conclusion,

NOTE Confidence: 0.820125292

 $00{:}27{:}55{.}940 \dashrightarrow 00{:}27{:}58{.}652$ but extend it a little bit and just

NOTE Confidence: 0.820125292

 $00{:}27{:}58.652 \dashrightarrow 00{:}28{:}01.249$ point out that our collaborators Uchen

NOTE Confidence: 0.820125292

00:28:01.249
 $\operatorname{-->}$ 00:28:04.472 and Ekta Karana who was formerly a

NOTE Confidence: 0.820125292

00:28:04.472 --> 00:28:06.794 trainee and Mark Burstein is here.

NOTE Confidence: 0.820125292

 $00:28:06.800 \longrightarrow 00:28:08.998$ I had a very nice paper in

NOTE Confidence: 0.820125292

 $00:28:08.998 \rightarrow 00:28:10.849$ science where they used a taxi,

NOTE Confidence: 0.820125292

 $00:28:10.850 \longrightarrow 00:28:12.640$ so an epigenetic approach to

NOTE Confidence: 0.820125292

 $00:28:12.640 \longrightarrow 00:28:14.430$ classify prostate cancer and I

- NOTE Confidence: 0.820125292
- $00:28:14.497 \longrightarrow 00:28:16.315$ won't go into all the details,
- NOTE Confidence: 0.820125292
- $00{:}28{:}16{.}320 \dashrightarrow 00{:}28{:}19{.}014$ but against essentially in addition to
- NOTE Confidence: 0.820125292
- $00:28:19.014 \rightarrow 00:28:21.340$ AR sensitive advanced prostate cancer,
- NOTE Confidence: 0.820125292
- $00:28:21.340 \longrightarrow 00:28:23.594$ they also came up with the wind
- NOTE Confidence: 0.820125292
- 00:28:23.594 --> 00:28:24.948 signaling pathway, a stem.
- NOTE Confidence: 0.820125292
- $00:28:24.948 \longrightarrow 00:28:26.010$ Like and neuroendocrine.
- NOTE Confidence: 0.820125292
- 00:28:26.010 --> 00:28:28.362 So I think it's a good working
- NOTE Confidence: 0.820125292
- $00{:}28{:}28{.}362 \dashrightarrow 00{:}28{:}29{.}830$ classification for these advanced
- NOTE Confidence: 0.820125292
- $00{:}28{:}29{.}830 \dashrightarrow 00{:}28{:}32{.}188$ cancers more than just air negative,
- NOTE Confidence: 0.820125292
- $00{:}28{:}32{.}190 \dashrightarrow 00{:}28{:}34{.}206$ but air negative could be stem like it
- NOTE Confidence: 0.820125292
- $00:28:34.206 \rightarrow 00:28:36.480$ could be when singling or neuroendocrine.
- NOTE Confidence: 0.820125292
- $00{:}28{:}36{.}480 \dashrightarrow 00{:}28{:}37{.}780$ I'm sure this will change,
- NOTE Confidence: 0.82381292125
- 00:28:37.780 --> 00:28:39.468 but I think it's a very nice study.
- NOTE Confidence: 0.82381292125
- $00{:}28{:}39{.}470 \dashrightarrow 00{:}28{:}42{.}260$ So when we applied this classification
- NOTE Confidence: 0.82381292125
- $00{:}28{:}42{.}260 \dashrightarrow 00{:}28{:}45{.}795$ and used a protect that we had
- NOTE Confidence: 0.82381292125

 $00:28:45.795 \longrightarrow 00:28:47.915$ acquired in collaboration with

NOTE Confidence: 0.82381292125

 $00{:}28{:}47{.}915 \dashrightarrow 00{:}28{:}49{.}970$ Genentech that was recently published

NOTE Confidence: 0.82381292125

00:28:49.970 --> 00:28:52.732 for lung cancer and very nice study,

NOTE Confidence: 0.82381292125

 $00{:}28{:}52{.}732 \dashrightarrow 00{:}28{:}55{.}624$ we were also able to demonstrate.

NOTE Confidence: 0.82381292125

 $00{:}28{:}55{.}630 \dashrightarrow 00{:}28{:}58{.}100$ Exquisite sensitivity to air positive,

NOTE Confidence: 0.82381292125

 $00{:}28{:}58{.}100 \dashrightarrow 00{:}29{:}01{.}036$ but also to some of the other subclasses, NOTE Confidence: 0.82381292125

 $00:29:01.040 \rightarrow 00:29:03.260$ so extending it beyond air sensitivity.

NOTE Confidence: 0.82381292125

 $00{:}29{:}03.260 \dashrightarrow 00{:}29{:}06.852$ So we think that these are very useful

NOTE Confidence: 0.82381292125

 $00:29:06.852 \rightarrow 00:29:09.112$ approaches of unfortunately that toxicity

NOTE Confidence: 0.82381292125

 $00{:}29{:}09{.}112 \dashrightarrow 00{:}29{:}12{.}340$ at least in our hands is very high.

NOTE Confidence: 0.82381292125

 $00{:}29{:}12.340 \dashrightarrow 00{:}29{:}14.986$ And so I think the strategy now is really

NOTE Confidence: 0.82381292125

 $00{:}29{:}14.986 \dashrightarrow 00{:}29{:}17.628$ to try to come up with more specific.

NOTE Confidence: 0.82381292125

00:29:17.630 --> 00:29:19.838 They're smart K2 inhibitors,

NOTE Confidence: 0.82381292125

 $00:29:19.838 \longrightarrow 00:29:21.494$ but for prostate,

NOTE Confidence: 0.82381292125

 $00{:}29{:}21{.}500 \dashrightarrow 00{:}29{:}23{.}453$ the question is should we also be

NOTE Confidence: 0.82381292125

00:29:23.453 --> 00:29:25.060 looking for smart K4 inhibitor?

- NOTE Confidence: 0.82381292125
- 00:29:25.060 00:29:26.300 And so that's something that's
- NOTE Confidence: 0.82381292125
- $00:29:26.300 \longrightarrow 00:29:27.044$ of great interest.
- NOTE Confidence: 0.82381292125
- 00:29:27.050 --> 00:29:28.615 So just to summarize this
- NOTE Confidence: 0.82381292125
- $00:29:28.615 \longrightarrow 00:29:29.867$ part of the presentation,
- NOTE Confidence: 0.82381292125
- $00{:}29{:}29{.}870 \dashrightarrow 00{:}29{:}31.662$ I wanted to just give you sort
- NOTE Confidence: 0.82381292125
- $00:29:31.662 \longrightarrow 00:29:33.381$ of the landscape of what's going
- NOTE Confidence: 0.82381292125
- $00:29:33.381 \longrightarrow 00:29:34.565$ on in prostate cancer.
- NOTE Confidence: 0.82381292125
- 00:29:34.570 --> 00:29:37.910 And with regards to resistance,
- NOTE Confidence: 0.82381292125
- $00:29:37.910 \rightarrow 00:29:40.590$ there's genomic and epigenetic players,
- NOTE Confidence: 0.82381292125
- $00{:}29{:}40.590 \dashrightarrow 00{:}29{:}43.842$ which I I mention are B and P53
- NOTE Confidence: 0.82381292125
- $00:29:43.842 \longrightarrow 00:29:46.854$ being two of the main players.
- NOTE Confidence: 0.82381292125
- 00:29:46.860 --> 00:29:48.788 Which are probably necessary
- NOTE Confidence: 0.82381292125
- 00:29:48.788 --> 00:29:50.234 but not sufficient.
- NOTE Confidence: 0.82381292125
- $00{:}29{:}50{.}240 \dashrightarrow 00{:}29{:}53{.}054$ And then there's a very interesting stories
- NOTE Confidence: 0.82381292125
- $00:29:53.054 \rightarrow 00:29:54.980$ developing in epigenetic regulation.
- NOTE Confidence: 0.82381292125

00:29:54.980 --> 00:29:57.374 I didn't talk about rest for the first part.

NOTE Confidence: 0.82381292125

 $00{:}29{:}57{.}380 \dashrightarrow 00{:}29{:}59{.}298$ I'll talk about rest which is an

NOTE Confidence: 0.82381292125

 $00:29:59.298 \rightarrow 00:30:01.020$ inhibitor of neural differentiation.

NOTE Confidence: 0.82381292125

 $00:30:01.020 \dashrightarrow 00:30:02.940$ I'll talk about that in the second part.

NOTE Confidence: 0.82381292125

 $00{:}30{:}02{.}940 \dashrightarrow 00{:}30{:}05{.}180$ And then I think that this is

NOTE Confidence: 0.82381292125

 $00{:}30{:}05{.}180 \dashrightarrow 00{:}30{:}07{.}637$ now emerging where based on these

NOTE Confidence: 0.82381292125

 $00:30:07.637 \rightarrow 00:30:09.533$ different alterations there may

NOTE Confidence: 0.82381292125

 $00:30:09.533 \longrightarrow 00:30:10.955$ be different subclasses.

NOTE Confidence: 0.82381292125

 $00{:}30{:}10.960 \dashrightarrow 00{:}30{:}12.298$ So I just want to highlight,

NOTE Confidence: 0.82381292125

 $00{:}30{:}12.300 \dashrightarrow 00{:}30{:}14.183$ we've modified a little bit of review

NOTE Confidence: 0.82381292125

 $00{:}30{:}14.183 \dashrightarrow 00{:}30{:}16.695$ that we had a few years ago where I think.

NOTE Confidence: 0.82381292125

 $00{:}30{:}16.700 \dashrightarrow 00{:}30{:}18.852$ Microenvironment plays an important

NOTE Confidence: 0.82381292125

 $00{:}30{:}18.852 \dashrightarrow 00{:}30{:}21.542$ role and there are different

NOTE Confidence: 0.82381292125

 $00:30:21.542 \longrightarrow 00:30:23.270$ pathways that are taken.

NOTE Confidence: 0.82381292125

 $00:30:23.270 \rightarrow 00:30:25.910$ Are they unidirectional, are they reversible?

NOTE Confidence: 0.82381292125

 $00:30:25.910 \longrightarrow 00:30:28.046$ I think that's going to be a very

 $00:30:28.046 \longrightarrow 00:30:28.910$ important translational issue.

NOTE Confidence: 0.82381292125

 $00{:}30{:}28{.}910 \dashrightarrow 00{:}30{:}31{.}066$ And I think for those treating patients,

NOTE Confidence: 0.82381292125

00:30:31.070 --> 00:30:33.218 obviously wanting to identify the time

NOTE Confidence: 0.82381292125

 $00:30:33.218 \dashrightarrow 00:30:35.438$ point where people will best respond

NOTE Confidence: 0.82381292125

 $00:30:35.438 \longrightarrow 00:30:37.604$ to novel the rapies will be important.

NOTE Confidence: 0.82381292125

 $00:30:37.610 \longrightarrow 00:30:38.534$ So that's one.

NOTE Confidence: 0.82381292125

 $00{:}30{:}38{.}534 \dashrightarrow 00{:}30{:}40{.}690$ Thing I wanted to tell you about

NOTE Confidence: 0.82381292125

 $00{:}30{:}40.765 \dashrightarrow 00{:}30{:}42.830$ this morning and now I want to

NOTE Confidence: 0.82381292125

 $00{:}30{:}42.830 \dashrightarrow 00{:}30{:}45.145$ tell you about something that's

NOTE Confidence: 0.82381292125

00:30:45.145 --> 00:30:48.307 that's entirely new to our group.

NOTE Confidence: 0.82381292125

00:30:48.307 --> 00:30:50.825 And I when I go for bike rides

NOTE Confidence: 0.82381292125

00:30:50.825 --> 00:30:52.812 around my house, I don't know,

NOTE Confidence: 0.82381292125

 $00{:}30{:}52.812 \dashrightarrow 00{:}30{:}54.520$ there are a lot of bike riders.

NOTE Confidence: 0.82381292125

00:30:54.520 --> 00:30:55.810 I know David Rim might be

NOTE Confidence: 0.82381292125

 $00{:}30{:}55{.}810 \dashrightarrow 00{:}30{:}57{.}240$ listening and he's a bike rider,

 $00:30:57.240 \rightarrow 00:30:59.832$ but when you are biking and you see

NOTE Confidence: 0.82381292125

 $00:30:59.832 \rightarrow 00:31:02.038$ that there's a slope of 27 degrees,

NOTE Confidence: 0.82381292125

 $00:31:02.040 \longrightarrow 00:31:03.087$ that's really steep.

NOTE Confidence: 0.82381292125

 $00{:}31{:}03.087 \dashrightarrow 00{:}31{:}06.798$ I mean so in the in the Tour de France,

NOTE Confidence: 0.82381292125

00:31:06.800 - 00:31:09.476 20 is starting to become extremely.

NOTE Confidence: 0.82381292125

00:31:09.480 --> 00:31:09.722 Challenging.

NOTE Confidence: 0.82381292125

 $00{:}31{:}09{.}722 \dashrightarrow 00{:}31{:}12{.}090$ I've been in races where I can't go up 20.

NOTE Confidence: 0.82381292125

00:31:12.090 --> 00:31:12.610 I'm walking.

NOTE Confidence: 0.82381292125

 $00{:}31{:}12.610 \dashrightarrow 00{:}31{:}14.690$ So when I see this I'm always thinking

NOTE Confidence: 0.82381292125

00:31:14.746 --> 00:31:16.458 one day I'm going to go down and

NOTE Confidence: 0.82381292125

00:31:16.458 --> 00:31:17.896 try going up this, but I haven't.

NOTE Confidence: 0.82381292125

00:31:17.896 --> 00:31:18.988 I haven't reached that day yet

NOTE Confidence: 0.82381292125

 $00:31:18.988 \longrightarrow 00:31:20.026$ but I'm going to try that.

NOTE Confidence: 0.82381292125

00:31:20.030 - 00:31:21.848 Maybe I'll have to wait for an E bike,

NOTE Confidence: 0.82381292125

 $00:31:21.850 \longrightarrow 00:31:23.750$ but I'm not there yet.

NOTE Confidence: 0.82381292125

 $00{:}31{:}23.750 \dashrightarrow 00{:}31{:}26.977$ But so I I think in our lab we'd like to

00:31:26.977 --> 00:31:29.889 take our challenges and when Anka Outback,

NOTE Confidence: 0.82381292125

 $00:31:29.890 \longrightarrow 00:31:31.472$ who's a postdoc in my lab who

NOTE Confidence: 0.82381292125

00:31:31.472 --> 00:31:32.150 had been working

NOTE Confidence: 0.772385457142857

00:31:32.200 --> 00:31:34.385 in Switch sniff Project, said what she

NOTE Confidence: 0.772385457142857

00:31:34.385 --> 00:31:36.730 really wants to work on is splicing.

NOTE Confidence: 0.772385457142857

 $00{:}31{:}36{.}730 \dashrightarrow 00{:}31{:}39{.}466$ And she said I'm particularly interested

NOTE Confidence: 0.772385457142857

00:31:39.466 --> 00:31:41.780 in minor splicing. I had a problem,

NOTE Confidence: 0.772385457142857

 $00:31:41.780 \rightarrow 00:31:43.777$ which was one I knew nothing about minor

NOTE Confidence: 0.772385457142857

00:31:43.777 --> 00:31:45.639 splicing and I had no idea whether

NOTE Confidence: 0.772385457142857

 $00:31:45.639 \rightarrow 00:31:47.739$ this was really a good use of her time.

NOTE Confidence: 0.772385457142857

 $00:31:47.740 \longrightarrow 00:31:49.444$ So I think this is always

NOTE Confidence: 0.772385457142857

00:31:49.444 --> 00:31:51.239 important point for Pi to decide,

NOTE Confidence: 0.772385457142857

00:31:51.240 --> 00:31:53.328 OK, are we really going to?

NOTE Confidence: 0.772385457142857

00:31:53.330 --> 00:31:53.915 Take this arm.

NOTE Confidence: 0.772385457142857

 $00{:}31{:}53{.}915 \dashrightarrow 00{:}31{:}55{.}565$ So I learned a lot and I'm going

 $00:31:55.565 \rightarrow 00:31:57.224$ to tell you about what we learned.

NOTE Confidence: 0.772385457142857

00:31:57.230 --> 00:31:59.494 It's a it's a work in progress but

NOTE Confidence: 0.772385457142857

 $00:31:59.494 \longrightarrow 00:32:01.540$ I think it's a potentially it's

NOTE Confidence: 0.772385457142857

 $00:32:01.540 \rightarrow 00:32:04.103$ exciting new area for us and helping

NOTE Confidence: 0.772385457142857

 $00:32:04.103 \longrightarrow 00:32:06.798$ me with my process of education was NOTE Confidence: 0.772385457142857

 $00{:}32{:}06{.}798 \dashrightarrow 00{:}32{:}08{.}770$ Rahul Canadia who's close by so he's NOTE Confidence: 0.772385457142857

 $00:32:08.770 \longrightarrow 00:32:11.059$ up just up the road at UConn and his NOTE Confidence: 0.772385457142857

 $00{:}32{:}11.059 \dashrightarrow 00{:}32{:}13.000$ post dot Kyle Drake who very helpful

NOTE Confidence: 0.772385457142857

 $00{:}32{:}13.000 \dashrightarrow 00{:}32{:}15.022$ and this is also a collaboration

NOTE Confidence: 0.772385457142857

 $00{:}32{:}15{.}022 \dashrightarrow 00{:}32{:}17{.}196$ with Mark Gerson's lab here at Yale.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}17.196 \dashrightarrow 00{:}32{:}18.641$ So there's a very strong

NOTE Confidence: 0.772385457142857

00:32:18.641 -> 00:32:19.530 Connecticut component.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}19{.}530 \dashrightarrow 00{:}32{:}21{.}217$ So what I did know about splicing

NOTE Confidence: 0.772385457142857

 $00{:}32{:}21{.}217 \dashrightarrow 00{:}32{:}23{.}367$ was I knew from Gunner Rich's group.

