WEBVTT

- NOTE duration:"01:01:10.5710000"
- NOTE language:en-us
- NOTE Confidence: 0.8283998
- $00:00:00.000 \rightarrow 00:00:01.950$  We have two speakers today covering
- NOTE Confidence: 0.8283998
- 00:00:01.950 --> 00:00:03.879 quite a diverse array of topics,
- NOTE Confidence: 0.8283998
- $00{:}00{:}03.880 \dashrightarrow 00{:}00{:}05.480$  which is terrific. Both internal
- NOTE Confidence: 0.8283998
- $00{:}00{:}05{.}480 \dashrightarrow 00{:}00{:}07{.}080$  speakers and I encourage people.
- NOTE Confidence: 0.8283998
- $00{:}00{:}07{.}080 \dashrightarrow 00{:}00{:}09{.}010$  If you have questions to
- NOTE Confidence: 0.8283998
- $00:00:09.010 \longrightarrow 00:00:10.940$  type them into the chat.
- NOTE Confidence: 0.8283998
- $00{:}00{:}10{.}940 \dashrightarrow 00{:}00{:}12{.}734$  And then we'll get those questions
- NOTE Confidence: 0.8283998
- $00{:}00{:}12.734 \dashrightarrow 00{:}00{:}14.870$  answered when the talks are are finished.
- NOTE Confidence: 0.8283998
- $00:00:14.870 \dashrightarrow 00:00:16.977$  So our first speaker is Antonio Omuro.
- NOTE Confidence: 0.8283998
- 00:00:16.980 --> 00:00:19.390 You may you may know he he is a professor
- NOTE Confidence: 0.8283998
- $00:00:19.451 \dashrightarrow 00:00:21.628$  of neurology and the chief of Neuro
- NOTE Confidence: 0.8283998
- 00:00:21.628 --> 00:00:23.651 Oncology here and Clinical Leader Program
- NOTE Confidence: 0.8283998
- $00{:}00{:}23.651 \dashrightarrow 00{:}00{:}26.038$  leader of the shin of your family,
- NOTE Confidence: 0.8283998
- $00:00:26.040 \longrightarrow 00:00:27.512$  can bring tumor center,

- NOTE Confidence: 0.8283998
- $00{:}00{:}27{.}512 \dashrightarrow 00{:}00{:}29{.}720$  which is a new program here.

 $00:00:29.720 \longrightarrow 00:00:30.948$  He received his initial

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00:00:30.948 --> 00:00:32.176 medical training in Brazil,

NOTE Confidence: 0.8283998

 $00{:}00{:}32.180 \dashrightarrow 00{:}00{:}33.404$  then worked at Memorial

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00:00:33.404 --> 00:00:34.934 Sloan Kettering for a while,

NOTE Confidence: 0.8283998

 $00:00:34.940 \longrightarrow 00:00:36.805$  and began his faculty career

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00:00:36.805 --> 00:00:38.297 at University of Miami.

NOTE Confidence: 0.8283998

 $00:00:38.300 \longrightarrow 00:00:39.810$  He joined us in 2012.

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 $00{:}00{:}39.810 \dashrightarrow 00{:}00{:}42.066$  He's an international leader in their

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 $00{:}00{:}42.066 \dashrightarrow 00{:}00{:}44.569$  clinical care and research on brain tumors.

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 $00:00:44.570 \rightarrow 00:00:45.854$  Leading leading pivotal research

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 $00{:}00{:}45.854 \dashrightarrow 00{:}00{:}47.780$  programs and treatment of these cancers,

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 $00{:}00{:}47.780 \dashrightarrow 00{:}00{:}49.980$  the Genevier family Brain Tumor Center is a

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 $00{:}00{:}49{.}980 \dashrightarrow 00{:}00{:}52{.}270$  new yellow initiative for the Comprehensive,

NOTE Confidence: 0.8283998

 $00:00:52.270 \dashrightarrow 00:00:53.287$  multidisciplinary brain tumor.

00:00:53.287 -> 00:00:55.321 Karen, perhaps you might hear a

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 $00:00:55.321 \dashrightarrow 00:00:57.088$  little bit about that from Antonio,

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00:00:57.090 - 00:00:59.016 so Antonio, the floor is yours.

NOTE Confidence: 0.8283998

00:00:59.020 --> 00:01:00.620 Thank you for speaking today.

NOTE Confidence: 0.84176815

00:01:02.690 --> 00:01:03.902 Thank you very much,

NOTE Confidence: 0.84176815

 $00{:}01{:}03{.}902 \dashrightarrow 00{:}01{:}05{.}720$  then super like to thank the

NOTE Confidence: 0.84176815

 $00:01:05.784 \longrightarrow 00:01:07.359$  organizers for inviting me to

NOTE Confidence: 0.84176815

 $00:01:07.359 \rightarrow 00:01:09.619$  talk to you today and for today.

NOTE Confidence: 0.84176815

00:01:09.620 --> 00:01:11.195 Specifically, I was asked to

NOTE Confidence: 0.84176815

 $00{:}01{:}11.195 \dashrightarrow 00{:}01{:}12.770$  share with you what's happening.

NOTE Confidence: 0.84176815

 $00{:}01{:}12.770 \dashrightarrow 00{:}01{:}14.552$  Our division in terms of clinical

NOTE Confidence: 0.84176815

00:01:14.552 --> 00:01:16.458 trials and how we're tapping into

NOTE Confidence: 0.84176815

00:01:16.458 --> 00:01:18.438 Yale talent to build our portfolio,

NOTE Confidence: 0.84176815

00:01:18.440 --> 00:01:20.323 but I would also like to share

NOTE Confidence: 0.84176815

 $00:01:20.323 \rightarrow 00:01:22.418$  with you the state of our fields

NOTE Confidence: 0.84176815

 $00:01:22.418 \longrightarrow 00:01:24.679$  and the spirit of almost like an

 $00:01:24.679 \rightarrow 00:01:26.459$  invitation to even more investigators

NOTE Confidence: 0.84176815

 $00{:}01{:}26.459 \dashrightarrow 00{:}01{:}29.150$  and labs to join us in this task.

NOTE Confidence: 0.81148463

 $00:01:32.980 \longrightarrow 00:01:35.350$  So today we're going to concentrate

NOTE Confidence: 0.81148463

 $00:01:35.350 \rightarrow 00:01:38.439$  on gliomas and the reason for that is

NOTE Confidence: 0.81148463

 $00:01:38.439 \dashrightarrow 00:01:41.012$  that they account for the vast majority NOTE Confidence: 0.81148463

 $00:01:41.012 \longrightarrow 00:01:43.764$  of the brain tumors and as you can

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 $00:01:43.764 \rightarrow 00:01:46.630$  see here this is a fight chart showing

NOTE Confidence: 0.81148463

 $00:01:46.630 \longrightarrow 00:01:48.190$  all malignant intracranial tumors,

NOTE Confidence: 0.81148463

 $00:01:48.190 \longrightarrow 00:01:51.060$  and the vast majority of the patients

NOTE Confidence: 0.81148463

 $00:01:51.060 \dashrightarrow 00:01:53.004$  have either glioblastoma or other

NOTE Confidence: 0.81148463

 $00:01:53.004 \longrightarrow 00:01:54.948$  forms of gliomas which for the

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 $00{:}01{:}54{.}948 \dashrightarrow 00{:}01{:}56{.}718$  most part our IDH mutants,

NOTE Confidence: 0.81148463

 $00{:}01{:}56.720 \dashrightarrow 00{:}01{:}59.415$  which account for grades two and three

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 $00{:}01{:}59{.}415 \dashrightarrow 00{:}02{:}01{.}659$  others like Thomas and grades too.

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 $00{:}02{:}01{.}660 \dashrightarrow 00{:}02{:}04{.}418$  In three algorithms, this is 3 or

 $00:02:04.418 \rightarrow 00:02:06.950$  by semester form as many Germans.

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 $00{:}02{:}06{.}950 \dashrightarrow 00{:}02{:}08{.}506$  In order rare tumors.

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 $00:02:08.506 \longrightarrow 00:02:11.347$  But the bottom line here is that

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00:02:11.347 - 00:02:13.867 this even the most common tumor,

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 $00:02:13.870 \longrightarrow 00:02:15.900$  which is unfortunately the great

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00:02:15.900 --> 00:02:17.524 for glioma or glioblastoma,

NOTE Confidence: 0.81148463

00:02:17.530 --> 00:02:19.906 still is a relatively rare disease

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 $00:02:19.906 \rightarrow 00:02:22.396$  with only three point 1 patients

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 $00:02:22.396 \longrightarrow 00:02:24.048$  for each 100,000 people.

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 $00:02:24.050 \rightarrow 00:02:26.892$  So it is again relatively rare disease

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00:02:26.892 --> 00:02:29.736 Fortunately, but it is, as you know,

NOTE Confidence: 0.81148463

 $00:02:29.740 \longrightarrow 00:02:31.850$  a very devastating disease and.

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 $00:02:31.850 \rightarrow 00:02:34.850$  The reason why this is such a charming

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 $00{:}02{:}34.850 \dashrightarrow 00{:}02{:}37.411$  diseases that you know the anatomic

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 $00:02:37.411 \longrightarrow 00:02:39.576$  location really doesn't help us.

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 $00:02:39.580 \longrightarrow 00:02:41.926$  So these are places that presents

- NOTE Confidence: 0.81148463
- $00{:}02{:}41{.}926 \dashrightarrow 00{:}02{:}43{.}987$  with these large tumors with

 $00:02:43.987 \rightarrow 00:02:45.687$  lots of surrounding edema,

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 $00:02:45.690 \dashrightarrow 00:02:47.314$  an infiltrative microscopic disease.

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 $00:02:47.314 \rightarrow 00:02:49.344$  These terms are highly vascularized,

NOTE Confidence: 0.81148463

 $00{:}02{:}49{.}350 \dashrightarrow 00{:}02{:}51{.}940$  so we're at the same time dealing

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 $00:02:51.940 \longrightarrow 00:02:54.240$  with an uncle logic disease,

NOTE Confidence: 0.81148463

 $00:02:54.240 \longrightarrow 00:02:56.275$  but truly we're dealing with

NOTE Confidence: 0.81148463

00:02:56.275 --> 00:02:58.310 a neurologic disease as well,

NOTE Confidence: 0.81148463

 $00:02:58.310 \rightarrow 00:03:00.824$  and you can imagine how challenging

NOTE Confidence: 0.81148463

 $00:03:00.824 \longrightarrow 00:03:02.500$  it is to manage.

NOTE Confidence: 0.81148463

 $00:03:02.500 \rightarrow 00:03:04.318$  All of these symptoms were still

NOTE Confidence: 0.81148463

 $00{:}03{:}04{.}318 \dashrightarrow 00{:}03{:}06{.}288$  trying to make a difference in

NOTE Confidence: 0.81148463

 $00:03:06.288 \dashrightarrow 00:03:07.970$  terms of uncle logic treatments.

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00:03:11.060 --> 00:03:12.975 Ends reflecting this challenge is

NOTE Confidence: 0.7932129

00:03:12.975 --> 00:03:15.634 the fact that the only drug that NOTE Confidence: 0.7932129

 $00:03:15.634 \rightarrow 00:03:17.644$  has shown to improve survival so

NOTE Confidence: 0.7932129

 $00:03:17.644 \rightarrow 00:03:19.601$  far is this alkylating alkylating

NOTE Confidence: 0.7932129

 $00{:}03{:}19{.}601$  -->  $00{:}03{:}22{.}770$  agent that is more than 20 years old.

NOTE Confidence: 0.7932129

00:03:22.770 --> 00:03:25.490 So this is the most dolomite and in

NOTE Confidence: 0.7932129

 $00{:}03{:}25{.}490 \dashrightarrow 00{:}03{:}27{.}755$  controllers here is saying that the

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00:03:27.755 --> 00:03:29.615 Missouri might improves both work

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 $00:03:29.687 \dashrightarrow 00:03:31.907$  for survival and overall survival,

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 $00{:}03{:}31{.}910 \dashrightarrow 00{:}03{:}33{.}800$  but even the experimental arm

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 $00{:}03{:}33{.}800 \dashrightarrow 00{:}03{:}35{.}312$  in the pivotal trial,

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 $00:03:35.320 \longrightarrow 00:03:38.300$  which was published in 2005.

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 $00:03:38.300 \dashrightarrow 00:03:41.275$  Survival remained only 15 months for again,

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 $00:03:41.280 \rightarrow 00:03:43.400$  newly diagnosed disease and further

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 $00{:}03{:}43{.}400 \dashrightarrow 00{:}03{:}46{.}415$  analysis of this data has shown that

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 $00{:}03{:}46{.}415 \dashrightarrow 00{:}03{:}48{.}875$  this survivor benefit is mostly driven

NOTE Confidence: 0.7932129

 $00:03:48.875 \rightarrow 00:03:51.510$  by tumors that have this afternoon.

NOTE Confidence: 0.7932129

 $00{:}03{:}51{.}510 \dashrightarrow 00{:}03{:}54{.}084$  Check silence of the Mt gene

- NOTE Confidence: 0.7932129
- $00:03:54.084 \rightarrow 00:03:56.323$  promoter by methylation so these

 $00{:}03{:}56{.}323 \dashrightarrow 00{:}03{:}58{.}987$  patients with math Laden GMT tend

NOTE Confidence: 0.7932129

00:03:58.987 --> 00:04:01.728 to respond better to Tim's or mine,

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 $00:04:01.730 \longrightarrow 00:04:03.855$  but they account for only

NOTE Confidence: 0.7932129

00:04:03.855 --> 00:04:06.024 about 30% of the patients.

NOTE Confidence: 0.7932129

 $00:04:06.024 \rightarrow 00:04:09.090$  So for the remainder of the patients.

NOTE Confidence: 0.7932129

 $00:04:09.090 \longrightarrow 00:04:10.865$  The only real treatment that

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 $00:04:10.865 \longrightarrow 00:04:12.285$  is available is radiation.

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00:04:15.370 --> 00:04:18.306 And we did try a lot of agents,

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 $00{:}04{:}18.310 \dashrightarrow 00{:}04{:}20.599$  and here you're looking at a slide

NOTE Confidence: 0.8231038

 $00:04:20.599 \longrightarrow 00:04:22.691$  from 2005 where we were talking

NOTE Confidence: 0.8231038

00:04:22.691 --> 00:04:25.120 about all of these clinical trials in

NOTE Confidence: 0.8231038

 $00{:}04{:}25.187 \dashrightarrow 00{:}04{:}27.477$  glioblastoma and in other diseases.

NOTE Confidence: 0.8231038

 $00:04:27.480 \dashrightarrow 00:04:29.320$  Testing these novel target the rapist.

NOTE Confidence: 0.8231038

 $00:04:29.320 \longrightarrow 00:04:31.078$  So we're very excited that for

 $00:04:31.078 \longrightarrow 00:04:33.361$  the first time in would be able

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 $00{:}04{:}33{.}361 \dashrightarrow 00{:}04{:}35{.}101$  to treat these patients with

NOTE Confidence: 0.8231038

 $00:04:35.101 \longrightarrow 00:04:37.305$  therapies that would carry minimal

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 $00:04:37.305 \rightarrow 00:04:39.225$  toxicities and tremendous efficacy,

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 $00{:}04{:}39{.}230 \dashrightarrow 00{:}04{:}43{.}838$  but as you know, the story was much more.

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00:04:43.840 --> 00:04:46.654 You know, harder than than what we

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 $00:04:46.654 \rightarrow 00:04:49.228$  originally thought, and one by one.

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 $00{:}04{:}49{.}228 \dashrightarrow 00{:}04{:}52{.}604$  All of these stars went on to

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 $00{:}04{:}52{.}604 \dashrightarrow 00{:}04{:}55{.}048$  fail in recurrent disease.

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 $00{:}04{:}55{.}050 \dashrightarrow 00{:}04{:}57{.}354$  The sad thing is that or may be the

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 $00{:}04{:}57{.}354 \dashrightarrow 00{:}04{:}59{.}695$  lucky thing for other diseases is that

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 $00{:}04{:}59.695 \dashrightarrow 00{:}05{:}02.277$  the majority of these drugs ended up

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 $00{:}05{:}02.277 \dashrightarrow 00{:}05{:}04.337$  being approved for other indications,

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 $00{:}05{:}04{.}340 \dashrightarrow 00{:}05{:}08{.}064$  but all of that rise in glucose

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 $00{:}05{:}08.064 \dashrightarrow 00{:}05{:}09.660$  Thomas have failed.

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 $00:05:09.660 \rightarrow 00:05:12.474$  And more challenging is the fact that

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- $00:05:12.474 \rightarrow 00:05:15.360$  we're not really sure what is it about

 $00:05:15.360 \longrightarrow 00:05:17.897$  the omens that all of these drugs

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 $00:05:17.897 \rightarrow 00:05:20.465$  actually fail one after the other,

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 $00:05:20.470 \longrightarrow 00:05:22.780$  is that because we are targeting

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 $00:05:22.780 \longrightarrow 00:05:23.935$  the wrong targets,

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 $00:05:23.940 \longrightarrow 00:05:25.484$  maybe they're not sufficiently

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00:05:25.484 --> 00:05:27.028 relevant for Uncle Genesis,

NOTE Confidence: 0.8231038

 $00{:}05{:}27{.}030 \dashrightarrow 00{:}05{:}29{.}196$  or there are too many feedback

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 $00:05:29.196 \dashrightarrow 00:05:31.110$  loops and redundant pathways were

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 $00{:}05{:}31{.}110 \dashrightarrow 00{:}05{:}33{.}534$  now more and more learning about

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 $00:05:33.534 \longrightarrow 00:05:34.746$  temporal spatial variations?

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 $00{:}05{:}34.750 \dashrightarrow 00{:}05{:}37.180$  Or is it be 'cause these

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 $00:05:37.180 \longrightarrow 00:05:39.260$  are the wrong drugs and?

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 $00:05:39.260 \longrightarrow 00:05:41.580$  We have problems you know,

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 $00:05:41.580 \rightarrow 00:05:43.436$  of achieving adequate concentrations,

- $00:05:43.436 \rightarrow 00:05:44.828$  especially for drugs.
- NOTE Confidence: 0.8231038
- $00{:}05{:}44{.}830 \dashrightarrow 00{:}05{:}47{.}150$  They are not very potent.
- NOTE Confidence: 0.8231038
- $00{:}05{:}47.150 \dashrightarrow 00{:}05{:}50.538$  We do need to have better blood
- NOTE Confidence: 0.8231038
- $00{:}05{:}50{.}538 \dashrightarrow 00{:}05{:}53{.}012$  brain barrier penetration because a
- NOTE Confidence: 0.8231038
- $00{:}05{:}53.012 \dashrightarrow 00{:}05{:}55.814$  lot of these microscopic disease is
- NOTE Confidence: 0.8231038
- $00:05:55.814 \dashrightarrow 00:05:59.128$  behind an intact blood brain barrier.
- NOTE Confidence: 0.8231038
- 00:05:59.130 --> 00:05:59.454 Also,
- NOTE Confidence: 0.8231038
- $00:05:59.454 \rightarrow 00:06:01.398$  we still don't know how to
- NOTE Confidence: 0.8231038
- $00{:}06{:}01{.}398 \dashrightarrow 00{:}06{:}03{.}230$  select basis for these drugs.
- NOTE Confidence: 0.8231038
- $00{:}06{:}03{.}230 \dashrightarrow 00{:}06{:}05{.}502$  We're still not sure if it should select
- NOTE Confidence: 0.8231038
- $00:06:05.502 \rightarrow 00:06:07.729$  based on specific mutations or should
- NOTE Confidence: 0.8231038
- $00{:}06{:}07{.}729 \dashrightarrow 00{:}06{:}10{.}420$  we go through transcription subgroups or not?
- NOTE Confidence: 0.8231038
- $00:06:10.420 \rightarrow 00:06:12.250$  Do any selection whatsoever and treat
- NOTE Confidence: 0.8231038
- $00{:}06{:}12.250 \dashrightarrow 00{:}06{:}14.528$  a large number of patients then then
- NOTE Confidence: 0.8231038
- $00:06:14.528 \rightarrow 00:06:16.859$  identify the responders and then go after
- NOTE Confidence: 0.8231038
- $00:06:16.916 \rightarrow 00:06:18.966$  the phenotypes that predict response.

- NOTE Confidence: 0.8231038
- $00:06:18.970 \longrightarrow 00:06:20.334$  So in other words,
- NOTE Confidence: 0.8231038
- $00:06:20.334 \rightarrow 00:06:22.039$  regardless of what we do,
- NOTE Confidence: 0.8231038
- $00:06:22.040 \longrightarrow 00:06:24.092$  we certainly need to improve translation
- NOTE Confidence: 0.8231038
- $00{:}06{:}24.092 \dashrightarrow 00{:}06{:}25.460$  components within our trials,
- NOTE Confidence: 0.8231038
- 00:06:25.460 00:06:27.170 improve the science before, during,
- NOTE Confidence: 0.8231038
- $00:06:27.170 \longrightarrow 00:06:29.676$  and after the trial and this is.
- NOTE Confidence: 0.8231038
- 00:06:29.680 --> 00:06:30.017 Actually,
- NOTE Confidence: 0.8231038
- $00{:}06{:}30{.}017 \dashrightarrow 00{:}06{:}31{.}365$  paradigm that we have
- NOTE Confidence: 0.8231038
- 00:06:31.365 --> 00:06:32.376 been following artificial.
- NOTE Confidence: 0.7912263
- $00:06:36.310 \longrightarrow 00:06:38.750$  So the low hanging fruit is to try
- NOTE Confidence: 0.7912263
- $00{:}06{:}38.750 \dashrightarrow 00{:}06{:}40.915$  to use the genomic information
- NOTE Confidence: 0.7912263
- $00:06:40.915 \longrightarrow 00:06:43.380$  that is now widely available.
- NOTE Confidence: 0.7912263
- $00:06:43.380 \longrightarrow 00:06:45.738$  Only streamers to see if we
- NOTE Confidence: 0.7912263
- $00{:}06{:}45.738 \dashrightarrow 00{:}06{:}47.310$  can improve our outcomes.
- NOTE Confidence: 0.7912263
- $00:06:47.310 \longrightarrow 00:06:50.604$  So as you know, global someone was the very
- NOTE Confidence: 0.7912263

 $00:06:50.604 \rightarrow 00:06:53.598$  first tumor sequenced by the TSJ effort, NOTE Confidence: 0.7912263  $00{:}06{:}53{.}600 \dashrightarrow 00{:}06{:}55{.}340$  and since then gene sequencing NOTE Confidence: 0.7912263  $00:06:55.340 \rightarrow 00:06:57.504$  has become the norm when managing NOTE Confidence: 0.7912263  $00:06:57.504 \rightarrow 00:06:59.274$  these patients and here looking NOTE Confidence: 0.7912263  $00:06:59.274 \rightarrow 00:07:02.149$  at all types of biome's and these NOTE Confidence: 0.7912263  $00:07:02.149 \rightarrow 00:07:03.997$  different colors here represents NOTE Confidence: 0.7912263  $00:07:03.997 \longrightarrow 00:07:06.382$  the different subtypes of gliomas. NOTE Confidence: 0.7912263  $00:07:06.382 \rightarrow 00:07:10.350$  And you have no difficulty to see that. NOTE Confidence: 0.7912263 00:07:10.350 --> 00:07:12.905 The genomic signatures are very NOTE Confidence: 0.7912263  $00{:}07{:}12.905 \dashrightarrow 00{:}07{:}14.949$  distinct across the different NOTE Confidence: 0.7912263  $00:07:14.949 \longrightarrow 00:07:16.730$  histologies you can see here. NOTE Confidence: 0.7912263  $00:07:16.730 \longrightarrow 00:07:19.015$  The quintessential signature of the NOTE Confidence: 0.7912263  $00:07:19.015 \rightarrow 00:07:21.994$  algal blooms, which is more penalty? NOTE Confidence: 0.7912263  $00:07:21.994 \rightarrow 00:07:24.574$  Q coalition ideate mutation Sir NOTE Confidence: 0.7912263  $00:07:24.574 \dashrightarrow 00:07:26.808$  promoter mutation and see I see NOTE Confidence: 0.7912263  $00:07:26.808 \longrightarrow 00:07:30.559$  and if you put P1 and here is the

- NOTE Confidence: 0.7912263
- $00{:}07{:}30.559 \dashrightarrow 00{:}07{:}32.587$  quintessential signature of Astros

 $00:07:32.587 \rightarrow 00:07:34.975$  with guided meditation AT Rex,

NOTE Confidence: 0.7912263

 $00:07:34.975 \longrightarrow 00:07:37.250$  Magician or lost interpretive fermentation.

NOTE Confidence: 0.7912263

 $00:07:37.250 \rightarrow 00:07:39.680$  And here's this essential signatures

NOTE Confidence: 0.7912263

 $00{:}07{:}39{.}680 \dashrightarrow 00{:}07{:}41{.}138$  of global stoma.

NOTE Confidence: 0.7912263

 $00{:}07{:}41.140 \dashrightarrow 00{:}07{:}43.513$  Now we start to see Jeff Farm

NOTE Confidence: 0.7912263

00:07:43.513 --> 00:07:45.690 to fication or mutation Pete.

NOTE Confidence: 0.7912263

 $00{:}07{:}45.690 \dashrightarrow 00{:}07{:}48.660$  Then loss or mutation and lots

NOTE Confidence: 0.7912263

 $00{:}07{:}48.660 \dashrightarrow 00{:}07{:}51.230$  of formalities in CD case.

