

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 --> 00:00:04.260 to introduce Doctor Mark Rubin,

NOTE Confidence: 0.753344047

00:00:04.260 --> 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 --> 00:00:09.190 Research and Burn Center for

NOTE Confidence: 0.753344047

00:00:09.190 --> 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 --> 00:00:19.172 Weill Cornell Medicine Institution that

NOTE Confidence: 0.830048071428571

00:00:19.172 --> 00:00:21.638 remained engaged to the prostate spore

NOTE Confidence: 0.8936092275

00:00:21.710 --> 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 --> 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 --> 00:00:32.230 doctor Rubin's laboratory led a series  
NOTE Confidence: 0.845784318571429

00:00:32.230 --> 00:00:34.100 of landmark studies defining distinct  
NOTE Confidence: 0.845784318571429

00:00:34.100 --> 00:00:36.150 molecular features of prostate cancer,  
NOTE Confidence: 0.845784318571429

00:00:36.150 --> 00:00:37.555 revealing pathways that are  
NOTE Confidence: 0.845784318571429

00:00:37.555 --> 00:00:39.230 perturbed and drive different types  
NOTE Confidence: 0.845784318571429

00:00:39.230 --> 00:00:40.814 of different types of this cancer.  
NOTE Confidence: 0.845784318571429

00:00:40.814 --> 00:00:42.998 Furthermore, he has translated many of  
NOTE Confidence: 0.845784318571429

00:00:42.998 --> 00:00:44.790 the genomic discoveries into clinical  
NOTE Confidence: 0.845784318571429

00:00:44.790 --> 00:00:46.610 tests that are currently patented  
NOTE Confidence: 0.845784318571429

00:00:46.610 --> 00:00:48.680 and Stanley used in the diagnosis  
NOTE Confidence: 0.845784318571429

00:00:48.680 --> 00:00:49.993 and treatment of prostate cancer.  
NOTE Confidence: 0.845784318571429

00:00:49.993 --> 00:00:52.160 He founded the Angler Institute for  
NOTE Confidence: 0.845784318571429

00:00:52.160 --> 00:00:53.506 Precision Medicine and most recently,

NOTE Confidence: 0.845784318571429  
00:00:53.506 --> 00:00:54.102 the Burn.  
NOTE Confidence: 0.845784318571429  
00:00:54.102 --> 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 --> 00:01:00.980 including those in major top journals.  
NOTE Confidence: 0.845784318571429  
00:01:00.980 --> 00:01:02.884 Today will tell us about his latest  
NOTE Confidence: 0.845784318571429  
00:01:02.884 --> 00:01:05.615 work in the minor spy summit exploring  
NOTE Confidence: 0.845784318571429  
00:01:05.615 --> 00:01:07.004 novel cancer vulnerabilities,  
NOTE Confidence: 0.845784318571429  
00:01:07.070 --> 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 --> 00:01:23.886 would want to say something again.  
NOTE Confidence: 0.5709378  
00:01:28.380 --> 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 --> 00:01:36.200 definitely over 10 years ago.  
NOTE Confidence: 0.5709378

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 --> 00:01:40.681 visit and hopefully I can figure out how  
NOTE Confidence: 0.5709378

00:01:40.681 --> 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 --> 00:01:51.328 mostly non relevant disclosures.  
NOTE Confidence: 0.856139078571429

00:01:51.328 --> 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 --> 00:02:00.338 what I was going to do and why I was going.  
NOTE Confidence: 0.856139078571429

00:02:00.340 --> 00:02:02.384 And so you heard that there were  
NOTE Confidence: 0.856139078571429

00:02:02.384 --> 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 --> 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 --> 00:02:11.051 new department and reorganizing a  
NOTE Confidence: 0.856139078571429

00:02:11.051 --> 00:02:12.458 department biomedical research.  
NOTE Confidence: 0.856139078571429

00:02:12.460 --> 00:02:14.371 But one of the decisions I made

NOTE Confidence: 0.856139078571429

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

NOTE Confidence: 0.856139078571429

00:02:16.230 --> 00:02:18.174 of taking projects that I had,

NOTE Confidence: 0.856139078571429

00:02:18.180 --> 00:02:21.480 I would start from scratch and.

NOTE Confidence: 0.856139078571429

00:02:21.480 --> 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 --> 00:02:28.138 of trainees in the audience and I

NOTE Confidence: 0.856139078571429

00:02:28.138 --> 00:02:30.130 just think it's a it was a very.

NOTE Confidence: 0.856139078571429

00:02:30.130 --> 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 --> 00:02:35.832 but it's certainly been an exciting

NOTE Confidence: 0.856139078571429

00:02:35.832 --> 00:02:37.450 time to think about new projects,

NOTE Confidence: 0.856139078571429

00:02:37.450 --> 00:02:39.592 what you think is important and

NOTE Confidence: 0.856139078571429

00:02:39.592 --> 00:02:42.344 actually going in places that feel a

NOTE Confidence: 0.856139078571429

00:02:42.344 --> 00:02:44.024 bit uncomfortable scientifically just

NOTE Confidence: 0.856139078571429

00:02:44.024 --> 00:02:46.627 because you need to learn new things.

NOTE Confidence: 0.856139078571429

00:02:46.630 --> 00:02:48.550 And so I think I left all the  
NOTE Confidence: 0.856139078571429

00:02:48.550 --> 00:02:49.994 projects with this prostate spore  
NOTE Confidence: 0.856139078571429

00:02:49.994 --> 00:02:51.812 and we started a new project.  
NOTE Confidence: 0.856139078571429

00:02:51.820 --> 00:02:53.980 So I'll tell you a little bit about  
NOTE Confidence: 0.856139078571429

00:02:53.980 --> 00:02:55.932 two things that we worked on more  
NOTE Confidence: 0.856139078571429

00:02:55.932 --> 00:02:57.667 recently just as way of background  
NOTE Confidence: 0.856139078571429

00:02:57.667 --> 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 --> 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 --> 00:03:09.821 therapy has really changed dramatically  
NOTE Confidence: 0.856139078571429

00:03:09.821 --> 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 --> 00:03:19.320 it was relatively androgen deprivation  
NOTE Confidence: 0.856139078571429

00:03:19.320 --> 00:03:22.180 therapy based with the taxanes.

NOTE Confidence: 0.856139078571429  
00:03:22.180 --> 00:03:24.268 But it's a very different than  
NOTE Confidence: 0.856139078571429  
00:03:24.268 --> 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 --> 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 --> 00:03:33.284 but just to point out that  
NOTE Confidence: 0.856139078571429  
00:03:33.284 --> 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 --> 00:03:40.137 what's going on just all the time,  
NOTE Confidence: 0.856139078571429  
00:03:40.140 --> 00:03:41.400 they're new opportunities.  
NOTE Confidence: 0.856139078571429  
00:03:41.400 --> 00:03:44.340 The one thing I would point out  
NOTE Confidence: 0.856139078571429  
00:03:44.419 --> 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 --> 00:03:51.300 various types of more potent  
NOTE Confidence: 0.856139078571429

00:03:51.300 --> 00:03:53.556 antiandrogen therapies such as  
NOTE Confidence: 0.856139078571429

00:03:53.556 --> 00:03:55.380 enzalutamide and abiraterone  
NOTE Confidence: 0.856139078571429

00:03:55.380 --> 00:03:57.164 resistances obviously an inevitable.  
NOTE Confidence: 0.856139078571429

00:03:57.164 --> 00:04:00.737 So patients can do well that for a short  
NOTE Confidence: 0.856139078571429

00:04:00.737 --> 00:04:03.419 time or they can do well for long time.  
NOTE Confidence: 0.856139078571429

00:04:03.420 --> 00:04:04.596 Eventually they'll fail,  
NOTE Confidence: 0.856139078571429

00:04:04.596 --> 00:04:06.556 but there are other opportunities.  
NOTE Confidence: 0.856139078571429

00:04:06.560 --> 00:04:07.840 Now there's PARP inhibitors,  
NOTE Confidence: 0.856139078571429

00:04:07.840 --> 00:04:09.120 so that's quite exciting.  
NOTE Confidence: 0.856139078571429

00:04:09.120 --> 00:04:10.470 Obviously there's immunotherapy  
NOTE Confidence: 0.856139078571429

00:04:10.470 --> 00:04:12.720 for such a small subset.  
NOTE Confidence: 0.856139078571429

00:04:12.720 --> 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 --> 00:04:21.902 or imaging and and and treatment and  
NOTE Confidence: 0.856139078571429

00:04:21.902 --> 00:04:25.589 these are again really more therapies.



NOTE Confidence: 0.856139078571429

00:04:25.590 --> 00:04:27.828 There's problems with all of them,

NOTE Confidence: 0.856139078571429

00:04:27.830 --> 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 --> 00:04:36.473 Resistance remains a major focus of our

NOTE Confidence: 0.856139078571429

00:04:36.473 --> 00:04:39.870 labs work and and other labs now to

NOTE Confidence: 0.856139078571429

00:04:39.870 --> 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 --> 00:04:46.872 is to think about in all of

NOTE Confidence: 0.856139078571429

00:04:46.872 --> 00:04:48.522 these settings what is the key

NOTE Confidence: 0.876171274545455

00:04:48.583 --> 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 --> 00:04:53.860 therapies or introduce new therapies.

NOTE Confidence: 0.876171274545455

00:04:53.860 --> 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 --> 00:04:58.940 make a few comments about lineage,

NOTE Confidence: 0.876171274545455

00:04:58.940 --> 00:05:00.785 plasticity and the resistance framework  
NOTE Confidence: 0.876171274545455

00:05:00.785 --> 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 --> 00:05:09.324 to the lung spore in the context of  
NOTE Confidence: 0.876171274545455

00:05:09.324 --> 00:05:11.690 switch sniff and epigenetic modulation.  
NOTE Confidence: 0.876171274545455

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

00:05:14.337 --> 00:05:16.157 that's unpublished that has connections  
NOTE Confidence: 0.876171274545455

00:05:16.157 --> 00:05:18.750 with both Yale and and Connecticut.  
NOTE Confidence: 0.876171274545455

00:05:18.750 --> 00:05:21.070 And it's our minor splicing.  
NOTE Confidence: 0.876171274545455

00:05:21.070 --> 00:05:23.527 So I have my main goal today will be  
NOTE Confidence: 0.876171274545455

00:05:23.527 --> 00:05:25.612 hopefully to tell you about something that  
NOTE Confidence: 0.876171274545455

00:05:25.612 --> 00:05:28.146 you may not know a lot about and maybe,  
NOTE Confidence: 0.876171274545455

00:05:28.150 --> 00:05:30.185 maybe we'll all learn something  
NOTE Confidence: 0.876171274545455

00:05:30.185 --> 00:05:31.813 together about minor splicing  
NOTE Confidence: 0.876171274545455

00:05:31.813 --> 00:05:33.848 and maybe also some insights.  
NOTE Confidence: 0.876171274545455

00:05:33.850 --> 00:05:36.334 As well and that we can talk about them.

NOTE Confidence: 0.876171274545455  
00:05:36.340 --> 00:05:38.716 So just a few comments about  
NOTE Confidence: 0.876171274545455  
00:05:38.716 --> 00:05:40.300 resistance and lineage plasticity.  
NOTE Confidence: 0.876171274545455  
00:05:40.300 --> 00:05:42.197 I've been showing these slides for a  
NOTE Confidence: 0.876171274545455  
00:05:42.197 --> 00:05:44.514 few years and I think it it helps me a  
NOTE Confidence: 0.876171274545455  
00:05:44.514 --> 00:05:46.304 lot of giving a framework for thinking  
NOTE Confidence: 0.876171274545455  
00:05:46.304 --> 00:05:48.458 about what we do clinically in the  
NOTE Confidence: 0.876171274545455  
00:05:48.458 --> 00:05:51.324 setting that most in the in the context  
NOTE Confidence: 0.876171274545455  
00:05:51.324 --> 00:05:53.893 that most of the types of therapies  
NOTE Confidence: 0.876171274545455  
00:05:53.893 --> 00:05:56.899 are very index oncogenic pathway driven.  
NOTE Confidence: 0.876171274545455  
00:05:56.900 --> 00:05:58.916 So if you have estrogen receptor,  
NOTE Confidence: 0.876171274545455  
00:05:58.920 --> 00:06:00.040 if you have her too,  
NOTE Confidence: 0.876171274545455  
00:06:00.040 --> 00:06:03.659 if you have EGFR as a main  
NOTE Confidence: 0.876171274545455  
00:06:03.659 --> 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 --> 00:06:07.770 the main,  
NOTE Confidence: 0.876171274545455

00:06:07.770 --> 00:06:09.620 the index oncogenic output is  
NOTE Confidence: 0.876171274545455

00:06:09.620 --> 00:06:11.942 being targeted and so then you  
NOTE Confidence: 0.876171274545455

00:06:11.942 --> 00:06:13.927 have resistance related to that.  
NOTE Confidence: 0.876171274545455

00:06:13.930 --> 00:06:15.826 But there are alternate effectors and  
NOTE Confidence: 0.876171274545455

00:06:15.826 --> 00:06:17.850 they're also alternate states that can occur.  
NOTE Confidence: 0.876171274545455

00:06:17.850 --> 00:06:20.930 So in the context of prostate cancer,  
NOTE Confidence: 0.876171274545455

00:06:20.930 --> 00:06:23.660 the Androgen receptor is the main  
NOTE Confidence: 0.876171274545455

00:06:23.660 --> 00:06:26.759 oncogenic target for most of the therapy,  
NOTE Confidence: 0.876171274545455

00:06:26.760 --> 00:06:29.736 whether it's Androgen and deprivation therapy  
NOTE Confidence: 0.876171274545455

00:06:29.736 --> 00:06:32.630 or targeted ligand targeted therapy or  
NOTE Confidence: 0.876171274545455

00:06:32.630 --> 00:06:35.594 therapy based on decreasing synthesis.  
NOTE Confidence: 0.876171274545455

00:06:35.594 --> 00:06:38.138 With androgens or hormones.  
NOTE Confidence: 0.876171274545455

00:06:38.140 --> 00:06:40.172 So you'd expect and and it is the  
NOTE Confidence: 0.876171274545455

00:06:40.172 --> 00:06:42.433 case that most of the mutations are  
NOTE Confidence: 0.876171274545455

00:06:42.433 --> 00:06:44.720 resistance occur in the ANDROGEN receptor.  
NOTE Confidence: 0.876171274545455

00:06:44.720 --> 00:06:46.865 So there's amplifications mutations and

NOTE Confidence: 0.876171274545455  
00:06:46.865 --> 00:06:50.627 so this is this is what you expect but  
NOTE Confidence: 0.876171274545455  
00:06:50.627 --> 00:06:53.469 what we also are seeing emerging more  
NOTE Confidence: 0.876171274545455  
00:06:53.469 --> 00:06:56.217 and more frequently with very potent  
NOTE Confidence: 0.876171274545455  
00:06:56.217 --> 00:06:58.446 anti ancient therapy are alternate  
NOTE Confidence: 0.876171274545455  
00:06:58.446 --> 00:07:00.984 pathways and this is getting into  
NOTE Confidence: 0.876171274545455  
00:07:00.984 --> 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 --> 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 --> 00:07:11.187 so you're a RH negative.  
NOTE Confidence: 0.876171274545455  
00:07:11.190 --> 00:07:13.206 And what are the mechanisms then that  
NOTE Confidence: 0.876171274545455  
00:07:13.206 --> 00:07:15.469 lead to this resistance is what we're  
NOTE Confidence: 0.876171274545455  
00:07:15.469 --> 00:07:17.839 trying to understand and a number of  
NOTE Confidence: 0.876171274545455  
00:07:17.839 --> 00:07:20.247 other groups are doing the same in prostate.  
NOTE Confidence: 0.876171274545455  
00:07:20.250 --> 00:07:22.086 Now obviously this is very interesting  
NOTE Confidence: 0.876171274545455

00:07:22.086 --> 00:07:23.770 in other cancers like bladder,  
NOTE Confidence: 0.876171274545455

00:07:23.770 --> 00:07:26.089 lung and breast.  
NOTE Confidence: 0.876171274545455

00:07:26.090 --> 00:07:28.010 So just to be specific,  
NOTE Confidence: 0.876171274545455

00:07:28.010 --> 00:07:30.522 as a pathologist we look under the microscope  
NOTE Confidence: 0.876171274545455

00:07:30.522 --> 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 --> 00:07:36.620 The cells have a lot of cytoplasm  
NOTE Confidence: 0.876171274545455

00:07:36.702 --> 00:07:39.122 and after antiandrogen therapy a  
NOTE Confidence: 0.876171274545455

00:07:39.122 --> 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 --> 00:07:44.513 just the types of therapies that  
NOTE Confidence: 0.876171274545455

00:07:44.513 --> 00:07:45.845 that patients may receive,  
NOTE Confidence: 0.876171274545455

00:07:45.850 --> 00:07:48.268 very strong potent anti entrant therapy,  
NOTE Confidence: 0.876171274545455

00:07:48.270 --> 00:07:49.710 but after these therapies  
NOTE Confidence: 0.876171274545455

00:07:49.710 --> 00:07:50.790 where most patients,  
NOTE Confidence: 0.876171274545455

00:07:50.790 --> 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 --> 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 --> 00:07:59.268 the most common,

NOTE Confidence: 0.866359873333333

00:07:59.268 --> 00:08:00.710 so I don't want to mislead you.

NOTE Confidence: 0.866359873333333

00:08:00.710 --> 00:08:02.929 The most common is probably still something

NOTE Confidence: 0.866359873333333

00:08:02.929 --> 00:08:04.909 that looks like an adenocarcinoma.

NOTE Confidence: 0.866359873333333

00:08:04.910 --> 00:08:07.584 It still can be responsive to more

NOTE Confidence: 0.866359873333333

00:08:07.584 --> 00:08:09.412 potent antiandrogens, but a subset,

NOTE Confidence: 0.866359873333333

00:08:09.412 --> 00:08:11.378 maybe 10 to 15% will have

NOTE Confidence: 0.866359873333333

00:08:11.378 --> 00:08:12.748 something that looks like this.