NOTE Confidence: 0.772385457142857

 $00:32:23.370 \longrightarrow 00:32:25.740$ The TCGA that splicing is is

NOTE Confidence: 0.772385457142857

 $00:32:25.740 \longrightarrow 00:32:27.773$ occurring very often in cancer

 $00:32:27.773 \longrightarrow 00:32:30.363$ that it can lead to NEO epitope.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}30{.}370 \dashrightarrow 00{:}32{:}33{.}130$ So I was more familiar with aberrant splicing

NOTE Confidence: 0.772385457142857

 $00:32:33.130 \rightarrow 00:32:36.348$ in the context of potentially immunotherapy.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}36{.}350 \dashrightarrow 00{:}32{:}39{.}260$ What I was also aware is that the IT plays

NOTE Confidence: 0.772385457142857

 $00:32:39.335 \rightarrow 00:32:42.389$ initially important role in the regulations.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}42{.}390 \dashrightarrow 00{:}32{:}44{.}273$ So this is a hallmark like figure

NOTE Confidence: 0.772385457142857

 $00:32:44.273 \longrightarrow 00:32:46.202$ showing all the different areas where

NOTE Confidence: 0.772385457142857

00:32:46.202 --> 00:32:48.326 splicing can play an important role.

NOTE Confidence: 0.772385457142857

00:32:48.330 --> 00:32:50.269 But I didn't know anything about minor

NOTE Confidence: 0.772385457142857

00:32:50.269 --> 00:32:52.386 splicing so I had to learn from Anka,

NOTE Confidence: 0.772385457142857

 $00:32:52.390 \longrightarrow 00:32:53.965$ Rahul and others.

NOTE Confidence: 0.772385457142857

 $00{:}32{:}53{.}965 \dashrightarrow 00{:}32{:}57{.}640$ And so I knew that when gene

NOTE Confidence: 0.772385457142857

 $00{:}32{:}57{.}640$ --> $00{:}32{:}59{.}000$ genes create messenger RNA.

NOTE Confidence: 0.772385457142857

 $00:32:59.000 \longrightarrow 00:33:01.775$ But in order to do that you have

NOTE Confidence: 0.772385457142857

 $00{:}33{:}01.775 \dashrightarrow 00{:}33{:}04.106$ to take the exons and somehow the

 $00:33:04.106 \longrightarrow 00:33:06.107$ introns have to be spliced out to

NOTE Confidence: 0.772385457142857

 $00{:}33{:}06{.}107 \dashrightarrow 00{:}33{:}08{.}552$ get to go from a preeminent M RNA

NOTE Confidence: 0.772385457142857

 $00{:}33{:}08{.}552 \dashrightarrow 00{:}33{:}11{.}640$ to an MRA that can be translated.

NOTE Confidence: 0.772385457142857

 $00:33:11.640 \longrightarrow 00:33:13.880$ And so the question is how does

NOTE Confidence: 0.772385457142857

 $00:33:13.880 \longrightarrow 00:33:14.840$ that actually occur?

NOTE Confidence: 0.772385457142857

 $00{:}33{:}14.840 \dashrightarrow 00{:}33{:}17.444$ And I'm not expert but I have

NOTE Confidence: 0.772385457142857

 $00:33:17.444 \dashrightarrow 00:33:20.241$ learned that the vast majority of

NOTE Confidence: 0.772385457142857

 $00:33:20.241 \rightarrow 00:33:23.439$ introns are excised through the major

NOTE Confidence: 0.772385457142857

 $00:33:23.439 \longrightarrow 00:33:25.678$ spliceosome which is U2 splices.

NOTE Confidence: 0.772385457142857

 $00:33:25.680 \rightarrow 00:33:27.558$ And in this place is home.

NOTE Confidence: 0.772385457142857

 $00{:}33{:}27.560 \dashrightarrow 00{:}33{:}30.704$ There are small nuclear RNA's that

NOTE Confidence: 0.772385457142857

00:33:30.704 --> 00:33:32.276 recognize consensus sequences,

NOTE Confidence: 0.772385457142857

 $00:33:32.280 \rightarrow 00:33:35.259$ both of the three prime and the five prime,

NOTE Confidence: 0.772385457142857

 $00:33:35.260 \longrightarrow 00:33:36.725$ but also branching points that

NOTE Confidence: 0.772385457142857

 $00:33:36.725 \rightarrow 00:33:38.560$ allow for this placing to occur.

NOTE Confidence: 0.772385457142857

 $00:33:38.560 \rightarrow 00:33:41.736$ So that's the vast majority of all proteins.

- NOTE Confidence: 0.772385457142857
- $00:33:41.740 \longrightarrow 00:33:42.636$ And it turns out,
- NOTE Confidence: 0.772385457142857
- $00{:}33{:}42.636 \dashrightarrow 00{:}33{:}44.596$ and this is what Anka was interested in
- NOTE Confidence: 0.772385457142857
- $00{:}33{:}44.596 \dashrightarrow 00{:}33{:}47.136$ because of work she had done, her pH.
- NOTE Confidence: 0.772385457142857
- 00:33:47.136 --> 00:33:47.564 D,
- NOTE Confidence: 0.772385457142857
- $00{:}33{:}47{.}564 \dashrightarrow 00{:}33{:}49{.}704$ That there's a minor spliceosome
- NOTE Confidence: 0.772385457142857
- $00{:}33{:}49{.}704 \dashrightarrow 00{:}33{:}52{.}139$ which recognizes introns that have
- NOTE Confidence: 0.772385457142857
- $00:33:52.139 \dashrightarrow 00:33:54.139$ a different consensus sequence.
- NOTE Confidence: 0.772385457142857
- $00:33:54.140 \longrightarrow 00:33:55.214$ And it's also.
- NOTE Confidence: 0.772385457142857
- $00:33:55.214 \dashrightarrow 00:33:57.874$ Referred to as the U-12 splicer zone.
- NOTE Confidence: 0.772385457142857
- $00:33:57.874 \rightarrow 00:34:00.730$ And so this is something that's really
- NOTE Confidence: 0.772385457142857
- $00:34:00.809 \rightarrow 00:34:03.389$ very understudied in in homeostasis.
- NOTE Confidence: 0.772385457142857
- 00:34:03.390 --> 00:34:04.916 I'll tell you a little bit about
- NOTE Confidence: 0.772385457142857
- $00:34:04.916 \longrightarrow 00:34:06.814$ what it we think it does or what
- NOTE Confidence: 0.772385457142857
- $00{:}34{:}06{.}814 \dashrightarrow 00{:}34{:}08{.}004$ it's it's believed to do.
- NOTE Confidence: 0.772385457142857
- $00{:}34{:}08{.}010 \dashrightarrow 00{:}34{:}10{.}929$ But it's very important in cutting out
- NOTE Confidence: 0.772385457142857

 $00:34:10.929 \longrightarrow 00:34:13.573$ minor introns that make that are part

NOTE Confidence: 0.772385457142857

 $00:34:13.573 \rightarrow 00:34:16.649$ of of genes that also have major introns.

NOTE Confidence: 0.772385457142857

 $00:34:16.650 \longrightarrow 00:34:18.186$ So I'll show you what that

NOTE Confidence: 0.772385457142857

 $00:34:18.186 \longrightarrow 00:34:19.790$ what that means in a moment.

NOTE Confidence: 0.772385457142857

 $00:34:19.790 \longrightarrow 00:34:22.130$ So the idea is that in a typical gene that

NOTE Confidence: 0.854723949090909

 $00{:}34{:}22.191 \dashrightarrow 00{:}34{:}23.799$ has a minor intron which we're

NOTE Confidence: 0.854723949090909

 $00:34:23.799 \rightarrow 00:34:25.429$ going to refer to as minor.

NOTE Confidence: 0.854723949090909

 $00:34:25.430 \longrightarrow 00:34:27.626$ Intron gene or Mig.

NOTE Confidence: 0.854723949090909

00:34:27.626 --> 00:34:30.920 These genes have one minor intron,

NOTE Confidence: 0.854723949090909

 $00:34:30.920 \rightarrow 00:34:32.760$ usually not more than one,

NOTE Confidence: 0.854723949090909

 $00:34:32.760 \longrightarrow 00:34:35.004$ and that it requires a specific

NOTE Confidence: 0.854723949090909

 $00:34:35.004 \rightarrow 00:34:37.778$ machinery to cut this minor intron out.

NOTE Confidence: 0.854723949090909

 $00:34:37.780 \longrightarrow 00:34:40.606$ Now I just will focus for most of the

NOTE Confidence: 0.854723949090909

 $00{:}34{:}40.606 \dashrightarrow 00{:}34{:}43.066$ presentation on one element of the minor

NOTE Confidence: 0.854723949090909

 $00:34:43.066 \rightarrow 00:34:45.269$ spliceosome which is called Usix attack,

NOTE Confidence: 0.854723949090909

 $00:34:45.270 \longrightarrow 00:34:47.958$ which is one of the catalytic components

- NOTE Confidence: 0.854723949090909
- $00{:}34{:}47{.}958 \dashrightarrow 00{:}34{:}50{.}773$ of the minor splice osome and that
- NOTE Confidence: 0.854723949090909
- $00{:}34{:}50{.}773 \dashrightarrow 00{:}34{:}53{.}418$ in homeostasis believed that under
- NOTE Confidence: 0.854723949090909
- $00{:}34{:}53{.}418 \dashrightarrow 00{:}34{:}55{.}629$ stress situations the conditions are.
- NOTE Confidence: 0.854723949090909
- $00:34:55.629 \longrightarrow 00:34:57.927$ Such that that you six attack
- NOTE Confidence: 0.854723949090909
- $00{:}34{:}57{.}927 \dashrightarrow 00{:}35{:}00{.}647$ is is not degraded and it allows
- NOTE Confidence: 0.854723949090909
- $00:35:00.647 \rightarrow 00:35:02.670$ for minor splicing to occur.
- NOTE Confidence: 0.854723949090909
- $00:35:02.670 \longrightarrow 00:35:04.470$ So whatever this gene is,
- NOTE Confidence: 0.854723949090909
- $00:35:04.470 \rightarrow 00:35:06.870$ it might be important in a stress situation.
- NOTE Confidence: 0.854723949090909
- 00:35:06.870 --> 00:35:09.192 It allows now map kinase signaling
- NOTE Confidence: 0.854723949090909
- $00{:}35{:}09{.}192 \dashrightarrow 00{:}35{:}11{.}437$ occurs and allows for the excision
- NOTE Confidence: 0.854723949090909
- $00:35:11.437 \rightarrow 00:35:13.925$ of this minor intron M RNA to be
- NOTE Confidence: 0.854723949090909
- $00{:}35{:}13.999 \dashrightarrow 00{:}35{:}15.715$ produced and then translation
- NOTE Confidence: 0.854723949090909
- 00:35:15.715 -> 00:35:18.289 of whatever that protein of that
- NOTE Confidence: 0.854723949090909
- $00{:}35{:}18{.}290 \dashrightarrow 00{:}35{:}20{.}390$ whatever that protein will be.
- NOTE Confidence: 0.854723949090909
- $00{:}35{:}20{.}390 \dashrightarrow 00{:}35{:}21{.}730$ So that's an important component.
- NOTE Confidence: 0.854723949090909

 $00:35:21.730 \rightarrow 00:35:23.960$ This is an evolutionary conserved.

NOTE Confidence: 0.76776221

00:35:26.160 --> 00:35:27.872 Events of minor splicing

NOTE Confidence: 0.76776221

 $00:35:27.872 \longrightarrow 00:35:30.012$ is not only in humans,

NOTE Confidence: 0.76776221

 $00:35:30.020 \dashrightarrow 00:35:33.940$ but also throughout the evolution.

NOTE Confidence: 0.76776221

 $00{:}35{:}33{.}940 \dashrightarrow 00{:}35{:}36{.}706$ My inner splicing has been maintained

NOTE Confidence: 0.76776221

 $00:35:36.706 \rightarrow 00:35:39.390$ and there's some interesting exceptions.

NOTE Confidence: 0.76776221

 $00:35:39.390 \longrightarrow 00:35:43.536$ The main role of minor splicing.

NOTE Confidence: 0.76776221

 $00:35:43.540 \longrightarrow 00:35:45.192$ Is seen in development.

NOTE Confidence: 0.76776221

00:35:45.192 --> 00:35:47.670 So Rahul who's our collaborator is

NOTE Confidence: 0.76776221

 $00:35:47.742 \dashrightarrow 00:35:50.520$ really an expert in neural development.

NOTE Confidence: 0.76776221

 $00{:}35{:}50{.}520 \dashrightarrow 00{:}35{:}53{.}310$ And so in patients who have

NOTE Confidence: 0.76776221

 $00{:}35{:}53{.}310 \dashrightarrow 00{:}35{:}55{.}170$ germline alterations or other

NOTE Confidence: 0.76776221

 $00:35:55.252 \rightarrow 00:35:57.700$ alterations in minor splicing,

NOTE Confidence: 0.76776221

 $00:35:57.700 \longrightarrow 00:36:00.241$ they see developmental problems and there are

NOTE Confidence: 0.76776221

00:36:00.241 --> 00:36:02.129 many developmental diseases that described,

NOTE Confidence: 0.76776221

 $00:36:02.130 \longrightarrow 00:36:04.442$ described or attributed to

- NOTE Confidence: 0.76776221
- $00:36:04.442 \longrightarrow 00:36:06.754$ errors in minor splicing.

 $00:36:06.760 \longrightarrow 00:36:07.614$ For cancer,

NOTE Confidence: 0.76776221

 $00:36:07.614 \rightarrow 00:36:10.176$ there's only two really known diseases,

NOTE Confidence: 0.76776221

 $00:36:10.180 \longrightarrow 00:36:12.215$ so put Sieger and myelodysplastic

NOTE Confidence: 0.76776221

 $00:36:12.215 \longrightarrow 00:36:13.436$ syndrome that are.

NOTE Confidence: 0.76776221

 $00{:}36{:}13{.}440 \dashrightarrow 00{:}36{:}15{.}600$ Associated with minor splicing alterations

NOTE Confidence: 0.76776221

 $00:36:15.600 \rightarrow 00:36:19.232$ and in total in Toto they're around 750,

NOTE Confidence: 0.76776221

 $00:36:19.232 \rightarrow 00:36:22.688$ maybe 800 genes that have a minor intron,

NOTE Confidence: 0.76776221

 $00{:}36{:}22.690 \dashrightarrow 00{:}36{:}26.227$ which we can refer to as minor in tron genes.

NOTE Confidence: 0.76776221

 $00{:}36{:}26{.}230 \dashrightarrow 00{:}36{:}28{.}502$ So Anka asked some questions that I think

NOTE Confidence: 0.76776221

 $00{:}36{:}28{.}502 \dashrightarrow 00{:}36{:}30{.}590$ are are pretty straightforward questions to

NOTE Confidence: 0.76776221

 $00{:}36{:}30{.}590 \dashrightarrow 00{:}36{:}33{.}769$ ask in the in the beginning of this project.

NOTE Confidence: 0.76776221

 $00{:}36{:}33{.}770 \dashrightarrow 00{:}36{:}34{.}452$ That is,

NOTE Confidence: 0.76776221

00:36:34.452 --> 00:36:36.839 do we see any evidence of minor

NOTE Confidence: 0.76776221

 $00{:}36{:}36{.}839 \dashrightarrow 00{:}36{:}38{.}789$ splicing alterations in cancer,

 $00:36:38.790 \rightarrow 00:36:40.082$ cancer progression?

NOTE Confidence: 0.76776221

00:36:40.082 --> 00:36:43.958 If so, is it preferentially during?

NOTE Confidence: 0.76776221

00:36:43.960 - 00:36:44.640 Disease progression.

NOTE Confidence: 0.76776221

 $00:36:44.640 \rightarrow 00:36:47.783$ So is this something that you see a more

NOTE Confidence: 0.76776221

 $00:36:47.783 \longrightarrow 00:36:49.919$ so in advanced or resistant disease?

NOTE Confidence: 0.76776221

 $00{:}36{:}49{.}920 \dashrightarrow 00{:}36{:}53{.}056$ Is this an active functionally active event?

