WEBVTT

NOTE duration: ”01:06:21.866”

NOTE Confidence: 0.948604

00:00:00.240 --> 00:00:02.320 So doctor Frank McCormick is

NOTE Confidence: 0.948604

00:00:02.320 --> 00:00:03.679 the chair of tumor biology

NOTE Confidence: 0.948604

00:00:03.679 --> 00:00:05.299 and cancer research at UCSF.

NOTE Confidence: 0.9633486

00:00:06.000 --> 00:00:07.120 He's had a long and

NOTE Confidence: 0.9633486

00:00:07.120 --> 00:00:09.280 storied career in biotech before

NOTE Confidence: 0.9633486

00:00:09.280 --> 00:00:11.039 coming back to academia, perhaps

NOTE Confidence: 0.9633486

00:00:11.039 --> 00:00:11.700 most notably,

NOTE Confidence: 0.9011051

00:00:12.639 --> 00:00:14.799 founder and CSO at Onyx

NOTE Confidence: 0.9011051

00:00:14.799 --> 00:00:15.299 Pharmaceuticals,

NOTE Confidence: 0.91319346

00:00:15.995 --> 00:00:18.075 which, develops sorafenib, the RAF

NOTE Confidence: 0.91319346

00:00:18.075 --> 00:00:19.775 inhibitor, and also palbasiclib,

NOTE Confidence: 0.9819434

00:00:20.075 --> 00:00:21.695 the CDK four six inhibitor.

NOTE Confidence: 0.9809869

00:00:23.755 --> 00:00:24.795 On top of that, he's

NOTE Confidence: 0.9809869

00:00:24.795 --> 00:00:26.555 been leading the RAS initiative

NOTE Confidence: 0.9809869

00:00:26.555 --> 00:00:27.915 at the NCI for over

NOTE Confidence: 0.9809869

00:00:27.915 --> 00:00:28.974 a decade now.

NOTE Confidence: 0.9851055

00:00:29.520 --> 00:00:31.200 And, I think, you know,

NOTE Confidence: 0.9851055

00:00:31.200 --> 00:00:33.040 most notably not most notably,

NOTE Confidence: 0.9851055

00:00:33.040 --> 00:00:34.580 but outside of his contributions

NOTE Confidence: 0.9851055

00:00:34.800 --> 00:00:35.380 to research,

NOTE Confidence: 0.98377335

00:00:36.720 --> 00:00:37.600 in my short time with

NOTE Confidence: 0.98377335

00:00:37.600 --> 00:00:38.560 him, I've learned that he's

NOTE Confidence: 0.98377335

00:00:38.560 --> 00:00:40.260 a a staunch proponent for,

NOTE Confidence: 0.9835978

00:00:41.120 --> 00:00:42.960 cancer research and for funding

NOTE Confidence: 0.9835978

00:00:42.960 --> 00:00:44.585 of scientists, which is more

NOTE Confidence: 0.9835978

00:00:44.585 --> 00:00:46.104 important now perhaps than ever.

NOTE Confidence: 0.9835978

00:00:46.104 --> 00:00:46.925 So please,

NOTE Confidence: 0.9782397

00:00:47.465 --> 00:00:48.585 join me in welcoming doctor

NOTE Confidence: 0.9782397

00:00:48.585 --> 00:00:49.325 Frank McCormack.

NOTE Confidence: 0.83274084

00:00:49.864 --> 00:00:50.845 Okay. That's awesome.

NOTE Confidence: 0.96899706

00:00:55.785 --> 00:00:57.065 That's a great introduction. Really

NOTE Confidence: 0.96899706

00:00:57.065 --> 00:00:57.945 brief. I like that. Thank

NOTE Confidence: 0.96899706

00:00:57.945 --> 00:00:58.445 you.

NOTE Confidence: 0.9793385

00:00:59.470 --> 00:01:00.110 And thanks a lot for

NOTE Confidence: 0.9793385

00:01:00.110 --> 00:01:00.910 inviting me. It's a real

NOTE Confidence: 0.9793385

00:01:00.910 --> 00:01:01.710 honor to be invited to

NOTE Confidence: 0.9793385

00:01:01.710 --> 00:01:02.450 come and talk

NOTE Confidence: 0.9128527

00:01:02.990 --> 00:01:04.030 back here again. But I

NOTE Confidence: 0.9128527

00:01:04.030 --> 00:01:05.390 came back here in, twenty

NOTE Confidence: 0.9128527

00:01:05.390 --> 00:01:06.270 nineteen was the last time

NOTE Confidence: 0.9128527

00:01:06.270 --> 00:01:07.390 I talked here. This is

NOTE Confidence: 0.9128527

00:01:07.390 --> 00:01:08.910 before the pandemic, which seems

NOTE Confidence: 0.9128527

00:01:08.910 --> 00:01:10.130 like a different world.

NOTE Confidence: 0.9104031

00:01:10.670 --> 00:01:12.050 But we survived the pandemic.

NOTE Confidence: 0.9104031

00:01:12.110 --> 00:01:13.390 We all survived Trump, I

NOTE Confidence: 0.9104031

00:01:13.390 --> 00:01:14.930 I hope. That's all.

NOTE Confidence: 0.76749945

00:01:16.975 --> 00:01:17.475 Anyway.

NOTE Confidence: 0.9347399

00:01:18.015 --> 00:01:18.975 Okay. So today, I'm gonna

NOTE Confidence: 0.9347399

00:01:18.975 --> 00:01:19.535 talk about,

NOTE Confidence: 0.8704829

00:01:20.495 --> 00:01:21.775 the the RAS pathway and

NOTE Confidence: 0.8704829

00:01:21.775 --> 00:01:22.275 specifically

NOTE Confidence: 0.8918756

00:01:22.575 --> 00:01:23.535 about a couple of drugs

NOTE Confidence: 0.8918756

00:01:23.535 --> 00:01:25.295 we developed that target KRAS

NOTE Confidence: 0.8918756

00:01:25.295 --> 00:01:25.795 cancers.

NOTE Confidence: 0.96382236

00:01:26.255 --> 00:01:27.135 But before I get into

NOTE Confidence: 0.96382236

00:01:27.135 --> 00:01:28.895 the drug, development and discovery

NOTE Confidence: 0.96382236

00:01:28.895 --> 00:01:29.909 part, I wanna give you

NOTE Confidence: 0.96382236

00:01:29.909 --> 00:01:30.990 a bit of background on

NOTE Confidence: 0.96382236

00:01:30.990 --> 00:01:32.590 the MAP kinase pathway in

NOTE Confidence: 0.96382236

00:01:32.590 --> 00:01:33.630 a few contexts, which are

NOTE Confidence: 0.96382236

00:01:33.630 --> 00:01:35.229 slightly outside of cancer and

NOTE Confidence: 0.96382236

00:01:35.229 --> 00:01:36.110 areas you may not be

NOTE Confidence: 0.96382236

00:01:36.110 --> 00:01:37.390 as familiar with because this

NOTE Confidence: 0.96382236

00:01:37.390 --> 00:01:39.149 pathway is involved in, in

NOTE Confidence: 0.96382236

00:01:39.149 --> 00:01:40.289 several different indications,

NOTE Confidence: 0.99085444

00:01:41.390 --> 00:01:42.829 beyond its well known role

NOTE Confidence: 0.99085444

00:01:42.829 --> 00:01:43.649 in in cancer.

NOTE Confidence: 0.91870034

00:01:44.935 --> 00:01:46.455 So that's, San Francisco as

NOTE Confidence: 0.91870034

00:01:46.455 --> 00:01:47.335 you can see, and,

NOTE Confidence: 0.980669

00:01:48.215 --> 00:01:49.815 these are my disclosures. And

NOTE Confidence: 0.980669

00:01:49.815 --> 00:01:51.015 to distract you from reading

NOTE Confidence: 0.980669

00:01:51.015 --> 00:01:52.375 them, the picture below is

NOTE Confidence: 0.980669

00:01:52.375 --> 00:01:53.815 the is the building,

NOTE Confidence: 0.9449405

00:01:54.215 --> 00:01:55.975 in Frederick, Maryland, where I've

NOTE Confidence: 0.9449405

00:01:55.975 --> 00:01:57.015 been spending a week a

NOTE Confidence: 0.9449405

00:01:57.015 --> 00:01:58.190 month for the last ten

NOTE Confidence: 0.9449405

00:01:58.190 --> 00:01:59.630 years, working on a project

NOTE Confidence: 0.9449405

00:01:59.630 --> 00:02:00.590 that Harold Varmus,

NOTE Confidence: 0.9297391

00:02:01.550 --> 00:02:03.409 initiated, really, to target,

NOTE Confidence: 0.9298796

00:02:03.870 --> 00:02:05.950 pancreas cancer primarily, another KRAS

NOTE Confidence: 0.9298796

00:02:05.950 --> 00:02:07.470 driven, cancers. Because at that

NOTE Confidence: 0.9298796

00:02:07.470 --> 00:02:08.990 time in twenty thirteen when

NOTE Confidence: 0.9298796

00:02:08.990 --> 00:02:10.110 we started, we had nothing

NOTE Confidence: 0.9298796

00:02:10.110 --> 00:02:11.490 for those patients at all.

NOTE Confidence: 0.9298796

00:02:11.745 --> 00:02:13.444 So he basically assigned

NOTE Confidence: 0.91788596

00:02:13.905 --> 00:02:15.745 fifty people from an from

NOTE Confidence: 0.91788596

00:02:15.745 --> 00:02:17.185 a a contract with the

NOTE Confidence: 0.91788596

00:02:17.185 --> 00:02:17.685 NCI

NOTE Confidence: 0.93992525

00:02:18.065 --> 00:02:19.185 and told them, okay. You

NOTE Confidence: 0.93992525

00:02:19.185 --> 00:02:19.985 guys are gonna work on

NOTE Confidence: 0.93992525

00:02:19.985 --> 00:02:21.584 RAS, and, he asked me

NOTE Confidence: 0.93992525

00:02:21.584 --> 00:02:22.885 to be the project leader.

NOTE Confidence: 0.93992525

00:02:23.025 --> 00:02:24.065 So I've been going there

NOTE Confidence: 0.93992525

00:02:24.065 --> 00:02:24.625 every every,

NOTE Confidence: 0.9744959

00:02:25.185 --> 00:02:26.065 every month or so for

NOTE Confidence: 0.9744959

00:02:26.065 --> 00:02:27.284 the last, ten years.

NOTE Confidence: 0.95447564

00:02:27.960 --> 00:02:29.080 And I'm very proud to

NOTE Confidence: 0.95447564

00:02:29.080 --> 00:02:30.280 say that we have actually

NOTE Confidence: 0.95447564

00:02:30.280 --> 00:02:32.440 developed three drugs from that

NOTE Confidence: 0.95447564

00:02:32.440 --> 00:02:34.040 initiative, which are now in

NOTE Confidence: 0.95447564

00:02:34.040 --> 00:02:35.160 clinical trials, and I'll tell

NOTE Confidence: 0.95447564

00:02:35.160 --> 00:02:36.120 you about two of them

NOTE Confidence: 0.95447564

00:02:36.120 --> 00:02:37.000 in the second part of

NOTE Confidence: 0.95447564

00:02:37.000 --> 00:02:38.600 my talk. So just as

NOTE Confidence: 0.95447564

00:02:38.600 --> 00:02:39.945 a preview, one is a

NOTE Confidence: 0.95447564

00:02:40.185 --> 00:02:42.025 a KRAS G12 c inhibitor,

NOTE Confidence: 0.95447564

00:02:42.025 --> 00:02:43.145 which is the on stage

NOTE Confidence: 0.95447564

00:02:43.145 --> 00:02:44.665 of of KRAS, which hasn't

NOTE Confidence: 0.95447564

00:02:44.665 --> 00:02:46.105 hasn't been done before. And

NOTE Confidence: 0.95447564

00:02:46.105 --> 00:02:46.745 the other one is a

NOTE Confidence: 0.95447564

00:02:46.745 --> 00:02:47.805 drug that prevents

NOTE Confidence: 0.9494652

00:02:48.105 --> 00:02:49.625 RAS proteins activating p I

NOTE Confidence: 0.9494652

00:02:49.625 --> 00:02:50.985 three kinase, and we think

NOTE Confidence: 0.9494652

00:02:50.985 --> 00:02:52.025 will be useful in a

NOTE Confidence: 0.9494652

00:02:52.025 --> 00:02:53.460 whole range of indications. The

NOTE Confidence: 0.9494652

00:02:53.460 --> 00:02:54.340 third one, which I won't

NOTE Confidence: 0.9494652

00:02:54.340 --> 00:02:55.700 talk about, is a pan

NOTE Confidence: 0.9494652

00:02:55.700 --> 00:02:57.320 KRAS drug, which is, also

NOTE Confidence: 0.9494652

00:02:57.460 --> 00:02:58.520 now in the clinic.

NOTE Confidence: 0.7946709

00:03:00.740 --> 00:03:01.560 K. So,

NOTE Confidence: 0.7476016

00:03:09.925 --> 00:03:10.985 Oh, I'm I'm sorry.

NOTE Confidence: 0.89491826

00:03:11.445 --> 00:03:13.205 Using the wrong advancing system.

NOTE Confidence: 0.89491826

00:03:13.205 --> 00:03:13.705 Okay.

NOTE Confidence: 0.9967356

00:03:15.685 --> 00:03:16.185 Okay.

NOTE Confidence: 0.9776497

00:03:16.965 --> 00:03:17.865 Now I'm set.

NOTE Confidence: 0.92788595

00:03:18.245 --> 00:03:18.745 So,

NOTE Confidence: 0.95052093

00:03:19.410 --> 00:03:21.090 again, introduction to the, the

NOTE Confidence: 0.95052093

00:03:21.090 --> 00:03:22.770 RAS pathway in normal cells.

NOTE Confidence: 0.95052093

00:03:22.770 --> 00:03:23.889 And I wanna stress that

NOTE Confidence: 0.95052093

00:03:23.889 --> 00:03:25.330 the only pathway that RAS

NOTE Confidence: 0.95052093

00:03:25.330 --> 00:03:27.169 proteins activates in normal cells

NOTE Confidence: 0.95052093

00:03:27.169 --> 00:03:28.370 is the RAS MAP kinase

NOTE Confidence: 0.95052093

00:03:28.370 --> 00:03:29.330 pathway as far as I

NOTE Confidence: 0.95052093

00:03:29.330 --> 00:03:30.690 know. No evidence for any

NOTE Confidence: 0.95052093

00:03:30.690 --> 00:03:32.630 other RAS effectors being important

NOTE Confidence: 0.95052093

00:03:32.770 --> 00:03:34.185 in normal cells. If anybody

NOTE Confidence: 0.95052093

00:03:34.185 --> 00:03:35.485 has information or,

NOTE Confidence: 0.9614311

00:03:35.865 --> 00:03:37.065 wants to contradict that, I'd

NOTE Confidence: 0.9614311

00:03:37.065 --> 00:03:37.945 be delighted to hear about

NOTE Confidence: 0.9614311

00:03:37.945 --> 00:03:39.225 it, but, I'm pretty sure

NOTE Confidence: 0.9614311

00:03:39.225 --> 00:03:40.585 that's the only pathway the

NOTE Confidence: 0.9614311

00:03:40.585 --> 00:03:41.405 RAS activates.

NOTE Confidence: 0.9808615

00:03:42.265 --> 00:03:42.505 So,

NOTE Confidence: 0.7938001

00:03:43.385 --> 00:03:44.345 you're all being familiar with

NOTE Confidence: 0.7938001

00:03:44.345 --> 00:03:45.545 the general concept here that

NOTE Confidence: 0.7938001

00:03:45.545 --> 00:03:46.765 RTKs activate,

NOTE Confidence: 0.90442234

00:03:47.430 --> 00:03:49.349 Sos one and other related

NOTE Confidence: 0.90442234

00:03:49.349 --> 00:03:50.550 proteins to put RAS from

NOTE Confidence: 0.90442234

00:03:50.550 --> 00:03:51.370 the off state,

NOTE Confidence: 0.92221236

00:03:51.750 --> 00:03:53.430 into the on state where

NOTE Confidence: 0.92221236

00:03:53.430 --> 00:03:54.709 RAS engages the map kinase

NOTE Confidence: 0.92221236

00:03:54.709 --> 00:03:55.209 pathway,

NOTE Confidence: 0.9608798

00:03:55.910 --> 00:03:57.190 and then gets turned off

NOTE Confidence: 0.9608798

00:03:57.190 --> 00:03:58.470 by gaps such as these

NOTE Confidence: 0.9608798

00:03:58.470 --> 00:03:59.670 three here, which I'll talk

NOTE Confidence: 0.9608798

00:03:59.670 --> 00:04:00.629 a bit more about in

NOTE Confidence: 0.9608798

00:04:00.629 --> 00:04:01.769 just in just a moment.