NOTE Confidence: 0.866359873333333

00:08:12.750 --> 00:08:14.980 So it's a neuroendocrine prostate

NOTE Confidence: 0.866359873333333

00:08:14.980 --> 00:08:17.210 cancer that's no longer responding

NOTE Confidence: 0.866359873333333

00:08:17.283 --> 00:08:19.283 to AR therapy and something

NOTE Confidence: 0.866359873333333

00:08:19.283 --> 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: 0.8663598733333333

00:08:22.514 --> 00:08:24.962 If you look under the microscope  
NOTE Confidence: 0.8663598733333333

00:08:24.962 --> 00:08:27.390 and perform immunohistochemistry,  
NOTE Confidence: 0.8663598733333333

00:08:27.390 --> 00:08:30.288 you'll see that you have the adenocarcinomas  
NOTE Confidence: 0.8663598733333333

00:08:30.288 --> 00:08:33.008 are very positive for Antrim receptor  
NOTE Confidence: 0.8663598733333333

00:08:33.008 --> 00:08:35.816 expression and are not positive for  
NOTE Confidence: 0.8663598733333333

00:08:35.816 --> 00:08:38.357 neuroendocrine markers such as synaptophysin.  
NOTE Confidence: 0.8663598733333333

00:08:38.360 --> 00:08:40.420 And for neuroendocrine cancers,  
NOTE Confidence: 0.8663598733333333

00:08:40.420 --> 00:08:42.995 you lose AR protein expression.  
NOTE Confidence: 0.8663598733333333

00:08:43.000 --> 00:08:43.855 Now that's important,  
NOTE Confidence: 0.8663598733333333

00:08:43.855 --> 00:08:45.618 just one important point, and this is  
NOTE Confidence: 0.8663598733333333

00:08:45.618 --> 00:08:46.854 probably true in many other cancers.  
NOTE Confidence: 0.8663598733333333

00:08:46.860 --> 00:08:48.900 If you block A R and now you  
NOTE Confidence: 0.8663598733333333

00:08:48.900 --> 00:08:51.019 have a neuroendocrine tumor,  
NOTE Confidence: 0.8663598733333333

00:08:51.020 --> 00:08:52.132 the pathways for AR,  
NOTE Confidence: 0.8663598733333333

00:08:52.132 --> 00:08:54.560 so you might see at the transcript.



NOTE Confidence: 0.866359873333333

00:08:54.560 --> 00:08:56.936 Level an attempts for Andrew receptor

NOTE Confidence: 0.866359873333333

00:08:56.936 --> 00:08:59.312 to produce protein but but protein

NOTE Confidence: 0.866359873333333

00:08:59.312 --> 00:09:01.490 levels are are usually very low.

NOTE Confidence: 0.866359873333333

00:09:01.490 --> 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 --> 00:09:08.648 These patients have a very poor outcome.

NOTE Confidence: 0.866359873333333

00:09:08.650 --> 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 --> 00:09:16.732 or by biopsy usually have anywhere

NOTE Confidence: 0.866359873333333

00:09:16.732 --> 00:09:19.490 from 7 to 12 months median survival.

NOTE Confidence: 0.866359873333333

00:09:19.490 --> 00:09:22.178 So very poor and there are

NOTE Confidence: 0.866359873333333

00:09:22.178 --> 00:09:23.970 very few therapy options.

NOTE Confidence: 0.866359873333333

00:09:23.970 --> 00:09:25.354 In showing this slide,

NOTE Confidence: 0.866359873333333

00:09:25.354 --> 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 adenocarcinoma all

NOTE Confidence: 0.866359873333333

00:09:29.549 --> 00:09:32.190 the way to small cell cancer.  
NOTE Confidence: 0.8663598733333333

00:09:32.190 --> 00:09:34.500 You can see in the adenocarcinoma it's  
NOTE Confidence: 0.8663598733333333

00:09:34.500 --> 00:09:36.846 positive for PSA which is a surrogate  
NOTE Confidence: 0.8663598733333333

00:09:36.846 --> 00:09:38.790 for antron singling and that it's  
NOTE Confidence: 0.8663598733333333

00:09:38.850 --> 00:09:41.310 negative for neuroendocrine markers here.  
NOTE Confidence: 0.8663598733333333

00:09:41.310 --> 00:09:43.676 And then as the tumor seems to,  
NOTE Confidence: 0.8663598733333333

00:09:43.680 --> 00:09:45.252 as we see different tumors where  
NOTE Confidence: 0.8663598733333333

00:09:45.252 --> 00:09:46.610 you have this neuroendocrine tumor,  
NOTE Confidence: 0.8663598733333333

00:09:46.610 --> 00:09:48.692 we see a positivity for the  
NOTE Confidence: 0.8663598733333333

00:09:48.692 --> 00:09:49.386 neuroendocrine markers.  
NOTE Confidence: 0.8663598733333333

00:09:49.390 --> 00:09:51.638 Now I think the important point here is  
NOTE Confidence: 0.8663598733333333

00:09:51.638 --> 00:09:53.526 an additional comment is that this is.  
NOTE Confidence: 0.8663598733333333

00:09:53.530 --> 00:09:55.240 All from the same patient.  
NOTE Confidence: 0.8663598733333333

00:09:55.240 --> 00:09:57.180 This patient had metastatic prostate  
NOTE Confidence: 0.8663598733333333

00:09:57.180 --> 00:09:59.564 cancer and these are from almost  
NOTE Confidence: 0.8663598733333333

00:09:59.564 --> 00:10:01.820 the same lesion in different areas.

NOTE Confidence: 0.8663598733333333  
00:10:01.820 --> 00:10:04.333 And so it's possible that you not  
NOTE Confidence: 0.8663598733333333  
00:10:04.333 --> 00:10:06.803 only have this trans differentiation  
NOTE Confidence: 0.8663598733333333  
00:10:06.803 --> 00:10:08.777 or lineage plasticity,  
NOTE Confidence: 0.8663598733333333  
00:10:08.780 --> 00:10:11.188 but it may be in the context  
NOTE Confidence: 0.8663598733333333  
00:10:11.188 --> 00:10:12.220 of mixed Histology.  
NOTE Confidence: 0.8663598733333333  
00:10:12.220 --> 00:10:15.620 So I think it's important to just remember  
NOTE Confidence: 0.8663598733333333  
00:10:15.620 --> 00:10:17.936 that heterogeneities obviously were is  
NOTE Confidence: 0.8663598733333333  
00:10:17.936 --> 00:10:20.256 an important component of resistance.  
NOTE Confidence: 0.8663598733333333  
00:10:20.260 --> 00:10:21.944 A few years ago,  
NOTE Confidence: 0.8663598733333333  
00:10:21.944 --> 00:10:23.879 probably around 2013 we started  
NOTE Confidence: 0.8663598733333333  
00:10:23.879 --> 00:10:25.694 a stand up to cancer.  
NOTE Confidence: 0.8663598733333333  
00:10:25.700 --> 00:10:28.275 PCF funded prostate Cancer Foundation  
NOTE Confidence: 0.8663598733333333  
00:10:28.275 --> 00:10:32.235 funded trial which was one of the first  
NOTE Confidence: 0.8663598733333333  
00:10:32.235 --> 00:10:34.839 precision oncology trials or number of  
NOTE Confidence: 0.8663598733333333  
00:10:34.839 --> 00:10:37.500 of PI's leading this Charles Sawyers,  
NOTE Confidence: 0.8663598733333333

00:10:37.500 --> 00:10:38.450 Real Shanian,  
NOTE Confidence: 0.8663598733333333

00:10:38.450 --> 00:10:41.300 Levi Garraway among others if Phil  
NOTE Confidence: 0.8663598733333333

00:10:41.300 --> 00:10:44.750 Kantoff and in this study one of the  
NOTE Confidence: 0.8663598733333333

00:10:44.750 --> 00:10:47.479 things that as pathologist was great is,  
NOTE Confidence: 0.8663598733333333

00:10:47.480 --> 00:10:49.552 is that we're able to look at now  
NOTE Confidence: 0.8663598733333333

00:10:49.552 --> 00:10:51.784 over 1000 cases of patients that  
NOTE Confidence: 0.8663598733333333

00:10:51.784 --> 00:10:53.428 were prospectively collected who  
NOTE Confidence: 0.8663598733333333

00:10:53.428 --> 00:10:55.639 were failing Andrew and decoration.  
NOTE Confidence: 0.8663598733333333

00:10:55.640 --> 00:10:58.480 Therapy and one sort or the other from  
NOTE Confidence: 0.8663598733333333

00:10:58.480 --> 00:11:00.176 multiple institutions and we could  
NOTE Confidence: 0.8663598733333333

00:11:00.176 --> 00:11:02.030 ask the question as a pathologist.  
NOTE Confidence: 0.8663598733333333

00:11:02.030 --> 00:11:04.074 If we used AR signaling as one  
NOTE Confidence: 0.8663598733333333

00:11:04.074 --> 00:11:05.977 score to look how adenocarcinoma  
NOTE Confidence: 0.8663598733333333

00:11:05.977 --> 00:11:07.889 tumor was and neuroendocrine  
NOTE Confidence: 0.8663598733333333

00:11:07.889 --> 00:11:09.801 signaling because we had  
NOTE Confidence: 0.818726499285714

00:11:09.874 --> 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 --> 00:11:15.756 we might expect to see 2A division

NOTE Confidence: 0.818726499285714

00:11:15.756 --> 00:11:18.376 into 2 camps and we could expect that

NOTE Confidence: 0.818726499285714

00:11:18.376 --> 00:11:20.838 there might be a third gradient of

NOTE Confidence: 0.818726499285714

00:11:20.838 --> 00:11:23.226 what tumors that are in transition.

NOTE Confidence: 0.818726499285714

00:11:23.230 --> 00:11:24.730 This is the real data.

NOTE Confidence: 0.818726499285714

00:11:24.730 --> 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 --> 00:11:33.166 many of the cases are sitting here,

NOTE Confidence: 0.818726499285714

00:11:33.170 --> 00:11:36.450 so high anger receptor signaling

NOTE Confidence: 0.818726499285714

00:11:36.450 --> 00:11:37.574 only some of them.

NOTE Confidence: 0.818726499285714

00:11:37.574 --> 00:11:39.260 So I mentioned about 15 percent,

NOTE Confidence: 0.818726499285714

00:11:39.260 --> 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 --> 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 --> 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 --> 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 --> 00:11:57.515 these very blue cells and neuroendocrine.  
NOTE Confidence: 0.818726499285714

00:11:57.520 --> 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 --> 00:12:02.080 neuroendocrine prostate cancer,  
NOTE Confidence: 0.818726499285714

00:12:02.080 --> 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 --> 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 --> 00:12:11.448 typical neuroendocrine tumor.

NOTE Confidence: 0.818726499285714  
00:12:11.450 --> 00:12:13.991 And then in area where we see  
NOTE Confidence: 0.818726499285714  
00:12:13.991 --> 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 --> 00:12:20.150 not just Andrew receptor but signaling,  
NOTE Confidence: 0.818726499285714  
00:12:20.150 --> 00:12:21.435 we see something that looks  
NOTE Confidence: 0.818726499285714  
00:12:21.435 --> 00:12:22.463 like a neuroendocrine cancer.  
NOTE Confidence: 0.818726499285714  
00:12:22.470 --> 00:12:23.610 These were not mixed up.  
NOTE Confidence: 0.818726499285714  
00:12:23.610 --> 00:12:24.612 We confirmed everything.  
NOTE Confidence: 0.818726499285714  
00:12:24.612 --> 00:12:27.190 So I think what is very important is,  
NOTE Confidence: 0.818726499285714  
00:12:27.190 --> 00:12:28.886 is that the Histology,  
NOTE Confidence: 0.818726499285714  
00:12:28.886 --> 00:12:31.430 so the phenotype and the genotype  
NOTE Confidence: 0.818726499285714  
00:12:31.513 --> 00:12:33.485 don't necessarily correlate that  
NOTE Confidence: 0.818726499285714  
00:12:33.485 --> 00:12:37.065 well and this causes obviously a lot  
NOTE Confidence: 0.818726499285714  
00:12:37.065 --> 00:12:39.249 of confusion for classification,  
NOTE Confidence: 0.818726499285714  
00:12:39.250 --> 00:12:41.638 which is very important for treatment.  
NOTE Confidence: 0.818726499285714

00:12:41.640 --> 00:12:43.576 This is a case that's in the middle  
NOTE Confidence: 0.818726499285714

00:12:43.576 --> 00:12:45.917 and it shows a very unusual Histology.  
NOTE Confidence: 0.818726499285714

00:12:45.920 --> 00:12:47.960 So for somebody doing prostate  
NOTE Confidence: 0.818726499285714

00:12:47.960 --> 00:12:50.000 pathology for many years now,  
NOTE Confidence: 0.818726499285714

00:12:50.000 --> 00:12:52.184 we usually see certain morphologies but  
NOTE Confidence: 0.818726499285714

00:12:52.184 --> 00:12:54.900 we don't see these odd looking nuclei.  
NOTE Confidence: 0.818726499285714

00:12:54.900 --> 00:12:57.042 And I think this is really related  
NOTE Confidence: 0.818726499285714

00:12:57.042 --> 00:12:58.600 to a few factors,  
NOTE Confidence: 0.818726499285714

00:12:58.600 --> 00:13:01.432 but at least one factor is that patients  
NOTE Confidence: 0.818726499285714

00:13:01.432 --> 00:13:04.057 are getting very potent anti androgens.  
NOTE Confidence: 0.818726499285714

00:13:04.060 --> 00:13:06.314 Another factor is that they're living longer,  
NOTE Confidence: 0.818726499285714

00:13:06.320 --> 00:13:08.300 so they're able to survive longer.  
NOTE Confidence: 0.818726499285714

00:13:08.300 --> 00:13:10.040 So we're seeing changes that  
NOTE Confidence: 0.818726499285714

00:13:10.040 --> 00:13:11.432 we previously hadn't seen.  
NOTE Confidence: 0.818726499285714

00:13:11.440 --> 00:13:13.328 So I think this is part of the  
NOTE Confidence: 0.818726499285714

00:13:13.328 --> 00:13:14.538 natural evolution of the cancer.



NOTE Confidence: 0.818726499285714  
00:13:14.540 --> 00:13:16.556 It's just that maybe we haven't seen this.  
NOTE Confidence: 0.818726499285714  
00:13:16.560 --> 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 --> 00:13:22.380 metastatic biopsies are not the norm.  
NOTE Confidence: 0.818726499285714  
00:13:22.380 --> 00:13:24.270 So usually we're not actually seeing  
NOTE Confidence: 0.818726499285714  
00:13:24.270 --> 00:13:26.680 what's going on as you treat patients.  
NOTE Confidence: 0.818726499285714  
00:13:26.680 --> 00:13:29.158 So this was eye opening for me  
NOTE Confidence: 0.818726499285714  
00:13:29.158 --> 00:13:30.220 as a pathologist.  
NOTE Confidence: 0.818726499285714  
00:13:30.220 --> 00:13:31.822 When we looked at the molecular  
NOTE Confidence: 0.818726499285714  
00:13:31.822 --> 00:13:33.539 alterations in some of these cases,  
NOTE Confidence: 0.818726499285714  
00:13:33.540 --> 00:13:36.424 they tended to have P53 and RB  
NOTE Confidence: 0.818726499285714  
00:13:36.424 --> 00:13:38.692 alterations in these cases as  
NOTE Confidence: 0.818726499285714  
00:13:38.692 --> 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 --> 00:13:42.274 About that.  
NOTE Confidence: 0.818726499285714

00:13:42.274 --> 00:13:44.633 But this leaves us with a picture  
NOTE Confidence: 0.818726499285714

00:13:44.633 --> 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 --> 00:13:50.890 under the microscope to classify it.  
NOTE Confidence: 0.818726499285714

00:13:50.890 --> 00:13:52.416 So it really suggested to us that  
NOTE Confidence: 0.818726499285714

00:13:52.416 --> 00:13:54.164 we need to come up with other  
NOTE Confidence: 0.818726499285714

00:13:54.164 --> 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 --> 00:14:01.165 but we don't really have  
NOTE Confidence: 0.876687335555556

00:14:01.165 --> 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 --> 00:14:07.824 the phenotype and the scores or  
NOTE Confidence: 0.876687335555556

00:14:07.824 --> 00:14:10.115 the signaling scores that you have  
NOTE Confidence: 0.876687335555556

00:14:10.115 --> 00:14:11.807 from transcriptomics don't match.  
NOTE Confidence: 0.876687335555556

00:14:11.810 --> 00:14:14.276 Perfectly so. And we also recognize

NOTE Confidence: 0.876687335555556  
00:14:14.276 --> 00:14:15.920 they're probably intermediate states.  
NOTE Confidence: 0.876687335555556  
00:14:15.920 --> 00:14:18.174 So I think those are important observations.  
NOTE Confidence: 0.876687335555556  
00:14:18.180 --> 00:14:21.042 So we start out with a model where we  
NOTE Confidence: 0.876687335555556  
00:14:21.042 --> 00:14:24.116 wanted to look at very discrete differences,  
NOTE Confidence: 0.876687335555556  
00:14:24.120 --> 00:14:26.524 adenocarcinoma and neuroendocrine tumors.  
NOTE Confidence: 0.876687335555556  
00:14:26.524 --> 00:14:28.940 In fact, when we look more carefully,  
NOTE Confidence: 0.876687335555556  
00:14:28.940 --> 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 --> 00:14:35.888 genotype and also transcriptomic  
NOTE Confidence: 0.876687335555556  
00:14:35.888 --> 00:14:38.416 and probably epigenetic alterations  
NOTE Confidence: 0.876687335555556  
00:14:38.416 --> 00:14:41.869 about the same time we wanted to do.  
NOTE Confidence: 0.876687335555556  
00:14:41.870 --> 00:14:43.802 A very focused study at looking  
NOTE Confidence: 0.876687335555556  
00:14:43.802 --> 00:14:45.784 at these extremes to ask the  
NOTE Confidence: 0.876687335555556  
00:14:45.784 --> 00:14:47.989 question what are some of the other  
NOTE Confidence: 0.876687335555556  
00:14:47.989 --> 00:14:49.800 factors that might play a role.  
NOTE Confidence: 0.876687335555556

00:14:49.800 --> 00:14:54.264 So genomics but also epigenetics and  
NOTE Confidence: 0.876687335555556

00:14:54.264 --> 00:14:57.670 transcriptomics were applied then to.  
NOTE Confidence: 0.876687335555556

00:14:57.670 --> 00:14:58.381 A set of,  
NOTE Confidence: 0.876687335555556

00:14:58.381 --> 00:15:01.002 I think at the time 50 or 60 cases  
NOTE Confidence: 0.876687335555556

00:15:01.002 --> 00:15:03.237 where we had bonafide neuroendocrine  
NOTE Confidence: 0.876687335555556

00:15:03.237 --> 00:15:05.632 cancers diagnosed by pathology and  
NOTE Confidence: 0.876687335555556

00:15:05.632 --> 00:15:08.097 adenocarcinomas 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 --> 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 --> 00:15:14.130 I think the important finding for us  
NOTE Confidence: 0.876687335555556

00:15:14.130 --> 00:15:17.757 was that we expected to see some some  
NOTE Confidence: 0.876687335555556

00:15:17.760 --> 00:15:19.935 really exciting genomic alteration that  
NOTE Confidence: 0.876687335555556