NOTE Confidence: 0.76776221

 $00{:}36{:}53.060 \dashrightarrow 00{:}36{:}55.232$ And that would be very important

NOTE Confidence: 0.76776221

 $00:36:55.232 \rightarrow 00:36:57.420$ if we're going to attribute this

NOTE Confidence: 0.76776221

 $00{:}36{:}57{.}420 \dashrightarrow 00{:}36{:}59{.}504$ as a key causative role or playing

NOTE Confidence: 0.76776221

 $00{:}36{:}59{.}504 \dashrightarrow 00{:}37{:}01{.}659$ a part in the cause of cancer

NOTE Confidence: 0.76776221

 $00{:}37{:}01.659 \dashrightarrow 00{:}37{:}03.057$ progression or resistance.

NOTE Confidence: 0.76776221

 $00{:}37{:}03.060 \dashrightarrow 00{:}37{:}04.789$ And is there what happens if you

NOTE Confidence: 0.76776221

 $00{:}37{:}04.789 \dashrightarrow 00{:}37{:}06.613$ inhibit this and what do you can

NOTE Confidence: 0.76776221

 $00:37:06.613 \rightarrow 00:37:08.155$ you reverse some of these features?

NOTE Confidence: 0.76776221

 $00{:}37{:}08{.}160 \dashrightarrow 00{:}37{:}09{.}483$ And so I'll show you some of

NOTE Confidence: 0.76776221

 $00:37:09.483 \longrightarrow 00:37:10.340$ the work we have.

- NOTE Confidence: 0.76776221
- 00:37:10.340 --> 00:37:11.260 It's a as a,
- NOTE Confidence: 0.76776221
- $00{:}37{:}11.260 \dashrightarrow 00{:}37{:}12.410$ as I mentioned this is
- NOTE Confidence: 0.76776221
- $00:37:12.410 \longrightarrow 00:37:14.008$ a work in progress but.
- NOTE Confidence: 0.76776221
- $00:37:14.010 \rightarrow 00:37:16.908$ But we do have a first paper in revision,
- NOTE Confidence: 0.76776221
- $00{:}37{:}16{.}910 \dashrightarrow 00{:}37{:}18{.}450$ which seems like it's been a revision
- NOTE Confidence: 0.76776221
- $00:37:18.450 \longrightarrow 00:37:19.968$ for I think almost a year now,
- NOTE Confidence: 0.76776221
- $00:37:19.970 \longrightarrow 00:37:21.530$ but hopefully we're getting
- NOTE Confidence: 0.76776221
- $00:37:21.530 \longrightarrow 00:37:23.090$ closer to that point.
- NOTE Confidence: 0.76776221
- $00{:}37{:}23.090 \dashrightarrow 00{:}37{:}25.988$ And so first study was in silico.
- NOTE Confidence: 0.76776221
- $00{:}37{:}25{.}990 \dashrightarrow 00{:}37{:}30{.}406$ So one of our collaborators for this
- NOTE Confidence: 0.76776221
- $00:37:30.406 \rightarrow 00:37:32.998$ project looked at computationally
- NOTE Confidence: 0.76776221
- $00{:}37{:}32{.}998 \dashrightarrow 00{:}37{:}35{.}590$ at protein protein interactions,
- NOTE Confidence: 0.76776221
- $00:37:35.590 \dashrightarrow 00:37:38.404$ taking 26 of the most well described NOTE Confidence: 0.76776221
- $00{:}37{:}38{.}404 \dashrightarrow 00{:}37{:}40{.}826$ prostate cancer genes and ask the
- NOTE Confidence: 0.76776221
- $00:37{:}40.826 \dashrightarrow 00{:}37{:}43.112$ question what is the direct protein
- NOTE Confidence: 0.76776221

 $00{:}37{:}43.112 \dashrightarrow 00{:}37{:}45.580$ protein interaction with these minor?

NOTE Confidence: 0.76776221

 $00{:}37{:}45{.}580 \dashrightarrow 00{:}37{:}47{.}482$ And try and containing genes and

NOTE Confidence: 0.76776221

 $00{:}37{:}47{.}482 \dashrightarrow 00{:}37{:}50{.}414$ as you can see on the right some NOTE Confidence: 0.76776221

 $00:37:50.414 \rightarrow 00:37:52.404$ very interesting genes and just

NOTE Confidence: 0.76776221

00:37:52.404 --> 00:37:54.221 highlight BRACA for example here

NOTE Confidence: 0.76776221

 $00{:}37{:}54{.}221$ --> $00{:}37{:}56{.}585$ are kinase a Mick which are genes NOTE Confidence: 0.76776221

 $00{:}37{:}56{.}585 \dashrightarrow 00{:}37{:}58{.}595$ that are very much associated with

NOTE Confidence: 0.76776221

 $00{:}37{:}58{.}595 \dashrightarrow 00{:}38{:}01{.}077$ prostate but also other cancers have

NOTE Confidence: 0.76776221

00:38:01.077 --> 00:38:05.019 as a very close relationship direct

NOTE Confidence: 0.76776221

 $00{:}38{:}05{.}019 \dashrightarrow 00{:}38{:}07{.}820$ interactions with minor intron.

NOTE Confidence: 0.76776221

 $00{:}38{:}07{.}820 \dashrightarrow 00{:}38{:}08{.}752$ Containing genes.

NOTE Confidence: 0.76776221

 $00:38:08.752 \rightarrow 00:38:12.480$ So that's sort of a first interesting hint.

NOTE Confidence: 0.76776221

 $00{:}38{:}12{.}480 \dashrightarrow 00{:}38{:}14{.}706$ I'm going to tell you about minor

NOTE Confidence: 0.76776221

00:38:14.706 --> 00:38:16.440 splicing in disease progression,

NOTE Confidence: 0.76776221

 $00{:}38{:}16{.}440 \dashrightarrow 00{:}38{:}18{.}352$ but before I just want to emphasize why

NOTE Confidence: 0.76776221

00:38:18.352 --> 00:38:20.196 I'm going to focus on you six attack.

- NOTE Confidence: 0.76776221
- $00:38:20.200 \rightarrow 00:38:22.454$ I mentioned that it's a catalytic component.

 $00{:}38{:}22{.}460 \dashrightarrow 00{:}38{:}24{.}612$ So if you have a gene that has

NOTE Confidence: 0.76776221

00:38:24.612 --> 00:38:25.720 a minor intron,

NOTE Confidence: 0.76776221

 $00:38:25.720 \rightarrow 00:38:27.495$ somehow the machinery comes together

NOTE Confidence: 0.76776221

 $00{:}38{:}27{.}495 \dashrightarrow 00{:}38{:}30{.}498$ and has to cut out this minor intron.

NOTE Confidence: 0.76776221

00:38:30.500 -> 00:38:32.670 And the reason why U-6 attack we

NOTE Confidence: 0.76776221

 $00:38:32.670 \rightarrow 00:38:34.857$ think is very important is because

NOTE Confidence: 0.76776221

00:38:34.857 --> 00:38:37.189 it's a dynamic component of this,

NOTE Confidence: 0.76776221

 $00{:}38{:}37{.}189 \dashrightarrow 00{:}38{:}39{.}104$ of this process where it's

NOTE Confidence: 0.76776221

 $00:38:39.104 \rightarrow 00:38:40.878$ really like the last step.

NOTE Confidence: 0.76776221

 $00{:}38{:}40{.}880 \dashrightarrow 00{:}38{:}42{.}680$ So it has to come together with you.

NOTE Confidence: 0.843054783333333

 $00{:}38{:}42.680 \dashrightarrow 00{:}38{:}44.815$ Four attack and this catalytic

NOTE Confidence: 0.843054783333333

 $00{:}38{:}44{.}815 \dashrightarrow 00{:}38{:}47{.}527$ subunit now cuts out the intron

NOTE Confidence: 0.843054783333333

 $00:38:47.527 \rightarrow 00:38:50.467$ and that's why it's probably very

NOTE Confidence: 0.843054783333333

 $00:38:50.467 \rightarrow 00:38:52.950$ carefully regulated in homeostasis.

 $00:38:52.950 \longrightarrow 00:38:54.372$ So that's the reason why we're

NOTE Confidence: 0.843054783333333

 $00{:}38{:}54{.}372 \dashrightarrow 00{:}38{:}55{.}710$ focusing on you six attack.

NOTE Confidence: 0.843054783333333

 $00:38:55.710 \longrightarrow 00:38:56.774$ And the idea is,

NOTE Confidence: 0.843054783333333

 $00:38:56.774 \rightarrow 00:38:58.681$ as I mentioned that in stress we

NOTE Confidence: 0.843054783333333

 $00:38:58.681 \dashrightarrow 00:39:00.459$ think that you six attack is used

NOTE Confidence: 0.843054783333333

 $00:39:00.459 \longrightarrow 00:39:02.474$ to help remove the minor intron for NOTE Confidence: 0.843054783333333

 $00:39:02.474 \rightarrow 00:39:04.614$ a subset of genes that are probably

NOTE Confidence: 0.843054783333333

 $00:39:04.614 \rightarrow 00:39:06.349$ important in responding to stress.

NOTE Confidence: 0.843054783333333

 $00:39:06.350 \longrightarrow 00:39:07.415$ That's our hypothesis.

NOTE Confidence: 0.843054783333333

 $00:39:07.415 \longrightarrow 00:39:09.545$ So what happens if you look

NOTE Confidence: 0.843054783333333

00:39:09.545 --> 00:39:11.050 in prostate cancer,

NOTE Confidence: 0.843054783333333

 $00:39:11.050 \rightarrow 00:39:12.954$ this is probably also true for other.

NOTE Confidence: 0.843054783333333

 $00:39:12.960 \longrightarrow 00:39:15.242$ This is, but we focus on prostate

NOTE Confidence: 0.843054783333333

 $00:39:15.242 \dashrightarrow 00:39:17.249$ cancer using some of the common

NOTE Confidence: 0.843054783333333

 $00:39:17.249 \rightarrow 00:39:18.849$ cell lines and patient Dr.

NOTE Confidence: 0.843054783333333

 $00:39:18.850 \rightarrow 00:39:20.342$ Organoids and arranging them

- NOTE Confidence: 0.843054783333333
- $00:39:20.342 \longrightarrow 00:39:22.580$ going from benign all the way

 $00:39:22.654 \rightarrow 00:39:24.328$ to neuroendocrine disease.

NOTE Confidence: 0.843054783333333

00:39:24.330 - > 00:39:26.406 So trying to cover the spectrum,

NOTE Confidence: 0.843054783333333

 $00:39:26.410 \longrightarrow 00:39:29.810$ we see an increase in U-6 attack expression.

NOTE Confidence: 0.843054783333333

 $00{:}39{:}29{.}810 \dashrightarrow 00{:}39{:}31{.}304$ As I mentioned there are other

NOTE Confidence: 0.843054783333333

 $00:39:31.304 \dashrightarrow 00:39:32.910$ components of the minor splice osome.

NOTE Confidence: 0.843054783333333

 $00{:}39{:}32{.}910 \dashrightarrow 00{:}39{:}36{.}170$ They also show similar overexpression.

NOTE Confidence: 0.843054783333333

 $00{:}39{:}36{.}170 \dashrightarrow 00{:}39{:}38{.}648$ We were able to then show this

NOTE Confidence: 0.843054783333333

 $00{:}39{:}38{.}648 \dashrightarrow 00{:}39{:}41{.}086$ insight to using RNA ISH and we're

NOTE Confidence: 0.843054783333333

 $00:39:41.086 \longrightarrow 00:39:43.410$ able to show that you can see.

NOTE Confidence: 0.843054783333333

 $00:39:43.410 \rightarrow 00:39:46.938$ Higher expression of these of the U-6 attack,

NOTE Confidence: 0.843054783333333

00:39:46.940 --> 00:39:49.880 but also other components as you

NOTE Confidence: 0.843054783333333

 $00:39:49.880 \dashrightarrow 00:39:52.620$ look at primary prostate cancers,

NOTE Confidence: 0.843054783333333

 $00{:}39{:}52.620 \dashrightarrow 00{:}39{:}55.356$ but also higher in primary prostate

NOTE Confidence: 0.843054783333333

 $00{:}39{:}55{.}356 \dashrightarrow 00{:}39{:}58{.}327$ cancers that go on to metastasize

 $00:39:58.327 \rightarrow 00:40:01.495$ and then in metastases even higher.

NOTE Confidence: 0.843054783333333

 $00:40:01.500 \longrightarrow 00:40:02.970$ What's important is,

NOTE Confidence: 0.843054783333333

00:40:02.970 --> 00:40:05.910 is this actually functionally doing anything?

NOTE Confidence: 0.843054783333333

 $00{:}40{:}05{.}910 \dashrightarrow 00{:}40{:}08{.}502$ And So what Anka did was she used

NOTE Confidence: 0.843054783333333

 $00{:}40{:}08.502 \dashrightarrow 00{:}40{:}10.824$ two vector systems that are designed

NOTE Confidence: 0.843054783333333

 $00:40:10.824 \longrightarrow 00:40:14.015$ so they have either 1 intron and the

NOTE Confidence: 0.843054783333333

 $00:40:14.015 \rightarrow 00:40:16.903$ intron is either a minor or major intron.

NOTE Confidence: 0.843054783333333

 $00:40:16.910 \longrightarrow 00:40:18.200$ And with luciferous,

NOTE Confidence: 0.843054783333333

 $00{:}40{:}18.200 \dashrightarrow 00{:}40{:}21.210$ with this luciferous as say she's able to

NOTE Confidence: 0.843054783333333

 $00:40:21.281 \rightarrow 00:40:24.026$ demonstrate expression if it's working,

NOTE Confidence: 0.843054783333333

 $00{:}40{:}24.030 \dashrightarrow 00{:}40{:}28.314$ so if it's working as a minor

NOTE Confidence: 0.843054783333333

 $00:40:28.314 \rightarrow 00:40:29.538$ intron excising.

NOTE Confidence: 0.843054783333333

 $00:40:29.540 \longrightarrow 00:40:32.570$ Machinery or is there a major

NOTE Confidence: 0.843054783333333

00:40:32.570 --> 00:40:34.590 intron excising machinery working?

NOTE Confidence: 0.843054783333333

 $00:40:34.590 \rightarrow 00:40:37.215$ And I think importantly when she looked

NOTE Confidence: 0.843054783333333

 $00:40:37.215 \rightarrow 00:40:40.590$ at the major insurance splicing activity,
- NOTE Confidence: 0.843054783333333
- $00:40:40.590 \longrightarrow 00:40:42.582$ it remained fairly similar
- NOTE Confidence: 0.843054783333333
- $00:40:42.582 \rightarrow 00:40:45.072$ throughout all the different types
- NOTE Confidence: 0.843054783333333
- $00:40:45.072 \longrightarrow 00:40:48.067$ of of model systems she looked at,
- NOTE Confidence: 0.843054783333333
- $00:40:48.070 \longrightarrow 00:40:50.206$ but only highly expressed for minor
- NOTE Confidence: 0.843054783333333
- $00:40:50.206 \rightarrow 00:40:52.709$ entrance splicing in the advanced cancers,
- NOTE Confidence: 0.843054783333333
- $00:40:52.710 \rightarrow 00:40:54.350$ which is intriguing suggesting
- NOTE Confidence: 0.843054783333333
- $00:40:54.350 \longrightarrow 00:40:56.400$ that this activity is increased.
- NOTE Confidence: 0.843054783333333
- $00:40:56.400 \rightarrow 00:40:58.269$ And this is a very simple vector
- NOTE Confidence: 0.843054783333333
- $00{:}40{:}58.269 \dashrightarrow 00{:}40{:}59.999$ system and we've since developed.
- NOTE Confidence: 0.843054783333333
- $00:41:00.000 \rightarrow 00:41:02.110$ More complex vector systems that
- NOTE Confidence: 0.843054783333333
- $00:41:02.110 \longrightarrow 00:41:04.220$ I could tell you about.
- NOTE Confidence: 0.843054783333333
- $00:41:04.220 \longrightarrow 00:41:05.360$ At the transcript level,
- NOTE Confidence: 0.843054783333333
- $00{:}41{:}05{.}360 \dashrightarrow 00{:}41{:}07{.}984$ we see and these are just some of the
- NOTE Confidence: 0.843054783333333
- $00{:}41{:}07{.}984 \dashrightarrow 00{:}41{:}09{.}979$ the the cell lines in prostate cancer,
- NOTE Confidence: 0.843054783333333
- $00{:}41{:}09{.}980 \dashrightarrow 00{:}41{:}13{.}276$ we see very high expression of U-6 attack
- NOTE Confidence: 0.843054783333333

 $00:41:13.276 \rightarrow 00:41:16.210$ but also other minor splicing components,

NOTE Confidence: 0.843054783333333

 $00:41:16.210 \longrightarrow 00:41:18.060$ but then also the MIGS.

NOTE Confidence: 0.843054783333333

00:41:18.060 - 00:41:20.220 So the minor intron containing

NOTE Confidence: 0.843054783333333

 $00:41:20.220 \rightarrow 00:41:22.380$ genes are more highly expressed.

NOTE Confidence: 0.843054783333333

 $00{:}41{:}22.380 \dashrightarrow 00{:}41{:}25.863$ So as we might expect now Mark Burstein's

NOTE Confidence: 0.843054783333333

 $00{:}41{:}25{.}863 \dashrightarrow 00{:}41{:}28{.}847$ lab helped us with I think a important

NOTE Confidence: 0.843054783333333

 $00:41:28.847 \rightarrow 00:41:31.489$ part which is also extending this to

NOTE Confidence: 0.843054783333333

 $00:41:31.489 \rightarrow 00:41:34.340$ other cancers and the question really is?