NOTE Confidence: 0.7912263

 $00:07:51.230 \dashrightarrow 00:07:53.830$  So putting those patients now,

NOTE Confidence: 0.7912263

 $00{:}07{:}53.830 \dashrightarrow 00{:}07{:}56.924$  arranging them into what kind of pathways

NOTE Confidence: 0.7912263

 $00:07:56.924 \dashrightarrow 00:08:00.070$  ended up being abnormally disturbers,

NOTE Confidence: 0.7912263

 $00:08:00.070 \longrightarrow 00:08:03.563$  we can see the vast majority of

NOTE Confidence: 0.7912263

 $00{:}08{:}03.563 \dashrightarrow 00{:}08{:}06.310$  patients follow this cake recipe.

NOTE Confidence: 0.7912263

 $00{:}08{:}06{.}310 \dashrightarrow 00{:}08{:}09{.}640$  So basically 1000 kinase pathway with

00:08:09.640 --> 00:08:13.275 PKU KTM Tor pathway activation and F1

NOTE Confidence: 0.7912263

 $00:08:13.275 \dashrightarrow 00:08:17.006$  you see also a lot of these patients

NOTE Confidence: 0.7912263

 $00{:}08{:}17.006 \dashrightarrow 00{:}08{:}21.510$  with arousing in the T3 pathway leading to.

NOTE Confidence: 0.7912263

00:08:21.510 --> 00:08:24.090 Abnormalities in senescence and a pop

NOTE Confidence: 0.7912263

 $00{:}08{:}24.090 \dashrightarrow 00{:}08{:}27.354$  ptosis and a lot of these patients

NOTE Confidence: 0.7912263

 $00:08:27.354 \rightarrow 00:08:30.756$  having a normality's in cell cycle control.

NOTE Confidence: 0.7912263

00:08:30.760 --> 00:08:33.560 But then when we put all of these

NOTE Confidence: 0.7912263

 $00:08:33.560 \dashrightarrow 00:08:36.120$  patients a match to actually which

NOTE Confidence: 0.7912263

 $00{:}08{:}36{.}120 \dashrightarrow 00{:}08{:}38{.}790$  mutations have a track record of

NOTE Confidence: 0.7912263

 $00{:}08{:}38{.}874 \dashrightarrow 00{:}08{:}42{.}242$  being drug and what you can see is

NOTE Confidence: 0.7912263

 $00{:}08{:}42.242 \dashrightarrow 00{:}08{:}44.245$  unfortunately each of these mutations

NOTE Confidence: 0.7912263

 $00:08:44.245 \rightarrow 00:08:46.555$  is actually very where we're not

NOTE Confidence: 0.7912263

00:08:46.555 --> 00:08:48.717 being very good at identifying

NOTE Confidence: 0.7912263

 $00{:}08{:}48.717 \dashrightarrow 00{:}08{:}50.847$  drugs for those specific phenotypes

NOTE Confidence: 0.7912263

00:08:50.847 --> 00:08:53.366 we heavily rely on basket trials.

NOTE Confidence: 0.7912263

 $00:08:53.370 \rightarrow 00:08:55.306$  But unfortunately basket trials

- NOTE Confidence: 0.7912263
- $00{:}08{:}55{.}306 \dashrightarrow 00{:}08{:}57{.}242$  typically exclude patients with

 $00:08:57.242 \longrightarrow 00:08:59.622$  brain tumors were left with no

NOTE Confidence: 0.7912263

 $00:08:59.622 \rightarrow 00:09:01.644$  trials or very trials that address.

NOTE Confidence: 0.7912263

 $00{:}09{:}01{.}650 \dashrightarrow 00{:}09{:}03{.}325$  These questions we do have

NOTE Confidence: 0.7912263

 $00:09:03.325 \longrightarrow 00:09:04.665$  some low hanging fruits.

NOTE Confidence: 0.7912263

 $00:09:04.670 \longrightarrow 00:09:06.310$  Of course ideas mutation will

NOTE Confidence: 0.7912263

 $00:09:06.310 \longrightarrow 00:09:08.710$  talk a little bit more about that,

NOTE Confidence: 0.7912263

 $00:09:08.710 \longrightarrow 00:09:09.368$  but again,

NOTE Confidence: 0.7912263

 $00{:}09{:}09{.}368 \dashrightarrow 00{:}09{:}11.671$  the message here is that it is

NOTE Confidence: 0.7912263

00:09:11.671 -> 00:09:13.737 very difficult to run start

NOTE Confidence: 0.7912263

 $00:09:13.737 \longrightarrow 00:09:15.807$  therapy trials of these days.

NOTE Confidence: 0.7912263

 $00{:}09{:}15{.}810 \dashrightarrow 00{:}09{:}18{.}180$  Because you really need to have

NOTE Confidence: 0.7912263

 $00:09:18.180 \longrightarrow 00:09:20.249$  strategies to tackle the rarity

NOTE Confidence: 0.7912263

 $00:09:20.249 \longrightarrow 00:09:22.309$  of each of these phenotypes.

NOTE Confidence: 0.808799

 $00{:}09{:}24.330 \dashrightarrow 00{:}09{:}27.382$  And adding to our challenges are how

 $00:09:27.382 \rightarrow 00:09:30.181$  these tumors evolve overtime and how NOTE Confidence: 0.808799  $00{:}09{:}30{.}181 \dashrightarrow 00{:}09{:}32{.}989$  they are heterogeneous to begin with. NOTE Confidence: 0.808799  $00:09:32.990 \rightarrow 00:09:36.118$  So this is a patient, for example, NOTE Confidence: 0.808799  $00:09:36.118 \rightarrow 00:09:39.086$  that at diagnosis she was enrolled in NOTE Confidence: 0.808799  $00:09:39.086 \rightarrow 00:09:42.065$  one of my trials of a notch inhibitor NOTE Confidence: 0.808799  $00:09:42.065 \rightarrow 00:09:45.503$  and she had a very typical signature NOTE Confidence: 0.808799  $00:09:45.503 \rightarrow 00:09:47.795$  of astrocytomas with identification NOTE Confidence: 0.808799 00:09:47.795 --> 00:09:50.630 interaxon to 53 mutations and several NOTE Confidence: 0.808799  $00{:}09{:}50{.}630 \dashrightarrow 00{:}09{:}52{.}310$  potential target targetable abnormalities NOTE Confidence: 0.808799  $00:09:52.310 \rightarrow 00:09:54.490$  with other abnormalities, but. NOTE Confidence: 0.808799  $00:09:54.490 \rightarrow 00:09:56.570$  When this patient again, NOTE Confidence: 0.808799  $00:09:56.570 \rightarrow 00:10:00.760$  she received the nearly diagnosed. NOTE Confidence: 0.808799 00:10:00.760 --> 00:10:02.968 Trial and then when she recovered, NOTE Confidence: 0.808799  $00:10:02.970 \longrightarrow 00:10:04.820$  she was operated on again, NOTE Confidence: 0.808799  $00:10:04.820 \rightarrow 00:10:07.764$  even though she had a very small tumor. NOTE Confidence: 0.808799  $00:10:07.770 \longrightarrow 00:10:10.614$  And what we found is that all of those

- NOTE Confidence: 0.808799
- 00:10:10.614 --> 00:10:13.307 potential target mutations are actually gone.

 $00{:}10{:}13{.}310 \dashrightarrow 00{:}10{:}15{.}150$  We're seeing some passengers here.

NOTE Confidence: 0.808799

 $00:10:15.150 \longrightarrow 00:10:17.160$  But the reality that's what's driving

NOTE Confidence: 0.808799

 $00{:}10{:}17{.}160 \dashrightarrow 00{:}10{:}19{.}761$  this tumor now is actually probably about

NOTE Confidence: 0.808799

00:10:19.761 --> 00:10:22.155 Melanie's at the OBGYN attic level,

NOTE Confidence: 0.808799

 $00{:}10{:}22.160 \dashrightarrow 00{:}10{:}25.024$  and you can imagine that if at this

NOTE Confidence: 0.808799

 $00:10:25.024 \rightarrow 00:10:27.971$  point in time of her disease we work

NOTE Confidence: 0.808799

 $00:10:27.971 \longrightarrow 00:10:30.869$  to enroll her in a clinical trial.

NOTE Confidence: 0.808799

 $00{:}10{:}30{.}870 \dashrightarrow 00{:}10{:}33{.}145$  Most patients do not have another brain

NOTE Confidence: 0.808799

 $00{:}10{:}33.145 \dashrightarrow 00{:}10{:}35.190$  surgery to have another sequence,

NOTE Confidence: 0.808799

 $00{:}10{:}35{.}190 \dashrightarrow 00{:}10{:}37{.}678$  so you go to archive tissue and we

NOTE Confidence: 0.808799

00:10:37.678 --> 00:10:40.063 would have selected her for trials

NOTE Confidence: 0.808799

 $00:10:40.063 \rightarrow 00:10:42.173$  that probably were irrelevant for

NOTE Confidence: 0.808799

 $00{:}10{:}42.173 \dashrightarrow 00{:}10{:}44.187$  her at this point in time.

NOTE Confidence: 0.808799

00:10:44.190 --> 00:10:44.653 Again,

 $00:10:44.653 \rightarrow 00:10:47.431$  those are males that we thought

NOTE Confidence: 0.808799

 $00{:}10{:}47{.}431 \dashrightarrow 00{:}10{:}50{.}069$  were present were actually gone.

NOTE Confidence: 0.808799

 $00:10:50.070 \longrightarrow 00:10:53.640$  This is another example of potentially

NOTE Confidence: 0.808799

 $00{:}10{:}53.640 \dashrightarrow 00{:}10{:}56.569$  targetable mutations that actually were

NOTE Confidence: 0.808799

 $00:10:56.569 \rightarrow 00:10:59.845$  very different at the time of recurrence.

NOTE Confidence: 0.808799

 $00{:}10{:}59{.}850 \dashrightarrow 00{:}11{:}00{.}438$  And.

NOTE Confidence: 0.808799

 $00{:}11{:}00{.}438 \dashrightarrow 00{:}11{:}02{.}790$  Another difficult challenge are

NOTE Confidence: 0.808799

 $00:11:02.790 \longrightarrow 00:11:04.554$  these patients here.

NOTE Confidence: 0.808799

 $00{:}11{:}04.560 \dashrightarrow 00{:}11{:}08.216$  So these are patients that we serve created.

NOTE Confidence: 0.808799

 $00:11:08.220 \longrightarrow 00:11:11.541$  These is a result of the use of the

NOTE Confidence: 0.808799

 $00{:}11{:}11{.}541$  -->  $00{:}11{:}14{.}987$  Mozilla might that can cause mutations in NOTE Confidence: 0.808799

 $00:11:14.987 \rightarrow 00:11:18.269$  mismatch repair genes at typically MSH.

NOTE Confidence: 0.808799

 $00{:}11{:}18{.}270 \dashrightarrow 00{:}11{:}21{.}598$ 6 and what happens is that these patients

NOTE Confidence: 0.808799

 $00:11:21.598 \rightarrow 00:11:23.959$  with mismatch repair defects start

NOTE Confidence: 0.808799

 $00:11:23.959 \longrightarrow 00:11:26.379$  accumulating all of these mutations

NOTE Confidence: 0.808799

 $00:11:26.379 \rightarrow 00:11:29.473$  and you can imagine that developing

- NOTE Confidence: 0.808799
- $00:11:29.473 \longrightarrow 00:11:32.033$  target therapies for these folks.

 $00:11:32.040 \longrightarrow 00:11:33.312$  Is much harder.

NOTE Confidence: 0.808799

 $00{:}11{:}33{.}312 \dashrightarrow 00{:}11{:}35{.}856$  And one of the surprising findings

NOTE Confidence: 0.808799

 $00:11:35.856 \longrightarrow 00:11:38.560$  of our studies have been that

NOTE Confidence: 0.808799

 $00:11:38.560 \rightarrow 00:11:41.384$  these are actually much more common

NOTE Confidence: 0.808799

 $00:11:41.384 \rightarrow 00:11:43.560$  than we previously thought.

NOTE Confidence: 0.84145206

 $00:11:46.580 \rightarrow 00:11:49.044$  So in moving forward what we're trying to

NOTE Confidence: 0.84145206

 $00{:}11{:}49{.}044 \dashrightarrow 00{:}11{:}52{.}286$  do is to again improve the science linked

NOTE Confidence: 0.84145206

 $00:11:52.286 \rightarrow 00:11:54.520$  through the early development trials,

NOTE Confidence: 0.84145206

00:11:54.520 - 00:11:57.005 so we more and more relying Phase

NOTE Confidence: 0.84145206

 $00{:}11{:}57.005 \dashrightarrow 00{:}12{:}00.040$  Zero tries to show us if our drugs

NOTE Confidence: 0.84145206

 $00{:}12{:}00{.}040 \dashrightarrow 00{:}12{:}02{.}460$  are actually getting into the brain,

NOTE Confidence: 0.84145206

 $00:12:02.460 \longrightarrow 00:12:04.345$  especially in areas with intact

NOTE Confidence: 0.84145206

 $00{:}12{:}04{.}345 \dashrightarrow 00{:}12{:}05{.}476$  blood brain barrier.

NOTE Confidence: 0.84145206

 $00{:}12{:}05{.}480 \dashrightarrow 00{:}12{:}09{.}309$  We also want to see if the.

00:12:09.310 --> 00:12:11.536 The drugs are hitting their targets and

NOTE Confidence: 0.84145206

00:12:11.536 --> 00:12:14.373 we like to look at the pharmacodynamic

NOTE Confidence: 0.84145206

 $00{:}12{:}14.373 \dashrightarrow 00{:}12{:}16.638$  effects in these resected specimens.

NOTE Confidence: 0.84145206

00:12:16.640 --> 00:12:18.912 Be more and more have we have to

NOTE Confidence: 0.84145206

00:12:18.912 --> 00:12:21.390 work with their companies to have

NOTE Confidence: 0.84145206

 $00{:}12{:}21{.}390 \dashrightarrow 00{:}12{:}23{.}690$  basket trials that actually include NOTE Confidence: 0.84145206

 $00:12:23.690 \rightarrow 00:12:25.910$  patients with our rare phenotypes.

NOTE Confidence: 0.84145206

 $00{:}12{:}25{.}910 \dashrightarrow 00{:}12{:}27{.}840$  There's a shift towards more

NOTE Confidence: 0.84145206

 $00{:}12{:}27{.}840 \dashrightarrow 00{:}12{:}29{.}770$  of a newly diagnosed disease.

NOTE Confidence: 0.84145206

 $00{:}12{:}29.770 \dashrightarrow 00{:}12{:}32.080$  Be 'cause these are easier patients,

NOTE Confidence: 0.84145206

 $00{:}12{:}32.080 \dashrightarrow 00{:}12{:}34.015$  and the genomics information is

NOTE Confidence: 0.84145206

 $00:12:34.015 \rightarrow 00:12:35.945$  actually fresh, and where we're

NOTE Confidence: 0.84145206

 $00{:}12{:}35{.}945 \dashrightarrow 00{:}12{:}37{.}485$  dealing with recurrent disease,

NOTE Confidence: 0.84145206

 $00:12:37.490 \longrightarrow 00:12:39.475$  we typically like to re

NOTE Confidence: 0.84145206

 $00{:}12{:}39{.}475 \dashrightarrow 00{:}12{:}41{.}063$  sample specials for target.

NOTE Confidence: 0.84145206

00:12:41.070 --> 00:12:41.949 Therapies, if anything,

- NOTE Confidence: 0.84145206
- $00:12:41.949 \rightarrow 00:12:44.000$  at least to exclude the hypermedia phenotype.
- NOTE Confidence: 0.84145206
- $00{:}12{:}44.000 \dashrightarrow 00{:}12{:}46.232$  And we also like to of course update the
- NOTE Confidence: 0.84145206
- $00:12:46.232 \rightarrow 00:12:48.686$  gene sequencing and the Uncle Genic trimers.
- NOTE Confidence: 0.84145206
- 00:12:48.690 --> 00:12:50.734 Another trend in our field, this try
- NOTE Confidence: 0.84145206
- $00:12:50.734 \rightarrow 00:12:52.194$  to target these strong communications,
- NOTE Confidence: 0.84145206
- $00:12:52.200 \longrightarrow 00:12:53.958$  but that's not an easy task.
- NOTE Confidence: 0.84145206
- 00:12:53.960 --> 00:12:54.632 And again,
- NOTE Confidence: 0.84145206
- $00:12:54.632 \rightarrow 00:12:56.648$  we're going to talk a little
- NOTE Confidence: 0.84145206
- $00:12:56.648 \longrightarrow 00:12:58.160$  bit more about that.
- NOTE Confidence: 0.84145206
- $00:12:58.160 \rightarrow 00:13:01.976$  But the vast majority of trials right now
- NOTE Confidence: 0.84145206
- $00{:}13{:}01{.}976 \dashrightarrow 00{:}13{:}05{.}580$  is actually trying to find alternative
- NOTE Confidence: 0.84145206
- $00:13:05.580 \longrightarrow 00:13:09.414$  strategies that address more stable targets.
- NOTE Confidence: 0.84145206
- $00:13:09.420 \dashrightarrow 00:13:11.940$  So the low hanging fruit of stable
- NOTE Confidence: 0.84145206
- $00:13:11.940 \longrightarrow 00:13:14.219$  targets is actually immuno the rapies.
- NOTE Confidence: 0.84145206
- $00:13:14.220 \longrightarrow 00:13:16.620$  So we do know that blue,
- NOTE Confidence: 0.84145206

00:13:16.620 --> 00:13:19.020 blasphemous do grow in a very

NOTE Confidence: 0.84145206

 $00:13:19.020 \rightarrow 00:13:20.220$  human suppressive microenvironment.

NOTE Confidence: 0.84145206

 $00{:}13{:}20{.}220 \dashrightarrow 00{:}13{:}22{.}225$  And we have identified several

NOTE Confidence: 0.84145206

00:13:22.225 --> 00:13:25.075 emergent points that seem to be very

NOTE Confidence: 0.84145206

 $00{:}13{:}25.075 \dashrightarrow 00{:}13{:}26.615$  important in this disease.

NOTE Confidence: 0.84145206

 $00:13:26.620 \longrightarrow 00:13:28.620$  But on top of identifying

NOTE Confidence: 0.84145206

00:13:28.620 --> 00:13:30.220 the right even checkpoint,

NOTE Confidence: 0.84145206

 $00:13:30.220 \longrightarrow 00:13:32.620$  we have the challenges of the

NOTE Confidence: 0.84145206

 $00:13:32.620 \longrightarrow 00:13:33.820$  anatomic location itself.

NOTE Confidence: 0.84145206

 $00{:}13{:}33{.}820 \dashrightarrow 00{:}13{:}36{.}836$  So you can imagine that it's much harder

NOTE Confidence: 0.84145206

 $00{:}13{:}36{.}836 \dashrightarrow 00{:}13{:}39{.}517$  to trigger him and logical response.

NOTE Confidence: 0.84145206

 $00:13:39.520 \longrightarrow 00:13:40.528$  In the brain,

NOTE Confidence: 0.84145206

00:13:40.528 --> 00:13:41.200 which is,

NOTE Confidence: 0.84145206

00:13:41.200 --> 00:13:41.958 you know,

NOTE Confidence: 0.84145206

 $00:13:41.958 \longrightarrow 00:13:43.474$  traditionally considered the so-called

NOTE Confidence: 0.84145206

 $00:13:43.474 \rightarrow 00:13:45.789$  sanctuary sites for the immune system.

- NOTE Confidence: 0.84145206
- $00:13:45.790 \longrightarrow 00:13:48.401$  And we have to get these email

 $00{:}13{:}48{.}401 \dashrightarrow 00{:}13{:}50{.}934$  responses to act fast because these

NOTE Confidence: 0.84145206

 $00{:}13{:}50{.}934 \dashrightarrow 00{:}13{:}53{.}598$  are tumors that grow very rapidly

NOTE Confidence: 0.84145206

 $00{:}13{:}53{.}598 \dashrightarrow 00{:}13{:}56{.}154$  and they cause symptoms and we

NOTE Confidence: 0.84145206

 $00:13:56.154 \rightarrow 00:13:58.592$  don't have the luxury of waiting

NOTE Confidence: 0.84145206

 $00:13:58.592 \rightarrow 00:14:01.064$  several months or years to react.

NOTE Confidence: 0.84145206

 $00:14:01.070 \longrightarrow 00:14:03.954$  The benefits of the email of the rapies.

NOTE Confidence: 0.84145206

00:14:03.960 --> 00:14:05.190 And of course,

NOTE Confidence: 0.84145206

00:14:05.190 --> 00:14:06.830 if you're triggering inflammatory

NOTE Confidence: 0.84145206

 $00:14:06.830 \longrightarrow 00:14:08.510$  responses in the brain,

NOTE Confidence: 0.84145206

 $00{:}14{:}08{.}510 \dashrightarrow 00{:}14{:}11{.}054$  we have to deal with the risks of

NOTE Confidence: 0.84145206

 $00{:}14{:}11.054 \dashrightarrow 00{:}14{:}13.870$  new log symptoms and neurotoxicity.

NOTE Confidence: 0.84145206

 $00{:}14{:}13.870 \dashrightarrow 00{:}14{:}16.210$  An another important thing is.

NOTE Confidence: 0.84145206

 $00{:}14{:}16{.}210 \dashrightarrow 00{:}14{:}17{.}758$  That this information could

NOTE Confidence: 0.84145206

 $00{:}14{:}17.758 \dashrightarrow 00{:}14{:}19.306$  potentially mimic some aggression,

 $00:14:19.310 \longrightarrow 00:14:21.390$  so managing these patients can

NOTE Confidence: 0.84145206

 $00:14:21.390 \longrightarrow 00:14:23.470$  be challenging because we have

NOTE Confidence: 0.84145206

 $00:14:23.541 \longrightarrow 00:14:25.515$  to learn to how to recognize,

NOTE Confidence: 0.84145206

00:14:25.520 --> 00:14:27.460 see the progression versus real

NOTE Confidence: 0.84145206

 $00{:}14{:}27{.}460 \dashrightarrow 00{:}14{:}29{.}400$  tumor progression on the MRI.

NOTE Confidence: 0.7355124

 $00{:}14{:}34{.}080 \dashrightarrow 00{:}14{:}36{.}383$  But we did try and here you're NOTE Confidence: 0.7355124

00:14:36.383 --> 00:14:38.594 looking at the very first results

NOTE Confidence: 0.7355124

 $00:14:38.594 \longrightarrow 00:14:41.261$  of the very first phase one trial

NOTE Confidence: 0.7355124

00:14:41.334 --> 00:14:43.266 utilizing image checkpoint inhibitors NOTE Confidence: 0.7355124

 $00{:}14{:}43{.}266$  -->  $00{:}14{:}46{.}870$  in global stoma and this was done in NOTE Confidence: 0.7355124

 $00{:}14{:}46{.}870 \dashrightarrow 00{:}14{:}49{.}670$  with VMS and in this trial we treated NOTE Confidence: 0.7355124

 $00{:}14{:}49.755 \dashrightarrow 00{:}14{:}52.605$  40 patients both with nivolumab or NOTE Confidence: 0.7355124

00:14:52.605 --> 00:14:54.950 two combinations of Nivola Bintulu

NOTE Confidence: 0.7355124

 $00{:}14{:}54{.}950 \dashrightarrow 00{:}14{:}57{.}854$  map and what we found is that yes,

NOTE Confidence: 0.7355124

 $00{:}14{:}57{.}860 \dashrightarrow 00{:}14{:}59{.}875$  the target definitely was present

NOTE Confidence: 0.7355124

 $00:14:59.875 \longrightarrow 00:15:01.890$  in the majority of patients,

- NOTE Confidence: 0.7355124
- $00{:}15{:}01.890 \dashrightarrow 00{:}15{:}04.632$  so 60% of the patients had

 $00:15:04.632 \longrightarrow 00:15:06.003$  PDL one expression.

NOTE Confidence: 0.7355124

 $00{:}15{:}06{.}010 \dashrightarrow 00{:}15{:}07{.}942$  But we didn't see any brain toxicities

NOTE Confidence: 0.7355124

 $00{:}15{:}07{.}942 \dashrightarrow 00{:}15{:}10{.}169$  which is good and perhaps bad because

NOTE Confidence: 0.7355124

 $00:15:10.169 \longrightarrow 00:15:11.844$  this could potentially reflect the

NOTE Confidence: 0.7355124

 $00{:}15{:}11{.}844 \dashrightarrow 00{:}15{:}13{.}694$  fact that we are not achieving

NOTE Confidence: 0.7355124

 $00:15:13.694 \rightarrow 00:15:15.466$  much and overall survival was very

NOTE Confidence: 0.7355124

00:15:15.466 --> 00:15:16.690 similar to historical controls,

NOTE Confidence: 0.7355124

00:15:16.690 --> 00:15:18.652 although some places it seemed to

NOTE Confidence: 0.7355124

 $00{:}15{:}18.652 \dashrightarrow 00{:}15{:}21.010$  Mount more of an email response.

