WEBVTT

NOTE duration:"01:01:10.5710000"

NOTE language:en-us

NOTE Confidence: 0.8283998

00:00:00.000 --> 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 --> 00:00:05.480 which is terrific. Both internal

NOTE Confidence: 0.8283998

00:00:05.480 --> 00:00:07.080 speakers and I encourage people.

NOTE Confidence: 0.8283998

00:00:07.080 --> 00:00:09.010 If you have questions to

NOTE Confidence: 0.8283998

00:00:09.010 --> 00:00:10.940 type them into the chat.

NOTE Confidence: 0.8283998

00:00:10.940 --> 00:00:12.734 And then we'll get those questions

NOTE Confidence: 0.8283998

00:00:12.734 --> 00:00:14.870 answered when the talks are are finished.

NOTE Confidence: 0.8283998

00:00:14.870 --> 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 --> 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 --> 00:00:26.038 leader of the shin of your family,

NOTE Confidence: 0.8283998

00:00:26.040 --> 00:00:27.512 can bring tumor center,

NOTE Confidence: 0.8283998

00:00:27.512 --> 00:00:29.720 which is a new program here.

NOTE Confidence: 0.8283998

00:00:29.720 --> 00:00:30.948 He received his initial

NOTE Confidence: 0.8283998

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

NOTE Confidence: 0.8283998

00:00:32.180 --> 00:00:33.404 then worked at Memorial

NOTE Confidence: 0.8283998

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

NOTE Confidence: 0.8283998

00:00:34.940 --> 00:00:36.805 and began his faculty career

NOTE Confidence: 0.8283998

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

NOTE Confidence: 0.8283998

00:00:38.300 --> 00:00:39.810 He joined us in 2012.

NOTE Confidence: 0.8283998

00:00:39.810 --> 00:00:42.066 He's an international leader in their

NOTE Confidence: 0.8283998

00:00:42.066 --> 00:00:44.569 clinical care and research on brain tumors.

NOTE Confidence: 0.8283998

00:00:44.570 --> 00:00:45.854 Leading leading pivotal research

NOTE Confidence: 0.8283998

00:00:45.854 --> 00:00:47.780 programs and treatment of these cancers,

NOTE Confidence: 0.8283998

00:00:47.780 --> 00:00:49.980 the Genevier family Brain Tumor Center is a

NOTE Confidence: 0.8283998

00:00:49.980 --> 00:00:52.270 new yellow initiative for the Comprehensive,

NOTE Confidence: 0.8283998

00:00:52.270 --> 00:00:53.287 multidisciplinary brain tumor.

NOTE Confidence: 0.8283998

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

NOTE Confidence: 0.8283998

00:00:55.321 --> 00:00:57.088 little bit about that from Antonio,

NOTE Confidence: 0.8283998

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 --> 00:01:05.720 then super like to thank the

NOTE Confidence: 0.84176815

00:01:05.784 --> 00:01:07.359 organizers for inviting me to

NOTE Confidence: 0.84176815

00:01:07.359 --> 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 --> 00:01:12.770 share with you what's happening.

NOTE Confidence: 0.84176815

00:01:12.770 --> 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 --> 00:01:22.418 with you the state of our fields

NOTE Confidence: 0.84176815

00:01:22.418 --> 00:01:24.679 and the spirit of almost like an

NOTE Confidence: 0.84176815

00:01:24.679 --> 00:01:26.459 invitation to even more investigators

NOTE Confidence: 0.84176815

00:01:26.459 --> 00:01:29.150 and labs to join us in this task.

NOTE Confidence: 0.81148463

00:01:32.980 --> 00:01:35.350 So today we're going to concentrate

NOTE Confidence: 0.81148463

00:01:35.350 --> 00:01:38.439 on gliomas and the reason for that is

NOTE Confidence: 0.81148463

00:01:38.439 --> 00:01:41.012 that they account for the vast majority

NOTE Confidence: 0.81148463

00:01:41.012 --> 00:01:43.764 of the brain tumors and as you can

NOTE Confidence: 0.81148463

00:01:43.764 --> 00:01:46.630 see here this is a fight chart showing

NOTE Confidence: 0.81148463

00:01:46.630 --> 00:01:48.190 all malignant intracranial tumors,

NOTE Confidence: 0.81148463

00:01:48.190 --> 00:01:51.060 and the vast majority of the patients

NOTE Confidence: 0.81148463

00:01:51.060 --> 00:01:53.004 have either glioblastoma or other

NOTE Confidence: 0.81148463

00:01:53.004 --> 00:01:54.948 forms of gliomas which for the

NOTE Confidence: 0.81148463

00:01:54.948 --> 00:01:56.718 most part our IDH mutants,

NOTE Confidence: 0.81148463

00:01:56.720 --> 00:01:59.415 which account for grades two and three

NOTE Confidence: 0.81148463

00:01:59.415 --> 00:02:01.659 others like Thomas and grades too.

NOTE Confidence: 0.81148463

00:02:01.660 --> 00:02:04.418 In three algorithms, this is 3 or

NOTE Confidence: 0.81148463

00:02:04.418 --> 00:02:06.950 by semester form as many Germans.

NOTE Confidence: 0.81148463

00:02:06.950 --> 00:02:08.506 In order rare tumors.

NOTE Confidence: 0.81148463

00:02:08.506 --> 00:02:11.347 But the bottom line here is that

NOTE Confidence: 0.81148463

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

NOTE Confidence: 0.81148463

00:02:13.870 --> 00:02:15.900 which is unfortunately the great

NOTE Confidence: 0.81148463

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

NOTE Confidence: 0.81148463

00:02:19.906 --> 00:02:22.396 with only three point 1 patients

NOTE Confidence: 0.81148463

00:02:22.396 --> 00:02:24.048 for each 100,000 people.

NOTE Confidence: 0.81148463

00:02:24.050 --> 00:02:26.892 So it is again relatively rare disease

NOTE Confidence: 0.81148463

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

NOTE Confidence: 0.81148463

00:02:29.740 --> 00:02:31.850 a very devastating disease and.

NOTE Confidence: 0.81148463

00:02:31.850 --> 00:02:34.850 The reason why this is such a charming

NOTE Confidence: 0.81148463

00:02:34.850 --> 00:02:37.411 diseases that you know the anatomic

NOTE Confidence: 0.81148463

00:02:37.411 --> 00:02:39.576 location really doesn't help us.

NOTE Confidence: 0.81148463

00:02:39.580 --> 00:02:41.926 So these are places that presents

NOTE Confidence: 0.81148463

00:02:41.926 --> 00:02:43.987 with these large tumors with

NOTE Confidence: 0.81148463

00:02:43.987 --> 00:02:45.687 lots of surrounding edema,

NOTE Confidence: 0.81148463

00:02:45.690 --> 00:02:47.314 an infiltrative microscopic disease.

NOTE Confidence: 0.81148463

00:02:47.314 --> 00:02:49.344 These terms are highly vascularized,

NOTE Confidence: 0.81148463

00:02:49.350 --> 00:02:51.940 so we're at the same time dealing

NOTE Confidence: 0.81148463

00:02:51.940 --> 00:02:54.240 with an uncle logic disease,

NOTE Confidence: 0.81148463

00:02:54.240 --> 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 --> 00:03:00.824 and you can imagine how challenging

NOTE Confidence: 0.81148463

00:03:00.824 --> 00:03:02.500 it is to manage.

NOTE Confidence: 0.81148463

00:03:02.500 --> 00:03:04.318 All of these symptoms were still

NOTE Confidence: 0.81148463

00:03:04.318 --> 00:03:06.288 trying to make a difference in

NOTE Confidence: 0.81148463

00:03:06.288 --> 00:03:07.970 terms of uncle logic treatments.

NOTE Confidence: 0.7932129

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 --> 00:03:17.644 has shown to improve survival so

NOTE Confidence: 0.7932129

00:03:17.644 --> 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 --> 00:03:27.755 controllers here is saying that the

NOTE Confidence: 0.7932129

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

NOTE Confidence: 0.7932129

00:03:29.687 --> 00:03:31.907 for survival and overall survival,

NOTE Confidence: 0.7932129

00:03:31.910 --> 00:03:33.800 but even the experimental arm

NOTE Confidence: 0.7932129

00:03:33.800 --> 00:03:35.312 in the pivotal trial,

NOTE Confidence: 0.7932129

00:03:35.320 --> 00:03:38.300 which was published in 2005.

NOTE Confidence: 0.7932129

00:03:38.300 --> 00:03:41.275 Survival remained only 15 months for again,

NOTE Confidence: 0.7932129

00:03:41.280 --> 00:03:43.400 newly diagnosed disease and further

NOTE Confidence: 0.7932129

00:03:43.400 --> 00:03:46.415 analysis of this data has shown that

NOTE Confidence: 0.7932129

00:03:46.415 --> 00:03:48.875 this survivor benefit is mostly driven

NOTE Confidence: 0.7932129

00:03:48.875 --> 00:03:51.510 by tumors that have this afternoon.

NOTE Confidence: 0.7932129

00:03:51.510 --> 00:03:54.084 Check silence of the Mt gene

NOTE Confidence: 0.7932129

00:03:54.084 --> 00:03:56.323 promoter by methylation so these

NOTE Confidence: 0.7932129

00:03:56.323 --> 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,

NOTE Confidence: 0.7932129

00:04:01.730 --> 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 --> 00:04:09.090 So for the remainder of the patients.

NOTE Confidence: 0.7932129

00:04:09.090 --> 00:04:10.865 The only real treatment that

NOTE Confidence: 0.7932129

00:04:10.865 --> 00:04:12.285 is available is radiation.

NOTE Confidence: 0.8231038

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

NOTE Confidence: 0.8231038

00:04:18.310 --> 00:04:20.599 and here you're looking at a slide

NOTE Confidence: 0.8231038

00:04:20.599 --> 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 --> 00:04:27.477 glioblastoma and in other diseases.

NOTE Confidence: 0.8231038

00:04:27.480 --> 00:04:29.320 Testing these novel target therapist.

NOTE Confidence: 0.8231038

00:04:29.320 --> 00:04:31.078 So we're very excited that for

NOTE Confidence: 0.8231038

00:04:31.078 --> 00:04:33.361 the first time in would be able

NOTE Confidence: 0.8231038

00:04:33.361 --> 00:04:35.101 to treat these patients with

NOTE Confidence: 0.8231038

00:04:35.101 --> 00:04:37.305 therapies that would carry minimal

NOTE Confidence: 0.8231038

00:04:37.305 --> 00:04:39.225 toxicities and tremendous efficacy,

NOTE Confidence: 0.8231038

00:04:39.230 --> 00:04:43.838 but as you know, the story was much more.

NOTE Confidence: 0.8231038

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

NOTE Confidence: 0.8231038

00:04:46.654 --> 00:04:49.228 originally thought, and one by one.

NOTE Confidence: 0.8231038

00:04:49.228 --> 00:04:52.604 All of these stars went on to

NOTE Confidence: 0.8231038

00:04:52.604 --> 00:04:55.048 fail in recurrent disease.

NOTE Confidence: 0.8231038

00:04:55.050 --> 00:04:57.354 The sad thing is that or maybe the

NOTE Confidence: 0.8231038

00:04:57.354 --> 00:04:59.695 lucky thing for other diseases is that

NOTE Confidence: 0.8231038

00:04:59.695 --> 00:05:02.277 the majority of these drugs ended up

NOTE Confidence: 0.8231038

00:05:02.277 --> 00:05:04.337 being approved for other indications,

NOTE Confidence: 0.8231038

00:05:04.340 --> 00:05:08.064 but all of that rise in glucose

NOTE Confidence: 0.8231038

00:05:08.064 --> 00:05:09.660 Thomas have failed.

NOTE Confidence: 0.8231038

00:05:09.660 --> 00:05:12.474 And more challenging is the fact that

NOTE Confidence: 0.8231038

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

NOTE Confidence: 0.8231038

00:05:15.360 --> 00:05:17.897 the omens that all of these drugs

NOTE Confidence: 0.8231038

00:05:17.897 --> 00:05:20.465 actually fail one after the other,

NOTE Confidence: 0.8231038

00:05:20.470 --> 00:05:22.780 is that because we are targeting

NOTE Confidence: 0.8231038

00:05:22.780 --> 00:05:23.935 the wrong targets,

NOTE Confidence: 0.8231038

00:05:23.940 --> 00:05:25.484 maybe they're not sufficiently

NOTE Confidence: 0.8231038

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

NOTE Confidence: 0.8231038

00:05:27.030 --> 00:05:29.196 or there are too many feedback

NOTE Confidence: 0.8231038

00:05:29.196 --> 00:05:31.110 loops and redundant pathways were

NOTE Confidence: 0.8231038

00:05:31.110 --> 00:05:33.534 now more and more learning about

NOTE Confidence: 0.8231038

00:05:33.534 --> 00:05:34.746 temporal spatial variations?

NOTE Confidence: 0.8231038

00:05:34.750 --> 00:05:37.180 Or is it be 'cause these

NOTE Confidence: 0.8231038

00:05:37.180 --> 00:05:39.260 are the wrong drugs and?

NOTE Confidence: 0.8231038

00:05:39.260 --> 00:05:41.580 We have problems you know,

NOTE Confidence: 0.8231038

00:05:41.580 --> 00:05:43.436 of achieving adequate concentrations,

NOTE Confidence: 0.8231038

00:05:43.436 --> 00:05:44.828 especially for drugs.

NOTE Confidence: 0.8231038

00:05:44.830 --> 00:05:47.150 They are not very potent.

NOTE Confidence: 0.8231038

00:05:47.150 --> 00:05:50.538 We do need to have better blood

NOTE Confidence: 0.8231038

00:05:50.538 --> 00:05:53.012 brain barrier penetration because a

NOTE Confidence: 0.8231038

00:05:53.012 --> 00:05:55.814 lot of these microscopic disease is

NOTE Confidence: 0.8231038

00:05:55.814 --> 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 --> 00:06:01.398 we still don't know how to

NOTE Confidence: 0.8231038

00:06:01.398 --> 00:06:03.230 select basis for these drugs.

NOTE Confidence: 0.8231038

00:06:03.230 --> 00:06:05.502 We're still not sure if it should select

NOTE Confidence: 0.8231038

00:06:05.502 --> 00:06:07.729 based on specific mutations or should

NOTE Confidence: 0.8231038

00:06:07.729 --> 00:06:10.420 we go through transcription subgroups or not?

NOTE Confidence: 0.8231038

00:06:10.420 --> 00:06:12.250 Do any selection whatsoever and treat

NOTE Confidence: 0.8231038

00:06:12.250 --> 00:06:14.528 a large number of patients then then

NOTE Confidence: 0.8231038

00:06:14.528 --> 00:06:16.859 identify the responders and then go after

NOTE Confidence: 0.8231038

00:06:16.916 --> 00:06:18.966 the phenotypes that predict response.

NOTE Confidence: 0.8231038

00:06:18.970 --> 00:06:20.334 So in other words,

NOTE Confidence: 0.8231038

00:06:20.334 --> 00:06:22.039 regardless of what we do,

NOTE Confidence: 0.8231038

00:06:22.040 --> 00:06:24.092 we certainly need to improve translation

NOTE Confidence: 0.8231038

00:06:24.092 --> 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 --> 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 --> 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 --> 00:06:38.750 So the low hanging fruit is to try

NOTE Confidence: 0.7912263

00:06:38.750 --> 00:06:40.915 to use the genomic information

NOTE Confidence: 0.7912263

00:06:40.915 --> 00:06:43.380 that is now widely available.