NOTE Confidence: 0.843054783333333

 $00{:}41{:}34{.}340 \dashrightarrow 00{:}41{:}37.625$ Are these Migs that we see that are altered

NOTE Confidence: 0.843054783333333

 $00{:}41{:}37.625 \dashrightarrow 00{:}41{:}41.007$ or alternatively expressed in in cancer,

NOTE Confidence: 0.843054783333333

 $00{:}41{:}41.010 \dashrightarrow 00{:}41{:}44.058$ are they potentially very useful in

NOTE Confidence: 0.843054783333333

00:41:44.058 --> 00:41:46.090 distinguishing different cancer types.

NOTE Confidence: 0.843054783333333

 $00{:}41{:}46.090 \dashrightarrow 00{:}41{:}47.800$ So we would hypothesize that the

NOTE Confidence: 0.843054783333333

00:41:47.800 --> 00:41:49.301 makes are expressed but probably

NOTE Confidence: 0.843054783333333

 $00:41:49.301 \rightarrow 00:41:50.851$ different in different tissue types

NOTE Confidence: 0.843054783333333

00:41:50.851 - 00:41:52.909 just like we see in progression.

- NOTE Confidence: 0.843054783333333
- 00:41:52.910 --> 00:41:55.241 And so in Mark's group is able
- NOTE Confidence: 0.843054783333333
- $00{:}41{:}55{.}241 \dashrightarrow 00{:}41{:}57{.}195$ to create these silhouette plot
- NOTE Confidence: 0.843054783333333
- $00:41:57.195 \longrightarrow 00:41:59.841$ here looking at 23 different tumor
- NOTE Confidence: 0.843054783333333
- 00:41:59.841 00:42:02.218 types from a pan cancer analysis
- NOTE Confidence: 0.843054783333333
- $00:42:02.218 \longrightarrow 00:42:04.342$ and they were able to show.
- NOTE Confidence: 0.90923169
- $00{:}42{:}04{.}350 \dashrightarrow 00{:}42{:}07{.}297$ That in this experiment where you go
- NOTE Confidence: 0.90923169
- $00{:}42{:}07{.}297 \dashrightarrow 00{:}42{:}10{.}485$ from 0% MIGS and then so there's a
- NOTE Confidence: 0.90923169
- $00:42:10.485 \rightarrow 00:42:12.822$ dilution experiment all the way to 100%.
- NOTE Confidence: 0.90923169
- $00:42:12.822 \rightarrow 00:42:15.076$ So this is done by doing many,
- NOTE Confidence: 0.90923169
- $00:42:15.080 \rightarrow 00:42:15.960$ many iterations.
- NOTE Confidence: 0.90923169
- $00:42:15.960 \longrightarrow 00:42:19.040$ You can demonstrate that the best model
- NOTE Confidence: 0.90923169
- $00{:}42{:}19{.}040 \dashrightarrow 00{:}42{:}20{.}920$ is a model where you include the mix.
- NOTE Confidence: 0.90923169
- $00:42:20.920 \longrightarrow 00:42:23.744$ So it shows that they have a very
- NOTE Confidence: 0.90923169
- $00:42:23.744 \longrightarrow 00:42:25.558$ strong ability to distinguish
- NOTE Confidence: 0.90923169
- $00{:}42{:}25{.}558 \dashrightarrow 00{:}42{:}27{.}016$ different cancer types.
- NOTE Confidence: 0.90923169

00:42:27.020 --> 00:42:28.272 But specifically for prostate,

NOTE Confidence: 0.90923169

 $00{:}42{:}28{.}272 \dashrightarrow 00{:}42{:}29{.}837$ when we ask the question,

NOTE Confidence: 0.90923169

 $00:42:29.840 \longrightarrow 00:42:32.858$ if we look at benign prostate

NOTE Confidence: 0.90923169

00:42:32.858 --> 00:42:34.367 tissue from GTX.

NOTE Confidence: 0.90923169

 $00{:}42{:}34{.}370 \dashrightarrow 00{:}42{:}36{.}786$ Database versus localized prostate

NOTE Confidence: 0.90923169

 $00{:}42{:}36.786 \dashrightarrow 00{:}42{:}39.806$ cancer or advanced prostate cancer.

NOTE Confidence: 0.90923169

 $00{:}42{:}39{.}810 \dashrightarrow 00{:}42{:}42{.}879$ We see that the MIG genes do a very

NOTE Confidence: 0.90923169

 $00:42:42.879 \rightarrow 00:42:45.213$ nice job without in any selection

NOTE Confidence: 0.90923169

 $00{:}42{:}45{.}213 \dashrightarrow 00{:}42{:}48{.}045$ of a subclass of of the Migs to

NOTE Confidence: 0.90923169

 $00:42:48.045 \rightarrow 00:42:50.097$ distinguish the different groups.

NOTE Confidence: 0.90923169

 $00:42:50.100 \longrightarrow 00:42:51.540$ I think it's important because

NOTE Confidence: 0.90923169

 $00:42:51.540 \longrightarrow 00:42:53.355$ it suggests that I think that

NOTE Confidence: 0.90923169

 $00{:}42{:}53{.}355 \dashrightarrow 00{:}42{:}54{.}970$ these genes for whatever reason,

NOTE Confidence: 0.90923169

 $00:42:54.970 \rightarrow 00:42:55.894$ for evolutionary reasons,

NOTE Confidence: 0.90923169

 $00:42:55.894 \rightarrow 00:42:57.126$ are important and stress,

NOTE Confidence: 0.90923169

 $00:42:57.130 \longrightarrow 00:43:00.244$ but they also are probably reactivated

- NOTE Confidence: 0.90923169
- $00:43:00.244 \rightarrow 00:43:03.470$ or useful for cancer progression.
- NOTE Confidence: 0.90923169
- 00:43:03.470 --> 00:43:05.694 And as I mentioned in the first part
- NOTE Confidence: 0.90923169
- $00:43:05.694 \rightarrow 00:43:08.098$ of the presentation is very important
- NOTE Confidence: 0.90923169
- $00:43:08.098 \rightarrow 00:43:10.323$ when we think about resistance,
- NOTE Confidence: 0.90923169
- $00:43:10.330 \rightarrow 00:43:12.808$ think about probably two types of resistance.
- NOTE Confidence: 0.90923169
- $00{:}43{:}12.810 \dashrightarrow 00{:}43{:}15.162$ One is still related to AR
- NOTE Confidence: 0.90923169
- $00:43:15.162 \longrightarrow 00:43:17.131$ signaling active tumors and we
- NOTE Confidence: 0.90923169
- $00:43:17.131 \rightarrow 00:43:19.413$ have to find ways to attack them,
- NOTE Confidence: 0.90923169
- $00:43:19.420 \longrightarrow 00:43:22.030$ but also AR negative tumors.
- NOTE Confidence: 0.90923169
- $00:43:22.030 \longrightarrow 00:43:23.615$ And I mentioned that there
- NOTE Confidence: 0.90923169
- $00:43:23.615 \longrightarrow 00:43:24.883$ are these four categories.
- NOTE Confidence: 0.90923169
- $00{:}43{:}24.890 \dashrightarrow 00{:}43{:}28.140$ So the question really is.
- NOTE Confidence: 0.90923169
- $00:43:28.140 \longrightarrow 00:43:30.660$ How can we gain any insight into that?
- NOTE Confidence: 0.90923169
- 00:43:30.660 --> 00:43:31.002 Well,
- NOTE Confidence: 0.90923169
- $00{:}43{:}31{.}002 \dashrightarrow 00{:}43{:}33{.}396$ one of the things that Anka had
- NOTE Confidence: 0.90923169

00:43:33.396 - > 00:43:35.938 read about and was known is that

NOTE Confidence: 0.90923169

00:43:35.938 --> 00:43:37.718 map kinase signaling is very

NOTE Confidence: 0.90923169

00:43:37.799 --> 00:43:40.439 important for you 6 attack stability.

NOTE Confidence: 0.90923169

00:43:40.440 --> 00:43:42.618 And so she asks a question,

NOTE Confidence: 0.90923169

00:43:42.620 --> 00:43:45.386 I'm using a A an antibiotic

NOTE Confidence: 0.90923169

 $00{:}43{:}45{.}386 \dashrightarrow 00{:}43{:}47{.}792$ that stimulates map sign kinase

NOTE Confidence: 0.90923169

 $00{:}43{:}47.792 \dashrightarrow 00{:}43{:}50.612$ signaling and ask them and also

NOTE Confidence: 0.90923169

 $00{:}43{:}50.612 \dashrightarrow 00{:}43{:}53.710$ myosin and was able to demonstrate

NOTE Confidence: 0.90923169

 $00{:}43{:}53{.}710 \dashrightarrow 00{:}43{:}56{.}556$ that when you activate MAP kinase

NOTE Confidence: 0.90923169

 $00{:}43{:}56{.}556$ --> $00{:}43{:}58{.}346$ signaling or Jack stat signaling.

NOTE Confidence: 0.90923169

 $00{:}43{:}58.350 \dashrightarrow 00{:}44{:}01.997$ You see only increased expression of of

NOTE Confidence: 0.90923169

 $00{:}44{:}01{.}997 \dashrightarrow 00{:}44{:}06{.}029$ minor splicing in the neuroendocrine tumors,

NOTE Confidence: 0.90923169

 $00:44:06.030 \rightarrow 00:44:07.060$ which is sort of interesting,

NOTE Confidence: 0.90923169

 $00{:}44{:}07.060 \dashrightarrow 00{:}44{:}10.456$ not in the AR sensitive tumors

NOTE Confidence: 0.90923169

 $00:44:10.460 \longrightarrow 00:44:12.040$ when she knocked it down,

NOTE Confidence: 0.90923169

 $00:44:12.040 \longrightarrow 00:44:13.140$ it was the same thing.

- NOTE Confidence: 0.90923169
- $00:44:13.140 \longrightarrow 00:44:15.010$ So I think that's important.
- NOTE Confidence: 0.90923169
- $00{:}44{:}15{.}010 \dashrightarrow 00{:}44{:}18{.}188$ And then in a separate study looking
- NOTE Confidence: 0.90923169
- $00:44:18.188 \rightarrow 00:44:21.819$ at the effect of and rogen stimulation,
- NOTE Confidence: 0.90923169
- $00:44:21.820 \longrightarrow 00:44:23.902$ she was able to demonstrate in
- NOTE Confidence: 0.90923169
- $00{:}44{:}23.902 \dashrightarrow 00{:}44{:}25.290$ different model systems whether
- NOTE Confidence: 0.90923169
- $00{:}44{:}25{.}355 \dashrightarrow 00{:}44{:}26{.}933$ it's a lineat cell line which
- NOTE Confidence: 0.90923169
- $00:44:26.933 \rightarrow 00:44:28.610$ is very angry and sensitive.
- NOTE Confidence: 0.90923169
- $00:44:28.610 \longrightarrow 00:44:31.578$ Or a line cap cell line that
- NOTE Confidence: 0.90923169
- $00{:}44{:}31{.}578 \dashrightarrow 00{:}44{:}32{.}850$ over expresses AR.
- NOTE Confidence: 0.90923169
- $00{:}44{:}32.850 \dashrightarrow 00{:}44{:}35.575$ She's able to demonstrate that
- NOTE Confidence: 0.90923169
- $00{:}44{:}35{.}575 \dashrightarrow 00{:}44{:}38{.}300$ minor intron activity is increased
- NOTE Confidence: 0.90923169
- $00{:}44{:}38{.}383 \dashrightarrow 00{:}44{:}41{.}047$ when you increase AR and and
- NOTE Confidence: 0.90923169
- $00:44:41.047 \longrightarrow 00:44:43.330$ can be modulated through that,
- NOTE Confidence: 0.90923169
- $00{:}44{:}43{.}330 \dashrightarrow 00{:}44{:}45{.}530$ but not major entrance splicing.
- NOTE Confidence: 0.90923169
- $00{:}44{:}45{.}530 \dashrightarrow 00{:}44{:}50{.}532$ So basically I'm trying to think about how a.
- NOTE Confidence: 0.90923169

 $00:44:50.532 \rightarrow 00:44:53.184$ ASICS attack could be stabilizer or

NOTE Confidence: 0.90923169

 $00:44:53.184 \rightarrow 00:44:55.738$ modulated AR signaling could play a

NOTE Confidence: 0.90923169

 $00{:}44{:}55{.}738$ --> $00{:}44{:}58{.}426$ role but also maps map kinase signaling. NOTE Confidence: 0.90923169

00:44:58.430 --> 00:45:01.027 And so she started developing a working NOTE Confidence: 0.90923169

 $00{:}45{:}01{.}027 \dashrightarrow 00{:}45{:}03{.}964$ framework of of how to think about

NOTE Confidence: 0.90923169

 $00{:}45{:}03{.}964 \dashrightarrow 00{:}45{:}05{.}716$ this thinking that neuroendocrine

NOTE Confidence: 0.90923169

00:45:05.716 --> 00:45:07.883 tumors might require map kinase

NOTE Confidence: 0.90923169

 $00{:}45{:}07.883 \dashrightarrow 00{:}45{:}09.908$ signaling to stabilize you six

NOTE Confidence: 0.90923169

00:45:09.908 --> 00:45:12.555 attack and allow for a minor intron

NOTE Confidence: 0.90923169

 $00{:}45{:}12.555 \dashrightarrow 00{:}45{:}14.390$ containing genes to be expressed

NOTE Confidence: 0.90923169

00:45:14.463 --> 00:45:16.268 whereas AR sensitive tumors might

NOTE Confidence: 0.90923169

 $00{:}45{:}16.268 \dashrightarrow 00{:}45{:}18.849$ do it in different way through air

NOTE Confidence: 0.90923169

 $00{:}45{:}18.849 \dashrightarrow 00{:}45{:}20.973$ signaling and we have more data.

NOTE Confidence: 0.90923169

 $00:45:20.980 \longrightarrow 00:45:22.072$ That helps support this.

NOTE Confidence: 0.90923169

 $00:45:22.072 \rightarrow 00:45:24.634$ One thing that was nice is there are two

NOTE Confidence: 0.90923169

 $00:45:24.634 \rightarrow 00:45:26.657$ high impact papers that came out talking

 $00:45:26.715 \longrightarrow 00:45:28.545$ about a subclass of prostate cancer

NOTE Confidence: 0.847652321

 $00{:}45{:}28.545 \dashrightarrow 00{:}45{:}30.544$ that is really driven by Jack stat.

NOTE Confidence: 0.847652321

 $00{:}45{:}30{.}544 \dashrightarrow 00{:}45{:}31{.}834$ So this is quite interesting.

NOTE Confidence: 0.847652321

 $00{:}45{:}31{.}840 \dashrightarrow 00{:}45{:}34{.}605$ And these are stem like tumors which

NOTE Confidence: 0.847652321

 $00:45:34.605 \longrightarrow 00:45:37.707$ would fit in nicely with with the

NOTE Confidence: 0.847652321

00:45:37.707 --> 00:45:40.461 model of minor splicing being driven

NOTE Confidence: 0.847652321

 $00:45:40.548 \dashrightarrow 00:45:43.369$ by a map sign map kinase signaling.

NOTE Confidence: 0.847652321

 $00{:}45{:}43{.}370 \dashrightarrow 00{:}45{:}47{.}194$ So in just the last part I now I

NOTE Confidence: 0.847652321

 $00:45:47.194 \longrightarrow 00:45:49.281$ want to go into what happens if

NOTE Confidence: 0.847652321

 $00:45:49.281 \longrightarrow 00:45:51.360$ we try to target you 6 attacks.

NOTE Confidence: 0.847652321

 $00:45:51.360 \longrightarrow 00:45:51.944$ Specifically.

NOTE Confidence: 0.847652321

 $00{:}45{:}51{.}944 \dashrightarrow 00{:}45{:}54{.}864$ And we hypothesize that this

NOTE Confidence: 0.847652321

00:45:54.864 --> 00:45:58.900 will have an A direct effect on

NOTE Confidence: 0.847652321

 $00{:}45{:}58{.}900 \dashrightarrow 00{:}46{:}01{.}780$ the ability to to exercise these

NOTE Confidence: 0.847652321

 $00{:}46{:}01.780 \dashrightarrow 00{:}46{:}03.930$ introns that are minor introns.

 $00:46:03.930 \longrightarrow 00:46:05.430$ And in fact that's the case.

NOTE Confidence: 0.847652321

 $00:46:05.430 \rightarrow 00:46:11.150$ So when when Anka used a small interfering

NOTE Confidence: 0.847652321

00:46:11.150 --> 00:46:13.610 RNA's to knock down U-6 attack,

NOTE Confidence: 0.847652321

 $00:46:13.610 \longrightarrow 00:46:17.418$ she demonstrated using a a minor splicing

NOTE Confidence: 0.847652321

 $00:46:17.418 \rightarrow 00:46:20.530$ index which looks for misplacing.

NOTE Confidence: 0.847652321

 $00{:}46{:}20{.}530 \dashrightarrow 00{:}46{:}22{.}186$ So now now the introns are

NOTE Confidence: 0.847652321

00:46:22.186 --> 00:46:23.290 no longer being spliced.