NOTE Confidence: 0.7355124

 $00{:}15{:}21.010 \dashrightarrow 00{:}15{:}23.850$  But this went on to be tested in

NOTE Confidence: 0.7355124

 $00{:}15{:}23.850 \dashrightarrow 00{:}15{:}26.079$  randomized trials and we are now

NOTE Confidence: 0.7355124

 $00{:}15{:}26.079 \dashrightarrow 00{:}15{:}27.889$  reporting the final results of

NOTE Confidence: 0.7355124

 $00{:}15{:}27.889 \dashrightarrow 00{:}15{:}30.321$  these shows and one by one they

NOTE Confidence: 0.7355124

 $00{:}15{:}30{.}321 \dashrightarrow 00{:}15{:}32{.}015$  all failed to improve survival,

 $00{:}15{:}32.015 \dashrightarrow 00{:}15{:}34.145$  both newly diagnose and recurrent disease.

NOTE Confidence: 0.8497241

00:15:37.040 --> 00:15:39.238 So we're not giving up on immunotherapy,

NOTE Confidence: 0.8497241

 $00{:}15{:}39{.}240 \dashrightarrow 00{:}15{:}42{.}230$  so I think our task now is to try to

NOTE Confidence: 0.8497241

 $00:15:42.320 \longrightarrow 00:15:45.148$  send what is that about the brain?

NOTE Confidence: 0.8497241

00:15:45.150 --> 00:15:48.146 That in spite of PDL one expression

NOTE Confidence: 0.8497241

 $00{:}15{:}48{.}146 \dashrightarrow 00{:}15{:}50{.}865$  we're not seeing any help from Anti NOTE Confidence: 0.8497241

 $00{:}15{:}50.865 \dashrightarrow 00{:}15{:}53.818$  PD one or anti PDL one the rapies and NOTE Confidence: 0.8497241

 $00:15:53.818 \rightarrow 00:15:57.178$  I think for for this question I think

NOTE Confidence: 0.8497241

 $00{:}15{:}57{.}180 \dashrightarrow 00{:}16{:}00{.}375$  it is great to have a helping hand of NOTE Confidence: 0.8497241

 $00:16:00.375 \longrightarrow 00:16:02.993$  people that study the CNS immunology

NOTE Confidence: 0.8497241

 $00{:}16{:}02{.}993 \dashrightarrow 00{:}16{:}06{.}834$  and in this project what we did is to NOTE Confidence: 0.8497241

 $00{:}16{:}06{.}834 \dashrightarrow 00{:}16{:}09{.}204$  partner with Doctor David Hoffer and NOTE Confidence: 0.8497241

00:16:09.210 --> 00:16:12.266 I'll also Liliana Luca to look at how

NOTE Confidence: 0.8497241

 $00{:}16{:}12.266 \dashrightarrow 00{:}16{:}15.646$  can we actually come up with better.

NOTE Confidence: 0.8497241

 $00{:}16{:}15{.}650 \dashrightarrow 00{:}16{:}18{.}070$  Image checkpoint inhibition that is

NOTE Confidence: 0.8497241

 $00{:}16{:}18.070 \dashrightarrow 00{:}16{:}20.981$  relevant for for this Mike environment

- NOTE Confidence: 0.8497241
- $00:16:20.981 \longrightarrow 00:16:24.229$  and what the heifers lab came up with
- NOTE Confidence: 0.8497241
- $00{:}16{:}24{.}229 \dashrightarrow 00{:}16{:}27{.}400$  is that this image of point called digit
- NOTE Confidence: 0.8497241
- $00{:}16{:}27{.}400 \dashrightarrow 00{:}16{:}31{.}130$  seems to be much more relevant in the brain.
- NOTE Confidence: 0.8497241
- $00:16:31.130 \longrightarrow 00:16:33.578$  It was very interesting that in
- NOTE Confidence: 0.8497241
- $00{:}16{:}33{.}578 \dashrightarrow 00{:}16{:}36{.}289$  their studies they found a lot of
- NOTE Confidence: 0.8497241
- $00{:}16{:}36{.}289 \dashrightarrow 00{:}16{:}38{.}299$  teacher expression in DBMS and not
- NOTE Confidence: 0.8497241
- $00:16:38.299 \longrightarrow 00:16:41.370$  so much digit expression in the
- NOTE Confidence: 0.8497241
- $00:16:41.370 \longrightarrow 00:16:42.966$  quintessential inflammatory disease
- NOTE Confidence: 0.8497241
- $00{:}16{:}42.966 \dashrightarrow 00{:}16{:}45.335$  which is multiple sclerosis and.
- NOTE Confidence: 0.8497241
- $00:16:45.335 \longrightarrow 00:16:47.510$  They went on to perform
- NOTE Confidence: 0.8497241
- 00:16:47.510 --> 00:16:49.150 several studies utilizing,
- NOTE Confidence: 0.8497241
- $00{:}16{:}49{.}150 \dashrightarrow 00{:}16{:}51{.}796$  so sequencing that sort of confirmed
- NOTE Confidence: 0.8497241
- $00:16:51.796 \rightarrow 00:16:54.930$  that T cell dysfunction was being driven
- NOTE Confidence: 0.8497241
- $00{:}16{:}54{.}930 \dashrightarrow 00{:}16{:}57{.}522$  by digit in this particular disease.
- NOTE Confidence: 0.8497241
- $00:16:57.530 \longrightarrow 00:17:00.176$  So to test this hypothesis in
- NOTE Confidence: 0.8497241

 $00:17:00.176 \longrightarrow 00:17:01.499$  patients with design,

NOTE Confidence: 0.8497241

 $00:17:01.500 \longrightarrow 00:17:06.316$  this clinical trial where we are looking at.

NOTE Confidence: 0.8497241

 $00{:}17{:}06{.}320 \dashrightarrow 00{:}17{:}08{.}768$  A different cohorts of patients prior

NOTE Confidence: 0.8497241

00:17:08.768 --> 00:17:11.527 to surgery where they will be treated

NOTE Confidence: 0.8497241

00:17:11.527 --> 00:17:13.991 with either infected or anti PD one

NOTE Confidence: 0.8497241

 $00{:}17{:}14.068 \dashrightarrow 00{:}17{:}16.474$  or the combination or placebo and NOTE Confidence: 0.8497241

 $00:17:16.474 \rightarrow 00:17:19.064$  then these patients will be brought to

NOTE Confidence: 0.8497241

00:17:19.064 --> 00:17:21.837 surgery and then we will do a tumor

NOTE Confidence: 0.8497241

00:17:21.837 --> 00:17:24.219 single cell RNA sequencing with an

NOTE Confidence: 0.8497241

 $00:17:24.219 \rightarrow 00:17:27.662$  axe as well as some studies to produce NOTE Confidence: 0.8497241

 $00:17:27.662 \rightarrow 00:17:30.291$  some spatial validation of the findings.

NOTE Confidence: 0.8497241

 $00{:}17{:}30{.}291 \dashrightarrow 00{:}17{:}32{.}997$  And there will also follow these

NOTE Confidence: 0.8497241

 $00:17:32.997 \longrightarrow 00:17:35.444$  patients longitudinally to see if we

NOTE Confidence: 0.8497241

 $00{:}17{:}35{.}444 \dashrightarrow 00{:}17{:}37{.}824$  can monitor what's happening in the tumor.

NOTE Confidence: 0.8497241

 $00{:}17{:}37.830 \dashrightarrow 00{:}17{:}40.566$  By analyzing the T cells in the periphery.

NOTE Confidence: 0.8497241

 $00:17:40.570 \longrightarrow 00:17:42.616$  So it's a very exciting trial.

- NOTE Confidence: 0.8497241
- $00{:}17{:}42.620 \dashrightarrow 00{:}17{:}44.860$  So I wish we had started the

 $00{:}17{:}44.860 \dashrightarrow 00{:}17{:}47.376$  development of Inter PD one this way

NOTE Confidence: 0.8497241

 $00:17:47.376 \rightarrow 00:17:49.236$  by understanding the science before

NOTE Confidence: 0.8497241

 $00:17:49.236 \rightarrow 00:17:51.598$  going to more or larger studies that

NOTE Confidence: 0.8497241

00:17:51.598 --> 00:17:53.221 would end up being negative,

NOTE Confidence: 0.8497241

 $00{:}17{:}53{.}221 \dashrightarrow 00{:}17{:}55{.}608$  but we're very excited about this mechanism.

NOTE Confidence: 0.8497241

 $00{:}17{:}55.610 \dashrightarrow 00{:}17{:}58.166$  Action also is important to emphasize

NOTE Confidence: 0.8497241

 $00{:}17{:}58.166 \dashrightarrow 00{:}18{:}00.554$  that this combination of anti teachers

NOTE Confidence: 0.8497241

 $00:18:00.554 \rightarrow 00:18:03.329$  and in fact PD one is very hot in

NOTE Confidence: 0.8497241

 $00:18:03.329 \longrightarrow 00:18:05.585$  the fields right now as you know it

NOTE Confidence: 0.8497241

00:18:05.585 --> 00:18:07.302 is already in phase 3IN.

NOTE Confidence: 0.8497241

00:18:07.302 --> 00:18:09.092 Non small cell lung cancer.

NOTE Confidence: 0.8497241

00:18:09.100 --> 00:18:11.320 And we're very excited to bring

NOTE Confidence: 0.8497241

 $00:18:11.320 \longrightarrow 00:18:13.170$  this trial here to you.

NOTE Confidence: 0.8553554

 $00{:}18{:}15{.}700 \dashrightarrow 00{:}18{:}17{.}550$  Also, to understand a little

00:18:17.550 --> 00:18:19.990 bit more of the immune system,

NOTE Confidence: 0.8553554

 $00:18:19.990 \longrightarrow 00:18:23.595$  we need a good models that are

NOTE Confidence: 0.8553554

00:18:23.595 --> 00:18:25.910 immunocompetent and one of the.

NOTE Confidence: 0.8553554

 $00{:}18{:}25{.}910 \dashrightarrow 00{:}18{:}27{.}815$  A richness of our environment

NOTE Confidence: 0.8553554

 $00{:}18{:}27.815 \dashrightarrow 00{:}18{:}30.180$  here is Doctor City chains work

NOTE Confidence: 0.8553554

 $00{:}18{:}30{.}180$  -->  $00{:}18{:}32{.}508$  producing these jam models of global NOTE Confidence: 0.8553554

 $00{:}18{:}32{.}508 \dashrightarrow 00{:}18{:}34{.}945$  stom as where he can pretty much

NOTE Confidence: 0.8553554

 $00:18:34.945 \longrightarrow 00:18:37.351$  produce avatars for all of these

NOTE Confidence: 0.8553554

00:18:37.351 --> 00:18:39.740 phenotypes that I just showed you,

NOTE Confidence: 0.8553554

 $00{:}18{:}39{.}740 \dashrightarrow 00{:}18{:}42{.}008$  and one of the ideas here is to see

NOTE Confidence: 0.8553554

 $00{:}18{:}42.008 \dashrightarrow 00{:}18{:}44.585$  how these different phenotypes respond NOTE Confidence: 0.8553554

 $00:18:44.585 \rightarrow 00:18:46.845$  to these different immunotherapy's.

NOTE Confidence: 0.8553554

 $00{:}18{:}46.850 \dashrightarrow 00{:}18{:}49.268$  So this is very exciting data

NOTE Confidence: 0.8553554

 $00:18:49.268 \rightarrow 00:18:51.744$  which again illustrates how we can

NOTE Confidence: 0.8553554

 $00:18:51.744 \rightarrow 00:18:53.724$  concomitantly to the development in

NOTE Confidence: 0.8553554

 $00:18:53.724 \rightarrow 00:18:56.607$  the clinic to also try to understand.

 $00:18:56.610 \rightarrow 00:18:59.610$  Are these treatments in parallel in the lab?

NOTE Confidence: 0.80247504

 $00:19:02.490 \longrightarrow 00:19:06.558$  Now another barrier for.

NOTE Confidence: 0.80247504

 $00{:}19{:}06{.}560 \dashrightarrow 00{:}19{:}09{.}095$  For the development of effective

NOTE Confidence: 0.80247504

 $00:19:09.095 \rightarrow 00:19:11.630$  even responses is the work

NOTE Confidence: 0.80247504

 $00:19:11.716 \longrightarrow 00:19:14.380$  being done by the Iwasaki slab.

NOTE Confidence: 0.80247504

 $00{:}19{:}14.380 \dashrightarrow 00{:}19{:}17.176$  So Akiko has been working with

NOTE Confidence: 0.80247504

00:19:17.176 --> 00:19:19.760 Eric Song and General Thomas,

NOTE Confidence: 0.80247504

 $00:19:19.760 \rightarrow 00:19:23.757$  and she has recently had this nature

NOTE Confidence: 0.80247504

 $00:19:23.757 \longrightarrow 00:19:26.869$  paper where they showed that.

NOTE Confidence: 0.80247504

 $00{:}19{:}26.870 \dashrightarrow 00{:}19{:}29.075$  There is a defective lymphatic

NOTE Confidence: 0.80247504

00:19:29.075 --> 00:19:31.788 drainage from the brain that you

NOTE Confidence: 0.80247504

 $00:19:31.788 \longrightarrow 00:19:33.908$  can correct utilizing the GFC.

NOTE Confidence: 0.80247504

 $00{:}19{:}33{.}910 \dashrightarrow 00{:}19{:}36{.}416$  So in her models that the combination

NOTE Confidence: 0.80247504

 $00{:}19{:}36.416 \dashrightarrow 00{:}19{:}39.667$  of Veg FC and Anti PD one actually

NOTE Confidence: 0.80247504

 $00{:}19{:}39.667 \dashrightarrow 00{:}19{:}41.762$  improves survival and was also

 $00:19:41.845 \rightarrow 00:19:44.475$  interesting that they also produce

NOTE Confidence: 0.80247504

00:19:44.475 --> 00:19:47.105 some experiments by injecting anti

NOTE Confidence: 0.80247504

 $00{:}19{:}47{.}110$  -->  $00{:}19{:}50{.}518$  PD one directly into the CSF and also NOTE Confidence: 0.80247504

 $00{:}19{:}50{.}518 \dashrightarrow 00{:}19{:}53{.}933$  the results seem to be better than

NOTE Confidence: 0.80247504

 $00{:}19{:}53{.}933 \dashrightarrow 00{:}19{:}56{.}850$  systemic administration of anti PD one.

NOTE Confidence: 0.80247504

 $00{:}19{:}56.850 \dashrightarrow 00{:}19{:}59.906$  So this is all giving rise to another

NOTE Confidence: 0.80247504

 $00:19:59.906 \longrightarrow 00:20:01.634$  generation of characterizing and

NOTE Confidence: 0.80247504

 $00{:}20{:}01{.}634 \dashrightarrow 00{:}20{:}04{.}728$  some new compounds that we hope to

NOTE Confidence: 0.80247504

 $00{:}20{:}04.728 \dashrightarrow 00{:}20{:}07.200$  bring to clinic in the mid term.

NOTE Confidence: 0.7626056

 $00:20:09.870 \longrightarrow 00:20:12.050$  Now also again another important

NOTE Confidence: 0.7626056

00:20:12.050 --> 00:20:14.230 barrier in Spanish solid tumors,

NOTE Confidence: 0.7626056

00:20:14.230 --> 00:20:15.878 but particularly in glomus,

NOTE Confidence: 0.7626056

 $00:20:15.878 \rightarrow 00:20:18.883$  is the role of tumor associated macrophages

NOTE Confidence: 0.7626056

 $00:20:18.883 \rightarrow 00:20:21.637$  and how they produce these emails.

NOTE Confidence: 0.7626056

 $00{:}20{:}21{.}640 \dashrightarrow 00{:}20{:}22{.}948$  Suppressive tumor convergence

NOTE Confidence: 0.7626056

 $00:20:22.948 \rightarrow 00:20:26.548$  and one of the ways that we could

- NOTE Confidence: 0.7626056
- $00:20:26.548 \rightarrow 00:20:28.883$  potentially intervene in this was

 $00:20:28.883 \rightarrow 00:20:31.668$  discovered by an item here at go,

NOTE Confidence: 0.7626056

 $00{:}20{:}31.670 \dashrightarrow 00{:}20{:}34.729$  where she's looking at the role of

NOTE Confidence: 0.7626056

 $00:20:34.729 \rightarrow 00:20:36.975$  this little Robo one, signaling

NOTE Confidence: 0.7626056

 $00{:}20{:}36{.}975 \dashrightarrow 00{:}20{:}40{.}005$  which seems to attract and polarize.

NOTE Confidence: 0.7626056

00:20:40.010 --> 00:20:42.320 Save Microfridge is in the

NOTE Confidence: 0.7626056

 $00:20:42.320 \longrightarrow 00:20:43.475$  brain microenvironment and

NOTE Confidence: 0.7626056

00:20:43.475 --> 00:20:44.709 Livingstone my confirming.

NOTE Confidence: 0.7626056

 $00:20:44.710 \rightarrow 00:20:47.846$  And when she did experiments to knock down,

NOTE Confidence: 0.7626056

00:20:47.850 --> 00:20:50.587 slid to, or to block this pathway,

NOTE Confidence: 0.7626056

 $00:20:50.590 \rightarrow 00:20:52.590$  she achieved better immune responses

NOTE Confidence: 0.7626056

 $00{:}20{:}52{.}590 \dashrightarrow 00{:}20{:}54{.}910$  and inflammation of anti PD one.

NOTE Confidence: 0.7626056

 $00{:}20{:}54{.}910 \dashrightarrow 00{:}20{:}57{.}202$  She had a really significant improvement

NOTE Confidence: 0.7626056

 $00{:}20{:}57{.}202 \dashrightarrow 00{:}21{:}00{.}389$  in survival or in this tumor bearing mice.

NOTE Confidence: 0.7626056

 $00{:}21{:}00{.}390 \dashrightarrow 00{:}21{:}03{.}270$  So the idea here is now to generate

 $00:21:03.270 \rightarrow 00:21:05.824$  enter Robo Nanobodies one of the

NOTE Confidence: 0.7626056

 $00{:}21{:}05{.}824 \dashrightarrow 00{:}21{:}08{.}014$  barriers project would be then

NOTE Confidence: 0.7626056

 $00:21:08.014 \rightarrow 00:21:10.338$  how can we get this number?

NOTE Confidence: 0.7626056

 $00:21:10.340 \longrightarrow 00:21:12.888$  At least to penetrate into the brain.

NOTE Confidence: 0.7626056

00:21:12.890 --> 00:21:14.710 And since she's very resourceful,

NOTE Confidence: 0.7626056

 $00:21:14.710 \longrightarrow 00:21:16.810$  she has the answer.

NOTE Confidence: 0.7626056

 $00{:}21{:}16.810 \dashrightarrow 00{:}21{:}18.385$  It looks like.

NOTE Confidence: 0.7626056

00:21:18.390 --> 00:21:19.938 If you block antibodies,

NOTE Confidence: 0.7626056

00:21:19.938 --> 00:21:21.873 if you use antibodies blocking

NOTE Confidence: 0.7626056

 $00:21:21.873 \rightarrow 00:21:23.817$  this receptor called UNC 5B,

NOTE Confidence: 0.7626056

 $00:21:23.820 \longrightarrow 00:21:26.148$  you conserve produce an on demand

NOTE Confidence: 0.7626056

00:21:26.148 --> 00:21:27.700 blood brain barrier opening,

NOTE Confidence: 0.7626056

 $00{:}21{:}27{.}700 \dashrightarrow 00{:}21{:}30.868$  so this is less a few hours and it's

NOTE Confidence: 0.7626056

00:21:30.868 --> 00:21:33.907 great for drugs up to 40 kilodaltons.

NOTE Confidence: 0.7626056

 $00{:}21{:}33{.}910 \dashrightarrow 00{:}21{:}37{.}402$  So the idea here is that if this is

NOTE Confidence: 0.7626056

 $00:21:37.402 \rightarrow 00:21:39.238$  successful, we could combine this.

- NOTE Confidence: 0.7626056
- $00:21:39.238 \longrightarrow 00:21:41.410$  These agents with many of the

 $00:21:41.484 \rightarrow 00:21:43.644$  chemotherapies in order target therapies

NOTE Confidence: 0.7626056

 $00:21:43.644 \rightarrow 00:21:46.961$  that we are trying to use to treat

NOTE Confidence: 0.7626056

 $00:21:46.961 \rightarrow 00:21:49.495$  these patients in a more efficient way.

NOTE Confidence: 0.7626056

 $00:21:49.500 \longrightarrow 00:21:51.456$  And overcome the problem of living

NOTE Confidence: 0.7626056

 $00{:}21{:}51{.}456 \dashrightarrow 00{:}21{:}53{.}080$  there countries so very exciting

NOTE Confidence: 0.7626056

 $00:21:53.080 \rightarrow 00:21:55.176$  work that we hope to see more of.

NOTE Confidence: 0.74804413

 $00{:}21{:}57{.}340 \dashrightarrow 00{:}21{:}59{.}216$  No moving on into.

NOTE Confidence: 0.74804413

00:21:59.216 --> 00:22:02.030 It's still sticking to the Mockingbird,

NOTE Confidence: 0.74804413

 $00:22:02.030 \rightarrow 00:22:05.306$  but moving on to partnerships with pharma.

NOTE Confidence: 0.74804413

 $00{:}22{:}05{.}310 \dashrightarrow 00{:}22{:}08{.}350$  One of the our partnerships

NOTE Confidence: 0.74804413

 $00{:}22{:}08{.}350 \dashrightarrow 00{:}22{:}10{.}782$  is with this drug.

NOTE Confidence: 0.74804413

 $00{:}22{:}10.790 \dashrightarrow 00{:}22{:}13.250$  This company called In Pharmaceuticals

NOTE Confidence: 0.74804413

 $00{:}22{:}13.250 \dashrightarrow 00{:}22{:}15.710$  and these folks have discovered

NOTE Confidence: 0.74804413

 $00{:}22{:}15.781 \dashrightarrow 00{:}22{:}17.929$  a novel receptor with within the
$00:22:17.929 \rightarrow 00:22:20.124$  Alpha V beta three integrin that

NOTE Confidence: 0.74804413

 $00:22:20.124 \longrightarrow 00:22:22.532$  is started by this FP PMT drug

NOTE Confidence: 0.74804413

 $00{:}22{:}22{.}532 \dashrightarrow 00{:}22{:}24{.}895$  that seems to have an amazing

NOTE Confidence: 0.74804413

00:22:24.895 - 00:22:26.910 activity in their mouse models.

NOTE Confidence: 0.74804413

 $00:22:26.910 \longrightarrow 00:22:28.798$  Really melting the mice.

NOTE Confidence: 0.74804413

 $00{:}22{:}28.798 \dashrightarrow 00{:}22{:}31.158$  And this was the first.

NOTE Confidence: 0.74804413

00:22:31.160 --> 00:22:33.488 Now we're now designing the 1st

NOTE Confidence: 0.74804413

00:22:33.488 --> 00:22:35.500 in human trial here GAIL,

NOTE Confidence: 0.74804413

 $00{:}22{:}35{.}500 \dashrightarrow 00{:}22{:}38{.}660$  that will start in a couple of months.

NOTE Confidence: 0.74804413

 $00{:}22{:}38.660 \dashrightarrow 00{:}22{:}41.144$  But to understand this better we

NOTE Confidence: 0.74804413

 $00{:}22{:}41.144 \dashrightarrow 00{:}22{:}43.800$ did bring Yellow Labs into the mix NOTE Confidence: 0.74804413

 $00:22:43.800 \rightarrow 00:22:46.325$  to better define how is this rug

NOTE Confidence: 0.74804413

 $00:22:46.325 \longrightarrow 00:22:48.215$  really working and who are the

NOTE Confidence: 0.74804413

 $00{:}22{:}48.215 \dashrightarrow 00{:}22{:}50.205$  best candidates by understand a

NOTE Confidence: 0.74804413

 $00{:}22{:}50{.}205 \dashrightarrow 00{:}22{:}52{.}617$  little bit more about the effects

NOTE Confidence: 0.74804413

 $00:22:52.686 \rightarrow 00:22:55.031$  on cell invasion signaling networks

- NOTE Confidence: 0.74804413
- $00:22:55.031 \longrightarrow 00:22:56.438$  and gene expression.

 $00:22:56.440 \longrightarrow 00:22:59.386$  So one of the assets that.

NOTE Confidence: 0.74804413

 $00{:}22{:}59{.}390 \dashrightarrow 00{:}23{:}01{.}685$  We're realizing in partnership with

NOTE Confidence: 0.74804413

 $00{:}23{:}01.685 \dashrightarrow 00{:}23{:}04.710$  under left ankle is looking at these.

NOTE Confidence: 0.74804413

 $00{:}23{:}04.710 \dashrightarrow 00{:}23{:}07.356$  The use of his integrated platform,

NOTE Confidence: 0.74804413

 $00{:}23{:}07{.}360 \dashrightarrow 00{:}23{:}09{.}726$  which is the so called race essay

NOTE Confidence: 0.74804413

 $00{:}23{:}09{.}726 \dashrightarrow 00{:}23{:}12{.}753$  which is a disrupted analysis of cell

NOTE Confidence: 0.74804413

 $00{:}23{:}12.753 \dashrightarrow 00{:}23{:}15.173$  phenotype extremes where he uses

NOTE Confidence: 0.74804413

 $00{:}23{:}15{.}173 \dashrightarrow 00{:}23{:}18{.}188$  the cell migration as a surrogate

NOTE Confidence: 0.74804413

00:23:18.188 --> 00:23:20.643 marker of tumor aggressiveness and

NOTE Confidence: 0.74804413

 $00{:}23{:}20.650 \dashrightarrow 00{:}23{:}23.870$  and then you can test the multiple

NOTE Confidence: 0.74804413

 $00{:}23{:}23{.}870 \dashrightarrow 00{:}23{:}26{.}154$  drugs utilizing this essay as

NOTE Confidence: 0.74804413

 $00{:}23{:}26{.}154 \dashrightarrow 00{:}23{:}28{.}184$  a form of drug screening,

NOTE Confidence: 0.74804413

 $00{:}23{:}28{.}190 \dashrightarrow 00{:}23{:}30{.}910$  and he's applying this rug.