00:15:19.935 --> 00:15:21.675 would characterize the difference,  
NOTE Confidence: 0.876687335555556

00:15:21.680 --> 00:15:22.640 but we didn't.  
NOTE Confidence: 0.876687335555556

00:15:22.640 --> 00:15:24.880 What we really see is a commonality

NOTE Confidence: 0.876687335555556  
00:15:24.944 --> 00:15:27.960 that RB1 and P53 are very commonly.  
NOTE Confidence: 0.876687335555556  
00:15:27.960 --> 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 --> 00:15:36.152 but we do see it and that in general  
NOTE Confidence: 0.876687335555556  
00:15:36.152 --> 00:15:38.488 the overlap in genomic alterations,  
NOTE Confidence: 0.876687335555556  
00:15:38.490 --> 00:15:40.518 copy number alterations is very similar  
NOTE Confidence: 0.876687335555556  
00:15:40.518 --> 00:15:42.618 except for let's say the Andrew  
NOTE Confidence: 0.876687335555556  
00:15:42.618 --> 00:15:44.682 receptor where that would be something  
NOTE Confidence: 0.876687335555556  
00:15:44.682 --> 00:15:46.778 that's very different and altered in  
NOTE Confidence: 0.876687335555556  
00:15:46.778 --> 00:15:50.470 adenocarcinoma but not in the small cell.  
NOTE Confidence: 0.876687335555556  
00:15:50.470 --> 00:15:52.886 When we looked at the data in combination,  
NOTE Confidence: 0.876687335555556  
00:15:52.890 --> 00:15:54.474 so looking at DNA,  
NOTE Confidence: 0.876687335555556  
00:15:54.474 --> 00:15:56.850 RNA and epigenetics and then asking  
NOTE Confidence: 0.876687335555556  
00:15:56.926 --> 00:15:59.491 the question what which element  
NOTE Confidence: 0.876687335555556  
00:15:59.491 --> 00:16:01.543 best explained the differences  
NOTE Confidence: 0.876687335555556

00:16:01.543 --> 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 --> 00:16:08.788 configuration of the of the population.  
NOTE Confidence: 0.876687335555556

00:16:08.790 --> 00:16:11.470 But certainly epigenetics or methylation  
NOTE Confidence: 0.876687335555556

00:16:11.470 --> 00:16:14.150 helped explain the difference quite,  
NOTE Confidence: 0.876687335555556

00:16:14.150 --> 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 --> 00:16:18.210 much more about that,  
NOTE Confidence: 0.876687335555556

00:16:18.210 --> 00:16:20.250 but we think methylation or epigenetic.  
NOTE Confidence: 0.876687335555556

00:16:20.250 --> 00:16:22.250 Alterations are very important.  
NOTE Confidence: 0.876687335555556

00:16:22.250 --> 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 --> 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 --> 00:16:34.121 there's an inflection point where

NOTE Confidence: 0.876687335555556  
00:16:34.121 --> 00:16:35.509 adenocarcinomas maybe go through  
NOTE Confidence: 0.876687335555556  
00:16:35.509 --> 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 --> 00:16:40.898 Now I think for people in the  
NOTE Confidence: 0.876687335555556  
00:16:40.898 --> 00:16:41.720 lung cancer field,  
NOTE Confidence: 0.876687335555556  
00:16:41.720 --> 00:16:44.180 this was something not unexpected,  
NOTE Confidence: 0.876687335555556  
00:16:44.180 --> 00:16:46.623 but this is something we wanted to  
NOTE Confidence: 0.876687335555556  
00:16:46.623 --> 00:16:48.671 explore in prostate as well because  
NOTE Confidence: 0.876687335555556  
00:16:48.671 --> 00:16:50.841 we think that at some point he's  
NOTE Confidence: 0.876687335555556  
00:16:50.914 --> 00:16:53.159 around 10 to 15% of the cases.  
NOTE Confidence: 0.876687335555556  
00:16:53.159 --> 00:16:55.980 Are no longer responding to AR driven  
NOTE Confidence: 0.876687335555556  
00:16:56.065 --> 00:16:58.435 therapies and become a RH negative  
NOTE Confidence: 0.876687335555556  
00:16:58.435 --> 00:17:01.998 in a sense that then they will then  
NOTE Confidence: 0.876687335555556  
00:17:01.998 --> 00:17:04.368 either trans differentiate to small  
NOTE Confidence: 0.876687335555556  
00:17:04.368 --> 00:17:08.170 cell or AR negative neuroendocrine negative.  
NOTE Confidence: 0.876687335555556

00:17:08.170 --> 00:17:10.384 So another type of air negative  
NOTE Confidence: 0.876687335555556

00:17:10.384 --> 00:17:12.687 phenotype and that's I think that  
NOTE Confidence: 0.876687335555556

00:17:12.687 --> 00:17:14.943 was supported by some of the  
NOTE Confidence: 0.876687335555556

00:17:14.943 --> 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: 0.835506886666667

00:17:18.390 --> 00:17:20.315 I'll just very briefly make a few  
NOTE Confidence: 0.835506886666667

00:17:20.315 --> 00:17:21.879 comments about the Polycom gene,  
NOTE Confidence: 0.835506886666667

00:17:21.880 --> 00:17:24.218 so easy H2. And also the switch  
NOTE Confidence: 0.835506886666667

00:17:24.218 --> 00:17:26.079 sniff work that we've done,  
NOTE Confidence: 0.835506886666667

00:17:26.080 --> 00:17:28.744 but I I think others are are quite  
NOTE Confidence: 0.835506886666667

00:17:28.744 --> 00:17:30.977 interested also for the lung cancer spore.  
NOTE Confidence: 0.835506886666667

00:17:30.980 --> 00:17:32.916 It's probably quite interesting  
NOTE Confidence: 0.835506886666667

00:17:32.916 --> 00:17:34.852 thinking about epigenetic regulation  
NOTE Confidence: 0.835506886666667

00:17:34.852 --> 00:17:36.818 and where we stand today.  
NOTE Confidence: 0.835506886666667

00:17:36.820 --> 00:17:39.367 So I think this is a very nice review.  
NOTE Confidence: 0.835506886666667

00:17:39.370 --> 00:17:42.156 They came out after two papers were



NOTE Confidence: 0.835506886666667

00:17:42.156 --> 00:17:44.276 published in science suggesting that

NOTE Confidence: 0.835506886666667

00:17:44.276 --> 00:17:47.258 there's a stem like state that occurs

NOTE Confidence: 0.835506886666667

00:17:47.258 --> 00:17:49.211 before you go to neuroendocrine

NOTE Confidence: 0.835506886666667

00:17:49.211 --> 00:17:51.716 or to a negative state and that

NOTE Confidence: 0.835506886666667

00:17:51.716 --> 00:17:53.346 one of the key players.

NOTE Confidence: 0.835506886666667

00:17:53.350 --> 00:17:56.738 It's probably easy H2 so a Polycom

NOTE Confidence: 0.835506886666667

00:17:56.738 --> 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: 0.835506886666667

00:18:02.280 --> 00:18:04.700 associated with AR signaling.

NOTE Confidence: 0.835506886666667

00:18:04.700 --> 00:18:06.541 And this is just one key experiment

NOTE Confidence: 0.835506886666667

00:18:06.541 --> 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: 0.835506886666667

00:18:13.363 --> 00:18:16.040 in a mouse model P53 and RB and

NOTE Confidence: 0.835506886666667

00:18:16.040 --> 00:18:18.200 that's what's shown here the the

NOTE Confidence: 0.835506886666667

00:18:18.279 --> 00:18:21.543 tumors are no longer sensitive to  
NOTE Confidence: 0.835506886666667

00:18:21.543 --> 00:18:23.719 the potent antiandrogen enzalutamide.  
NOTE Confidence: 0.835506886666667

00:18:23.720 --> 00:18:25.752 And so you could see that the tumors  
NOTE Confidence: 0.835506886666667

00:18:25.752 --> 00:18:27.754 are now continuing to grow even  
NOTE Confidence: 0.835506886666667

00:18:27.754 --> 00:18:29.549 in the presence of enzalutamide.  
NOTE Confidence: 0.835506886666667

00:18:29.550 --> 00:18:31.558 If you use EH2,  
NOTE Confidence: 0.835506886666667

00:18:31.558 --> 00:18:34.068 you can reactivate or resensitize  
NOTE Confidence: 0.835506886666667

00:18:34.068 --> 00:18:37.353 these tumors to the epigenetic drugs  
NOTE Confidence: 0.835506886666667

00:18:37.353 --> 00:18:40.616 that are used now clinically for  
NOTE Confidence: 0.835506886666667

00:18:40.616 --> 00:18:43.934 as easy as two inhibitors and you  
NOTE Confidence: 0.835506886666667

00:18:43.934 --> 00:18:45.570 can reactivate air sensitivity.  
NOTE Confidence: 0.835506886666667

00:18:45.570 --> 00:18:48.724 So this is just a concept that this is  
NOTE Confidence: 0.835506886666667

00:18:48.724 --> 00:18:50.920 a stem like state that's potentially  
NOTE Confidence: 0.835506886666667

00:18:50.920 --> 00:18:53.920 reversible and I think that's an interesting.  
NOTE Confidence: 0.835506886666667

00:18:53.920 --> 00:18:54.628 Concept there.  
NOTE Confidence: 0.835506886666667

00:18:54.628 --> 00:18:57.106 I'm happy to discuss more about those.

NOTE Confidence: 0.835506886666667

00:18:57.110 --> 00:18:58.850 There's some controversy a little

NOTE Confidence: 0.835506886666667

00:18:58.850 --> 00:18:59.894 bit about that,

NOTE Confidence: 0.835506886666667

00:18:59.900 --> 00:19:02.528 but I'll just leave it at that for now.

NOTE Confidence: 0.835506886666667

00:19:02.530 --> 00:19:04.030 We were interested in the other,

NOTE Confidence: 0.835506886666667

00:19:04.030 --> 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: 0.835506886666667

00:19:08.175 --> 00:19:10.190 looking at the switch sniff complex

NOTE Confidence: 0.835506886666667

00:19:10.190 --> 00:19:12.633 and the things that really were of

NOTE Confidence: 0.835506886666667

00:19:12.633 --> 00:19:14.238 particular interest to us were one,

NOTE Confidence: 0.835506886666667

00:19:14.240 --> 00:19:16.270 that there's an embryonic switch

NOTE Confidence: 0.835506886666667

00:19:16.270 --> 00:19:18.799 sniff complex that goes to other

NOTE Confidence: 0.835506886666667

00:19:18.799 --> 00:19:20.089 types of complexes.

NOTE Confidence: 0.835506886666667

00:19:20.090 --> 00:19:22.835 So you can have this a stem like complex,

NOTE Confidence: 0.835506886666667

00:19:22.840 --> 00:19:23.818 but it also.

NOTE Confidence: 0.835506886666667

00:19:23.818 --> 00:19:25.774 A neuronal complex and the idea

NOTE Confidence: 0.835506886666667

00:19:25.774 --> 00:19:28.177 was that in development it's very  
NOTE Confidence: 0.835506886666667

00:19:28.177 --> 00:19:30.700 important that you're able to have  
NOTE Confidence: 0.835506886666667

00:19:30.700 --> 00:19:32.940 neural development and switch sniff  
NOTE Confidence: 0.835506886666667

00:19:32.940 --> 00:19:35.326 complex activates and can facilitate  
NOTE Confidence: 0.835506886666667

00:19:35.326 --> 00:19:38.256 a neural development and playing  
NOTE Confidence: 0.835506886666667

00:19:38.256 --> 00:19:42.394 an important role that H3K27 marks  
NOTE Confidence: 0.835506886666667

00:19:42.394 --> 00:19:44.188 of escalation.  
NOTE Confidence: 0.835506886666667

00:19:44.190 --> 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: 0.835506886666667

00:19:49.088 --> 00:19:51.620 that that the switch sniff,  
NOTE Confidence: 0.835506886666667

00:19:51.620 --> 00:19:52.583 particularly the ATP,  
NOTE Confidence: 0.835506886666667

00:19:52.583 --> 00:19:55.222 Asus market two and Smart K for are  
NOTE Confidence: 0.835506886666667

00:19:55.222 --> 00:19:57.184 often altered and a particular interest  
NOTE Confidence: 0.835506886666667

00:19:57.184 --> 00:19:59.987 in many of the synthetic lethal screens.  
NOTE Confidence: 0.835506886666667

00:19:59.990 --> 00:20:02.286 So Mark four and smart K2 come  
NOTE Confidence: 0.835506886666667

00:20:02.286 --> 00:20:05.433 up as sort of key findings and so

NOTE Confidence: 0.835506886666667

00:20:05.433 --> 00:20:08.216 there's been a great interest in

NOTE Confidence: 0.835506886666667

00:20:08.216 --> 00:20:10.696 translationally developing drugs that

NOTE Confidence: 0.835506886666667

00:20:10.696 --> 00:20:13.726 would knockout smarca 2 specifically.

NOTE Confidence: 0.835506886666667

00:20:13.726 --> 00:20:17.807 In smart key for ultra tumors and

NOTE Confidence: 0.835506886666667

00:20:17.807 --> 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: 0.835506886666667

00:20:23.310 --> 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: 0.835506886666667

00:20:27.030 --> 00:20:29.858 So most of whether it's an ATP

NOTE Confidence: 0.835506886666667

00:20:29.858 --> 00:20:31.930 ACE inhibitor or a protac,

NOTE Confidence: 0.835506886666667

00:20:31.930 --> 00:20:33.080 this has been a difficult,

NOTE Confidence: 0.835506886666667

00:20:33.080 --> 00:20:33.884 it's been challenging.

NOTE Confidence: 0.835506886666667

00:20:33.884 --> 00:20:35.760 So most of the work is is

NOTE Confidence: 0.88847246047619

00:20:35.824 --> 00:20:37.840 really focused on knocking out both

NOTE Confidence: 0.88847246047619

00:20:37.840 --> 00:20:39.800 and creating a synthetic lethality.

NOTE Confidence: 0.811509029285714

00:20:41.930 --> 00:20:44.562 What we found in a sort of as  
NOTE Confidence: 0.811509029285714

00:20:44.562 --> 00:20:47.570 as is very common in prostate,  
NOTE Confidence: 0.811509029285714

00:20:47.570 --> 00:20:49.880 so prostate tends to prostate cancer.  
NOTE Confidence: 0.811509029285714

00:20:49.880 --> 00:20:51.710 Research tends to look at things  
NOTE Confidence: 0.811509029285714

00:20:51.710 --> 00:20:52.930 differently because for whatever  
NOTE Confidence: 0.811509029285714

00:20:52.983 --> 00:20:54.699 reason prostate is a little bit  
NOTE Confidence: 0.811509029285714

00:20:54.699 --> 00:20:55.843 different than other cancers.  
NOTE Confidence: 0.811509029285714

00:20:55.850 --> 00:20:58.643 And we were interested in looking at  
NOTE Confidence: 0.811509029285714

00:20:58.643 --> 00:21:00.739 the overexpression of smart Guy 4,  
NOTE Confidence: 0.811509029285714

00:21:00.740 --> 00:21:02.721 which is not usually the case in  
NOTE Confidence: 0.811509029285714

00:21:02.721 --> 00:21:05.165 in many of the tumors that have  
NOTE Confidence: 0.811509029285714

00:21:05.165 --> 00:21:07.070 lost smart gave for expression.  
NOTE Confidence: 0.811509029285714

00:21:07.070 --> 00:21:09.435 So these are complicated complexes  
NOTE Confidence: 0.811509029285714

00:21:09.435 --> 00:21:11.327 and I'll simplify it.  
NOTE Confidence: 0.811509029285714

00:21:11.330 --> 00:21:13.448 By just saying that there's a  
NOTE Confidence: 0.811509029285714

00:21:13.448 --> 00:21:15.224 working component which is a

NOTE Confidence: 0.811509029285714

00:21:15.224 --> 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 --> 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 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 --> 00:21:27.975 And the idea is that most of the work

NOTE Confidence: 0.811509029285714

00:21:27.975 --> 00:21:29.927 is going and targeting these and we

NOTE Confidence: 0.811509029285714

00:21:29.927 --> 00:21:31.863 were interested to see what happens

NOTE Confidence: 0.811509029285714

00:21:31.863 --> 00:21:33.367 in prostate cancer progression,

NOTE Confidence: 0.811509029285714

00:21:33.370 --> 00:21:35.680 whether there were mutations or

NOTE Confidence: 0.811509029285714

00:21:35.680 --> 00:21:38.510 alterations in these in the ATP Aces.

NOTE Confidence: 0.811509029285714

00:21:38.510 --> 00:21:39.950 What we found is,

NOTE Confidence: 0.811509029285714

00:21:39.950 --> 00:21:41.774 is that when we look there's as you

NOTE Confidence: 0.811509029285714

00:21:41.774 --> 00:21:43.769 look in prostate cancer progression,

NOTE Confidence: 0.811509029285714

00:21:43.770 --> 00:21:46.458 we sent to see an increase in smart

NOTE Confidence: 0.811509029285714

00:21:46.458 --> 00:21:49.050 K4 and a decrease in smart K2.  
NOTE Confidence: 0.811509029285714

00:21:49.050 --> 00:21:51.444 So that's a little bit different than  
NOTE Confidence: 0.811509029285714

00:21:51.444 --> 00:21:53.790 what's seen in some other cancers,  
NOTE Confidence: 0.811509029285714

00:21:53.790 --> 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 --> 00:22:02.768 we also see an increase in some  
NOTE Confidence: 0.811509029285714

00:22:02.768 --> 00:22:05.285 of the neural components of the  
NOTE Confidence: 0.811509029285714

00:22:05.285 --> 00:22:07.655 switch sniff complex that are there  
NOTE Confidence: 0.811509029285714

00:22:07.655 --> 00:22:09.431 associated with the the neural  
NOTE Confidence: 0.811509029285714

00:22:09.431 --> 00:22:11.574 complex which is called back 53B as  
NOTE Confidence: 0.811509029285714

00:22:11.574 --> 00:22:13.550 one of the as one of the proteins.  
NOTE Confidence: 0.811509029285714

00:22:13.550 --> 00:22:16.350 So just to visualize this as a pathologist  
NOTE Confidence: 0.811509029285714

00:22:16.350 --> 00:22:18.638 their core complexes don't change.  
NOTE Confidence: 0.811509029285714

00:22:18.640 --> 00:22:21.226 So going from localized disease or  
NOTE Confidence: 0.811509029285714

00:22:21.226 --> 00:22:23.638 benign tissue to advanced disease



NOTE Confidence: 0.811509029285714

00:22:23.638 --> 00:22:26.106 that's neuroendocrine positive you.