NOTE Confidence: 0.9182158

00:04:02.265 --> 00:04:04.105 But although its pathway is

NOTE Confidence: 0.9182158

00:04:04.105 --> 00:04:05.224 well trodden, it's in the

NOTE Confidence: 0.9182158

00:04:05.224 --> 00:04:06.504 textbooks, there's still lots of

NOTE Confidence: 0.9182158

00:04:06.504 --> 00:04:07.465 elements to this pathway we

NOTE Confidence: 0.9182158

00:04:07.465 --> 00:04:08.905 don't really understand. In fact,

NOTE Confidence: 0.9182158

00:04:08.905 --> 00:04:09.784 most of it we don't

NOTE Confidence: 0.9182158

00:04:09.784 --> 00:04:11.485 understand really in in-depth.

NOTE Confidence: 0.94661754

00:04:12.584 --> 00:04:14.265 For example, a critical part

NOTE Confidence: 0.94661754

00:04:14.265 --> 00:04:15.224 of this pathway is the

NOTE Confidence: 0.94661754

00:04:15.224 --> 00:04:17.005 tyrosine phosphatase SHIP two,

NOTE Confidence: 0.9202849

00:04:17.440 --> 00:04:18.820 which is thought to dephosphorylate

NOTE Confidence: 0.9202849

00:04:18.960 --> 00:04:20.880 a critical substrate and enable

NOTE Confidence: 0.9202849

00:04:20.880 --> 00:04:21.860 all this to happen.

NOTE Confidence: 0.98937136

00:04:22.400 --> 00:04:23.440 We don't think that's true.

NOTE Confidence: 0.98937136

00:04:23.440 --> 00:04:24.560 We don't think SHIP two

NOTE Confidence: 0.98937136

00:04:24.560 --> 00:04:25.860 phosphatase is actually,

NOTE Confidence: 0.9808802

00:04:26.480 --> 00:04:27.760 important as an activity, but

NOTE Confidence: 0.9808802

00:04:27.760 --> 00:04:29.300 the protein definitely is important,

NOTE Confidence: 0.9808802

00:04:29.600 --> 00:04:30.820 and we don't really understand,

NOTE Confidence: 0.9808802

00:04:30.960 --> 00:04:31.779 how it works.

NOTE Confidence: 0.8609334

00:04:32.414 --> 00:04:33.634 We don't really understand,

NOTE Confidence: 0.97005415

00:04:34.414 --> 00:04:35.455 which gaps are in play

NOTE Confidence: 0.97005415

00:04:35.455 --> 00:04:37.055 in different cell types. We

NOTE Confidence: 0.97005415

00:04:37.055 --> 00:04:38.735 don't really understand how this

NOTE Confidence: 0.97005415

00:04:38.735 --> 00:04:40.414 complex is regulated to regulate

NOTE Confidence: 0.97005415

00:04:40.414 --> 00:04:42.175 BAP kinase, and so on.

NOTE Confidence: 0.97005415

00:04:42.175 --> 00:04:43.375 And if you actually understand

NOTE Confidence: 0.97005415

00:04:43.375 --> 00:04:44.095 or or look at the

NOTE Confidence: 0.97005415

00:04:44.095 --> 00:04:45.634 details by which RAS activates

NOTE Confidence: 0.97005415

00:04:45.775 --> 00:04:47.134 RAF, for example, it's really

NOTE Confidence: 0.97005415

00:04:47.134 --> 00:04:48.870 complicated. There's multiple steps.

NOTE Confidence: 0.92398816

00:04:49.250 --> 00:04:50.950 This is a massive oversimplification.

NOTE Confidence: 0.94775444

00:04:51.810 --> 00:04:53.250 But still, the the hierarchy

NOTE Confidence: 0.94775444

00:04:53.250 --> 00:04:54.450 is definitely correct, but the

NOTE Confidence: 0.94775444

00:04:54.450 --> 00:04:55.730 details are yet to be

NOTE Confidence: 0.94775444

00:04:55.730 --> 00:04:56.470 filled in.

NOTE Confidence: 0.9064087

00:04:57.089 --> 00:04:57.970 So just to get you

NOTE Confidence: 0.9064087

00:04:57.970 --> 00:04:58.690 all on the same page,

NOTE Confidence: 0.9064087

00:04:58.690 --> 00:04:59.490 if you take a cell

NOTE Confidence: 0.9064087

00:04:59.490 --> 00:05:01.110 line, add EGF, for example,

NOTE Confidence: 0.9064087

00:05:01.404 --> 00:05:02.945 you activate RAS GDP

NOTE Confidence: 0.9000193

00:05:03.565 --> 00:05:04.925 levels within about about one

NOTE Confidence: 0.9000193

00:05:04.925 --> 00:05:06.365 minute. So this pathway gets

NOTE Confidence: 0.9000193

00:05:06.365 --> 00:05:07.404 kicked on, and then it

NOTE Confidence: 0.9000193

00:05:07.404 --> 00:05:08.525 gets turned off again in

NOTE Confidence: 0.9000193

00:05:08.525 --> 00:05:09.985 about the same time frame,

NOTE Confidence: 0.95745337

00:05:10.285 --> 00:05:10.604 by,

NOTE Confidence: 0.82392514

00:05:11.324 --> 00:05:12.945 in in the gaps such

NOTE Confidence: 0.82392514

00:05:13.005 --> 00:05:14.764 as neurofibromine and RAS, a

NOTE Confidence: 0.82392514

00:05:14.764 --> 00:05:16.225 two, turning off again.

NOTE Confidence: 0.98168564

00:05:16.550 --> 00:05:17.589 And the spike of RAS

NOTE Confidence: 0.98168564

00:05:17.589 --> 00:05:18.089 activity

NOTE Confidence: 0.95938206

00:05:18.470 --> 00:05:19.670 translates to a spike of

NOTE Confidence: 0.95938206

00:05:19.670 --> 00:05:20.570 phospho work,

NOTE Confidence: 0.90805167

00:05:21.110 --> 00:05:22.070 as a as a signal

NOTE Confidence: 0.90805167

00:05:22.070 --> 00:05:23.270 goes down the pathway, and

NOTE Confidence: 0.90805167

00:05:23.270 --> 00:05:24.390 the end result of this,

NOTE Confidence: 0.90805167

00:05:24.710 --> 00:05:25.210 pathway,

NOTE Confidence: 0.9840727

00:05:25.670 --> 00:05:26.950 can affect all kinds of

NOTE Confidence: 0.9840727

00:05:26.950 --> 00:05:28.310 different aspects of cell growth

NOTE Confidence: 0.9840727

00:05:28.310 --> 00:05:28.970 and metabolism

NOTE Confidence: 0.5615036

00:05:29.430 --> 00:05:29.930 differentiation

NOTE Confidence: 0.94877476

00:05:30.230 --> 00:05:31.589 and even cognition, as I'll

NOTE Confidence: 0.94877476

00:05:31.589 --> 00:05:33.015 mention later. But the output

NOTE Confidence: 0.94877476

00:05:33.015 --> 00:05:33.975 of the pathway is very

NOTE Confidence: 0.94877476

00:05:33.975 --> 00:05:35.495 much context dependent even though

NOTE Confidence: 0.94877476

00:05:35.495 --> 00:05:36.615 the pathway is, you know,

NOTE Confidence: 0.94877476

00:05:36.615 --> 00:05:38.395 highly conserved between different tissues.

NOTE Confidence: 0.928947

00:05:39.255 --> 00:05:40.535 Using a phospho ERK sensor,

NOTE Confidence: 0.928947

00:05:40.535 --> 00:05:41.335 you can see that when

NOTE Confidence: 0.928947

00:05:41.335 --> 00:05:42.375 you add growth factors to

NOTE Confidence: 0.928947

00:05:42.375 --> 00:05:43.255 cells, you get a spike

NOTE Confidence: 0.928947

00:05:43.255 --> 00:05:44.455 of signaling down the pathway.

NOTE Confidence: 0.928947

00:05:44.455 --> 00:05:45.860 This is phospho ERK coming

NOTE Confidence: 0.928947

00:05:45.860 --> 00:05:46.660 on and off again in

NOTE Confidence: 0.928947

00:05:46.660 --> 00:05:48.200 a very nice controlled spike.

NOTE Confidence: 0.98981

00:05:48.740 --> 00:05:49.800 If you add more EGF,

NOTE Confidence: 0.98981

00:05:49.860 --> 00:05:51.300 you get more spikes. So

NOTE Confidence: 0.98981

00:05:51.300 --> 00:05:52.260 each of these spikes is

NOTE Confidence: 0.98981

00:05:52.260 --> 00:05:53.720 the same size and duration,

NOTE Confidence: 0.9243591

00:05:54.339 --> 00:05:55.940 and is highly regulated. It's

NOTE Confidence: 0.9243591

00:05:55.940 --> 00:05:57.000 just you get more,

NOTE Confidence: 0.9397259

00:05:57.805 --> 00:05:59.004 spikes if you have more

NOTE Confidence: 0.9397259

00:05:59.004 --> 00:06:00.365 more growth factors. So in

NOTE Confidence: 0.9397259

00:06:00.365 --> 00:06:01.724 normal cells, this pathway is

NOTE Confidence: 0.9397259

00:06:01.724 --> 00:06:03.724 extremely precisely regulated, so on

NOTE Confidence: 0.9397259

00:06:03.724 --> 00:06:05.245 and off very quickly. And

NOTE Confidence: 0.9397259

00:06:05.245 --> 00:06:05.745 this,

NOTE Confidence: 0.9199698

00:06:06.125 --> 00:06:07.164 pattern will be different with

NOTE Confidence: 0.9199698

00:06:07.164 --> 00:06:08.525 different growth factors. The duration

NOTE Confidence: 0.9199698

00:06:08.525 --> 00:06:09.724 will be different and so

NOTE Confidence: 0.9199698

00:06:09.724 --> 00:06:10.525 on, but,

NOTE Confidence: 0.99316996

00:06:11.085 --> 00:06:12.384 a whole number of proteins

NOTE Confidence: 0.91160923

00:06:12.960 --> 00:06:14.080 jump in to regulate this

NOTE Confidence: 0.91160923

00:06:14.080 --> 00:06:15.540 pathway with great precision.

NOTE Confidence: 0.90712136

00:06:17.200 --> 00:06:18.640 We've studied this pathway in

NOTE Confidence: 0.90712136

00:06:18.640 --> 00:06:20.000 cancer, obviously, but also in,

NOTE Confidence: 0.90712136

00:06:20.320 --> 00:06:21.300 in Noonan syndrome,

NOTE Confidence: 0.94347084

00:06:21.920 --> 00:06:23.520 which is, a disease in

NOTE Confidence: 0.94347084

00:06:23.520 --> 00:06:24.420 which individuals,

NOTE Confidence: 0.9723017

00:06:25.425 --> 00:06:27.105 inherit a germline mutation in

NOTE Confidence: 0.9723017

00:06:27.105 --> 00:06:27.904 one of the genes in

NOTE Confidence: 0.9723017

00:06:27.904 --> 00:06:28.565 this pathway.

NOTE Confidence: 0.92586577

00:06:29.025 --> 00:06:30.065 And we like this studying

NOTE Confidence: 0.92586577

00:06:30.065 --> 00:06:31.665 this disease because these are

NOTE Confidence: 0.92586577

00:06:31.665 --> 00:06:33.185 slightly activated versions of a

NOTE Confidence: 0.92586577

00:06:33.185 --> 00:06:34.705 normal counterpart but in a

NOTE Confidence: 0.92586577

00:06:34.705 --> 00:06:36.464 normal cell background. So unlike

NOTE Confidence: 0.92586577

00:06:36.464 --> 00:06:37.585 cancer where everything has gone

NOTE Confidence: 0.92586577

00:06:37.585 --> 00:06:39.250 to hell, these are wild

NOTE Confidence: 0.92586577

00:06:39.250 --> 00:06:40.770 type cells with just one

NOTE Confidence: 0.92586577

00:06:40.770 --> 00:06:42.230 slight gain of function mutation.

NOTE Confidence: 0.91257805

00:06:42.610 --> 00:06:43.650 And these gain of functions

NOTE Confidence: 0.91257805

00:06:43.650 --> 00:06:44.850 can happen in pretty much

NOTE Confidence: 0.91257805

00:06:44.850 --> 00:06:46.550 every part of this pathway.

NOTE Confidence: 0.8995763

00:06:46.930 --> 00:06:48.290 And they're all weak alleles

NOTE Confidence: 0.8995763

00:06:48.290 --> 00:06:50.210 that don't cause cancer, and,

NOTE Confidence: 0.9870076

00:06:50.930 --> 00:06:52.690 individuals can survive these activating

NOTE Confidence: 0.9870076

00:06:52.690 --> 00:06:53.875 events, but they end up

NOTE Confidence: 0.9870076

00:06:53.875 --> 00:06:54.995 with a very similar kind

NOTE Confidence: 0.9870076

00:06:54.995 --> 00:06:55.574 of phenotype.

NOTE Confidence: 0.96686584

00:06:56.275 --> 00:06:58.115 These individuals have distinct facial

NOTE Confidence: 0.96686584

00:06:58.115 --> 00:06:59.074 features, as you can see

NOTE Confidence: 0.96686584

00:06:59.074 --> 00:07:00.754 here. They have some cardiac

NOTE Confidence: 0.96686584

00:07:00.754 --> 00:07:02.115 problems, and they have short

NOTE Confidence: 0.96686584

00:07:02.115 --> 00:07:02.615 stature.

NOTE Confidence: 0.96649724

00:07:03.314 --> 00:07:04.435 This is a very common

NOTE Confidence: 0.96649724

00:07:04.435 --> 00:07:05.714 disease. Actually, one in a

NOTE Confidence: 0.96649724

00:07:05.714 --> 00:07:07.235 thousand people or more have

NOTE Confidence: 0.96649724

00:07:07.235 --> 00:07:09.190 Noonan syndrome. It's mild, not

NOTE Confidence: 0.96649724

00:07:09.190 --> 00:07:10.230 life threatening, but it does

NOTE Confidence: 0.96649724

00:07:10.230 --> 00:07:11.930 have phenotypes and consequences.

NOTE Confidence: 0.91624147

00:07:12.710 --> 00:07:13.669 So based on this, you

NOTE Confidence: 0.91624147

00:07:13.669 --> 00:07:14.710 say this pathway is involved

NOTE Confidence: 0.91624147

00:07:14.870 --> 00:07:15.990 the RAS pathway is involved

NOTE Confidence: 0.91624147

00:07:15.990 --> 00:07:18.230 in differentiation and development because

NOTE Confidence: 0.91624147

00:07:18.230 --> 00:07:19.190 these are the effects you

NOTE Confidence: 0.91624147

00:07:19.190 --> 00:07:20.250 see when you hyperactivate

NOTE Confidence: 0.7130652

00:07:20.870 --> 00:07:21.530 this pathway.

NOTE Confidence: 0.956684

00:07:22.845 --> 00:07:23.724 And the frequency of this

NOTE Confidence: 0.956684

00:07:23.724 --> 00:07:24.764 disease is much more than

NOTE Confidence: 0.956684

00:07:24.764 --> 00:07:25.965 you'd expect just from the

NOTE Confidence: 0.956684

00:07:25.965 --> 00:07:28.365 mutation rate, in in, in

NOTE Confidence: 0.956684

00:07:28.365 --> 00:07:29.565 any particular gene in the

NOTE Confidence: 0.956684

00:07:29.565 --> 00:07:30.065 genome.

NOTE Confidence: 0.94079536

00:07:30.444 --> 00:07:32.205 And the the, the reason

NOTE Confidence: 0.94079536

00:07:32.205 --> 00:07:33.884 for that, or a potential

NOTE Confidence: 0.94079536

00:07:33.884 --> 00:07:35.405 reason was revealed recently by

NOTE Confidence: 0.94079536

00:07:35.405 --> 00:07:36.305 a paper that

NOTE Confidence: 0.91584927

00:07:36.670 --> 00:07:37.970 is, I think, the really

NOTE Confidence: 0.91584927

00:07:38.190 --> 00:07:39.630 game changing paper to me,

NOTE Confidence: 0.91584927

00:07:39.630 --> 00:07:41.390 and it's slightly gross. So

NOTE Confidence: 0.91584927

00:07:41.390 --> 00:07:42.290 hang with me.

NOTE Confidence: 0.966486

00:07:42.990 --> 00:07:43.950 So this is a study

NOTE Confidence: 0.966486

00:07:43.950 --> 00:07:44.610 in which,

NOTE Confidence: 0.7855523

00:07:45.230 --> 00:07:46.690 Anne Gereilly in Oxford,

NOTE Confidence: 0.97280616

00:07:47.150 --> 00:07:48.190 did a study in which

NOTE Confidence: 0.97280616

00:07:48.190 --> 00:07:48.510 she,

NOTE Confidence: 0.9955842

00:07:48.990 --> 00:07:49.515 looked at

NOTE Confidence: 0.9959089

00:07:50.155 --> 00:07:52.235 clonal expansion of cells in

NOTE Confidence: 0.9959089

00:07:52.235 --> 00:07:53.535 aging male testes.