NOTE Confidence: 0.847652321

 $00:46:23.290 \longrightarrow 00:46:23.616$ Out.

NOTE Confidence: 0.847652321

 $00{:}46{:}23.616 \dashrightarrow 00{:}46{:}26.224$ And so the data is analyzed and it

NOTE Confidence: 0.847652321

 $00{:}46{:}26{.}224$ --> $00{:}46{:}28{.}251$ consistently shows in all the different

NOTE Confidence: 0.847652321

 $00{:}46{:}28.251 \dashrightarrow 00{:}46{:}30.580$ model systems that if you knock out,

NOTE Confidence: 0.847652321

 $00{:}46{:}30{.}580 \dashrightarrow 00{:}46{:}33{.}740$ if you knock down your six pack it

NOTE Confidence: 0.847652321

 $00:46:33.740 \longrightarrow 00:46:36.437$ functionally has the effect of of

NOTE Confidence: 0.847652321

 $00:46:36.437 \longrightarrow 00:46:38.722$ not allowing these minor intron

NOTE Confidence: 0.847652321

 $00{:}46{:}38.722 \dashrightarrow 00{:}46{:}41.628$ containing genes to to excise out the

NOTE Confidence: 0.847652321

 $00:46:41.628 \rightarrow 00:46:43.892$ entrance for the experts in splicing.

- NOTE Confidence: 0.847652321
- $00{:}46{:}43.892 \dashrightarrow 00{:}46{:}45.597$ I won't go into that.
- NOTE Confidence: 0.847652321
- $00{:}46{:}45{.}600 \dashrightarrow 00{:}46{:}46{.}896$ I'm not an expert in splicing,
- NOTE Confidence: 0.847652321
- 00:46:46.900 --> 00:46:48.940 but cryptic cryptic splice site
- NOTE Confidence: 0.847652321
- $00{:}46{:}48{.}940 \dashrightarrow 00{:}46{:}51{.}899$ alterations seem to be the most common.
- NOTE Confidence: 0.847652321
- $00{:}46{:}51{.}900 \dashrightarrow 00{:}46{:}53{.}540$ But here you can actually.
- NOTE Confidence: 0.847652321
- $00{:}46{:}53{.}540 \dashrightarrow 00{:}46{:}55{.}969$ Determine the specific types of splice sites.
- NOTE Confidence: 0.847652321
- $00:46:55.970 \longrightarrow 00:46:57.150$ So we have experts here,
- NOTE Confidence: 0.847652321
- $00{:}46{:}57{.}150 \dashrightarrow 00{:}47{:}01{.}182$ but I'm not an expert to talk about that.
- NOTE Confidence: 0.847652321
- $00{:}47{:}01{.}190 \dashrightarrow 00{:}47{:}02{.}866$ Anka performed transcriptomics and
- NOTE Confidence: 0.847652321
- $00{:}47{:}02.866 \dashrightarrow 00{:}47{:}05.380$ proteomics and in the context of
- NOTE Confidence: 0.847652321
- $00:47:05.449 \longrightarrow 00:47:07.435$ knocking down you six attack the
- NOTE Confidence: 0.847652321
- $00{:}47{:}07{.}435 \dashrightarrow 00{:}47{:}10{.}155$ main finding I think are that in the NOTE Confidence: 0.847652321
- 00:47:10.155 --> 00:47:12.141 different cell lines we saw different
- NOTE Confidence: 0.847652321
- 00:47:12.150 --> 00:47:14.019 genes that are altered which I think
- NOTE Confidence: 0.847652321
- $00:47:14.019 \longrightarrow 00:47:16.015$ goes in the to the view that this
- NOTE Confidence: 0.847652321

 $00:47:16.015 \rightarrow 00:47:17.975$ is going to be very context specific

NOTE Confidence: 0.847652321

 $00:47:17.975 \longrightarrow 00:47:20.267$ what the regulation of minor splicing.

NOTE Confidence: 0.847652321

 $00{:}47{:}20{.}270$ --> $00{:}47{:}22{.}028$ There were certain the mes that emerged NOTE Confidence: 0.847652321

 $00{:}47{:}22.028 \dashrightarrow 00{:}47{:}23.966$ and I think the important theme

NOTE Confidence: 0.847652321

 $00:47:23.966 \longrightarrow 00:47:26.071$ that should highlight would be 2.

NOTE Confidence: 0.847652321

 $00{:}47{:}26.071$ --> $00{:}47{:}28.639$ So one would be cell cycle and also NOTE Confidence: 0.847652321

00:47:28.639 --> 00:47:31.190 DNA repair were two themes that.

NOTE Confidence: 0.847652321

 $00{:}47{:}31{.}190 \dashrightarrow 00{:}47{:}33{.}185$ Came out when we look at the

NOTE Confidence: 0.847652321

00:47:33.185 --> 00:47:35.304 common genes that are altered in

NOTE Confidence: 0.847652321

 $00:47:35.304 \rightarrow 00:47:36.900$ these different model systems,

NOTE Confidence: 0.847652321

 $00{:}47{:}36{.}900 \dashrightarrow 00{:}47{:}39{.}175$ and so here's an example of the

NOTE Confidence: 0.847652321

00:47:39.175 --> 00:47:41.158 David analysis where it shows some

NOTE Confidence: 0.847652321

 $00{:}47{:}41.158$ --> $00{:}47{:}43.349$ of the common themes and cell cycle.

NOTE Confidence: 0.726276324

 $00:47:45.380 \longrightarrow 00:47:48.380$ As well as DNA alterations,

NOTE Confidence: 0.726276324

 $00{:}47{:}48.380 \dashrightarrow 00{:}47{:}51.369$ came came out as being altered when

NOTE Confidence: 0.726276324

 $00{:}47{:}51{.}369 \dashrightarrow 00{:}47{:}53{.}970$ you knocked down you six attack.

 $00:47:53.970 \longrightarrow 00:47:56.238$ In single cell sequencing fact fax

NOTE Confidence: 0.726276324

00:47:56.238 --> 00:47:58.409 analysis not showing all the data

NOTE Confidence: 0.726276324

 $00{:}47{:}58{.}409 \dashrightarrow 00{:}48{:}00{.}474$ just to just to highlight that we

NOTE Confidence: 0.726276324

00:48:00.474 --> 00:48:02.641 see at G1 arrest when you knock

NOTE Confidence: 0.726276324

 $00:48:02.641 \rightarrow 00:48:04.694$ down you six attack supporting the

NOTE Confidence: 0.726276324

00:48:04.694 --> 00:48:07.226 view that that minor splicing plays

NOTE Confidence: 0.726276324

 $00{:}48{:}07{.}226 \dashrightarrow 00{:}48{:}09{.}512$ an important role in cell cycle

NOTE Confidence: 0.726276324

 $00{:}48{:}09{.}512 \dashrightarrow 00{:}48{:}11{.}564$ in a series of experiments where

NOTE Confidence: 0.726276324

 $00{:}48{:}11.633 \dashrightarrow 00{:}48{:}13.775$ she looked at both cancer cells.

NOTE Confidence: 0.726276324

00:48:13.780 --> 00:48:18.645 So this is a Antrim receptor sensitive

NOTE Confidence: 0.726276324

 $00{:}48{:}18.650 \dashrightarrow 00{:}48{:}21.434$ cast ration resistant tumor that is still

NOTE Confidence: 0.726276324

 $00{:}48{:}21{.}434 \dashrightarrow 00{:}48{:}24{.}080$ probably sensitive to AR signaling.

NOTE Confidence: 0.726276324

00:48:24.080 --> 00:48:26.456 And you knocked down you six attack you

NOTE Confidence: 0.726276324

 $00{:}48{:}26{.}456 \dashrightarrow 00{:}48{:}29{.}560$ see a decrease in in growth of tumor cells.

NOTE Confidence: 0.726276324

 $00{:}48{:}29.560 \dashrightarrow 00{:}48{:}31.800$ We see no change when you look at

 $00:48:31.800 \rightarrow 00:48:33.536$ either mouse fibroblasts or human

NOTE Confidence: 0.726276324

 $00:48:33.536 \rightarrow 00:48:35.391$ fibroblasts and in cocultures one

NOTE Confidence: 0.726276324

00:48:35.391 --> 00:48:37.772 of the reviewers I think is a good

NOTE Confidence: 0.726276324

 $00:48:37.772 \rightarrow 00:48:39.752$ point do we see preferential changes

NOTE Confidence: 0.726276324

 $00{:}48{:}39{.}752 \dashrightarrow 00{:}48{:}44{.}003$ occurring in a Co culture and we we we

NOTE Confidence: 0.726276324

 $00{:}48{:}44.003 \dashrightarrow 00{:}48{:}47.034$ actually see only the tumor cells are

NOTE Confidence: 0.726276324

 $00{:}48{:}47.034 \dashrightarrow 00{:}48{:}50.317$ affected by by you six attack knockdown.

NOTE Confidence: 0.726276324

 $00:48:50.320 \longrightarrow 00:48:52.680$ This is probably the key

NOTE Confidence: 0.726276324

00:48:52.680 --> 00:48:54.096 the rapeutic translational slide.

NOTE Confidence: 0.726276324

 $00:48:54.100 \longrightarrow 00:48:56.050$ Which is that in air sensitive

NOTE Confidence: 0.726276324

 $00{:}48{:}56.050 \dashrightarrow 00{:}48{:}58.251$ tumors if you treat with enzalutamide

NOTE Confidence: 0.726276324

00:48:58.251 --> 00:49:00.747 or knockdown usix attack you see

NOTE Confidence: 0.726276324

 $00{:}49{:}00{.}747 \dashrightarrow 00{:}49{:}03{.}082$ basically the same result which is

NOTE Confidence: 0.726276324

 $00:49:03.082 \longrightarrow 00:49:05.230$ a decrease in confluence of cells.

NOTE Confidence: 0.726276324

 $00{:}49{:}05{.}230 \dashrightarrow 00{:}49{:}07{.}200$ So this is using Incyte.

NOTE Confidence: 0.726276324

 $00:49:07.200 \longrightarrow 00:49:09.152$ If you then go to cell lines that

 $00{:}49{:}09{.}152 \dashrightarrow 00{:}49{:}11.065$ are AR resistant and there's just

NOTE Confidence: 0.726276324

 $00:49:11.065 \longrightarrow 00:49:13.690$ two cell lines but we've done it or

NOTE Confidence: 0.726276324

00:49:13.690 --> 00:49:15.738 more are you see that the tumors are

NOTE Confidence: 0.726276324

00:49:15.740 --> 00:49:17.800 no longer sensitive to enzalutamide

NOTE Confidence: 0.726276324

 $00{:}49{:}17.800 \dashrightarrow 00{:}49{:}19.860$ or the antiandrogen the rapy but

NOTE Confidence: 0.726276324

 $00:49:19.930 \longrightarrow 00:49:21.922$ continue to be very sensitive to

NOTE Confidence: 0.726276324

00:49:21.922 --> 00:49:24.119 knocking down you six attack which.

NOTE Confidence: 0.726276324

 $00:49:24.120 \longrightarrow 00:49:26.521$ Is A is a promising first step

NOTE Confidence: 0.726276324

 $00{:}49{:}26{.}521 \dashrightarrow 00{:}49{:}29{.}123$ for thinking about does this have

NOTE Confidence: 0.726276324

 $00:49:29.123 \longrightarrow 00:49:30.626$ any therapeutic translation,

NOTE Confidence: 0.726276324

00:49:30.630 --> 00:49:31.578 although many,

NOTE Confidence: 0.726276324

00:49:31.578 --> 00:49:33.948 many steps away from actually

NOTE Confidence: 0.726276324

 $00{:}49{:}33{.}948 \dashrightarrow 00{:}49{:}35{.}370$ having the rapeutic translation.

NOTE Confidence: 0.726276324

 $00{:}49{:}35{.}370 \dashrightarrow 00{:}49{:}38{.}100$ We extended this to the Memorial Sloan

NOTE Confidence: 0.726276324

 $00:49:38.100 \rightarrow 00:49:40.049$ Kettering and Cornell patient Dr.

 $00:49:40.050 \rightarrow 00:49:42.335$ Organoids that represent a range

NOTE Confidence: 0.726276324

 $00{:}49{:}42{.}335 \dashrightarrow 00{:}49{:}45{.}166$ of air positive and air negative

NOTE Confidence: 0.726276324

00:49:45.166 --> 00:49:48.421 prostate cancers and we see the same

NOTE Confidence: 0.726276324

 $00{:}49{:}48{.}421 \dashrightarrow 00{:}49{:}51{.}350$ effect that you can by knocking down

NOTE Confidence: 0.726276324

 $00{:}49{:}51{.}350 \dashrightarrow 00{:}49{:}53{.}908$ you six attack you can decrease.

NOTE Confidence: 0.726276324

 $00:49:53.908 \longrightarrow 00:49:56.460$ Cell viability and confluence.

NOTE Confidence: 0.726276324

 $00:49:56.460 \longrightarrow 00:49:57.676$ I'll skip the videos,

NOTE Confidence: 0.726276324

 $00{:}49{:}57.676 \dashrightarrow 00{:}50{:}00.262$ but we can also see this in benign

NOTE Confidence: 0.726276324

 $00{:}50{:}00{.}262 \dashrightarrow 00{:}50{:}03{.}014$ prostate cell lines that are that we have,

NOTE Confidence: 0.726276324

 $00:50:03.020 \longrightarrow 00:50:04.530$ as well as the cancer cell lines.

NOTE Confidence: 0.88153776

00:50:08.210 --> 00:50:08.678 If you can

NOTE Confidence: 0.789957396

00:50:08.690 --> 00:50:11.090 move, OK. So the last,

NOTE Confidence: 0.789957396

 $00{:}50{:}11.090 \dashrightarrow 00{:}50{:}13.648$ the very last piece I just want to bring

NOTE Confidence: 0.789957396

 $00{:}50{:}13.648 \dashrightarrow 00{:}50{:}16.294$ up is a interesting concept and this

NOTE Confidence: 0.789957396

 $00:50:16.294 \rightarrow 00:50:18.768$ is something we call poison peptides.

NOTE Confidence: 0.789957396

 $00:50:18.770 \rightarrow 00:50:20.354$ Maybe somebody's used this in another

- NOTE Confidence: 0.789957396
- $00:50:20.354 \rightarrow 00:50:22.428$ context and maybe it's not the right context,
- NOTE Confidence: 0.789957396
- 00:50:22.430 --> 00:50:24.782 but right now we're just working
- NOTE Confidence: 0.789957396
- $00:50:24.782 \longrightarrow 00:50:26.350$ title is poison peptides.
- NOTE Confidence: 0.789957396
- $00:50:26.350 \longrightarrow 00:50:28.014$ And the idea is,
- NOTE Confidence: 0.789957396
- $00{:}50{:}28.014 \dashrightarrow 00{:}50{:}30.510$ is that when the minor introns
- NOTE Confidence: 0.789957396
- $00{:}50{:}30{.}601 \dashrightarrow 00{:}50{:}33{.}662$ splicing occurs it it performs a
- NOTE Confidence: 0.789957396
- $00:50:33.662 \rightarrow 00:50:35.827$ protein that it potentially plays
- NOTE Confidence: 0.789957396
- $00:50:35.827 \rightarrow 00:50:38.718$ an important role in cell cycle.
- NOTE Confidence: 0.789957396
- $00{:}50{:}38.720 \dashrightarrow 00{:}50{:}41.066$ And help stabilize the cancer cells,
- NOTE Confidence: 0.789957396
- $00:50:41.070 \longrightarrow 00:50:43.390$ but when it's not excised,
- NOTE Confidence: 0.789957396
- $00{:}50{:}43{.}390 \dashrightarrow 00{:}50{:}45{.}736$ the question is what what's happening
- NOTE Confidence: 0.789957396
- $00{:}50{:}45.736 \dashrightarrow 00{:}50{:}47.824$ with these message and is it,
- NOTE Confidence: 0.789957396
- $00:50:47.824 \rightarrow 00:50:49.128$ is it becoming just,
- NOTE Confidence: 0.789957396
- $00:50:49.130 \rightarrow 00:50:50.975$ is it just undergoing degradation
- NOTE Confidence: 0.789957396
- $00{:}50{:}50{.}975 \dashrightarrow 00{:}50{:}53{.}605$ or are there some sort of aberrant
- NOTE Confidence: 0.789957396

 $00:50:53.605 \rightarrow 00:50:56.097$ or other types of isoforms that are

NOTE Confidence: 0.789957396

 $00{:}50{:}56{.}097 \dashrightarrow 00{:}50{:}58{.}555$ formed and just want to show you an

NOTE Confidence: 0.789957396

00:50:58.555 --> 00:51:00.621 example that we were quite intrigued

NOTE Confidence: 0.789957396

 $00:51:00.621 \longrightarrow 00:51:03.003$ with which is related to rest.

NOTE Confidence: 0.789957396

 $00:51:03.010 \longrightarrow 00:51:05.754$ So rest is a transcription factor plays

NOTE Confidence: 0.789957396

 $00:51:05.754 \rightarrow 00:51:08.789$ an important role in neural fate regulation.