NOTE Confidence: 0.74804413

 $00:23:30.910 \rightarrow 00:23:33.406$  Your days were very interesting results

 $00:23:33.406 \rightarrow 00:23:36.928$  and we hope to then identify partners.

NOTE Confidence: 0.74804413

 $00{:}23{:}36{.}930 \dashrightarrow 00{:}23{:}39{.}498$  Which are the best genomic candidates

NOTE Confidence: 0.74804413

 $00{:}23{:}39{.}498 \dashrightarrow 00{:}23{:}42{.}268$  and then see if we can optimize

NOTE Confidence: 0.74804413

 $00:23:42.268 \rightarrow 00:23:45.254$  the trial as we go by in reaching

NOTE Confidence: 0.74804413

 $00{:}23{:}45{.}254 \dashrightarrow 00{:}23{:}48{.}444$  with either best candidates or

NOTE Confidence: 0.74804413

 $00:23:48.444 \rightarrow 00:23:50.358$  potentially novel combinations.

NOTE Confidence: 0.74804413

00:23:50.360 --> 00:23:51.226 So again,

NOTE Confidence: 0.74804413

 $00:23:51.226 \longrightarrow 00:23:53.391$  that's just to illustrate that

NOTE Confidence: 0.74804413

00:23:53.391 --> 00:23:55.782 it's very important to really

NOTE Confidence: 0.74804413

 $00:23:55.782 \longrightarrow 00:23:57.300$  involve our laboratories.

NOTE Confidence: 0.74804413

 $00{:}23{:}57{.}300 \dashrightarrow 00{:}24{:}00{.}660$  Even in trials that are

NOTE Confidence: 0.74804413

00:24:00.660 - 00:24:03.348 being conducted by pharma.

NOTE Confidence: 0.74804413

 $00:24:03.350 \longrightarrow 00:24:04.415$  Now sticking again,

NOTE Confidence: 0.74804413

 $00:24:04.415 \longrightarrow 00:24:06.545$  not now moving on to other

NOTE Confidence: 0.74804413

00:24:06.545 --> 00:24:08.020 more stable targets,

NOTE Confidence: 0.74804413

 $00:24:08.020 \rightarrow 00:24:10.908$  and one of them is ideas with patient

- NOTE Confidence: 0.74804413
- $00{:}24{:}10{.}908 \dashrightarrow 00{:}24{:}13{.}751$  and this story came out of Doctor

 $00:24:13.751 \rightarrow 00:24:16.579$  Kendra's lab where he found it ideas.

NOTE Confidence: 0.74804413

 $00:24:16.580 \rightarrow 00:24:18.746$  Mutations change DNA repair through the

NOTE Confidence: 0.74804413

00:24:18.746 --> 00:24:20.860 production of two hydroxy obliterate,

NOTE Confidence: 0.74804413

 $00:24:20.860 \rightarrow 00:24:23.576$  which is the byproduct of this mutation,

NOTE Confidence: 0.74804413

 $00{:}24{:}23.580 \dashrightarrow 00{:}24{:}26.100$  and this results in sort of brokenness

NOTE Confidence: 0.74804413

 $00:24:26.100 \rightarrow 00:24:29.408$  that then can be targeted by PARP inhibitors.

NOTE Confidence: 0.74804413

 $00{:}24{:}29{.}410 \dashrightarrow 00{:}24{:}31{.}770$  So he has several clinical

NOTE Confidence: 0.74804413

 $00{:}24{:}31{.}770 \dashrightarrow 00{:}24{:}34{.}130$  trials of these park inhibitors.

NOTE Confidence: 0.74804413

 $00:24:34.130 \longrightarrow 00:24:36.748$  And we are now hoping to see

NOTE Confidence: 0.74804413

 $00:24:36.748 \longrightarrow 00:24:39.331$  if this will actually improve

NOTE Confidence: 0.74804413

 $00{:}24{:}39{.}331 \dashrightarrow 00{:}24{:}42{.}067$  outcomes for these patients.

NOTE Confidence: 0.75027966

00:24:44.290 --> 00:24:47.786 Also, again sticking to the DNA repair thing,

NOTE Confidence: 0.75027966

 $00{:}24{:}47.790 \dashrightarrow 00{:}24{:}50.541$  we recently submitted a United team led

NOTE Confidence: 0.75027966

 $00{:}24{:}50{.}541 \dashrightarrow 00{:}24{:}53{.}702$  by Mayo Clinic and John Jennifer Correa

 $00:24:53.702 \rightarrow 00:24:56.087$  in partnership with even colonies.

NOTE Confidence: 0.75027966

 $00{:}24{:}56.090 \dashrightarrow 00{:}24{:}57.834$  Doctor Bindra and I.

NOTE Confidence: 0.75027966

 $00:24:57.834 \rightarrow 00:25:00.014$  So we have two projects.

NOTE Confidence: 0.75027966

 $00{:}25{:}00{.}020 \dashrightarrow 00{:}25{:}03{.}009$  One is trying to optimize MDM two

NOTE Confidence: 0.75027966

 $00{:}25{:}03.009 \dashrightarrow 00{:}25{:}05.690$  inhibition for these patients and 80

NOTE Confidence: 0.75027966

 $00{:}25{:}05{.}690 \dashrightarrow 00{:}25{:}08{.}324$  Rd in ambition for these patients.

NOTE Confidence: 0.75027966

 $00{:}25{:}08{.}330 \dashrightarrow 00{:}25{:}11{.}347$  And this will again bring two other

NOTE Confidence: 0.75027966

 $00:25:11.347 \longrightarrow 00:25:14.318$  Phase 0 slash 1 clinical trials.

NOTE Confidence: 0.75027966

 $00{:}25{:}14.320 \dashrightarrow 00{:}25{:}16.570$  To our portfolio, hopefully soon.

NOTE Confidence: 0.8357312

 $00{:}25{:}20.570 \dashrightarrow 00{:}25{:}22.544$  Now we don't have time to

NOTE Confidence: 0.8357312

 $00:25:22.544 \longrightarrow 00:25:24.710$  review all of our portfolio,

NOTE Confidence: 0.8357312

00:25:24.710 --> 00:25:27.122 but we do have partnerships with

NOTE Confidence: 0.8357312

 $00{:}25{:}27{.}122 \dashrightarrow 00{:}25{:}29{.}139$  industry for opening other tries

NOTE Confidence: 0.8357312

 $00{:}25{:}29{.}139 \dashrightarrow 00{:}25{:}31{.}463$  to fill in gaps in our portfolio.

NOTE Confidence: 0.8357312

 $00{:}25{:}31{.}470 \dashrightarrow 00{:}25{:}33{.}305$  Doctor Blundin has activated the

NOTE Confidence: 0.8357312

00:25:33.305 - 00:25:36.048 Agile trial which is a multi drug

- NOTE Confidence: 0.8357312
- $00{:}25{:}36{.}048 \dashrightarrow 00{:}25{:}38{.}568$  multi arm clinical trial that is

 $00{:}25{:}38{.}568 \dashrightarrow 00{:}25{:}40{.}787$  happening worldwide so we have access

NOTE Confidence: 0.8357312

 $00:25:40.787 \longrightarrow 00:25:42.749$  to these drugs for our patients

NOTE Confidence: 0.8357312

 $00:25:42.750 \longrightarrow 00:25:45.389$  and have a bunch of other choice.

NOTE Confidence: 0.8357312

 $00{:}25{:}45{.}390 \dashrightarrow 00{:}25{:}47{.}766$  But the theme here is really to focus on

NOTE Confidence: 0.8357312

 $00{:}25{:}47.766$  -->  $00{:}25{:}50.181$  early the rapeutic development and then

NOTE Confidence: 0.8357312

 $00:25:50.181 \rightarrow 00:25:52.273$  participating inside cooperative groups.

NOTE Confidence: 0.8357312

00:25:52.280 --> 00:25:55.040 Please, for those extremely rare phenotypes,

NOTE Confidence: 0.8357312

 $00:25:55.040 \longrightarrow 00:25:55.960$  for example,

NOTE Confidence: 0.8357312

 $00:25:55.960 \rightarrow 00:25:57.800$  by ref mutant craniopharyngioma switch,

NOTE Confidence: 0.8357312

 $00{:}25{:}57{.}800 \dashrightarrow 00{:}26{:}00{.}992$  again very difficult to find patience

NOTE Confidence: 0.8357312

 $00{:}26{:}00{.}992 \dashrightarrow 00{:}26{:}05{.}425$  and for those we do need to partner

NOTE Confidence: 0.8357312

 $00{:}26{:}05{.}425 \dashrightarrow 00{:}26{:}08{.}731$  with other places around the country.

NOTE Confidence: 0.8357312

 $00{:}26{:}08.740 \dashrightarrow 00{:}26{:}11.452$  And I could go on and on talking

NOTE Confidence: 0.8357312

 $00{:}26{:}11.452 \dashrightarrow 00{:}26{:}13.801$  about all of the years signs

 $00:26:13.801 \longrightarrow 00:26:16.177$  that is going in brain tumors.

NOTE Confidence: 0.8357312

00:26:16.180 --> 00:26:18.412 I select a few stories that

NOTE Confidence: 0.8357312

 $00{:}26{:}18{.}412 \dashrightarrow 00{:}26{:}19{.}900$  are closest to clinic,

NOTE Confidence: 0.8357312

 $00{:}26{:}19{.}900 \dashrightarrow 00{:}26{:}22{.}315$  but all these people in this picture

NOTE Confidence: 0.8357312

 $00{:}26{:}22{.}315 \dashrightarrow 00{:}26{:}25{.}041$  and many others that I'm not even

NOTE Confidence: 0.8357312

00:26:25.041 --> 00:26:27.066 mentioning today are producing a mazing

NOTE Confidence: 0.8357312

 $00{:}26{:}27.066 \dashrightarrow 00{:}26{:}29.651$  size that we can actually use into

NOTE Confidence: 0.8357312

 $00:26:29.651 \rightarrow 00:26:32.128$  our portfolio and bring it in anymore.

NOTE Confidence: 0.8357312

00:26:32.128 --> 00:26:33.552 Let's say intelligent trials

NOTE Confidence: 0.8357312

 $00:26:33.552 \rightarrow 00:26:35.150$  ranging from data science,

NOTE Confidence: 0.8357312

 $00{:}26{:}35{.}150 \dashrightarrow 00{:}26{:}37{.}290$  junior imaging and all sorts

NOTE Confidence: 0.8357312

 $00:26:37.290 \longrightarrow 00:26:38.574$  of the rapeutic approaches.

NOTE Confidence: 0.8357312

 $00:26:38.580 \longrightarrow 00:26:39.600$  So in conclusion,

NOTE Confidence: 0.8357312

 $00:26:39.600 \rightarrow 00:26:41.980$  so we're lucky enough to have this

NOTE Confidence: 0.8357312

 $00{:}26{:}42.051 \dashrightarrow 00{:}26{:}44.536$  unique breath of scientific expertise.

NOTE Confidence: 0.8357312

 $00:26:44.540 \rightarrow 00:26:46.832$  Our focus is really on investigating

- NOTE Confidence: 0.8357312
- $00{:}26{:}46.832 \dashrightarrow 00{:}26{:}49.189$  shaded trials that are home grown

 $00{:}26{:}49{.}189 \dashrightarrow 00{:}26{:}51{.}863$  and our other focuses on early stage

NOTE Confidence: 0.8357312

 $00:26:51.863 \rightarrow 00:26:53.669$  development with former partners,

NOTE Confidence: 0.8357312

 $00:26:53.670 \longrightarrow 00:26:55.650$  but also bringing along our

NOTE Confidence: 0.8357312

 $00:26:55.650 \longrightarrow 00:26:57.234$  own labs email collagen,

NOTE Confidence: 0.8357312

 $00:26:57.240 \rightarrow 00:27:00.019$  a repair have emerged as leading teams,

NOTE Confidence: 0.8357312

 $00:27:00.020 \rightarrow 00:27:03.188$  but here there we have many patents about,

NOTE Confidence: 0.8357312

00:27:03.190 - 00:27:05.390 although many are not ready

NOTE Confidence: 0.8357312

 $00{:}27{:}05{.}390 \dashrightarrow 00{:}27{:}07{.}590$  for complication and need a

NOTE Confidence: 0.8357312

 $00:27:07.670 \longrightarrow 00:27:09.910$  lot of help for development.

NOTE Confidence: 0.8357312

 $00:27:09.910 \longrightarrow 00:27:11.630$  We certainly need more work

NOTE Confidence: 0.8357312

 $00{:}27{:}11.630 \dashrightarrow 00{:}27{:}13.006$  on existing available drugs,

NOTE Confidence: 0.8357312

 $00{:}27{:}13.010 \dashrightarrow 00{:}27{:}14.675$  for example coming from Seatac

NOTE Confidence: 0.8357312

 $00{:}27{:}14.675 \dashrightarrow 00{:}27{:}17.435$  and Pharma and a lot of work in

NOTE Confidence: 0.8357312

 $00{:}27{:}17.435 \dashrightarrow 00{:}27{:}19.135$  functional genomics so that we

 $00:27:19.135 \longrightarrow 00:27:21.585$  can figure out finally how to

NOTE Confidence: 0.8357312

 $00{:}27{:}21.585 \dashrightarrow 00{:}27{:}23.285$  target these undruggable targets.

NOTE Confidence: 0.8357312

 $00{:}27{:}23.290 \dashrightarrow 00{:}27{:}25.754$  So that I would like to finish

NOTE Confidence: 0.8357312

 $00:27:25.754 \longrightarrow 00:27:27.959$  by thanking all of the people.

NOTE Confidence: 0.8357312

 $00:27:27.960 \longrightarrow 00:27:30.108$  So when we talk clinical trials,

NOTE Confidence: 0.8357312

 $00{:}27{:}30{.}110 \dashrightarrow 00{:}27{:}33{.}755$  really the merit is all of others of the

NOTE Confidence: 0.8357312

 $00{:}27{:}33.755 \dashrightarrow 00{:}27{:}37.220$  labs of the all of the infra structure.

NOTE Confidence: 0.8357312

 $00:27:37.220 \longrightarrow 00:27:39.554$  I would also like to acknowledge

NOTE Confidence: 0.8357312

 $00{:}27{:}39{.}554 \dashrightarrow 00{:}27{:}41{.}500$  our division attendings and aips,

NOTE Confidence: 0.8357312

 $00{:}27{:}41.500 \dashrightarrow 00{:}27{:}43.052$  or actually managing treating

NOTE Confidence: 0.8357312

 $00{:}27{:}43.052 \dashrightarrow 00{:}27{:}44.992$  these patients in the trials.

NOTE Confidence: 0.8357312

 $00{:}27{:}45{.}000 \dashrightarrow 00{:}27{:}48{.}492$  I would like to thank again the Cito staff.

NOTE Confidence: 0.8357312

 $00{:}27{:}48.500 \dashrightarrow 00{:}27{:}50.450$  They're going through rough times,

NOTE Confidence: 0.8357312

 $00{:}27{:}50{.}450 \dashrightarrow 00{:}27{:}53{.}446$  but right Decker is navigating and it's

NOTE Confidence: 0.8357312

 $00{:}27{:}53.446 \dashrightarrow 00{:}27{:}56.879$  going to get us out of this situation.

NOTE Confidence: 0.8357312

 $00{:}27{:}56.880 \dashrightarrow 00{:}27{:}59.162$  A big thanks to the PRC reviewers

- NOTE Confidence: 0.8357312
- $00:27:59.162 \rightarrow 00:28:01.845$  'cause one of my hats is actually as

 $00:28:01.845 \rightarrow 00:28:04.370$  the Pearcey chair and we we acknowledge

NOTE Confidence: 0.8357312

 $00{:}28{:}04{.}370 \dashrightarrow 00{:}28{:}06{.}830$  along with Barbara Burtness that there

NOTE Confidence: 0.8357312

 $00:28:06.830 \longrightarrow 00:28:09.420$  was a lot of work that goes into

NOTE Confidence: 0.8357312

 $00{:}28{:}09{.}420 \dashrightarrow 00{:}28{:}12{.}357$  this and that I would like to thank

NOTE Confidence: 0.8357312

 $00:28:12.357 \rightarrow 00:28:14.462$  them publicly at this opportunity.

NOTE Confidence: 0.8357312

 $00:28:14.470 \longrightarrow 00:28:15.289$  Lots of things.

NOTE Confidence: 0.8357312

 $00:28:15.289 \longrightarrow 00:28:17.200$  So why CCI that help us with

NOTE Confidence: 0.8357312

 $00{:}28{:}17.264 \dashrightarrow 00{:}28{:}19.500$  investigating share clinical trials.

NOTE Confidence: 0.8357312

 $00:28:19.500 \longrightarrow 00:28:22.104$  All of the people that have been

NOTE Confidence: 0.8357312

 $00:28:22.104 \rightarrow 00:28:23.885$  enabling this research and finally

NOTE Confidence: 0.8357312

 $00{:}28{:}23.885 \dashrightarrow 00{:}28{:}26.261$  a big thank to the YCC and Smile

NOTE Confidence: 0.8357312

 $00{:}28{:}26{.}337 \dashrightarrow 00{:}28{:}28{.}297$  leadership with more Pickens.

NOTE Confidence: 0.8357312

00:28:28.300 --> 00:28:30.350 Kevin versus Kevin Beans loosely,

NOTE Confidence: 0.8357312

 $00{:}28{:}30{.}350 \dashrightarrow 00{:}28{:}32{.}954$  and neither will all understand importance

 $00:28:32.954 \rightarrow 00:28:35.430$  of our clinical trials portfolio.

NOTE Confidence: 0.8357312

00:28:35.430 --> 00:28:37.030 Last but not least, again,

NOTE Confidence: 0.8413786

00:28:37.030 --> 00:28:39.294 I would like to thank the show her

NOTE Confidence: 0.8413786

 $00{:}28{:}39{.}294 \dashrightarrow 00{:}28{:}41{.}189$  family for their generous gift.

NOTE Confidence: 0.8413786

 $00{:}28{:}41{.}190 \dashrightarrow 00{:}28{:}43{.}122$  In fact, then I'm not going to

NOTE Confidence: 0.8413786

 $00{:}28{:}43{.}122 \dashrightarrow 00{:}28{:}45{.}111$  talk about this today because we're NOTE Confidence: 0.8413786

00:28:45.111 --> 00:28:46.946 still working on the details,

NOTE Confidence: 0.8413786

 $00{:}28{:}46{.}950 \dashrightarrow 00{:}28{:}49{.}470$  but the word is out of the receive a

NOTE Confidence: 0.8413786

00:28:49.470 --> 00:28:51.428 generous gift from that foundation,

NOTE Confidence: 0.8413786

 $00{:}28{:}51{.}430 \dashrightarrow 00{:}28{:}53{.}516$  and we're hoping to put together a NOTE Confidence: 0.8413786

 $00:28:53.516 \rightarrow 00:28:55.481$  nice program that will again enable NOTE Confidence: 0.8413786

 $00{:}28{:}55{.}481 \dashrightarrow 00{:}28{:}57{.}503$  and expand on our research efforts. NOTE Confidence: 0.8413786

 $00{:}28{:}57{.}510 \dashrightarrow 00{:}28{:}59{.}729$  Thank you very much and I'll take

NOTE Confidence: 0.8413786

 $00:28:59.729 \longrightarrow 00:29:01.670$  some points if you have time.

NOTE Confidence: 0.85210776

00:29:02.790 --> 00:29:04.596 OK, thank you very much Antonio.

NOTE Confidence: 0.85210776

 $00:29:04.600 \rightarrow 00:29:05.941$  Very interesting work.

- NOTE Confidence: 0.85210776
- $00:29:05.941 \rightarrow 00:29:08.623$  Are there any questions that people
- NOTE Confidence: 0.85210776
- $00:29:08.623 \longrightarrow 00:29:10.776$  want to enter into the chat?
- NOTE Confidence: 0.85210776
- $00:29:10.780 \longrightarrow 00:29:11.698$  While we're waiting,
- NOTE Confidence: 0.85210776
- 00:29:11.698 --> 00:29:13.228 I have a quick question.
- NOTE Confidence: 0.85210776
- 00:29:13.230 --> 00:29:14.450 You mentioned this idea
- NOTE Confidence: 0.85210776
- $00:29:14.450 \longrightarrow 00:29:15.975$  of opening up the bread.
- NOTE Confidence: 0.85210776
- $00{:}29{:}15{.}980 \dashrightarrow 00{:}29{:}17{.}788$  The blood brain barrier
- NOTE Confidence: 0.85210776
- $00:29:17.788 \longrightarrow 00:29:19.596$  by targeting a molecule.
- NOTE Confidence: 0.85210776
- $00:29:19.600 \rightarrow 00:29:21.343$  Is it worth going back to some
- NOTE Confidence: 0.85210776
- $00:29:21.343 \longrightarrow 00:29:22.810$  of the earlier drugs that
- NOTE Confidence: 0.85210776
- $00:29:22.810 \longrightarrow 00:29:24.138$  weren't terribly effective to
- NOTE Confidence: 0.85210776
- $00:29:24.138 \longrightarrow 00:29:26.106$  see that whether or not that
- NOTE Confidence: 0.85210776
- $00:29:26.106 \longrightarrow 00:29:27.566$  might help them work better?
- NOTE Confidence: 0.71716356
- $00{:}29{:}28{.}430 \dashrightarrow 00{:}29{:}33{.}020$  Yes, I think there is a whole list of drugs
- NOTE Confidence: 0.71716356
- $00:29:33.132 \longrightarrow 00:29:37.297$  that perhaps will need to be revisited.
- NOTE Confidence: 0.71716356

 $00:29:37.300 \rightarrow 00:29:39.544$  Although most of these drugs would

NOTE Confidence: 0.71716356

 $00{:}29{:}39{.}544 \dashrightarrow 00{:}29{:}42{.}199$  actually be again in rare phenotypes,

NOTE Confidence: 0.71716356

00:29:42.200 --> 00:29:44.240 because I think those are,

NOTE Confidence: 0.71716356

 $00{:}29{:}44{.}240 \dashrightarrow 00{:}29{:}46{.}688$  we still need to select them

NOTE Confidence: 0.71716356

 $00{:}29{:}46.688 \dashrightarrow 00{:}29{:}48.320$  by those specific mutations.

NOTE Confidence: 0.71716356

 $00{:}29{:}48{.}320 \dashrightarrow 00{:}29{:}50{.}768$  The problem of copy number remains

NOTE Confidence: 0.71716356

00:29:50.768 --> 00:29:52.400 regardless of flipping connectors.

NOTE Confidence: 0.71716356

 $00:29:52.400 \rightarrow 00:29:55.256$  I don't think blood brain barrier penetration

NOTE Confidence: 0.71716356

 $00{:}29{:}55{.}256 \dashrightarrow 00{:}29{:}58{.}152$  was the reason why we couldn't target

NOTE Confidence: 0.71716356

 $00{:}29{:}58.152 \dashrightarrow 00{:}30{:}00.558$  EGFR amplification or Pete and loss.

NOTE Confidence: 0.71716356

 $00:30:00.560 \longrightarrow 00:30:03.409$  I think that is a different question,

NOTE Confidence: 0.71716356

 $00:30:03.410 \longrightarrow 00:30:06.308$  but if we are to even answer

NOTE Confidence: 0.71716356

 $00:30:06.308 \longrightarrow 00:30:08.130$  those we still need.

NOTE Confidence: 0.71716356

 $00:30:08.130 \longrightarrow 00:30:09.038$  This kind of approach,

NOTE Confidence: 0.71716356

 $00{:}30{:}09{.}038 \dashrightarrow 00{:}30{:}10{.}999$  'cause it makes our life so much easier.

NOTE Confidence: 0.8856998

 $00:30:13.660 \rightarrow 00:30:15.550$  Are there any questions from the audience?