NOTE Confidence: 0.9157818

00:07:54.235 --> 00:07:55.195 So what she did was

NOTE Confidence: 0.9157818

00:07:55.195 --> 00:07:56.635 took slice of testes from,

NOTE Confidence: 0.9157818

00:07:56.875 --> 00:07:58.315 from elder men. This is

NOTE Confidence: 0.9157818

00:07:58.315 --> 00:07:59.055 a seventy,

NOTE Confidence: 0.9125354

00:07:59.595 --> 00:08:00.555 eighty year old, ninety year

NOTE Confidence: 0.9125354

00:08:00.555 --> 00:08:01.915 old guy, and then did

NOTE Confidence: 0.9125354

00:08:01.915 --> 00:08:03.355 deep sequencing on little regions

NOTE Confidence: 0.9125354

00:08:03.355 --> 00:08:04.175 of the testis,

NOTE Confidence: 0.931018

00:08:05.060 --> 00:08:06.180 sequencing for genes in the

NOTE Confidence: 0.931018

00:08:06.180 --> 00:08:07.780 MAP kinase pathway, so, like,

NOTE Confidence: 0.931018

00:08:07.780 --> 00:08:09.540 sixty different genes. So each

NOTE Confidence: 0.931018

00:08:09.540 --> 00:08:11.220 of these circles here represents

NOTE Confidence: 0.931018

00:08:11.220 --> 00:08:13.140 clonal expansion of a cell

NOTE Confidence: 0.931018

00:08:13.140 --> 00:08:14.520 in the testis. Okay?

NOTE Confidence: 0.94823086

00:08:15.140 --> 00:08:16.340 And the colors are coded

NOTE Confidence: 0.94823086

00:08:16.340 --> 00:08:17.400 by which of the genes

NOTE Confidence: 0.92203075

00:08:17.860 --> 00:08:19.220 are named on this list

NOTE Confidence: 0.92203075

00:08:19.220 --> 00:08:21.005 here. So in this particular,

NOTE Confidence: 0.89640576

00:08:21.544 --> 00:08:23.384 slice to this test, as

NOTE Confidence: 0.89640576

00:08:23.384 --> 00:08:24.185 you can see, there are

NOTE Confidence: 0.89640576

00:08:24.185 --> 00:08:25.805 all kinds of focal amplifications

NOTE Confidence: 0.8170507

00:08:26.185 --> 00:08:28.044 of, of these cells,

NOTE Confidence: 0.99140763

00:08:28.505 --> 00:08:29.725 and the genes involved

NOTE Confidence: 0.68128866

00:08:30.425 --> 00:08:31.705 are genes in might may

NOTE Confidence: 0.68128866

00:08:31.705 --> 00:08:33.245 be a spec, FGF receptor,

NOTE Confidence: 0.68128866

00:08:33.304 --> 00:08:33.804 FGFR2,

NOTE Confidence: 0.9670347

00:08:34.425 --> 00:08:34.925 FGFR3,

NOTE Confidence: 0.9312119

00:08:36.120 --> 00:08:37.160 and most of the genes

NOTE Confidence: 0.9312119

00:08:37.160 --> 00:08:38.780 involved in syndrome, including,

NOTE Confidence: 0.55271375

00:08:39.400 --> 00:08:39.900 PTKN11,

NOTE Confidence: 0.8385575

00:08:40.280 --> 00:08:41.900 SHIP2, and and RAS.

NOTE Confidence: 0.9219421

00:08:42.920 --> 00:08:44.040 So the really interesting thing

NOTE Confidence: 0.9219421

00:08:44.040 --> 00:08:45.240 about this is that just

NOTE Confidence: 0.9219421

00:08:45.240 --> 00:08:46.679 like as in any other

NOTE Confidence: 0.9219421

00:08:46.679 --> 00:08:47.800 tissue, as you age, you

NOTE Confidence: 0.9219421

00:08:47.800 --> 00:08:49.304 get point mutations in RAS

NOTE Confidence: 0.9219421

00:08:49.304 --> 00:08:50.505 which and and RAS pathway,

NOTE Confidence: 0.9219421

00:08:50.505 --> 00:08:51.865 which cause clonal expansion of

NOTE Confidence: 0.9219421

00:08:51.865 --> 00:08:53.084 your cells in your body.

NOTE Confidence: 0.9219421

00:08:53.304 --> 00:08:54.184 These are the cells that

NOTE Confidence: 0.9219421

00:08:54.184 --> 00:08:55.005 make sperm.

NOTE Confidence: 0.9491853

00:08:55.625 --> 00:08:57.065 So these mutations, which are

NOTE Confidence: 0.9491853

00:08:57.065 --> 00:08:58.824 selected for for amplification in

NOTE Confidence: 0.9491853

00:08:58.824 --> 00:09:00.345 the testes, are transmitted to

NOTE Confidence: 0.9491853

00:09:00.345 --> 00:09:01.084 the offspring.

NOTE Confidence: 0.92415655

00:09:01.690 --> 00:09:03.050 And there, they they cause

NOTE Confidence: 0.92415655

00:09:03.050 --> 00:09:04.330 the syndrome, but the selection

NOTE Confidence: 0.92415655

00:09:04.330 --> 00:09:05.470 was actually in the testis

NOTE Confidence: 0.92415655

00:09:05.530 --> 00:09:07.050 of the, of the aging

NOTE Confidence: 0.92415655

00:09:07.050 --> 00:09:08.170 individual. So that's why they're

NOTE Confidence: 0.92415655

00:09:08.170 --> 00:09:09.130 much more frequent than you'd

NOTE Confidence: 0.92415655

00:09:09.130 --> 00:09:10.330 expect, and these are then

NOTE Confidence: 0.92415655

00:09:10.330 --> 00:09:12.250 disseminated throughout the population. So

NOTE Confidence: 0.92415655

00:09:12.250 --> 00:09:13.790 here we have human evolution,

NOTE Confidence: 0.99886984

00:09:14.330 --> 00:09:14.990 at work.

NOTE Confidence: 0.89292103

00:09:15.765 --> 00:09:18.005 So, again, Noonan syndrome is

NOTE Confidence: 0.89292103

00:09:18.005 --> 00:09:19.305 probably caused by these

NOTE Confidence: 0.8376129

00:09:19.684 --> 00:09:20.985 mutations in aging

NOTE Confidence: 0.8243284

00:09:21.445 --> 00:09:21.945 testes.

NOTE Confidence: 0.8946805

00:09:22.405 --> 00:09:23.305 Also, FGFR3

NOTE Confidence: 0.9986733

00:09:23.684 --> 00:09:24.184 mutations

NOTE Confidence: 0.9163684

00:09:24.485 --> 00:09:26.105 cause dwarfism, achondroplasia.

NOTE Confidence: 0.77133507

00:09:27.045 --> 00:09:28.265 And just as a sidebar,

NOTE Confidence: 0.77133507

00:09:28.565 --> 00:09:29.445 the company a company I

NOTE Confidence: 0.77133507

00:09:29.445 --> 00:09:30.665 cofounding for BridgeBio

NOTE Confidence: 0.92336917

00:09:31.070 --> 00:09:31.890 has an FTFR3 inhibitor,

NOTE Confidence: 0.9909571

00:09:32.990 --> 00:09:34.050 in clinical trials,

NOTE Confidence: 0.9783087

00:09:34.510 --> 00:09:36.589 for people with dwarfism, and

NOTE Confidence: 0.9783087

00:09:36.589 --> 00:09:38.910 amazingly, the drug accelerates growth

NOTE Confidence: 0.9783087

00:09:38.910 --> 00:09:40.350 of these individuals to normal

NOTE Confidence: 0.9783087

00:09:40.350 --> 00:09:42.209 growth rates without any toxicity

NOTE Confidence: 0.9783087

00:09:42.270 --> 00:09:43.230 because it's used at a

NOTE Confidence: 0.9783087

00:09:43.230 --> 00:09:44.455 very low dose. That'll be

NOTE Confidence: 0.9783087

00:09:44.455 --> 00:09:46.054 coming out soon, but that's

NOTE Confidence: 0.9783087

00:09:46.054 --> 00:09:47.115 just sidebar.

NOTE Confidence: 0.9318697

00:09:47.815 --> 00:09:49.115 Anyway, so,

NOTE Confidence: 0.92540514

00:09:50.615 --> 00:09:52.054 that that's the Nuna syndrome,

NOTE Confidence: 0.92540514

00:09:52.054 --> 00:09:53.015 and we've we've looked at

NOTE Confidence: 0.92540514

00:09:53.015 --> 00:09:54.135 all the genes that involved

NOTE Confidence: 0.92540514

00:09:54.135 --> 00:09:55.175 in the syndrome and have

NOTE Confidence: 0.92540514

00:09:55.175 --> 00:09:56.455 now have a mechanism for

NOTE Confidence: 0.92540514

00:09:56.455 --> 00:09:57.415 how each of these are

NOTE Confidence: 0.92540514

00:09:57.415 --> 00:09:58.774 activated except for SHIP two,

NOTE Confidence: 0.92540514

00:09:58.774 --> 00:10:00.500 which we're still working on.

NOTE Confidence: 0.93179435

00:10:01.760 --> 00:10:03.200 Now another another disease which

NOTE Confidence: 0.93179435

00:10:03.200 --> 00:10:04.400 is much more clinically serious

NOTE Confidence: 0.93179435

00:10:04.400 --> 00:10:04.980 is neurofibromasosis

NOTE Confidence: 0.9780353

00:10:05.679 --> 00:10:07.280 type one. So in this

NOTE Confidence: 0.9780353

00:10:07.280 --> 00:10:09.760 disease, individuals either inherit or

NOTE Confidence: 0.9780353

00:10:09.760 --> 00:10:10.800 acquire a,

NOTE Confidence: 0.9960395

00:10:11.360 --> 00:10:12.660 mutation in the neurofibromine

NOTE Confidence: 0.8728914

00:10:13.120 --> 00:10:13.620 gene.

NOTE Confidence: 0.9594818

00:10:13.955 --> 00:10:15.075 That's a gap that turns

NOTE Confidence: 0.9594818

00:10:15.075 --> 00:10:15.575 RAS

NOTE Confidence: 0.97353745

00:10:16.035 --> 00:10:17.155 off. So through loss of,

NOTE Confidence: 0.97353745

00:10:17.715 --> 00:10:18.215 neurofibromine,

NOTE Confidence: 0.8690197

00:10:18.915 --> 00:10:20.355 RAS protein starts to accumulate

NOTE Confidence: 0.8690197

00:10:20.355 --> 00:10:21.715 in the GTP bound state

NOTE Confidence: 0.8690197

00:10:21.715 --> 00:10:22.595 just as they as they

NOTE Confidence: 0.8690197

00:10:22.595 --> 00:10:23.715 do in cancer, but not

NOTE Confidence: 0.8690197

00:10:23.715 --> 00:10:24.995 as severe. Okay? So I've

NOTE Confidence: 0.8690197

00:10:24.995 --> 00:10:26.775 given a partial break here.

NOTE Confidence: 0.9503327

00:10:27.260 --> 00:10:28.220 So this is also pretty

NOTE Confidence: 0.9503327

00:10:28.220 --> 00:10:29.500 common. One in three thousand

NOTE Confidence: 0.9503327

00:10:29.500 --> 00:10:30.620 five hundred people. That's a

NOTE Confidence: 0.9503327

00:10:30.620 --> 00:10:31.899 hundred thousand people in the

NOTE Confidence: 0.9503327

00:10:31.899 --> 00:10:33.500 US have NF one disease

NOTE Confidence: 0.9503327

00:10:33.500 --> 00:10:34.720 of varying severity.

NOTE Confidence: 0.9966197

00:10:35.179 --> 00:10:36.640 The heterozygous state,

NOTE Confidence: 0.7762857

00:10:37.179 --> 00:10:39.040 the the phenotype is cognitive

NOTE Confidence: 0.7762857

00:10:39.260 --> 00:10:39.760 defects,

NOTE Confidence: 0.7662074

00:10:40.415 --> 00:10:41.875 vascular disease and osteoporosis.

NOTE Confidence: 0.89988923

00:10:43.214 --> 00:10:43.454 But,

NOTE Confidence: 0.9280754

00:10:44.334 --> 00:10:45.615 these, by far, the most

NOTE Confidence: 0.9280754

00:10:45.615 --> 00:10:46.894 problematic for the kids and

NOTE Confidence: 0.9280754

00:10:46.894 --> 00:10:48.334 the families are the cognitive

NOTE Confidence: 0.9280754

00:10:48.334 --> 00:10:50.035 defects because these kids have,

NOTE Confidence: 0.9280754

00:10:50.334 --> 00:10:52.175 autistic like phenotypes and that

NOTE Confidence: 0.9280754

00:10:52.175 --> 00:10:53.554 they have a disruptive behavior

NOTE Confidence: 0.9280754

00:10:53.750 --> 00:10:54.630 and are very difficult to

NOTE Confidence: 0.9280754

00:10:54.630 --> 00:10:55.829 deal with in a family

NOTE Confidence: 0.9280754

00:10:55.829 --> 00:10:57.110 situation. So this is a

NOTE Confidence: 0.9280754

00:10:57.110 --> 00:10:58.089 big problem.

NOTE Confidence: 0.8885479

00:10:59.110 --> 00:11:00.389 But worst yet for the

NOTE Confidence: 0.8885479

00:11:00.389 --> 00:11:01.910 kids, they lose a second

NOTE Confidence: 0.8885479

00:11:01.910 --> 00:11:02.410 allele,

NOTE Confidence: 0.81293404

00:11:02.790 --> 00:11:03.290 randomly.

NOTE Confidence: 0.9725998

00:11:03.750 --> 00:11:05.269 They get clonal growth of

NOTE Confidence: 0.9725998

00:11:05.269 --> 00:11:06.584 benign tumors, which can be

NOTE Confidence: 0.9725998

00:11:06.584 --> 00:11:08.024 either on the skin such

NOTE Confidence: 0.9725998

00:11:08.024 --> 00:11:09.165 as these dermal neurofibromas

NOTE Confidence: 0.98331356

00:11:09.865 --> 00:11:11.245 or plexiform neurofibromas

NOTE Confidence: 0.9936725

00:11:11.704 --> 00:11:12.925 that grow around nerves.

NOTE Confidence: 0.9590678

00:11:13.545 --> 00:11:14.745 Now these are benign, but

NOTE Confidence: 0.9590678

00:11:14.745 --> 00:11:16.105 as they grow over time,

NOTE Confidence: 0.9590678

00:11:16.105 --> 00:11:17.464 they can be extremely painful,

NOTE Confidence: 0.9590678

00:11:17.464 --> 00:11:18.505 and they can't often be

NOTE Confidence: 0.9590678

00:11:18.505 --> 00:11:19.785 surgically removed because they grow

NOTE Confidence: 0.9590678

00:11:19.785 --> 00:11:21.460 around nerves. So this is

NOTE Confidence: 0.9590678

00:11:21.460 --> 00:11:22.900 a really, awful disease, and

NOTE Confidence: 0.9590678

00:11:22.900 --> 00:11:24.260 it's a lifelong disease because,

NOTE Confidence: 0.9590678

00:11:24.580 --> 00:11:25.220 you know, this is a

NOTE Confidence: 0.9590678

00:11:25.220 --> 00:11:25.720 germline,

NOTE Confidence: 0.7613672

00:11:26.260 --> 00:11:26.760 mutation,

NOTE Confidence: 0.96688884

00:11:27.140 --> 00:11:28.020 and it just sort of

NOTE Confidence: 0.96688884

00:11:28.020 --> 00:11:29.559 get gets worse over time.

NOTE Confidence: 0.96688884

00:11:29.620 --> 00:11:30.760 These kids are also,

NOTE Confidence: 0.8306034

00:11:31.620 --> 00:11:33.000 at risk of some malignancies,

NOTE Confidence: 0.93027866

00:11:33.380 --> 00:11:33.880 including,

NOTE Confidence: 0.95482445

00:11:34.260 --> 00:11:35.965 those listed here. But the

NOTE Confidence: 0.95482445

00:11:35.965 --> 00:11:37.245 worst, which happens in about

NOTE Confidence: 0.95482445

00:11:37.245 --> 00:11:38.465 ten percent of the cases,

NOTE Confidence: 0.95482445

00:11:38.765 --> 00:11:40.125 they can lose genes in

NOTE Confidence: 0.95482445

00:11:40.125 --> 00:11:42.605 the polycomb repressive complex and,

NOTE Confidence: 0.8912431

00:11:43.005 --> 00:11:44.605 become, malignant. And these are

NOTE Confidence: 0.8912431

00:11:44.605 --> 00:11:46.785 malignant peripheral nerve seed tumors,

NOTE Confidence: 0.8912431

00:11:46.845 --> 00:11:48.065 and these are fatal.

NOTE Confidence: 0.9395155

00:11:49.399 --> 00:11:50.600 So, this is a disease

NOTE Confidence: 0.9395155

00:11:50.600 --> 00:11:51.720 which has been known for

NOTE Confidence: 0.9395155

00:11:51.720 --> 00:11:52.679 a very long time when

NOTE Confidence: 0.9395155

00:11:52.679 --> 00:11:54.120 gene was discovered and shown

NOTE Confidence: 0.9395155

00:11:54.120 --> 00:11:55.480 to be a protein that

NOTE Confidence: 0.9395155

00:11:55.480 --> 00:11:56.920 regulates RAS, as we showed

NOTE Confidence: 0.9395155

00:11:56.920 --> 00:11:57.899 in nineteen ninety.