NOTE Confidence: 0.811509029285714

00:22:26.110 --> 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 --> 00:22:32.385 here back 53B is only expressed in

NOTE Confidence: 0.811509029285714

00:22:32.385 --> 00:22:34.450 their endocrine tumor as you'd expect.

NOTE Confidence: 0.811509029285714

00:22:34.450 --> 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 --> 00:22:41.613 paralogs is very highly expressed

NOTE Confidence: 0.811509029285714

00:22:41.613 --> 00:22:43.793 in the neuroendocrine tumors or

NOTE Confidence: 0.811509029285714

00:22:43.793 --> 00:22:46.252 maybe the stem like type tumors that

NOTE Confidence: 0.811509029285714

00:22:46.252 --> 00:22:48.399 we see smart K2 is not expressed.

NOTE Confidence: 0.811509029285714

00:22:48.399 --> 00:22:50.097 So we were originally thinking that

NOTE Confidence: 0.811509029285714

00:22:50.097 --> 00:22:51.870 for us would be very interesting,

NOTE Confidence: 0.811509029285714

00:22:51.870 --> 00:22:53.850 interesting to modulate smart K4

NOTE Confidence: 0.811509029285714

00:22:53.850 --> 00:22:56.370 in the context of prostate cancer.

NOTE Confidence: 0.811509029285714

00:22:56.370 --> 00:22:57.510 And just as an aside,  
NOTE Confidence: 0.811509029285714

00:22:57.510 --> 00:23:00.330 we don't see any mutations that are  
NOTE Confidence: 0.811509029285714

00:23:00.330 --> 00:23:02.780 seen in other cancers in either of  
NOTE Confidence: 0.811509029285714

00:23:02.780 --> 00:23:05.541 the of the paralogs or in any of the  
NOTE Confidence: 0.811509029285714

00:23:05.541 --> 00:23:08.288 of the Swiss sniff complex members.  
NOTE Confidence: 0.811509029285714

00:23:08.290 --> 00:23:10.250 When we look at pathology,  
NOTE Confidence: 0.811509029285714

00:23:10.250 --> 00:23:13.036 again if you look at cases where  
NOTE Confidence: 0.811509029285714

00:23:13.036 --> 00:23:14.948 you have adenocarcinoma here and  
NOTE Confidence: 0.811509029285714

00:23:14.948 --> 00:23:16.604 then you have some neuroendocrine  
NOTE Confidence: 0.811509029285714

00:23:16.604 --> 00:23:18.848 cancer in the exact same tumor,  
NOTE Confidence: 0.811509029285714

00:23:18.850 --> 00:23:20.313 you can very nicely see some of  
NOTE Confidence: 0.811509029285714

00:23:20.313 --> 00:23:21.809 the things I'm telling you about.  
NOTE Confidence: 0.811509029285714

00:23:21.810 --> 00:23:24.642 So the small cell expression of  
NOTE Confidence: 0.811509029285714

00:23:24.642 --> 00:23:26.530 synaptophysin the scene here.  
NOTE Confidence: 0.811509029285714

00:23:26.530 --> 00:23:27.616 The BAT 53B,  
NOTE Confidence: 0.811509029285714

00:23:27.616 --> 00:23:29.788 which again is a neural component,

NOTE Confidence: 0.811509029285714

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

NOTE Confidence: 0.811509029285714

00:23:33.120 --> 00:23:35.950 sniff complex is expressed there,

NOTE Confidence: 0.811509029285714

00:23:35.950 --> 00:23:37.710 but not in the adenocarcinoma.

NOTE Confidence: 0.811509029285714

00:23:37.710 --> 00:23:38.760 So that's important.

NOTE Confidence: 0.811509029285714

00:23:38.760 --> 00:23:41.210 And then here is I think a

NOTE Confidence: 0.830189032666667

00:23:41.286 --> 00:23:44.408 very important finding at least in the

NOTE Confidence: 0.830189032666667

00:23:44.408 --> 00:23:47.558 published paper where we took an organoid

NOTE Confidence: 0.830189032666667

00:23:47.558 --> 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 --> 00:23:54.190 now this we're seeing heterogeneity.

NOTE Confidence: 0.830189032666667

00:23:54.190 --> 00:23:55.335 So that's one thing that's

NOTE Confidence: 0.830189032666667

00:23:55.335 --> 00:23:56.910 important is even in a patient.

NOTE Confidence: 0.830189032666667

00:23:56.910 --> 00:23:58.502 Private organoid this passage

NOTE Confidence: 0.830189032666667

00:23:58.502 --> 00:24:00.492 many times we see heterogeneity.

NOTE Confidence: 0.830189032666667

00:24:00.500 --> 00:24:02.348 And what's interesting here is smart

NOTE Confidence: 0.830189032666667

00:24:02.348 --> 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 --> 00:24:09.618 much involved in stemness is expressed.  
NOTE Confidence: 0.830189032666667

00:24:09.620 --> 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 --> 00:24:16.520 but they are expressed in  
NOTE Confidence: 0.830189032666667

00:24:16.520 --> 00:24:18.580 the Smart Gate 2 area.  
NOTE Confidence: 0.830189032666667

00:24:18.580 --> 00:24:21.044 So it looks like the paralogs play a  
NOTE Confidence: 0.830189032666667

00:24:21.044 --> 00:24:22.878 different role in modulating them.  
NOTE Confidence: 0.830189032666667

00:24:22.880 --> 00:24:24.760 May do something very different.  
NOTE Confidence: 0.830189032666667

00:24:24.760 --> 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 --> 00:24:31.070 you have some cells that are more  
NOTE Confidence: 0.830189032666667

00:24:31.136 --> 00:24:33.251 poised to be neuroendocrine and  
NOTE Confidence: 0.830189032666667

00:24:33.251 --> 00:24:35.425 others that are potentially that  
NOTE Confidence: 0.830189032666667

00:24:35.425 --> 00:24:37.800 are potentially still very stem

NOTE Confidence: 0.830189032666667

00:24:37.800 --> 00:24:39.700 like and potentially reversible.

NOTE Confidence: 0.746438354

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

NOTE Confidence: 0.746438354

00:24:47.860 --> 00:24:50.121 has shared some of the organizers he's

NOTE Confidence: 0.746438354

00:24:50.121 --> 00:24:52.320 developed through some of these mouse models.

NOTE Confidence: 0.746438354

00:24:52.320 --> 00:24:54.070 So I mentioned that he's

NOTE Confidence: 0.746438354

00:24:54.070 --> 00:24:55.470 developed mouse models where

NOTE Confidence: 0.746438354

00:24:55.470 --> 00:24:58.029 he's done knockout of P53 and RB.

NOTE Confidence: 0.746438354

00:24:58.029 --> 00:24:59.994 They've also knocked out P-10.

NOTE Confidence: 0.746438354

00:25:00.000 --> 00:25:02.928 And so in black we have P-10 knocked

NOTE Confidence: 0.746438354

00:25:02.928 --> 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 knockout in

NOTE Confidence: 0.746438354

00:25:10.020 --> 00:25:11.460 these various mouse models.

NOTE Confidence: 0.746438354

00:25:11.460 --> 00:25:13.440 And you can see that in the mouse models.

NOTE Confidence: 0.746438354

00:25:13.440 --> 00:25:16.359 You also have the same observation that

NOTE Confidence: 0.746438354

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 --> 00:25:21.885 And a little bit of the controversy is

NOTE Confidence: 0.746438354

00:25:21.885 --> 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 --> 00:25:28.581 but that's a sort of another

NOTE Confidence: 0.746438354

00:25:28.581 --> 00:25:30.410 discussion and then smart.

NOTE Confidence: 0.746438354

00:25:30.410 --> 00:25:31.890 The two goes down dramatically

NOTE Confidence: 0.746438354

00:25:31.890 --> 00:25:33.370 when you knock out either

NOTE Confidence: 0.820125292

00:25:35.400 --> 00:25:37.960 P53RB alone or with P53.

NOTE Confidence: 0.820125292

00:25:37.960 --> 00:25:40.600 There's some other interesting findings.

NOTE Confidence: 0.820125292

00:25:40.600 --> 00:25:42.235 The methyl transferases

NOTE Confidence: 0.820125292

00:25:42.235 --> 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 --> 00:25:48.754 but there's I think an interesting

NOTE Confidence: 0.820125292

00:25:48.754 --> 00:25:51.588 story related to the epigenetic side of

NOTE Confidence: 0.820125292

00:25:51.588 --> 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 --> 00:25:57.790 point is in this mouse model,

NOTE Confidence: 0.820125292

00:25:57.790 --> 00:26:00.709 we then did proteomics on the patient

NOTE Confidence: 0.820125292

00:26:00.709 --> 00:26:02.799 derived organoids from this model.

NOTE Confidence: 0.820125292

00:26:02.800 --> 00:26:04.475 And what's interesting and what

NOTE Confidence: 0.820125292

00:26:04.475 --> 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 --> 00:26:10.790 that we see overexpression of socks too,

NOTE Confidence: 0.820125292

00:26:10.790 --> 00:26:12.488 which I showed you in the

NOTE Confidence: 0.820125292

00:26:12.488 --> 00:26:13.620 in the human samples.

NOTE Confidence: 0.820125292

00:26:13.620 --> 00:26:16.245 We also have smart K fours overexpressed.

NOTE Confidence: 0.820125292

00:26:16.250 --> 00:26:17.660 But what's quite interesting is,

NOTE Confidence: 0.820125292

00:26:17.660 --> 00:26:20.210 is that if you take this model out of the

NOTE Confidence: 0.820125292

00:26:20.281 --> 00:26:22.831 mouse and now put it and just grow it in,

NOTE Confidence: 0.820125292

00:26:22.840 --> 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 --> 00:26:27.599 not in vivo.  
NOTE Confidence: 0.820125292

00:26:27.599 --> 00:26:29.177 What ends up happening is you  
NOTE Confidence: 0.820125292

00:26:29.177 --> 00:26:30.930 don't see these changes anymore.  
NOTE Confidence: 0.820125292

00:26:30.930 --> 00:26:32.988 So just one other comment that environment  
NOTE Confidence: 0.820125292

00:26:32.988 --> 00:26:34.865 we think is very important and I  
NOTE Confidence: 0.820125292

00:26:34.865 --> 00:26:37.330 think when do a lot of us when we're  
NOTE Confidence: 0.820125292

00:26:37.330 --> 00:26:39.000 doing the our organoid experiments,  
NOTE Confidence: 0.820125292

00:26:39.000 --> 00:26:40.645 we have to be mindful that the  
NOTE Confidence: 0.820125292

00:26:40.645 --> 00:26:42.150 results could be very different.  
NOTE Confidence: 0.820125292

00:26:42.150 --> 00:26:44.589 And there's I think more to come about this.  
NOTE Confidence: 0.820125292

00:26:44.590 --> 00:26:46.912 I think Walter Carter who's was  
NOTE Confidence: 0.820125292

00:26:46.912 --> 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 --> 00:26:54.019 in this area.  
NOTE Confidence: 0.820125292

00:26:54.019 --> 00:26:58.160 So just a final comments about switch sniffs.



NOTE Confidence: 0.820125292

00:26:58.160 --> 00:27:01.220 So we were sort of surprised

NOTE Confidence: 0.820125292

00:27:01.220 --> 00:27:04.240 at the end of 21,

NOTE Confidence: 0.820125292

00:27:04.240 --> 00:27:06.352 so beginning of 22 to see a paper

NOTE Confidence: 0.820125292

00:27:06.352 --> 00:27:08.386 from rural Shanes group because we

NOTE Confidence: 0.820125292

00:27:08.386 --> 00:27:10.546 were we've been following this field

NOTE Confidence: 0.820125292

00:27:10.613 --> 00:27:12.839 for awhile and we've known about the

NOTE Confidence: 0.820125292

00:27:12.839 --> 00:27:15.192 toxicity for the Protex if you try

NOTE Confidence: 0.820125292

00:27:15.192 --> 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 --> 00:27:22.777 a protech that was not a toxic.

NOTE Confidence: 0.820125292

00:27:22.780 --> 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 --> 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 --> 00:27:35.145 they show and that the switch sniff

NOTE Confidence: 0.820125292

00:27:35.145 --> 00:27:38.895 protect for a combined smart A4  
NOTE Confidence: 0.820125292

00:27:38.895 --> 00:27:42.455 and smart K2 are exquisitely potent  
NOTE Confidence: 0.820125292

00:27:42.455 --> 00:27:45.530 against AR sensitive prostate cancer.  
NOTE Confidence: 0.820125292

00:27:45.530 --> 00:27:47.910 And so we found that quite interesting.  
NOTE Confidence: 0.820125292

00:27:47.910 --> 00:27:50.381 We we have been following up we  
NOTE Confidence: 0.820125292

00:27:50.381 --> 00:27:52.385 had actually been working on  
NOTE Confidence: 0.820125292

00:27:52.385 --> 00:27:54.550 something similar and and have.  
NOTE Confidence: 0.820125292

00:27:54.550 --> 00:27:55.940 Come to a similar conclusion,  
NOTE Confidence: 0.820125292

00:27:55.940 --> 00:27:58.652 but extend it a little bit and just  
NOTE Confidence: 0.820125292

00:27:58.652 --> 00:28:01.249 point out that our collaborators Uchen  
NOTE Confidence: 0.820125292

00:28:01.249 --> 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 --> 00:28:08.998 I had a very nice paper in  
NOTE Confidence: 0.820125292

00:28:08.998 --> 00:28:10.849 science where they used a taxi,  
NOTE Confidence: 0.820125292

00:28:10.850 --> 00:28:12.640 so an epigenetic approach to  
NOTE Confidence: 0.820125292

00:28:12.640 --> 00:28:14.430 classify prostate cancer and I

NOTE Confidence: 0.820125292

00:28:14.497 --> 00:28:16.315 won't go into all the details,

NOTE Confidence: 0.820125292

00:28:16.320 --> 00:28:19.014 but against essentially in addition to

NOTE Confidence: 0.820125292

00:28:19.014 --> 00:28:21.340 AR sensitive advanced prostate cancer,

NOTE Confidence: 0.820125292

00:28:21.340 --> 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 --> 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 --> 00:28:29.830 classification for these advanced

NOTE Confidence: 0.820125292

00:28:29.830 --> 00:28:32.188 cancers more than just air negative,

NOTE Confidence: 0.820125292

00:28:32.190 --> 00:28:34.206 but air negative could be stem like it

NOTE Confidence: 0.820125292

00:28:34.206 --> 00:28:36.480 could be when singling or neuroendocrine.

NOTE Confidence: 0.820125292

00:28:36.480 --> 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 --> 00:28:42.260 So when we applied this classification

NOTE Confidence: 0.82381292125

00:28:42.260 --> 00:28:45.795 and used a protect that we had

NOTE Confidence: 0.82381292125

00:28:45.795 --> 00:28:47.915 acquired in collaboration with  
NOTE Confidence: 0.82381292125

00:28:47.915 --> 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 --> 00:28:55.624 we were also able to demonstrate.  
NOTE Confidence: 0.82381292125

00:28:55.630 --> 00:28:58.100 Exquisite sensitivity to air positive,  
NOTE Confidence: 0.82381292125

00:28:58.100 --> 00:29:01.036 but also to some of the other subclasses,  
NOTE Confidence: 0.82381292125

00:29:01.040 --> 00:29:03.260 so extending it beyond air sensitivity.  
NOTE Confidence: 0.82381292125

00:29:03.260 --> 00:29:06.852 So we think that these are very useful  
NOTE Confidence: 0.82381292125

00:29:06.852 --> 00:29:09.112 approaches of unfortunately that toxicity  
NOTE Confidence: 0.82381292125

00:29:09.112 --> 00:29:12.340 at least in our hands is very high.  
NOTE Confidence: 0.82381292125

00:29:12.340 --> 00:29:14.986 And so I think the strategy now is really  
NOTE Confidence: 0.82381292125

00:29:14.986 --> 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 --> 00:29:21.494 but for prostate,  
NOTE Confidence: 0.82381292125

00:29:21.500 --> 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 --> 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 --> 00:29:29.867 part of the presentation,

NOTE Confidence: 0.82381292125

00:29:29.870 --> 00:29:31.662 I wanted to just give you sort

NOTE Confidence: 0.82381292125

00:29:31.662 --> 00:29:33.381 of the landscape of what's going

NOTE Confidence: 0.82381292125

00:29:33.381 --> 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 --> 00:29:40.590 there's genomic and epigenetic players,

NOTE Confidence: 0.82381292125

00:29:40.590 --> 00:29:43.842 which I I mention are B and P53

NOTE Confidence: 0.82381292125

00:29:43.842 --> 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 --> 00:29:53.054 And then there's a very interesting stories

NOTE Confidence: 0.82381292125

00:29:53.054 --> 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 --> 00:29:59.298 I'll talk about rest which is an  
NOTE Confidence: 0.82381292125

00:29:59.298 --> 00:30:01.020 inhibitor of neural differentiation.  
NOTE Confidence: 0.82381292125

00:30:01.020 --> 00:30:02.940 I'll talk about that in the second part.  
NOTE Confidence: 0.82381292125

00:30:02.940 --> 00:30:05.180 And then I think that this is  
NOTE Confidence: 0.82381292125

00:30:05.180 --> 00:30:07.637 now emerging where based on these  
NOTE Confidence: 0.82381292125

00:30:07.637 --> 00:30:09.533 different alterations there may  
NOTE Confidence: 0.82381292125

00:30:09.533 --> 00:30:10.955 be different subclasses.  
NOTE Confidence: 0.82381292125

00:30:10.960 --> 00:30:12.298 So I just want to highlight,  
NOTE Confidence: 0.82381292125

00:30:12.300 --> 00:30:14.183 we've modified a little bit of review  
NOTE Confidence: 0.82381292125

00:30:14.183 --> 00:30:16.695 that we had a few years ago where I think.  
NOTE Confidence: 0.82381292125

00:30:16.700 --> 00:30:18.852 Microenvironment plays an important  
NOTE Confidence: 0.82381292125

00:30:18.852 --> 00:30:21.542 role and there are different  
NOTE Confidence: 0.82381292125

00:30:21.542 --> 00:30:23.270 pathways that are taken.  
NOTE Confidence: 0.82381292125

00:30:23.270 --> 00:30:25.910 Are they unidirectional, are they reversible?  
NOTE Confidence: 0.82381292125

00:30:25.910 --> 00:30:28.046 I think that's going to be a very

NOTE Confidence: 0.82381292125

00:30:28.046 --> 00:30:28.910 important translational issue.

NOTE Confidence: 0.82381292125

00:30:28.910 --> 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 --> 00:30:35.438 point where people will best respond

NOTE Confidence: 0.82381292125

00:30:35.438 --> 00:30:37.604 to novel therapies will be important.

NOTE Confidence: 0.82381292125

00:30:37.610 --> 00:30:38.534 So that's one.