NOTE Confidence: 0.7912263

00:06:43.380 --> 00:06:45.738 Only streamers to see if we

NOTE Confidence: 0.7912263

00:06:45.738 --> 00:06:47.310 can improve our outcomes.

NOTE Confidence: 0.7912263

00:06:47.310 --> 00:06:50.604 So as you know, global someone was the very

NOTE Confidence: 0.7912263

00:06:50.604 --> 00:06:53.598 first tumor sequenced by the TSJ effort,

NOTE Confidence: 0.7912263

00:06:53.600 --> 00:06:55.340 and since then gene sequencing

NOTE Confidence: 0.7912263

00:06:55.340 --> 00:06:57.504 has become the norm when managing

NOTE Confidence: 0.7912263

00:06:57.504 --> 00:06:59.274 these patients and here looking

NOTE Confidence: 0.7912263

00:06:59.274 --> 00:07:02.149 at all types of biome's and these

NOTE Confidence: 0.7912263

00:07:02.149 --> 00:07:03.997 different colors here represents

NOTE Confidence: 0.7912263

00:07:03.997 --> 00:07:06.382 the different subtypes of gliomas.

NOTE Confidence: 0.7912263

00:07:06.382 --> 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 --> 00:07:14.949 distinct across the different

NOTE Confidence: 0.7912263

00:07:14.949 --> 00:07:16.730 histologies you can see here.

NOTE Confidence: 0.7912263

00:07:16.730 --> 00:07:19.015 The quintessential signature of the

NOTE Confidence: 0.7912263

00:07:19.015 --> 00:07:21.994 algal blooms, which is more penalty?

NOTE Confidence: 0.7912263

00:07:21.994 --> 00:07:24.574 Q coalition ideate mutation Sir

NOTE Confidence: 0.7912263

00:07:24.574 --> 00:07:26.808 promoter mutation and see I see

NOTE Confidence: 0.7912263

00:07:26.808 --> 00:07:30.559 and if you put P1 and here is the

NOTE Confidence: 0.7912263

00:07:30.559 --> 00:07:32.587 quintessential signature of Astros

NOTE Confidence: 0.7912263

00:07:32.587 --> 00:07:34.975 with guided meditation AT Rex,

NOTE Confidence: 0.7912263

00:07:34.975 --> 00:07:37.250 Magician or lost interpretive fermentation.

NOTE Confidence: 0.7912263

00:07:37.250 --> 00:07:39.680 And here's this essential signatures

NOTE Confidence: 0.7912263

00:07:39.680 --> 00:07:41.138 of global stoma.

NOTE Confidence: 0.7912263

00:07:41.140 --> 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 --> 00:07:48.660 Then loss or mutation and lots

NOTE Confidence: 0.7912263

00:07:48.660 --> 00:07:51.230 of formalities in CD case.

NOTE Confidence: 0.7912263

00:07:51.230 --> 00:07:53.830 So putting those patients now,

NOTE Confidence: 0.7912263

00:07:53.830 --> 00:07:56.924 arranging them into what kind of pathways

NOTE Confidence: 0.7912263

00:07:56.924 --> 00:08:00.070 ended up being abnormally disturbers,

NOTE Confidence: 0.7912263

00:08:00.070 --> 00:08:03.563 we can see the vast majority of

NOTE Confidence: 0.7912263

00:08:03.563 --> 00:08:06.310 patients follow this cake recipe.

NOTE Confidence: 0.7912263

00:08:06.310 --> 00:08:09.640 So basically 1000 kinase pathway with

NOTE Confidence: 0.7912263

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

NOTE Confidence: 0.7912263

00:08:13.275 --> 00:08:17.006 you see also a lot of these patients

NOTE Confidence: 0.7912263

00:08:17.006 --> 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 --> 00:08:27.354 ptosis and a lot of these patients

NOTE Confidence: 0.7912263

00:08:27.354 --> 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 --> 00:08:36.120 patients a match to actually which

NOTE Confidence: 0.7912263

00:08:36.120 --> 00:08:38.790 mutations have a track record of

NOTE Confidence: 0.7912263

00:08:38.874 --> 00:08:42.242 being drug and what you can see is

NOTE Confidence: 0.7912263

00:08:42.242 --> 00:08:44.245 unfortunately each of these mutations

NOTE Confidence: 0.7912263

00:08:44.245 --> 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 --> 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 --> 00:08:55.306 But unfortunately basket trials

NOTE Confidence: 0.7912263

00:08:55.306 --> 00:08:57.242 typically exclude patients with

NOTE Confidence: 0.7912263

00:08:57.242 --> 00:08:59.622 brain tumors were left with no

NOTE Confidence: 0.7912263

00:08:59.622 --> 00:09:01.644 trials or very trials that address.

NOTE Confidence: 0.7912263

00:09:01.650 --> 00:09:03.325 These questions we do have

NOTE Confidence: 0.7912263

00:09:03.325 --> 00:09:04.665 some low hanging fruits.

NOTE Confidence: 0.7912263

00:09:04.670 --> 00:09:06.310 Of course ideas mutation will

NOTE Confidence: 0.7912263

00:09:06.310 --> 00:09:08.710 talk a little bit more about that,

NOTE Confidence: 0.7912263

00:09:08.710 --> 00:09:09.368 but again,

NOTE Confidence: 0.7912263

00:09:09.368 --> 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 --> 00:09:15.807 therapy trials of these days.

NOTE Confidence: 0.7912263

00:09:15.810 --> 00:09:18.180 Because you really need to have

NOTE Confidence: 0.7912263

00:09:18.180 --> 00:09:20.249 strategies to tackle the rarity

NOTE Confidence: 0.7912263

00:09:20.249 --> 00:09:22.309 of each of these phenotypes.

NOTE Confidence: 0.808799

00:09:24.330 --> 00:09:27.382 And adding to our challenges are how

NOTE Confidence: 0.808799

00:09:27.382 --> 00:09:30.181 these tumors evolve overtime and how

NOTE Confidence: 0.808799

00:09:30.181 --> 00:09:32.989 they are heterogeneous to begin with.

NOTE Confidence: 0.808799

00:09:32.990 --> 00:09:36.118 So this is a patient, for example,

NOTE Confidence: 0.808799

00:09:36.118 --> 00:09:39.086 that at diagnosis she was enrolled in

NOTE Confidence: 0.808799

00:09:39.086 --> 00:09:42.065 one of my trials of a notch inhibitor

NOTE Confidence: 0.808799

00:09:42.065 --> 00:09:45.503 and she had a very typical signature

NOTE Confidence: 0.808799

00:09:45.503 --> 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 --> 00:09:52.310 potential target targetable abnormalities

NOTE Confidence: 0.808799

00:09:52.310 --> 00:09:54.490 with other abnormalities, but.

NOTE Confidence: 0.808799

00:09:54.490 --> 00:09:56.570 When this patient again,

NOTE Confidence: 0.808799

00:09:56.570 --> 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 --> 00:10:04.820 she was operated on again,

NOTE Confidence: 0.808799

00:10:04.820 --> 00:10:07.764 even though she had a very small tumor.

NOTE Confidence: 0.808799

00:10:07.770 --> 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.

NOTE Confidence: 0.808799

00:10:13.310 --> 00:10:15.150 We're seeing some passengers here.

NOTE Confidence: 0.808799

00:10:15.150 --> 00:10:17.160 But the reality that's what's driving

NOTE Confidence: 0.808799

00:10:17.160 --> 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 --> 00:10:25.024 and you can imagine that if at this

NOTE Confidence: 0.808799

00:10:25.024 --> 00:10:27.971 point in time of her disease we work

NOTE Confidence: 0.808799

00:10:27.971 --> 00:10:30.869 to enroll her in a clinical trial.

NOTE Confidence: 0.808799

00:10:30.870 --> 00:10:33.145 Most patients do not have another brain

NOTE Confidence: 0.808799

00:10:33.145 --> 00:10:35.190 surgery to have another sequence,

NOTE Confidence: 0.808799

00:10:35.190 --> 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 --> 00:10:42.173 that probably were irrelevant for

NOTE Confidence: 0.808799

00:10:42.173 --> 00:10:44.187 her at this point in time.

NOTE Confidence: 0.808799

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

NOTE Confidence: 0.808799

00:10:44.653 --> 00:10:47.431 those are males that we thought

NOTE Confidence: 0.808799

00:10:47.431 --> 00:10:50.069 were present were actually gone.

NOTE Confidence: 0.808799

00:10:50.070 --> 00:10:53.640 This is another example of potentially

NOTE Confidence: 0.808799

00:10:53.640 --> 00:10:56.569 targetable mutations that actually were

NOTE Confidence: 0.808799

00:10:56.569 --> 00:10:59.845 very different at the time of recurrence.

NOTE Confidence: 0.808799

00:10:59.850 --> 00:11:00.438 And.

NOTE Confidence: 0.808799

00:11:00.438 --> 00:11:02.790 Another difficult challenge are

NOTE Confidence: 0.808799

00:11:02.790 --> 00:11:04.554 these patients here.

NOTE Confidence: 0.808799

00:11:04.560 --> 00:11:08.216 So these are patients that we serve created.

NOTE Confidence: 0.808799

00:11:08.220 --> 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 --> 00:11:18.269 mismatch repair genes at typically MSH.

NOTE Confidence: 0.808799

00:11:18.270 --> 00:11:21.598 6 and what happens is that these patients

NOTE Confidence: 0.808799

00:11:21.598 --> 00:11:23.959 with mismatch repair defects start

NOTE Confidence: 0.808799

00:11:23.959 --> 00:11:26.379 accumulating all of these mutations

NOTE Confidence: 0.808799

00:11:26.379 --> 00:11:29.473 and you can imagine that developing

NOTE Confidence: 0.808799

00:11:29.473 --> 00:11:32.033 target therapies for these folks.

NOTE Confidence: 0.808799

00:11:32.040 --> 00:11:33.312 Is much harder.

NOTE Confidence: 0.808799

00:11:33.312 --> 00:11:35.856 And one of the surprising findings

NOTE Confidence: 0.808799

00:11:35.856 --> 00:11:38.560 of our studies have been that

NOTE Confidence: 0.808799

00:11:38.560 --> 00:11:41.384 these are actually much more common

NOTE Confidence: 0.808799

00:11:41.384 --> 00:11:43.560 than we previously thought.

NOTE Confidence: 0.84145206

00:11:46.580 --> 00:11:49.044 So in moving forward what we're trying to

NOTE Confidence: 0.84145206

00:11:49.044 --> 00:11:52.286 do is to again improve the science linked

NOTE Confidence: 0.84145206

00:11:52.286 --> 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 --> 00:12:00.040 Zero tries to show us if our drugs

NOTE Confidence: 0.84145206

00:12:00.040 --> 00:12:02.460 are actually getting into the brain,

NOTE Confidence: 0.84145206

00:12:02.460 --> 00:12:04.345 especially in areas with intact

NOTE Confidence: 0.84145206

00:12:04.345 --> 00:12:05.476 blood brain barrier.

NOTE Confidence: 0.84145206

00:12:05.480 --> 00:12:09.309 We also want to see if the.

NOTE Confidence: 0.84145206

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 --> 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 --> 00:12:23.690 basket trials that actually include

NOTE Confidence: 0.84145206

00:12:23.690 --> 00:12:25.910 patients with our rare phenotypes.

NOTE Confidence: 0.84145206

00:12:25.910 --> 00:12:27.840 There's a shift towards more

NOTE Confidence: 0.84145206

00:12:27.840 --> 00:12:29.770 of a newly diagnosed disease.

NOTE Confidence: 0.84145206

00:12:29.770 --> 00:12:32.080 Be 'cause these are easier patients,

NOTE Confidence: 0.84145206

00:12:32.080 --> 00:12:34.015 and the genomics information is

NOTE Confidence: 0.84145206

00:12:34.015 --> 00:12:35.945 actually fresh, and where we're

NOTE Confidence: 0.84145206

00:12:35.945 --> 00:12:37.485 dealing with recurrent disease,

NOTE Confidence: 0.84145206

00:12:37.490 --> 00:12:39.475 we typically like to re

NOTE Confidence: 0.84145206

00:12:39.475 --> 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 --> 00:12:44.000 at least to exclude the hypermedia phenotype.

NOTE Confidence: 0.84145206

00:12:44.000 --> 00:12:46.232 And we also like to of course update the

NOTE Confidence: 0.84145206

00:12:46.232 --> 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 --> 00:12:52.194 to target these strong communications,

NOTE Confidence: 0.84145206

00:12:52.200 --> 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 --> 00:12:56.648 we're going to talk a little

NOTE Confidence: 0.84145206

00:12:56.648 --> 00:12:58.160 bit more about that.

NOTE Confidence: 0.84145206

00:12:58.160 --> 00:13:01.976 But the vast majority of trials right now

NOTE Confidence: 0.84145206

00:13:01.976 --> 00:13:05.580 is actually trying to find alternative

NOTE Confidence: 0.84145206

00:13:05.580 --> 00:13:09.414 strategies that address more stable targets.

NOTE Confidence: 0.84145206

00:13:09.420 --> 00:13:11.940 So the low hanging fruit of stable

NOTE Confidence: 0.84145206

00:13:11.940 --> 00:13:14.219 targets is actually immuno therapies.

NOTE Confidence: 0.84145206

00:13:14.220 --> 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 --> 00:13:20.220 human suppressive microenvironment.

NOTE Confidence: 0.84145206

00:13:20.220 --> 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 --> 00:13:26.615 important in this disease.

NOTE Confidence: 0.84145206

00:13:26.620 --> 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 --> 00:13:32.620 we have the challenges of the

NOTE Confidence: 0.84145206

00:13:32.620 --> 00:13:33.820 anatomic location itself.

NOTE Confidence: 0.84145206

00:13:33.820 --> 00:13:36.836 So you can imagine that it's much harder

NOTE Confidence: 0.84145206

00:13:36.836 --> 00:13:39.517 to trigger him and logical response.

NOTE Confidence: 0.84145206

00:13:39.520 --> 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 --> 00:13:43.474 traditionally considered the so-called

NOTE Confidence: 0.84145206

00:13:43.474 --> 00:13:45.789 sanctuary sites for the immune system.

NOTE Confidence: 0.84145206

00:13:45.790 --> 00:13:48.401 And we have to get these email

NOTE Confidence: 0.84145206

00:13:48.401 --> 00:13:50.934 responses to act fast because these

NOTE Confidence: 0.84145206

00:13:50.934 --> 00:13:53.598 are tumors that grow very rapidly

NOTE Confidence: 0.84145206

00:13:53.598 --> 00:13:56.154 and they cause symptoms and we

NOTE Confidence: 0.84145206

00:13:56.154 --> 00:13:58.592 don't have the luxury of waiting

NOTE Confidence: 0.84145206

00:13:58.592 --> 00:14:01.064 several months or years to react.

NOTE Confidence: 0.84145206

00:14:01.070 --> 00:14:03.954 The benefits of the email of therapies.

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 --> 00:14:08.510 responses in the brain,

NOTE Confidence: 0.84145206

00:14:08.510 --> 00:14:11.054 we have to deal with the risks of

NOTE Confidence: 0.84145206

00:14:11.054 --> 00:14:13.870 new log symptoms and neurotoxicity.

NOTE Confidence: 0.84145206

00:14:13.870 --> 00:14:16.210 An another important thing is.