NOTE Confidence: 0.9258746

00:11:58.519 --> 00:12:00.199 All the complex phenotypes here

NOTE Confidence: 0.9258746

00:12:00.199 --> 00:12:01.500 turn out to be probably

NOTE Confidence: 0.9258746

00:12:01.559 --> 00:12:03.179 just too much active RAS.

NOTE Confidence: 0.979637

00:12:03.665 --> 00:12:04.945 A little too much in

NOTE Confidence: 0.979637

00:12:04.945 --> 00:12:06.245 the in the, heterozygotes,

NOTE Confidence: 0.9444621

00:12:06.785 --> 00:12:07.825 and way too much in

NOTE Confidence: 0.9444621

00:12:07.825 --> 00:12:09.425 the clonal cells would lose

NOTE Confidence: 0.9444621

00:12:09.425 --> 00:12:10.485 a second allele.

NOTE Confidence: 0.9412732

00:12:11.585 --> 00:12:12.385 So we put a lot

NOTE Confidence: 0.9412732

00:12:12.385 --> 00:12:13.665 of work into understanding how

NOTE Confidence: 0.9412732

00:12:13.665 --> 00:12:15.445 the NF1 protein is regulated.

NOTE Confidence: 0.9412732

00:12:15.665 --> 00:12:15.905 It's,

NOTE Confidence: 0.95815825

00:12:17.320 --> 00:12:18.600 it's a really interesting protein.

NOTE Confidence: 0.95815825

00:12:18.600 --> 00:12:19.880 It's a gigantic protein. It's

NOTE Confidence: 0.95815825

00:12:19.880 --> 00:12:20.920 two thousand eight hundred amino

NOTE Confidence: 0.95815825

00:12:20.920 --> 00:12:22.440 acids long. For a long

NOTE Confidence: 0.95815825

00:12:22.440 --> 00:12:23.480 time, it was just drawn

NOTE Confidence: 0.95815825

00:12:23.480 --> 00:12:24.520 as a stick like this

NOTE Confidence: 0.95815825

00:12:24.520 --> 00:12:25.559 with the gap domain in

NOTE Confidence: 0.95815825

00:12:25.559 --> 00:12:26.920 the middle, a sec fourteen

NOTE Confidence: 0.95815825

00:12:26.920 --> 00:12:28.040 domain, which is involved in

NOTE Confidence: 0.95815825

00:12:28.040 --> 00:12:30.140 membrane localization, and then unknown

NOTE Confidence: 0.95815825

00:12:30.200 --> 00:12:31.640 territory all across the whole

NOTE Confidence: 0.95815825

00:12:31.640 --> 00:12:33.285 gene. But then we and

NOTE Confidence: 0.95815825

00:12:33.285 --> 00:12:34.485 others solve the cryo EM

NOTE Confidence: 0.95815825

00:12:34.485 --> 00:12:36.245 structure of the protein, and

NOTE Confidence: 0.95815825

00:12:36.245 --> 00:12:37.045 it turns out to be

NOTE Confidence: 0.95815825

00:12:37.045 --> 00:12:38.485 a really beautiful structure. It's

NOTE Confidence: 0.95815825

00:12:38.485 --> 00:12:39.785 actually a head to tail,

NOTE Confidence: 0.79404753

00:12:40.405 --> 00:12:40.905 dimer,

NOTE Confidence: 0.8585465

00:12:41.445 --> 00:12:42.485 in this sort of infinity

NOTE Confidence: 0.8585465

00:12:42.485 --> 00:12:43.845 shaped protein, which is mostly

NOTE Confidence: 0.8585465

00:12:43.845 --> 00:12:45.205 made up of coils of

NOTE Confidence: 0.8585465

00:12:45.205 --> 00:12:46.840 alpha helices. And then there's

NOTE Confidence: 0.8585465

00:12:46.840 --> 00:12:47.880 RAS binding that main from

NOTE Confidence: 0.8585465

00:12:47.880 --> 00:12:49.080 one protein here and then

NOTE Confidence: 0.8585465

00:12:49.080 --> 00:12:49.820 one here.

NOTE Confidence: 0.85668916

00:12:50.280 --> 00:12:52.200 And this gigantic protein is

NOTE Confidence: 0.85668916

00:12:52.200 --> 00:12:53.240 taken to RAS in the

NOTE Confidence: 0.85668916

00:12:53.240 --> 00:12:55.160 membrane through as adapt to

NOTE Confidence: 0.85668916

00:12:55.160 --> 00:12:56.300 protein called SPREAD1,

NOTE Confidence: 0.95098436

00:12:56.920 --> 00:12:57.660 and SPREAD2,

NOTE Confidence: 0.92074275

00:12:58.520 --> 00:13:00.475 and also through binding directly

NOTE Confidence: 0.92074275

00:13:00.475 --> 00:13:02.154 to activated receptors like c

NOTE Confidence: 0.92074275

00:13:02.154 --> 00:13:03.675 kit. And once this gets

NOTE Confidence: 0.92074275

00:13:03.675 --> 00:13:04.714 to the membrane, it turns

NOTE Confidence: 0.92074275

00:13:04.714 --> 00:13:06.475 RAS off. This whole process

NOTE Confidence: 0.92074275

00:13:06.475 --> 00:13:07.135 is extremely

NOTE Confidence: 0.9672885

00:13:07.514 --> 00:13:08.415 tightly regulated.

NOTE Confidence: 0.94599104

00:13:08.875 --> 00:13:09.834 Let's say a level of

NOTE Confidence: 0.94599104

00:13:09.834 --> 00:13:12.074 expression spreads and phosphorylation probably

NOTE Confidence: 0.94599104

00:13:12.074 --> 00:13:13.755 of NF one, and binding

NOTE Confidence: 0.94599104

00:13:13.755 --> 00:13:14.954 to the receptor and so

NOTE Confidence: 0.94599104

00:13:14.954 --> 00:13:16.290 on. Because we know from

NOTE Confidence: 0.94599104

00:13:16.290 --> 00:13:17.730 genetics, if you have half

NOTE Confidence: 0.94599104

00:13:17.730 --> 00:13:18.770 as much of its protein

NOTE Confidence: 0.94599104

00:13:18.770 --> 00:13:19.809 as normal, you have a

NOTE Confidence: 0.94599104

00:13:19.809 --> 00:13:20.870 major disease.

NOTE Confidence: 0.85555744

00:13:21.170 --> 00:13:22.050 So it's got to be

NOTE Confidence: 0.85555744

00:13:22.050 --> 00:13:23.190 very precisely regulated.

NOTE Confidence: 0.9694219

00:13:23.730 --> 00:13:24.610 So we're doing a lot

NOTE Confidence: 0.9694219

00:13:24.610 --> 00:13:25.510 of work on that.

NOTE Confidence: 0.94442993

00:13:26.690 --> 00:13:27.570 Now there's not much good

NOTE Confidence: 0.94442993

00:13:27.570 --> 00:13:28.610 news in the NF one

NOTE Confidence: 0.94442993

00:13:28.610 --> 00:13:30.325 world, but there was some,

NOTE Confidence: 0.94442993

00:13:30.645 --> 00:13:32.005 a few years ago when

NOTE Confidence: 0.94442993

00:13:32.005 --> 00:13:33.625 Brigitte Wideman of the NCI

NOTE Confidence: 0.94442993

00:13:33.684 --> 00:13:35.765 pediatric oncology group performed a

NOTE Confidence: 0.94442993

00:13:35.765 --> 00:13:36.965 clinical trial on a MEK

NOTE Confidence: 0.94442993

00:13:36.965 --> 00:13:37.465 inhibitor

NOTE Confidence: 0.8940479

00:13:37.845 --> 00:13:38.804 to turn down the MAP

NOTE Confidence: 0.8940479

00:13:38.804 --> 00:13:39.705 kinase pathway,

NOTE Confidence: 0.9722013

00:13:40.085 --> 00:13:41.045 in patients with,

NOTE Confidence: 0.92953455

00:13:42.245 --> 00:13:43.465 plexiform neurofibromas.

NOTE Confidence: 0.9404644

00:13:44.270 --> 00:13:45.470 So this is a brilliant

NOTE Confidence: 0.9404644

00:13:45.470 --> 00:13:47.150 clinical trial because this is

NOTE Confidence: 0.9404644

00:13:47.150 --> 00:13:48.350 not a disease which is

NOTE Confidence: 0.9404644

00:13:48.350 --> 00:13:49.710 life threatening. So we're not

NOTE Confidence: 0.9404644

00:13:49.710 --> 00:13:51.230 measuring clinical endpoints in terms

NOTE Confidence: 0.9404644

00:13:51.230 --> 00:13:52.990 of survival or progressive free

NOTE Confidence: 0.9404644

00:13:52.990 --> 00:13:55.230 survival. This these endpoints were

NOTE Confidence: 0.9404644

00:13:55.230 --> 00:13:56.670 a reduction of tumor burden

NOTE Confidence: 0.9404644

00:13:56.670 --> 00:13:58.350 and also reduction of pain

NOTE Confidence: 0.9404644

00:13:58.350 --> 00:13:59.470 and other quality of life

NOTE Confidence: 0.9404644

00:13:59.470 --> 00:14:00.565 issues. But she got the

NOTE Confidence: 0.9404644

00:14:00.565 --> 00:14:01.925 drug approved, and this is

NOTE Confidence: 0.9404644

00:14:01.925 --> 00:14:03.285 now, widely used with kids

NOTE Confidence: 0.9404644

00:14:03.285 --> 00:14:04.184 for NF one.

NOTE Confidence: 0.9717056

00:14:04.644 --> 00:14:06.165 So the effects can be

NOTE Confidence: 0.9717056

00:14:06.165 --> 00:14:07.225 dramatic, but,

NOTE Confidence: 0.9274707

00:14:07.764 --> 00:14:08.725 those of you who've been

NOTE Confidence: 0.9274707

00:14:08.725 --> 00:14:09.845 involved in clinical use of

NOTE Confidence: 0.9274707

00:14:09.845 --> 00:14:11.285 mecadipid does know these drugs

NOTE Confidence: 0.9274707

00:14:11.285 --> 00:14:12.804 are toxic. And most kids

NOTE Confidence: 0.9274707

00:14:12.804 --> 00:14:13.845 go off this drug after

NOTE Confidence: 0.9274707

00:14:13.845 --> 00:14:14.725 a few months because of

NOTE Confidence: 0.9274707

00:14:14.725 --> 00:14:15.545 the side effects,

NOTE Confidence: 0.8884731

00:14:16.459 --> 00:14:17.740 are really bad and and

NOTE Confidence: 0.8884731

00:14:17.740 --> 00:14:18.620 to the GI and other

NOTE Confidence: 0.8884731

00:14:18.620 --> 00:14:19.899 issues. So we need a

NOTE Confidence: 0.8884731

00:14:19.899 --> 00:14:20.860 better way of dealing with

NOTE Confidence: 0.8884731

00:14:20.860 --> 00:14:21.440 this disease.

NOTE Confidence: 0.9882569

00:14:22.139 --> 00:14:22.639 And

NOTE Confidence: 0.989054

00:14:23.100 --> 00:14:24.319 hope is on the way,

NOTE Confidence: 0.91036654

00:14:24.620 --> 00:14:25.899 and it is just hope

NOTE Confidence: 0.91036654

00:14:25.899 --> 00:14:26.639 at this point.

NOTE Confidence: 0.9073841

00:14:27.259 --> 00:14:28.220 But we think that most

NOTE Confidence: 0.9073841

00:14:28.220 --> 00:14:29.600 of the, activity

NOTE Confidence: 0.9281088

00:14:30.084 --> 00:14:31.285 that's activated when you lose

NOTE Confidence: 0.9281088

00:14:31.285 --> 00:14:33.205 your neurofibromine protein is actually

NOTE Confidence: 0.9281088

00:14:33.205 --> 00:14:33.705 KRAS,

NOTE Confidence: 0.922514

00:14:34.404 --> 00:14:35.605 and we think that because

NOTE Confidence: 0.922514

00:14:35.605 --> 00:14:37.125 if we measure the ability

NOTE Confidence: 0.922514

00:14:37.125 --> 00:14:38.325 of RAS family proteins to

NOTE Confidence: 0.922514

00:14:38.325 --> 00:14:39.845 bind to neurofibromine, the NF

NOTE Confidence: 0.922514

00:14:39.845 --> 00:14:40.505 one protein,

NOTE Confidence: 0.9739879

00:14:40.885 --> 00:14:42.584 KRAS is the major partner.

NOTE Confidence: 0.9829177

00:14:42.885 --> 00:14:43.850 And if we knock out

NOTE Confidence: 0.9829177

00:14:43.850 --> 00:14:45.769 NF one cells, KRAS is

NOTE Confidence: 0.9829177

00:14:45.769 --> 00:14:46.570 the one that comes to

NOTE Confidence: 0.9829177

00:14:46.570 --> 00:14:48.490 life, most actively as we

NOTE Confidence: 0.9829177

00:14:48.490 --> 00:14:49.790 and others have shown.

NOTE Confidence: 0.952776

00:14:50.410 --> 00:14:51.769 So this all hangs together.

NOTE Confidence: 0.952776

00:14:51.769 --> 00:14:52.810 This means the drugs that

NOTE Confidence: 0.952776

00:14:52.810 --> 00:14:53.850 are now being developed for

NOTE Confidence: 0.952776

00:14:53.850 --> 00:14:54.350 cancer,

NOTE Confidence: 0.95673335

00:14:55.475 --> 00:14:56.835 which have the ability to

NOTE Confidence: 0.95673335

00:14:56.835 --> 00:14:58.675 target wild type KRAS could

NOTE Confidence: 0.95673335

00:14:58.675 --> 00:14:59.875 be tested in NF one

NOTE Confidence: 0.95673335

00:14:59.875 --> 00:15:01.395 disease, and we we are

NOTE Confidence: 0.95673335

00:15:01.395 --> 00:15:02.755 planning on doing exactly that

NOTE Confidence: 0.95673335

00:15:02.755 --> 00:15:04.215 with a pan KRAS inhibitor.

NOTE Confidence: 0.92500836

00:15:04.675 --> 00:15:05.715 And the theory is that,

NOTE Confidence: 0.92500836

00:15:06.195 --> 00:15:07.235 it should be as potent

NOTE Confidence: 0.92500836

00:15:07.235 --> 00:15:08.435 as a MEK inhibitor but

NOTE Confidence: 0.92500836

00:15:08.435 --> 00:15:09.475 without all the side effects

NOTE Confidence: 0.92500836

00:15:09.475 --> 00:15:10.915 because we're only eating KRAS

NOTE Confidence: 0.92500836

00:15:10.915 --> 00:15:11.900 and not all the RAS

NOTE Confidence: 0.92500836

00:15:11.900 --> 00:15:13.200 proteins that MEK,

NOTE Confidence: 0.9453277

00:15:13.660 --> 00:15:15.100 would deal with. So we

NOTE Confidence: 0.9453277

00:15:15.100 --> 00:15:16.220 hope that would be, heading

NOTE Confidence: 0.9453277

00:15:16.220 --> 00:15:17.180 for the clinic, in the

NOTE Confidence: 0.9453277

00:15:17.180 --> 00:15:18.460 next, year or two, one

NOTE Confidence: 0.9453277

00:15:18.460 --> 00:15:20.380 of several KRAS drugs, which,

NOTE Confidence: 0.9453277

00:15:20.780 --> 00:15:21.740 hit wild type as well

NOTE Confidence: 0.9453277

00:15:21.740 --> 00:15:22.800 as mutant alleles.

NOTE Confidence: 0.948654

00:15:25.935 --> 00:15:27.855 Now I mentioned that, that

NOTE Confidence: 0.948654

00:15:27.855 --> 00:15:29.295 autism and behavioral problems are

NOTE Confidence: 0.948654

00:15:29.295 --> 00:15:30.415 a big issue with NF1

NOTE Confidence: 0.948654

00:15:30.415 --> 00:15:32.175 patients. These issues are even

NOTE Confidence: 0.948654

00:15:32.175 --> 00:15:33.775 more severe in people who

NOTE Confidence: 0.948654

00:15:33.775 --> 00:15:35.154 have lost one copy,

NOTE Confidence: 0.9324198

00:15:35.615 --> 00:15:37.440 of the, SYNGAP gene, which

NOTE Confidence: 0.9324198

00:15:37.520 --> 00:15:39.280 is another gap related protein

NOTE Confidence: 0.9324198

00:15:39.280 --> 00:15:40.400 shown down here. This one

NOTE Confidence: 0.9324198

00:15:40.400 --> 00:15:41.460 is brain specific,

NOTE Confidence: 0.9311196

00:15:41.840 --> 00:15:43.200 but people lose this by

NOTE Confidence: 0.9311196

00:15:43.200 --> 00:15:44.660 chance head in the in

NOTE Confidence: 0.9311196

00:15:44.720 --> 00:15:45.940 heterozygous state,

NOTE Confidence: 0.9201549

00:15:46.400 --> 00:15:48.320 and, they they then succumb

NOTE Confidence: 0.9201549

00:15:48.320 --> 00:15:49.840 to, very severe forms of,

NOTE Confidence: 0.9201549

00:15:50.080 --> 00:15:51.860 autism, including, epilepsy.