NOTE Confidence: 0.82381292125

00:30:38.534 --> 00:30:40.690 Thing I wanted to tell you about

NOTE Confidence: 0.82381292125

00:30:40.765 --> 00:30:42.830 this morning and now I want to

NOTE Confidence: 0.82381292125

00:30:42.830 --> 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 --> 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 --> 00:30:57.240 listening and he's a bike rider,

NOTE Confidence: 0.82381292125

00:30:57.240 --> 00:30:59.832 but when you are biking and you see  
NOTE Confidence: 0.82381292125

00:30:59.832 --> 00:31:02.038 that there's a slope of 27 degrees,  
NOTE Confidence: 0.82381292125

00:31:02.040 --> 00:31:03.087 that's really steep.  
NOTE Confidence: 0.82381292125

00:31:03.087 --> 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 --> 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 --> 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 --> 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 --> 00:31:23.750 but I'm not there yet.  
NOTE Confidence: 0.82381292125

00:31:23.750 --> 00:31:26.977 But so I I think in our lab we'd like to



NOTE Confidence: 0.82381292125  
00:31:26.977 --> 00:31:29.889 take our challenges and when Anka Outback,  
NOTE Confidence: 0.82381292125  
00:31:29.890 --> 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 --> 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 --> 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 --> 00:31:47.739 this was really a good use of her time.  
NOTE Confidence: 0.772385457142857  
00:31:47.740 --> 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 --> 00:31:55.565 So I learned a lot and I'm going  
NOTE Confidence: 0.772385457142857

00:31:55.565 --> 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 --> 00:32:01.540 I think it's a potentially it's  
NOTE Confidence: 0.772385457142857

00:32:01.540 --> 00:32:04.103 exciting new area for us and helping  
NOTE Confidence: 0.772385457142857

00:32:04.103 --> 00:32:06.798 me with my process of education was  
NOTE Confidence: 0.772385457142857

00:32:06.798 --> 00:32:08.770 Rahul Canadia who's close by so he's  
NOTE Confidence: 0.772385457142857

00:32:08.770 --> 00:32:11.059 up just up the road at UConn and his  
NOTE Confidence: 0.772385457142857

00:32:11.059 --> 00:32:13.000 post dot Kyle Drake who very helpful  
NOTE Confidence: 0.772385457142857

00:32:13.000 --> 00:32:15.022 and this is also a collaboration  
NOTE Confidence: 0.772385457142857

00:32:15.022 --> 00:32:17.196 with Mark Gerson's lab here at Yale.  
NOTE Confidence: 0.772385457142857

00:32:17.196 --> 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 --> 00:32:21.217 So what I did know about splicing  
NOTE Confidence: 0.772385457142857

00:32:21.217 --> 00:32:23.367 was I knew from Gunner Rich's group.  
NOTE Confidence: 0.772385457142857

00:32:23.370 --> 00:32:25.740 The TCGA that splicing is is  
NOTE Confidence: 0.772385457142857

00:32:25.740 --> 00:32:27.773 occurring very often in cancer

NOTE Confidence: 0.772385457142857  
00:32:27.773 --> 00:32:30.363 that it can lead to NEO epitope.  
NOTE Confidence: 0.772385457142857  
00:32:30.370 --> 00:32:33.130 So I was more familiar with aberrant splicing  
NOTE Confidence: 0.772385457142857  
00:32:33.130 --> 00:32:36.348 in the context of potentially immunotherapy.  
NOTE Confidence: 0.772385457142857  
00:32:36.350 --> 00:32:39.260 What I was also aware is that the IT plays  
NOTE Confidence: 0.772385457142857  
00:32:39.335 --> 00:32:42.389 initially important role in the regulations.  
NOTE Confidence: 0.772385457142857  
00:32:42.390 --> 00:32:44.273 So this is a hallmark like figure  
NOTE Confidence: 0.772385457142857  
00:32:44.273 --> 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 --> 00:32:53.965 Rahul and others.  
NOTE Confidence: 0.772385457142857  
00:32:53.965 --> 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 --> 00:33:01.775 But in order to do that you have  
NOTE Confidence: 0.772385457142857  
00:33:01.775 --> 00:33:04.106 to take the exons and somehow the  
NOTE Confidence: 0.772385457142857

00:33:04.106 --> 00:33:06.107 introns have to be spliced out to  
NOTE Confidence: 0.772385457142857

00:33:06.107 --> 00:33:08.552 get to go from a preeminent M RNA  
NOTE Confidence: 0.772385457142857

00:33:08.552 --> 00:33:11.640 to an MRA that can be translated.  
NOTE Confidence: 0.772385457142857

00:33:11.640 --> 00:33:13.880 And so the question is how does  
NOTE Confidence: 0.772385457142857

00:33:13.880 --> 00:33:14.840 that actually occur?  
NOTE Confidence: 0.772385457142857

00:33:14.840 --> 00:33:17.444 And I'm not expert but I have  
NOTE Confidence: 0.772385457142857

00:33:17.444 --> 00:33:20.241 learned that the vast majority of  
NOTE Confidence: 0.772385457142857

00:33:20.241 --> 00:33:23.439 introns are excised through the major  
NOTE Confidence: 0.772385457142857

00:33:23.439 --> 00:33:25.678 spliceosome which is U2 splices.  
NOTE Confidence: 0.772385457142857

00:33:25.680 --> 00:33:27.558 And in this place is home.  
NOTE Confidence: 0.772385457142857

00:33:27.560 --> 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 --> 00:33:35.259 both of the three prime and the five prime,  
NOTE Confidence: 0.772385457142857

00:33:35.260 --> 00:33:36.725 but also branching points that  
NOTE Confidence: 0.772385457142857

00:33:36.725 --> 00:33:38.560 allow for this placing to occur.  
NOTE Confidence: 0.772385457142857

00:33:38.560 --> 00:33:41.736 So that's the vast majority of all proteins.

NOTE Confidence: 0.772385457142857  
00:33:41.740 --> 00:33:42.636 And it turns out,  
NOTE Confidence: 0.772385457142857  
00:33:42.636 --> 00:33:44.596 and this is what Anka was interested in  
NOTE Confidence: 0.772385457142857  
00:33:44.596 --> 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 --> 00:33:49.704 That there's a minor spliceosome  
NOTE Confidence: 0.772385457142857  
00:33:49.704 --> 00:33:52.139 which recognizes introns that have  
NOTE Confidence: 0.772385457142857  
00:33:52.139 --> 00:33:54.139 a different consensus sequence.  
NOTE Confidence: 0.772385457142857  
00:33:54.140 --> 00:33:55.214 And it's also.  
NOTE Confidence: 0.772385457142857  
00:33:55.214 --> 00:33:57.874 Referred to as the U-12 splicer zone.  
NOTE Confidence: 0.772385457142857  
00:33:57.874 --> 00:34:00.730 And so this is something that's really  
NOTE Confidence: 0.772385457142857  
00:34:00.809 --> 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 --> 00:34:06.814 what it we think it does or what  
NOTE Confidence: 0.772385457142857  
00:34:06.814 --> 00:34:08.004 it's it's believed to do.  
NOTE Confidence: 0.772385457142857  
00:34:08.010 --> 00:34:10.929 But it's very important in cutting out  
NOTE Confidence: 0.772385457142857

00:34:10.929 --> 00:34:13.573 minor introns that make that are part  
NOTE Confidence: 0.772385457142857

00:34:13.573 --> 00:34:16.649 of of genes that also have major introns.  
NOTE Confidence: 0.772385457142857

00:34:16.650 --> 00:34:18.186 So I'll show you what that  
NOTE Confidence: 0.772385457142857

00:34:18.186 --> 00:34:19.790 what that means in a moment.  
NOTE Confidence: 0.772385457142857

00:34:19.790 --> 00:34:22.130 So the idea is that in a typical gene that  
NOTE Confidence: 0.854723949090909

00:34:22.191 --> 00:34:23.799 has a minor intron which we're  
NOTE Confidence: 0.854723949090909

00:34:23.799 --> 00:34:25.429 going to refer to as minor.  
NOTE Confidence: 0.854723949090909

00:34:25.430 --> 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 --> 00:34:32.760 usually not more than one,  
NOTE Confidence: 0.854723949090909

00:34:32.760 --> 00:34:35.004 and that it requires a specific  
NOTE Confidence: 0.854723949090909

00:34:35.004 --> 00:34:37.778 machinery to cut this minor intron out.  
NOTE Confidence: 0.854723949090909

00:34:37.780 --> 00:34:40.606 Now I just will focus for most of the  
NOTE Confidence: 0.854723949090909

00:34:40.606 --> 00:34:43.066 presentation on one element of the minor  
NOTE Confidence: 0.854723949090909

00:34:43.066 --> 00:34:45.269 spliceosome which is called Unix attack,  
NOTE Confidence: 0.854723949090909

00:34:45.270 --> 00:34:47.958 which is one of the catalytic components

NOTE Confidence: 0.854723949090909

00:34:47.958 --> 00:34:50.773 of the minor spliceosome and that

NOTE Confidence: 0.854723949090909

00:34:50.773 --> 00:34:53.418 in homeostasis believed that under

NOTE Confidence: 0.854723949090909

00:34:53.418 --> 00:34:55.629 stress situations the conditions are.

NOTE Confidence: 0.854723949090909

00:34:55.629 --> 00:34:57.927 Such that that you six attack

NOTE Confidence: 0.854723949090909

00:34:57.927 --> 00:35:00.647 is is not degraded and it allows

NOTE Confidence: 0.854723949090909

00:35:00.647 --> 00:35:02.670 for minor splicing to occur.

NOTE Confidence: 0.854723949090909

00:35:02.670 --> 00:35:04.470 So whatever this gene is,

NOTE Confidence: 0.854723949090909

00:35:04.470 --> 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 --> 00:35:11.437 occurs and allows for the excision

NOTE Confidence: 0.854723949090909

00:35:11.437 --> 00:35:13.925 of this minor intron M RNA to be

NOTE Confidence: 0.854723949090909

00:35:13.999 --> 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 --> 00:35:20.390 whatever that protein will be.

NOTE Confidence: 0.854723949090909

00:35:20.390 --> 00:35:21.730 So that's an important component.

NOTE Confidence: 0.854723949090909

00:35:21.730 --> 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 --> 00:35:30.012 is not only in humans,  
NOTE Confidence: 0.76776221

00:35:30.020 --> 00:35:33.940 but also throughout the evolution.  
NOTE Confidence: 0.76776221

00:35:33.940 --> 00:35:36.706 My inner splicing has been maintained  
NOTE Confidence: 0.76776221

00:35:36.706 --> 00:35:39.390 and there's some interesting exceptions.  
NOTE Confidence: 0.76776221

00:35:39.390 --> 00:35:43.536 The main role of minor splicing.  
NOTE Confidence: 0.76776221

00:35:43.540 --> 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 --> 00:35:50.520 really an expert in neural development.  
NOTE Confidence: 0.76776221

00:35:50.520 --> 00:35:53.310 And so in patients who have  
NOTE Confidence: 0.76776221

00:35:53.310 --> 00:35:55.170 germline alterations or other  
NOTE Confidence: 0.76776221

00:35:55.252 --> 00:35:57.700 alterations in minor splicing,  
NOTE Confidence: 0.76776221

00:35:57.700 --> 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 --> 00:36:04.442 described or attributed to



NOTE Confidence: 0.76776221

00:36:04.442 --> 00:36:06.754 errors in minor splicing.

NOTE Confidence: 0.76776221

00:36:06.760 --> 00:36:07.614 For cancer,

NOTE Confidence: 0.76776221

00:36:07.614 --> 00:36:10.176 there's only two really known diseases,

NOTE Confidence: 0.76776221

00:36:10.180 --> 00:36:12.215 so put Sieger and myelodysplastic

NOTE Confidence: 0.76776221

00:36:12.215 --> 00:36:13.436 syndrome that are.

NOTE Confidence: 0.76776221

00:36:13.440 --> 00:36:15.600 Associated with minor splicing alterations

NOTE Confidence: 0.76776221

00:36:15.600 --> 00:36:19.232 and in total in Toto they're around 750,

NOTE Confidence: 0.76776221

00:36:19.232 --> 00:36:22.688 maybe 800 genes that have a minor intron,

NOTE Confidence: 0.76776221

00:36:22.690 --> 00:36:26.227 which we can refer to as minor intron genes.

NOTE Confidence: 0.76776221

00:36:26.230 --> 00:36:28.502 So Anka asked some questions that I think

NOTE Confidence: 0.76776221

00:36:28.502 --> 00:36:30.590 are are pretty straightforward questions to

NOTE Confidence: 0.76776221

00:36:30.590 --> 00:36:33.769 ask in the in the beginning of this project.

NOTE Confidence: 0.76776221

00:36:33.770 --> 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 --> 00:36:38.789 splicing alterations in cancer,

NOTE Confidence: 0.76776221

00:36:38.790 --> 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 --> 00:36:47.783 So is this something that you see a more  
NOTE Confidence: 0.76776221

00:36:47.783 --> 00:36:49.919 so in advanced or resistant disease?  
NOTE Confidence: 0.76776221

00:36:49.920 --> 00:36:53.056 Is this an active functionally active event?  
NOTE Confidence: 0.76776221

00:36:53.060 --> 00:36:55.232 And that would be very important  
NOTE Confidence: 0.76776221

00:36:55.232 --> 00:36:57.420 if we're going to attribute this  
NOTE Confidence: 0.76776221

00:36:57.420 --> 00:36:59.504 as a key causative role or playing  
NOTE Confidence: 0.76776221

00:36:59.504 --> 00:37:01.659 a part in the cause of cancer  
NOTE Confidence: 0.76776221

00:37:01.659 --> 00:37:03.057 progression or resistance.  
NOTE Confidence: 0.76776221

00:37:03.060 --> 00:37:04.789 And is there what happens if you  
NOTE Confidence: 0.76776221

00:37:04.789 --> 00:37:06.613 inhibit this and what do you can  
NOTE Confidence: 0.76776221

00:37:06.613 --> 00:37:08.155 you reverse some of these features?  
NOTE Confidence: 0.76776221

00:37:08.160 --> 00:37:09.483 And so I'll show you some of  
NOTE Confidence: 0.76776221

00:37:09.483 --> 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 --> 00:37:12.410 as I mentioned this is

NOTE Confidence: 0.76776221

00:37:12.410 --> 00:37:14.008 a work in progress but.

NOTE Confidence: 0.76776221

00:37:14.010 --> 00:37:16.908 But we do have a first paper in revision,

NOTE Confidence: 0.76776221

00:37:16.910 --> 00:37:18.450 which seems like it's been a revision

NOTE Confidence: 0.76776221

00:37:18.450 --> 00:37:19.968 for I think almost a year now,

NOTE Confidence: 0.76776221

00:37:19.970 --> 00:37:21.530 but hopefully we're getting

NOTE Confidence: 0.76776221

00:37:21.530 --> 00:37:23.090 closer to that point.

NOTE Confidence: 0.76776221

00:37:23.090 --> 00:37:25.988 And so first study was in silico.

NOTE Confidence: 0.76776221

00:37:25.990 --> 00:37:30.406 So one of our collaborators for this

NOTE Confidence: 0.76776221

00:37:30.406 --> 00:37:32.998 project looked at computationally

NOTE Confidence: 0.76776221

00:37:32.998 --> 00:37:35.590 at protein protein interactions,

NOTE Confidence: 0.76776221

00:37:35.590 --> 00:37:38.404 taking 26 of the most well described

NOTE Confidence: 0.76776221

00:37:38.404 --> 00:37:40.826 prostate cancer genes and ask the

NOTE Confidence: 0.76776221

00:37:40.826 --> 00:37:43.112 question what is the direct protein

NOTE Confidence: 0.76776221

00:37:43.112 --> 00:37:45.580 protein interaction with these minor?  
NOTE Confidence: 0.76776221

00:37:45.580 --> 00:37:47.482 And try and containing genes and  
NOTE Confidence: 0.76776221

00:37:47.482 --> 00:37:50.414 as you can see on the right some  
NOTE Confidence: 0.76776221

00:37:50.414 --> 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 --> 00:37:58.595 that are very much associated with  
NOTE Confidence: 0.76776221

00:37:58.595 --> 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 --> 00:38:07.820 interactions with minor intron.  
NOTE Confidence: 0.76776221

00:38:07.820 --> 00:38:08.752 Containing genes.  
NOTE Confidence: 0.76776221

00:38:08.752 --> 00:38:12.480 So that's sort of a first interesting hint.  
NOTE Confidence: 0.76776221

00:38:12.480 --> 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 --> 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 --> 00:38:22.454 I mentioned that it's a catalytic component.

NOTE Confidence: 0.76776221

00:38:22.460 --> 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 --> 00:38:27.495 somehow the machinery comes together

NOTE Confidence: 0.76776221

00:38:27.495 --> 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 --> 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 --> 00:38:39.104 of this process where it's

NOTE Confidence: 0.76776221

00:38:39.104 --> 00:38:40.878 really like the last step.

NOTE Confidence: 0.76776221

00:38:40.880 --> 00:38:42.680 So it has to come together with you.

NOTE Confidence: 0.8430547833333333

00:38:42.680 --> 00:38:44.815 Four attack and this catalytic

NOTE Confidence: 0.8430547833333333

00:38:44.815 --> 00:38:47.527 subunit now cuts out the intron

NOTE Confidence: 0.8430547833333333

00:38:47.527 --> 00:38:50.467 and that's why it's probably very

NOTE Confidence: 0.8430547833333333

00:38:50.467 --> 00:38:52.950 carefully regulated in homeostasis.