- NOTE Confidence: 0.79346305
- $00:30:22.920 \rightarrow 00:30:26.412$  I was also struck by the lots of different
- NOTE Confidence: 0.79346305
- $00{:}30{:}26.412 \dashrightarrow 00{:}30{:}28.850$  mutations upon recurrence. He showed.
- NOTE Confidence: 0.7935335
- $00:30:31.150 \longrightarrow 00:30:33.060$  What is that thought to
- NOTE Confidence: 0.7935335
- $00:30:33.060 \longrightarrow 00:30:35.719$  be due to is just so high
- NOTE Confidence: 0.7935335
- $00:30:35.720 \rightarrow 00:30:37.630$  perforation rate of these tumors.
- NOTE Confidence: 0.7935335
- $00{:}30{:}37{.}630 \dashrightarrow 00{:}30{:}39{.}530$  Yeah, well, I think so.
- NOTE Confidence: 0.7935335
- $00:30:39.530 \longrightarrow 00:30:42.183$  First of all, these tumors are very
- NOTE Confidence: 0.7935335
- $00:30:42.183 \rightarrow 00:30:44.084$  heterogeneous to begin with, right?
- NOTE Confidence: 0.7935335
- $00{:}30{:}44.084 \dashrightarrow 00{:}30{:}46.268$  So these are guns that are
- NOTE Confidence: 0.7935335
- $00:30:46.268 \rightarrow 00:30:48.300$  were there to begin with,
- NOTE Confidence: 0.7935335
- $00{:}30{:}48{.}300 \dashrightarrow 00{:}30{:}50{.}960$  but it looks like the treatment process
- NOTE Confidence: 0.7935335
- $00:30:50.960 \longrightarrow 00:30:54.038$  ends up eliminating a lot of this so
- NOTE Confidence: 0.7935335
- $00{:}30{:}54.038 \dashrightarrow 00{:}30{:}55.530$  called cancer associated mutations.
- NOTE Confidence: 0.7935335
- $00:30:55.530 \rightarrow 00:30:57.612$  Another unknown mutations emerge and also
- NOTE Confidence: 0.7935335
- $00:30:57.612 \longrightarrow 00:31:00.548$  a lot of these are actually epigenetic.
- NOTE Confidence: 0.7935335

- $00:31:00.550 \rightarrow 00:31:00.971$  Changes.
- NOTE Confidence: 0.7935335
- $00{:}31{:}00{.}971 \dashrightarrow 00{:}31{:}03{.}918$  So there's a whole line of research
- NOTE Confidence: 0.7935335
- 00:31:03.918 --> 00:31:06.623 trying to then understand this and
- NOTE Confidence: 0.7935335
- $00{:}31{:}06.623 \dashrightarrow 00{:}31{:}09.737$  more can als are interested in in that
- NOTE Confidence: 0.7935335
- $00{:}31{:}09{.}737 \dashrightarrow 00{:}31{:}12{.}299$  line of research and other labs to
- NOTE Confidence: 0.7935335
- 00:31:12.299 --> 00:31:15.005 see how we can target these tumors
- NOTE Confidence: 0.7935335
- $00:31:15.005 \rightarrow 00:31:17.270$  at recurrence that are sort of,
- NOTE Confidence: 0.7935335
- 00:31:17.270 --> 00:31:18.040 you know,
- NOTE Confidence: 0.7935335
- $00:31:18.040 \rightarrow 00:31:20.350$  very simple from a genomic standpoint,
- NOTE Confidence: 0.7935335
- $00:31:20.350 \rightarrow 00:31:23.430$  but not so simple at the epigenetic level.
- NOTE Confidence: 0.7935335
- $00:31:23.430 \longrightarrow 00:31:24.970$  Well, thank you very
- NOTE Confidence: 0.83255094
- 00:31:24.970 --> 00:31:26.338 much. Very interesting.
- NOTE Confidence: 0.83255094
- $00:31:26.338 \rightarrow 00:31:31.030$  We have to move on to the second speaker.
- NOTE Confidence: 0.83255094
- 00:31:31.030 --> 00:31:33.598 In our second stewartii climb down
- NOTE Confidence: 0.83255094
- 00:31:33.598 --> 00:31:36.166 from the Hill from Science Hill,
- NOTE Confidence: 0.83255094
- $00:31:36.170 \longrightarrow 00:31:38.970$  is Seth hairs on who's the Milton

- NOTE Confidence: 0.83255094
- 00:31:38.970 --> 00:31:40.663 Harris professor of Chemistry

 $00{:}31{:}40.663 \dashrightarrow 00{:}31{:}43.568$  received his PhD at Harvard and then

NOTE Confidence: 0.83255094

00:31:43.568 --> 00:31:46.437 post Doc at University of Illinois,

NOTE Confidence: 0.83255094

 $00:31:46.440 \longrightarrow 00:31:49.290$  and he's interested in natural

NOTE Confidence: 0.83255094

 $00:31:49.290 \longrightarrow 00:31:51.570$  product's particular products that

NOTE Confidence: 0.83255094

 $00{:}31{:}51{.}570$  -->  $00{:}31{:}54{.}518$  affect the synthesis or damaged DNA.

NOTE Confidence: 0.83255094

 $00:31:54.520 \longrightarrow 00:31:55.988$  And he's received numerous

NOTE Confidence: 0.83255094

00:31:55.988 --> 00:31:57.456 multiple Young Investigator awards

NOTE Confidence: 0.83255094

 $00{:}31{:}57{.}456 \dashrightarrow 00{:}31{:}59{.}279$  and working with Jason Crawford

NOTE Confidence: 0.83255094

 $00{:}31{:}59{.}279 \dashrightarrow 00{:}32{:}00{.}659$  is a terrific collaboration.

NOTE Confidence: 0.83255094

00:32:00.660 --> 00:32:01.749 Looking at them,

NOTE Confidence: 0.83255094

00:32:01.749 $\operatorname{-->}$ 00:32:03.927 the metabolites made by the human

NOTE Confidence: 0.83255094

 $00{:}32{:}03{.}927 \dashrightarrow 00{:}32{:}05{.}762$  microbiota and identified some of

NOTE Confidence: 0.83255094

 $00{:}32{:}05{.}762 \dashrightarrow 00{:}32{:}07{.}880$  them that actually damaged DNA and

NOTE Confidence: 0.83255094

 $00:32:07.880 \dashrightarrow 00:32:09.328$  therefore contribute to cancer.

00:32:09.328 --> 00:32:11.148 So Seth, we're looking forward

NOTE Confidence: 0.83255094

 $00:32:11.148 \longrightarrow 00:32:12.930$  to hearing about your work.

NOTE Confidence: 0.83255094

 $00:32:12.930 \longrightarrow 00:32:13.650$  Thank you.

NOTE Confidence: 0.8794826

00:32:15.060 --> 00:32:16.875 OK, thanks Dan,

NOTE Confidence: 0.8794826

 $00{:}32{:}16.875 \dashrightarrow 00{:}32{:}19.295$  thanks for the introduction.

NOTE Confidence: 0.8794826

 $00{:}32{:}19{.}300 \dashrightarrow 00{:}32{:}20{.}955$  And thanks to all to

NOTE Confidence: 0.8794826

 $00{:}32{:}20{.}955 \dashrightarrow 00{:}32{:}22{.}280$  every one for the invocation.

NOTE Confidence: 0.8794826

 $00:32:22.280 \rightarrow 00:32:25.538$  Comment for attending the lecture.

NOTE Confidence: 0.8794826

00:32:25.540 --> 00:32:27.360 I will talk today about work we've

NOTE Confidence: 0.8794826

 $00:32:27.360 \longrightarrow 00:32:29.340$  been doing in the human microbiome,

NOTE Confidence: 0.8794826

 $00:32:29.340 \longrightarrow 00:32:30.500$  but actually ignore it.

NOTE Confidence: 0.70541836

00:32:33.350 --> 00:32:37.570 Just calling on ever. Snap because.

NOTE Confidence: 0.70541836

 $00{:}32{:}37{.}570 \dashrightarrow 00{:}32{:}40{.}216$  Cave against drug resistant TMZ resistant.

NOTE Confidence: 0.70541836

 $00{:}32{:}40{.}220 \dashrightarrow 00{:}32{:}43{.}314$  GBM that we're very excited about but

NOTE Confidence: 0.70541836

 $00:32:43.314 \longrightarrow 00:32:46.850$  that will be a story for another day.

NOTE Confidence: 0.88522273

00:32:48.900 --> 00:32:51.572 And so right. So today I'll talk

 $00:32:51.572 \rightarrow 00:32:53.928$  about a project that's been ongoing

NOTE Confidence: 0.88522273

 $00{:}32{:}53{.}928 \dashrightarrow 00{:}32{:}56{.}469$  in my group for about 6 years.

NOTE Confidence: 0.88522273

 $00{:}32{:}56{.}470 \dashrightarrow 00{:}32{:}59{.}668$  And we've been looking to understand

NOTE Confidence: 0.88522273

 $00{:}32{:}59.668 \dashrightarrow 00{:}33{:}03.200$  the molecular basis of a carcinogen

NOTE Confidence: 0.88522273

 $00:33:03.200 \dashrightarrow 00:33:05.820$  carcinogenic phenotype that was

NOTE Confidence: 0.88522273

 $00{:}33{:}05{.}820 \dashrightarrow 00{:}33{:}09{.}048$  observed from certain gut bacteria so.

NOTE Confidence: 0.88522273

 $00{:}33{:}09{.}048 \dashrightarrow 00{:}33{:}11{.}631$  I'll go through sort of the sequence

NOTE Confidence: 0.88522273

 $00:33:11.631 \longrightarrow 00:33:14.631$  of events to kind of outline sequence

NOTE Confidence: 0.88522273

 $00{:}33{:}14.631 \dashrightarrow 00{:}33{:}17.260$  of discoveries to outline the problem,

NOTE Confidence: 0.88522273

 $00:33:17.260 \longrightarrow 00:33:20.923$  and so in 2006 this was the paper that NOTE Confidence: 0.88522273

 $00:33:20.923 \dashrightarrow 00:33:24.825$  set off a lot of interest in this area.

NOTE Confidence: 0.88522273

 $00{:}33{:}24{.}830 \dashrightarrow 00{:}33{:}27{.}920$  Eric Oswald and coworkers identified

NOTE Confidence: 0.88522273

 $00{:}33{:}27{.}920 \dashrightarrow 00{:}33{:}31{.}010$  certain strains of commensal and

NOTE Confidence: 0.88522273

 $00:33:31.102 \dashrightarrow 00:33:34.861$  pathogenic E coli that had a biosynthetic NOTE Confidence: 0.88522273

 $00:33:34.861 \dashrightarrow 00:33:38.268$  gene cluster known as the CLB cluster.

 $00:33:38.270 \longrightarrow 00:33:42.270$  So by that I mean that gene genetic

NOTE Confidence: 0.88522273

 $00{:}33{:}42.270 \dashrightarrow 00{:}33{:}45.730$  locus contains the coding for enzymes

NOTE Confidence: 0.88522273

 $00{:}33{:}45{.}730$  -->  $00{:}33{:}49{.}270$  that make a secondary metabolite and NOTE Confidence: 0.88522273

 $00:33:49.370 \rightarrow 00:33:52.790$  he took these CLB containing bacteria NOTE Confidence: 0.88522273

 $00:33:52.790 \rightarrow 00:33:55.535$  and did a transient infection.

NOTE Confidence: 0.88522273

 $00{:}33{:}55{.}535 \dashrightarrow 00{:}33{:}58{.}325$  HeLa cells with them and then

NOTE Confidence: 0.88522273

 $00:33:58.325 \longrightarrow 00:34:01.527$  looked at the effect on the cells,

NOTE Confidence: 0.88522273

 $00{:}34{:}01{.}530 \dashrightarrow 00{:}34{:}04{.}158$  and he found that they underwent

NOTE Confidence: 0.88522273

00:34:04.158 --> 00:34:05.472 cell cycle arrest.

NOTE Confidence: 0.88522273

 $00:34:05.480 \dashrightarrow 00:34:08.546$  Meglos cytosis and using a comet assay.

NOTE Confidence: 0.88522273

 $00{:}34{:}08.550 \dashrightarrow 00{:}34{:}12.358$  Another Gamage to XD he saw that

NOTE Confidence: 0.88522273

 $00{:}34{:}12{.}358 \dashrightarrow 00{:}34{:}14{.}619$  they accumulated double strand

NOTE Confidence: 0.88522273

 $00{:}34{:}14.619 \dashrightarrow 00{:}34{:}16.719$  breaks in their DNA.

NOTE Confidence: 0.88522273

 $00:34:16.720 \rightarrow 00:34:18.960$  And so this is a very interesting phenotype.

NOTE Confidence: 0.88522273

 $00{:}34{:}18{.}960 \dashrightarrow 00{:}34{:}21{.}760$  It's not the first time.

NOTE Confidence: 0.88522273

00:34:21.760 --> 00:34:23.260 Microbes, have, you know,

- NOTE Confidence: 0.88522273
- $00:34:23.260 \longrightarrow 00:34:24.385$  produced Gina toxins,

 $00{:}34{:}24{.}390 \dashrightarrow 00{:}34{:}27{.}510$  but it was was a very interesting

NOTE Confidence: 0.88522273

 $00{:}34{:}27{.}510 \dashrightarrow 00{:}34{:}30{.}758$  example and I'll come to in a second wait.

NOTE Confidence: 0.88522273

 $00:34:30.760 \rightarrow 00:34:34.348$  Why it's attracting so much attention?

NOTE Confidence: 0.88522273

 $00:34:34.350 \longrightarrow 00:34:36.942$  Subsequent to that report,

NOTE Confidence: 0.88522273

 $00{:}34{:}36{.}942 \dashrightarrow 00{:}34{:}39{.}534$  there's been numerous studies

NOTE Confidence: 0.88522273

 $00{:}34{:}39{.}534 \dashrightarrow 00{:}34{:}42{.}899$  trying to ascertain whether or not

NOTE Confidence: 0.88522273

 $00{:}34{:}42.899 \dashrightarrow 00{:}34{:}46.567$  there is a role for these bacteria

NOTE Confidence: 0.88522273

 $00{:}34{:}46{.}567 \dashrightarrow 00{:}34{:}49{.}043$  in colorectal cancer formation

NOTE Confidence: 0.88522273

 $00:34:49.043 \rightarrow 00:34:53.554$  and from the same group in 2010.

NOTE Confidence: 0.88522273

 $00{:}34{:}53{.}554 \dashrightarrow 00{:}34{:}57{.}796$  It was shown that in in

NOTE Confidence: 0.88522273

 $00{:}34{:}57.796 \dashrightarrow 00{:}35{:}00.839$  intestinal loop models of.

NOTE Confidence: 0.88522273

 $00{:}35{:}00{.}840 \dashrightarrow 00{:}35{:}04{.}319$  My step or infected with CLB bacteria

NOTE Confidence: 0.88522273

 $00{:}35{:}04{.}319 \dashrightarrow 00{:}35{:}07{.}288$  they observe DNA damage in vivo.

NOTE Confidence: 0.88522273

00:35:07.290 --> 00:35:10.580 They observed gamma H2 X they observed

 $00:35:10.580 \dashrightarrow 00:35:13.663$  increased mutations in the HP RT&TK

NOTE Confidence: 0.88522273

 $00:35:13.663 \rightarrow 00:35:16.318$  loci and then also hyperproliferation

NOTE Confidence: 0.88522273

 $00:35:16.318 \dashrightarrow 00:35:18.699$  following exposure to the bacteria.

NOTE Confidence: 0.88522273

 $00{:}35{:}18.700 \dashrightarrow 00{:}35{:}21.899$  So they seem to be driving tumorigenesis

NOTE Confidence: 0.88522273

 $00{:}35{:}21.899 \dashrightarrow 00{:}35{:}24.424$  and then there were subsequent

NOTE Confidence: 0.88522273

 $00:35:24.424 \rightarrow 00:35:27.084$  studies following up looking at

NOTE Confidence: 0.88522273

 $00:35:27.084 \rightarrow 00:35:30.098$  similar types of in vivo effects.

NOTE Confidence: 0.88522273

00:35:30.100 --> 00:35:31.798 So using IL.

NOTE Confidence: 0.88522273

00:35:31.798 --> 00:35:32.930 Knockout mice,

NOTE Confidence: 0.88522273

 $00:35:32.930 \dashrightarrow 00:35:35.936$  it was shown that infection with

NOTE Confidence: 0.88522273

 $00{:}35{:}35{.}936 \dashrightarrow 00{:}35{:}38{.}960$  these bacteria leads to a higher

NOTE Confidence: 0.88522273

00:35:38.960 --> 00:35:41.750 rate of tumor formation and then NOTE Confidence: 0.88522273

00:35:41.750 - 00:35:44.740 there were three groups that did.

NOTE Confidence: 0.88522273

00:35:44.740 --> 00:35:47.719 Meta analysis of of \*\*\*\*\* samples

NOTE Confidence: 0.88522273

00:35:47.719 --> 00:35:50.833 from from CRC patients and what NOTE Confidence: 0.88522273

 $00:35:50.833 \longrightarrow 00:35:55.073$  we find is that about 60 to 70% of

 $00:35:55.073 \rightarrow 00:35:57.538$  CRC patients have these bacteria

NOTE Confidence: 0.88522273

 $00{:}35{:}57{.}538 \dashrightarrow 00{:}36{:}00{.}518$  and that's and that's versus about

NOTE Confidence: 0.88522273

 $00:36:00.518 \longrightarrow 00:36:02.368 20\%$  in the healthy population.

NOTE Confidence: 0.88522273

 $00:36:02.368 \longrightarrow 00:36:05.314$  And the other sort of bit is that

NOTE Confidence: 0.88522273

 $00{:}36{:}05{.}314 \dashrightarrow 00{:}36{:}07{.}284$  the preponderance of these bacteria

NOTE Confidence: 0.88522273

 $00{:}36{:}07{.}284 \dashrightarrow 00{:}36{:}10{.}077$  tracks with the severity of the cancer,

NOTE Confidence: 0.88522273

 $00:36:10.080 \rightarrow 00:36:12.285$  so people with more advanced CRC were

NOTE Confidence: 0.88522273

 $00:36:12.285 \rightarrow 00:36:14.840$  at the high end of that correlation,

NOTE Confidence: 0.88522273

 $00{:}36{:}14.840 \dashrightarrow 00{:}36{:}17.300$  whereas people with early stage

NOTE Confidence: 0.88522273

 $00{:}36{:}17{.}300 \dashrightarrow 00{:}36{:}20{.}810$  CRC were more at the lower end.

NOTE Confidence: 0.88522273

 $00{:}36{:}20{.}810 \dashrightarrow 00{:}36{:}23{.}099$  And so it wasn't really until last

NOTE Confidence: 0.88522273

 $00{:}36{:}23.099 \dashrightarrow 00{:}36{:}25.575$  year that a causal relationship

NOTE Confidence: 0.88522273

 $00{:}36{:}25{.}575 \dashrightarrow 00{:}36{:}27{.}708$  was unequivocally established.

NOTE Confidence: 0.88522273

00:36:27.710 --> 00:36:30.584 There were two studies from mayor

NOTE Confidence: 0.88522273

 $00{:}36{:}30{.}584 \dashrightarrow 00{:}36{:}33{.}619$  and then Boxtel and Cleavers an

 $00:36:33.619 \rightarrow 00:36:35.667$  in the Cleavers study.

NOTE Confidence: 0.88522273

 $00{:}36{:}35{.}670 \dashrightarrow 00{:}36{:}39{.}515$  They generated an organoid and

NOTE Confidence: 0.88522273

 $00:36:39.515 \dashrightarrow 00:36:43.360$  infected that organoid chronically for NOTE Confidence: 0.88522273

 $00{:}36{:}43{.}472 \dashrightarrow 00{:}36{:}47{.}917$  about three or four months with the

NOTE Confidence: 0.88522273

 $00{:}36{:}47{.}917 \dashrightarrow 00{:}36{:}51{.}640$  CLB positive bacteria and what they

NOTE Confidence: 0.88522273

 $00{:}36{:}51{.}640 \dashrightarrow 00{:}36{:}55{.}616$  showed is that you get the mutational

NOTE Confidence: 0.88522273

 $00{:}36{:}55{.}620 \dashrightarrow 00{:}36{:}58{.}764$  signature transformation and proliferation.

NOTE Confidence: 0.88522273

 $00{:}36{:}58.764 \dashrightarrow 00{:}37{:}03.480$  We also find that that mutational

NOTE Confidence: 0.84878147

 $00{:}37{:}03.589 \dashrightarrow 00{:}37{:}05.530$  signature is found.

NOTE Confidence: 0.84878147

00:37:05.530 --> 00:37:08.379 Enriched in in CRC patients as well,

NOTE Confidence: 0.84878147

 $00{:}37{:}08{.}380 \dashrightarrow 00{:}37{:}10{.}816$  and so the mayor study came

NOTE Confidence: 0.84878147

 $00:37:10.816 \longrightarrow 00:37:12.034$  to similar conclusions,

NOTE Confidence: 0.84878147

 $00:37:12.040 \longrightarrow 00:37:14.889$  and essentially these two papers you know,

NOTE Confidence: 0.84878147

 $00{:}37{:}14.890 \dashrightarrow 00{:}37{:}17.722$  this is a rare example in the microbiome

NOTE Confidence: 0.84878147

 $00{:}37{:}17.722 \dashrightarrow 00{:}37{:}20.185$  where you actually establish causation.

NOTE Confidence: 0.84878147

 $00:37:20.185 \rightarrow 00:37:22.880$  So these two papers brought this

- NOTE Confidence: 0.84878147
- $00:37:22.880 \longrightarrow 00:37:25.608$  phenotype to the two sort of

 $00:37:25.608 \longrightarrow 00:37:28.058$  a causal level and what my lab

NOTE Confidence: 0.84878147

00:37:28.058 --> 00:37:30.758 has been trying to do of course,

NOTE Confidence: 0.84878147

 $00{:}37{:}30.760 \dashrightarrow 00{:}37{:}32.452$  is understand the molecular

NOTE Confidence: 0.84878147

 $00{:}37{:}32{.}452 \dashrightarrow 00{:}37{:}35{.}649$  basis for all of this OK and so.

NOTE Confidence: 0.83618563

 $00:37:38.520 \longrightarrow 00:37:41.530$  Oswald, in his initial paper,

NOTE Confidence: 0.83618563

00:37:41.530 --> 00:37:47.550 had done a series of very nice and you know,

NOTE Confidence: 0.83618563

 $00:37:47.550 \longrightarrow 00:37:50.970$  robust control experiments to establish

NOTE Confidence: 0.83618563

 $00:37:50.970 \dashrightarrow 00:37:53.706$  that this genotoxic phenotype.

NOTE Confidence: 0.83618563

 $00{:}37{:}53{.}710 \dashrightarrow 00{:}37{:}56{.}068$  Is due to the final biosynthetic

NOTE Confidence: 0.83618563

 $00{:}37{:}56.068 \dashrightarrow 00{:}37{:}58.579$  product product of the CLB cluster.

NOTE Confidence: 0.83618563

 $00{:}37{:}58{.}580 \dashrightarrow 00{:}38{:}01{.}422$  In other words, if one modifies any

NOTE Confidence: 0.83618563

 $00:38:01.422 \longrightarrow 00:38:04.270$  of the enzymes in the CLB pathway,

NOTE Confidence: 0.83618563

 $00{:}38{:}04{.}270 \dashrightarrow 00{:}38{:}06{.}700$  you lose this genotoxic phenotype OK,

NOTE Confidence: 0.83618563

 $00{:}38{:}06{.}700 \dashrightarrow 00{:}38{:}09{.}661$  and so the implication then is that

 $00:38:09.661 \rightarrow 00:38:12.720$  it's the fully elaborated molecule.

NOTE Confidence: 0.83618563

 $00{:}38{:}12.720 \dashrightarrow 00{:}38{:}14.920$  That is the active toxin,

NOTE Confidence: 0.83618563

 $00:38:14.920 \longrightarrow 00:38:18.000$  not something in route to

NOTE Confidence: 0.83618563

00:38:18.000 - 00:38:19.848 another another product.

NOTE Confidence: 0.83618563

 $00:38:19.850 \dashrightarrow 00:38:23.000$  And we call that molecule Coley bactine.

NOTE Confidence: 0.83618563

 $00{:}38{:}23.000 \dashrightarrow 00{:}38{:}25.875$  And. So the field basically

NOTE Confidence: 0.83618563

 $00:38:25.875 \rightarrow 00:38:30.260$  set out to do what we do best,

NOTE Confidence: 0.83618563

 $00{:}38{:}30{.}260 \dashrightarrow 00{:}38{:}32{.}900$  which is isolate compounds and the

NOTE Confidence: 0.83618563

00:38:32.900 --> 00:38:35.240 classic way of isolating natural

NOTE Confidence: 0.83618563

 $00:38:35.240 \rightarrow 00:38:37.740$  product secondary metabolites is to

NOTE Confidence: 0.83618563

 $00{:}38{:}37{.}740 \dashrightarrow 00{:}38{:}40{.}490$  culture the Organism of interest.

NOTE Confidence: 0.83618563

 $00:38:40.490 \longrightarrow 00:38:42.925$  In the case of bacterial

NOTE Confidence: 0.83618563

00:38:42.925 --> 00:38:43.899 secondary metabolite,

NOTE Confidence: 0.83618563

00:38:43.900 --> 00:38:47.309 you might grow it in liquid culture,

NOTE Confidence: 0.83618563

 $00{:}38{:}47{.}310 \dashrightarrow 00{:}38{:}50{.}049$  growing on scale.

NOTE Confidence: 0.83618563

00:38:50.050 - 00:38:52.155 Extract start to fractionate by

00:38:52.155 --> 00:38:54.560 HPLC and then we typically do.

NOTE Confidence: 0.83618563

 $00{:}38{:}54{.}560 \dashrightarrow 00{:}38{:}57{.}020$  It's known as activity guided fractionation,

NOTE Confidence: 0.83618563

 $00:38:57.020 \rightarrow 00:38:59.198$  where you're essentially testing each of

NOTE Confidence: 0.83618563

 $00{:}38{:}59{.}198$  -->  $00{:}39{:}01{.}940$  these fractions for a particular phenotype.