NOTE Confidence: 0.789957396

 $00{:}51{:}08.790 \dashrightarrow 00{:}51{:}10.635$ In development and so most

NOTE Confidence: 0.789957396

00:51:10.635 - 00:51:12.480 of us know about rest,

NOTE Confidence: 0.789957396

 $00{:}51{:}12{.}480 \dashrightarrow 00{:}51{:}14{.}735$ rest when rest expression is

NOTE Confidence: 0.789957396

 $00:51:14.735 \rightarrow 00:51:16.990$ present in in cancer types,

NOTE Confidence: 0.789957396

 $00:51:16.990 \longrightarrow 00:51:19.498$ we know that it it prevents

NOTE Confidence: 0.789957396

 $00:51:19.498 \longrightarrow 00:51:20.334$ neural differentiation.

NOTE Confidence: 0.789957396

 $00:51:20.340 \longrightarrow 00:51:21.436$ And when it's down,

NOTE Confidence: 0.789957396

 $00:51:21.436 \longrightarrow 00:51:23.528$ we expect that you may see neural

NOTE Confidence: 0.789957396

 $00{:}51{:}23.528 \dashrightarrow 00{:}51{:}25.826$ differentiation and this is in cancer.

NOTE Confidence: 0.789957396

 $00:51:25.830 \rightarrow 00:51:28.056$ We see this occurring quite often.

- NOTE Confidence: 0.789957396
- $00:51:28.060 \dashrightarrow 00:51:31.462$ There's also a isoform that's that's
- NOTE Confidence: 0.789957396
- $00{:}51{:}31{.}462 \dashrightarrow 00{:}51{:}35{.}158$ known but little known and that's called
- NOTE Confidence: 0.789957396
- $00{:}51{:}35{.}158 \dashrightarrow 00{:}51{:}38{.}930$ rest four and rest 4 forms a dimer.
- NOTE Confidence: 0.789957396
- $00:51:38.930 \rightarrow 00:51:41.359$ With rest one and prevents it from
- NOTE Confidence: 0.789957396
- $00{:}51{:}41{.}359 \dashrightarrow 00{:}51{:}44{.}133$ binding to DNA and therefore it
- NOTE Confidence: 0.789957396
- $00{:}51{:}44{.}133 \dashrightarrow 00{:}51{:}45{.}795$ allows neural differentiation.
- NOTE Confidence: 0.789957396
- 00:51:45.800 --> 00:51:47.558 So if risk four is present,
- NOTE Confidence: 0.789957396
- $00:51:47.560 \longrightarrow 00:51:49.260$ you do have neural differentiation
- NOTE Confidence: 0.789957396
- $00{:}51{:}49{.}260 \dashrightarrow 00{:}51{:}51{.}347$ and this is just showing in
- NOTE Confidence: 0.789957396
- $00:51:51.347 \longrightarrow 00:51:52.639$ a slightly different way.
- NOTE Confidence: 0.789957396
- $00:51:52.640 \longrightarrow 00:51:55.880$ So there's a small there.
- NOTE Confidence: 0.789957396
- 00:51:55.880 --> 00:51:59.284 There's a small mini intron here,
- NOTE Confidence: 0.789957396
- $00{:}51{:}59{.}284 \dashrightarrow 00{:}52{:}02{.}296$ a small Exx on here that needs
- NOTE Confidence: 0.789957396
- $00:52:02.296 \longrightarrow 00:52:05.606$ to be excised in order for you
- NOTE Confidence: 0.789957396
- $00:52:05.606 \rightarrow 00:52:09.170$ to go from rest 4 to rest one.
- NOTE Confidence: 0.789957396

 $00:52:09.170 \longrightarrow 00:52:11.162$ So what I wanted to show you is

NOTE Confidence: 0.789957396

 $00{:}52{:}11{.}162 \dashrightarrow 00{:}52{:}13{.}129$ that then Anka asks the question,

NOTE Confidence: 0.789957396

 $00{:}52{:}13.130 \dashrightarrow 00{:}52{:}15.560$ well what does she see as far as rest NOTE Confidence: 0.789957396

 $00:52:15.560 \rightarrow 00:52:17.802$ expression as expected it's very low

NOTE Confidence: 0.789957396

00:52:17.802 --> 00:52:19.330 in neuroendocrine prostate cancers,

NOTE Confidence: 0.789957396

 $00{:}52{:}19{.}330 \dashrightarrow 00{:}52{:}22{.}249$ this from our stand up cancer data,

NOTE Confidence: 0.789957396

 $00:52:22.250 \longrightarrow 00:52:24.415$ but she sees higher expression

NOTE Confidence: 0.789957396

 $00:52:24.415 \longrightarrow 00:52:27.180$ of risk for in these cases.

NOTE Confidence: 0.789957396

 $00{:}52{:}27.180 \dashrightarrow 00{:}52{:}28.755$ So that's something we had never looked

NOTE Confidence: 0.789957396

 $00{:}52{:}28.755 \dashrightarrow 00{:}52{:}30.333$ at because we never thought about

NOTE Confidence: 0.789957396

 $00{:}52{:}30{.}333 \dashrightarrow 00{:}52{:}31{.}763$ looking at the different isoforms.

NOTE Confidence: 0.789957396

 $00:52:31.770 \longrightarrow 00:52:33.528$ And if you think about the

NOTE Confidence: 0.789957396

00:52:33.528 --> 00:52:34.700 endogenous expression of risk

NOTE Confidence: 0.789957396

 $00:52:34.754 \longrightarrow 00:52:36.428$ for in the different cell lines,

NOTE Confidence: 0.789957396

 $00:52:36.430 \longrightarrow 00:52:37.606$ we also see the same thing.

NOTE Confidence: 0.789957396

 $00:52:37.610 \longrightarrow 00:52:39.510$ So very low risk 4.

- NOTE Confidence: 0.789957396
- $00:52:39.510 \longrightarrow 00:52:41.540$ Expression in the neuroendocrine tumors
- NOTE Confidence: 0.789957396
- 00:52:41.540 --> 00:52:44.339 when she knocks down you six attack,
- NOTE Confidence: 0.789957396
- $00:52:44.340 \longrightarrow 00:52:48.300$ she increases rest rest expression.
- NOTE Confidence: 0.789957396
- $00:52:48.300 \rightarrow 00:52:49.950$ But I think what's really interesting
- NOTE Confidence: 0.789957396
- $00{:}52{:}49{.}950 \dashrightarrow 00{:}52{:}51{.}896$ is if you look at the protein
- NOTE Confidence: 0.789957396
- $00{:}52{:}51{.}896 \dashrightarrow 00{:}52{:}53{.}744$ level and you look at the different
- NOTE Confidence: 0.789957396
- $00{:}52{:}53.802 \dashrightarrow 00{:}52{:}55.517$ isoform she's able to demonstrate
- NOTE Confidence: 0.789957396
- $00{:}52{:}55{.}517 \dashrightarrow 00{:}52{:}57{.}595$ in neuroendocrine model said if you
- NOTE Confidence: 0.789957396
- $00{:}52{:}57{.}595 \dashrightarrow 00{:}52{:}59{.}725$ knocked down Usix attack and again
- NOTE Confidence: 0.789957396
- $00:52:59.725 \longrightarrow 00:53:02.354$ this is not a perfect but it's a
- NOTE Confidence: 0.789957396
- $00{:}53{:}02{.}354 \dashrightarrow 00{:}53{:}04{.}318$ it's a beginning of a developing
- NOTE Confidence: 0.789957396
- 00:53:04.318 --> 00:53:06.706 a hypothesis that she sees a
- NOTE Confidence: 0.789957396
- $00{:}53{:}06{.}706 \dashrightarrow 00{:}53{:}08{.}662$ decrease in rest for so.
- NOTE Confidence: 0.789957396
- 00:53:08.662 --> 00:53:10.948 At least the hypothesis is developing
- NOTE Confidence: 0.789957396
- $00{:}53{:}10{.}948 \dashrightarrow 00{:}53{:}14{.}033$ that we can think that in the normal
- NOTE Confidence: 0.789957396

 $00:53:14.033 \rightarrow 00:53:16.197$ state of these advanced prostate

NOTE Confidence: 0.789957396

 $00{:}53{:}16.197 \dashrightarrow 00{:}53{:}18.557$ cancers that are neuroendocrine,

NOTE Confidence: 0.789957396

 $00:53:18.560 \longrightarrow 00:53:20.714$ they have high levels of rest

NOTE Confidence: 0.789957396

 $00:53:20.714 \rightarrow 00:53:22.150$ four which prevent arrest

NOTE Confidence: 0.845042928888889

 $00{:}53{:}22{.}216 \dashrightarrow 00{:}53{:}24.856$ from being functional and allow

NOTE Confidence: 0.845042928888889

00:53:24.856 --> 00:53:26.440 for neuroendocrine maintenance

NOTE Confidence: 0.845042928888889

 $00:53:26.440 \longrightarrow 00:53:28.277$ or differentiation and that

NOTE Confidence: 0.845042928888889

00:53:28.277 --> 00:53:30.047 knocking down you six attack.

NOTE Confidence: 0.845042928888889

 $00{:}53{:}30{.}050 \dashrightarrow 00{:}53{:}32{.}054$ But clearly other ways of modulating

NOTE Confidence: 0.845042928888889

 $00{:}53{:}32{.}054 \dashrightarrow 00{:}53{:}34{.}285$ rest could also lead to a situation

NOTE Confidence: 0.845042928888889

 $00{:}53{:}34{.}285 \dashrightarrow 00{:}53{:}36{.}217$ where you knock down rest for it

NOTE Confidence: 0.845042928888889

00:53:36.277 --> 00:53:37.977 and you increase rest anyway.

NOTE Confidence: 0.845042928888889

 $00:53:37.980 \longrightarrow 00:53:40.300$ So I'll I'll leave you with just nice.

NOTE Confidence: 0.845042928888889

00:53:40.300 --> 00:53:41.305 Image of Switzerland,

NOTE Confidence: 0.845042928888889

 $00:53:41.305 \longrightarrow 00:53:44.059$ so Nice Lake that we like to go

NOTE Confidence: 0.845042928888889

 $00:53:44.059 \rightarrow 00:53:46.404$ hiking around and just a summary.

- NOTE Confidence: 0.845042928888889
- 00:53:46.410 --> 00:53:48.790 So I've told you about minor splicing
- NOTE Confidence: 0.845042928888889
- $00:53:48.790 \longrightarrow 00:53:51.401$ how there's a it's really a very
- NOTE Confidence: 0.845042928888889
- $00:53:51.401 \rightarrow 00:53:53.301$ small component of the spliceosome
- NOTE Confidence: 0.845042928888889
- $00:53:53.301 \longrightarrow 00:53:55.990$ and that we think U-6 attack is
- NOTE Confidence: 0.845042928888889
- $00{:}53{:}55{.}990 \dashrightarrow 00{:}53{:}57{.}981$ is quite interesting because it
- NOTE Confidence: 0.845042928888889
- 00:53:57.981 --> 00:54:00.436 plays an important catalytic role
- NOTE Confidence: 0.845042928888889
- $00:54:00.436 \longrightarrow 00:54:02.400$ and potentially represents an
- NOTE Confidence: 0.845042928888889
- $00:54:02.479 \rightarrow 00:54:05.007$ important opportunity for therapy.
- NOTE Confidence: 0.845042928888889
- $00{:}54{:}05{.}010 \dashrightarrow 00{:}54{:}06{.}762$ And most important slide is just
- NOTE Confidence: 0.845042928888889
- 00:54:06.762 --> 00:54:08.988 to make sure I acknowledge all
- NOTE Confidence: 0.845042928888889
- $00:54:08.988 \longrightarrow 00:54:10.479$ our great collaborators.
- NOTE Confidence: 0.845042928888889
- $00{:}54{:}10{.}480 \dashrightarrow 00{:}54{:}11{.}880$ So in addition to.
- NOTE Confidence: 0.845042928888889
- $00{:}54{:}11{.}880 \dashrightarrow 00{:}54{:}13{.}980$ Bronco with the Ruben Lab members
- NOTE Confidence: 0.845042928888889
- $00{:}54{:}14.048 \dashrightarrow 00{:}54{:}16.064$ as well as members from Rahul
- NOTE Confidence: 0.845042928888889
- $00:54:16.064 \rightarrow 00:54:18.615$ Canali's group at at the at the
- NOTE Confidence: 0.845042928888889

 $00{:}54{:}18.615 \dashrightarrow 00{:}54{:}20.505$ University of Connecticut and Mark

NOTE Confidence: 0.845042928888889

 $00{:}54{:}20{.}510 \dashrightarrow 00{:}54{:}21{.}870$ Gerstein's group here at Yale.

NOTE Confidence: 0.845042928888889

 $00:54:21.870 \longrightarrow 00:54:23.007$ They've been really,

NOTE Confidence: 0.845042928888889

 $00{:}54{:}23.007 \dashrightarrow 00{:}54{:}25.281$ really helpful in letting us think

NOTE Confidence: 0.845042928888889

 $00{:}54{:}25{.}281 \dashrightarrow 00{:}54{:}27{.}715$ about this and and really broad terms.

NOTE Confidence: 0.845042928888889

 $00:54:27.720 \rightarrow 00:54:29.448$ Thank you very much for your attention today.

NOTE Confidence: 0.8141235

00:54:34.160 -> 00:54:35.940 Happy to take any questions.

NOTE Confidence: 0.96253157

00:54:39.240 --> 00:54:43.348 OK. Questions. So yeah.

NOTE Confidence: 0.96253157

 $00{:}54{:}43{.}348 \dashrightarrow 00{:}54{:}46{.}928$ So the floor is open.

NOTE Confidence: 0.96253157

 $00:54:46.930 \longrightarrow 00:54:51.709$ Questions for mark.

NOTE Confidence: 0.96253157

 $00{:}54{:}51{.}710 \dashrightarrow 00{:}54{:}54{.}139$ I I can get started with a

NOTE Confidence: 0.96253157

 $00{:}54{:}54{.}139 \dashrightarrow 00{:}54{:}56{.}209$ question that was really nice.

NOTE Confidence: 0.96253157

 $00:54:56.210 \longrightarrow 00:54:58.118$ Thank you very much and wonderful

NOTE Confidence: 0.96253157

 $00{:}54{:}58{.}118 \dashrightarrow 00{:}55{:}00{.}371$ to hear about both of those stories

NOTE Confidence: 0.96253157

 $00{:}55{:}00{.}371 \dashrightarrow 00{:}55{:}02{.}513$ on the Swiss knife complex and on

NOTE Confidence: 0.96253157

 $00:55:02.574 \dashrightarrow 00:55:04.409$ the the minor intron splicing.

 $00{:}55{:}04{.}410 \dashrightarrow 00{:}55{:}07{.}418$ So one of the questions that I have

NOTE Confidence: 0.96253157

 $00{:}55{:}07{.}418$ --> $00{:}55{:}10{.}488$ and it's something that that's

NOTE Confidence: 0.96253157

 $00{:}55{:}10.490 \dashrightarrow 00{:}55{:}13.577$ something that we think about a lot NOTE Confidence: 0.96253157

 $00:55:13.577 \rightarrow 00:55:16.977$ as well is the sensitivity of of

NOTE Confidence: 0.96253157

 $00{:}55{:}16{.}977 \dashrightarrow 00{:}55{:}19{.}546$ tumors to smarka for modulation for NOTE Confidence: 0.96253157

 $00:55:19.546 \dashrightarrow 00:55:22.340$ example and one of the things that.

NOTE Confidence: 0.96253157

 $00{:}55{:}22{.}340 \dashrightarrow 00{:}55{:}26{.}078$ You mentioned was or what it seems

NOTE Confidence: 0.96253157

 $00{:}55{:}26.078 \dashrightarrow 00{:}55{:}29.365$ like these protax seemed to be

NOTE Confidence: 0.96253157

 $00{:}55{:}29{.}365 \dashrightarrow 00{:}55{:}31{.}990$ most effective in tumors that

NOTE Confidence: 0.96253157

 $00{:}55{:}31{.}990 \dashrightarrow 00{:}55{:}35{.}070$ are AR sensitive to which is kind

NOTE Confidence: 0.96253157

 $00{:}55{:}35{.}070 \dashrightarrow 00{:}55{:}37{.}911$ of interesting if we think about

NOTE Confidence: 0.96253157

 $00:55:37.911 \rightarrow 00:55:40.546$ smart before perhaps exerting its

NOTE Confidence: 0.96253157

 $00{:}55{:}40{.}546{\:}-{\:}>00{:}55{:}43{.}660$ functions in the resistant tumors.

NOTE Confidence: 0.96253157

 $00{:}55{:}43{.}660 \dashrightarrow 00{:}55{:}45{.}711$ And I was wondering if you have NOTE Confidence: 0.96253157

 $00{:}55{:}45{.}711 \dashrightarrow 00{:}55{:}48{.}163$ if if if you have any thoughts

 $00:55:48.163 \longrightarrow 00:55:50.033$ on sort of that paradox?

NOTE Confidence: 0.96253157

 $00{:}55{:}50{.}040 \dashrightarrow 00{:}55{:}52{.}348$ Well, if it is a paradox,

NOTE Confidence: 0.65090655875

 $00:55:52.400 \longrightarrow 00:55:55.920$ yeah. So I'll just expand a little bit.