NOTE Confidence: 0.9459988

00:15:52.815 --> 00:15:53.855 So these are some of

NOTE Confidence: 0.9459988

00:15:53.855 --> 00:15:55.135 the mutations, which have been

NOTE Confidence: 0.9459988

00:15:55.135 --> 00:15:56.755 mapped to cause, autism.

NOTE Confidence: 0.9153572

00:15:57.375 --> 00:15:58.495 So this is not proven

NOTE Confidence: 0.9153572

00:15:58.495 --> 00:15:59.615 really formally yet, but it

NOTE Confidence: 0.9153572

00:15:59.615 --> 00:16:01.295 looks like too much map

NOTE Confidence: 0.9153572

00:16:01.295 --> 00:16:02.975 plan is pathway in specific

NOTE Confidence: 0.9153572

00:16:02.975 --> 00:16:03.955 parts of the brain,

NOTE Confidence: 0.9714905

00:16:04.335 --> 00:16:05.535 can lead to, these kind

NOTE Confidence: 0.9714905

00:16:05.535 --> 00:16:06.195 of behaviors.

NOTE Confidence: 0.9686217

00:16:07.079 --> 00:16:08.199 Again, it hasn't been formally

NOTE Confidence: 0.9686217

00:16:08.199 --> 00:16:09.240 proven, but now we have

NOTE Confidence: 0.9686217

00:16:09.240 --> 00:16:10.440 drugs actually to test that

NOTE Confidence: 0.9686217

00:16:10.440 --> 00:16:10.940 possibility,

NOTE Confidence: 0.9427018

00:16:11.399 --> 00:16:12.920 very specific KRAS and other

NOTE Confidence: 0.9427018

00:16:12.920 --> 00:16:13.740 RAS pathway,

NOTE Confidence: 0.99883795

00:16:14.279 --> 00:16:14.779 inhibitors.

NOTE Confidence: 0.9994646

00:16:15.319 --> 00:16:15.819 So

NOTE Confidence: 0.9802252

00:16:16.360 --> 00:16:17.560 I believe that the RAS

NOTE Confidence: 0.9802252

00:16:17.560 --> 00:16:19.160 field will will now start

NOTE Confidence: 0.9802252

00:16:19.160 --> 00:16:20.360 to pay more attention to

NOTE Confidence: 0.9802252

00:16:20.360 --> 00:16:21.660 the effects of RAS signaling

NOTE Confidence: 0.9802252

00:16:21.800 --> 00:16:23.425 in the brain. Ras proteins

NOTE Confidence: 0.9802252

00:16:23.425 --> 00:16:24.144 have always been known to

NOTE Confidence: 0.9802252

00:16:24.144 --> 00:16:25.024 be very abundant in the

NOTE Confidence: 0.9802252

00:16:25.024 --> 00:16:27.204 brain, but, since obviously,

NOTE Confidence: 0.57061046

00:16:27.931 --> 00:16:28.431 these

NOTE Confidence: 0.8760152

00:16:28.785 --> 00:16:29.825 until recently were thought to

NOTE Confidence: 0.8760152

00:16:29.825 --> 00:16:31.204 be non proliferative tissues,

NOTE Confidence: 0.8755275

00:16:31.985 --> 00:16:33.024 there's always been a question

NOTE Confidence: 0.8755275

00:16:33.024 --> 00:16:33.745 as why do we why

NOTE Confidence: 0.8755275

00:16:33.745 --> 00:16:34.385 do you have so much

NOTE Confidence: 0.8755275

00:16:34.385 --> 00:16:35.745 map size activity in the

NOTE Confidence: 0.8755275

00:16:35.745 --> 00:16:37.060 in the brain? So that

NOTE Confidence: 0.8755275

00:16:37.060 --> 00:16:38.360 needs to be revisited.

NOTE Confidence: 0.99311316

00:16:40.819 --> 00:16:41.319 Anyway,

NOTE Confidence: 0.8301468

00:16:42.500 --> 00:16:43.639 move towards cancer.

NOTE Confidence: 0.949158

00:16:44.100 --> 00:16:45.779 So, in cancer, we have

NOTE Confidence: 0.949158

00:16:45.779 --> 00:16:47.540 a different situation again. Now,

NOTE Confidence: 0.949158

00:16:47.779 --> 00:16:49.779 mutations occur in KRAS, codons

NOTE Confidence: 0.949158

00:16:49.779 --> 00:16:50.740 twelve, and sixty one as

NOTE Confidence: 0.949158

00:16:50.740 --> 00:16:52.120 you definitely all know.

NOTE Confidence: 0.94565827

00:16:52.505 --> 00:16:53.325 These mutations,

NOTE Confidence: 0.944508

00:16:53.865 --> 00:16:56.024 make RAS proteins resistant to

NOTE Confidence: 0.944508

00:16:56.024 --> 00:16:57.305 all gaps, so they get

NOTE Confidence: 0.944508

00:16:57.305 --> 00:16:58.425 turned off by any any

NOTE Confidence: 0.944508

00:16:58.425 --> 00:16:59.545 gaps in the cell can

NOTE Confidence: 0.944508

00:16:59.545 --> 00:17:01.144 no longer, turn off this

NOTE Confidence: 0.944508

00:17:01.144 --> 00:17:01.644 protein.

NOTE Confidence: 0.9088847

00:17:02.425 --> 00:17:04.025 So these proteins accumulate in

NOTE Confidence: 0.9088847

00:17:04.025 --> 00:17:05.720 a GTP bound state as

NOTE Confidence: 0.9088847

00:17:05.720 --> 00:17:06.280 shown by this,

NOTE Confidence: 0.85407215

00:17:07.080 --> 00:17:08.040 t l c analysis of

NOTE Confidence: 0.85407215

00:17:08.040 --> 00:17:09.900 nucleotides bound to RAS for

NOTE Confidence: 0.85407215

00:17:10.040 --> 00:17:11.960 wild type RAS, mostly GDP

NOTE Confidence: 0.85407215

00:17:11.960 --> 00:17:13.240 bound, q g

NOTE Confidence: 0.83297026

00:17:13.720 --> 00:17:15.000 q sixty one no. G

NOTE Confidence: 0.83297026

00:17:15.000 --> 00:17:17.100 twelve c, mostly GDP bound,

NOTE Confidence: 0.97898275

00:17:17.734 --> 00:17:18.395 and then,

NOTE Confidence: 0.9328108

00:17:18.935 --> 00:17:20.135 g twelve c and v

NOTE Confidence: 0.9328108

00:17:20.135 --> 00:17:21.494 and q sixty one. So

NOTE Confidence: 0.9328108

00:17:21.494 --> 00:17:22.935 the mutant pure proteins accumulate

NOTE Confidence: 0.9328108

00:17:22.935 --> 00:17:24.395 in the GTP bound state,

NOTE Confidence: 0.9328108

00:17:24.455 --> 00:17:25.015 and that's,

NOTE Confidence: 0.99136317

00:17:25.575 --> 00:17:27.195 part of what causes cancer.

NOTE Confidence: 0.9503373

00:17:27.734 --> 00:17:28.855 But the consequence of this

NOTE Confidence: 0.9503373

00:17:28.855 --> 00:17:30.369 lack of regulation is we've

NOTE Confidence: 0.9503373

00:17:30.369 --> 00:17:32.130 lost that pulsatile spike of

NOTE Confidence: 0.9503373

00:17:32.130 --> 00:17:33.169 signaling that you see in

NOTE Confidence: 0.9503373

00:17:33.169 --> 00:17:34.770 response to EGF. And now

NOTE Confidence: 0.9503373

00:17:34.770 --> 00:17:35.649 we have a situation where

NOTE Confidence: 0.9503373

00:17:35.649 --> 00:17:37.090 you have tonic activation of

NOTE Confidence: 0.9503373

00:17:37.090 --> 00:17:37.990 phospho work.

NOTE Confidence: 0.93173057

00:17:38.369 --> 00:17:40.210 These spikes actually, obviously, this

NOTE Confidence: 0.93173057

00:17:40.210 --> 00:17:42.150 tonic activity is not necessarily

NOTE Confidence: 0.93173057

00:17:42.210 --> 00:17:43.169 as as high as a

NOTE Confidence: 0.93173057

00:17:43.169 --> 00:17:44.210 spike in in a normal

NOTE Confidence: 0.93173057

00:17:44.210 --> 00:17:45.570 cell. It's just on the

NOTE Confidence: 0.93173057

00:17:45.570 --> 00:17:47.494 whole time. And this persistent

NOTE Confidence: 0.93173057

00:17:47.555 --> 00:17:48.675 activation of the MAP kinase

NOTE Confidence: 0.93173057

00:17:48.675 --> 00:17:49.175 pathway,

NOTE Confidence: 0.9026088

00:17:49.795 --> 00:17:50.755 from as you can see

NOTE Confidence: 0.9026088

00:17:50.755 --> 00:17:52.115 from RAS GDP levels or

NOTE Confidence: 0.9026088

00:17:52.115 --> 00:17:52.855 from fossil

NOTE Confidence: 0.9770202

00:17:53.315 --> 00:17:54.215 work, this causes

NOTE Confidence: 0.89794195

00:17:54.675 --> 00:17:56.135 massive change in the transcriptional

NOTE Confidence: 0.88593316

00:17:56.435 --> 00:17:58.195 profile in cells and can

NOTE Confidence: 0.88593316

00:17:58.195 --> 00:17:59.635 lead to their, change of

NOTE Confidence: 0.88593316

00:17:59.635 --> 00:18:00.675 a normal cell into a

NOTE Confidence: 0.88593316

00:18:00.675 --> 00:18:01.494 tumor cell.

NOTE Confidence: 0.93242186

00:18:01.850 --> 00:18:02.990 So that is the basis

NOTE Confidence: 0.93242186

00:18:03.130 --> 00:18:04.990 of RAS driven cancer, persistent

NOTE Confidence: 0.93242186

00:18:05.050 --> 00:18:06.730 tonic activation of the MAP

NOTE Confidence: 0.93242186

00:18:06.730 --> 00:18:07.550 kinase pathway.

NOTE Confidence: 0.96349037

00:18:07.930 --> 00:18:09.050 Pathway is not on fire.

NOTE Confidence: 0.96349037

00:18:09.050 --> 00:18:10.490 It's just always on, and

NOTE Confidence: 0.96349037

00:18:10.490 --> 00:18:11.790 that's a very different signal

NOTE Confidence: 0.96349037

00:18:11.850 --> 00:18:13.070 for the cell to interpret.

NOTE Confidence: 0.9786993

00:18:13.450 --> 00:18:14.570 And, that, I think, is

NOTE Confidence: 0.9786993

00:18:14.570 --> 00:18:15.369 the basis of the whole

NOTE Confidence: 0.9786993

00:18:15.369 --> 00:18:15.869 thing.

NOTE Confidence: 0.93929297

00:18:16.244 --> 00:18:17.525 But RAS proteins do more

NOTE Confidence: 0.93929297

00:18:17.525 --> 00:18:18.565 than that in cancer as

NOTE Confidence: 0.93929297

00:18:18.565 --> 00:18:19.785 I'm sure you all appreciate.

NOTE Confidence: 0.90422994

00:18:20.645 --> 00:18:21.525 If you ask,

NOTE Confidence: 0.99300134

00:18:22.085 --> 00:18:22.585 Google

NOTE Confidence: 0.9697115

00:18:23.125 --> 00:18:24.325 what RAS proteins do in

NOTE Confidence: 0.9697115

00:18:24.325 --> 00:18:25.685 cancer cells, you'll probably find

NOTE Confidence: 0.9697115

00:18:25.685 --> 00:18:27.045 a picture like this, which

NOTE Confidence: 0.9697115

00:18:27.045 --> 00:18:27.925 is based on, you know,

NOTE Confidence: 0.9697115

00:18:27.925 --> 00:18:29.460 one of fifty diagrams for

NOTE Confidence: 0.9697115

00:18:29.460 --> 00:18:30.820 literature in which RAS proteins

NOTE Confidence: 0.9697115

00:18:30.820 --> 00:18:33.240 can activate multiple downstream effectors

NOTE Confidence: 0.9697115

00:18:33.300 --> 00:18:34.440 from various publications

NOTE Confidence: 0.99931735

00:18:34.820 --> 00:18:35.720 over the years.

NOTE Confidence: 0.9592257

00:18:36.820 --> 00:18:37.859 At the RAS initiative, we

NOTE Confidence: 0.9592257

00:18:37.859 --> 00:18:38.920 did a sort of crowdsourcing

NOTE Confidence: 0.9592257

00:18:39.140 --> 00:18:40.100 version of this and asked

NOTE Confidence: 0.9592257

00:18:40.100 --> 00:18:41.619 the community of RAS people,

NOTE Confidence: 0.9592257

00:18:41.619 --> 00:18:42.580 what do you think RAS

NOTE Confidence: 0.9592257

00:18:42.580 --> 00:18:44.095 proteins do? And, of course,

NOTE Confidence: 0.9592257

00:18:44.095 --> 00:18:45.615 they all voted for their

NOTE Confidence: 0.9592257

00:18:45.615 --> 00:18:46.654 favorite protein in the in

NOTE Confidence: 0.9592257

00:18:46.654 --> 00:18:47.234 the pathway,

NOTE Confidence: 0.9498538

00:18:47.934 --> 00:18:48.734 and you get a sort

NOTE Confidence: 0.9498538

00:18:48.734 --> 00:18:50.174 of conglomerate picture like this

NOTE Confidence: 0.9498538

00:18:50.174 --> 00:18:51.455 in which RAS is here.

NOTE Confidence: 0.9498538

00:18:51.455 --> 00:18:52.835 Here's the map kinase pathway.

NOTE Confidence: 0.9498538

00:18:52.975 --> 00:18:54.515 The RAS proteins also activate

NOTE Confidence: 0.9498538

00:18:54.575 --> 00:18:55.315 other downstream

NOTE Confidence: 0.68950677

00:18:55.774 --> 00:18:57.234 effect as shown here.

NOTE Confidence: 0.8788034

00:18:57.679 --> 00:18:58.580 Now all of these,

NOTE Confidence: 0.9441057

00:18:59.280 --> 00:19:01.039 pathways are based on data

NOTE Confidence: 0.9441057

00:19:01.039 --> 00:19:02.880 from cell lines, and the

NOTE Confidence: 0.9441057

00:19:02.880 --> 00:19:03.919 bottom line is that,

NOTE Confidence: 0.9182723

00:19:04.640 --> 00:19:06.240 the RAS always engages MAP

NOTE Confidence: 0.9182723

00:19:06.240 --> 00:19:06.740 kinase,

NOTE Confidence: 0.95313394

00:19:07.119 --> 00:19:08.640 and can activate other effectors

NOTE Confidence: 0.95313394

00:19:08.640 --> 00:19:09.600 in different cell lines, and

NOTE Confidence: 0.95313394

00:19:09.600 --> 00:19:10.480 that's the answer that you

NOTE Confidence: 0.95313394

00:19:10.480 --> 00:19:11.919 get from CHaT GPT if

NOTE Confidence: 0.95313394

00:19:11.919 --> 00:19:13.140 you ask the same question.

NOTE Confidence: 0.80776834

00:19:13.695 --> 00:19:15.635 MAP kinase pathway, yes, always.

NOTE Confidence: 0.92643034

00:19:16.335 --> 00:19:18.015 Most tumor cells also activate

NOTE Confidence: 0.92643034

00:19:18.015 --> 00:19:19.455 p I three kinase. Some

NOTE Confidence: 0.92643034

00:19:19.455 --> 00:19:21.375 activate RAL GDS and some

NOTE Confidence: 0.92643034

00:19:21.375 --> 00:19:22.894 additional effectors, which are kind

NOTE Confidence: 0.92643034

00:19:22.894 --> 00:19:23.774 of more rare, but they're

NOTE Confidence: 0.92643034

00:19:23.774 --> 00:19:24.975 still real. They're just less

NOTE Confidence: 0.92643034

00:19:24.975 --> 00:19:25.475 common.

NOTE Confidence: 0.9554458

00:19:26.720 --> 00:19:28.160 So that's the situation in

NOTE Confidence: 0.9554458

00:19:28.160 --> 00:19:28.740 in cancer.