NOTE Confidence: 0.83618563

 $00{:}39{:}01{.}940 \dashrightarrow 00{:}39{:}04{.}978$  And then you keep purifying and testing

NOTE Confidence: 0.83618563

 $00{:}39{:}04{.}978$  -->  $00{:}39{:}07{.}916$  and purifying testing until you get to

NOTE Confidence: 0.83618563

 $00:39:07.916 \rightarrow 00:39:10.550$  a single compound and you characterize it.

NOTE Confidence: 0.83618563

 $00:39:10.550 \longrightarrow 00:39:12.530$  The problem is that this

NOTE Confidence: 0.83618563

 $00{:}39{:}12{.}530 \dashrightarrow 00{:}39{:}15{.}060$  approach does not work for Kohli.

NOTE Confidence: 0.83618563

00:39:15.060 --> 00:39:16.130 Bakhtin, OK,

NOTE Confidence: 0.83618563

 $00{:}39{:}16.130 \dashrightarrow 00{:}39{:}19.340$  so the molecule is very unstable.

NOTE Confidence: 0.83618563

 $00{:}39{:}19{.}340 \dashrightarrow 00{:}39{:}23{.}612$  It is very difficult to get the bacteria

NOTE Confidence: 0.83618563

 $00{:}39{:}23.612 \dashrightarrow 00{:}39{:}27.296$  to express the CLB pathway ex vivo.

NOTE Confidence: 0.83618563

 $00{:}39{:}27{.}300 \dashrightarrow 00{:}39{:}32{.}016$  And what we find is that because of the.

NOTE Confidence: 0.83618563

00:39:32.020 --> 00:39:32.880 You know,

 $00:39:32.880 \rightarrow 00:39:35.460$  primarily anaerobic environment of the gut.

NOTE Confidence: 0.83618563

 $00:39:35.460 \longrightarrow 00:39:37.675$  The molecule actually undergoes oxidative

NOTE Confidence: 0.83618563

 $00:39:37.675 \longrightarrow 00:39:40.620$  degradation when you attempt to isolate it.

NOTE Confidence: 0.83618563

 $00:39:40.620 \longrightarrow 00:39:43.630$  Sort of on the bench under air,

NOTE Confidence: 0.83618563

 $00:39:43.630 \longrightarrow 00:39:46.578$  and just to to.

NOTE Confidence: 0.83618563

 $00:39:46.580 \longrightarrow 00:39:48.110$  Give you an example of how

NOTE Confidence: 0.83618563

 $00:39:48.110 \longrightarrow 00:39:48.875$  challenging this is.

NOTE Confidence: 0.83618563

 $00:39:48.880 \rightarrow 00:39:50.920$  This is not work from our own laboratory.

NOTE Confidence: 0.83618563

 $00{:}39{:}50{.}920 \dashrightarrow 00{:}39{:}54{.}898$  This is a group at at Berkeley and scripts.

NOTE Confidence: 0.83618563

00:39:54.900 - 00:39:56.680 They've been pursuing Cali,

NOTE Confidence: 0.83618563

 $00:39:56.680 \longrightarrow 00:39:59.350$  backed in in the isolated this.

NOTE Confidence: 0.83618563

 $00:39:59.350 \longrightarrow 00:40:03.032$  Molecule here in 2019 they obtained 50

NOTE Confidence: 0.83618563

 $00{:}40{:}03.032 \dashrightarrow 00{:}40{:}06.958$  micrograms from a 2000 liter fermentation.

NOTE Confidence: 0.83618563

 $00:40:06.960 \longrightarrow 00:40:09.880$  If anyone can imagine that,

NOTE Confidence: 0.83618563

 $00:40:09.880 \longrightarrow 00:40:12.805$  so we're talking about literally

NOTE Confidence: 0.83618563

 $00:40:12.805 \rightarrow 00:40:14.560$  vanishingly small quantities.

 $00:40:16.940 \longrightarrow 00:40:18.950$  And they they advanced this molecule

NOTE Confidence: 0.84360933

 $00:40:18.950 \longrightarrow 00:40:20.640$  as a candidate calling back,

NOTE Confidence: 0.84360933

 $00{:}40{:}20.640 \dashrightarrow 00{:}40{:}22.950$  and unfortunately this was derived from a

NOTE Confidence: 0.84360933

 $00{:}40{:}22.950 \dashrightarrow 00{:}40{:}24.670$ triple mutant Frankenstein like bacteria,

NOTE Confidence: 0.84360933

 $00{:}40{:}24.670 \dashrightarrow 00{:}40{:}26.350$  and I wrote a commentary.

NOTE Confidence: 0.84360933

 $00{:}40{:}26.350 \dashrightarrow 00{:}40{:}28.282$  If you're interested on this at

NOTE Confidence: 0.84360933

 $00:40:28.282 \rightarrow 00:40:30.208$  the general thinking in the field

NOTE Confidence: 0.84360933

 $00:40:30.208 \longrightarrow 00:40:31.930$  is this is probably not relevant

NOTE Confidence: 0.84360933

 $00:40:31.930 \longrightarrow 00:40:33.739$  to the genotoxic phenotype.

NOTE Confidence: 0.84360933

 $00:40:33.740 \longrightarrow 00:40:35.044$  But the point is,

NOTE Confidence: 0.84360933

 $00{:}40{:}35{.}044 \dashrightarrow 00{:}40{:}37{.}000$  these are the links that people

NOTE Confidence: 0.84360933

 $00:40:37.070 \longrightarrow 00:40:39.163$  are willing to go to to try

NOTE Confidence: 0.84360933

 $00{:}40{:}39.163 \dashrightarrow 00{:}40{:}40.800$  and isolate these molecules.

NOTE Confidence: 0.8315405

 $00:40:43.630 \longrightarrow 00:40:46.696$  And so, how do we approach this?

NOTE Confidence: 0.8315405

 $00{:}40{:}46{.}700 \dashrightarrow 00{:}40{:}48{.}452$  So, as Dan mentioned,

 $00:40:48.452 \rightarrow 00:40:51.080$  we've been collaborating with Jason Crawford.

NOTE Confidence: 0.8315405

 $00{:}40{:}51.080 \dashrightarrow 00{:}40{:}53.702$  Jason is one of the leaders

NOTE Confidence: 0.8315405

 $00:40:53.702 \longrightarrow 00:40:55.013$  in understanding Kohli,

NOTE Confidence: 0.8315405

 $00:40:55.020 \longrightarrow 00:40:56.184$  backed in biosynthesis.

NOTE Confidence: 0.8315405

 $00{:}40{:}56{.}184 \dashrightarrow 00{:}40{:}59{.}443$  And So what we've been doing is really

NOTE Confidence: 0.8315405

 $00{:}40{:}59{.}443 \dashrightarrow 00{:}41{:}01{.}803$  taking knowledge from the biosynthetic NOTE Confidence: 0.8315405

 $00{:}41{:}01.803 \dashrightarrow 00{:}41{:}05.086$  pathway and trying to infer what types

NOTE Confidence: 0.8315405

 $00:41:05.086 \rightarrow 00:41:07.720$  of substructures might be within Kohli.

NOTE Confidence: 0.8315405

 $00{:}41{:}07{.}720 \dashrightarrow 00{:}41{:}10{.}160$  Backed in itself and how

NOTE Confidence: 0.8315405

 $00:41:10.160 \longrightarrow 00:41:11.624$  those might interact.

NOTE Confidence: 0.8315405

 $00{:}41{:}11{.}630 \dashrightarrow 00{:}41{:}14{.}526$  With DNA and so one of the sort

NOTE Confidence: 0.8315405

 $00{:}41{:}14.526 \dashrightarrow 00{:}41{:}17.778$  of models that came out of these

NOTE Confidence: 0.8315405

 $00{:}41{:}17.778 \dashrightarrow 00{:}41{:}20.208$  biosynthetic studies is that you

NOTE Confidence: 0.8315405

00:41:20.305 --> 00:41:23.135 have these fully linear products

NOTE Confidence: 0.8315405

 $00:41:23.135 \rightarrow 00:41:26.470$  offloaded from the PKS assembly line.

NOTE Confidence: 0.8315405

 $00:41:26.470 \longrightarrow 00:41:28.970$  There's a searing protease that

- NOTE Confidence: 0.8315405
- $00:41:28.970 \longrightarrow 00:41:32.179$  removes this residue and blew this ACL.

00:41:32.180 --> 00:41:34.230 Asparagine residue.

NOTE Confidence: 0.8315405

00:41:34.230 --> 00:41:36.250 That generates a primary amine,

NOTE Confidence: 0.8315405

 $00{:}41{:}36{.}250 \dashrightarrow 00{:}41{:}38{.}742$  and once you form at that can start

NOTE Confidence: 0.8315405

 $00:41:38.742 \longrightarrow 00:41:41.666$  to wrap up and ultimately lead to

NOTE Confidence: 0.8315405

 $00:41:41.666 \longrightarrow 00:41:44.324$  this compound on the bottom here,

NOTE Confidence: 0.8315405

 $00{:}41{:}44{.}330 \dashrightarrow 00{:}41{:}46{.}784$  which has a cyclopropane ring in

NOTE Confidence: 0.8315405

 $00:41:46.784 \rightarrow 00:41:49.578$  conjugation with with it with the Alpha,

NOTE Confidence: 0.8315405

 $00{:}41{:}49{.}580 \dashrightarrow 00{:}41{:}51{.}575$  beta unsaturated imming and for

NOTE Confidence: 0.8315405

 $00{:}41{:}51{.}575 \dashrightarrow 00{:}41{:}54{.}042$  those in the audience that have

NOTE Confidence: 0.8315405

 $00{:}41{:}54.042 \dashrightarrow 00{:}41{:}55.638$  worked with Gina toxins,

NOTE Confidence: 0.8315405

 $00{:}41{:}55.640 \dashrightarrow 00{:}41{:}57.660$  you know that these electrophilic

NOTE Confidence: 0.8315405

 $00{:}41{:}57.660 \dashrightarrow 00{:}41{:}59.276$  cyclopropane's are not uncommon.

NOTE Confidence: 0.8315405

 $00{:}41{:}59{.}280 \dashrightarrow 00{:}42{:}02{.}264$  This is a sort of a pharmacophore that's

NOTE Confidence: 0.8315405

 $00:42:02.264 \rightarrow 00:42:05.460$  found in a variety of genotoxic natural.

00:42:05.460 --> 00:42:07.170 Products and so this was,

NOTE Confidence: 0.8315405

00:42:07.170 --> 00:42:07.828 you know,

NOTE Confidence: 0.8315405

00:42:07.828 --> 00:42:09.473 sort of very logically following

NOTE Confidence: 0.8315405

 $00:42:09.473 \longrightarrow 00:42:11.269$  from that type of precedent.

NOTE Confidence: 0.8315405

 $00:42:11.270 \longrightarrow 00:42:14.006$  The problem is that the problem is this.

NOTE Confidence: 0.8315405

 $00{:}42{:}14.010 \dashrightarrow 00{:}42{:}16.056$  No one had isolated these imines.

NOTE Confidence: 0.8315405

00:42:16.060 --> 00:42:18.796 No one had any spectroscopic data on them.

NOTE Confidence: 0.8315405

 $00:42:18.800 \longrightarrow 00:42:20.510$  All we had was this.

NOTE Confidence: 0.8315405

 $00{:}42{:}20{.}510 \dashrightarrow 00{:}42{:}23.876$  This kind of this mechanistic hypothesis.

NOTE Confidence: 0.8315405

 $00:42:23.880 \longrightarrow 00:42:26.448$  And so we set out to make it,

NOTE Confidence: 0.8315405

 $00{:}42{:}26{.}450 \dashrightarrow 00{:}42{:}28{.}898$  and I'm not going to have time to go

NOTE Confidence: 0.8315405

 $00{:}42{:}28.898 \dashrightarrow 00{:}42{:}31.313$  through all of the synthetic work that

NOTE Confidence: 0.8315405

 $00{:}42{:}31{.}313$  -->  $00{:}42{:}33{.}509$  that went into developing these roots.

NOTE Confidence: 0.8315405

 $00:42:33.510 \longrightarrow 00:42:35.757$  But the key steps are shown here.

NOTE Confidence: 0.8315405

 $00{:}42{:}35{.}760 \dashrightarrow 00{:}42{:}37{.}923$  So we start from this linear precursor

NOTE Confidence: 0.8315405

 $00:42:37.923 \longrightarrow 00:42:40.519$  and what we find is that if we

- NOTE Confidence: 0.8315405
- $00:42:40.519 \rightarrow 00:42:42.500$  concentrate this down from dilute acid,

 $00:42:42.500 \longrightarrow 00:42:45.148$  we can get this.

NOTE Confidence: 0.8315405

00:42:45.150 -> 00:42:46.860 Carbon and nitrogen to condense

NOTE Confidence: 0.8315405

 $00:42:46.860 \longrightarrow 00:42:48.919$  onto the ketone. You found this.

NOTE Confidence: 0.8315405

 $00:42:48.919 \longrightarrow 00:42:49.948$  Finally this image.

NOTE Confidence: 0.8315405

 $00:42:49.950 \longrightarrow 00:42:52.116$  We then do a bond formation

NOTE Confidence: 0.8315405

 $00:42:52.116 \longrightarrow 00:42:54.254$  deprotect the Bach route to get

NOTE Confidence: 0.8315405

 $00:42:54.254 \rightarrow 00:42:56.126$  to this compound on the left,

NOTE Confidence: 0.8315405

 $00{:}42{:}56{.}130 \dashrightarrow 00{:}42{:}59{.}698$  we isolate this as as it's TFA salt.

NOTE Confidence: 0.8315405

00:42:59.700 --> 00:43:01.730 But if you neutralize this,

NOTE Confidence: 0.8315405

 $00:43:01.730 \longrightarrow 00:43:03.755$  it's snapshot and so this

NOTE Confidence: 0.8315405

00:43:03.755 --> 00:43:05.375 carbon attacks this ketone,

NOTE Confidence: 0.8315405

 $00:43:05.380 \longrightarrow 00:43:08.050$  you lose water, any formatting.

NOTE Confidence: 0.8315405

 $00{:}43{:}08{.}050 \dashrightarrow 00{:}43{:}08{.}830$  And.

NOTE Confidence: 0.8187508

 $00{:}43{:}10{.}920 \dashrightarrow 00{:}43{:}12{.}838$  The assay that we use, that's 'cause

 $00:43:12.838 \rightarrow 00:43:15.400$  it's nice to give us a lot of detail.

NOTE Confidence: 0.8187508

00:43:15.400 --> 00:43:17.080 It's inexpensive, it's fast, is is.

NOTE Confidence: 0.808242

 $00{:}43{:}19{.}250 \dashrightarrow 00{:}43{:}20{.}934$  Taking linearized plasmid DNA

NOTE Confidence: 0.808242

 $00:43:20.934 \rightarrow 00:43:22.618$  incubating with the molecule,

NOTE Confidence: 0.808242

00:43:22.620 --> 00:43:24.300 running a denaturing gel,

NOTE Confidence: 0.808242

 $00:43:24.300 \longrightarrow 00:43:26.820$  and basically if you look at

NOTE Confidence: 0.808242

 $00:43:26.905 \longrightarrow 00:43:28.930$  the right hand lanes here,

NOTE Confidence: 0.808242

 $00:43:28.930 \longrightarrow 00:43:31.597$  you see these streaks on the gel

NOTE Confidence: 0.808242

 $00{:}43{:}31{.}597 \dashrightarrow 00{:}43{:}34{.}742$  going down to about 100 animal or what

NOTE Confidence: 0.808242

 $00{:}43{:}34{.}742 \dashrightarrow 00{:}43{:}38{.}229$  that tells us is that at 100 animal

NOTE Confidence: 0.808242

 $00{:}43{:}38{.}229 \dashrightarrow 00{:}43{:}40{.}719$  or concentration of this compound,

NOTE Confidence: 0.808242

 $00:43:40.720 \longrightarrow 00:43:41.983$  we're getting extensive

NOTE Confidence: 0.808242

 $00:43:41.983 \rightarrow 00:43:43.667$  degradation of the DNA.

NOTE Confidence: 0.808242

 $00{:}43{:}43.670 \dashrightarrow 00{:}43{:}46.190$  These are smaller fragments that

NOTE Confidence: 0.808242

 $00:43:46.190 \longrightarrow 00:43:49.140$  have higher mobility on the gel.

NOTE Confidence: 0.808242

 $00:43:49.140 \rightarrow 00:43:52.436$  And so that was very exciting to us.

- NOTE Confidence: 0.808242
- 00:43:52.440 --> 00:43:53.607 And you know,
- NOTE Confidence: 0.808242
- $00{:}43{:}53{.}607 \dashrightarrow 00{:}43{:}55{.}552$  we hypothesized again that it
- NOTE Confidence: 0.808242
- $00{:}43{:}55{.}552 \dashrightarrow 00{:}43{:}57{.}840$  was this nucleotide addition to
- NOTE Confidence: 0.808242
- $00:43:57.840 \rightarrow 00:44:00.230$  the cyclopropane that was leading
- NOTE Confidence: 0.808242
- $00:44:00.230 \longrightarrow 00:44:02.989$  to this degradation of the DNA.
- NOTE Confidence: 0.808242
- $00:44:02.990 \longrightarrow 00:44:05.806$  And so to probe that in a little
- NOTE Confidence: 0.808242
- 00:44:05.806 --> 00:44:07.200 bit more detail,
- NOTE Confidence: 0.808242
- $00:44:07.200 \rightarrow 00:44:09.874$  we made a couple of control compounds.
- NOTE Confidence: 0.808242
- $00:44:09.880 \longrightarrow 00:44:11.924$  So the first one.
- NOTE Confidence: 0.808242
- $00:44:11.924 \longrightarrow 00:44:14.479$  Was this dimeric structure up
- NOTE Confidence: 0.808242
- $00{:}44{:}14{.}479 \dashrightarrow 00{:}44{:}17{.}804$  top here and so the hypothesis is
- NOTE Confidence: 0.808242
- $00:44:17.804 \rightarrow 00:44:21.219$  that if this is alkylating DNA,
- NOTE Confidence: 0.808242
- $00:44:21.220 \longrightarrow 00:44:24.166$  perhaps we can induce two fold
- NOTE Confidence: 0.808242
- $00{:}44{:}24.166 \dashrightarrow 00{:}44{:}27.451$  alkylation and perhaps we can then
- NOTE Confidence: 0.808242
- $00:44:27.451 \rightarrow 00:44:29.907$  detect and interstrand crosslink?
- NOTE Confidence: 0.808242

 $00:44:29.910 \longrightarrow 00:44:32.815$  And when you incubate with that compound,

NOTE Confidence: 0.808242

00:44:32.820 --> 00:44:36.140 indeed you can see down here Crosslink Band.

NOTE Confidence: 0.808242

 $00{:}44{:}36{.}140 \dashrightarrow 00{:}44{:}38{.}780$  This corresponds to our positive

NOTE Confidence: 0.808242

 $00:44:38.780 \rightarrow 00:44:40.892$  control for crosslinking cisplatin.

NOTE Confidence: 0.808242

 $00{:}44{:}40{.}900 \dashrightarrow 00{:}44{:}43{.}300$  And then the other thing we did was

NOTE Confidence: 0.808242

 $00{:}44{:}43{.}300 \dashrightarrow 00{:}44{:}46{.}209$  we made a negative control where we NOTE Confidence: 0.808242

 $00{:}44{:}46{.}209 \dashrightarrow 00{:}44{:}48{.}444$  took that cyclopropane and converted

NOTE Confidence: 0.808242

00:44:48.515 --> 00:44:50.957 it to the gem dimethyl substituent.

NOTE Confidence: 0.808242

 $00{:}44{:}50{.}960 \dashrightarrow 00{:}44{:}52{.}895$  The hypothesis being if the

NOTE Confidence: 0.808242

 $00:44:52.895 \rightarrow 00:44:54.443$  cyclopropane is truly involved,

NOTE Confidence: 0.808242

 $00{:}44{:}54{.}450 \dashrightarrow 00{:}44{:}56{.}180$  this compound should be inactive

NOTE Confidence: 0.808242

00:44:56.180 --> 00:44:58.700 and going up to half millimolar.

NOTE Confidence: 0.808242

00:44:58.700 --> 00:45:00.681 We don't detect any damage in our

NOTE Confidence: 0.808242

 $00{:}45{:}00{.}681 \dashrightarrow 00{:}45{:}02{.}517$  as say and so without characterizing

NOTE Confidence: 0.808242

 $00{:}45{:}02.517 \dashrightarrow 00{:}45{:}04.822$  the product without even having

NOTE Confidence: 0.808242

 $00:45:04.822 \rightarrow 00:45:06.830$  isolated the natural products,

- NOTE Confidence: 0.808242
- $00{:}45{:}06{.}830 \dashrightarrow 00{:}45{:}09{.}926$  we were able to sort of formulate this

 $00{:}45{:}09{.}926 \dashrightarrow 00{:}45{:}12{.}758$  proposal for how these things might be.

NOTE Confidence: 0.808242

 $00:45:12.760 \longrightarrow 00:45:14.528$  Might be alkylating DNA.

NOTE Confidence: 0.826165012

 $00:45:16.690 \rightarrow 00:45:19.610$  And. We are, you know,

NOTE Confidence: 0.826165012

 $00:45:19.610 \longrightarrow 00:45:21.518$  we sort of at that point.

NOTE Confidence: 0.826165012

 $00:45:21.520 \longrightarrow 00:45:23.188$  Got stocks so that was around

NOTE Confidence: 0.826165012

 $00:45:23.188 \longrightarrow 00:45:25.340$  2018 when we had identified this.

NOTE Confidence: 0.826165012

 $00:45:25.340 \longrightarrow 00:45:26.925$  You know, this DNA reactive

NOTE Confidence: 0.826165012

 $00:45:26.925 \longrightarrow 00:45:28.193$  substructure in the molecule.

NOTE Confidence: 0.826165012

 $00{:}45{:}28{.}200 \dashrightarrow 00{:}45{:}30{.}108$  We knew that it was incomplete.

NOTE Confidence: 0.826165012

 $00:45:30.110 \longrightarrow 00:45:31.061$  In other words,

NOTE Confidence: 0.826165012

 $00{:}45{:}31.061 \dashrightarrow 00{:}45{:}32.646$  there were other functional groups,

NOTE Confidence: 0.826165012

 $00:45:32.650 \rightarrow 00:45:35.186$  other rings and things with in Cali bactine.

NOTE Confidence: 0.826165012

 $00{:}45{:}35{.}190 \dashrightarrow 00{:}45{:}38{.}144$  But we didn't know what they were.

NOTE Confidence: 0.826165012

 $00{:}45{:}38.150 \dashrightarrow 00{:}45{:}40.544$  And as I mentioned in the beginning,
$00:45:40.550 \longrightarrow 00:45:42.230$  the you know the classical

NOTE Confidence: 0.826165012

00:45:42.230 --> 00:45:43.910 isolation approach is not very

NOTE Confidence: 0.826165012

 $00:45:43.974 \longrightarrow 00:45:46.038$  successful in this in this context,

NOTE Confidence: 0.826165012

 $00:45:46.040 \rightarrow 00:45:48.850$  and so we were stuck.

NOTE Confidence: 0.826165012

 $00:45:48.850 \longrightarrow 00:45:51.010$  Until this paper came out,

NOTE Confidence: 0.826165012

 $00:45:51.010 \rightarrow 00:45:54.880$  and so this is also from the Oswald Group.

NOTE Confidence: 0.826165012

 $00{:}45{:}54{.}880 \dashrightarrow 00{:}45{:}57{.}035$  They did a beautiful experiment

NOTE Confidence: 0.826165012

 $00:45:57.035 \longrightarrow 00:45:59.190$  where they took the collie,

NOTE Confidence: 0.826165012

 $00{:}45{:}59{.}190 \dashrightarrow 00{:}46{:}00{.}914$  backed in producing bacteria,

NOTE Confidence: 0.826165012

 $00:46:00.914 \rightarrow 00:46:03.500$  grew them up in liquid media,

NOTE Confidence: 0.826165012

 $00:46:03.500 \longrightarrow 00:46:04.793$  added exogeneous DNA,

NOTE Confidence: 0.826165012

 $00:46:04.793 \rightarrow 00:46:06.948$  isolated that DNA following incubation,

NOTE Confidence: 0.826165012

 $00{:}46{:}06{.}950 \dashrightarrow 00{:}46{:}10.078$  and ran a denaturing gel and the point

NOTE Confidence: 0.826165012

 $00:46:10.078 \rightarrow 00:46:12.609$  is that they observed interstrand

NOTE Confidence: 0.826165012

 $00{:}46{:}12.609 \dashrightarrow 00{:}46{:}15.927$  crosslinks in that DNA that was

NOTE Confidence: 0.826165012

 $00:46:15.927 \rightarrow 00:46:18.949$  exposed to these bacteria OK and so.

- NOTE Confidence: 0.826165012
- $00{:}46{:}18.950 \dashrightarrow 00{:}46{:}21.970$  I have a note here at the bottom to remind

 $00{:}46{:}22.044 \dashrightarrow 00{:}46{:}24.844$  me you know if you're paying attention.

NOTE Confidence: 0.826165012

 $00:46:24.850 \rightarrow 00:46:26.238$  The original female phenotype

NOTE Confidence: 0.826165012

 $00:46:26.238 \longrightarrow 00:46:27.626$  was double strand breaks.

NOTE Confidence: 0.826165012

00:46:27.630 --> 00:46:29.706 Now I'm talking about cross links.