NOTE Confidence: 0.84145206

00:14:16.210 --> 00:14:17.758 That this information could

NOTE Confidence: 0.84145206

00:14:17.758 --> 00:14:19.306 potentially mimic some aggression,

NOTE Confidence: 0.84145206

00:14:19.310 --> 00:14:21.390 so managing these patients can

NOTE Confidence: 0.84145206

00:14:21.390 --> 00:14:23.470 be challenging because we have

NOTE Confidence: 0.84145206

00:14:23.541 --> 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 --> 00:14:29.400 tumor progression on the MRI.

NOTE Confidence: 0.7355124

00:14:34.080 --> 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 --> 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 --> 00:14:49.670 with VMS and in this trial we treated

NOTE Confidence: 0.7355124

00:14:49.755 --> 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 --> 00:14:57.854 map and what we found is that yes,

NOTE Confidence: 0.7355124

00:14:57.860 --> 00:14:59.875 the target definitely was present

NOTE Confidence: 0.7355124

00:14:59.875 --> 00:15:01.890 in the majority of patients,

NOTE Confidence: 0.7355124

00:15:01.890 --> 00:15:04.632 so 60% of the patients had

NOTE Confidence: 0.7355124

00:15:04.632 --> 00:15:06.003 PDL one expression.

NOTE Confidence: 0.7355124

00:15:06.010 --> 00:15:07.942 But we didn't see any brain toxicities

NOTE Confidence: 0.7355124

00:15:07.942 --> 00:15:10.169 which is good and perhaps bad because

NOTE Confidence: 0.7355124

00:15:10.169 --> 00:15:11.844 this could potentially reflect the

NOTE Confidence: 0.7355124

00:15:11.844 --> 00:15:13.694 fact that we are not achieving

NOTE Confidence: 0.7355124

00:15:13.694 --> 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 --> 00:15:21.010 Mount more of an email response.

NOTE Confidence: 0.7355124

00:15:21.010 --> 00:15:23.850 But this went on to be tested in

NOTE Confidence: 0.7355124

00:15:23.850 --> 00:15:26.079 randomized trials and we are now

NOTE Confidence: 0.7355124

00:15:26.079 --> 00:15:27.889 reporting the final results of

NOTE Confidence: 0.7355124

00:15:27.889 --> 00:15:30.321 these shows and one by one they

NOTE Confidence: 0.7355124

00:15:30.321 --> 00:15:32.015 all failed to improve survival,

NOTE Confidence: 0.7355124

00:15:32.015 --> 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 --> 00:15:42.230 so I think our task now is to try to

NOTE Confidence: 0.8497241

00:15:42.320 --> 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 --> 00:15:50.865 we're not seeing any help from Anti

NOTE Confidence: 0.8497241

00:15:50.865 --> 00:15:53.818 PD one or anti PDL one therapies and

NOTE Confidence: 0.8497241

00:15:53.818 --> 00:15:57.178 I think for for this question I think

NOTE Confidence: 0.8497241

00:15:57.180 --> 00:16:00.375 it is great to have a helping hand of

NOTE Confidence: 0.8497241

00:16:00.375 --> 00:16:02.993 people that study the CNS immunology

NOTE Confidence: 0.8497241

00:16:02.993 --> 00:16:06.834 and in this project what we did is to

NOTE Confidence: 0.8497241

00:16:06.834 --> 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 --> 00:16:15.646 can we actually come up with better.

NOTE Confidence: 0.8497241

00:16:15.650 --> 00:16:18.070 Image checkpoint inhibition that is

NOTE Confidence: 0.8497241

00:16:18.070 --> 00:16:20.981 relevant for for this Mike environment

NOTE Confidence: 0.8497241

00:16:20.981 --> 00:16:24.229 and what the heifers lab came up with

NOTE Confidence: 0.8497241

00:16:24.229 --> 00:16:27.400 is that this image of point called digit

NOTE Confidence: 0.8497241

00:16:27.400 --> 00:16:31.130 seems to be much more relevant in the brain.

NOTE Confidence: 0.8497241

00:16:31.130 --> 00:16:33.578 It was very interesting that in

NOTE Confidence: 0.8497241

00:16:33.578 --> 00:16:36.289 their studies they found a lot of

NOTE Confidence: 0.8497241

00:16:36.289 --> 00:16:38.299 teacher expression in DBMS and not

NOTE Confidence: 0.8497241

00:16:38.299 --> 00:16:41.370 so much digit expression in the

NOTE Confidence: 0.8497241

00:16:41.370 --> 00:16:42.966 quintessential inflammatory disease

NOTE Confidence: 0.8497241

00:16:42.966 --> 00:16:45.335 which is multiple sclerosis and.

NOTE Confidence: 0.8497241

00:16:45.335 --> 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 --> 00:16:51.796 so sequencing that sort of confirmed

NOTE Confidence: 0.8497241

00:16:51.796 --> 00:16:54.930 that T cell dysfunction was being driven

NOTE Confidence: 0.8497241

00:16:54.930 --> 00:16:57.522 by digit in this particular disease.

NOTE Confidence: 0.8497241

00:16:57.530 --> 00:17:00.176 So to test this hypothesis in

NOTE Confidence: 0.8497241

00:17:00.176 --> 00:17:01.499 patients with design,

NOTE Confidence: 0.8497241

00:17:01.500 --> 00:17:06.316 this clinical trial where we are looking at.

NOTE Confidence: 0.8497241

00:17:06.320 --> 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 --> 00:17:16.474 or the combination or placebo and

NOTE Confidence: 0.8497241

00:17:16.474 --> 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 --> 00:17:27.662 axe as well as some studies to produce

NOTE Confidence: 0.8497241

00:17:27.662 --> 00:17:30.291 some spatial validation of the findings.

NOTE Confidence: 0.8497241

00:17:30.291 --> 00:17:32.997 And there will also follow these

NOTE Confidence: 0.8497241

00:17:32.997 --> 00:17:35.444 patients longitudinally to see if we

NOTE Confidence: 0.8497241

00:17:35.444 --> 00:17:37.824 can monitor what's happening in the tumor.

NOTE Confidence: 0.8497241

00:17:37.830 --> 00:17:40.566 By analyzing the T cells in the periphery.

NOTE Confidence: 0.8497241

00:17:40.570 --> 00:17:42.616 So it's a very exciting trial.

NOTE Confidence: 0.8497241

00:17:42.620 --> 00:17:44.860 So I wish we had started the

NOTE Confidence: 0.8497241

00:17:44.860 --> 00:17:47.376 development of Inter PD one this way

NOTE Confidence: 0.8497241

00:17:47.376 --> 00:17:49.236 by understanding the science before

NOTE Confidence: 0.8497241

00:17:49.236 --> 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 --> 00:17:55.608 but we're very excited about this mechanism.

NOTE Confidence: 0.8497241

00:17:55.610 --> 00:17:58.166 Action also is important to emphasize

NOTE Confidence: 0.8497241

00:17:58.166 --> 00:18:00.554 that this combination of anti teachers

NOTE Confidence: 0.8497241

00:18:00.554 --> 00:18:03.329 and in fact PD one is very hot in

NOTE Confidence: 0.8497241

00:18:03.329 --> 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 --> 00:18:13.170 this trial here to you.

NOTE Confidence: 0.8553554

00:18:15.700 --> 00:18:17.550 Also, to understand a little

NOTE Confidence: 0.8553554

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

NOTE Confidence: 0.8553554

00:18:19.990 --> 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 --> 00:18:27.815 A richness of our environment

NOTE Confidence: 0.8553554

00:18:27.815 --> 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 --> 00:18:34.945 stomas where he can pretty much

NOTE Confidence: 0.8553554

00:18:34.945 --> 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 --> 00:18:42.008 and one of the ideas here is to see

NOTE Confidence: 0.8553554

00:18:42.008 --> 00:18:44.585 how these different phenotypes respond

NOTE Confidence: 0.8553554

00:18:44.585 --> 00:18:46.845 to these different immunotherapy's.

NOTE Confidence: 0.8553554

00:18:46.850 --> 00:18:49.268 So this is very exciting data

NOTE Confidence: 0.8553554

00:18:49.268 --> 00:18:51.744 which again illustrates how we can

NOTE Confidence: 0.8553554

00:18:51.744 --> 00:18:53.724 concomitantly to the development in

NOTE Confidence: 0.8553554

00:18:53.724 --> 00:18:56.607 the clinic to also try to understand.

NOTE Confidence: 0.8553554

00:18:56.610 --> 00:18:59.610 Are these treatments in parallel in the lab?

NOTE Confidence: 0.80247504

00:19:02.490 --> 00:19:06.558 Now another barrier for.

NOTE Confidence: 0.80247504

00:19:06.560 --> 00:19:09.095 For the development of effective

NOTE Confidence: 0.80247504

00:19:09.095 --> 00:19:11.630 even responses is the work

NOTE Confidence: 0.80247504

00:19:11.716 --> 00:19:14.380 being done by the Iwasaki slab.

NOTE Confidence: 0.80247504

00:19:14.380 --> 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 --> 00:19:23.757 and she has recently had this nature

NOTE Confidence: 0.80247504

00:19:23.757 --> 00:19:26.869 paper where they showed that.

NOTE Confidence: 0.80247504

00:19:26.870 --> 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 --> 00:19:33.908 can correct utilizing the GFC.

NOTE Confidence: 0.80247504

00:19:33.910 --> 00:19:36.416 So in her models that the combination

NOTE Confidence: 0.80247504

00:19:36.416 --> 00:19:39.667 of Veg FC and Anti PD one actually

NOTE Confidence: 0.80247504

00:19:39.667 --> 00:19:41.762 improves survival and was also

NOTE Confidence: 0.80247504

00:19:41.845 --> 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 --> 00:19:53.933 the results seem to be better than

NOTE Confidence: 0.80247504

00:19:53.933 --> 00:19:56.850 systemic administration of anti PD one.

NOTE Confidence: 0.80247504

00:19:56.850 --> 00:19:59.906 So this is all giving rise to another

NOTE Confidence: 0.80247504

00:19:59.906 --> 00:20:01.634 generation of characterizing and

NOTE Confidence: 0.80247504

00:20:01.634 --> 00:20:04.728 some new compounds that we hope to

NOTE Confidence: 0.80247504

00:20:04.728 --> 00:20:07.200 bring to clinic in the mid term.

NOTE Confidence: 0.7626056

00:20:09.870 --> 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 --> 00:20:18.883 is the role of tumor associated macrophages

NOTE Confidence: 0.7626056

00:20:18.883 --> 00:20:21.637 and how they produce these emails.

NOTE Confidence: 0.7626056

00:20:21.640 --> 00:20:22.948 Suppressive tumor convergence

NOTE Confidence: 0.7626056

00:20:22.948 --> 00:20:26.548 and one of the ways that we could

NOTE Confidence: 0.7626056

00:20:26.548 --> 00:20:28.883 potentially intervene in this was

NOTE Confidence: 0.7626056

00:20:28.883 --> 00:20:31.668 discovered by an item here at go,

NOTE Confidence: 0.7626056

00:20:31.670 --> 00:20:34.729 where she's looking at the role of

NOTE Confidence: 0.7626056

00:20:34.729 --> 00:20:36.975 this little Robo one, signaling

NOTE Confidence: 0.7626056

00:20:36.975 --> 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 in the

NOTE Confidence: 0.7626056

00:20:42.320 --> 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 --> 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 --> 00:20:52.590 she achieved better immune responses

NOTE Confidence: 0.7626056

00:20:52.590 --> 00:20:54.910 and inflammation of anti PD one.

NOTE Confidence: 0.7626056

00:20:54.910 --> 00:20:57.202 She had a really significant improvement

NOTE Confidence: 0.7626056

00:20:57.202 --> 00:21:00.389 in survival or in this tumor bearing mice.

NOTE Confidence: 0.7626056

00:21:00.390 --> 00:21:03.270 So the idea here is now to generate

NOTE Confidence: 0.7626056

00:21:03.270 --> 00:21:05.824 enter Robo Nanobodies one of the

NOTE Confidence: 0.7626056

00:21:05.824 --> 00:21:08.014 barriers project would be then

NOTE Confidence: 0.7626056

00:21:08.014 --> 00:21:10.338 how can we get this number?

NOTE Confidence: 0.7626056

00:21:10.340 --> 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 --> 00:21:16.810 she has the answer.

NOTE Confidence: 0.7626056

00:21:16.810 --> 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 --> 00:21:23.817 this receptor called UNC 5B,

NOTE Confidence: 0.7626056

00:21:23.820 --> 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 --> 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 --> 00:21:37.402 So the idea here is that if this is

NOTE Confidence: 0.7626056

00:21:37.402 --> 00:21:39.238 successful, we could combine this.

NOTE Confidence: 0.7626056

00:21:39.238 --> 00:21:41.410 These agents with many of the

NOTE Confidence: 0.7626056

00:21:41.484 --> 00:21:43.644 chemotherapies in order target therapies

NOTE Confidence: 0.7626056

00:21:43.644 --> 00:21:46.961 that we are trying to use to treat

NOTE Confidence: 0.7626056

00:21:46.961 --> 00:21:49.495 these patients in a more efficient way.

NOTE Confidence: 0.7626056

00:21:49.500 --> 00:21:51.456 And overcome the problem of living

NOTE Confidence: 0.7626056

00:21:51.456 --> 00:21:53.080 there countries so very exciting

NOTE Confidence: 0.7626056

00:21:53.080 --> 00:21:55.176 work that we hope to see more of.

NOTE Confidence: 0.74804413

00:21:57.340 --> 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 --> 00:22:05.306 but moving on to partnerships with pharma.

NOTE Confidence: 0.74804413

00:22:05.310 --> 00:22:08.350 One of the our partnerships

NOTE Confidence: 0.74804413

00:22:08.350 --> 00:22:10.782 is with this drug.

NOTE Confidence: 0.74804413

00:22:10.790 --> 00:22:13.250 This company called In Pharmaceuticals

NOTE Confidence: 0.74804413

00:22:13.250 --> 00:22:15.710 and these folks have discovered

NOTE Confidence: 0.74804413

00:22:15.781 --> 00:22:17.929 a novel receptor with within the

NOTE Confidence: 0.74804413

00:22:17.929 --> 00:22:20.124 Alpha V beta three integrin that

NOTE Confidence: 0.74804413

00:22:20.124 --> 00:22:22.532 is started by this FP PMT drug

NOTE Confidence: 0.74804413

00:22:22.532 --> 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 --> 00:22:28.798 Really melting the mice.

NOTE Confidence: 0.74804413

00:22:28.798 --> 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 --> 00:22:38.660 that will start in a couple of months.

NOTE Confidence: 0.74804413

00:22:38.660 --> 00:22:41.144 But to understand this better we

NOTE Confidence: 0.74804413

00:22:41.144 --> 00:22:43.800 did bring Yellow Labs into the mix

NOTE Confidence: 0.74804413

00:22:43.800 --> 00:22:46.325 to better define how is this rug

NOTE Confidence: 0.74804413

00:22:46.325 --> 00:22:48.215 really working and who are the

NOTE Confidence: 0.74804413

00:22:48.215 --> 00:22:50.205 best candidates by understand a

NOTE Confidence: 0.74804413

00:22:50.205 --> 00:22:52.617 little bit more about the effects

NOTE Confidence: 0.74804413

00:22:52.686 --> 00:22:55.031 on cell invasion signaling networks

NOTE Confidence: 0.74804413

00:22:55.031 --> 00:22:56.438 and gene expression.