NOTE Confidence: 0.93270475

00:19:29.119 --> 00:19:29.920 But then as as a

NOTE Confidence: 0.93270475

00:19:29.920 --> 00:19:31.200 biochemist, you can ask, well,

NOTE Confidence: 0.93270475

00:19:31.200 --> 00:19:32.160 how does a small protein

NOTE Confidence: 0.93270475

00:19:32.160 --> 00:19:33.119 like RAS, which has a

NOTE Confidence: 0.93270475

00:19:33.119 --> 00:19:34.880 very small effective binding region,

NOTE Confidence: 0.93270475

00:19:34.880 --> 00:19:36.320 so twenty to ten amino

NOTE Confidence: 0.93270475

00:19:36.320 --> 00:19:37.760 acids, how can it possibly

NOTE Confidence: 0.93270475

00:19:37.760 --> 00:19:39.359 engage so many different downstream

NOTE Confidence: 0.93270475

00:19:39.359 --> 00:19:41.040 proteins effectively and turn them

NOTE Confidence: 0.93270475

00:19:41.040 --> 00:19:41.385 on,

NOTE Confidence: 0.9298516

00:19:41.865 --> 00:19:43.484 to engage downstream pathways.

NOTE Confidence: 0.84181154

00:19:44.825 --> 00:19:45.325 So,

NOTE Confidence: 0.95949596

00:19:46.744 --> 00:19:47.545 this is what I think

NOTE Confidence: 0.95949596

00:19:47.545 --> 00:19:48.984 is happening. So in normal

NOTE Confidence: 0.95949596

00:19:48.984 --> 00:19:51.005 cells, RAS proteins only activate,

NOTE Confidence: 0.81460124

00:19:51.865 --> 00:19:53.720 pathways pathway I mean, RAS

NOTE Confidence: 0.81460124

00:19:53.720 --> 00:19:54.220 proteins.

NOTE Confidence: 0.98709106

00:19:54.520 --> 00:19:56.619 However, RAS proteins have cousins,

NOTE Confidence: 0.9206111

00:19:57.080 --> 00:19:58.060 such as rRAS2

NOTE Confidence: 0.9040721

00:19:58.440 --> 00:20:00.220 and MRAS and and RAL.

NOTE Confidence: 0.9040721

00:20:00.440 --> 00:20:01.340 And if you overexpress

NOTE Confidence: 0.92139953

00:20:01.880 --> 00:20:03.080 a mutant form of RAS

NOTE Confidence: 0.92139953

00:20:03.080 --> 00:20:04.280 at high levels, it can

NOTE Confidence: 0.92139953

00:20:04.280 --> 00:20:05.100 cross over,

NOTE Confidence: 0.8867989

00:20:05.640 --> 00:20:07.420 and then interact with PI3

NOTE Confidence: 0.8867989

00:20:07.480 --> 00:20:07.980 kinase

NOTE Confidence: 0.93118346

00:20:08.415 --> 00:20:09.775 or with SHOCK two or

NOTE Confidence: 0.93118346

00:20:09.775 --> 00:20:10.735 with other members of these

NOTE Confidence: 0.93118346

00:20:10.735 --> 00:20:11.235 proteins

NOTE Confidence: 0.9895724

00:20:11.615 --> 00:20:12.815 just because the proteins are

NOTE Confidence: 0.9895724

00:20:12.815 --> 00:20:13.475 so similar.

NOTE Confidence: 0.9762821

00:20:14.175 --> 00:20:14.575 So,

NOTE Confidence: 0.8741725

00:20:15.055 --> 00:20:15.695 as I'll show you in

NOTE Confidence: 0.8741725

00:20:15.695 --> 00:20:17.055 just a moment, the binding

NOTE Confidence: 0.8741725

00:20:17.055 --> 00:20:18.415 size of these proteins are

NOTE Confidence: 0.8741725

00:20:18.415 --> 00:20:19.075 are very

NOTE Confidence: 0.7992668

00:20:19.615 --> 00:20:20.115 similar.

NOTE Confidence: 0.89026165

00:20:20.790 --> 00:20:22.030 So this is like sort

NOTE Confidence: 0.89026165

00:20:22.030 --> 00:20:23.530 of, unwanted inappropriate,

NOTE Confidence: 0.8779485

00:20:24.550 --> 00:20:26.150 interactions of RAS with other

NOTE Confidence: 0.8779485

00:20:26.150 --> 00:20:26.650 effectors.

NOTE Confidence: 0.8611745

00:20:27.110 --> 00:20:28.150 It kind of reminds me

NOTE Confidence: 0.8611745

00:20:28.150 --> 00:20:29.670 of, Donald Trump at a

NOTE Confidence: 0.8611745

00:20:29.670 --> 00:20:30.410 beauty patent.

NOTE Confidence: 0.9514701

00:20:31.670 --> 00:20:32.390 If I can use that

NOTE Confidence: 0.9514701

00:20:32.390 --> 00:20:32.890 analogy.

NOTE Confidence: 0.79023695

00:20:33.975 --> 00:20:34.475 So,

NOTE Confidence: 0.95332247

00:20:36.135 --> 00:20:37.815 inappropriate rations, which shouldn't happen

NOTE Confidence: 0.95332247

00:20:37.815 --> 00:20:38.855 normally, but do because we

NOTE Confidence: 0.95332247

00:20:38.855 --> 00:20:39.734 have a high level of

NOTE Confidence: 0.95332247

00:20:39.734 --> 00:20:41.095 mutant RAS in the GTP

NOTE Confidence: 0.95332247

00:20:41.095 --> 00:20:41.835 bound state.

NOTE Confidence: 0.9570004

00:20:42.375 --> 00:20:43.414 And, actually, this sort of

NOTE Confidence: 0.9570004

00:20:43.414 --> 00:20:44.455 goes the other way as

NOTE Confidence: 0.9570004

00:20:44.455 --> 00:20:46.135 well. Mutations in our RAS

NOTE Confidence: 0.9570004

00:20:46.135 --> 00:20:47.335 and our RAS two proteins

NOTE Confidence: 0.9570004

00:20:47.335 --> 00:20:48.054 that cause,

NOTE Confidence: 0.9097258

00:20:48.615 --> 00:20:50.500 Luna syndrome can crossover and

NOTE Confidence: 0.9097258

00:20:50.500 --> 00:20:51.960 activate in that kinase pathway.

NOTE Confidence: 0.9097258

00:20:52.100 --> 00:20:52.980 And that's why they all

NOTE Confidence: 0.9097258

00:20:52.980 --> 00:20:54.260 can do that, whereas they

NOTE Confidence: 0.9097258

00:20:54.260 --> 00:20:55.380 don't do that in normal

NOTE Confidence: 0.9097258

00:20:55.380 --> 00:20:56.420 tissue. Okay? This is a

NOTE Confidence: 0.9097258

00:20:56.420 --> 00:20:57.700 gain of function as a

NOTE Confidence: 0.9097258

00:20:57.700 --> 00:20:59.059 result of over expression and

NOTE Confidence: 0.9097258

00:20:59.059 --> 00:21:00.600 mutation in in the target.

NOTE Confidence: 0.87591606

00:21:01.220 --> 00:21:02.260 So that's what we think

NOTE Confidence: 0.87591606

00:21:02.260 --> 00:21:02.740 how,

NOTE Confidence: 0.9858643

00:21:03.365 --> 00:21:04.405 RAS proteins can pick up

NOTE Confidence: 0.9858643

00:21:04.405 --> 00:21:05.765 all these different interactions by

NOTE Confidence: 0.9858643

00:21:05.765 --> 00:21:07.045 sort of barging in on

NOTE Confidence: 0.9858643

00:21:07.045 --> 00:21:07.865 their cousins,

NOTE Confidence: 0.9260545

00:21:08.244 --> 00:21:10.005 which look very similar. So

NOTE Confidence: 0.9260545

00:21:10.005 --> 00:21:10.965 just for those of you

NOTE Confidence: 0.9260545

00:21:10.965 --> 00:21:12.244 who like details, this is

NOTE Confidence: 0.9260545

00:21:12.244 --> 00:21:12.565 a

NOTE Confidence: 0.8654416

00:21:13.125 --> 00:21:14.744 the the RAS, g domain.

NOTE Confidence: 0.8965328

00:21:15.710 --> 00:21:16.670 This is the effect of

NOTE Confidence: 0.8965328

00:21:16.670 --> 00:21:18.109 binding region of the RAS

NOTE Confidence: 0.8965328

00:21:18.109 --> 00:21:19.310 protein. So h n and

NOTE Confidence: 0.8965328

00:21:19.310 --> 00:21:20.910 K RAS are identical, but

NOTE Confidence: 0.8965328

00:21:20.910 --> 00:21:23.070 so is, MRAS, RS, RS

NOTE Confidence: 0.8965328

00:21:23.070 --> 00:21:24.270 two, and RIT one. They

NOTE Confidence: 0.8965328

00:21:24.270 --> 00:21:25.250 all have the same,

NOTE Confidence: 0.91924304

00:21:25.710 --> 00:21:27.250 effect of binding region.

NOTE Confidence: 0.979552

00:21:27.790 --> 00:21:29.090 So all of these cousins

NOTE Confidence: 0.979552

00:21:29.310 --> 00:21:30.770 can interact with RAF,

NOTE Confidence: 0.88464034

00:21:31.234 --> 00:21:33.315 for example, but only canonical

NOTE Confidence: 0.88464034

00:21:33.315 --> 00:21:34.855 RAS proteins activate it,

NOTE Confidence: 0.9720547

00:21:35.395 --> 00:21:36.755 and that's because activation has

NOTE Confidence: 0.9720547

00:21:36.755 --> 00:21:37.635 a is a two step

NOTE Confidence: 0.9720547

00:21:37.635 --> 00:21:39.555 process, binding followed by a

NOTE Confidence: 0.9720547

00:21:39.555 --> 00:21:40.994 second engagement of a different

NOTE Confidence: 0.9720547

00:21:40.994 --> 00:21:42.035 part of the protein to

NOTE Confidence: 0.9720547

00:21:42.035 --> 00:21:43.494 turn on the actual activity,

NOTE Confidence: 0.9720547

00:21:43.555 --> 00:21:44.675 and that's unique to the

NOTE Confidence: 0.9720547

00:21:44.675 --> 00:21:45.975 canonical RAS proteins.

NOTE Confidence: 0.91407984

00:21:47.450 --> 00:21:48.570 So, in the case of,

NOTE Confidence: 0.86034584

00:21:49.369 --> 00:21:50.590 of of RAS and RAF,

NOTE Confidence: 0.9466687

00:21:51.130 --> 00:21:52.650 this is the, the minimal

NOTE Confidence: 0.9466687

00:21:52.650 --> 00:21:53.770 binding domain of,

NOTE Confidence: 0.87050015

00:21:54.490 --> 00:21:55.450 of RAS and RAF that

NOTE Confidence: 0.87050015

00:21:55.450 --> 00:21:56.010 we solved,

NOTE Confidence: 0.8784097

00:21:56.890 --> 00:21:57.869 many years ago.

NOTE Confidence: 0.9437754

00:21:58.330 --> 00:21:59.369 In addition to that, we

NOTE Confidence: 0.9437754

00:21:59.369 --> 00:22:00.410 solved a bigger piece of

NOTE Confidence: 0.9437754

00:22:00.410 --> 00:22:01.885 RAF, including the sister enriched

NOTE Confidence: 0.9437754

00:22:01.885 --> 00:22:03.025 domain shown here,

NOTE Confidence: 0.99878573

00:22:03.325 --> 00:22:04.145 which now

NOTE Confidence: 0.96519834

00:22:04.445 --> 00:22:06.225 extends the footprint on RAS

NOTE Confidence: 0.96519834

00:22:06.365 --> 00:22:07.665 to a much bigger footprint,

NOTE Confidence: 0.96519834

00:22:07.805 --> 00:22:09.885 and this CRD interaction with

NOTE Confidence: 0.96519834

00:22:09.885 --> 00:22:11.165 RAS is essential for the

NOTE Confidence: 0.96519834

00:22:11.165 --> 00:22:12.385 activation process.

NOTE Confidence: 0.93523264

00:22:12.980 --> 00:22:13.940 Okay? So if you don't

NOTE Confidence: 0.93523264

00:22:13.940 --> 00:22:14.820 have that, you can get

NOTE Confidence: 0.93523264

00:22:14.820 --> 00:22:16.119 binding, but nothing happens.

NOTE Confidence: 0.8769812

00:22:16.740 --> 00:22:18.260 And, so we think that's

NOTE Confidence: 0.8769812

00:22:18.260 --> 00:22:19.700 that's interaction here is actually

NOTE Confidence: 0.8769812

00:22:19.700 --> 00:22:21.240 really interesting, also interesting,

NOTE Confidence: 0.959799

00:22:22.980 --> 00:22:24.500 interesting drug target because this

NOTE Confidence: 0.959799

00:22:24.500 --> 00:22:25.955 direction is weaker than the

NOTE Confidence: 0.959799

00:22:25.955 --> 00:22:27.395 RBD, and it actually has

NOTE Confidence: 0.959799

00:22:27.395 --> 00:22:29.075 some specificity for different RAF

NOTE Confidence: 0.959799

00:22:29.075 --> 00:22:29.575 isoforms.

NOTE Confidence: 0.90869933

00:22:30.275 --> 00:22:31.475 But that's the general principle.

NOTE Confidence: 0.90869933

00:22:31.475 --> 00:22:32.435 We have a binding piece

NOTE Confidence: 0.90869933

00:22:32.435 --> 00:22:33.155 and then a sort of

NOTE Confidence: 0.90869933

00:22:33.155 --> 00:22:34.915 activation piece, and those are

NOTE Confidence: 0.90869933

00:22:34.915 --> 00:22:35.955 unique to different members of

NOTE Confidence: 0.90869933

00:22:35.955 --> 00:22:37.075 the RAF family, but they

NOTE Confidence: 0.90869933

00:22:37.075 --> 00:22:38.115 can cross over. If you

NOTE Confidence: 0.90869933

00:22:38.115 --> 00:22:39.335 over express proteins,

NOTE Confidence: 0.95130813

00:22:39.990 --> 00:22:40.950 too much. They can they

NOTE Confidence: 0.95130813

00:22:40.950 --> 00:22:42.310 can pick up interactions which

NOTE Confidence: 0.95130813

00:22:42.310 --> 00:22:43.770 are not supposed to happen.

NOTE Confidence: 0.9422506

00:22:45.830 --> 00:22:46.730 Okay. So,

NOTE Confidence: 0.95373476

00:22:47.430 --> 00:22:48.869 the, the world of,

NOTE Confidence: 0.9739444

00:22:49.670 --> 00:22:50.950 of drug discovery in the

NOTE Confidence: 0.9739444

00:22:50.950 --> 00:22:52.710 RAS world really started in

NOTE Confidence: 0.9739444

00:22:52.710 --> 00:22:53.990 a in a serious way

NOTE Confidence: 0.9739444

00:22:53.990 --> 00:22:55.210 in twenty thirteen

NOTE Confidence: 0.88345796

00:22:55.565 --> 00:22:57.025 when Kevan Shokat at UCSF,

NOTE Confidence: 0.94530165

00:22:57.645 --> 00:22:59.165 had the brilliant idea of

NOTE Confidence: 0.94530165

00:22:59.165 --> 00:23:00.445 targeting the g twelve c

NOTE Confidence: 0.94530165

00:23:00.445 --> 00:23:01.825 allele of KRAS.

NOTE Confidence: 0.9454685

00:23:02.525 --> 00:23:03.885 So g twelve c is

NOTE Confidence: 0.9454685

00:23:03.885 --> 00:23:05.005 common in non small cell

NOTE Confidence: 0.9454685

00:23:05.005 --> 00:23:06.285 lung cancer because it's a

NOTE Confidence: 0.9454685

00:23:06.285 --> 00:23:07.905 hallmark of cigarette smoke.

NOTE Confidence: 0.8344324

00:23:08.930 --> 00:23:10.390 But cystain is a reactive,

NOTE Confidence: 0.93404245

00:23:11.170 --> 00:23:12.930 residue, and by sheer good

NOTE Confidence: 0.93404245

00:23:12.930 --> 00:23:13.430 fortune,

NOTE Confidence: 0.9419449

00:23:13.890 --> 00:23:15.330 Kevan's lab is close to

NOTE Confidence: 0.9419449

00:23:15.330 --> 00:23:15.830 the,

NOTE Confidence: 0.89163435

00:23:16.530 --> 00:23:17.810 a group at, at at

NOTE Confidence: 0.89163435

00:23:17.810 --> 00:23:19.750 UCSF that developed a cystain

NOTE Confidence: 0.89163435

00:23:19.810 --> 00:23:21.490 tethering library for finding small

NOTE Confidence: 0.89163435

00:23:21.490 --> 00:23:23.010 molecules applying to cystains and

NOTE Confidence: 0.89163435

00:23:23.010 --> 00:23:23.510 proteins.