NOTE Confidence: 0.826165012

 $00{:}46{:}29{.}710 \dashrightarrow 00{:}46{:}32{.}139$  Those two lesions are are intimately related,

NOTE Confidence: 0.826165012

 $00{:}46{:}32{.}140 \dashrightarrow 00{:}46{:}34{.}162$  and I'll talk about that at

NOTE Confidence: 0.826165012

 $00{:}46{:}34{.}162 \dashrightarrow 00{:}46{:}35{.}950$  the end if there's time.

NOTE Confidence: 0.826165012

 $00:46:35.950 \longrightarrow 00:46:37.996$  But basically we're very excited about

NOTE Confidence: 0.826165012

 $00{:}46{:}37{.}996 \dashrightarrow 00{:}46{:}40{.}461$  this paper because you can imagine that

NOTE Confidence: 0.826165012

 $00:46:40.461 \rightarrow 00:46:42.890$  Kohli bactine is entrained in that crosslink,

NOTE Confidence: 0.826165012

00:46:42.890 --> 00:46:43.204 right?

NOTE Confidence: 0.826165012

00:46:43.204 --> 00:46:43.832 You know,

NOTE Confidence: 0.826165012

 $00{:}46{:}43.832 \dashrightarrow 00{:}46{:}46.474$  if that's what's causing the crossing at that

NOTE Confidence: 0.826165012

 $00{:}46{:}46{.}474 \dashrightarrow 00{:}46{:}48{.}790$  point wasn't completely certain that either,

- $00{:}46{:}48.790 \dashrightarrow 00{:}46{:}49.097$  but.
- NOTE Confidence: 0.826165012
- 00:46:49.097 -> 00:46:51.860 Assuming that it is all we have to do,
- NOTE Confidence: 0.826165012
- $00:46:51.860 \longrightarrow 00:46:53.804$  all we have to do is isolate that
- NOTE Confidence: 0.826165012
- $00{:}46{:}53.804 \dashrightarrow 00{:}46{:}55.180$  crosslink can characterize it.
- NOTE Confidence: 0.8377484
- $00{:}46{:}57{.}290 \dashrightarrow 00{:}47{:}01{.}560$  And so at this point in time, you know.
- NOTE Confidence: 0.8377484
- 00:47:01.560 --> 00:47:03.240 90% of the biosynthetic
- NOTE Confidence: 0.8377484
- $00:47:03.240 \longrightarrow 00:47:05.290$  pathway had been mapped out.
- NOTE Confidence: 0.8377484
- $00:47:05.290 \rightarrow 00:47:08.706$  We had a very good understanding of what
- NOTE Confidence: 0.8377484
- $00{:}47{:}08.706 \dashrightarrow 00{:}47{:}12.703$  went in of the amino acids that went into
- NOTE Confidence: 0.8377484
- $00:47:12.703 \rightarrow 00:47:15.880$  the pathway and where they ended up.
- NOTE Confidence: 0.8377484
- 00:47:15.880 --> 00:47:17.820 Following sort of offloading
- NOTE Confidence: 0.8377484
- 00:47:17.820 --> 00:47:19.760 of the biosynthetic products,
- NOTE Confidence: 0.8377484
- $00:47:19.760 \longrightarrow 00:47:23.640$  and so for example, it was known through
- NOTE Confidence: 0.8377484
- $00:47:23.640 \rightarrow 00:47:27.040$  work that Jason did very early on,
- NOTE Confidence: 0.8377484
- $00{:}47{:}27.040 \dashrightarrow 00{:}47{:}29.950$  and then others that this amino
- NOTE Confidence: 0.8377484
- $00:47:29.950 \rightarrow 00:47:31.890$  cyclopropane comes from methionine,

- NOTE Confidence: 0.8377484
- $00:47:31.890 \longrightarrow 00:47:34.230$  and these thia zole rings

 $00:47:34.230 \rightarrow 00:47:36.570$  derived from cysteine OK.

NOTE Confidence: 0.8377484

 $00:47:36.570 \longrightarrow 00:47:37.770$  And So what?

NOTE Confidence: 0.8377484

 $00{:}47{:}37{.}770 \dashrightarrow 00{:}47{:}40{.}570$  This allowed us to do is conduct

NOTE Confidence: 0.8377484

 $00:47:40.663 \rightarrow 00:47:43.823$  essentially isotope labeling experiments

NOTE Confidence: 0.8377484

 $00{:}47{:}43.823 \dashrightarrow 00{:}47{:}47.773$  where we generated auxotrophic strains,

NOTE Confidence: 0.8377484

 $00{:}47{:}47{.}780 \dashrightarrow 00{:}47{:}50{.}140$  either deficient in methionine

NOTE Confidence: 0.8377484

 $00:47:50.140 \longrightarrow 00:47:51.910$  or cysteine biosynthesis,

NOTE Confidence: 0.8377484

 $00:47:51.910 \longrightarrow 00:47:55.430$  and then supplemented those cultures

NOTE Confidence: 0.8377484

 $00:47:55.430 \longrightarrow 00:47:59.400$  with C13 labeled amino acid OK.

NOTE Confidence: 0.8377484

 $00:47:59.400 \longrightarrow 00:48:01.661$  And so we can take the wild

NOTE Confidence: 0.8377484

00:48:01.661 --> 00:48:03.680 type strain the oxygen riffs

NOTE Confidence: 0.8377484

 $00{:}48{:}03{.}680 \dashrightarrow 00{:}48{:}06{.}100$  with their amino acids incubate.

NOTE Confidence: 0.8377484

 $00{:}48{:}06{.}100 \dashrightarrow 00{:}48{:}08{.}858$  Here we're using linearized puck 19 DNA.

NOTE Confidence: 0.8377484

 $00:48:08.860 \longrightarrow 00:48:11.072$  We can run a gel to verify

 $00:48:11.072 \rightarrow 00:48:13.190$  that we got crosslinking,

NOTE Confidence: 0.8377484

 $00{:}48{:}13.190 \dashrightarrow 00{:}48{:}16.014$  and then we can try and isolate that

NOTE Confidence: 0.8377484

00:48:16.014 --> 00:48:18.310 cross link and characterize it,

NOTE Confidence: 0.8377484

 $00{:}48{:}18{.}310 \dashrightarrow 00{:}48{:}20.767$  and one of the things that's worth

NOTE Confidence: 0.8377484

 $00:48:20.767 \rightarrow 00:48:23.938$  pointing out is that to do these assays

NOTE Confidence: 0.8377484

 $00:48:23.938 \longrightarrow 00:48:25.978$  were talking about 250 microliters

NOTE Confidence: 0.8377484

 $00{:}48{:}26.049 \dashrightarrow 00{:}48{:}28.159$  of culture versus 2000 liters.

NOTE Confidence: 0.8377484

 $00:48:28.160 \longrightarrow 00:48:30.240$  You know using the old?

NOTE Confidence: 0.8377484

 $00{:}48{:}30{.}240 \dashrightarrow 00{:}48{:}32{.}585$  The sort of the old fashioned method,

NOTE Confidence: 0.8377484

 $00{:}48{:}32{.}590 \dashrightarrow 00{:}48{:}34{.}822$  and so to give you an idea of

NOTE Confidence: 0.8377484

 $00{:}48{:}34{.}822 \dashrightarrow 00{:}48{:}36{.}989$  what the data looks like and

NOTE Confidence: 0.8377484

 $00{:}48{:}36{.}989 \dashrightarrow 00{:}48{:}39{.}281$  why we do this isotope labeling.

NOTE Confidence: 0.8377484

 $00{:}48{:}39{.}290 \dashrightarrow 00{:}48{:}40{.}960$  I'll show you this slide.

NOTE Confidence: 0.8377484

00:48:40.960 --> 00:48:41.887 So for example,

NOTE Confidence: 0.8377484

 $00{:}48{:}41{.}887 \dashrightarrow 00{:}48{:}44{.}050$  we can spot these ions that I've

NOTE Confidence: 0.8377484

 $00:48:44.120 \longrightarrow 00:48:45.990$  marked in colored boxes here,

- NOTE Confidence: 0.8377484
- $00:48:45.990 \longrightarrow 00:48:48.095$  and the top chromatogram is

 $00:48:48.095 \longrightarrow 00:48:49.779$  the wild type strain.

NOTE Confidence: 0.8377484

 $00{:}48{:}49{.}780 \dashrightarrow 00{:}48{:}52{.}636$  And what you can see in the Sistine

NOTE Confidence: 0.8377484

 $00{:}48{:}52{.}636 \dashrightarrow 00{:}48{:}54{.}947$  Auxotroph the middle graph is that

NOTE Confidence: 0.8377484

 $00{:}48{:}54{.}947 \dashrightarrow 00{:}48{:}57{.}740$  those ions are shifted by three units,

NOTE Confidence: 0.8377484

 $00{:}48{:}57{.}740 \dashrightarrow 00{:}49{:}00{.}365$  and so that's very useful to us

NOTE Confidence: 0.8377484

 $00:49:00.365 \longrightarrow 00:49:02.669$  because it tells us two things.

NOTE Confidence: 0.8377484

 $00:49:02.670 \longrightarrow 00:49:05.372$  One is that that Ion is probably

NOTE Confidence: 0.8377484

 $00{:}49{:}05{.}372 \dashrightarrow 00{:}49{:}08{.}064$  contains Poly back in or the vestiges

NOTE Confidence: 0.8377484

 $00{:}49{:}08{.}064 \dashrightarrow 00{:}49{:}10{.}242$  of Cali Bactine and then two.

NOTE Confidence: 0.8377484

00:49:10.250 --> 00:49:12.140 It contains one thiazole residue,

NOTE Confidence: 0.8377484

 $00:49:12.140 \longrightarrow 00:49:14.870$  there was one cysteine incorporated

NOTE Confidence: 0.8377484

 $00{:}49{:}14.870 \dashrightarrow 00{:}49{:}16.508$  into that unit.

NOTE Confidence: 0.8377484

00:49:16.510 --> 00:49:18.274 And we can play the same game

NOTE Confidence: 0.8377484

 $00{:}49{:}18.274 \dashrightarrow 00{:}49{:}19.600$  with the methionine auxotroph.

 $00:49:19.600 \rightarrow 00:49:22.129$  So here we get a shift by plus four.

NOTE Confidence: 0.8377484

 $00{:}49{:}22{.}130 \dashrightarrow 00{:}49{:}24{.}118$  So that tells us there's 11 amino

NOTE Confidence: 0.8377484

 $00{:}49{:}24.118 \dashrightarrow 00{:}49{:}25.565$  cyclopropane and tells us it's

NOTE Confidence: 0.8377484

 $00{:}49{:}25{.}565 \dashrightarrow 00{:}49{:}26{.}905$  also related to Cali Bactine.

NOTE Confidence: 0.8377484

 $00{:}49{:}26{.}910 \dashrightarrow 00{:}49{:}30{.}870$  OK, so this was the initial work that we did.

NOTE Confidence: 0.8377484

 $00{:}49{:}30{.}870 \dashrightarrow 00{:}49{:}34{.}070$  We had to carry out a lot more

NOTE Confidence: 0.8377484

 $00:49:34.070 \longrightarrow 00:49:37.545$  labeling in order to get the full

NOTE Confidence: 0.8377484

 $00:49:37.545 \rightarrow 00:49:40.615$  structure assignment and So what we

NOTE Confidence: 0.8377484

00:49:40.615 --> 00:49:43.815 did was we generated a series of we

NOTE Confidence: 0.8377484

 $00{:}49{:}43.815 \dashrightarrow 00{:}49{:}46.450$  had our cysteine and methionine auxotroph.

NOTE Confidence: 0.8377484

 $00{:}49{:}46{.}450 \dashrightarrow 00{:}49{:}49{.}000$  We generated steering and glaci Knox

NOTE Confidence: 0.8377484

00:49:49.000 --> 00:49:51.694 A<br/>tros because those are also incorporated

NOTE Confidence: 0.8377484

 $00{:}49{:}51{.}694$  -->  $00{:}49{:}54{.}454$  into the into the natural product.

NOTE Confidence: 0.8377484

 $00{:}49{:}54{.}460 \dashrightarrow 00{:}49{:}58{.}060$  And then we also did Universal labeling C

NOTE Confidence: 0.8377484

 $00:49:58.060 \rightarrow 00:50:01.430$  13 labeling with glucose an 15 labeling.

NOTE Confidence: 0.8377484

 $00:50:01.430 \longrightarrow 00:50:02.864$  With ammonium chloride.

- NOTE Confidence: 0.8377484
- $00:50:02.864 \rightarrow 00:50:06.210$  And we can run the same experiment

00:50:06.301 - > 00:50:08.857 where we incubate with the DNA,

NOTE Confidence: 0.8377484

 $00:50:08.860 \longrightarrow 00:50:10.000$  isolate the crosslink,

NOTE Confidence: 0.8377484

 $00{:}50{:}10.000 \dashrightarrow 00{:}50{:}10.760$  digest it,

NOTE Confidence: 0.8377484

 $00{:}50{:}10.760 \dashrightarrow 00{:}50{:}13.964$  analyze it by 10MM S and we can then

NOTE Confidence: 0.8377484

 $00{:}50{:}13.964 \dashrightarrow 00{:}50{:}17.176$  see different shifts in those ions.

NOTE Confidence: 0.8377484

 $00{:}50{:}17.180 \dashrightarrow 00{:}50{:}19.484$  And this data turned out to

NOTE Confidence: 0.8377484

 $00:50:19.484 \longrightarrow 00:50:21.340$  be very powerful for us,

NOTE Confidence: 0.8377484

 $00:50:21.340 \longrightarrow 00:50:23.230$  because without isolating the compound

NOTE Confidence: 0.8377484

00:50:23.230 --> 00:50:25.120 without getting any spectroscopic data,

NOTE Confidence: 0.8377484

 $00:50:25.120 \longrightarrow 00:50:25.798$  we can,

NOTE Confidence: 0.8377484

 $00:50:25.798 \longrightarrow 00:50:28.510$  we can glean an incredible amount of insight

NOTE Confidence: 0.7990484

 $00{:}50{:}28{.}581 \dashrightarrow 00{:}50{:}30{.}409$  into the molecule structure.

NOTE Confidence: 0.7990484

 $00{:}50{:}30{.}410 \dashrightarrow 00{:}50{:}32{.}300$  So from the glucose labeling,

NOTE Confidence: 0.7990484

 $00:50:32.300 \longrightarrow 00:50:34.946$  we get a shift by 37 units.

 $00:50:34.950 \longrightarrow 00:50:36.840$  That tells us, of course,

NOTE Confidence: 0.7990484

 $00:50:36.840 \longrightarrow 00:50:38.730$  that it has 37 carbons.

NOTE Confidence: 0.7990484

00:50:38.730 --> 00:50:40.620 Ammonia shifts by 8 units,

NOTE Confidence: 0.7990484

 $00:50:40.620 \rightarrow 00:50:42.762$  we have eight nitrogens we can see

NOTE Confidence: 0.7990484

 $00:50:42.762 \dashrightarrow 00:50:45.149$  that in the methionine auxotroph,

NOTE Confidence: 0.7990484

 $00{:}50{:}45{.}150 \dashrightarrow 00{:}50{:}47{.}466$  and I'm talking about a higher

NOTE Confidence: 0.7990484

 $00:50:47.466 \longrightarrow 00:50:49.010$  molecular weight ion here.

NOTE Confidence: 0.7990484

 $00:50:49.010 \longrightarrow 00:50:51.422$  At the top we get a shift by 8

NOTE Confidence: 0.7990484

 $00{:}50{:}51{.}422 \dashrightarrow 00{:}50{:}53{.}372$  carbons and so that told us that

NOTE Confidence: 0.7990484

 $00{:}50{:}53{.}372 \dashrightarrow 00{:}50{:}55{.}348$  we had two of these cyclopropane NOTE Confidence: 0.7990484

 $00{:}50{:}55{.}348 \dashrightarrow 00{:}50{:}58{.}253$  residues or what was left of them.

NOTE Confidence: 0.7990484

 $00{:}50{:}58{.}260 \dashrightarrow 00{:}51{:}00{.}228$  Two thia zole rings based on A6

NOTE Confidence: 0.7990484

00:51:00.228 --> 00:51:02.195 carbon shift in this in the

NOTE Confidence: 0.7990484

00:51:02.195 --> 00:51:04.246 Sistine Extra if you get the idea,

NOTE Confidence: 0.7990484

 $00{:}51{:}04{.}250 \dashrightarrow 00{:}51{:}06{.}642$  and so we can basically tease out a

NOTE Confidence: 0.7990484

 $00:51:06.642 \longrightarrow 00:51:09.138$  lot of structural data to sort of

- NOTE Confidence: 0.7990484
- $00:51:09.138 \dashrightarrow 00:51:12.097$  see what pieces are need to be put

00:51:12.097 --> 00:51:14.233 together here to make the molecule.

NOTE Confidence: 0.7990484

 $00:51:14.240 \rightarrow 00:51:18.152$  And so at any rate we found this

NOTE Confidence: 0.7990484

 $00:51:18.152 \rightarrow 00:51:21.029$  higher molecular weight ion at 956.

NOTE Confidence: 0.7990484

 $00:51:21.030 \longrightarrow 00:51:22.298$  Using all that data,

NOTE Confidence: 0.7990484

 $00{:}51{:}22.298 \dashrightarrow 00{:}51{:}25.452$  we were able to fit it to this structure

NOTE Confidence: 0.7990484

 $00{:}51{:}25{.}452 \dashrightarrow 00{:}51{:}28{.}189$  here and so it contains one adenine

NOTE Confidence: 0.7990484

 $00:51:28.266 \rightarrow 00:51:31.320$  residue and have explicitly drawn the

NOTE Confidence: 0.7990484

 $00:51:31.320 \rightarrow 00:51:34.182$  Adenine without connectivity to the base,

NOTE Confidence: 0.7990484

 $00:51:34.182 \rightarrow 00:51:37.470$  because at the time that we did this,

NOTE Confidence: 0.7990484

 $00:51:37.470 \longrightarrow 00:51:39.114$  we couldn't specify where

NOTE Confidence: 0.7990484

 $00{:}51{:}39{.}114 \dashrightarrow 00{:}51{:}41{.}169$  it was bonded to a denine.

NOTE Confidence: 0.7990484

 $00:51:41.170 \longrightarrow 00:51:44.047$  We now know that that's in three,

NOTE Confidence: 0.7990484

 $00{:}51{:}44.050 \dashrightarrow 00{:}51{:}47.749$  but had one adenine on the right hand side.

NOTE Confidence: 0.7990484

 $00{:}51{:}47.750 \dashrightarrow 00{:}51{:}50.620$  You have a cyclopropane that's still intact,

- $00{:}51{:}50{.}620 \dashrightarrow 00{:}51{:}50{.}909$  OK.
- NOTE Confidence: 0.7990484
- $00{:}51{:}50{.}909 \dashrightarrow 00{:}51{:}53{.}510$  And then you've got the rest of the core
- NOTE Confidence: 0.7990484
- 00:51:53.583 --> 00:51:56.019 molecule sort of linking it together,
- NOTE Confidence: 0.7990484
- 00:51:56.020 --> 00:51:58.225 and so it's it's almost C2 symmetric,
- NOTE Confidence: 0.7990484
- $00{:}51{:}58{.}230 \dashrightarrow 00{:}51{:}59{.}820$  it's it's a hetero dimer.
- NOTE Confidence: 0.7990484
- $00:51:59.820 \longrightarrow 00:52:01.400$  It's not quite C2 symmetric.
- NOTE Confidence: 0.7990484
- $00:52:01.400 \longrightarrow 00:52:02.924$  If you look carefully at these
- NOTE Confidence: 0.7990484
- $00:52:02.924 \rightarrow 00:52:04.422$  thiazole rings they have different
- NOTE Confidence: 0.7990484
- $00:52:04.422 \rightarrow 00:52:06.158$  appendages in different connectivity,
- NOTE Confidence: 0.7990484
- 00:52:06.160 --> 00:52:07.740 but it's very close OK,
- NOTE Confidence: 0.7990484
- $00{:}52{:}07{.}740 \dashrightarrow 00{:}52{:}09{.}325$  and this structure fit RMS
- NOTE Confidence: 0.7990484
- 00:52:09.325 --> 00:52:10.593 data within one PPM,
- NOTE Confidence: 0.7990484
- 00:52:10.600 00:52:12.496 so we're very excited about that.
- NOTE Confidence: 0.7616281
- 00:52:14.640 --> 00:52:17.848 And so if that is simply a mono
- NOTE Confidence: 0.7616281
- $00:52:17.848 \rightarrow 00:52:20.657$  adenine addict and we're getting icy,
- NOTE Confidence: 0.7616281
- $00:52:20.660 \rightarrow 00:52:22.380$  else, presumably there's a

- NOTE Confidence: 0.7616281
- $00{:}52{:}22{.}380 \dashrightarrow 00{:}52{:}24.960$  dinucleotide add up and we went,

 $00{:}52{:}24.960 \dashrightarrow 00{:}52{:}29.260$  and we were able to find the dyad an addict.

NOTE Confidence: 0.7616281

 $00:52:29.260 \longrightarrow 00:52:33.130$  OK, and this fits, fits within 1/2 PPM error.

NOTE Confidence: 0.7616281

00:52:33.130 --> 00:52:35.280 OK, and so working backwards,

NOTE Confidence: 0.7616281

 $00:52:35.280 \rightarrow 00:52:38.720$  if that's the dyad, and in an act,

NOTE Confidence: 0.7616281

 $00:52:38.720 \longrightarrow 00:52:41.730$  then this is the structure of Kohli,

NOTE Confidence: 0.7616281

 $00:52:41.730 \longrightarrow 00:52:44.140$  bactine on the bottom here.

NOTE Confidence: 0.7616281

00:52:44.140 --> 00:52:47.899 OK, and so we've got two cyclopropane's.

NOTE Confidence: 0.7616281

 $00{:}52{:}47{.}900 \dashrightarrow 00{:}52{:}52{.}366$  And in the middle we have this

NOTE Confidence: 0.7616281

00:52:52.366 --> 00:52:54.770 1/2 dicarbonyl residue OK.

NOTE Confidence: 0.7616281

 $00:52:54.770 \longrightarrow 00:52:56.402$  There's a detail here

NOTE Confidence: 0.7616281

 $00:52:56.402 \dashrightarrow 00:52:58.034$  which is worth mentioning,

NOTE Confidence: 0.7616281

 $00:52:58.040 \rightarrow 00:53:01.712$  which is that this is this kind of compound.

NOTE Confidence: 0.7616281

 $00{:}53{:}01{.}720$  -->  $00{:}53{:}04{.}672$  On the bottom is what we characterized what

NOTE Confidence: 0.7616281

 $00{:}53{:}04.672 \dashrightarrow 00{:}53{:}07.858$  we expect based on the biosynthetic pathway.

 $00:53:07.860 \rightarrow 00:53:11.124$  Is the self amino ketone at the top,

NOTE Confidence: 0.7616281

00:53:11.130 --> 00:53:13.594 but we've done work that shown that

NOTE Confidence: 0.7616281

 $00{:}53{:}13{.}594$  -->  $00{:}53{:}16{.}116$  this thing is unstable towards aerobic NOTE Confidence: 0.7616281

00:53:16.116 --> 00:53:18.894 oxidation to an Alpha keto imine,

NOTE Confidence: 0.7616281

00:53:18.900 --> 00:53:21.959 and then hydrolysis 212 die ketone and

NOTE Confidence: 0.7616281

 $00{:}53{:}21{.}959 \dashrightarrow 00{:}53{:}24{.}697$  so working under air on the bench.

NOTE Confidence: 0.7616281

 $00{:}53{:}24.700 \dashrightarrow 00{:}53{:}27.171$  This is this is the compound that

NOTE Confidence: 0.7616281

 $00{:}53{:}27{.}171 \dashrightarrow 00{:}53{:}29{.}490$  you would have expected to get.

NOTE Confidence: 0.7616281

 $00{:}53{:}29{.}490 \dashrightarrow 00{:}53{:}31{.}620$  And still so no ones isolated

NOTE Confidence: 0.7616281

 $00:53:31.620 \longrightarrow 00:53:33.040$  calling back in yet.

NOTE Confidence: 0.7616281

 $00{:}53{:}33{.}040 \dashrightarrow 00{:}53{:}35{.}170$  And so how do you prove

NOTE Confidence: 0.7616281

 $00:53:35.170 \longrightarrow 00:53:36.235$  the structure assignment?

NOTE Confidence: 0.7616281

 $00{:}53{:}36{.}240 \dashrightarrow 00{:}53{:}39{.}426$  We can go back and try and make it,

NOTE Confidence: 0.7616281

 $00{:}53{:}39{.}430 \dashrightarrow 00{:}53{:}42{.}286$  and so we spent some time developing a

NOTE Confidence: 0.7616281

 $00{:}53{:}42.286 \dashrightarrow 00{:}53{:}44.757$  synthesis of the molecule and it was.

NOTE Confidence: 0.7616281

 $00{:}53{:}44{.}760 \dashrightarrow 00{:}53{:}46{.}890$  It was not straightforward because of

- NOTE Confidence: 0.7616281
- 00:53:46.890 00:53:50.210 its instability, but we could make it.

 $00{:}53{:}50{.}210 \dashrightarrow 00{:}53{:}54{.}107$  And then we can do an LCMS coinjection and

NOTE Confidence: 0.7616281

 $00{:}53{:}54{.}107 \dashrightarrow 00{:}53{:}58{.}207$  we see that has the same retention time.