NOTE Confidence: 0.65090655875

 $00:55:55.920 \longrightarrow 00:55:57.160$ So I think the things,

NOTE Confidence: 0.65090655875

 $00{:}55{:}57{.}160 \dashrightarrow 00{:}55{:}59{.}470$ just to reiterate what I said

NOTE Confidence: 0.65090655875

 $00:55:59.470 \longrightarrow 00:56:01.380$ though also and you're well

NOTE Confidence: 0.65090655875

 $00:56:01.380 \longrightarrow 00:56:03.748$ aware of is that if you do any.

NOTE Confidence: 0.65090655875

 $00:56:03.750 \longrightarrow 00:56:05.964$ Synthetic lethal screens, smart K4 and

NOTE Confidence: 0.65090655875

00:56:05.964 --> 00:56:08.740 Mark 2 come out as always winners,

NOTE Confidence: 0.65090655875

 $00:56:08.740 \rightarrow 00:56:10.312$ they're always there, right.

NOTE Confidence: 0.65090655875

 $00{:}56{:}10.312 \dashrightarrow 00{:}56{:}14.277$ And so I think that the Protex in effectively

NOTE Confidence: 0.65090655875

 $00:56:14.277 \longrightarrow 00:56:17.197$ you know hitting both regardless are

NOTE Confidence: 0.65090655875

 $00{:}56{:}17.197 \dashrightarrow 00{:}56{:}19.766$ you know great targets I think for.

NOTE Confidence: 0.65090655875

 $00:56:19.770 \longrightarrow 00:56:21.906$ So the question is why is it so?

NOTE Confidence: 0.65090655875

 $00:56:21.910 \dashrightarrow 00:56:23.980$ Why are the AR sensitive tumors.

NOTE Confidence: 0.65090655875

 $00:56:23.980 \longrightarrow 00:56:26.722$ So you know why are they

- NOTE Confidence: 0.65090655875
- $00:56:26.722 \rightarrow 00:56:28.550$ exquisitely sensitive to this.
- NOTE Confidence: 0.65090655875
- $00:56:28.550 \longrightarrow 00:56:31.364$ We think that that's not the case.
- NOTE Confidence: 0.65090655875
- $00:56:31.370 \rightarrow 00:56:33.210$ So we actually think that it extends beyond,
- NOTE Confidence: 0.65090655875
- $00:56:33.210 \longrightarrow 00:56:34.596$ it's not just.
- NOTE Confidence: 0.65090655875
- $00{:}56{:}34{.}596 \dashrightarrow 00{:}56{:}37{.}305$ They are and the the complexity we
- NOTE Confidence: 0.65090655875
- $00{:}56{:}37{.}305 \dashrightarrow 00{:}56{:}40{.}761$ have is is that we think that AR that
- NOTE Confidence: 0.65090655875
- 00:56:40.761 -> 00:56:43.564 smart K4 is something you want to
- NOTE Confidence: 0.65090655875
- $00{:}56{:}43.564 \dashrightarrow 00{:}56{:}46.220$ decrease and but we know that if we
- NOTE Confidence: 0.65090655875
- $00{:}56{:}46{.}220 \dashrightarrow 00{:}56{:}48{.}814$ do that smart K2 has to be maintained.
- NOTE Confidence: 0.65090655875
- $00:56:48.820 \longrightarrow 00:56:51.010$ So there's a problem with the
- NOTE Confidence: 0.65090655875
- $00{:}56{:}51{.}010 \dashrightarrow 00{:}56{:}53{.}160$ the Protex is extremely toxic and
- NOTE Confidence: 0.65090655875
- $00{:}56{:}53.160 \dashrightarrow 00{:}56{:}55.020$ so how to get around that.
- NOTE Confidence: 0.65090655875
- $00{:}56{:}55{.}020 \dashrightarrow 00{:}56{:}57{.}015$ The other thing also I'm sure you're
- NOTE Confidence: 0.65090655875
- 00:56:57.015 --> 00:56:58.985 aware and you've maybe seen this is NOTE Confidence: 0.65090655875
- 00:56:58.985 --> 00:57:00.924 that when you use the protects you
- NOTE Confidence: 0.65090655875

 $00:57:00.924 \rightarrow 00:57:02.429$ can actually get nice resistance

NOTE Confidence: 0.65090655875

 $00{:}57{:}02{.}429 \dashrightarrow 00{:}57{:}04{.}180$ very quickly and as you expect.

NOTE Confidence: 0.65090655875

 $00:57:04.180 \longrightarrow 00:57:05.530$ Where would the resistance be?

NOTE Confidence: 0.65090655875

 $00:57:05.530 \longrightarrow 00:57:07.514$ It's in VHL or and and one

NOTE Confidence: 0.65090655875

 $00{:}57{:}07{.}514 \dashrightarrow 00{:}57{:}09{.}757$ of the genes associated with how

NOTE Confidence: 0.65090655875

 $00{:}57{:}09{.}757 \dashrightarrow 00{:}57{:}11.847$ the protects are are designed.

NOTE Confidence: 0.65090655875

00:57:11.850 --> 00:57:14.048 So we have nice experiments I didn't

NOTE Confidence: 0.65090655875

 $00{:}57{:}14.048 \dashrightarrow 00{:}57{:}16.811$ show but where we've you know in cycle

NOTE Confidence: 0.65090655875

00:57:16.811 $\operatorname{-->}$ 00:57:18.954 through resistance which is going to

NOTE Confidence: 0.65090655875

 $00:57:18.954 \dashrightarrow 00:57:21.530$ be different than the ATP a type resistance.

NOTE Confidence: 0.65090655875

00:57:21.530 --> 00:57:23.722 So in a rules paper I think it

NOTE Confidence: 0.65090655875

 $00{:}57{:}23.722 \dashrightarrow 00{:}57{:}26.204$ was exciting to see that you can

NOTE Confidence: 0.65090655875

 $00:57:26.204 \rightarrow 00:57:27.326$ potentially target cancers.

NOTE Confidence: 0.65090655875

 $00{:}57{:}27{.}330 \dashrightarrow 00{:}57{:}29{.}731$ I think there's a bit of skepticism

NOTE Confidence: 0.65090655875

 $00:57:29.731 \longrightarrow 00:57:31.841$ in the issue of toxicity because

NOTE Confidence: 0.65090655875

00:57:31.841 - > 00:57:34.550 I think the field and in in Bob.

- NOTE Confidence: 0.65090655875
- 00:57:34.550 --> 00:57:36.220 The box paper from Genentech,
- NOTE Confidence: 0.65090655875
- $00{:}57{:}36{.}220 \dashrightarrow 00{:}57{:}38{.}458$ I think they nicely described that
- NOTE Confidence: 0.65090655875
- $00{:}57{:}38{.}458 \dashrightarrow 00{:}57{:}41{.}214$ the toxicity is a major issue and
- NOTE Confidence: 0.65090655875
- $00:57:41.214 \rightarrow 00:57:43.189$ so since a specificity whether
- NOTE Confidence: 0.65090655875
- $00:57:43.189 \longrightarrow 00:57:44.699$ it's for Smarca 2,
- NOTE Confidence: 0.65090655875
- $00{:}57{:}44.700 \dashrightarrow 00{:}57{:}46.820$ but we think it would be interesting to
- NOTE Confidence: 0.65090655875
- 00:57:46.820 --> 00:57:48.899 have smart K4 specificity for prostate.
- NOTE Confidence: 0.65090655875
- 00:57:48.900 --> 00:57:49.476 So I don't,
- NOTE Confidence: 0.65090655875
- 00:57:49.476 --> 00:57:51.313 I don't know I mean it's but we don't
- NOTE Confidence: 0.65090655875
- $00:57:51.313 \longrightarrow 00:57:52.846$ have either so at this point so.
- NOTE Confidence: 0.894762494
- 00:57:55.120 --> 00:57:58.930 Thank you. Yes. So yes, please go ahead.
- NOTE Confidence: 0.83852434
- $00{:}58{:}20{.}110 \dashrightarrow 00{:}58{:}21{.}350$ You might you might have to
- NOTE Confidence: 0.83852434
- $00:58:21.350 \longrightarrow 00:58:22.390$ repeat the question for me
- NOTE Confidence: 0.914617287333333
- 00:58:22.437 --> 00:58:23.477 because I didn't hear it.
- NOTE Confidence: 0.60060287
- $00{:}58{:}25{.}500 \dashrightarrow 00{:}58{:}25{.}870$ OK.
- NOTE Confidence: 0.887259296

00:58:36.350 --> 00:58:37.220 Do you think you could?

NOTE Confidence: 0.686882793333333

 $00{:}58{:}37{.}370 \dashrightarrow 00{:}58{:}38{.}450$ I think it would be hard.

NOTE Confidence: 0.686882793333333

 $00:58:38.450 \longrightarrow 00:58:39.428$ Would you like to come out?

NOTE Confidence: 0.788932177222222

 $00:58:39.440 \rightarrow 00:58:41.640$ I think you have to say it in the microphone

NOTE Confidence: 0.788932177222222

 $00{:}58{:}41{.}690 \dashrightarrow 00{:}58{:}43{.}690$ so people can hear it who are listening.

NOTE Confidence: 0.788932177222222

 $00{:}58{:}43.690 \dashrightarrow 00{:}58{:}46.310$ And also I I can't hear very well, so.

NOTE Confidence: 0.9340254166666667

00:58:48.750 --> 00:58:53.798 So this is thank you. So what's your name?

NOTE Confidence: 0.9340254166666667

00:58:53.800 - 00:58:55.046 So we have a guest speaker here.

NOTE Confidence: 0.631046205

00:58:56.000 --> 00:59:00.200 My question was about smarka force,

NOTE Confidence: 0.631046205

 $00{:}59{:}00{.}200 \dashrightarrow 00{:}59{:}02{.}230$ the sensitivity with the protests

NOTE Confidence: 0.631046205

 $00{:}59{:}02{.}230 \dashrightarrow 00{:}59{:}04{.}260$ and the prostate cancer cells.

NOTE Confidence: 0.631046205

 $00:59:04.260 \longrightarrow 00:59:07.026$ I'm wondering if you think that

NOTE Confidence: 0.631046205

 $00{:}59{:}07{.}026$ --> $00{:}59{:}09{.}919$ the smart effort like the BRG

NOTE Confidence: 0.631046205

 $00:59:09.920 \rightarrow 00:59:13.466$ catalytic subunit is active within us,

NOTE Confidence: 0.631046205

00:59:13.470 -> 00:59:15.406 why sniff chromatin remodeler?

NOTE Confidence: 0.631046205

00:59:15.406 - 00:59:18.310 Enzyme complex in the context

- NOTE Confidence: 0.631046205
- $00:59:18.390 \longrightarrow 00:59:20.466$ where it is being affected or
- NOTE Confidence: 0.631046205
- $00{:}59{:}20{.}466 \dashrightarrow 00{:}59{:}23{.}079$ if you think it has a separate.
- NOTE Confidence: 0.631046205
- $00:59:23.080 \rightarrow 00:59:25.450$ Activity and I'm wondering because
- NOTE Confidence: 0.631046205
- $00{:}59{:}25{.}450 \dashrightarrow 00{:}59{:}27{.}252$ you mentioned EH2 as well,
- NOTE Confidence: 0.631046205
- $00{:}59{:}27{.}252 \dashrightarrow 00{:}59{:}28{.}956$ I know can have Polycom independent
- NOTE Confidence: 0.631046205
- $00{:}59{:}28{.}956 \dashrightarrow 00{:}59{:}30{.}258$ functions where it associates
- NOTE Confidence: 0.631046205
- 00:59:30.258 --> 00:59:31.873 with the ENERGEN receptor or
- NOTE Confidence: 0.631046205
- $00:59:31.873 \rightarrow 00:59:33.449$ something similar might be going on.
- NOTE Confidence: 0.698803522
- $00{:}59{:}33{.}700 \dashrightarrow 00{:}59{:}34{.}760$ So that's a great question.
- NOTE Confidence: 0.698803522
- $00{:}59{:}34{.}760 \dashrightarrow 00{:}59{:}37{.}442$ So and and the way that I didn't show
- NOTE Confidence: 0.698803522
- $00{:}59{:}37{.}442 \dashrightarrow 00{:}59{:}39{.}997$ data but the way that I think we've
- NOTE Confidence: 0.698803522
- $00{:}59{:}39{.}997 \dashrightarrow 00{:}59{:}42{.}532$ been going at this has been to look
- NOTE Confidence: 0.698803522
- $00{:}59{:}42{.}532 \dashrightarrow 00{:}59{:}44{.}844$ at also there are ATP ace inhibitors.
- NOTE Confidence: 0.698803522
- $00{:}59{:}44{.}844 \dashrightarrow 00{:}59{:}47{.}196$ So we also have data for
- NOTE Confidence: 0.698803522
- $00{:}59{:}47{.}196 \dashrightarrow 00{:}59{:}49{.}290$ the ATP ACE inhibitors.
- NOTE Confidence: 0.698803522

 $00:59:49.290 \rightarrow 00:59:51.290$ The protects are more effective,

NOTE Confidence: 0.698803522

 $00{:}59{:}51{.}290 \dashrightarrow 00{:}59{:}55{.}196$ but they're more toxic and so

NOTE Confidence: 0.698803522

 $00:59:55.196 \rightarrow 00:59:58.590$ but inhibiting a TPA does.

NOTE Confidence: 0.698803522

 $00{:}59{:}58{.}590 \dashrightarrow 01{:}00{:}00{.}389$ You know make it have a similar

NOTE Confidence: 0.698803522

 $01:00:00.389 \rightarrow 01:00:02.104$ effect but again it's not specific

NOTE Confidence: 0.698803522

 $01{:}00{:}02{.}104 \dashrightarrow 01{:}00{:}03{.}886$ to this market force market too.

NOTE Confidence: 0.698803522

 $01{:}00{:}03.890 \dashrightarrow 01{:}00{:}05.584$ So it's hard to dissociate that and

NOTE Confidence: 0.698803522

 $01{:}00{:}05{.}584 \dashrightarrow 01{:}00{:}07{.}755$ we have SSI data with CRISPR data for

NOTE Confidence: 0.698803522

01:00:07.755 --> 01:00:09.767 knocking out what happens if you knock NOTE Confidence: 0.698803522

 $01:00:09.767 \longrightarrow 01:00:11.465$ out smart key forwards market too.

NOTE Confidence: 0.698803522

 $01:00:11.470 \longrightarrow 01:00:12.790$ So that's one problem.

NOTE Confidence: 0.698803522

01:00:12.790 $\operatorname{-->}$ 01:00:14.770 The other problem that we have

NOTE Confidence: 0.698803522

 $01:00:14.840 \longrightarrow 01:00:16.970$ which didn't discuss at all is

NOTE Confidence: 0.698803522

 $01:00:16.970 \longrightarrow 01:00:18.729$ that it's really difficult to

NOTE Confidence: 0.698803522

 $01:00:18.729 \longrightarrow 01:00:19.892$ chip these these proteins,

NOTE Confidence: 0.698803522

 $01:00:19.892 \longrightarrow 01:00:21.447$ some people can do it.

- NOTE Confidence: 0.698803522
- 01:00:21.450 --> 01:00:23.172 So Cigar Codex Group is is world
- NOTE Confidence: 0.698803522
- $01:00:23.172 \longrightarrow 01:00:25.219$ expert in that we we haven't been
- NOTE Confidence: 0.698803522
- $01:00:25.219 \rightarrow 01:00:26.789$ able to achieve that unfortunately.
- NOTE Confidence: 0.8956368866666667
- $01:00:30.410 \longrightarrow 01:00:31.628$ Other questions, yes.
- NOTE Confidence: 0.5780350866666667
- 01:00:39.070 --> 01:00:39.760 The role the
- NOTE Confidence: 0.759423952857143
- $01:00:39.770 \longrightarrow 01:00:41.830$ role of progesterones as
- NOTE Confidence: 0.759423952857143
- 01:00:41.830 --> 01:00:44.050 well as androgens. Estrogen,
- NOTE Confidence: 0.848446689
- $01:00:44.100 \longrightarrow 01:00:45.510$ OK. So that's a that's
- NOTE Confidence: 0.848446689
- $01:00:45.510 \longrightarrow 01:00:46.920$ one of my favorite topics.
- NOTE Confidence: 0.848446689
- $01:00:46.920 \longrightarrow 01:00:48.915$ I love that topics the role of
- NOTE Confidence: 0.848446689
- $01{:}00{:}48{.}915 \dashrightarrow 01{:}00{:}50{.}720$ estrogen in advanced prostate cancer.
- NOTE Confidence: 0.848446689
- $01{:}00{:}50.720 \dashrightarrow 01{:}00{:}53.368$ So I think it's it's it seems like
- NOTE Confidence: 0.848446689
- 01:00:53.368 --> 01:00:54.886 it's paradoxically it shouldn't
- NOTE Confidence: 0.848446689
- $01{:}00{:}54.886 \dashrightarrow 01{:}00{:}56.856$ be that important but estrogen
- NOTE Confidence: 0.848446689
- $01:00:56.856 \rightarrow 01:00:58.924$ receptor and antrum receptor they
- NOTE Confidence: 0.848446689

 $01:00:58.924 \rightarrow 01:01:00.979$ have very similar binding sites.