NOTE Confidence: 0.9043166

00:23:23.970 --> 00:23:24.984 So So K band put

NOTE Confidence: 0.9043166

00:23:24.984 --> 00:23:26.184 two and two together under

NOTE Confidence: 0.9043166

00:23:26.184 --> 00:23:27.565 the screen with that library

NOTE Confidence: 0.9043166

00:23:27.705 --> 00:23:28.744 to find compounds that were

NOTE Confidence: 0.9043166

00:23:28.744 --> 00:23:30.025 bind to g twelve c,

NOTE Confidence: 0.9043166

00:23:30.025 --> 00:23:31.225 and he found compounds, as

NOTE Confidence: 0.9043166

00:23:31.225 --> 00:23:32.265 you all know, I'm sure,

NOTE Confidence: 0.9043166

00:23:32.265 --> 00:23:33.244 and found a compound,

NOTE Confidence: 0.9523287

00:23:33.705 --> 00:23:34.905 that binds in the, in

NOTE Confidence: 0.9523287

00:23:34.905 --> 00:23:36.025 the pocket here that hadn't

NOTE Confidence: 0.9523287

00:23:36.025 --> 00:23:37.225 been seen previously. It's an

NOTE Confidence: 0.9523287

00:23:37.225 --> 00:23:38.525 induced pocket, actually.

NOTE Confidence: 0.9369211

00:23:39.225 --> 00:23:40.399 It's called the switch two

NOTE Confidence: 0.9369211

00:23:40.399 --> 00:23:41.760 pocket. It tucks in under

NOTE Confidence: 0.9369211

00:23:41.760 --> 00:23:43.539 here through covalent interaction.

NOTE Confidence: 0.9755583

00:23:44.559 --> 00:23:45.760 So with this experiment, he

NOTE Confidence: 0.9755583

00:23:45.760 --> 00:23:46.960 killed two birds with one

NOTE Confidence: 0.9755583

00:23:46.960 --> 00:23:47.460 stone.

NOTE Confidence: 0.8420396

00:23:47.760 --> 00:23:48.640 First of all, he got

NOTE Confidence: 0.8420396

00:23:48.640 --> 00:23:49.760 a a compound of binds

NOTE Confidence: 0.8420396

00:23:49.760 --> 00:23:50.960 to RAS with high affinity.

NOTE Confidence: 0.8420396

00:23:50.960 --> 00:23:51.619 It's covalent.

NOTE Confidence: 0.9521721

00:23:52.255 --> 00:23:54.015 And secondly, this is specific

NOTE Confidence: 0.9521721

00:23:54.015 --> 00:23:55.455 for the mutant allele, so

NOTE Confidence: 0.9521721

00:23:55.455 --> 00:23:56.335 it should be a safe

NOTE Confidence: 0.9521721

00:23:56.335 --> 00:23:58.655 drug. So, obviously, everybody jumped

NOTE Confidence: 0.9521721

00:23:58.655 --> 00:24:00.015 on this immediately and then,

NOTE Confidence: 0.93138367

00:24:00.575 --> 00:24:01.395 followed this

NOTE Confidence: 0.9263901

00:24:01.775 --> 00:24:03.135 this path, and now we

NOTE Confidence: 0.9263901

00:24:03.135 --> 00:24:05.075 have some fifteen different D12C

NOTE Confidence: 0.9263901

00:24:05.135 --> 00:24:05.635 inhibitors,

NOTE Confidence: 0.8589683

00:24:06.095 --> 00:24:07.660 in the clinic, And, also,

NOTE Confidence: 0.8589683

00:24:07.660 --> 00:24:09.100 having bust open the sort

NOTE Confidence: 0.8589683

00:24:09.100 --> 00:24:10.640 of the knot of RAS,

NOTE Confidence: 0.9535738

00:24:11.020 --> 00:24:11.980 now we see this pocket

NOTE Confidence: 0.9535738

00:24:11.980 --> 00:24:13.020 can be used for actually

NOTE Confidence: 0.9535738

00:24:13.020 --> 00:24:14.320 non covalent interactions,

NOTE Confidence: 0.9617669

00:24:15.100 --> 00:24:15.840 as well.

NOTE Confidence: 0.9432819

00:24:17.820 --> 00:24:19.420 So these this summarizes RAS

NOTE Confidence: 0.9432819

00:24:19.420 --> 00:24:20.800 inhibitors in the pipeline.

NOTE Confidence: 0.9964126

00:24:21.180 --> 00:24:21.680 The

NOTE Confidence: 0.9709918

00:24:22.315 --> 00:24:23.675 pink ones here are approved.

NOTE Confidence: 0.9709918

00:24:23.675 --> 00:24:25.055 That's from Amgen and Marathi.

NOTE Confidence: 0.9709918

00:24:25.195 --> 00:24:26.315 All the blue ones are

NOTE Confidence: 0.9709918

00:24:26.315 --> 00:24:27.755 in clinical trials right now.

NOTE Confidence: 0.9709918

00:24:27.755 --> 00:24:28.575 This is probably

NOTE Confidence: 0.8356546

00:24:29.115 --> 00:24:30.234 out of date after those

NOTE Confidence: 0.8356546

00:24:30.234 --> 00:24:31.295 of you went to ACR.

NOTE Confidence: 0.8512011

00:24:31.755 --> 00:24:33.835 Can't have, you know, escaped

NOTE Confidence: 0.8512011

00:24:33.835 --> 00:24:34.715 the fact that half a

NOTE Confidence: 0.8512011

00:24:34.715 --> 00:24:36.175 torsion KRAS inhibitors.

NOTE Confidence: 0.9022751

00:24:37.279 --> 00:24:38.080 So these are all in

NOTE Confidence: 0.9022751

00:24:38.080 --> 00:24:39.519 the clinic, but the majority

NOTE Confidence: 0.9022751

00:24:39.519 --> 00:24:40.960 of these are knockoffs of

NOTE Confidence: 0.9022751

00:24:40.960 --> 00:24:42.859 KVAN's original idea, the,

NOTE Confidence: 0.61479867

00:24:44.480 --> 00:24:44.980 compounds.

NOTE Confidence: 0.97015643

00:24:45.359 --> 00:24:47.200 And, by chance, the pocket

NOTE Confidence: 0.97015643

00:24:47.200 --> 00:24:49.119 that KVAN discovered is only

NOTE Confidence: 0.97015643

00:24:49.119 --> 00:24:49.619 accessible,

NOTE Confidence: 0.96597564

00:24:50.145 --> 00:24:51.665 apparently, at that time in

NOTE Confidence: 0.96597564

00:24:51.665 --> 00:24:52.865 the, off state of the

NOTE Confidence: 0.96597564

00:24:52.865 --> 00:24:54.645 protein, the GDP bound state.

NOTE Confidence: 0.96597564

00:24:54.785 --> 00:24:56.305 Okay? So these are all

NOTE Confidence: 0.96597564

00:24:56.305 --> 00:24:57.285 off state inhibitors.

NOTE Confidence: 0.9337503

00:24:58.385 --> 00:24:59.425 Now for those of you

NOTE Confidence: 0.9337503

00:24:59.425 --> 00:25:00.385 who think about RAS at

NOTE Confidence: 0.9337503

00:25:00.385 --> 00:25:01.585 all, you'll think, well, hang

NOTE Confidence: 0.9337503

00:25:01.585 --> 00:25:02.545 on. What's the point of

NOTE Confidence: 0.9337503

00:25:02.545 --> 00:25:03.665 inhibiting the the off state

NOTE Confidence: 0.9337503

00:25:03.665 --> 00:25:04.545 of RAS when you wanna

NOTE Confidence: 0.9337503

00:25:04.545 --> 00:25:05.790 hit inhibit the on state?

NOTE Confidence: 0.9337503

00:25:06.190 --> 00:25:07.550 But turns out RAS protein

NOTE Confidence: 0.9337503

00:25:07.550 --> 00:25:09.010 cycle between the two states.

NOTE Confidence: 0.9337503

00:25:09.150 --> 00:25:10.350 So a compound that traps

NOTE Confidence: 0.9337503

00:25:10.350 --> 00:25:11.310 the protein in the off

NOTE Confidence: 0.9337503

00:25:11.310 --> 00:25:13.650 state prevents it becoming activated

NOTE Confidence: 0.9337503

00:25:13.790 --> 00:25:14.910 is a very good strategy.

NOTE Confidence: 0.9337503

00:25:14.910 --> 00:25:16.030 Right? Trapping it in the

NOTE Confidence: 0.9337503

00:25:16.030 --> 00:25:17.150 off in the off state,

NOTE Confidence: 0.9337503

00:25:17.150 --> 00:25:18.050 so it's seen.

NOTE Confidence: 0.9023139

00:25:19.514 --> 00:25:21.195 However, there are compounds in

NOTE Confidence: 0.9023139

00:25:21.195 --> 00:25:22.315 the clinic now, including when

NOTE Confidence: 0.9023139

00:25:22.315 --> 00:25:24.315 I'll mention, just coming up,

NOTE Confidence: 0.9023139

00:25:24.315 --> 00:25:25.914 BBOA five twenty, which does

NOTE Confidence: 0.9023139

00:25:25.914 --> 00:25:26.414 actually,

NOTE Confidence: 0.79852325

00:25:27.434 --> 00:25:28.955 bind covenylate to cysteine in

NOTE Confidence: 0.79852325

00:25:28.955 --> 00:25:30.414 a GTP bound state.

NOTE Confidence: 0.95302737

00:25:31.140 --> 00:25:31.940 This is really hard to

NOTE Confidence: 0.95302737

00:25:31.940 --> 00:25:32.740 do. We did this at

NOTE Confidence: 0.95302737

00:25:32.740 --> 00:25:33.140 Frederick,

NOTE Confidence: 0.63124883

00:25:33.619 --> 00:25:35.160 Merrill Anderson collaboration with

NOTE Confidence: 0.58767194

00:25:35.540 --> 00:25:37.160 a partner of Bio Oncology,

NOTE Confidence: 0.9467841

00:25:37.780 --> 00:25:39.380 because the the the GTP

NOTE Confidence: 0.9467841

00:25:39.380 --> 00:25:40.500 bound state is much tighter

NOTE Confidence: 0.9467841

00:25:40.500 --> 00:25:41.859 than the GDP bound state.

NOTE Confidence: 0.9467841

00:25:41.859 --> 00:25:43.160 It took years of medicinal

NOTE Confidence: 0.9467841

00:25:43.220 --> 00:25:44.500 chemistry to find a compound

NOTE Confidence: 0.9467841

00:25:44.500 --> 00:25:45.619 that would fit in into

NOTE Confidence: 0.9467841

00:25:45.619 --> 00:25:46.515 that that pocket,

NOTE Confidence: 0.95425385

00:25:46.915 --> 00:25:48.115 but we we were able

NOTE Confidence: 0.95425385

00:25:48.115 --> 00:25:48.935 to do that.

NOTE Confidence: 0.9897011

00:25:49.875 --> 00:25:50.595 I'll come back to that

NOTE Confidence: 0.9897011

00:25:50.595 --> 00:25:51.315 in just a minute and

NOTE Confidence: 0.9897011

00:25:51.315 --> 00:25:52.295 tell you how it works.

NOTE Confidence: 0.9089483

00:25:52.994 --> 00:25:54.994 These hit, t twelve d,

NOTE Confidence: 0.9089483

00:25:54.994 --> 00:25:56.035 which is the most common

NOTE Confidence: 0.9089483

00:25:56.035 --> 00:25:57.815 allele overall in human cancer,

NOTE Confidence: 0.9465704

00:25:58.435 --> 00:25:59.635 and, these in the clinic,

NOTE Confidence: 0.9465704

00:25:59.635 --> 00:26:00.755 and these are preclinical, and

NOTE Confidence: 0.9465704

00:26:00.755 --> 00:26:02.115 there are many more behind

NOTE Confidence: 0.9465704

00:26:02.115 --> 00:26:03.450 this. These are not covalent

NOTE Confidence: 0.9465704

00:26:03.450 --> 00:26:04.330 for the most part. There's

NOTE Confidence: 0.9465704

00:26:04.330 --> 00:26:05.210 one but most of them

NOTE Confidence: 0.9465704

00:26:05.210 --> 00:26:06.030 is not covalent.

NOTE Confidence: 0.9148083

00:26:06.410 --> 00:26:07.210 But some of these, like

NOTE Confidence: 0.9148083

00:26:07.210 --> 00:26:08.570 this Murati compound, which is

NOTE Confidence: 0.9148083

00:26:08.570 --> 00:26:08.890 published

NOTE Confidence: 0.7949176

00:26:10.730 --> 00:26:12.109 this has a binding constant,

NOTE Confidence: 0.9453794

00:26:12.490 --> 00:26:14.109 to RAS, to the

NOTE Confidence: 0.90282893

00:26:14.535 --> 00:26:15.655 to RAS, which is in

NOTE Confidence: 0.90282893

00:26:15.815 --> 00:26:17.575 almost unmeasurably tight. It's it's,

NOTE Confidence: 0.90282893

00:26:17.734 --> 00:26:18.615 it's an off rate, which

NOTE Confidence: 0.90282893

00:26:18.615 --> 00:26:19.734 is, in a matter of

NOTE Confidence: 0.90282893

00:26:19.734 --> 00:26:20.234 hours.

NOTE Confidence: 0.8353755

00:26:20.535 --> 00:26:21.975 The binding constant is sub

NOTE Confidence: 0.8353755

00:26:22.055 --> 00:26:23.035 way sub picomolar,

NOTE Confidence: 0.9417074

00:26:23.575 --> 00:26:24.715 and it's non covalent.

NOTE Confidence: 0.9259316

00:26:25.575 --> 00:26:26.375 And it just goes to

NOTE Confidence: 0.9259316

00:26:26.375 --> 00:26:27.415 show, you know, someone has

NOTE Confidence: 0.9259316

00:26:27.415 --> 00:26:28.295 said, you know, ten years

NOTE Confidence: 0.9259316

00:26:28.295 --> 00:26:29.130 ago, do you think we'll

NOTE Confidence: 0.9259316

00:26:29.130 --> 00:26:30.810 ever find a picomolar compound

NOTE Confidence: 0.9259316

00:26:30.810 --> 00:26:32.490 that binds to RAS in,

NOTE Confidence: 0.9259316

00:26:32.490 --> 00:26:33.470 you know, noncovalently?

NOTE Confidence: 0.84678835

00:26:34.730 --> 00:26:36.410 It it said, well, no

NOTE Confidence: 0.84678835

00:26:36.410 --> 00:26:36.910 way.

NOTE Confidence: 0.9844356

00:26:37.850 --> 00:26:38.970 But it that's that's the

NOTE Confidence: 0.9844356

00:26:38.970 --> 00:26:40.650 way it is. So, it

NOTE Confidence: 0.9844356

00:26:40.650 --> 00:26:41.770 just sort of got cracked

NOTE Confidence: 0.9844356

00:26:41.770 --> 00:26:42.670 piece by piece.

NOTE Confidence: 0.9043471

00:26:43.054 --> 00:26:44.835 So these compounds are, again,

NOTE Confidence: 0.9043471

00:26:44.895 --> 00:26:46.275 in the clinic. These are,

NOTE Confidence: 0.9964625

00:26:46.815 --> 00:26:48.595 other versions of different alleles.

NOTE Confidence: 0.91297734

00:26:48.975 --> 00:26:50.255 These are PAN KRAS that

NOTE Confidence: 0.91297734

00:26:50.255 --> 00:26:51.535 I mentioned earlier, might be

NOTE Confidence: 0.91297734

00:26:51.535 --> 00:26:53.455 used for NF1 disease. We

NOTE Confidence: 0.91297734

00:26:53.455 --> 00:26:54.434 have one at BridgeBio,

NOTE Confidence: 0.9677938

00:26:54.815 --> 00:26:55.615 this one here, which is

NOTE Confidence: 0.9677938

00:26:55.615 --> 00:26:56.960 in the clinic now. And

NOTE Confidence: 0.9677938

00:26:56.960 --> 00:26:58.480 we're developing a a version

NOTE Confidence: 0.9677938

00:26:58.480 --> 00:26:59.200 of that for the for

NOTE Confidence: 0.9677938

00:26:59.200 --> 00:27:00.660 treating, NF one.

NOTE Confidence: 0.98819506

00:27:01.600 --> 00:27:03.060 So from, you know, nothing,

NOTE Confidence: 0.95821095

00:27:03.520 --> 00:27:04.720 twenty thirteen, we now have

NOTE Confidence: 0.95821095

00:27:04.720 --> 00:27:05.760 a whole, you know, whole

NOTE Confidence: 0.95821095

00:27:05.760 --> 00:27:08.100 pipeline of RAS, inhibitors. Okay.

NOTE Confidence: 0.9490168

00:27:10.315 --> 00:27:11.835 Okay. So, again, these are

NOTE Confidence: 0.9490168

00:27:11.835 --> 00:27:13.275 the the two, that were

NOTE Confidence: 0.9490168

00:27:13.275 --> 00:27:14.015 first approved.