NOTE Confidence: 0.8430547833333333

00:38:52.950 --> 00:38:54.372 So that's the reason why we're  
NOTE Confidence: 0.8430547833333333

00:38:54.372 --> 00:38:55.710 focusing on you six attack.  
NOTE Confidence: 0.8430547833333333

00:38:55.710 --> 00:38:56.774 And the idea is,  
NOTE Confidence: 0.8430547833333333

00:38:56.774 --> 00:38:58.681 as I mentioned that in stress we  
NOTE Confidence: 0.8430547833333333

00:38:58.681 --> 00:39:00.459 think that you six attack is used  
NOTE Confidence: 0.8430547833333333

00:39:00.459 --> 00:39:02.474 to help remove the minor intron for  
NOTE Confidence: 0.8430547833333333

00:39:02.474 --> 00:39:04.614 a subset of genes that are probably  
NOTE Confidence: 0.8430547833333333

00:39:04.614 --> 00:39:06.349 important in responding to stress.  
NOTE Confidence: 0.8430547833333333

00:39:06.350 --> 00:39:07.415 That's our hypothesis.  
NOTE Confidence: 0.8430547833333333

00:39:07.415 --> 00:39:09.545 So what happens if you look  
NOTE Confidence: 0.8430547833333333

00:39:09.545 --> 00:39:11.050 in prostate cancer,  
NOTE Confidence: 0.8430547833333333

00:39:11.050 --> 00:39:12.954 this is probably also true for other.  
NOTE Confidence: 0.8430547833333333

00:39:12.960 --> 00:39:15.242 This is, but we focus on prostate  
NOTE Confidence: 0.8430547833333333

00:39:15.242 --> 00:39:17.249 cancer using some of the common  
NOTE Confidence: 0.8430547833333333

00:39:17.249 --> 00:39:18.849 cell lines and patient Dr.  
NOTE Confidence: 0.8430547833333333

00:39:18.850 --> 00:39:20.342 Organoids and arranging them

NOTE Confidence: 0.8430547833333333  
00:39:20.342 --> 00:39:22.580 going from benign all the way  
NOTE Confidence: 0.8430547833333333  
00:39:22.654 --> 00:39:24.328 to neuroendocrine disease.  
NOTE Confidence: 0.8430547833333333  
00:39:24.330 --> 00:39:26.406 So trying to cover the spectrum,  
NOTE Confidence: 0.8430547833333333  
00:39:26.410 --> 00:39:29.810 we see an increase in U-6 attack expression.  
NOTE Confidence: 0.8430547833333333  
00:39:29.810 --> 00:39:31.304 As I mentioned there are other  
NOTE Confidence: 0.8430547833333333  
00:39:31.304 --> 00:39:32.910 components of the minor spliceosome.  
NOTE Confidence: 0.8430547833333333  
00:39:32.910 --> 00:39:36.170 They also show similar overexpression.  
NOTE Confidence: 0.8430547833333333  
00:39:36.170 --> 00:39:38.648 We were able to then show this  
NOTE Confidence: 0.8430547833333333  
00:39:38.648 --> 00:39:41.086 insight to using RNA ISH and we're  
NOTE Confidence: 0.8430547833333333  
00:39:41.086 --> 00:39:43.410 able to show that you can see.  
NOTE Confidence: 0.8430547833333333  
00:39:43.410 --> 00:39:46.938 Higher expression of these of the U-6 attack,  
NOTE Confidence: 0.8430547833333333  
00:39:46.940 --> 00:39:49.880 but also other components as you  
NOTE Confidence: 0.8430547833333333  
00:39:49.880 --> 00:39:52.620 look at primary prostate cancers,  
NOTE Confidence: 0.8430547833333333  
00:39:52.620 --> 00:39:55.356 but also higher in primary prostate  
NOTE Confidence: 0.8430547833333333  
00:39:55.356 --> 00:39:58.327 cancers that go on to metastasize  
NOTE Confidence: 0.8430547833333333

00:39:58.327 --> 00:40:01.495 and then in metastases even higher.  
NOTE Confidence: 0.8430547833333333

00:40:01.500 --> 00:40:02.970 What's important is,  
NOTE Confidence: 0.8430547833333333

00:40:02.970 --> 00:40:05.910 is this actually functionally doing anything?  
NOTE Confidence: 0.8430547833333333

00:40:05.910 --> 00:40:08.502 And So what Anka did was she used  
NOTE Confidence: 0.8430547833333333

00:40:08.502 --> 00:40:10.824 two vector systems that are designed  
NOTE Confidence: 0.8430547833333333

00:40:10.824 --> 00:40:14.015 so they have either 1 intron and the  
NOTE Confidence: 0.8430547833333333

00:40:14.015 --> 00:40:16.903 intron is either a minor or major intron.  
NOTE Confidence: 0.8430547833333333

00:40:16.910 --> 00:40:18.200 And with luciferous,  
NOTE Confidence: 0.8430547833333333

00:40:18.200 --> 00:40:21.210 with this luciferous assay she's able to  
NOTE Confidence: 0.8430547833333333

00:40:21.281 --> 00:40:24.026 demonstrate expression if it's working,  
NOTE Confidence: 0.8430547833333333

00:40:24.030 --> 00:40:28.314 so if it's working as a minor  
NOTE Confidence: 0.8430547833333333

00:40:28.314 --> 00:40:29.538 intron excising.  
NOTE Confidence: 0.8430547833333333

00:40:29.540 --> 00:40:32.570 Machinery or is there a major  
NOTE Confidence: 0.8430547833333333

00:40:32.570 --> 00:40:34.590 intron excising machinery working?  
NOTE Confidence: 0.8430547833333333

00:40:34.590 --> 00:40:37.215 And I think importantly when she looked  
NOTE Confidence: 0.8430547833333333

00:40:37.215 --> 00:40:40.590 at the major insurance splicing activity,



NOTE Confidence: 0.8430547833333333

00:40:40.590 --> 00:40:42.582 it remained fairly similar

NOTE Confidence: 0.8430547833333333

00:40:42.582 --> 00:40:45.072 throughout all the different types

NOTE Confidence: 0.8430547833333333

00:40:45.072 --> 00:40:48.067 of of model systems she looked at,

NOTE Confidence: 0.8430547833333333

00:40:48.070 --> 00:40:50.206 but only highly expressed for minor

NOTE Confidence: 0.8430547833333333

00:40:50.206 --> 00:40:52.709 entrance splicing in the advanced cancers,

NOTE Confidence: 0.8430547833333333

00:40:52.710 --> 00:40:54.350 which is intriguing suggesting

NOTE Confidence: 0.8430547833333333

00:40:54.350 --> 00:40:56.400 that this activity is increased.

NOTE Confidence: 0.8430547833333333

00:40:56.400 --> 00:40:58.269 And this is a very simple vector

NOTE Confidence: 0.8430547833333333

00:40:58.269 --> 00:40:59.999 system and we've since developed.

NOTE Confidence: 0.8430547833333333

00:41:00.000 --> 00:41:02.110 More complex vector systems that

NOTE Confidence: 0.8430547833333333

00:41:02.110 --> 00:41:04.220 I could tell you about.

NOTE Confidence: 0.8430547833333333

00:41:04.220 --> 00:41:05.360 At the transcript level,

NOTE Confidence: 0.8430547833333333

00:41:05.360 --> 00:41:07.984 we see and these are just some of the

NOTE Confidence: 0.8430547833333333

00:41:07.984 --> 00:41:09.979 the the cell lines in prostate cancer,

NOTE Confidence: 0.8430547833333333

00:41:09.980 --> 00:41:13.276 we see very high expression of U-6 attack

NOTE Confidence: 0.8430547833333333

00:41:13.276 --> 00:41:16.210 but also other minor splicing components,  
NOTE Confidence: 0.8430547833333333

00:41:16.210 --> 00:41:18.060 but then also the MIGS.  
NOTE Confidence: 0.8430547833333333

00:41:18.060 --> 00:41:20.220 So the minor intron containing  
NOTE Confidence: 0.8430547833333333

00:41:20.220 --> 00:41:22.380 genes are more highly expressed.  
NOTE Confidence: 0.8430547833333333

00:41:22.380 --> 00:41:25.863 So as we might expect now Mark Burstein's  
NOTE Confidence: 0.8430547833333333

00:41:25.863 --> 00:41:28.847 lab helped us with I think a important  
NOTE Confidence: 0.8430547833333333

00:41:28.847 --> 00:41:31.489 part which is also extending this to  
NOTE Confidence: 0.8430547833333333

00:41:31.489 --> 00:41:34.340 other cancers and the question really is?  
NOTE Confidence: 0.8430547833333333

00:41:34.340 --> 00:41:37.625 Are these Migs that we see that are altered  
NOTE Confidence: 0.8430547833333333

00:41:37.625 --> 00:41:41.007 or alternatively expressed in in cancer,  
NOTE Confidence: 0.8430547833333333

00:41:41.010 --> 00:41:44.058 are they potentially very useful in  
NOTE Confidence: 0.8430547833333333

00:41:44.058 --> 00:41:46.090 distinguishing different cancer types.  
NOTE Confidence: 0.8430547833333333

00:41:46.090 --> 00:41:47.800 So we would hypothesize that the  
NOTE Confidence: 0.8430547833333333

00:41:47.800 --> 00:41:49.301 makes are expressed but probably  
NOTE Confidence: 0.8430547833333333

00:41:49.301 --> 00:41:50.851 different in different tissue types  
NOTE Confidence: 0.8430547833333333

00:41:50.851 --> 00:41:52.909 just like we see in progression.

NOTE Confidence: 0.8430547833333333  
00:41:52.910 --> 00:41:55.241 And so in Mark's group is able  
NOTE Confidence: 0.8430547833333333  
00:41:55.241 --> 00:41:57.195 to create these silhouette plot  
NOTE Confidence: 0.8430547833333333  
00:41:57.195 --> 00:41:59.841 here looking at 23 different tumor  
NOTE Confidence: 0.8430547833333333  
00:41:59.841 --> 00:42:02.218 types from a pan cancer analysis  
NOTE Confidence: 0.8430547833333333  
00:42:02.218 --> 00:42:04.342 and they were able to show.  
NOTE Confidence: 0.90923169  
00:42:04.350 --> 00:42:07.297 That in this experiment where you go  
NOTE Confidence: 0.90923169  
00:42:07.297 --> 00:42:10.485 from 0% MIGS and then so there's a  
NOTE Confidence: 0.90923169  
00:42:10.485 --> 00:42:12.822 dilution experiment all the way to 100%.  
NOTE Confidence: 0.90923169  
00:42:12.822 --> 00:42:15.076 So this is done by doing many,  
NOTE Confidence: 0.90923169  
00:42:15.080 --> 00:42:15.960 many iterations.  
NOTE Confidence: 0.90923169  
00:42:15.960 --> 00:42:19.040 You can demonstrate that the best model  
NOTE Confidence: 0.90923169  
00:42:19.040 --> 00:42:20.920 is a model where you include the mix.  
NOTE Confidence: 0.90923169  
00:42:20.920 --> 00:42:23.744 So it shows that they have a very  
NOTE Confidence: 0.90923169  
00:42:23.744 --> 00:42:25.558 strong ability to distinguish  
NOTE Confidence: 0.90923169  
00:42:25.558 --> 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 --> 00:42:29.837 when we ask the question,  
NOTE Confidence: 0.90923169

00:42:29.840 --> 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 --> 00:42:36.786 Database versus localized prostate  
NOTE Confidence: 0.90923169

00:42:36.786 --> 00:42:39.806 cancer or advanced prostate cancer.  
NOTE Confidence: 0.90923169

00:42:39.810 --> 00:42:42.879 We see that the MIG genes do a very  
NOTE Confidence: 0.90923169

00:42:42.879 --> 00:42:45.213 nice job without in any selection  
NOTE Confidence: 0.90923169

00:42:45.213 --> 00:42:48.045 of a subclass of of the Migs to  
NOTE Confidence: 0.90923169

00:42:48.045 --> 00:42:50.097 distinguish the different groups.  
NOTE Confidence: 0.90923169

00:42:50.100 --> 00:42:51.540 I think it's important because  
NOTE Confidence: 0.90923169

00:42:51.540 --> 00:42:53.355 it suggests that I think that  
NOTE Confidence: 0.90923169

00:42:53.355 --> 00:42:54.970 these genes for whatever reason,  
NOTE Confidence: 0.90923169

00:42:54.970 --> 00:42:55.894 for evolutionary reasons,  
NOTE Confidence: 0.90923169

00:42:55.894 --> 00:42:57.126 are important and stress,  
NOTE Confidence: 0.90923169

00:42:57.130 --> 00:43:00.244 but they also are probably reactivated

NOTE Confidence: 0.90923169

00:43:00.244 --> 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 --> 00:43:08.098 of the presentation is very important

NOTE Confidence: 0.90923169

00:43:08.098 --> 00:43:10.323 when we think about resistance,

NOTE Confidence: 0.90923169

00:43:10.330 --> 00:43:12.808 think about probably two types of resistance.

NOTE Confidence: 0.90923169

00:43:12.810 --> 00:43:15.162 One is still related to AR

NOTE Confidence: 0.90923169

00:43:15.162 --> 00:43:17.131 signaling active tumors and we

NOTE Confidence: 0.90923169

00:43:17.131 --> 00:43:19.413 have to find ways to attack them,

NOTE Confidence: 0.90923169

00:43:19.420 --> 00:43:22.030 but also AR negative tumors.

NOTE Confidence: 0.90923169

00:43:22.030 --> 00:43:23.615 And I mentioned that there

NOTE Confidence: 0.90923169

00:43:23.615 --> 00:43:24.883 are these four categories.

NOTE Confidence: 0.90923169

00:43:24.890 --> 00:43:28.140 So the question really is.

NOTE Confidence: 0.90923169

00:43:28.140 --> 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 --> 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 --> 00:43:47.792 that stimulates map sign kinase  
NOTE Confidence: 0.90923169

00:43:47.792 --> 00:43:50.612 signaling and ask them and also  
NOTE Confidence: 0.90923169

00:43:50.612 --> 00:43:53.710 myosin and was able to demonstrate  
NOTE Confidence: 0.90923169

00:43:53.710 --> 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 --> 00:44:01.997 You see only increased expression of of  
NOTE Confidence: 0.90923169

00:44:01.997 --> 00:44:06.029 minor splicing in the neuroendocrine tumors,  
NOTE Confidence: 0.90923169

00:44:06.030 --> 00:44:07.060 which is sort of interesting,  
NOTE Confidence: 0.90923169

00:44:07.060 --> 00:44:10.456 not in the AR sensitive tumors  
NOTE Confidence: 0.90923169

00:44:10.460 --> 00:44:12.040 when she knocked it down,  
NOTE Confidence: 0.90923169

00:44:12.040 --> 00:44:13.140 it was the same thing.

NOTE Confidence: 0.90923169

00:44:13.140 --> 00:44:15.010 So I think that's important.

NOTE Confidence: 0.90923169

00:44:15.010 --> 00:44:18.188 And then in a separate study looking

NOTE Confidence: 0.90923169

00:44:18.188 --> 00:44:21.819 at the effect of androgen stimulation,

NOTE Confidence: 0.90923169

00:44:21.820 --> 00:44:23.902 she was able to demonstrate in

NOTE Confidence: 0.90923169

00:44:23.902 --> 00:44:25.290 different model systems whether

NOTE Confidence: 0.90923169

00:44:25.355 --> 00:44:26.933 it's a lincat cell line which

NOTE Confidence: 0.90923169

00:44:26.933 --> 00:44:28.610 is very angry and sensitive.

NOTE Confidence: 0.90923169

00:44:28.610 --> 00:44:31.578 Or a line cap cell line that

NOTE Confidence: 0.90923169

00:44:31.578 --> 00:44:32.850 over expresses AR.

NOTE Confidence: 0.90923169

00:44:32.850 --> 00:44:35.575 She's able to demonstrate that

NOTE Confidence: 0.90923169

00:44:35.575 --> 00:44:38.300 minor intron activity is increased

NOTE Confidence: 0.90923169

00:44:38.383 --> 00:44:41.047 when you increase AR and and

NOTE Confidence: 0.90923169

00:44:41.047 --> 00:44:43.330 can be modulated through that,

NOTE Confidence: 0.90923169

00:44:43.330 --> 00:44:45.530 but not major entrance splicing.

NOTE Confidence: 0.90923169

00:44:45.530 --> 00:44:50.532 So basically I'm trying to think about how a.

NOTE Confidence: 0.90923169

00:44:50.532 --> 00:44:53.184 ASICS attack could be stabilizer or  
NOTE Confidence: 0.90923169

00:44:53.184 --> 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 --> 00:45:03.964 framework of of how to think about  
NOTE Confidence: 0.90923169

00:45:03.964 --> 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 --> 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 --> 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 --> 00:45:18.849 do it in different way through air  
NOTE Confidence: 0.90923169

00:45:18.849 --> 00:45:20.973 signaling and we have more data.  
NOTE Confidence: 0.90923169

00:45:20.980 --> 00:45:22.072 That helps support this.  
NOTE Confidence: 0.90923169

00:45:22.072 --> 00:45:24.634 One thing that was nice is there are two  
NOTE Confidence: 0.90923169

00:45:24.634 --> 00:45:26.657 high impact papers that came out talking



NOTE Confidence: 0.847652321

00:45:26.715 --> 00:45:28.545 about a subclass of prostate cancer

NOTE Confidence: 0.847652321

00:45:28.545 --> 00:45:30.544 that is really driven by Jack stat.

NOTE Confidence: 0.847652321

00:45:30.544 --> 00:45:31.834 So this is quite interesting.

NOTE Confidence: 0.847652321

00:45:31.840 --> 00:45:34.605 And these are stem like tumors which

NOTE Confidence: 0.847652321

00:45:34.605 --> 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 --> 00:45:43.369 by a map sign map kinase signaling.

NOTE Confidence: 0.847652321

00:45:43.370 --> 00:45:47.194 So in just the last part I now I

NOTE Confidence: 0.847652321

00:45:47.194 --> 00:45:49.281 want to go into what happens if

NOTE Confidence: 0.847652321

00:45:49.281 --> 00:45:51.360 we try to target you 6 attacks.

NOTE Confidence: 0.847652321

00:45:51.360 --> 00:45:51.944 Specifically.

NOTE Confidence: 0.847652321

00:45:51.944 --> 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 --> 00:46:01.780 the ability to to exercise these

NOTE Confidence: 0.847652321

00:46:01.780 --> 00:46:03.930 introns that are minor introns.

NOTE Confidence: 0.847652321

00:46:03.930 --> 00:46:05.430 And in fact that's the case.  
NOTE Confidence: 0.847652321

00:46:05.430 --> 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 --> 00:46:17.418 she demonstrated using a a minor splicing  
NOTE Confidence: 0.847652321

00:46:17.418 --> 00:46:20.530 index which looks for misplacing.  
NOTE Confidence: 0.847652321

00:46:20.530 --> 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 --> 00:46:23.616 Out.  
NOTE Confidence: 0.847652321

00:46:23.616 --> 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 --> 00:46:30.580 model systems that if you knock out,  
NOTE Confidence: 0.847652321

00:46:30.580 --> 00:46:33.740 if you knock down your six pack it  
NOTE Confidence: 0.847652321

00:46:33.740 --> 00:46:36.437 functionally has the effect of of  
NOTE Confidence: 0.847652321

00:46:36.437 --> 00:46:38.722 not allowing these minor intron  
NOTE Confidence: 0.847652321

00:46:38.722 --> 00:46:41.628 containing genes to to excise out the  
NOTE Confidence: 0.847652321

00:46:41.628 --> 00:46:43.892 entrance for the experts in splicing.

NOTE Confidence: 0.847652321

00:46:43.892 --> 00:46:45.597 I won't go into that.

NOTE Confidence: 0.847652321

00:46:45.600 --> 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 --> 00:46:51.899 alterations seem to be the most common.