NOTE Confidence: 0.74804413

00:22:56.440 --> 00:22:59.386 So one of the assets that.

NOTE Confidence: 0.74804413

00:22:59.390 --> 00:23:01.685 We're realizing in partnership with

NOTE Confidence: 0.74804413

00:23:01.685 --> 00:23:04.710 under left ankle is looking at these.

NOTE Confidence: 0.74804413

00:23:04.710 --> 00:23:07.356 The use of his integrated platform,

NOTE Confidence: 0.74804413

00:23:07.360 --> 00:23:09.726 which is the so called race essay

NOTE Confidence: 0.74804413

00:23:09.726 --> 00:23:12.753 which is a disrupted analysis of cell

NOTE Confidence: 0.74804413

00:23:12.753 --> 00:23:15.173 phenotype extremes where he uses

NOTE Confidence: 0.74804413

00:23:15.173 --> 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 --> 00:23:23.870 and then you can test the multiple

NOTE Confidence: 0.74804413

00:23:23.870 --> 00:23:26.154 drugs utilizing this essay as

NOTE Confidence: 0.74804413

00:23:26.154 --> 00:23:28.184 a form of drug screening,

NOTE Confidence: 0.74804413

00:23:28.190 --> 00:23:30.910 and he's applying this rug.

NOTE Confidence: 0.74804413

00:23:30.910 --> 00:23:33.406 Your days were very interesting results

NOTE Confidence: 0.74804413

00:23:33.406 --> 00:23:36.928 and we hope to then identify partners.

NOTE Confidence: 0.74804413

00:23:36.930 --> 00:23:39.498 Which are the best genomic candidates

NOTE Confidence: 0.74804413

00:23:39.498 --> 00:23:42.268 and then see if we can optimize

NOTE Confidence: 0.74804413

00:23:42.268 --> 00:23:45.254 the trial as we go by in reaching

NOTE Confidence: 0.74804413

00:23:45.254 --> 00:23:48.444 with either best candidates or

NOTE Confidence: 0.74804413

00:23:48.444 --> 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 --> 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 --> 00:23:57.300 involve our laboratories.

NOTE Confidence: 0.74804413

00:23:57.300 --> 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 --> 00:24:04.415 Now sticking again,

NOTE Confidence: 0.74804413

00:24:04.415 --> 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 --> 00:24:10.908 and one of them is ideas with patient

NOTE Confidence: 0.74804413

00:24:10.908 --> 00:24:13.751 and this story came out of Doctor

NOTE Confidence: 0.74804413

00:24:13.751 --> 00:24:16.579 Kendra's lab where he found it ideas.

NOTE Confidence: 0.74804413

00:24:16.580 --> 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 --> 00:24:23.576 which is the byproduct of this mutation,

NOTE Confidence: 0.74804413

00:24:23.580 --> 00:24:26.100 and this results in sort of brokenness

NOTE Confidence: 0.74804413

00:24:26.100 --> 00:24:29.408 that then can be targeted by PARP inhibitors.

NOTE Confidence: 0.74804413

00:24:29.410 --> 00:24:31.770 So he has several clinical

NOTE Confidence: 0.74804413

00:24:31.770 --> 00:24:34.130 trials of these park inhibitors.

NOTE Confidence: 0.74804413

00:24:34.130 --> 00:24:36.748 And we are now hoping to see

NOTE Confidence: 0.74804413

00:24:36.748 --> 00:24:39.331 if this will actually improve

NOTE Confidence: 0.74804413

00:24:39.331 --> 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 --> 00:24:50.541 we recently submitted a United team led

NOTE Confidence: 0.75027966

00:24:50.541 --> 00:24:53.702 by Mayo Clinic and John Jennifer Correa

NOTE Confidence: 0.75027966

00:24:53.702 --> 00:24:56.087 in partnership with even colonies.

NOTE Confidence: 0.75027966

00:24:56.090 --> 00:24:57.834 Doctor Bindra and I.

NOTE Confidence: 0.75027966

00:24:57.834 --> 00:25:00.014 So we have two projects.

NOTE Confidence: 0.75027966

00:25:00.020 --> 00:25:03.009 One is trying to optimize MDM two

NOTE Confidence: 0.75027966

00:25:03.009 --> 00:25:05.690 inhibition for these patients and 80

NOTE Confidence: 0.75027966

00:25:05.690 --> 00:25:08.324 Rd in ambition for these patients.

NOTE Confidence: 0.75027966

00:25:08.330 --> 00:25:11.347 And this will again bring two other

NOTE Confidence: 0.75027966

00:25:11.347 --> 00:25:14.318 Phase 0 slash 1 clinical trials.

NOTE Confidence: 0.75027966

00:25:14.320 --> 00:25:16.570 To our portfolio, hopefully soon.

NOTE Confidence: 0.8357312

00:25:20.570 --> 00:25:22.544 Now we don't have time to

NOTE Confidence: 0.8357312

00:25:22.544 --> 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 --> 00:25:29.139 industry for opening other tries

NOTE Confidence: 0.8357312

00:25:29.139 --> 00:25:31.463 to fill in gaps in our portfolio.

NOTE Confidence: 0.8357312

00:25:31.470 --> 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 --> 00:25:38.568 multi arm clinical trial that is

NOTE Confidence: 0.8357312

00:25:38.568 --> 00:25:40.787 happening worldwide so we have access

NOTE Confidence: 0.8357312

00:25:40.787 --> 00:25:42.749 to these drugs for our patients

NOTE Confidence: 0.8357312

00:25:42.750 --> 00:25:45.389 and have a bunch of other choice.

NOTE Confidence: 0.8357312

00:25:45.390 --> 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 therapeutic development and then

NOTE Confidence: 0.8357312

00:25:50.181 --> 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 --> 00:25:55.960 for example,

NOTE Confidence: 0.8357312

00:25:55.960 --> 00:25:57.800 byref mutant craniopharyngioma switch,

NOTE Confidence: 0.8357312

00:25:57.800 --> 00:26:00.992 again very difficult to find patience

NOTE Confidence: 0.8357312

00:26:00.992 --> 00:26:05.425 and for those we do need to partner

NOTE Confidence: 0.8357312

00:26:05.425 --> 00:26:08.731 with other places around the country.

NOTE Confidence: 0.8357312

00:26:08.740 --> 00:26:11.452 And I could go on and on talking

NOTE Confidence: 0.8357312

00:26:11.452 --> 00:26:13.801 about all of the years signs

NOTE Confidence: 0.8357312

00:26:13.801 --> 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 --> 00:26:19.900 are closest to clinic,

NOTE Confidence: 0.8357312

00:26:19.900 --> 00:26:22.315 but all these people in this picture

NOTE Confidence: 0.8357312

00:26:22.315 --> 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 amazing

NOTE Confidence: 0.8357312

00:26:27.066 --> 00:26:29.651 size that we can actually use into

NOTE Confidence: 0.8357312

00:26:29.651 --> 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 --> 00:26:35.150 ranging from data science,

NOTE Confidence: 0.8357312

00:26:35.150 --> 00:26:37.290 junior imaging and all sorts

NOTE Confidence: 0.8357312

00:26:37.290 --> 00:26:38.574 of therapeutic approaches.

NOTE Confidence: 0.8357312

00:26:38.580 --> 00:26:39.600 So in conclusion,

NOTE Confidence: 0.8357312

00:26:39.600 --> 00:26:41.980 so we're lucky enough to have this

NOTE Confidence: 0.8357312

00:26:42.051 --> 00:26:44.536 unique breath of scientific expertise.

NOTE Confidence: 0.8357312

00:26:44.540 --> 00:26:46.832 Our focus is really on investigating

NOTE Confidence: 0.8357312

00:26:46.832 --> 00:26:49.189 shaded trials that are home grown

NOTE Confidence: 0.8357312

00:26:49.189 --> 00:26:51.863 and our other focuses on early stage

NOTE Confidence: 0.8357312

00:26:51.863 --> 00:26:53.669 development with former partners,

NOTE Confidence: 0.8357312

00:26:53.670 --> 00:26:55.650 but also bringing along our

NOTE Confidence: 0.8357312

00:26:55.650 --> 00:26:57.234 own labs email collagen,

NOTE Confidence: 0.8357312

00:26:57.240 --> 00:27:00.019 a repair have emerged as leading teams,

NOTE Confidence: 0.8357312

00:27:00.020 --> 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 --> 00:27:07.590 for complication and need a

NOTE Confidence: 0.8357312

00:27:07.670 --> 00:27:09.910 lot of help for development.

NOTE Confidence: 0.8357312

00:27:09.910 --> 00:27:11.630 We certainly need more work

NOTE Confidence: 0.8357312

00:27:11.630 --> 00:27:13.006 on existing available drugs,

NOTE Confidence: 0.8357312

00:27:13.010 --> 00:27:14.675 for example coming from Seatac

NOTE Confidence: 0.8357312

00:27:14.675 --> 00:27:17.435 and Pharma and a lot of work in

NOTE Confidence: 0.8357312

00:27:17.435 --> 00:27:19.135 functional genomics so that we

NOTE Confidence: 0.8357312

00:27:19.135 --> 00:27:21.585 can figure out finally how to

NOTE Confidence: 0.8357312

00:27:21.585 --> 00:27:23.285 target these undruggable targets.

NOTE Confidence: 0.8357312

00:27:23.290 --> 00:27:25.754 So that I would like to finish

NOTE Confidence: 0.8357312

00:27:25.754 --> 00:27:27.959 by thanking all of the people.

NOTE Confidence: 0.8357312

00:27:27.960 --> 00:27:30.108 So when we talk clinical trials,

NOTE Confidence: 0.8357312

00:27:30.110 --> 00:27:33.755 really the merit is all of others of the

NOTE Confidence: 0.8357312

00:27:33.755 --> 00:27:37.220 labs of the all of the infrastructure.

NOTE Confidence: 0.8357312

00:27:37.220 --> 00:27:39.554 I would also like to acknowledge

NOTE Confidence: 0.8357312

00:27:39.554 --> 00:27:41.500 our division attendings and aips,

NOTE Confidence: 0.8357312

00:27:41.500 --> 00:27:43.052 or actually managing treating

NOTE Confidence: 0.8357312

00:27:43.052 --> 00:27:44.992 these patients in the trials.

NOTE Confidence: 0.8357312

00:27:45.000 --> 00:27:48.492 I would like to thank again the Cito staff.

NOTE Confidence: 0.8357312

00:27:48.500 --> 00:27:50.450 They're going through rough times,

NOTE Confidence: 0.8357312

00:27:50.450 --> 00:27:53.446 but right Decker is navigating and it's

NOTE Confidence: 0.8357312

00:27:53.446 --> 00:27:56.879 going to get us out of this situation.

NOTE Confidence: 0.8357312

00:27:56.880 --> 00:27:59.162 A big thanks to the PRC reviewers

NOTE Confidence: 0.8357312

00:27:59.162 --> 00:28:01.845 'cause one of my hats is actually as

NOTE Confidence: 0.8357312

00:28:01.845 --> 00:28:04.370 the Pearcey chair and we we acknowledge

NOTE Confidence: 0.8357312

00:28:04.370 --> 00:28:06.830 along with Barbara Burtness that there

NOTE Confidence: 0.8357312

00:28:06.830 --> 00:28:09.420 was a lot of work that goes into

NOTE Confidence: 0.8357312

00:28:09.420 --> 00:28:12.357 this and that I would like to thank

NOTE Confidence: 0.8357312

00:28:12.357 --> 00:28:14.462 them publicly at this opportunity.

NOTE Confidence: 0.8357312

00:28:14.470 --> 00:28:15.289 Lots of things.

NOTE Confidence: 0.8357312

00:28:15.289 --> 00:28:17.200 So why CCI that help us with

NOTE Confidence: 0.8357312

00:28:17.264 --> 00:28:19.500 investigating share clinical trials.

NOTE Confidence: 0.8357312

00:28:19.500 --> 00:28:22.104 All of the people that have been

NOTE Confidence: 0.8357312

00:28:22.104 --> 00:28:23.885 enabling this research and finally

NOTE Confidence: 0.8357312

00:28:23.885 --> 00:28:26.261 a big thank to the YCC and Smile

NOTE Confidence: 0.8357312

00:28:26.337 --> 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 --> 00:28:32.954 and neither will all understand importance

NOTE Confidence: 0.8357312

00:28:32.954 --> 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 --> 00:28:41.189 family for their generous gift.

NOTE Confidence: 0.8413786

00:28:41.190 --> 00:28:43.122 In fact, then I'm not going to

NOTE Confidence: 0.8413786

00:28:43.122 --> 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 --> 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 --> 00:28:53.516 and we're hoping to put together a

NOTE Confidence: 0.8413786

00:28:53.516 --> 00:28:55.481 nice program that will again enable

NOTE Confidence: 0.8413786

00:28:55.481 --> 00:28:57.503 and expand on our research efforts.

NOTE Confidence: 0.8413786

00:28:57.510 --> 00:28:59.729 Thank you very much and I'll take

NOTE Confidence: 0.8413786

00:28:59.729 --> 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 --> 00:29:05.941 Very interesting work.

NOTE Confidence: 0.85210776

00:29:05.941 --> 00:29:08.623 Are there any questions that people

NOTE Confidence: 0.85210776

00:29:08.623 --> 00:29:10.776 want to enter into the chat?

NOTE Confidence: 0.85210776

00:29:10.780 --> 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 --> 00:29:15.975 of opening up the bread.

NOTE Confidence: 0.85210776

00:29:15.980 --> 00:29:17.788 The blood brain barrier

NOTE Confidence: 0.85210776

00:29:17.788 --> 00:29:19.596 by targeting a molecule.

NOTE Confidence: 0.85210776

00:29:19.600 --> 00:29:21.343 Is it worth going back to some

NOTE Confidence: 0.85210776

00:29:21.343 --> 00:29:22.810 of the earlier drugs that

NOTE Confidence: 0.85210776

00:29:22.810 --> 00:29:24.138 weren't terribly effective to

NOTE Confidence: 0.85210776

00:29:24.138 --> 00:29:26.106 see that whether or not that

NOTE Confidence: 0.85210776

00:29:26.106 --> 00:29:27.566 might help them work better?

NOTE Confidence: 0.71716356

00:29:28.430 --> 00:29:33.020 Yes, I think there is a whole list of drugs

NOTE Confidence: 0.71716356

00:29:33.132 --> 00:29:37.297 that perhaps will need to be revisited.

NOTE Confidence: 0.71716356

00:29:37.300 --> 00:29:39.544 Although most of these drugs would

NOTE Confidence: 0.71716356

00:29:39.544 --> 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 --> 00:29:46.688 we still need to select them

NOTE Confidence: 0.71716356

00:29:46.688 --> 00:29:48.320 by those specific mutations.

NOTE Confidence: 0.71716356

00:29:48.320 --> 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 --> 00:29:55.256 I don't think blood brain barrier penetration

NOTE Confidence: 0.71716356

00:29:55.256 --> 00:29:58.152 was the reason why we couldn't target

NOTE Confidence: 0.71716356

00:29:58.152 --> 00:30:00.558 EGFR amplification or Pete and loss.

NOTE Confidence: 0.71716356

00:30:00.560 --> 00:30:03.409 I think that is a different question,

NOTE Confidence: 0.71716356

00:30:03.410 --> 00:30:06.308 but if we are to even answer

NOTE Confidence: 0.71716356

00:30:06.308 --> 00:30:08.130 those we still need.