NOTE Confidence: 0.848446689

 $01:01:00.980 \longrightarrow 01:01:02.723$ So there's a lot of half binding

NOTE Confidence: 0.848446689

 $01:01:02.723 \longrightarrow 01:01:04.479$ sites that are are regulated.

NOTE Confidence: 0.848446689

 $01{:}01{:}04{.}480 \dashrightarrow 01{:}01{:}06{.}853$ So I think it's important role and

NOTE Confidence: 0.848446689

01:01:06.853 --> 01:01:09.254 that it's also known that other

NOTE Confidence: 0.848446689

 $01{:}01{:}09{.}254 \dashrightarrow 01{:}01{:}11{.}434$ nuclear hormones are activated and NOTE Confidence: 0.848446689

 $01:01:11.434 \longrightarrow 01:01:13.699$ the context of AR depletion so.

NOTE Confidence: 0.848446689

01:01:13.700 --> 01:01:15.278 Do you think it's important and

NOTE Confidence: 0.848446689

01:01:15.278 --> 01:01:16.770 in prior studies we've seen it,

NOTE Confidence: 0.848446689

01:01:16.770 --> 01:01:17.934 it's part of progression,

NOTE Confidence: 0.848446689

01:01:17.934 --> 01:01:19.389 but we didn't specifically focus

NOTE Confidence: 0.848446689

 $01:01:19.389 \longrightarrow 01:01:20.800$ on that here. So it's.

NOTE Confidence: 0.590920588333333

01:01:29.130 --> 01:01:31.920 In plasticity it's role in plasticity,

NOTE Confidence: 0.715208235714286

 $01:01:31.930 \longrightarrow 01:01:36.018$ so the role of estrogen and plasticity.

NOTE Confidence: 0.715208235714286

 $01:01:36.020 \rightarrow 01:01:38.520$ Or progestin or progesterone.

NOTE Confidence: 0.715208235714286

 $01{:}01{:}38.520 \dashrightarrow 01{:}01{:}41.355$ So I think I think in stem in stemness.

01:01:41.360 --> 01:01:43.334 So I think Charles Sawyers group

NOTE Confidence: 0.715208235714286

01:01:43.334 --> 01:01:45.610 has looked at that and I think

NOTE Confidence: 0.715208235714286

 $01:01:45.610 \rightarrow 01:01:47.689$ there's the view that it does play

NOTE Confidence: 0.715208235714286

 $01{:}01{:}47.756 \dashrightarrow 01{:}01{:}50.150$ a role in resistance and is seen

NOTE Confidence: 0.715208235714286

 $01{:}01{:}50{.}150$ --> $01{:}01{:}51{.}940$ associated with stem like state,

NOTE Confidence: 0.715208235714286

01:01:51.940 --> 01:01:54.250 but maybe not neuroendocrine state. So

NOTE Confidence: 0.718713145

 $01:01:54.820 \longrightarrow 01:01:56.588$ yeah. Thank you, Joe.

NOTE Confidence: 0.7995987

 $01:02:00.910 \longrightarrow 01:02:01.880$ Thank you for coming out.

NOTE Confidence: 0.6157551

 $01{:}02{:}06{.}500 \dashrightarrow 01{:}02{:}10{.}750$ My question is about the the rapies for.

NOTE Confidence: 0.90906139

 $01:02:10.750 \longrightarrow 01:02:15.260$ As you know. Ready for those people?

NOTE Confidence: 0.661346733333333

 $01:02:16.750 \longrightarrow 01:02:17.500$ Show that you're.

NOTE Confidence: 0.66546635

 $01{:}02{:}22.850 \dashrightarrow 01{:}02{:}26.740$ Or is there any incremental attrition? To.

NOTE Confidence: 0.552128935

 $01{:}02{:}28.590 \dashrightarrow 01{:}02{:}29.230$ Or any.

NOTE Confidence: 0.843472615555556

 $01{:}02{:}34{.}070 \dashrightarrow 01{:}02{:}35{.}290$ Well, I'm a pathologist.

NOTE Confidence: 0.843472615555556

 $01{:}02{:}35{.}290 \dashrightarrow 01{:}02{:}36{.}815$ I better not comment on,

 $01:02:36.820 \rightarrow 01:02:37.888$ on clinical oncology therapy.

NOTE Confidence: 0.843472615555556

 $01:02:37.888 \longrightarrow 01:02:39.490$ But the only thing I would

NOTE Confidence: 0.843472615555556

 $01:02:39.540 \longrightarrow 01:02:40.776$ say is that there's a lot,

NOTE Confidence: 0.843472615555556

 $01:02:40.780 \rightarrow 01:02:43.576$ there's great interest in you know

NOTE Confidence: 0.843472615555556

 $01:02:43.576 \rightarrow 01:02:45.940$ epigenetic regulation which are toxic.

NOTE Confidence: 0.843472615555556

01:02:45.940 --> 01:02:48.532 And you know close friend of mine Johann NOTE Confidence: 0.843472615555556

 $01:02:48.532 \rightarrow 01:02:50.755$ Debono was just with him the other day

NOTE Confidence: 0.843472615555556

 $01:02:50.755 \rightarrow 01:02:52.620$ in Basel and we were talking about this.

NOTE Confidence: 0.843472615555556

 $01{:}02{:}52{.}620 \dashrightarrow 01{:}02{:}53{.}956$ So I think there are a number of

NOTE Confidence: 0.843472615555556

 $01:02:53.956 \rightarrow 01:02:55.260$ studies that are coming down the line,

NOTE Confidence: 0.843472615555556

 $01:02:55.260 \rightarrow 01:02:57.416$ but it may not be you know,

NOTE Confidence: 0.843472615555556

 $01{:}02{:}57{.}420 \dashrightarrow 01{:}02{:}59{.}460$ so I presented these different categories,

NOTE Confidence: 0.843472615555556

 $01:02:59.460 \longrightarrow 01:03:01.728$ it may be for a R negative.

NOTE Confidence: 0.843472615555556

 $01:03:01.730 \rightarrow 01:03:04.327$ But not neuroendocrine tumors that there are,

NOTE Confidence: 0.843472615555556

 $01{:}03{:}04{.}330 \dashrightarrow 01{:}03{:}07{.}246$ you know, some new the rapeutic targets.

NOTE Confidence: 0.843472615555556

 $01:03:07.250 \longrightarrow 01:03:08.880$ Her three is the target.
NOTE Confidence: 0.843472615555556

 $01:03:08.880 \rightarrow 01:03:11.984$ There are other targets that are coming up,

NOTE Confidence: 0.843472615555556

01:03:11.990 - 01:03:15.028 some common to lung cancer as well,

NOTE Confidence: 0.843472615555556

 $01:03:15.030 \longrightarrow 01:03:17.050$ but no winners yet,

NOTE Confidence: 0.843472615555556

 $01:03:17.050 \rightarrow 01:03:18.565$ no successful winners.

NOTE Confidence: 0.843472615555556

 $01:03:18.570 \rightarrow 01:03:20.418$ And then hopefully I pointed out in

NOTE Confidence: 0.843472615555556

 $01{:}03{:}20{.}418 \dashrightarrow 01{:}03{:}22{.}535$ the first part of the presentation how

NOTE Confidence: 0.843472615555556

 $01:03:22.535 \rightarrow 01:03:24.810$ difficult it is to actually classify these.

NOTE Confidence: 0.843472615555556

01:03:24.810 --> 01:03:26.790 So once it's air negative,

NOTE Confidence: 0.843472615555556

01:03:26.790 --> 01:03:29.170 I think there's still complexity.

NOTE Confidence: 0.843472615555556

 $01:03:29.170 \longrightarrow 01:03:30.900$ So we're far behind breast

NOTE Confidence: 0.843472615555556

 $01:03:30.900 \longrightarrow 01:03:32.630$ cancer and maybe lung cancer.

NOTE Confidence: 0.843472615555556

 $01:03:32.630 \longrightarrow 01:03:35.073$ As far as being able to accurately

NOTE Confidence: 0.843472615555556

 $01{:}03{:}35{.}073 \dashrightarrow 01{:}03{:}37{.}088$ classify what needs to be treated.

NOTE Confidence: 0.843472615555556

 $01{:}03{:}37{.}090 \dashrightarrow 01{:}03{:}39{.}146$ So I think that in all the and

NOTE Confidence: 0.843472615555556

 $01:03:39.146 \longrightarrow 01:03:41.668$ so in the in the advisory boards,

NOTE Confidence: 0.843472615555556

 $01{:}03{:}41.670 \dashrightarrow 01{:}03{:}43.254$ I think the common conclusion after

NOTE Confidence: 0.843472615555556

 $01:03:43.254 \rightarrow 01:03:44.946$ two or three days of discussions

NOTE Confidence: 0.843472615555556

 $01:03:44.946 \longrightarrow 01:03:46.110$ are always the same,

NOTE Confidence: 0.843472615555556

 $01:03:46.110 \longrightarrow 01:03:48.990$ which is that we just need to treat

NOTE Confidence: 0.843472615555556

 $01:03:48.990 \rightarrow 01:03:51.187$ everybody and see who what works.

NOTE Confidence: 0.843472615555556

 $01:03:51.190 \rightarrow 01:03:52.450$ Which is sort of depressing,

NOTE Confidence: 0.843472615555556

 $01:03:52.450 \longrightarrow 01:03:53.690$ but it's that's that's sort

NOTE Confidence: 0.843472615555556

 $01:03:53.690 \longrightarrow 01:03:55.320$ of where we are I think.

NOTE Confidence: 0.804383019411765

 $01{:}03{:}55{.}790 \dashrightarrow 01{:}03{:}57{.}422$ I think we have similar issues

NOTE Confidence: 0.804383019411765

 $01:03:57.422 \rightarrow 01:03:58.895$ in lung cancer and resistant

NOTE Confidence: 0.804383019411765

 $01:03:58.895 \rightarrow 01:04:00.845$ tumors trying to figure it out.

NOTE Confidence: 0.77401228

 $01:04:02.140 \longrightarrow 01:04:03.845$ What pathologist. So that's just

NOTE Confidence: 0.77401228

 $01:04:03.845 \longrightarrow 01:04:05.778$ my personal opinion, not don't,

NOTE Confidence: 0.77401228

 $01:04:05.778 \longrightarrow 01:04:07.840$ don't take that. Beyond that,

NOTE Confidence: 0.7915238275

 $01:04:07.970 \longrightarrow 01:04:09.746$ we have one last question in the back.

NOTE Confidence: 0.71277517

 $01:04:12.330 \longrightarrow 01:04:13.900$ Roll off. Thank you.

- NOTE Confidence: 0.62965414
- $01:04:17.230 \longrightarrow 01:04:18.338$ So like the cluster.
- NOTE Confidence: 0.8756992116666667
- 01:04:22.580 --> 01:04:24.488 I'm sorry, I can't hear from
- NOTE Confidence: 0.818377945238095
- $01:04:24.660 \longrightarrow 01:04:27.068$ do you think there is a role
- NOTE Confidence: 0.818377945238095
- $01:04:27.068 \longrightarrow 01:04:28.100$ for differentiation the rapies
- NOTE Confidence: 0.818377945238095
- $01:04:28.161 \longrightarrow 01:04:29.851$ in prostate cancer kind of
- NOTE Confidence: 0.818377945238095
- $01{:}04{:}29{.}851 \dashrightarrow 01{:}04{:}31{.}780$ analogous to the retinoic acid and
- NOTE Confidence: 0.621062275
- $01:04:32.480 \longrightarrow 01:04:35.080$ there would be. So.
- NOTE Confidence: 0.621062275
- 01:04:35.080 --> 01:04:37.264 So one thing I just maybe not
- NOTE Confidence: 0.621062275
- $01{:}04{:}37{.}264 \dashrightarrow 01{:}04{:}39{.}439$ directly relate to your question but.
- NOTE Confidence: 0.621062275
- $01:04:39.440 \longrightarrow 01:04:42.065$ Being able to model differentiation
- NOTE Confidence: 0.621062275
- $01:04:42.065 \rightarrow 01:04:43.640$ would be phenomenal.
- NOTE Confidence: 0.621062275
- $01{:}04{:}43.640 \dashrightarrow 01{:}04{:}45.728$ So if we had model systems where it NOTE Confidence: 0.621062275
- NOTE Confidence. 0.021002275
- 01:04:45.728 --> 01:04:47.840 could show I know like in AML and
- NOTE Confidence: 0.621062275
- $01{:}04{:}47{.}840 \dashrightarrow 01{:}04{:}49{.}387$ other cancer and other hematopoietic NOTE Confidence: 0.621062275
- 01:04:49.387 --> 01:04:51.712 cancers you can show differentiation
- NOTE Confidence: 0.621062275

 $01:04:51.712 \rightarrow 01:04:53.851$ of blocking differentiation and I

NOTE Confidence: 0.621062275

 $01:04:53.851 \longrightarrow 01:04:55.477$ think we don't have those models.

NOTE Confidence: 0.621062275

01:04:55.480 --> 01:04:57.968 I think the closest thing we have right

NOTE Confidence: 0.621062275

 $01{:}04{:}57{.}968 \dashrightarrow 01{:}05{:}00{.}602$ now is develop of like the stem like

NOTE Confidence: 0.621062275

 $01{:}05{:}00.602 \dashrightarrow 01{:}05{:}03.061$ state and then you know ideally we'd

NOTE Confidence: 0.621062275

 $01{:}05{:}03.061 \dashrightarrow 01{:}05{:}05.254$ like to flux back between a denocarcinoma.

NOTE Confidence: 0.621062275

 $01{:}05{:}05{.}254 \dashrightarrow 01{:}05{:}07{.}498$ So we're starting to see some

NOTE Confidence: 0.621062275

 $01:05:07.498 \longrightarrow 01:05:09.359$ of the organoid models and.

NOTE Confidence: 0.621062275

01:05:09.360 --> 01:05:11.050 Mouse, but we don't really

NOTE Confidence: 0.621062275

 $01:05:11.050 \longrightarrow 01:05:12.402$ have that ability yet.

NOTE Confidence: 0.621062275

 $01{:}05{:}12{.}410 \dashrightarrow 01{:}05{:}14{.}642$ So I do think what you're saying is

NOTE Confidence: 0.621062275

 $01:05:14.642 \rightarrow 01:05:16.182$ interesting and we my view would

NOTE Confidence: 0.621062275

 $01:05:16.182 \longrightarrow 01:05:17.959$ be that if you could tell which

NOTE Confidence: 0.621062275

 $01{:}05{:}17.959 \dashrightarrow 01{:}05{:}19.649$ tumors are going to transition,

NOTE Confidence: 0.621062275

 $01:05:19.650 \rightarrow 01:05:22.098$ you'd want to treat them as early as

NOTE Confidence: 0.621062275

 $01{:}05{:}22.098 \dashrightarrow 01{:}05{:}24.221$ possible with the other element in

- NOTE Confidence: 0.621062275
- $01:05:24.221 \longrightarrow 01:05:26.387$ addition to AR targeted therapy before
- NOTE Confidence: 0.621062275
- $01:05:26.456 \rightarrow 01:05:28.969$ it goes down the road to differentiation.
- NOTE Confidence: 0.5343186
- $01:05:30.420 \longrightarrow 01:05:35.510$ Next. By those standards. Yeah.
- NOTE Confidence: 0.7234029075
- 01:05:38.890 --> 01:05:41.080 Have you tried like stemness
- NOTE Confidence: 0.7234029075
- $01:05:41.080 \longrightarrow 01:05:42.394$ targeted like therapies?
- NOTE Confidence: 0.777768090909091
- $01:05:42.410 \longrightarrow 01:05:43.900$ Yeah, we haven't, but that's
- NOTE Confidence: 0.777768090909091
- $01:05:43.900 \rightarrow 01:05:45.940$ obviously there's a lot of interest.
- NOTE Confidence: 0.777768090909091
- $01{:}05{:}45{.}940 \dashrightarrow 01{:}05{:}49{.}308$ So you saw the, I showed two papers
- NOTE Confidence: 0.777768090909091
- $01{:}05{:}49{.}308 \dashrightarrow 01{:}05{:}51{.}630$ from main paper from Charles Sawyers
- NOTE Confidence: 0.777768090909091
- 01:05:51.630 --> 01:05:54.000 Group and looking at Jack Stats.
- NOTE Confidence: 0.777768090909091
- $01:05:54.000 \rightarrow 01:05:56.615$ So they're very interested in
- NOTE Confidence: 0.777768090909091
- 01:05:56.615 --> 01:05:58.707 various the rapies related to
- NOTE Confidence: 0.777768090909091
- $01{:}05{:}58{.}707 \dashrightarrow 01{:}06{:}01{.}148$ that to targeting stemness.
- NOTE Confidence: 0.777768090909091
- 01:06:01.150 --> 01:06:02.915 I mean our approach was related to
- NOTE Confidence: 0.777768090909091
- $01{:}06{:}02{.}915 \dashrightarrow 01{:}06{:}04{.}350$ the epigenetic approach and you know.
- NOTE Confidence: 0.81549836

01:06:07.280 --> 01:06:09.149 Thank you, I.