NOTE Confidence: 0.847652321

00:46:51.900 --> 00:46:53.540 But here you can actually.

NOTE Confidence: 0.847652321

00:46:53.540 --> 00:46:55.969 Determine the specific types of splice sites.

NOTE Confidence: 0.847652321

00:46:55.970 --> 00:46:57.150 So we have experts here,

NOTE Confidence: 0.847652321

00:46:57.150 --> 00:47:01.182 but I'm not an expert to talk about that.

NOTE Confidence: 0.847652321

00:47:01.190 --> 00:47:02.866 Anka performed transcriptomics and

NOTE Confidence: 0.847652321

00:47:02.866 --> 00:47:05.380 proteomics and in the context of

NOTE Confidence: 0.847652321

00:47:05.449 --> 00:47:07.435 knocking down you six attack the

NOTE Confidence: 0.847652321

00:47:07.435 --> 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 --> 00:47:16.015 goes in the to the view that this

NOTE Confidence: 0.847652321

00:47:16.015 --> 00:47:17.975 is going to be very context specific  
NOTE Confidence: 0.847652321

00:47:17.975 --> 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 themes that emerged  
NOTE Confidence: 0.847652321

00:47:22.028 --> 00:47:23.966 and I think the important theme  
NOTE Confidence: 0.847652321

00:47:23.966 --> 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 --> 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 --> 00:47:36.900 these different model systems,  
NOTE Confidence: 0.847652321

00:47:36.900 --> 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 --> 00:47:48.380 As well as DNA alterations,  
NOTE Confidence: 0.726276324

00:47:48.380 --> 00:47:51.369 came came out as being altered when  
NOTE Confidence: 0.726276324

00:47:51.369 --> 00:47:53.970 you knocked down you six attack.

NOTE Confidence: 0.726276324

00:47:53.970 --> 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 --> 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 --> 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 --> 00:48:09.512 an important role in cell cycle

NOTE Confidence: 0.726276324

00:48:09.512 --> 00:48:11.564 in a series of experiments where

NOTE Confidence: 0.726276324

00:48:11.633 --> 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 --> 00:48:21.434 castration resistant tumor that is still

NOTE Confidence: 0.726276324

00:48:21.434 --> 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 --> 00:48:29.560 see a decrease in in growth of tumor cells.

NOTE Confidence: 0.726276324

00:48:29.560 --> 00:48:31.800 We see no change when you look at

NOTE Confidence: 0.726276324

00:48:31.800 --> 00:48:33.536 either mouse fibroblasts or human  
NOTE Confidence: 0.726276324

00:48:33.536 --> 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 --> 00:48:39.752 point do we see preferential changes  
NOTE Confidence: 0.726276324

00:48:39.752 --> 00:48:44.003 occurring in a Co culture and we we we  
NOTE Confidence: 0.726276324

00:48:44.003 --> 00:48:47.034 actually see only the tumor cells are  
NOTE Confidence: 0.726276324

00:48:47.034 --> 00:48:50.317 affected by by you six attack knockdown.  
NOTE Confidence: 0.726276324

00:48:50.320 --> 00:48:52.680 This is probably the key  
NOTE Confidence: 0.726276324

00:48:52.680 --> 00:48:54.096 therapeutic translational slide.  
NOTE Confidence: 0.726276324

00:48:54.100 --> 00:48:56.050 Which is that in air sensitive  
NOTE Confidence: 0.726276324

00:48:56.050 --> 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 --> 00:49:03.082 basically the same result which is  
NOTE Confidence: 0.726276324

00:49:03.082 --> 00:49:05.230 a decrease in confluence of cells.  
NOTE Confidence: 0.726276324

00:49:05.230 --> 00:49:07.200 So this is using Incyte.  
NOTE Confidence: 0.726276324

00:49:07.200 --> 00:49:09.152 If you then go to cell lines that

NOTE Confidence: 0.726276324

00:49:09.152 --> 00:49:11.065 are AR resistant and there's just

NOTE Confidence: 0.726276324

00:49:11.065 --> 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 --> 00:49:19.860 or the antiandrogen therapy but

NOTE Confidence: 0.726276324

00:49:19.930 --> 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 --> 00:49:26.521 Is A is a promising first step

NOTE Confidence: 0.726276324

00:49:26.521 --> 00:49:29.123 for thinking about does this have

NOTE Confidence: 0.726276324

00:49:29.123 --> 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 --> 00:49:35.370 having therapeutic translation.

NOTE Confidence: 0.726276324

00:49:35.370 --> 00:49:38.100 We extended this to the Memorial Sloan

NOTE Confidence: 0.726276324

00:49:38.100 --> 00:49:40.049 Kettering and Cornell patient Dr.

NOTE Confidence: 0.726276324

00:49:40.050 --> 00:49:42.335 Organoids that represent a range  
NOTE Confidence: 0.726276324

00:49:42.335 --> 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 --> 00:49:51.350 effect that you can by knocking down  
NOTE Confidence: 0.726276324

00:49:51.350 --> 00:49:53.908 you six attack you can decrease.  
NOTE Confidence: 0.726276324

00:49:53.908 --> 00:49:56.460 Cell viability and confluence.  
NOTE Confidence: 0.726276324

00:49:56.460 --> 00:49:57.676 I'll skip the videos,  
NOTE Confidence: 0.726276324

00:49:57.676 --> 00:50:00.262 but we can also see this in benign  
NOTE Confidence: 0.726276324

00:50:00.262 --> 00:50:03.014 prostate cell lines that are that we have,  
NOTE Confidence: 0.726276324

00:50:03.020 --> 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 --> 00:50:13.648 the very last piece I just want to bring  
NOTE Confidence: 0.789957396

00:50:13.648 --> 00:50:16.294 up is a interesting concept and this  
NOTE Confidence: 0.789957396

00:50:16.294 --> 00:50:18.768 is something we call poison peptides.  
NOTE Confidence: 0.789957396

00:50:18.770 --> 00:50:20.354 Maybe somebody's used this in another



NOTE Confidence: 0.789957396

00:50:20.354 --> 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 --> 00:50:26.350 title is poison peptides.

NOTE Confidence: 0.789957396

00:50:26.350 --> 00:50:28.014 And the idea is,

NOTE Confidence: 0.789957396

00:50:28.014 --> 00:50:30.510 is that when the minor introns

NOTE Confidence: 0.789957396

00:50:30.601 --> 00:50:33.662 splicing occurs it it performs a

NOTE Confidence: 0.789957396

00:50:33.662 --> 00:50:35.827 protein that it potentially plays

NOTE Confidence: 0.789957396

00:50:35.827 --> 00:50:38.718 an important role in cell cycle.

NOTE Confidence: 0.789957396

00:50:38.720 --> 00:50:41.066 And help stabilize the cancer cells,

NOTE Confidence: 0.789957396

00:50:41.070 --> 00:50:43.390 but when it's not excised,

NOTE Confidence: 0.789957396

00:50:43.390 --> 00:50:45.736 the question is what what's happening

NOTE Confidence: 0.789957396

00:50:45.736 --> 00:50:47.824 with these message and is it,

NOTE Confidence: 0.789957396

00:50:47.824 --> 00:50:49.128 is it becoming just,

NOTE Confidence: 0.789957396

00:50:49.130 --> 00:50:50.975 is it just undergoing degradation

NOTE Confidence: 0.789957396

00:50:50.975 --> 00:50:53.605 or are there some sort of aberrant

NOTE Confidence: 0.789957396

00:50:53.605 --> 00:50:56.097 or other types of isoforms that are  
NOTE Confidence: 0.789957396

00:50:56.097 --> 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 --> 00:51:03.003 with which is related to rest.  
NOTE Confidence: 0.789957396

00:51:03.010 --> 00:51:05.754 So rest is a transcription factor plays  
NOTE Confidence: 0.789957396

00:51:05.754 --> 00:51:08.789 an important role in neural fate regulation.  
NOTE Confidence: 0.789957396

00:51:08.790 --> 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 --> 00:51:14.735 rest when rest expression is  
NOTE Confidence: 0.789957396

00:51:14.735 --> 00:51:16.990 present in in cancer types,  
NOTE Confidence: 0.789957396

00:51:16.990 --> 00:51:19.498 we know that it it prevents  
NOTE Confidence: 0.789957396

00:51:19.498 --> 00:51:20.334 neural differentiation.  
NOTE Confidence: 0.789957396

00:51:20.340 --> 00:51:21.436 And when it's down,  
NOTE Confidence: 0.789957396

00:51:21.436 --> 00:51:23.528 we expect that you may see neural  
NOTE Confidence: 0.789957396

00:51:23.528 --> 00:51:25.826 differentiation and this is in cancer.  
NOTE Confidence: 0.789957396

00:51:25.830 --> 00:51:28.056 We see this occurring quite often.

NOTE Confidence: 0.789957396

00:51:28.060 --> 00:51:31.462 There's also a isoform that's that's

NOTE Confidence: 0.789957396

00:51:31.462 --> 00:51:35.158 known but little known and that's called

NOTE Confidence: 0.789957396

00:51:35.158 --> 00:51:38.930 rest four and rest 4 forms a dimer.

NOTE Confidence: 0.789957396

00:51:38.930 --> 00:51:41.359 With rest one and prevents it from

NOTE Confidence: 0.789957396

00:51:41.359 --> 00:51:44.133 binding to DNA and therefore it

NOTE Confidence: 0.789957396

00:51:44.133 --> 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 --> 00:51:49.260 you do have neural differentiation

NOTE Confidence: 0.789957396

00:51:49.260 --> 00:51:51.347 and this is just showing in

NOTE Confidence: 0.789957396

00:51:51.347 --> 00:51:52.639 a slightly different way.

NOTE Confidence: 0.789957396

00:51:52.640 --> 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 --> 00:52:02.296 a small Exxon here that needs

NOTE Confidence: 0.789957396

00:52:02.296 --> 00:52:05.606 to be excised in order for you

NOTE Confidence: 0.789957396

00:52:05.606 --> 00:52:09.170 to go from rest 4 to rest one.

NOTE Confidence: 0.789957396

00:52:09.170 --> 00:52:11.162 So what I wanted to show you is  
NOTE Confidence: 0.789957396

00:52:11.162 --> 00:52:13.129 that then Anka asks the question,  
NOTE Confidence: 0.789957396

00:52:13.130 --> 00:52:15.560 well what does she see as far as rest  
NOTE Confidence: 0.789957396

00:52:15.560 --> 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 --> 00:52:22.249 this from our stand up cancer data,  
NOTE Confidence: 0.789957396

00:52:22.250 --> 00:52:24.415 but she sees higher expression  
NOTE Confidence: 0.789957396

00:52:24.415 --> 00:52:27.180 of risk for in these cases.  
NOTE Confidence: 0.789957396

00:52:27.180 --> 00:52:28.755 So that's something we had never looked  
NOTE Confidence: 0.789957396

00:52:28.755 --> 00:52:30.333 at because we never thought about  
NOTE Confidence: 0.789957396

00:52:30.333 --> 00:52:31.763 looking at the different isoforms.  
NOTE Confidence: 0.789957396

00:52:31.770 --> 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 --> 00:52:36.428 for in the different cell lines,  
NOTE Confidence: 0.789957396

00:52:36.430 --> 00:52:37.606 we also see the same thing.  
NOTE Confidence: 0.789957396

00:52:37.610 --> 00:52:39.510 So very low risk 4.

NOTE Confidence: 0.789957396

00:52:39.510 --> 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 --> 00:52:48.300 she increases rest rest expression.

NOTE Confidence: 0.789957396

00:52:48.300 --> 00:52:49.950 But I think what's really interesting

NOTE Confidence: 0.789957396

00:52:49.950 --> 00:52:51.896 is if you look at the protein

NOTE Confidence: 0.789957396

00:52:51.896 --> 00:52:53.744 level and you look at the different

NOTE Confidence: 0.789957396

00:52:53.802 --> 00:52:55.517 isoform she's able to demonstrate

NOTE Confidence: 0.789957396

00:52:55.517 --> 00:52:57.595 in neuroendocrine model said if you

NOTE Confidence: 0.789957396

00:52:57.595 --> 00:52:59.725 knocked down Unix attack and again

NOTE Confidence: 0.789957396

00:52:59.725 --> 00:53:02.354 this is not a perfect but it's a

NOTE Confidence: 0.789957396

00:53:02.354 --> 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 --> 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 --> 00:53:14.033 that we can think that in the normal

NOTE Confidence: 0.789957396

00:53:14.033 --> 00:53:16.197 state of these advanced prostate  
NOTE Confidence: 0.789957396

00:53:16.197 --> 00:53:18.557 cancers that are neuroendocrine,  
NOTE Confidence: 0.789957396

00:53:18.560 --> 00:53:20.714 they have high levels of rest  
NOTE Confidence: 0.789957396

00:53:20.714 --> 00:53:22.150 four which prevent arrest  
NOTE Confidence: 0.845042928888889

00:53:22.216 --> 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 --> 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 --> 00:53:32.054 But clearly other ways of modulating  
NOTE Confidence: 0.845042928888889

00:53:32.054 --> 00:53:34.285 rest could also lead to a situation  
NOTE Confidence: 0.845042928888889

00:53:34.285 --> 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 --> 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 --> 00:53:44.059 so Nice Lake that we like to go  
NOTE Confidence: 0.845042928888889

00:53:44.059 --> 00:53:46.404 hiking around and 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 --> 00:53:51.401 how there's a it's really a very

NOTE Confidence: 0.845042928888889

00:53:51.401 --> 00:53:53.301 small component of the spliceosome

NOTE Confidence: 0.845042928888889

00:53:53.301 --> 00:53:55.990 and that we think U-6 attack is

NOTE Confidence: 0.845042928888889

00:53:55.990 --> 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 --> 00:54:02.400 and potentially represents an

NOTE Confidence: 0.845042928888889

00:54:02.479 --> 00:54:05.007 important opportunity for therapy.

NOTE Confidence: 0.845042928888889

00:54:05.010 --> 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 --> 00:54:10.479 our great collaborators.

NOTE Confidence: 0.845042928888889

00:54:10.480 --> 00:54:11.880 So in addition to.

NOTE Confidence: 0.845042928888889

00:54:11.880 --> 00:54:13.980 Bronco with the Ruben Lab members

NOTE Confidence: 0.845042928888889

00:54:14.048 --> 00:54:16.064 as well as members from Rahul

NOTE Confidence: 0.845042928888889

00:54:16.064 --> 00:54:18.615 Canali's group at at the at the

NOTE Confidence: 0.845042928888889

00:54:18.615 --> 00:54:20.505 University of Connecticut and Mark  
NOTE Confidence: 0.845042928888889

00:54:20.510 --> 00:54:21.870 Gerstein's group here at Yale.  
NOTE Confidence: 0.845042928888889

00:54:21.870 --> 00:54:23.007 They've been really,  
NOTE Confidence: 0.845042928888889

00:54:23.007 --> 00:54:25.281 really helpful in letting us think  
NOTE Confidence: 0.845042928888889

00:54:25.281 --> 00:54:27.715 about this and and really broad terms.  
NOTE Confidence: 0.845042928888889

00:54:27.720 --> 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 --> 00:54:46.928 So the floor is open.  
NOTE Confidence: 0.96253157

00:54:46.930 --> 00:54:51.709 Questions for mark.  
NOTE Confidence: 0.96253157

00:54:51.710 --> 00:54:54.139 I I can get started with a  
NOTE Confidence: 0.96253157

00:54:54.139 --> 00:54:56.209 question that was really nice.  
NOTE Confidence: 0.96253157

00:54:56.210 --> 00:54:58.118 Thank you very much and wonderful  
NOTE Confidence: 0.96253157

00:54:58.118 --> 00:55:00.371 to hear about both of those stories  
NOTE Confidence: 0.96253157

00:55:00.371 --> 00:55:02.513 on the Swiss knife complex and on  
NOTE Confidence: 0.96253157

00:55:02.574 --> 00:55:04.409 the the minor intron splicing.



NOTE Confidence: 0.96253157

00:55:04.410 --> 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 that's

NOTE Confidence: 0.96253157

00:55:10.490 --> 00:55:13.577 something that we think about a lot

NOTE Confidence: 0.96253157

00:55:13.577 --> 00:55:16.977 as well is the sensitivity of of

NOTE Confidence: 0.96253157

00:55:16.977 --> 00:55:19.546 tumors to smarka for modulation for

NOTE Confidence: 0.96253157

00:55:19.546 --> 00:55:22.340 example and one of the things that.

NOTE Confidence: 0.96253157

00:55:22.340 --> 00:55:26.078 You mentioned was or what it seems

NOTE Confidence: 0.96253157

00:55:26.078 --> 00:55:29.365 like these protax seemed to be

NOTE Confidence: 0.96253157

00:55:29.365 --> 00:55:31.990 most effective in tumors that

NOTE Confidence: 0.96253157

00:55:31.990 --> 00:55:35.070 are AR sensitive to which is kind

NOTE Confidence: 0.96253157

00:55:35.070 --> 00:55:37.911 of interesting if we think about

NOTE Confidence: 0.96253157

00:55:37.911 --> 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 --> 00:55:45.711 And I was wondering if you have

NOTE Confidence: 0.96253157

00:55:45.711 --> 00:55:48.163 if if if you have any thoughts

NOTE Confidence: 0.96253157

00:55:48.163 --> 00:55:50.033 on sort of that paradox?  
NOTE Confidence: 0.96253157

00:55:50.040 --> 00:55:52.348 Well, if it is a paradox,  
NOTE Confidence: 0.65090655875

00:55:52.400 --> 00:55:55.920 yeah. So I'll just expand a little bit.  
NOTE Confidence: 0.65090655875

00:55:55.920 --> 00:55:57.160 So I think the things,  
NOTE Confidence: 0.65090655875

00:55:57.160 --> 00:55:59.470 just to reiterate what I said  
NOTE Confidence: 0.65090655875

00:55:59.470 --> 00:56:01.380 though also and you're well  
NOTE Confidence: 0.65090655875

00:56:01.380 --> 00:56:03.748 aware of is that if you do any.  
NOTE Confidence: 0.65090655875

00:56:03.750 --> 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 --> 00:56:10.312 they're always there, right.  
NOTE Confidence: 0.65090655875

00:56:10.312 --> 00:56:14.277 And so I think that the Protex in effectively  
NOTE Confidence: 0.65090655875

00:56:14.277 --> 00:56:17.197 you know hitting both regardless are  
NOTE Confidence: 0.65090655875

00:56:17.197 --> 00:56:19.766 you know great targets I think for.  
NOTE Confidence: 0.65090655875

00:56:19.770 --> 00:56:21.906 So the question is why is it so?  
NOTE Confidence: 0.65090655875

00:56:21.910 --> 00:56:23.980 Why are the AR sensitive tumors.  
NOTE Confidence: 0.65090655875

00:56:23.980 --> 00:56:26.722 So you know why are they

NOTE Confidence: 0.65090655875

00:56:26.722 --> 00:56:28.550 exquisitely sensitive to this.