NOTE Confidence: 0.71716356

00:30:08.130 --> 00:30:09.038 This kind of approach,

NOTE Confidence: 0.71716356

00:30:09.038 --> 00:30:10.999 'cause it makes our life so much easier.

NOTE Confidence: 0.8856998

00:30:13.660 --> 00:30:15.550 Are there any questions from the audience?

NOTE Confidence: 0.79346305

00:30:22.920 --> 00:30:26.412 I was also struck by the lots of different

NOTE Confidence: 0.79346305

00:30:26.412 --> 00:30:28.850 mutations upon recurrence. He showed.

NOTE Confidence: 0.7935335

00:30:31.150 --> 00:30:33.060 What is that thought to

NOTE Confidence: 0.7935335

00:30:33.060 --> 00:30:35.719 be due to is just so high

NOTE Confidence: 0.7935335

00:30:35.720 --> 00:30:37.630 perforation rate of these tumors.

NOTE Confidence: 0.7935335

00:30:37.630 --> 00:30:39.530 Yeah, well, I think so.

NOTE Confidence: 0.7935335

00:30:39.530 --> 00:30:42.183 First of all, these tumors are very

NOTE Confidence: 0.7935335

00:30:42.183 --> 00:30:44.084 heterogeneous to begin with, right?

NOTE Confidence: 0.7935335

00:30:44.084 --> 00:30:46.268 So these are guns that are

NOTE Confidence: 0.7935335

00:30:46.268 --> 00:30:48.300 were there to begin with,

NOTE Confidence: 0.7935335

00:30:48.300 --> 00:30:50.960 but it looks like the treatment process

NOTE Confidence: 0.7935335

00:30:50.960 --> 00:30:54.038 ends up eliminating a lot of this so

NOTE Confidence: 0.7935335

00:30:54.038 --> 00:30:55.530 called cancer associated mutations.

NOTE Confidence: 0.7935335

00:30:55.530 --> 00:30:57.612 Another unknown mutations emerge and also

NOTE Confidence: 0.7935335

00:30:57.612 --> 00:31:00.548 a lot of these are actually epigenetic.

NOTE Confidence: 0.7935335

00:31:00.550 --> 00:31:00.971 Changes.

NOTE Confidence: 0.7935335

00:31:00.971 --> 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 --> 00:31:09.737 more canals are interested in in that

NOTE Confidence: 0.7935335

00:31:09.737 --> 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 --> 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 --> 00:31:20.350 very simple from a genomic standpoint,

NOTE Confidence: 0.7935335

00:31:20.350 --> 00:31:23.430 but not so simple at the epigenetic level.

NOTE Confidence: 0.7935335

00:31:23.430 --> 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 --> 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 --> 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

NOTE Confidence: 0.83255094

00:31:40.663 --> 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 --> 00:31:49.290 and he's interested in natural

NOTE Confidence: 0.83255094

00:31:49.290 --> 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 --> 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 --> 00:31:59.279 and working with Jason Crawford

NOTE Confidence: 0.83255094

00:31:59.279 --> 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 --> 00:32:03.927 the metabolites made by the human

NOTE Confidence: 0.83255094

00:32:03.927 --> 00:32:05.762 microbiota and identified some of

NOTE Confidence: 0.83255094

00:32:05.762 --> 00:32:07.880 them that actually damaged DNA and

NOTE Confidence: 0.83255094

00:32:07.880 --> 00:32:09.328 therefore contribute to cancer.

NOTE Confidence: 0.83255094

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

NOTE Confidence: 0.83255094

00:32:11.148 --> 00:32:12.930 to hearing about your work.

NOTE Confidence: 0.83255094

00:32:12.930 --> 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 --> 00:32:19.295 thanks for the introduction.

NOTE Confidence: 0.8794826

00:32:19.300 --> 00:32:20.955 And thanks to all to

NOTE Confidence: 0.8794826

00:32:20.955 --> 00:32:22.280 everyone for the invocation.

NOTE Confidence: 0.8794826

00:32:22.280 --> 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 --> 00:32:29.340 been doing in the human microbiome,

NOTE Confidence: 0.8794826

00:32:29.340 --> 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 --> 00:32:40.216 Cave against drug resistant TMZ resistant.

NOTE Confidence: 0.70541836

00:32:40.220 --> 00:32:43.314 GBM that we're very excited about but

NOTE Confidence: 0.70541836

00:32:43.314 --> 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

NOTE Confidence: 0.88522273

00:32:51.572 --> 00:32:53.928 about a project that's been ongoing

NOTE Confidence: 0.88522273

00:32:53.928 --> 00:32:56.469 in my group for about 6 years.

NOTE Confidence: 0.88522273

00:32:56.470 --> 00:32:59.668 And we've been looking to understand

NOTE Confidence: 0.88522273

00:32:59.668 --> 00:33:03.200 the molecular basis of a carcinogen

NOTE Confidence: 0.88522273

00:33:03.200 --> 00:33:05.820 carcinogenic phenotype that was

NOTE Confidence: 0.88522273

00:33:05.820 --> 00:33:09.048 observed from certain gut bacteria so.

NOTE Confidence: 0.88522273

00:33:09.048 --> 00:33:11.631 I'll go through sort of the sequence

NOTE Confidence: 0.88522273

00:33:11.631 --> 00:33:14.631 of events to kind of outline sequence

NOTE Confidence: 0.88522273

00:33:14.631 --> 00:33:17.260 of discoveries to outline the problem,

NOTE Confidence: 0.88522273

00:33:17.260 --> 00:33:20.923 and so in 2006 this was the paper that

NOTE Confidence: 0.88522273

00:33:20.923 --> 00:33:24.825 set off a lot of interest in this area.

NOTE Confidence: 0.88522273

00:33:24.830 --> 00:33:27.920 Eric Oswald and coworkers identified

NOTE Confidence: 0.88522273

00:33:27.920 --> 00:33:31.010 certain strains of commensal and

NOTE Confidence: 0.88522273

00:33:31.102 --> 00:33:34.861 pathogenic E coli that had a biosynthetic

NOTE Confidence: 0.88522273

00:33:34.861 --> 00:33:38.268 gene cluster known as the CLB cluster.

NOTE Confidence: 0.88522273

00:33:38.270 --> 00:33:42.270 So by that I mean that gene genetic

NOTE Confidence: 0.88522273

00:33:42.270 --> 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 --> 00:33:52.790 he took these CLB containing bacteria

NOTE Confidence: 0.88522273

00:33:52.790 --> 00:33:55.535 and did a transient infection.

NOTE Confidence: 0.88522273

00:33:55.535 --> 00:33:58.325 HeLa cells with them and then

NOTE Confidence: 0.88522273

00:33:58.325 --> 00:34:01.527 looked at the effect on the cells,

NOTE Confidence: 0.88522273

00:34:01.530 --> 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 --> 00:34:08.546 Meglos cytosis and using a comet assay.

NOTE Confidence: 0.88522273

00:34:08.550 --> 00:34:12.358 Another Gamage to XD he saw that

NOTE Confidence: 0.88522273

00:34:12.358 --> 00:34:14.619 they accumulated double strand

NOTE Confidence: 0.88522273

00:34:14.619 --> 00:34:16.719 breaks in their DNA.

NOTE Confidence: 0.88522273

00:34:16.720 --> 00:34:18.960 And so this is a very interesting phenotype.

NOTE Confidence: 0.88522273

00:34:18.960 --> 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 --> 00:34:24.385 produced Gina toxins,

NOTE Confidence: 0.88522273

00:34:24.390 --> 00:34:27.510 but it was was was a very interesting

NOTE Confidence: 0.88522273

00:34:27.510 --> 00:34:30.758 example and I'll come to in a second wait.

NOTE Confidence: 0.88522273

00:34:30.760 --> 00:34:34.348 Why it's attracting so much attention?

NOTE Confidence: 0.88522273

00:34:34.350 --> 00:34:36.942 Subsequent to that report,

NOTE Confidence: 0.88522273

00:34:36.942 --> 00:34:39.534 there's been numerous studies

NOTE Confidence: 0.88522273

00:34:39.534 --> 00:34:42.899 trying to ascertain whether or not

NOTE Confidence: 0.88522273

00:34:42.899 --> 00:34:46.567 there is a role for these bacteria

NOTE Confidence: 0.88522273

00:34:46.567 --> 00:34:49.043 in colorectal cancer formation

NOTE Confidence: 0.88522273

00:34:49.043 --> 00:34:53.554 and from the same group in 2010.

NOTE Confidence: 0.88522273

00:34:53.554 --> 00:34:57.796 It was shown that in in

NOTE Confidence: 0.88522273

00:34:57.796 --> 00:35:00.839 intestinal loop models of.

NOTE Confidence: 0.88522273

00:35:00.840 --> 00:35:04.319 My step or infected with CLB bacteria

NOTE Confidence: 0.88522273

00:35:04.319 --> 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

NOTE Confidence: 0.88522273

00:35:10.580 --> 00:35:13.663 increased mutations in the HP RT&TK

NOTE Confidence: 0.88522273

00:35:13.663 --> 00:35:16.318 loci and then also hyperproliferation

NOTE Confidence: 0.88522273

00:35:16.318 --> 00:35:18.699 following exposure to the bacteria.

NOTE Confidence: 0.88522273

00:35:18.700 --> 00:35:21.899 So they seem to be driving tumorigenesis

NOTE Confidence: 0.88522273

00:35:21.899 --> 00:35:24.424 and then there were subsequent

NOTE Confidence: 0.88522273

00:35:24.424 --> 00:35:27.084 studies following up looking at

NOTE Confidence: 0.88522273

00:35:27.084 --> 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 --> 00:35:35.936 it was shown that infection with

NOTE Confidence: 0.88522273

00:35:35.936 --> 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 --> 00:35:55.073 we find is that about 60 to 70% of

NOTE Confidence: 0.88522273

00:35:55.073 --> 00:35:57.538 CRC patients have these bacteria

NOTE Confidence: 0.88522273

00:35:57.538 --> 00:36:00.518 and that's and that's versus about

NOTE Confidence: 0.88522273

00:36:00.518 --> 00:36:02.368 20% in the healthy population.

NOTE Confidence: 0.88522273

00:36:02.368 --> 00:36:05.314 And the other sort of bit is that

NOTE Confidence: 0.88522273

00:36:05.314 --> 00:36:07.284 the preponderance of these bacteria

NOTE Confidence: 0.88522273

00:36:07.284 --> 00:36:10.077 tracks with the severity of the cancer,

NOTE Confidence: 0.88522273

00:36:10.080 --> 00:36:12.285 so people with more advanced CRC were

NOTE Confidence: 0.88522273

00:36:12.285 --> 00:36:14.840 at the high end of that correlation,

NOTE Confidence: 0.88522273

00:36:14.840 --> 00:36:17.300 whereas people with early stage

NOTE Confidence: 0.88522273

00:36:17.300 --> 00:36:20.810 CRC were more at the lower end.

NOTE Confidence: 0.88522273

00:36:20.810 --> 00:36:23.099 And so it wasn't really until last

NOTE Confidence: 0.88522273

00:36:23.099 --> 00:36:25.575 year that a causal relationship

NOTE Confidence: 0.88522273

00:36:25.575 --> 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 --> 00:36:33.619 and then Boxtel and Cleavers an

NOTE Confidence: 0.88522273

00:36:33.619 --> 00:36:35.667 in the Cleavers study.

NOTE Confidence: 0.88522273

00:36:35.670 --> 00:36:39.515 They generated an organoid and

NOTE Confidence: 0.88522273

00:36:39.515 --> 00:36:43.360 infected that organoid chronically for

NOTE Confidence: 0.88522273

00:36:43.472 --> 00:36:47.917 about three or four months with the

NOTE Confidence: 0.88522273

00:36:47.917 --> 00:36:51.640 CLB positive bacteria and what they

NOTE Confidence: 0.88522273

00:36:51.640 --> 00:36:55.616 showed is that you get the mutational

NOTE Confidence: 0.88522273

00:36:55.620 --> 00:36:58.764 signature transformation and proliferation.

NOTE Confidence: 0.88522273

00:36:58.764 --> 00:37:03.480 We also find that that mutational

NOTE Confidence: 0.84878147

00:37:03.589 --> 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 --> 00:37:10.816 and so the mayor study came

NOTE Confidence: 0.84878147

00:37:10.816 --> 00:37:12.034 to similar conclusions,

NOTE Confidence: 0.84878147

00:37:12.040 --> 00:37:14.889 and essentially these two papers you know,

NOTE Confidence: 0.84878147

00:37:14.890 --> 00:37:17.722 this is a rare example in the microbiome

NOTE Confidence: 0.84878147

00:37:17.722 --> 00:37:20.185 where you actually establish causation.

NOTE Confidence: 0.84878147

00:37:20.185 --> 00:37:22.880 So these two papers brought this

NOTE Confidence: 0.84878147

00:37:22.880 --> 00:37:25.608 phenotype to the two sort of

NOTE Confidence: 0.84878147

00:37:25.608 --> 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 --> 00:37:32.452 is understand the molecular

NOTE Confidence: 0.84878147

00:37:32.452 --> 00:37:35.649 basis for all of this OK and so.

NOTE Confidence: 0.83618563

00:37:38.520 --> 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 --> 00:37:50.970 robust control experiments to establish

NOTE Confidence: 0.83618563

00:37:50.970 --> 00:37:53.706 that this genotoxic phenotype.

NOTE Confidence: 0.83618563

00:37:53.710 --> 00:37:56.068 Is due to the final biosynthetic

NOTE Confidence: 0.83618563

00:37:56.068 --> 00:37:58.579 product product of the CLB cluster.

NOTE Confidence: 0.83618563

00:37:58.580 --> 00:38:01.422 In other words, if one modifies any

NOTE Confidence: 0.83618563

00:38:01.422 --> 00:38:04.270 of the enzymes in the CLB pathway,

NOTE Confidence: 0.83618563

00:38:04.270 --> 00:38:06.700 you lose this genotoxic phenotype OK,

NOTE Confidence: 0.83618563

00:38:06.700 --> 00:38:09.661 and so the implication then is that

NOTE Confidence: 0.83618563

00:38:09.661 --> 00:38:12.720 it's the fully elaborated molecule.

NOTE Confidence: 0.83618563

00:38:12.720 --> 00:38:14.920 That is the active toxin,

NOTE Confidence: 0.83618563

00:38:14.920 --> 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 --> 00:38:23.000 And we call that molecule Coley bactine.

NOTE Confidence: 0.83618563

00:38:23.000 --> 00:38:25.875 And. So the field basically

NOTE Confidence: 0.83618563

00:38:25.875 --> 00:38:30.260 set out to do what we do best,

NOTE Confidence: 0.83618563

00:38:30.260 --> 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 --> 00:38:37.740 product secondary metabolites is to

NOTE Confidence: 0.83618563

00:38:37.740 --> 00:38:40.490 culture the Organism of interest.

NOTE Confidence: 0.83618563

00:38:40.490 --> 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 --> 00:38:50.049 growing on scale.

NOTE Confidence: 0.83618563

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

NOTE Confidence: 0.83618563

00:38:52.155 --> 00:38:54.560 HPLC and then we typically do.

NOTE Confidence: 0.83618563

00:38:54.560 --> 00:38:57.020 It's known as activity guided fractionation,

NOTE Confidence: 0.83618563

00:38:57.020 --> 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 --> 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 --> 00:39:10.550 a single compound and you characterize it.