NOTE Confidence: 0.7616281

 $00:53:58.210 \longrightarrow 00:54:00.821$  It has the same tandem Ms as

NOTE Confidence: 0.7616281

 $00:54:00.821 \longrightarrow 00:54:03.670$  the as the natural material,

NOTE Confidence: 0.7616281

 $00{:}54{:}03.670 \dashrightarrow 00{:}54{:}06.645$  and then finally we did a crosslinking

NOTE Confidence: 0.7616281

 $00:54:06.645 \rightarrow 00:54:09.772$  assay where we basically ran that same

NOTE Confidence: 0.7616281

 $00:54:09.772 \rightarrow 00:54:13.230$  experiment that we ran with the bacteria,

NOTE Confidence: 0.7616281

00:54:13.230 --> 00:54:15.526 except replace the bacteria

NOTE Confidence: 0.7616281

 $00:54:15.526 \rightarrow 00:54:17.248$  with our compound.

NOTE Confidence: 0.7616281

 $00{:}54{:}17.250 \dashrightarrow 00{:}54{:}19.464$  And so this thing will crosslink

NOTE Confidence: 0.7616281

 $00{:}54{:}19{.}464 \dashrightarrow 00{:}54{:}21{.}676$  add up to about, you know,

NOTE Confidence: 0.7616281

 $00{:}54{:}21.676 \dashrightarrow 00{:}54{:}23.516$  down to about 500 nanomolar.

NOTE Confidence: 0.7616281

 $00{:}54{:}23.520 \dashrightarrow 00{:}54{:}26.200$  And then we can do the tandem Ms

NOTE Confidence: 0.7616281

 $00:54:26.200 \longrightarrow 00:54:28.320$  analysis of those cross links.

 $00{:}54{:}28{.}320 \dashrightarrow 00{:}54{:}31{.}632$  And so let me explain what's on this slide.

NOTE Confidence: 0.7616281

 $00{:}54{:}31{.}640 \dashrightarrow 00{:}54{:}34{.}209$  So when we do the bacterial experiment

NOTE Confidence: 0.7616281

 $00{:}54{:}34{.}209 \dashrightarrow 00{:}54{:}37{.}180$  where we treat the DNA with the bacteria,

NOTE Confidence: 0.7616281

 $00:54:37.180 \longrightarrow 00:54:39.020$  we can isolate the crosslink.

NOTE Confidence: 0.7616281

 $00{:}54{:}39{.}020 \dashrightarrow 00{:}54{:}40{.}870$  You then run tandem Ms,

NOTE Confidence: 0.7616281

 $00{:}54{:}40{.}870 \dashrightarrow 00{:}54{:}43{.}446$  you get a whole list of ions,

NOTE Confidence: 0.7616281

 $00{:}54{:}43.450 \dashrightarrow 00{:}54{:}45.802$  primary and secondary and tertiary ions

NOTE Confidence: 0.7616281

 $00:54:45.802 \rightarrow 00:54:49.098$  that you see from those crosslinks and so.

NOTE Confidence: 0.7616281

 $00{:}54{:}49{.}100 \dashrightarrow 00{:}54{:}50{.}790$  You know the argument is.

NOTE Confidence: 0.7616281

 $00{:}54{:}50{.}790 \dashrightarrow 00{:}54{:}53{.}022$  If we're making the same molecule

NOTE Confidence: 0.7616281

 $00:54:53.022 \longrightarrow 00:54:55.100$  that the bugs are making.

NOTE Confidence: 0.7616281

00:54:55.100 --> 00:54:57.425 Are synthetic compound oughta interact

NOTE Confidence: 0.7616281

 $00{:}54{:}57{.}425 \dashrightarrow 00{:}55{:}01{.}411$  with DNA in the same way and it ought to

NOTE Confidence: 0.7616281

 $00:55:01.411 \rightarrow 00:55:04.727$  blow apart in a mass spec in the same way?

NOTE Confidence: 0.7616281

 $00{:}55{:}04{.}730 \dashrightarrow 00{:}55{:}07{.}426$  And So what this plot shows on the

NOTE Confidence: 0.7616281

 $00:55:07.426 \longrightarrow 00:55:10.106$  X axis or all of the ions that

- NOTE Confidence: 0.7616281
- $00:55:10.106 \longrightarrow 00:55:13.494$  we found in the tenant and Ms of

 $00:55:13.494 \rightarrow 00:55:15.510$  the bacteria derived crosslinks,

NOTE Confidence: 0.7616281

 $00:55:15.510 \longrightarrow 00:55:18.709$  we see all of those ions with

NOTE Confidence: 0.7616281

00:55:18.709 - 00:55:20.080 our synthetic material.

NOTE Confidence: 0.7616281

 $00{:}55{:}20.080 \dashrightarrow 00{:}55{:}22.840$  And the Y axis is simply the experimental

NOTE Confidence: 0.7616281

 $00{:}55{:}22.840 \dashrightarrow 00{:}55{:}24.713$  minus theoretical error for those

NOTE Confidence: 0.7616281

 $00:55:24.713 \rightarrow 00:55:26.578$  ions using this synthetic material.

NOTE Confidence: 0.7616281

 $00:55:26.580 \longrightarrow 00:55:29.840$  And so the point is we get all the same

NOTE Confidence: 0.7616281

 $00{:}55{:}29{.}926 \dashrightarrow 00{:}55{:}33{.}436$  ions that we get when we use the bacteria.

NOTE Confidence: 0.7616281

 $00:55:33.440 \longrightarrow 00:55:35.320$  They're all within with the

NOTE Confidence: 0.7616281

00:55:35.320 --> 00:55:37.769 exception of 1 within two PPM OK,

NOTE Confidence: 0.7616281

 $00{:}55{:}37{.}770 \dashrightarrow 00{:}55{:}41{.}240$  and so we don't have an NMR of Cali bactine

NOTE Confidence: 0.7819776

 $00{:}55{:}41{.}328 \dashrightarrow 00{:}55{:}42{.}459$  to compare to.

NOTE Confidence: 0.7819776

 $00{:}55{:}42{.}460 \dashrightarrow 00{:}55{:}44{.}638$  But we can say that structure

NOTE Confidence: 0.7819776

 $00:55:44.638 \dashrightarrow 00:55:46.789$  that we made interacts with DNA.

 $00{:}55{:}46{.}790 \dashrightarrow 00{:}55{:}49{.}142$  It crosslinks DNA and then it blows

NOTE Confidence: 0.7819776

 $00{:}55{:}49{.}142 \dashrightarrow 00{:}55{:}51{.}210$  apart in attend imeson exactly.

NOTE Confidence: 0.7819776

 $00{:}55{:}51{.}210 \dashrightarrow 00{:}55{:}53{.}031$  In indistinguishable fashion.

NOTE Confidence: 0.7819776

 $00:55:53.031 \longrightarrow 00:55:56.066$  And So what about this?

NOTE Confidence: 0.7819776

00:55:56.070 --> 00:55:58.368 I see LDS be, you know,

NOTE Confidence: 0.7819776

 $00:55:58.370 \longrightarrow 00:55:59.104$  apparent contradiction,

NOTE Confidence: 0.7819776

 $00{:}55{:}59{.}104 \dashrightarrow 00{:}56{:}02{.}040$  so there's been a lot of debate in

NOTE Confidence: 0.7819776

 $00:56:02.105 \rightarrow 00:56:04.130$  the literature between you know,

NOTE Confidence: 0.7819776

00:56:04.130 $\operatorname{-->}$ 00:56:06.370 debating the mechanism of action

NOTE Confidence: 0.7819776

00:56:06.370 --> 00:56:08.610 because Oswald had originally observed

NOTE Confidence: 0.7819776

 $00{:}56{:}08.677$  -->  $00{:}56{:}11.015$  DNA double strand breaks using a comet NOTE Confidence: 0.7819776

00:56:11.015 - 00:56:13.347 assay and then came along and said,

NOTE Confidence: 0.7819776

00:56:13.350 --> 00:56:15.270 no wait, it's cross links,

NOTE Confidence: 0.7819776

 $00:56:15.270 \longrightarrow 00:56:17.974$  and for any of you that are familiar

NOTE Confidence: 0.7819776

 $00:56:17.974 \longrightarrow 00:56:19.879$  with these repair pathways,

NOTE Confidence: 0.7819776

 $00{:}56{:}19.880 \dashrightarrow 00{:}56{:}22.178$  you know that these two phenotypes

- NOTE Confidence: 0.7819776
- $00:56:22.178 \rightarrow 00:56:24.413$  are intimately linked, right? And so.

 $00{:}56{:}24{.}413 \dashrightarrow 00{:}56{:}26{.}940$  When you start to repair an ICL,

NOTE Confidence: 0.7819776

 $00:56:26.940 \longrightarrow 00:56:29.046$  you actually form a DSP that

NOTE Confidence: 0.7819776

 $00{:}56{:}29.046 \dashrightarrow 00{:}56{:}31.457$  leads to activation of HR and so

NOTE Confidence: 0.7819776

00:56:31.457 --> 00:56:33.662 you're going to see gamma, H2, X.

NOTE Confidence: 0.7819776

00:56:33.662 --> 00:56:35.292 You're going to see streaking

NOTE Confidence: 0.7819776

00:56:35.292 --> 00:56:36.710 in your comment essay,

NOTE Confidence: 0.7819776

 $00:56:36.710 \longrightarrow 00:56:38.885$  and so the two phenotypes

NOTE Confidence: 0.7819776

00:56:38.885 - 00:56:40.190 are entirely consistent.

NOTE Confidence: 0.7819776

 $00:56:40.190 \longrightarrow 00:56:42.896$  And we actually identified another pathway,

NOTE Confidence: 0.7819776

 $00{:}56{:}42.900 \dashrightarrow 00{:}56{:}45.606$  which is just a spontaneous pathway.

NOTE Confidence: 0.7819776

 $00{:}56{:}45.610 \dashrightarrow 00{:}56{:}48.522$  So it's well known in the old sort

NOTE Confidence: 0.7819776

 $00{:}56{:}48.522 \dashrightarrow 00{:}56{:}51.487$  of Gina toxin literature that N

NOTE Confidence: 0.7819776

 $00{:}56{:}51{.}487 \dashrightarrow 00{:}56{:}54{.}172$ 3 adenine addicts are unstable

NOTE Confidence: 0.7819776

 $00{:}56{:}54{.}172 \dashrightarrow 00{:}56{:}55{.}930$  towards depurination.

 $00:56:55.930 \rightarrow 00:56:58.667$  And if we run our crosslinking assay,

NOTE Confidence: 0.7819776

 $00:56:58.670 \longrightarrow 00:56:59.846$  we sort of.

NOTE Confidence: 0.7819776

 $00:56:59.846 \longrightarrow 00:57:02.590$  We modify the assay to be able

NOTE Confidence: 0.7819776

 $00:57:02.691 \longrightarrow 00:57:05.309$  to sort of get at this data,

NOTE Confidence: 0.7819776

 $00{:}57{:}05{.}310 \dashrightarrow 00{:}57{:}07{.}692$  but this is the conclusion is

NOTE Confidence: 0.7819776

 $00{:}57{:}07.692 \dashrightarrow 00{:}57{:}09.710$  essentially that these these Icl's

NOTE Confidence: 0.7819776

 $00:57:09.710 \longrightarrow 00:57:11.550$  undergo a slow, deep urination.

NOTE Confidence: 0.7819776

 $00{:}57{:}11{.}550 \dashrightarrow 00{:}57{:}13{.}830$  And then there's a second elimination

NOTE Confidence: 0.7819776

00:57:13.830 --> 00:57:16.047 of the phosphate that occurs to

NOTE Confidence: 0.7819776

 $00{:}57{:}16.047 \dashrightarrow 00{:}57{:}18.135$  lead to a single strand break.

NOTE Confidence: 0.7819776

 $00{:}57{:}18.140 \dashrightarrow 00{:}57{:}20.380$  And you can imagine then you know,

NOTE Confidence: 0.7819776

 $00{:}57{:}20{.}380 \dashrightarrow 00{:}57{:}22{.}204$  in tandem with the repair pathways

NOTE Confidence: 0.7819776

 $00{:}57{:}22.204 \dashrightarrow 00{:}57{:}23.880$  and also other alkylation lesions.

NOTE Confidence: 0.7819776

 $00{:}57{:}23.880 \dashrightarrow 00{:}57{:}26.568$  Eventually you're going to get those

NOTE Confidence: 0.7819776

 $00{:}57{:}26.568 \dashrightarrow 00{:}57{:}29.151$  single strand breaks close enough to

NOTE Confidence: 0.7819776

 $00:57:29.151 \longrightarrow 00:57:31.999$  each other to get a double strand break.

- NOTE Confidence: 0.7819776
- 00:57:32.000 > 00:57:33.813 And so this brings us to where

 $00:57:33.813 \rightarrow 00:57:35.960$  we're at in the project, and so.

NOTE Confidence: 0.8687447

 $00{:}57{:}38{.}700 \dashrightarrow 00{:}57{:}41{.}148$  What we're currently doing is working

NOTE Confidence: 0.8687447

 $00{:}57{:}41.148 \dashrightarrow 00{:}57{:}43.960$  with this molecule on the bottom here.

NOTE Confidence: 0.8687447

 $00{:}57{:}43.960 \dashrightarrow 00{:}57{:}46.504$  And this is not Kohli backed in itself.

NOTE Confidence: 0.8687447

00:57:46.510 --> 00:57:49.597 It is a analog of Kohli Bakhtin.

NOTE Confidence: 0.8687447

 $00:57:49.600 \rightarrow 00:57:51.868$  The differences are highlighted in green,

NOTE Confidence: 0.8687447

 $00{:}57{:}51{.}870 \dashrightarrow 00{:}57{:}54{.}355$  and so the dye ketonen Kohli backed

NOTE Confidence: 0.8687447

 $00{:}57{:}54{.}355 \dashrightarrow 00{:}57{:}57{.}560$  in on the top here is very unstable.

NOTE Confidence: 0.8687447

00:57:57.560 --> 00:57:59.828 You can't work with this compound,

NOTE Confidence: 0.8687447

 $00{:}57{:}59{.}830 \dashrightarrow 00{:}58{:}02{.}194$ it would be, you know Sufficient

NOTE Confidence: 0.8687447

 $00{:}58{:}02{.}194 \dashrightarrow 00{:}58{:}05{.}277$  asked to try and use this in a

NOTE Confidence: 0.8687447

 $00{:}58{:}05{.}277 \dashrightarrow 00{:}58{:}07{.}407$  series of essays to examine it.

NOTE Confidence: 0.8687447

00:58:07.410 --> 00:58:08.790 Sort of cellular activity.

NOTE Confidence: 0.8687447

 $00{:}58{:}08{.}790 \dashrightarrow 00{:}58{:}11{.}594$  And so we made what we call the

 $00:58:11.594 \rightarrow 00:58:13.911$  Dez di ketone analog on the bottom

NOTE Confidence: 0.8687447

 $00{:}58{:}13.911 \dashrightarrow 00{:}58{:}16.130$  and working with Christian Jobin

NOTE Confidence: 0.8687447

 $00{:}58{:}16{.}130 \dashrightarrow 00{:}58{:}18{.}400$  at the University of Florida.

NOTE Confidence: 0.8687447

00:58:18.400 --> 00:58:19.750 Christians been basically

NOTE Confidence: 0.8687447

 $00:58:19.750 \longrightarrow 00:58:21.100$  taking this compound.

NOTE Confidence: 0.8687447

 $00{:}58{:}21{.}100 \dashrightarrow 00{:}58{:}23{.}781$  Through all of the essays that have

NOTE Confidence: 0.8687447

 $00{:}58{:}23.781 \dashrightarrow 00{:}58{:}27.172$  been run by by Oswald and Box Tone

NOTE Confidence: 0.8687447

 $00{:}58{:}27.172 \dashrightarrow 00{:}58{:}29.878$  Cleavers and others looking at the

NOTE Confidence: 0.8687447

00:58:29.878 --> 00:58:32.662 genotoxic phenotype of the bacteria and

NOTE Confidence: 0.8687447

 $00{:}58{:}32.662 \dashrightarrow 00{:}58{:}34.922$  seeing if the molecule recapitulates

NOTE Confidence: 0.8687447

 $00:58:34.922 \longrightarrow 00:58:38.376$  it and up until now, it seems too

NOTE Confidence: 0.8687447

 $00{:}58{:}38{.}376 \dashrightarrow 00{:}58{:}41{.}400$  so we see we get activation again.

NOTE Confidence: 0.8687447

 $00:58:41.400 \longrightarrow 00:58:43.470$  My page 2X.

NOTE Confidence: 0.8687447

 $00:58:43.470 \longrightarrow 00:58:44.850$  Fancy D2.

NOTE Confidence: 0.8687447

 $00:58:44.850 \rightarrow 00:58:47.202$  What he's doing right now is basically

NOTE Confidence: 0.8687447

 $00:58:47.202 \longrightarrow 00:58:50.123$  looking to see if this induces the same

- NOTE Confidence: 0.8687447
- $00:58:50.123 \rightarrow 00:58:52.343$  type of mutational signature that one

 $00{:}58{:}52{.}343 \dashrightarrow 00{:}58{:}54{.}823$  gets with the bacteria and that will be,

NOTE Confidence: 0.8687447

 $00:58:54.830 \longrightarrow 00:58:56.888$  you know, sort of the end.

NOTE Confidence: 0.8687447

 $00:58:56.890 \longrightarrow 00:58:57.793$  The end point.

NOTE Confidence: 0.8687447

00:58:57.793 --> 00:58:59.298 Hopefully you know it will

NOTE Confidence: 0.8687447

 $00:58:59.298 \longrightarrow 00:59:01.019$  be a positive result,

NOTE Confidence: 0.8687447

 $00:59:01.020 \longrightarrow 00:59:03.694$  but whatever it is that will be

NOTE Confidence: 0.8687447

 $00:59:03.694 \rightarrow 00:59:06.529$  sort of the endpoint for this.

NOTE Confidence: 0.8687447

 $00{:}59{:}06{.}530 \dashrightarrow 00{:}59{:}08{.}420$  And so I just acknowledge all

NOTE Confidence: 0.8687447

 $00:59:08.420 \longrightarrow 00:59:10.330$  the people that did the work.

NOTE Confidence: 0.8687447

 $00:59:10.330 \longrightarrow 00:59:11.915$  I'll just go through this

NOTE Confidence: 0.8687447

 $00:59:11.915 \longrightarrow 00:59:13.183$  quickly to save time.

NOTE Confidence: 0.8687447

 $00:59:13.190 \rightarrow 00:59:15.086$  But this is my collaborator Jason.

NOTE Confidence: 0.8687447

00:59:15.090 --> 00:59:16.670 Many of you know him.

NOTE Confidence: 0.8687447

 $00{:}59{:}16.670 \dashrightarrow 00{:}59{:}18.590$  Many people from my group contributed

 $00:59:18.590 \longrightarrow 00:59:20.480$  to this project over the years,

NOTE Confidence: 0.8687447

 $00{:}59{:}20{.}480 \dashrightarrow 00{:}59{:}22{.}699$  acknowledged the NCI and Yale for funding.

NOTE Confidence: 0.8687447

 $00{:}59{:}22{.}700 \dashrightarrow 00{:}59{:}24{.}305$  Thanks again for the invitation

NOTE Confidence: 0.8687447

 $00:59:24.305 \longrightarrow 00:59:26.574$  and I'm happy to stay on and

NOTE Confidence: 0.8687447

 $00:59:26.574 \longrightarrow 00:59:28.084$  take any questions you have.

NOTE Confidence: 0.8345129

00:59:32.140 --> 00:59:33.570 Thank you Seth, very interesting.

NOTE Confidence: 0.8345129

 $00{:}59{:}33{.}570 \dashrightarrow 00{:}59{:}34{.}710$  It makes me appreciate

NOTE Confidence: 0.8345129

 $00:59:34.710 \longrightarrow 00:59:35.850$  that I'm a microbiologist.

NOTE Confidence: 0.8345129

 $00{:}59{:}35{.}850 \dashrightarrow 00{:}59{:}37{.}560$  It's not nowhere near as hard

NOTE Confidence: 0.8345129

 $00{:}59{:}37{.}560 \dashrightarrow 00{:}59{:}39{.}820$  as being a chemist, I think.

NOTE Confidence: 0.8345129

 $00:59:39.820 \dashrightarrow 00:59:43.180$  Are there other questions for process?

NOTE Confidence: 0.81077635

00:59:48.670 --> 00:59:50.930 I want question of course,

NOTE Confidence: 0.81077635

 $00{:}59{:}50{.}930 \dashrightarrow 00{:}59{:}53{.}636$  DNA damaging agents can cause cancer,

NOTE Confidence: 0.81077635

 $00{:}59{:}53{.}640 \dashrightarrow 00{:}59{:}57{.}630$  but there also used to treat cancer.

NOTE Confidence: 0.81077635

 $00:59:57.630 \longrightarrow 00:59:59.680$  Is there any thought? Is there

NOTE Confidence: 0.81077635

 $00:59:59.680 \rightarrow 01:00:01.380$  possibility of using these compounds

- NOTE Confidence: 0.8513931
- $01:00:01.380 \rightarrow 01:00:02.748$  therapeutically? Absolutely yeah, that's

 $01:00:02.750 \rightarrow 01:00:04.450$  something we're very excited about,

NOTE Confidence: 0.8513931

 $01:00:04.450 \longrightarrow 01:00:06.496$  so I didn't get into it.

NOTE Confidence: 0.8513931

 $01:00:06.500 \rightarrow 01:00:08.614$  You know, one of the challenges that

NOTE Confidence: 0.8513931

 $01:00:08.614 \rightarrow 01:00:11.608$  we in my group is always the chemistry.

NOTE Confidence: 0.8513931

01:00:11.610 --> 01:00:13.500 You know, the chemistry work is

NOTE Confidence: 0.8513931

 $01:00:13.500 \rightarrow 01:00:15.448$  a general chemistry to make these

NOTE Confidence: 0.8513931

 $01:00:15.448 \rightarrow 01:00:17.618$  molecules is very robust and we started

NOTE Confidence: 0.8513931

01:00:17.618 --> 01:00:19.799 to characterize them with Ranjeet,

NOTE Confidence: 0.8513931

01:00:19.800 --> 01:00:21.505 Bindra slab and he's found

NOTE Confidence: 0.8513931

01:00:21.505 --> 01:00:23.210 that in bracket two mutants,

NOTE Confidence: 0.8513931

 $01{:}00{:}23.210 \dashrightarrow 01{:}00{:}25.926$  these things are hyperactive and so that's

NOTE Confidence: 0.8513931

 $01{:}00{:}25{.}926$  -->  $01{:}00{:}28{.}030$  the immediate direction we're going in.

NOTE Confidence: 0.8513931

01:00:28.030 --> 01:00:30.748 Long term, we're looking to see if we can,

NOTE Confidence: 0.8513931

 $01{:}00{:}30{.}750 \dashrightarrow 01{:}00{:}32{.}616$  you know, optimize the properties of

 $01{:}00{:}32.616 \dashrightarrow 01{:}00{:}34.369$  these molecules a little bit more.

NOTE Confidence: 0.8513931

 $01{:}00{:}34{.}370 \dashrightarrow 01{:}00{:}36{.}568$  You know it's more than just another

NOTE Confidence: 0.8513931

01:00:36.568 --> 01:00:38.598 crosslinker because I didn't get into it,

NOTE Confidence: 0.8513931

 $01{:}00{:}38{.}600 \dashrightarrow 01{:}00{:}40{.}178$  but there's a mechanism by which

NOTE Confidence: 0.8513931

 $01:00:40.178 \longrightarrow 01:00:42.322$  we can gauge the activity of the

NOTE Confidence: 0.8513931

 $01:00:42.322 \rightarrow 01:00:44.037$  molecule and potentially target it,

NOTE Confidence: 0.8513931

 $01{:}00{:}44.040 \dashrightarrow 01{:}00{:}45.550$  and so there's a lot.

NOTE Confidence: 0.8513931

 $01:00:45.550 \rightarrow 01:00:47.958$  Yeah, there's a lot that we can do,

NOTE Confidence: 0.8513931

 $01{:}00{:}47{.}960 \dashrightarrow 01{:}00{:}49{.}778$  and that's sort of the phase

NOTE Confidence: 0.8513931

 $01{:}00{:}49.778 \dashrightarrow 01{:}00{:}51.280$  that we're entering into with

NOTE Confidence: 0.8546458

 $01{:}00{:}51.280 \dashrightarrow 01{:}00{:}53.092$  the project traffic we are after

NOTE Confidence: 0.8546458

 $01{:}00{:}53.092 \dashrightarrow 01{:}00{:}54.606$ 1:00 o'clock, so if people

NOTE Confidence: 0.8546458

 $01:00:54.606 \rightarrow 01:00:56.116$  have other questions for Seth,

NOTE Confidence: 0.8546458

 $01{:}00{:}56{.}120 \dashrightarrow 01{:}00{:}59{.}016$  just email him I'm sure. Be happy too.

NOTE Confidence: 0.8546458

 $01:00:59.016 \rightarrow 01:01:01.326$  Talking thank both speakers for

NOTE Confidence: 0.8546458

 $01:01:01.326 \rightarrow 01:01:03.600$  really stimulating talk today. Thank

 $01:01:03.600 \longrightarrow 01:01:05.049$  you thanks everyone.