NOTE Confidence: 0.65090655875

00:56:28.550 --> 00:56:31.364 We think that that's not the case.

NOTE Confidence: 0.65090655875

00:56:31.370 --> 00:56:33.210 So we actually think that it extends beyond,

NOTE Confidence: 0.65090655875

00:56:33.210 --> 00:56:34.596 it's not just.

NOTE Confidence: 0.65090655875

00:56:34.596 --> 00:56:37.305 They are and the the complexity we

NOTE Confidence: 0.65090655875

00:56:37.305 --> 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 --> 00:56:46.220 decrease and but we know that if we

NOTE Confidence: 0.65090655875

00:56:46.220 --> 00:56:48.814 do that smart K2 has to be maintained.

NOTE Confidence: 0.65090655875

00:56:48.820 --> 00:56:51.010 So there's a problem with the

NOTE Confidence: 0.65090655875

00:56:51.010 --> 00:56:53.160 the Protex is extremely toxic and

NOTE Confidence: 0.65090655875

00:56:53.160 --> 00:56:55.020 so how to get around that.

NOTE Confidence: 0.65090655875

00:56:55.020 --> 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 --> 00:57:02.429 can actually get nice resistance  
NOTE Confidence: 0.65090655875

00:57:02.429 --> 00:57:04.180 very quickly and as you expect.  
NOTE Confidence: 0.65090655875

00:57:04.180 --> 00:57:05.530 Where would the resistance be?  
NOTE Confidence: 0.65090655875

00:57:05.530 --> 00:57:07.514 It's in VHL or and and and one  
NOTE Confidence: 0.65090655875

00:57:07.514 --> 00:57:09.757 of the genes associated with how  
NOTE Confidence: 0.65090655875

00:57:09.757 --> 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 --> 00:57:16.811 show but where we've you know in cycle  
NOTE Confidence: 0.65090655875

00:57:16.811 --> 00:57:18.954 through resistance which is going to  
NOTE Confidence: 0.65090655875

00:57:18.954 --> 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 --> 00:57:26.204 was exciting to see that you can  
NOTE Confidence: 0.65090655875

00:57:26.204 --> 00:57:27.326 potentially target cancers.  
NOTE Confidence: 0.65090655875

00:57:27.330 --> 00:57:29.731 I think there's a bit of skepticism  
NOTE Confidence: 0.65090655875

00:57:29.731 --> 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 --> 00:57:38.458 I think they nicely described that  
NOTE Confidence: 0.65090655875  
00:57:38.458 --> 00:57:41.214 the toxicity is a major issue and  
NOTE Confidence: 0.65090655875  
00:57:41.214 --> 00:57:43.189 so since a specificity whether  
NOTE Confidence: 0.65090655875  
00:57:43.189 --> 00:57:44.699 it's for Smarca 2,  
NOTE Confidence: 0.65090655875  
00:57:44.700 --> 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 --> 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 --> 00:58:21.350 You might you might have to  
NOTE Confidence: 0.83852434  
00:58:21.350 --> 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 --> 00:58:25.870 OK.  
NOTE Confidence: 0.887259296

00:58:36.350 --> 00:58:37.220 Do you think you could?  
NOTE Confidence: 0.6868827933333333

00:58:37.370 --> 00:58:38.450 I think it would be hard.  
NOTE Confidence: 0.6868827933333333

00:58:38.450 --> 00:58:39.428 Would you like to come out?  
NOTE Confidence: 0.7889321772222222

00:58:39.440 --> 00:58:41.640 I think you have to say it in the microphone  
NOTE Confidence: 0.7889321772222222

00:58:41.690 --> 00:58:43.690 so people can hear it who are listening.  
NOTE Confidence: 0.7889321772222222

00:58:43.690 --> 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 --> 00:59:02.230 the sensitivity with the protests  
NOTE Confidence: 0.631046205

00:59:02.230 --> 00:59:04.260 and the prostate cancer cells.  
NOTE Confidence: 0.631046205

00:59:04.260 --> 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 the BRG  
NOTE Confidence: 0.631046205

00:59:09.920 --> 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 in the context

NOTE Confidence: 0.631046205

00:59:18.390 --> 00:59:20.466 where it is being affected or

NOTE Confidence: 0.631046205

00:59:20.466 --> 00:59:23.079 if you think it has a separate.

NOTE Confidence: 0.631046205

00:59:23.080 --> 00:59:25.450 Activity and I'm wondering because

NOTE Confidence: 0.631046205

00:59:25.450 --> 00:59:27.252 you mentioned EH2 as well,

NOTE Confidence: 0.631046205

00:59:27.252 --> 00:59:28.956 I know can have Polycom independent

NOTE Confidence: 0.631046205

00:59:28.956 --> 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 --> 00:59:33.449 something similar might be going on.

NOTE Confidence: 0.698803522

00:59:33.700 --> 00:59:34.760 So that's a great question.

NOTE Confidence: 0.698803522

00:59:34.760 --> 00:59:37.442 So and and the way that I didn't show

NOTE Confidence: 0.698803522

00:59:37.442 --> 00:59:39.997 data but the way that I think we've

NOTE Confidence: 0.698803522

00:59:39.997 --> 00:59:42.532 been going at this has been to look

NOTE Confidence: 0.698803522

00:59:42.532 --> 00:59:44.844 at also there are ATP ace inhibitors.

NOTE Confidence: 0.698803522

00:59:44.844 --> 00:59:47.196 So we also have data for

NOTE Confidence: 0.698803522

00:59:47.196 --> 00:59:49.290 the ATP ACE inhibitors.

NOTE Confidence: 0.698803522

00:59:49.290 --> 00:59:51.290 The protects are more effective,  
NOTE Confidence: 0.698803522

00:59:51.290 --> 00:59:55.196 but they're more toxic and so  
NOTE Confidence: 0.698803522

00:59:55.196 --> 00:59:58.590 but inhibiting a TPA does.  
NOTE Confidence: 0.698803522

00:59:58.590 --> 01:00:00.389 You know make it have a similar  
NOTE Confidence: 0.698803522

01:00:00.389 --> 01:00:02.104 effect but again it's not specific  
NOTE Confidence: 0.698803522

01:00:02.104 --> 01:00:03.886 to this market force market too.  
NOTE Confidence: 0.698803522

01:00:03.890 --> 01:00:05.584 So it's hard to dissociate that and  
NOTE Confidence: 0.698803522

01:00:05.584 --> 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 --> 01:00:11.465 out smart key forwards market too.  
NOTE Confidence: 0.698803522

01:00:11.470 --> 01:00:12.790 So that's one problem.  
NOTE Confidence: 0.698803522

01:00:12.790 --> 01:00:14.770 The other problem that we have  
NOTE Confidence: 0.698803522

01:00:14.840 --> 01:00:16.970 which didn't discuss at all is  
NOTE Confidence: 0.698803522

01:00:16.970 --> 01:00:18.729 that it's really difficult to  
NOTE Confidence: 0.698803522

01:00:18.729 --> 01:00:19.892 chip these these proteins,  
NOTE Confidence: 0.698803522

01:00:19.892 --> 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 --> 01:00:25.219 expert in that we we haven't been

NOTE Confidence: 0.698803522

01:00:25.219 --> 01:00:26.789 able to achieve that unfortunately.

NOTE Confidence: 0.895636886666667

01:00:30.410 --> 01:00:31.628 Other questions, yes.

NOTE Confidence: 0.578035086666667

01:00:39.070 --> 01:00:39.760 The role the

NOTE Confidence: 0.759423952857143

01:00:39.770 --> 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 --> 01:00:45.510 OK. So that's a that's

NOTE Confidence: 0.848446689

01:00:45.510 --> 01:00:46.920 one of my favorite topics.

NOTE Confidence: 0.848446689

01:00:46.920 --> 01:00:48.915 I love that topics the role of

NOTE Confidence: 0.848446689

01:00:48.915 --> 01:00:50.720 estrogen in advanced prostate cancer.

NOTE Confidence: 0.848446689

01:00:50.720 --> 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 --> 01:00:56.856 be that important but estrogen

NOTE Confidence: 0.848446689

01:00:56.856 --> 01:00:58.924 receptor and antrum receptor they

NOTE Confidence: 0.848446689

01:00:58.924 --> 01:01:00.979 have very similar binding sites.  
NOTE Confidence: 0.848446689

01:01:00.980 --> 01:01:02.723 So there's a lot of half binding  
NOTE Confidence: 0.848446689

01:01:02.723 --> 01:01:04.479 sites that are are are regulated.  
NOTE Confidence: 0.848446689

01:01:04.480 --> 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 --> 01:01:11.434 nuclear hormones are activated and  
NOTE Confidence: 0.848446689

01:01:11.434 --> 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 --> 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 --> 01:01:36.018 so the role of estrogen and plasticity.  
NOTE Confidence: 0.715208235714286

01:01:36.020 --> 01:01:38.520 Or progestin or progesterone.  
NOTE Confidence: 0.715208235714286

01:01:38.520 --> 01:01:41.355 So I think I think in stem in stemness.

NOTE Confidence: 0.715208235714286  
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 --> 01:01:47.689 there's the view that it does play  
NOTE Confidence: 0.715208235714286  
01:01:47.756 --> 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 --> 01:01:56.588 yeah. Thank you, Joe.  
NOTE Confidence: 0.7995987  
01:02:00.910 --> 01:02:01.880 Thank you for coming out.  
NOTE Confidence: 0.6157551  
01:02:06.500 --> 01:02:10.750 My question is about the therapies for.  
NOTE Confidence: 0.90906139  
01:02:10.750 --> 01:02:15.260 As you know. Ready for those people?  
NOTE Confidence: 0.6613467333333333  
01:02:16.750 --> 01:02:17.500 Show that you're.  
NOTE Confidence: 0.66546635  
01:02:22.850 --> 01:02:26.740 Or is there any incremental attrition? To.  
NOTE Confidence: 0.552128935  
01:02:28.590 --> 01:02:29.230 Or any.  
NOTE Confidence: 0.8434726155555556  
01:02:34.070 --> 01:02:35.290 Well, I'm a pathologist.  
NOTE Confidence: 0.8434726155555556  
01:02:35.290 --> 01:02:36.815 I better not comment on,  
NOTE Confidence: 0.8434726155555556

01:02:36.820 --> 01:02:37.888 on clinical oncology therapy.  
NOTE Confidence: 0.843472615555556

01:02:37.888 --> 01:02:39.490 But the only thing I would  
NOTE Confidence: 0.843472615555556

01:02:39.540 --> 01:02:40.776 say is that there's a lot,  
NOTE Confidence: 0.843472615555556

01:02:40.780 --> 01:02:43.576 there's great interest in you know  
NOTE Confidence: 0.843472615555556

01:02:43.576 --> 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 --> 01:02:50.755 Debono was just with him the other day  
NOTE Confidence: 0.843472615555556

01:02:50.755 --> 01:02:52.620 in Basel and we were talking about this.  
NOTE Confidence: 0.843472615555556

01:02:52.620 --> 01:02:53.956 So I think there are a number of  
NOTE Confidence: 0.843472615555556

01:02:53.956 --> 01:02:55.260 studies that are coming down the line,  
NOTE Confidence: 0.843472615555556

01:02:55.260 --> 01:02:57.416 but it may not be you know,  
NOTE Confidence: 0.843472615555556

01:02:57.420 --> 01:02:59.460 so I presented these different categories,  
NOTE Confidence: 0.843472615555556

01:02:59.460 --> 01:03:01.728 it may be for a R negative.  
NOTE Confidence: 0.843472615555556

01:03:01.730 --> 01:03:04.327 But not neuroendocrine tumors that there are,  
NOTE Confidence: 0.843472615555556

01:03:04.330 --> 01:03:07.246 you know, some new therapeutic targets.  
NOTE Confidence: 0.843472615555556

01:03:07.250 --> 01:03:08.880 Her three is the target.

NOTE Confidence: 0.843472615555556  
01:03:08.880 --> 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 --> 01:03:17.050 but no winners yet,  
NOTE Confidence: 0.843472615555556  
01:03:17.050 --> 01:03:18.565 no successful winners.  
NOTE Confidence: 0.843472615555556  
01:03:18.570 --> 01:03:20.418 And then hopefully I pointed out in  
NOTE Confidence: 0.843472615555556  
01:03:20.418 --> 01:03:22.535 the first part of the presentation how  
NOTE Confidence: 0.843472615555556  
01:03:22.535 --> 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 --> 01:03:30.900 So we're far behind breast  
NOTE Confidence: 0.843472615555556  
01:03:30.900 --> 01:03:32.630 cancer and maybe lung cancer.  
NOTE Confidence: 0.843472615555556  
01:03:32.630 --> 01:03:35.073 As far as being able to accurately  
NOTE Confidence: 0.843472615555556  
01:03:35.073 --> 01:03:37.088 classify what needs to be treated.  
NOTE Confidence: 0.843472615555556  
01:03:37.090 --> 01:03:39.146 So I think that in all the and  
NOTE Confidence: 0.843472615555556  
01:03:39.146 --> 01:03:41.668 so in the in the advisory boards,  
NOTE Confidence: 0.843472615555556

01:03:41.670 --> 01:03:43.254 I think the common conclusion after  
NOTE Confidence: 0.843472615555556

01:03:43.254 --> 01:03:44.946 two or three days of discussions  
NOTE Confidence: 0.843472615555556

01:03:44.946 --> 01:03:46.110 are always the same,  
NOTE Confidence: 0.843472615555556

01:03:46.110 --> 01:03:48.990 which is that we just need to treat  
NOTE Confidence: 0.843472615555556

01:03:48.990 --> 01:03:51.187 everybody and see who what works.  
NOTE Confidence: 0.843472615555556

01:03:51.190 --> 01:03:52.450 Which is sort of depressing,  
NOTE Confidence: 0.843472615555556

01:03:52.450 --> 01:03:53.690 but it's that's that's sort  
NOTE Confidence: 0.843472615555556

01:03:53.690 --> 01:03:55.320 of where we are I think.  
NOTE Confidence: 0.804383019411765

01:03:55.790 --> 01:03:57.422 I think we have similar issues  
NOTE Confidence: 0.804383019411765

01:03:57.422 --> 01:03:58.895 in lung cancer and resistant  
NOTE Confidence: 0.804383019411765

01:03:58.895 --> 01:04:00.845 tumors trying to figure it out.  
NOTE Confidence: 0.77401228

01:04:02.140 --> 01:04:03.845 What pathologist. So that's just  
NOTE Confidence: 0.77401228

01:04:03.845 --> 01:04:05.778 my personal opinion, not don't,  
NOTE Confidence: 0.77401228

01:04:05.778 --> 01:04:07.840 don't take that. Beyond that,  
NOTE Confidence: 0.7915238275

01:04:07.970 --> 01:04:09.746 we have one last question in the back.  
NOTE Confidence: 0.71277517

01:04:12.330 --> 01:04:13.900 Roll off. Thank you.

NOTE Confidence: 0.62965414

01:04:17.230 --> 01:04:18.338 So like the cluster.

NOTE Confidence: 0.875699211666667

01:04:22.580 --> 01:04:24.488 I'm sorry, I can't hear from

NOTE Confidence: 0.818377945238095

01:04:24.660 --> 01:04:27.068 do you think there is a role

NOTE Confidence: 0.818377945238095

01:04:27.068 --> 01:04:28.100 for differentiation therapies

NOTE Confidence: 0.818377945238095

01:04:28.161 --> 01:04:29.851 in prostate cancer kind of

NOTE Confidence: 0.818377945238095

01:04:29.851 --> 01:04:31.780 analogous to the retinoic acid and

NOTE Confidence: 0.621062275

01:04:32.480 --> 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 --> 01:04:39.439 directly relate to your question but.

NOTE Confidence: 0.621062275

01:04:39.440 --> 01:04:42.065 Being able to model differentiation

NOTE Confidence: 0.621062275

01:04:42.065 --> 01:04:43.640 would be phenomenal.

NOTE Confidence: 0.621062275

01:04:43.640 --> 01:04:45.728 So if we had model systems where it

NOTE Confidence: 0.621062275

01:04:45.728 --> 01:04:47.840 could show I know like in AML and

NOTE Confidence: 0.621062275

01:04:47.840 --> 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 --> 01:04:53.851 of blocking differentiation and I  
NOTE Confidence: 0.621062275

01:04:53.851 --> 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 --> 01:05:00.602 now is develop of like the stem like  
NOTE Confidence: 0.621062275

01:05:00.602 --> 01:05:03.061 state and then you know ideally we'd  
NOTE Confidence: 0.621062275

01:05:03.061 --> 01:05:05.254 like to flux back between adenocarcinoma.  
NOTE Confidence: 0.621062275

01:05:05.254 --> 01:05:07.498 So we're starting to see some  
NOTE Confidence: 0.621062275

01:05:07.498 --> 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 --> 01:05:12.402 have that ability yet.  
NOTE Confidence: 0.621062275

01:05:12.410 --> 01:05:14.642 So I do think what you're saying is  
NOTE Confidence: 0.621062275

01:05:14.642 --> 01:05:16.182 interesting and we my view would  
NOTE Confidence: 0.621062275

01:05:16.182 --> 01:05:17.959 be that if you could tell which  
NOTE Confidence: 0.621062275

01:05:17.959 --> 01:05:19.649 tumors are going to transition,  
NOTE Confidence: 0.621062275

01:05:19.650 --> 01:05:22.098 you'd want to treat them as early as  
NOTE Confidence: 0.621062275

01:05:22.098 --> 01:05:24.221 possible with the other element in



NOTE Confidence: 0.621062275

01:05:24.221 --> 01:05:26.387 addition to AR targeted therapy before

NOTE Confidence: 0.621062275

01:05:26.456 --> 01:05:28.969 it goes down the road to differentiation.

NOTE Confidence: 0.5343186

01:05:30.420 --> 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 --> 01:05:42.394 targeted like therapies?

NOTE Confidence: 0.777768090909091

01:05:42.410 --> 01:05:43.900 Yeah, we haven't, but that's

NOTE Confidence: 0.777768090909091

01:05:43.900 --> 01:05:45.940 obviously there's a lot of interest.

NOTE Confidence: 0.777768090909091

01:05:45.940 --> 01:05:49.308 So you saw the, I showed two papers

NOTE Confidence: 0.777768090909091

01:05:49.308 --> 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 --> 01:05:56.615 So they're very interested in

NOTE Confidence: 0.777768090909091

01:05:56.615 --> 01:05:58.707 various therapies related to

NOTE Confidence: 0.777768090909091

01:05:58.707 --> 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 --> 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.