NOTE Confidence: 0.83618563

00:39:10.550 --> 00:39:12.530 The problem is that this

NOTE Confidence: 0.83618563

00:39:12.530 --> 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 --> 00:39:19.340 so the molecule is very unstable.

NOTE Confidence: 0.83618563

00:39:19.340 --> 00:39:23.612 It is very difficult to get the bacteria

NOTE Confidence: 0.83618563

00:39:23.612 --> 00:39:27.296 to express the CLB pathway ex vivo.

NOTE Confidence: 0.83618563

00:39:27.300 --> 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,

NOTE Confidence: 0.83618563

00:39:32.880 --> 00:39:35.460 primarily anaerobic environment of the gut.

NOTE Confidence: 0.83618563

00:39:35.460 --> 00:39:37.675 The molecule actually undergoes oxidative

NOTE Confidence: 0.83618563

00:39:37.675 --> 00:39:40.620 degradation when you attempt to isolate it.

NOTE Confidence: 0.83618563

00:39:40.620 --> 00:39:43.630 Sort of on the bench under air,

NOTE Confidence: 0.83618563

00:39:43.630 --> 00:39:46.578 and just to to.

NOTE Confidence: 0.83618563

00:39:46.580 --> 00:39:48.110 Give you an example of how

NOTE Confidence: 0.83618563

00:39:48.110 --> 00:39:48.875 challenging this is.

NOTE Confidence: 0.83618563

00:39:48.880 --> 00:39:50.920 This is not work from our own laboratory.

NOTE Confidence: 0.83618563

00:39:50.920 --> 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 --> 00:39:59.350 backed in in the isolated this.

NOTE Confidence: 0.83618563

00:39:59.350 --> 00:40:03.032 Molecule here in 2019 they obtained 50

NOTE Confidence: 0.83618563

00:40:03.032 --> 00:40:06.958 micrograms from a 2000 liter fermentation.

NOTE Confidence: 0.83618563

00:40:06.960 --> 00:40:09.880 If anyone can imagine that,

NOTE Confidence: 0.83618563

00:40:09.880 --> 00:40:12.805 so we're talking about literally

NOTE Confidence: 0.83618563

00:40:12.805 --> 00:40:14.560 vanishingly small quantities.

NOTE Confidence: 0.84360933

00:40:16.940 --> 00:40:18.950 And they they advanced this molecule

NOTE Confidence: 0.84360933

00:40:18.950 --> 00:40:20.640 as a candidate calling back,

NOTE Confidence: 0.84360933

00:40:20.640 --> 00:40:22.950 and unfortunately this was derived from a

NOTE Confidence: 0.84360933

00:40:22.950 --> 00:40:24.670 triple mutant Frankenstein like bacteria,

NOTE Confidence: 0.84360933

00:40:24.670 --> 00:40:26.350 and I wrote a commentary.

NOTE Confidence: 0.84360933

00:40:26.350 --> 00:40:28.282 If you're interested on this at

NOTE Confidence: 0.84360933

00:40:28.282 --> 00:40:30.208 the general thinking in the field

NOTE Confidence: 0.84360933

00:40:30.208 --> 00:40:31.930 is this is probably not relevant

NOTE Confidence: 0.84360933

00:40:31.930 --> 00:40:33.739 to the genotoxic phenotype.

NOTE Confidence: 0.84360933

00:40:33.740 --> 00:40:35.044 But the point is,

NOTE Confidence: 0.84360933

00:40:35.044 --> 00:40:37.000 these are the links that people

NOTE Confidence: 0.84360933

00:40:37.070 --> 00:40:39.163 are willing to go to to try

NOTE Confidence: 0.84360933

00:40:39.163 --> 00:40:40.800 and isolate these molecules.

NOTE Confidence: 0.8315405

00:40:43.630 --> 00:40:46.696 And so, how do we approach this?

NOTE Confidence: 0.8315405

00:40:46.700 --> 00:40:48.452 So, as Dan mentioned,

NOTE Confidence: 0.8315405

00:40:48.452 --> 00:40:51.080 we've been collaborating with Jason Crawford.

NOTE Confidence: 0.8315405

00:40:51.080 --> 00:40:53.702 Jason is one of the leaders

NOTE Confidence: 0.8315405

00:40:53.702 --> 00:40:55.013 in understanding Kohli,

NOTE Confidence: 0.8315405

00:40:55.020 --> 00:40:56.184 backed in biosynthesis.

NOTE Confidence: 0.8315405

00:40:56.184 --> 00:40:59.443 And So what we've been doing is really

NOTE Confidence: 0.8315405

00:40:59.443 --> 00:41:01.803 taking knowledge from the biosynthetic

NOTE Confidence: 0.8315405

00:41:01.803 --> 00:41:05.086 pathway and trying to infer what types

NOTE Confidence: 0.8315405

00:41:05.086 --> 00:41:07.720 of substructures might be within Kohli.

NOTE Confidence: 0.8315405

00:41:07.720 --> 00:41:10.160 Backed in itself and how

NOTE Confidence: 0.8315405

00:41:10.160 --> 00:41:11.624 those might interact.

NOTE Confidence: 0.8315405

00:41:11.630 --> 00:41:14.526 With DNA and so one of the sort

NOTE Confidence: 0.8315405

00:41:14.526 --> 00:41:17.778 of models that came out of these

NOTE Confidence: 0.8315405

00:41:17.778 --> 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 --> 00:41:26.470 offloaded from the PKS assembly line.

NOTE Confidence: 0.8315405

00:41:26.470 --> 00:41:28.970 There's a searing protease that

NOTE Confidence: 0.8315405

00:41:28.970 --> 00:41:32.179 removes this residue and blew this ACL.

NOTE Confidence: 0.8315405

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 --> 00:41:38.742 and once you format that can start

NOTE Confidence: 0.8315405

00:41:38.742 --> 00:41:41.666 to wrap up and ultimately lead to

NOTE Confidence: 0.8315405

00:41:41.666 --> 00:41:44.324 this compound on the bottom here,

NOTE Confidence: 0.8315405

00:41:44.330 --> 00:41:46.784 which has a cyclopropane ring in

NOTE Confidence: 0.8315405

00:41:46.784 --> 00:41:49.578 conjugation with with it with the Alpha,

NOTE Confidence: 0.8315405

00:41:49.580 --> 00:41:51.575 beta unsaturated imming and for

NOTE Confidence: 0.8315405

00:41:51.575 --> 00:41:54.042 those in the audience that have

NOTE Confidence: 0.8315405

00:41:54.042 --> 00:41:55.638 worked with Gina toxins,

NOTE Confidence: 0.8315405

00:41:55.640 --> 00:41:57.660 you know that these electrophilic

NOTE Confidence: 0.8315405

00:41:57.660 --> 00:41:59.276 cyclopropane's are not uncommon.

NOTE Confidence: 0.8315405

00:41:59.280 --> 00:42:02.264 This is a sort of a pharmacophore that's

NOTE Confidence: 0.8315405

00:42:02.264 --> 00:42:05.460 found in a variety of genotoxic natural.

NOTE Confidence: 0.8315405

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 --> 00:42:11.269 from that type of precedent.

NOTE Confidence: 0.8315405

00:42:11.270 --> 00:42:14.006 The problem is that the problem is this.

NOTE Confidence: 0.8315405

00:42:14.010 --> 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 --> 00:42:20.510 All we had was this.

NOTE Confidence: 0.8315405

00:42:20.510 --> 00:42:23.876 This kind of this mechanistic hypothesis.

NOTE Confidence: 0.8315405

00:42:23.880 --> 00:42:26.448 And so we set out to make it,

NOTE Confidence: 0.8315405

00:42:26.450 --> 00:42:28.898 and I'm not going to have time to go

NOTE Confidence: 0.8315405

00:42:28.898 --> 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 --> 00:42:35.757 But the key steps are shown here.

NOTE Confidence: 0.8315405

00:42:35.760 --> 00:42:37.923 So we start from this linear precursor

NOTE Confidence: 0.8315405

00:42:37.923 --> 00:42:40.519 and what we find is that if we

NOTE Confidence: 0.8315405

00:42:40.519 --> 00:42:42.500 concentrate this down from dilute acid,

NOTE Confidence: 0.8315405

00:42:42.500 --> 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 --> 00:42:48.919 onto the ketone. You found this.

NOTE Confidence: 0.8315405

00:42:48.919 --> 00:42:49.948 Finally this image.

NOTE Confidence: 0.8315405

00:42:49.950 --> 00:42:52.116 We then do a bond formation

NOTE Confidence: 0.8315405

00:42:52.116 --> 00:42:54.254 deprotect the Bach route to get

NOTE Confidence: 0.8315405

00:42:54.254 --> 00:42:56.126 to this compound on the left,

NOTE Confidence: 0.8315405

00:42:56.130 --> 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 --> 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 --> 00:43:08.050 you lose water, any formatting.

NOTE Confidence: 0.8315405

00:43:08.050 --> 00:43:08.830 And.

NOTE Confidence: 0.8187508

00:43:10.920 --> 00:43:12.838 The assay that we use, that's 'cause

NOTE Confidence: 0.8187508

00:43:12.838 --> 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 --> 00:43:20.934 Taking linearized plasmid DNA

NOTE Confidence: 0.808242

00:43:20.934 --> 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 --> 00:43:26.820 and basically if you look at

NOTE Confidence: 0.808242

00:43:26.905 --> 00:43:28.930 the right hand lanes here,

NOTE Confidence: 0.808242

00:43:28.930 --> 00:43:31.597 you see these streaks on the gel

NOTE Confidence: 0.808242

00:43:31.597 --> 00:43:34.742 going down to about 100 animal or what

NOTE Confidence: 0.808242

00:43:34.742 --> 00:43:38.229 that tells us is that at 100 animal

NOTE Confidence: 0.808242

00:43:38.229 --> 00:43:40.719 or concentration of this compound,

NOTE Confidence: 0.808242

00:43:40.720 --> 00:43:41.983 we're getting extensive

NOTE Confidence: 0.808242

00:43:41.983 --> 00:43:43.667 degradation of the DNA.

NOTE Confidence: 0.808242

00:43:43.670 --> 00:43:46.190 These are smaller fragments that

NOTE Confidence: 0.808242

00:43:46.190 --> 00:43:49.140 have higher mobility on the gel.

NOTE Confidence: 0.808242

00:43:49.140 --> 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 --> 00:43:55.552 we hypothesized again that it

NOTE Confidence: 0.808242

00:43:55.552 --> 00:43:57.840 was this nucleotide addition to

NOTE Confidence: 0.808242

00:43:57.840 --> 00:44:00.230 the cyclopropane that was leading

NOTE Confidence: 0.808242

00:44:00.230 --> 00:44:02.989 to this degradation of the DNA.

NOTE Confidence: 0.808242

00:44:02.990 --> 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 --> 00:44:09.874 we made a couple of control compounds.

NOTE Confidence: 0.808242

00:44:09.880 --> 00:44:11.924 So the first one.

NOTE Confidence: 0.808242

00:44:11.924 --> 00:44:14.479 Was this dimeric structure up

NOTE Confidence: 0.808242

00:44:14.479 --> 00:44:17.804 top here and so the hypothesis is

NOTE Confidence: 0.808242

00:44:17.804 --> 00:44:21.219 that if this is alkylating DNA,

NOTE Confidence: 0.808242

00:44:21.220 --> 00:44:24.166 perhaps we can induce two fold

NOTE Confidence: 0.808242

00:44:24.166 --> 00:44:27.451 alkylation and perhaps we can then

NOTE Confidence: 0.808242

00:44:27.451 --> 00:44:29.907 detect and interstrand crosslink?

NOTE Confidence: 0.808242

00:44:29.910 --> 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 --> 00:44:38.780 This corresponds to our positive

NOTE Confidence: 0.808242

00:44:38.780 --> 00:44:40.892 control for crosslinking cisplatin.

NOTE Confidence: 0.808242

00:44:40.900 --> 00:44:43.300 And then the other thing we did was

NOTE Confidence: 0.808242

00:44:43.300 --> 00:44:46.209 we made a negative control where we

NOTE Confidence: 0.808242

00:44:46.209 --> 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 --> 00:44:52.895 The hypothesis being if the

NOTE Confidence: 0.808242

00:44:52.895 --> 00:44:54.443 cyclopropane is truly involved,

NOTE Confidence: 0.808242

00:44:54.450 --> 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 --> 00:45:02.517 assay and so without characterizing

NOTE Confidence: 0.808242

00:45:02.517 --> 00:45:04.822 the product without even having

NOTE Confidence: 0.808242

00:45:04.822 --> 00:45:06.830 isolated the natural products,

NOTE Confidence: 0.808242

00:45:06.830 --> 00:45:09.926 we were able to sort of formulate this

NOTE Confidence: 0.808242

00:45:09.926 --> 00:45:12.758 proposal for how these things might be.

NOTE Confidence: 0.808242

00:45:12.760 --> 00:45:14.528 Might be alkylating DNA.

NOTE Confidence: 0.826165012

00:45:16.690 --> 00:45:19.610 And. We are, you know,

NOTE Confidence: 0.826165012

00:45:19.610 --> 00:45:21.518 we sort of at that point.

NOTE Confidence: 0.826165012

00:45:21.520 --> 00:45:23.188 Got stocks so that was around

NOTE Confidence: 0.826165012

00:45:23.188 --> 00:45:25.340 2018 when we had identified this.

NOTE Confidence: 0.826165012

00:45:25.340 --> 00:45:26.925 You know, this DNA reactive

NOTE Confidence: 0.826165012

00:45:26.925 --> 00:45:28.193 substructure in the molecule.

NOTE Confidence: 0.826165012

00:45:28.200 --> 00:45:30.108 We knew that it was incomplete.

NOTE Confidence: 0.826165012

00:45:30.110 --> 00:45:31.061 In other words,

NOTE Confidence: 0.826165012

00:45:31.061 --> 00:45:32.646 there were other functional groups,

NOTE Confidence: 0.826165012

00:45:32.650 --> 00:45:35.186 other rings and things with in Cali bactine.

NOTE Confidence: 0.826165012

00:45:35.190 --> 00:45:38.144 But we didn't know what they were.

NOTE Confidence: 0.826165012

00:45:38.150 --> 00:45:40.544 And as I mentioned in the beginning,

NOTE Confidence: 0.826165012

00:45:40.550 --> 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 --> 00:45:46.038 successful in this in this context,

NOTE Confidence: 0.826165012

00:45:46.040 --> 00:45:48.850 and so we were stuck.

NOTE Confidence: 0.826165012

00:45:48.850 --> 00:45:51.010 Until this paper came out,

NOTE Confidence: 0.826165012

00:45:51.010 --> 00:45:54.880 and so this is also from the Oswald Group.

NOTE Confidence: 0.826165012

00:45:54.880 --> 00:45:57.035 They did a beautiful experiment

NOTE Confidence: 0.826165012

00:45:57.035 --> 00:45:59.190 where they took the collie,

NOTE Confidence: 0.826165012

00:45:59.190 --> 00:46:00.914 backed in producing bacteria,

NOTE Confidence: 0.826165012

00:46:00.914 --> 00:46:03.500 grew them up in liquid media,

NOTE Confidence: 0.826165012

00:46:03.500 --> 00:46:04.793 added exogeneous DNA,

NOTE Confidence: 0.826165012

00:46:04.793 --> 00:46:06.948 isolated that DNA following incubation,

NOTE Confidence: 0.826165012

00:46:06.950 --> 00:46:10.078 and ran a denaturing gel and the point

NOTE Confidence: 0.826165012

00:46:10.078 --> 00:46:12.609 is that they observed interstrand

NOTE Confidence: 0.826165012

00:46:12.609 --> 00:46:15.927 crosslinks in that DNA that was

NOTE Confidence: 0.826165012

00:46:15.927 --> 00:46:18.949 exposed to these bacteria OK and so.

NOTE Confidence: 0.826165012

00:46:18.950 --> 00:46:21.970 I have a note here at the bottom to remind

NOTE Confidence: 0.826165012

00:46:22.044 --> 00:46:24.844 me you know if you're paying attention.

NOTE Confidence: 0.826165012

00:46:24.850 --> 00:46:26.238 The original female phenotype

NOTE Confidence: 0.826165012

00:46:26.238 --> 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 --> 00:46:32.139 Those two lesions are are intimately related,

NOTE Confidence: 0.826165012

00:46:32.140 --> 00:46:34.162 and I'll talk about that at

NOTE Confidence: 0.826165012

00:46:34.162 --> 00:46:35.950 the end if there's time.

NOTE Confidence: 0.826165012

00:46:35.950 --> 00:46:37.996 But basically we're very excited about

NOTE Confidence: 0.826165012

00:46:37.996 --> 00:46:40.461 this paper because you can imagine that

NOTE Confidence: 0.826165012

00:46:40.461 --> 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 --> 00:46:46.474 if that's what's causing the crossing at that

NOTE Confidence: 0.826165012

00:46:46.474 --> 00:46:48.790 point wasn't completely certain that either,

NOTE Confidence: 0.826165012

00:46:48.790 --> 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 --> 00:46:53.804 all we have to do is isolate that

NOTE Confidence: 0.826165012

00:46:53.804 --> 00:46:55.180 crosslink can characterize it.

NOTE Confidence: 0.8377484

00:46:57.290 --> 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 --> 00:47:05.290 pathway had been mapped out.

NOTE Confidence: 0.8377484

00:47:05.290 --> 00:47:08.706 We had a very good understanding of what

NOTE Confidence: 0.8377484

00:47:08.706 --> 00:47:12.703 went in of the amino acids that went into

NOTE Confidence: 0.8377484

00:47:12.703 --> 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 --> 00:47:23.640 and so for example, it was known through

NOTE Confidence: 0.8377484

00:47:23.640 --> 00:47:27.040 work that Jason did very early on,

NOTE Confidence: 0.8377484

00:47:27.040 --> 00:47:29.950 and then others that this amino

NOTE Confidence: 0.8377484

00:47:29.950 --> 00:47:31.890 cyclopropane comes from methionine,

NOTE Confidence: 0.8377484

00:47:31.890 --> 00:47:34.230 and these thiazole rings

NOTE Confidence: 0.8377484

00:47:34.230 --> 00:47:36.570 derived from cysteine OK.

NOTE Confidence: 0.8377484

00:47:36.570 --> 00:47:37.770 And So what?

NOTE Confidence: 0.8377484

00:47:37.770 --> 00:47:40.570 This allowed us to do is conduct

NOTE Confidence: 0.8377484

00:47:40.663 --> 00:47:43.823 essentially isotope labeling experiments

NOTE Confidence: 0.8377484

00:47:43.823 --> 00:47:47.773 where we generated auxotrophic strains,

NOTE Confidence: 0.8377484

00:47:47.780 --> 00:47:50.140 either deficient in methionine

NOTE Confidence: 0.8377484

00:47:50.140 --> 00:47:51.910 or cysteine biosynthesis,

NOTE Confidence: 0.8377484

00:47:51.910 --> 00:47:55.430 and then supplemented those cultures

NOTE Confidence: 0.8377484

00:47:55.430 --> 00:47:59.400 with C13 labeled amino acid OK.

NOTE Confidence: 0.8377484

00:47:59.400 --> 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 --> 00:48:06.100 with their amino acids incubate.

NOTE Confidence: 0.8377484

00:48:06.100 --> 00:48:08.858 Here we're using linearized puck 19 DNA.

NOTE Confidence: 0.8377484

00:48:08.860 --> 00:48:11.072 We can run a gel to verify

NOTE Confidence: 0.8377484

00:48:11.072 --> 00:48:13.190 that we got crosslinking,

NOTE Confidence: 0.8377484

00:48:13.190 --> 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 --> 00:48:20.767 and one of the things that's worth

NOTE Confidence: 0.8377484

00:48:20.767 --> 00:48:23.938 pointing out is that to do these assays

NOTE Confidence: 0.8377484

00:48:23.938 --> 00:48:25.978 were talking about 250 microliters

NOTE Confidence: 0.8377484

00:48:26.049 --> 00:48:28.159 of culture versus 2000 liters.

NOTE Confidence: 0.8377484

00:48:28.160 --> 00:48:30.240 You know using the old?

NOTE Confidence: 0.8377484

00:48:30.240 --> 00:48:32.585 The sort of the old fashioned method,

NOTE Confidence: 0.8377484

00:48:32.590 --> 00:48:34.822 and so to give you an idea of

NOTE Confidence: 0.8377484

00:48:34.822 --> 00:48:36.989 what the data looks like and

NOTE Confidence: 0.8377484

00:48:36.989 --> 00:48:39.281 why we do this isotope labeling.

NOTE Confidence: 0.8377484

00:48:39.290 --> 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 --> 00:48:44.050 we can spot these ions that I've

NOTE Confidence: 0.8377484

00:48:44.120 --> 00:48:45.990 marked in colored boxes here,

NOTE Confidence: 0.8377484

00:48:45.990 --> 00:48:48.095 and the top chromatogram is

NOTE Confidence: 0.8377484

00:48:48.095 --> 00:48:49.779 the wild type strain.

NOTE Confidence: 0.8377484

00:48:49.780 --> 00:48:52.636 And what you can see in the Sistine

NOTE Confidence: 0.8377484

00:48:52.636 --> 00:48:54.947 Auxotroph the middle graph is that

NOTE Confidence: 0.8377484

00:48:54.947 --> 00:48:57.740 those ions are shifted by three units,

NOTE Confidence: 0.8377484

00:48:57.740 --> 00:49:00.365 and so that's very useful to us

NOTE Confidence: 0.8377484

00:49:00.365 --> 00:49:02.669 because it tells us two things.

NOTE Confidence: 0.8377484

00:49:02.670 --> 00:49:05.372 One is that that Ion is probably

NOTE Confidence: 0.8377484

00:49:05.372 --> 00:49:08.064 contains Poly back in or the vestiges

NOTE Confidence: 0.8377484

00:49:08.064 --> 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 --> 00:49:14.870 there was one cysteine incorporated

NOTE Confidence: 0.8377484

00:49:14.870 --> 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 --> 00:49:19.600 with the methionine auxotroph.

NOTE Confidence: 0.8377484

00:49:19.600 --> 00:49:22.129 So here we get a shift by plus four.

NOTE Confidence: 0.8377484

00:49:22.130 --> 00:49:24.118 So that tells us there's 11 amino

NOTE Confidence: 0.8377484

00:49:24.118 --> 00:49:25.565 cyclopropane and tells us it's

NOTE Confidence: 0.8377484

00:49:25.565 --> 00:49:26.905 also related to Cali Bactine.

NOTE Confidence: 0.8377484

00:49:26.910 --> 00:49:30.870 OK, so this was the initial work that we did.

NOTE Confidence: 0.8377484

00:49:30.870 --> 00:49:34.070 We had to carry out a lot more

NOTE Confidence: 0.8377484

00:49:34.070 --> 00:49:37.545 labeling in order to get the full

NOTE Confidence: 0.8377484

00:49:37.545 --> 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 --> 00:49:46.450 had our cysteine and methionine auxotroph.

NOTE Confidence: 0.8377484

00:49:46.450 --> 00:49:49.000 We generated steering and glaci Knox

NOTE Confidence: 0.8377484

00:49:49.000 --> 00:49:51.694 Atros 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 --> 00:49:58.060 And then we also did Universal labeling C

NOTE Confidence: 0.8377484

00:49:58.060 --> 00:50:01.430 13 labeling with glucose an 15 labeling.

NOTE Confidence: 0.8377484

00:50:01.430 --> 00:50:02.864 With ammonium chloride.

NOTE Confidence: 0.8377484

00:50:02.864 --> 00:50:06.210 And we can run the same experiment

NOTE Confidence: 0.8377484

00:50:06.301 --> 00:50:08.857 where we incubate with the DNA,

NOTE Confidence: 0.8377484

00:50:08.860 --> 00:50:10.000 isolate the crosslink,

NOTE Confidence: 0.8377484

00:50:10.000 --> 00:50:10.760 digest it,

NOTE Confidence: 0.8377484

00:50:10.760 --> 00:50:13.964 analyze it by 10MM S and we can then

NOTE Confidence: 0.8377484

00:50:13.964 --> 00:50:17.176 see different shifts in those ions.

NOTE Confidence: 0.8377484

00:50:17.180 --> 00:50:19.484 And this data turned out to

NOTE Confidence: 0.8377484

00:50:19.484 --> 00:50:21.340 be very powerful for us,

NOTE Confidence: 0.8377484

00:50:21.340 --> 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 --> 00:50:25.798 we can,

NOTE Confidence: 0.8377484

00:50:25.798 --> 00:50:28.510 we can glean an incredible amount of insight

NOTE Confidence: 0.7990484

00:50:28.581 --> 00:50:30.409 into the molecule structure.

NOTE Confidence: 0.7990484

00:50:30.410 --> 00:50:32.300 So from the glucose labeling,

NOTE Confidence: 0.7990484

00:50:32.300 --> 00:50:34.946 we get a shift by 37 units.

NOTE Confidence: 0.7990484

00:50:34.950 --> 00:50:36.840 That tells us, of course,

NOTE Confidence: 0.7990484

00:50:36.840 --> 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 --> 00:50:42.762 we have eight nitrogens we can see

NOTE Confidence: 0.7990484

00:50:42.762 --> 00:50:45.149 that in the methionine auxotroph,

NOTE Confidence: 0.7990484

00:50:45.150 --> 00:50:47.466 and I'm talking about a higher

NOTE Confidence: 0.7990484

00:50:47.466 --> 00:50:49.010 molecular weight ion here.

NOTE Confidence: 0.7990484

00:50:49.010 --> 00:50:51.422 At the top we get a shift by 8

NOTE Confidence: 0.7990484

00:50:51.422 --> 00:50:53.372 carbons and so that told us that

NOTE Confidence: 0.7990484

00:50:53.372 --> 00:50:55.348 we had two of these cyclopropane

NOTE Confidence: 0.7990484

00:50:55.348 --> 00:50:58.253 residues or what was left of them.

NOTE Confidence: 0.7990484

00:50:58.260 --> 00:51:00.228 Two thiazole 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 --> 00:51:06.642 and so we can basically tease out a

NOTE Confidence: 0.7990484

00:51:06.642 --> 00:51:09.138 lot of structural data to sort of

NOTE Confidence: 0.7990484

00:51:09.138 --> 00:51:12.097 see what pieces are need to be put

NOTE Confidence: 0.7990484

00:51:12.097 --> 00:51:14.233 together here to make the molecule.

NOTE Confidence: 0.7990484

00:51:14.240 --> 00:51:18.152 And so at any rate we found this

NOTE Confidence: 0.7990484

00:51:18.152 --> 00:51:21.029 higher molecular weight ion at 956.

NOTE Confidence: 0.7990484

00:51:21.030 --> 00:51:22.298 Using all that data,

NOTE Confidence: 0.7990484

00:51:22.298 --> 00:51:25.452 we were able to fit it to this structure

NOTE Confidence: 0.7990484

00:51:25.452 --> 00:51:28.189 here and so it contains one adenine

NOTE Confidence: 0.7990484

00:51:28.266 --> 00:51:31.320 residue and have explicitly drawn the

NOTE Confidence: 0.7990484

00:51:31.320 --> 00:51:34.182 Adenine without connectivity to the base,

NOTE Confidence: 0.7990484

00:51:34.182 --> 00:51:37.470 because at the time that we did this,

NOTE Confidence: 0.7990484

00:51:37.470 --> 00:51:39.114 we couldn't specify where

NOTE Confidence: 0.7990484

00:51:39.114 --> 00:51:41.169 it was bonded to adenine.

NOTE Confidence: 0.7990484

00:51:41.170 --> 00:51:44.047 We now know that that's in three,

NOTE Confidence: 0.7990484

00:51:44.050 --> 00:51:47.749 but had one adenine on the right hand side.

NOTE Confidence: 0.7990484

00:51:47.750 --> 00:51:50.620 You have a cyclopropane that's still intact,

NOTE Confidence: 0.7990484

00:51:50.620 --> 00:51:50.909 OK.

NOTE Confidence: 0.7990484

00:51:50.909 --> 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 --> 00:51:59.820 it's it's a hetero dimer.

NOTE Confidence: 0.7990484

00:51:59.820 --> 00:52:01.400 It's not quite C2 symmetric.

NOTE Confidence: 0.7990484

00:52:01.400 --> 00:52:02.924 If you look carefully at these

NOTE Confidence: 0.7990484

00:52:02.924 --> 00:52:04.422 thiazole rings they have different

NOTE Confidence: 0.7990484

00:52:04.422 --> 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 --> 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 --> 00:52:20.657 adenine addict and we're getting icy,

NOTE Confidence: 0.7616281

00:52:20.660 --> 00:52:22.380 else, presumably there's a

NOTE Confidence: 0.7616281

00:52:22.380 --> 00:52:24.960 dinucleotide add up and we went,

NOTE Confidence: 0.7616281

00:52:24.960 --> 00:52:29.260 and we were able to find the dyad an addict.

NOTE Confidence: 0.7616281

00:52:29.260 --> 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 --> 00:52:38.720 if that's the dyad, and in an act,

NOTE Confidence: 0.7616281

00:52:38.720 --> 00:52:41.730 then this is the structure of Kohli,

NOTE Confidence: 0.7616281

00:52:41.730 --> 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 --> 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 --> 00:52:56.402 There's a detail here

NOTE Confidence: 0.7616281

00:52:56.402 --> 00:52:58.034 which is worth mentioning,

NOTE Confidence: 0.7616281

00:52:58.040 --> 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 --> 00:53:07.858 we expect based on the biosynthetic pathway.

NOTE Confidence: 0.7616281

00:53:07.860 --> 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 --> 00:53:24.697 so working under air on the bench.

NOTE Confidence: 0.7616281

00:53:24.700 --> 00:53:27.171 This is this is the compound that

NOTE Confidence: 0.7616281

00:53:27.171 --> 00:53:29.490 you would have expected to get.

NOTE Confidence: 0.7616281

00:53:29.490 --> 00:53:31.620 And still so no ones isolated

NOTE Confidence: 0.7616281

00:53:31.620 --> 00:53:33.040 calling back in yet.

NOTE Confidence: 0.7616281

00:53:33.040 --> 00:53:35.170 And so how do you prove

NOTE Confidence: 0.7616281

00:53:35.170 --> 00:53:36.235 the structure assignment?

NOTE Confidence: 0.7616281

00:53:36.240 --> 00:53:39.426 We can go back and try and make it,

NOTE Confidence: 0.7616281

00:53:39.430 --> 00:53:42.286 and so we spent some time developing a

NOTE Confidence: 0.7616281

00:53:42.286 --> 00:53:44.757 synthesis of the molecule and it was.

NOTE Confidence: 0.7616281

00:53:44.760 --> 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.

NOTE Confidence: 0.7616281

00:53:50.210 --> 00:53:54.107 And then we can do an LCMS coinjection and

NOTE Confidence: 0.7616281

00:53:54.107 --> 00:53:58.207 we see that has the same retention time.

NOTE Confidence: 0.7616281

00:53:58.210 --> 00:54:00.821 It has the same tandem Ms as

NOTE Confidence: 0.7616281

00:54:00.821 --> 00:54:03.670 the as the natural material,

NOTE Confidence: 0.7616281

00:54:03.670 --> 00:54:06.645 and then finally we did a crosslinking

NOTE Confidence: 0.7616281

00:54:06.645 --> 00:54:09.772 assay where we basically ran that same

NOTE Confidence: 0.7616281

00:54:09.772 --> 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 --> 00:54:17.248 with our compound.

NOTE Confidence: 0.7616281

00:54:17.250 --> 00:54:19.464 And so this thing will crosslink

NOTE Confidence: 0.7616281

00:54:19.464 --> 00:54:21.676 add up to about, you know,

NOTE Confidence: 0.7616281

00:54:21.676 --> 00:54:23.516 down to about 500 nanomolar.

NOTE Confidence: 0.7616281

00:54:23.520 --> 00:54:26.200 And then we can do the tandem Ms

NOTE Confidence: 0.7616281

00:54:26.200 --> 00:54:28.320 analysis of those cross links.

NOTE Confidence: 0.7616281

00:54:28.320 --> 00:54:31.632 And so let me explain what's on this slide.

NOTE Confidence: 0.7616281

00:54:31.640 --> 00:54:34.209 So when we do the bacterial experiment

NOTE Confidence: 0.7616281

00:54:34.209 --> 00:54:37.180 where we treat the DNA with the bacteria,

NOTE Confidence: 0.7616281

00:54:37.180 --> 00:54:39.020 we can isolate the crosslink.

NOTE Confidence: 0.7616281

00:54:39.020 --> 00:54:40.870 You then run tandem Ms,

NOTE Confidence: 0.7616281

00:54:40.870 --> 00:54:43.446 you get a whole list of ions,

NOTE Confidence: 0.7616281

00:54:43.450 --> 00:54:45.802 primary and secondary and tertiary ions

NOTE Confidence: 0.7616281

00:54:45.802 --> 00:54:49.098 that you see from those crosslinks and so.

NOTE Confidence: 0.7616281

00:54:49.100 --> 00:54:50.790 You know the argument is.

NOTE Confidence: 0.7616281

00:54:50.790 --> 00:54:53.022 If we're making the same molecule

NOTE Confidence: 0.7616281

00:54:53.022 --> 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 --> 00:55:01.411 with DNA in the same way and it ought to

NOTE Confidence: 0.7616281

00:55:01.411 --> 00:55:04.727 blow apart in a mass spec in the same way?

NOTE Confidence: 0.7616281

00:55:04.730 --> 00:55:07.426 And So what this plot shows on the

NOTE Confidence: 0.7616281

00:55:07.426 --> 00:55:10.106 X axis or all of the ions that

NOTE Confidence: 0.7616281

00:55:10.106 --> 00:55:13.494 we found in the tenant and Ms of

NOTE Confidence: 0.7616281

00:55:13.494 --> 00:55:15.510 the bacteria derived crosslinks,

NOTE Confidence: 0.7616281

00:55:15.510 --> 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 --> 00:55:22.840 And the Y axis is simply the experimental

NOTE Confidence: 0.7616281

00:55:22.840 --> 00:55:24.713 minus theoretical error for those

NOTE Confidence: 0.7616281

00:55:24.713 --> 00:55:26.578 ions using this synthetic material.

NOTE Confidence: 0.7616281

00:55:26.580 --> 00:55:29.840 And so the point is we get all the same

NOTE Confidence: 0.7616281

00:55:29.926 --> 00:55:33.436 ions that we get when we use the bacteria.

NOTE Confidence: 0.7616281

00:55:33.440 --> 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 --> 00:55:41.240 and so we don't have an NMR of Cali bactine

NOTE Confidence: 0.7819776

00:55:41.328 --> 00:55:42.459 to compare to.

NOTE Confidence: 0.7819776

00:55:42.460 --> 00:55:44.638 But we can say that structure

NOTE Confidence: 0.7819776

00:55:44.638 --> 00:55:46.789 that we made interacts with DNA.

NOTE Confidence: 0.7819776

00:55:46.790 --> 00:55:49.142 It crosslinks DNA and then it blows

NOTE Confidence: 0.7819776

00:55:49.142 --> 00:55:51.210 apart in attend imeson exactly.

NOTE Confidence: 0.7819776

00:55:51.210 --> 00:55:53.031 In indistinguishable fashion.

NOTE Confidence: 0.7819776

00:55:53.031 --> 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 --> 00:55:59.104 apparent contradiction,

NOTE Confidence: 0.7819776

00:55:59.104 --> 00:56:02.040 so there's been a lot of debate in

NOTE Confidence: 0.7819776

00:56:02.105 --> 00:56:04.130 the literature between you know,

NOTE Confidence: 0.7819776

00:56:04.130 --> 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 --> 00:56:17.974 and for any of you that are familiar

NOTE Confidence: 0.7819776

00:56:17.974 --> 00:56:19.879 with these repair pathways,

NOTE Confidence: 0.7819776

00:56:19.880 --> 00:56:22.178 you know that these two phenotypes

NOTE Confidence: 0.7819776

00:56:22.178 --> 00:56:24.413 are intimately linked, right? And so.

NOTE Confidence: 0.7819776

00:56:24.413 --> 00:56:26.940 When you start to repair an ICL,

NOTE Confidence: 0.7819776

00:56:26.940 --> 00:56:29.046 you actually form a DSP that

NOTE Confidence: 0.7819776

00:56:29.046 --> 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 --> 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 --> 00:56:42.896 And we actually identified another pathway,

NOTE Confidence: 0.7819776

00:56:42.900 --> 00:56:45.606 which is just a spontaneous pathway.

NOTE Confidence: 0.7819776

00:56:45.610 --> 00:56:48.522 So it's well known in the old sort

NOTE Confidence: 0.7819776

00:56:48.522 --> 00:56:51.487 of Gina toxin literature that N

NOTE Confidence: 0.7819776

00:56:51.487 --> 00:56:54.172 3 adenine addicts are unstable

NOTE Confidence: 0.7819776

00:56:54.172 --> 00:56:55.930 towards depurination.

NOTE Confidence: 0.7819776

00:56:55.930 --> 00:56:58.667 And if we run our crosslinking assay,

NOTE Confidence: 0.7819776

00:56:58.670 --> 00:56:59.846 we sort of.

NOTE Confidence: 0.7819776

00:56:59.846 --> 00:57:02.590 We modify the assay to be able

NOTE Confidence: 0.7819776

00:57:02.691 --> 00:57:05.309 to sort of get at this data,

NOTE Confidence: 0.7819776

00:57:05.310 --> 00:57:07.692 but this is the conclusion is

NOTE Confidence: 0.7819776

00:57:07.692 --> 00:57:09.710 essentially that these these Icl's

NOTE Confidence: 0.7819776

00:57:09.710 --> 00:57:11.550 undergo a slow, deep urination.

NOTE Confidence: 0.7819776

00:57:11.550 --> 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 --> 00:57:18.135 lead to a single strand break.

NOTE Confidence: 0.7819776

00:57:18.140 --> 00:57:20.380 And you can imagine then you know,

NOTE Confidence: 0.7819776

00:57:20.380 --> 00:57:22.204 in tandem with the repair pathways

NOTE Confidence: 0.7819776

00:57:22.204 --> 00:57:23.880 and also other alkylation lesions.

NOTE Confidence: 0.7819776

00:57:23.880 --> 00:57:26.568 Eventually you're going to get those

NOTE Confidence: 0.7819776

00:57:26.568 --> 00:57:29.151 single strand breaks close enough to

NOTE Confidence: 0.7819776

00:57:29.151 --> 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

NOTE Confidence: 0.7819776

00:57:33.813 --> 00:57:35.960 we're at in the project, and so.

NOTE Confidence: 0.8687447

00:57:38.700 --> 00:57:41.148 What we're currently doing is working

NOTE Confidence: 0.8687447

00:57:41.148 --> 00:57:43.960 with this molecule on the bottom here.

NOTE Confidence: 0.8687447

00:57:43.960 --> 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 --> 00:57:51.868 The differences are highlighted in green,

NOTE Confidence: 0.8687447

00:57:51.870 --> 00:57:54.355 and so the dye ketonen Kohli backed

NOTE Confidence: 0.8687447

00:57:54.355 --> 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 --> 00:58:02.194 it would be, you know Suffiecient

NOTE Confidence: 0.8687447

00:58:02.194 --> 00:58:05.277 asked to try and use this in a

NOTE Confidence: 0.8687447

00:58:05.277 --> 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 --> 00:58:11.594 And so we made what we call the

NOTE Confidence: 0.8687447

00:58:11.594 --> 00:58:13.911 Dez di ketone analog on the bottom

NOTE Confidence: 0.8687447

00:58:13.911 --> 00:58:16.130 and working with Christian Jobin

NOTE Confidence: 0.8687447

00:58:16.130 --> 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 --> 00:58:21.100 taking this compound.

NOTE Confidence: 0.8687447

00:58:21.100 --> 00:58:23.781 Through all of the essays that have

NOTE Confidence: 0.8687447

00:58:23.781 --> 00:58:27.172 been run by by Oswald and Box Tone

NOTE Confidence: 0.8687447

00:58:27.172 --> 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 --> 00:58:34.922 seeing if the molecule recapitulates

NOTE Confidence: 0.8687447

00:58:34.922 --> 00:58:38.376 it and up until now, it seems too

NOTE Confidence: 0.8687447

00:58:38.376 --> 00:58:41.400 so we see we get activation again.

NOTE Confidence: 0.8687447

00:58:41.400 --> 00:58:43.470 My page 2X.

NOTE Confidence: 0.8687447

00:58:43.470 --> 00:58:44.850 Fancy D2.

NOTE Confidence: 0.8687447

00:58:44.850 --> 00:58:47.202 What he's doing right now is basically

NOTE Confidence: 0.8687447

00:58:47.202 --> 00:58:50.123 looking to see if this induces the same

NOTE Confidence: 0.8687447

00:58:50.123 --> 00:58:52.343 type of mutational signature that one

NOTE Confidence: 0.8687447

00:58:52.343 --> 00:58:54.823 gets with the bacteria and that will be,

NOTE Confidence: 0.8687447

00:58:54.830 --> 00:58:56.888 you know, sort of the end.

NOTE Confidence: 0.8687447

00:58:56.890 --> 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 --> 00:59:01.019 be a positive result,

NOTE Confidence: 0.8687447

00:59:01.020 --> 00:59:03.694 but whatever it is that will be

NOTE Confidence: 0.8687447

00:59:03.694 --> 00:59:06.529 sort of the endpoint for this.

NOTE Confidence: 0.8687447

00:59:06.530 --> 00:59:08.420 And so I just acknowledge all

NOTE Confidence: 0.8687447

00:59:08.420 --> 00:59:10.330 the people that did the work.

NOTE Confidence: 0.8687447

00:59:10.330 --> 00:59:11.915 I'll just go through this

NOTE Confidence: 0.8687447

00:59:11.915 --> 00:59:13.183 quickly to save time.

NOTE Confidence: 0.8687447

00:59:13.190 --> 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 --> 00:59:18.590 Many people from my group contributed

NOTE Confidence: 0.8687447

00:59:18.590 --> 00:59:20.480 to this project over the years,

NOTE Confidence: 0.8687447

00:59:20.480 --> 00:59:22.699 acknowledged the NCI and Yale for funding.

NOTE Confidence: 0.8687447

00:59:22.700 --> 00:59:24.305 Thanks again for the invitation

NOTE Confidence: 0.8687447

00:59:24.305 --> 00:59:26.574 and I'm happy to stay on and

NOTE Confidence: 0.8687447

00:59:26.574 --> 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 --> 00:59:34.710 It makes me appreciate

NOTE Confidence: 0.8345129

00:59:34.710 --> 00:59:35.850 that I'm a microbiologist.

NOTE Confidence: 0.8345129

00:59:35.850 --> 00:59:37.560 It's not nowhere near as hard

NOTE Confidence: 0.8345129

00:59:37.560 --> 00:59:39.820 as being a chemist, I think.

NOTE Confidence: 0.8345129

00:59:39.820 --> 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 --> 00:59:53.636 DNA damaging agents can cause cancer,

NOTE Confidence: 0.81077635

00:59:53.640 --> 00:59:57.630 but there also used to treat cancer.

NOTE Confidence: 0.81077635

00:59:57.630 --> 00:59:59.680 Is there any thought? Is there

NOTE Confidence: 0.81077635

00:59:59.680 --> 01:00:01.380 possibility of using these compounds

NOTE Confidence: 0.8513931

01:00:01.380 --> 01:00:02.748 therapeutically? Absolutely yeah, that's

NOTE Confidence: 0.8513931

01:00:02.750 --> 01:00:04.450 something we're very excited about,

NOTE Confidence: 0.8513931

01:00:04.450 --> 01:00:06.496 so I didn't get into it.

NOTE Confidence: 0.8513931

01:00:06.500 --> 01:00:08.614 You know, one of the challenges that

NOTE Confidence: 0.8513931

01:00:08.614 --> 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 --> 01:00:15.448 a general chemistry to make these

NOTE Confidence: 0.8513931

01:00:15.448 --> 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 --> 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 --> 01:00:32.616 you know, optimize the properties of

NOTE Confidence: 0.8513931

01:00:32.616 --> 01:00:34.369 these molecules a little bit more.

NOTE Confidence: 0.8513931

01:00:34.370 --> 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 --> 01:00:40.178 but there's a mechanism by which

NOTE Confidence: 0.8513931

01:00:40.178 --> 01:00:42.322 we can gauge the activity of the

NOTE Confidence: 0.8513931

01:00:42.322 --> 01:00:44.037 molecule and potentially target it,

NOTE Confidence: 0.8513931

01:00:44.040 --> 01:00:45.550 and so there's a lot.

NOTE Confidence: 0.8513931

01:00:45.550 --> 01:00:47.958 Yeah, there's a lot that we can do,

NOTE Confidence: 0.8513931

01:00:47.960 --> 01:00:49.778 and that's sort of the phase

NOTE Confidence: 0.8513931

01:00:49.778 --> 01:00:51.280 that we're entering into with

NOTE Confidence: 0.8546458

01:00:51.280 --> 01:00:53.092 the project traffic we are after

NOTE Confidence: 0.8546458

01:00:53.092 --> 01:00:54.606 1:00 o'clock, so if people

NOTE Confidence: 0.8546458

01:00:54.606 --> 01:00:56.116 have other questions for Seth,

NOTE Confidence: 0.8546458

01:00:56.120 --> 01:00:59.016 just email him I'm sure. Be happy too.

NOTE Confidence: 0.8546458

01:00:59.016 --> 01:01:01.326 Talking thank both speakers for

NOTE Confidence: 0.8546458

01:01:01.326 --> 01:01:03.600 really stimulating talk today. Thank

NOTE Confidence: 0.8330914

01:01:03.600 --> 01:01:05.049 you thanks everyone.