NOTE Confidence: 0.9479566

00:27:14.875 --> 00:27:16.175 I think these went into

NOTE Confidence: 0.9479566

00:27:16.234 --> 00:27:17.515 clinic pretty quickly, and and,

NOTE Confidence: 0.9479566

00:27:17.835 --> 00:27:18.895 Amgen and

NOTE Confidence: 0.75624764

00:27:19.275 --> 00:27:20.315 and and Marathi had these

NOTE Confidence: 0.75624764

00:27:20.315 --> 00:27:21.215 drugs approved,

NOTE Confidence: 0.8377153

00:27:22.234 --> 00:27:23.515 as a single agents or

NOTE Confidence: 0.8377153

00:27:23.515 --> 00:27:24.895 in this case, in combination,

NOTE Confidence: 0.8377153

00:27:25.035 --> 00:27:25.775 with cetuximab

NOTE Confidence: 0.9572813

00:27:26.230 --> 00:27:26.889 in twenty

NOTE Confidence: 0.88349736

00:27:27.269 --> 00:27:28.009 four. However,

NOTE Confidence: 0.8438297

00:27:28.549 --> 00:27:30.230 although there was somewhat somewhat

NOTE Confidence: 0.8438297

00:27:30.230 --> 00:27:31.750 of an advantage in of

NOTE Confidence: 0.8438297

00:27:31.750 --> 00:27:33.609 progression free survival early on,

NOTE Confidence: 0.8438297

00:27:33.750 --> 00:27:34.250 overall,

NOTE Confidence: 0.9853167

00:27:34.710 --> 00:27:36.490 there's no real survival benefit

NOTE Confidence: 0.9853167

00:27:36.549 --> 00:27:38.470 of using these drugs, compared

NOTE Confidence: 0.9853167

00:27:38.470 --> 00:27:40.009 with standard of care chemotherapy.

NOTE Confidence: 0.97708523

00:27:41.145 --> 00:27:42.685 So this was obviously disappointing.

NOTE Confidence: 0.9651404

00:27:43.625 --> 00:27:44.905 In some ways, not too

NOTE Confidence: 0.9651404

00:27:44.905 --> 00:27:46.025 surprising because we know that

NOTE Confidence: 0.9651404

00:27:46.025 --> 00:27:46.984 if you inhibit the RAS

NOTE Confidence: 0.9651404

00:27:46.984 --> 00:27:49.305 pathway, you activate upstream signaling

NOTE Confidence: 0.9651404

00:27:49.305 --> 00:27:50.905 pathway by de repressing EGF

NOTE Confidence: 0.9651404

00:27:50.905 --> 00:27:52.505 receptor, for example, and and

NOTE Confidence: 0.9651404

00:27:52.505 --> 00:27:53.305 that has to be dealt

NOTE Confidence: 0.9651404

00:27:53.305 --> 00:27:54.330 with. But I think most

NOTE Confidence: 0.9651404

00:27:54.330 --> 00:27:55.690 people were expecting a much

NOTE Confidence: 0.9651404

00:27:55.690 --> 00:27:57.309 more dramatic response than this.

NOTE Confidence: 0.95756775

00:27:57.770 --> 00:27:59.770 And, the problem is these,

NOTE Confidence: 0.95756775

00:27:59.929 --> 00:28:01.150 tumors acquire resistance,

NOTE Confidence: 0.91129553

00:28:01.609 --> 00:28:02.350 very quickly,

NOTE Confidence: 0.98468006

00:28:02.890 --> 00:28:04.090 and this has been studied

NOTE Confidence: 0.98468006

00:28:04.090 --> 00:28:04.910 quite carefully.

NOTE Confidence: 0.93432724

00:28:05.450 --> 00:28:06.855 About at least, I think,

NOTE Confidence: 0.93432724

00:28:06.855 --> 00:28:08.395 the current betting is about

NOTE Confidence: 0.93432724

00:28:08.535 --> 00:28:09.815 two thirds of the all

NOTE Confidence: 0.93432724

00:28:09.815 --> 00:28:11.275 the, resistance mechanisms

NOTE Confidence: 0.96473247

00:28:11.575 --> 00:28:13.675 relate to upstream signaling. Okay?

NOTE Confidence: 0.97939

00:28:14.055 --> 00:28:15.175 And that's because of a

NOTE Confidence: 0.97939

00:28:15.175 --> 00:28:16.935 of a fundamental flaw in

NOTE Confidence: 0.97939

00:28:16.935 --> 00:28:18.455 the original concept. Although it's

NOTE Confidence: 0.97939

00:28:18.455 --> 00:28:20.250 a brilliant concept, the floor

NOTE Confidence: 0.97939

00:28:20.250 --> 00:28:21.130 is that the drug has

NOTE Confidence: 0.97939

00:28:21.130 --> 00:28:22.270 to bind to the inactive

NOTE Confidence: 0.97939

00:28:22.330 --> 00:28:23.630 state of the

NOTE Confidence: 0.99404496

00:28:29.690 --> 00:28:30.190 sorry.

NOTE Confidence: 0.9288646

00:28:30.650 --> 00:28:31.530 The drug has to bind

NOTE Confidence: 0.9288646

00:28:31.530 --> 00:28:32.490 to the inactive state of

NOTE Confidence: 0.9288646

00:28:32.490 --> 00:28:33.550 the of the RAS protein,

NOTE Confidence: 0.97476673

00:28:34.115 --> 00:28:35.015 which is fine.

NOTE Confidence: 0.9470013

00:28:35.475 --> 00:28:36.595 So the drug binds here

NOTE Confidence: 0.9470013

00:28:36.595 --> 00:28:38.035 and then, basically, locks it

NOTE Confidence: 0.9470013

00:28:38.035 --> 00:28:39.075 in this state and prevents

NOTE Confidence: 0.9470013

00:28:39.075 --> 00:28:40.195 it going back to the

NOTE Confidence: 0.9470013

00:28:40.195 --> 00:28:42.035 active state. The problem is

NOTE Confidence: 0.9470013

00:28:42.035 --> 00:28:43.555 the tumors can quite easily,

NOTE Confidence: 0.9470013

00:28:43.555 --> 00:28:45.795 apparently, find ways of increasing

NOTE Confidence: 0.9470013

00:28:45.795 --> 00:28:46.695 upstream signaling.

NOTE Confidence: 0.9685642

00:28:47.350 --> 00:28:48.889 So if SARS is activated

NOTE Confidence: 0.9685642

00:28:49.110 --> 00:28:50.230 and gets to the inactive

NOTE Confidence: 0.9685642

00:28:50.230 --> 00:28:51.830 form of RAS first, it'll

NOTE Confidence: 0.9685642

00:28:51.830 --> 00:28:52.870 kick the protein back to

NOTE Confidence: 0.9685642

00:28:52.870 --> 00:28:54.149 the active state, and off

NOTE Confidence: 0.9685642

00:28:54.149 --> 00:28:55.269 we go again down this

NOTE Confidence: 0.9685642

00:28:55.269 --> 00:28:55.769 pathway.

NOTE Confidence: 0.99454045

00:28:56.309 --> 00:28:57.269 So the drug has to

NOTE Confidence: 0.99454045

00:28:57.269 --> 00:28:58.649 compete with endogenous

NOTE Confidence: 0.9249064

00:28:58.950 --> 00:28:59.929 RTK signaling.

NOTE Confidence: 0.90659237

00:29:00.365 --> 00:29:01.325 And tumors have found ways

NOTE Confidence: 0.90659237

00:29:01.325 --> 00:29:03.105 of amplifying RTK signaling,

NOTE Confidence: 0.89981514

00:29:04.045 --> 00:29:05.425 or even making more KRAS

NOTE Confidence: 0.89981514

00:29:05.645 --> 00:29:06.765 so the drug can't keep

NOTE Confidence: 0.89981514

00:29:06.765 --> 00:29:07.885 up and can't it can't

NOTE Confidence: 0.89981514

00:29:07.885 --> 00:29:09.245 hold back the protein in

NOTE Confidence: 0.89981514

00:29:09.245 --> 00:29:10.445 and out of state because

NOTE Confidence: 0.89981514

00:29:10.445 --> 00:29:12.605 there's tremendous pressure on upstream

NOTE Confidence: 0.89981514

00:29:12.605 --> 00:29:13.965 to get the to get

NOTE Confidence: 0.89981514

00:29:13.965 --> 00:29:15.165 the protein back into the

NOTE Confidence: 0.89981514

00:29:15.165 --> 00:29:15.825 on state.

NOTE Confidence: 0.99548227

00:29:17.039 --> 00:29:18.100 So the initial

NOTE Confidence: 0.92490715

00:29:18.720 --> 00:29:20.000 once this was realized, the

NOTE Confidence: 0.92490715

00:29:20.000 --> 00:29:21.200 number of clinical trials were

NOTE Confidence: 0.92490715

00:29:21.200 --> 00:29:22.360 started with drugs that hit

NOTE Confidence: 0.92490715

00:29:22.480 --> 00:29:23.919 inhibit SHIFT two to try

NOTE Confidence: 0.92490715

00:29:23.919 --> 00:29:25.600 and prevent upstream signaling or

NOTE Confidence: 0.92490715

00:29:25.600 --> 00:29:27.299 SARS or RTK signaling,

NOTE Confidence: 0.9386322

00:29:28.159 --> 00:29:29.305 and for the most part,

NOTE Confidence: 0.9386322

00:29:29.305 --> 00:29:30.345 except in lung in the

NOTE Confidence: 0.9386322

00:29:30.345 --> 00:29:31.325 colorectal cancer,

NOTE Confidence: 0.9593173

00:29:31.705 --> 00:29:33.465 for different reasons maybe, this

NOTE Confidence: 0.9593173

00:29:33.465 --> 00:29:34.665 has not been very successful

NOTE Confidence: 0.9593173

00:29:34.665 --> 00:29:36.105 because these drugs are just

NOTE Confidence: 0.9593173

00:29:36.105 --> 00:29:37.385 toxic. They're just they're like

NOTE Confidence: 0.9593173

00:29:37.385 --> 00:29:39.305 growth factor signaling inhibitors that

NOTE Confidence: 0.9593173

00:29:39.305 --> 00:29:41.065 don't have any any, any

NOTE Confidence: 0.9593173

00:29:41.065 --> 00:29:42.205 specificity. So

NOTE Confidence: 0.9993672

00:29:42.809 --> 00:29:43.309 combining

NOTE Confidence: 0.98085314

00:29:43.769 --> 00:29:45.289 the off state with upstream

NOTE Confidence: 0.98085314

00:29:45.289 --> 00:29:46.409 inhibitors has not been a

NOTE Confidence: 0.98085314

00:29:46.409 --> 00:29:48.029 successful strategy, I would say.

NOTE Confidence: 0.9218273

00:29:48.330 --> 00:29:49.690 So a better strategy would

NOTE Confidence: 0.9218273

00:29:49.690 --> 00:29:50.490 be to find a compound

NOTE Confidence: 0.9218273

00:29:50.490 --> 00:29:51.769 that hits the GTP bound

NOTE Confidence: 0.9218273

00:29:51.769 --> 00:29:53.690 state directly, and then, you

NOTE Confidence: 0.9218273

00:29:53.690 --> 00:29:54.830 wouldn't have this problem

NOTE Confidence: 0.8944001

00:29:55.335 --> 00:29:56.475 in in theory.

NOTE Confidence: 0.9194389

00:29:58.934 --> 00:29:59.735 So that's what we did.

NOTE Confidence: 0.9194389

00:29:59.735 --> 00:30:00.534 As I said, this took

NOTE Confidence: 0.9194389

00:30:00.534 --> 00:30:02.135 a long time, for we

NOTE Confidence: 0.9194389

00:30:02.135 --> 00:30:03.495 did this in collaboration with

NOTE Confidence: 0.9194389

00:30:03.495 --> 00:30:04.534 the group at, at British

NOTE Confidence: 0.9194389

00:30:04.534 --> 00:30:05.595 British Bio Oncology.

NOTE Confidence: 0.96428156

00:30:06.534 --> 00:30:07.414 We were able to do

NOTE Confidence: 0.96428156

00:30:07.414 --> 00:30:08.455 this because right from the

NOTE Confidence: 0.96428156

00:30:08.455 --> 00:30:09.174 get go in the RAS

NOTE Confidence: 0.96428156

00:30:09.174 --> 00:30:09.674 initiative,

NOTE Confidence: 0.99569076

00:30:10.000 --> 00:30:11.279 our mandate was to attack

NOTE Confidence: 0.99569076

00:30:11.279 --> 00:30:12.419 pancreatic cancer,

NOTE Confidence: 0.97358173

00:30:13.039 --> 00:30:14.240 not g twelve c lung

NOTE Confidence: 0.97358173

00:30:14.240 --> 00:30:16.240 cancer. But pancreatic cancer is

NOTE Confidence: 0.97358173

00:30:16.240 --> 00:30:17.679 mostly g twelve d and

NOTE Confidence: 0.97358173

00:30:17.679 --> 00:30:18.960 v, which are much more

NOTE Confidence: 0.97358173

00:30:18.960 --> 00:30:20.400 GTP bound than g twelve

NOTE Confidence: 0.97358173

00:30:20.400 --> 00:30:21.679 c, and we wouldn't be

NOTE Confidence: 0.97358173

00:30:21.679 --> 00:30:22.659 able to use the covalent

NOTE Confidence: 0.97358173

00:30:22.720 --> 00:30:23.220 approach.

NOTE Confidence: 0.92957705

00:30:23.674 --> 00:30:24.875 Right from the start, we

NOTE Confidence: 0.92957705

00:30:24.875 --> 00:30:25.615 worked on

NOTE Confidence: 0.91434956

00:30:25.995 --> 00:30:27.275 drugs that hit the GTP

NOTE Confidence: 0.91434956

00:30:27.275 --> 00:30:29.375 form of mutant RAS proteins.

NOTE Confidence: 0.91434956

00:30:29.674 --> 00:30:30.335 And, eventually,

NOTE Confidence: 0.92541134

00:30:30.794 --> 00:30:31.934 as we're making drugs,

NOTE Confidence: 0.95192915

00:30:32.235 --> 00:30:34.255 for to target pancreatic cancer,

NOTE Confidence: 0.95192915

00:30:34.315 --> 00:30:35.355 we realized we could quickly

NOTE Confidence: 0.95192915

00:30:35.434 --> 00:30:36.315 quite easily make one of

NOTE Confidence: 0.95192915

00:30:36.315 --> 00:30:37.034 those into a g two

NOTE Confidence: 0.95192915

00:30:37.034 --> 00:30:38.395 l c compound because cystine

NOTE Confidence: 0.95192915

00:30:38.395 --> 00:30:39.540 was right close by to

NOTE Confidence: 0.95192915

00:30:39.620 --> 00:30:41.220 our active site. So we

NOTE Confidence: 0.95192915

00:30:41.220 --> 00:30:42.740 have some experience in targeting

NOTE Confidence: 0.95192915

00:30:42.740 --> 00:30:44.100 the on the on state,

NOTE Confidence: 0.95192915

00:30:44.100 --> 00:30:45.700 which we translated into this

NOTE Confidence: 0.95192915

00:30:45.700 --> 00:30:46.200 compound.

NOTE Confidence: 0.9498279

00:30:46.820 --> 00:30:47.860 So here's some specs. This

NOTE Confidence: 0.9498279

00:30:47.860 --> 00:30:49.220 is all published so, recently,

NOTE Confidence: 0.9498279

00:30:49.220 --> 00:30:50.020 so I won't go into

NOTE Confidence: 0.9498279

00:30:50.020 --> 00:30:51.780 any detail. It's extremely potent

NOTE Confidence: 0.9498279

00:30:51.780 --> 00:30:52.100 with,

NOTE Confidence: 0.7531848

00:30:52.815 --> 00:30:53.855 seventy, p q m l

NOTE Confidence: 0.7531848

00:30:53.855 --> 00:30:54.894 I c fifty and cell

NOTE Confidence: 0.7531848

00:30:54.894 --> 00:30:56.894 lines, very, very clean, good

NOTE Confidence: 0.7531848

00:30:56.894 --> 00:30:58.115 good drug like properties,

NOTE Confidence: 0.90652597

00:30:58.735 --> 00:30:59.054 and,

NOTE Confidence: 0.97082204

00:30:59.774 --> 00:31:00.595 off we go.

NOTE Confidence: 0.8386537

00:31:02.414 --> 00:31:03.934 Of course, there's twenty other

NOTE Confidence: 0.8386537

00:31:03.934 --> 00:31:05.235 Rasnovas in the clinics.

NOTE Confidence: 0.9542804

00:31:06.090 --> 00:31:07.049 So showing this is better

NOTE Confidence: 0.9542804

00:31:07.049 --> 00:31:07.850 than the other ones is

NOTE Confidence: 0.9542804

00:31:07.850 --> 00:31:09.370 is our challenge, but, we

NOTE Confidence: 0.9542804

00:31:09.370 --> 00:31:10.410 believe that the on state

NOTE Confidence: 0.9542804

00:31:10.410 --> 00:31:11.690 will be more effective, but

NOTE Confidence: 0.9542804

00:31:11.690 --> 00:31:12.750 we need to prove it.

NOTE Confidence: 0.9542804

00:31:13.049 --> 00:31:13.929 But you can ask, okay.

NOTE Confidence: 0.9542804

00:31:13.929 --> 00:31:14.970 Well, the the off state,

NOTE Confidence: 0.9542804

00:31:14.970 --> 00:31:15.690 we can now sort of

NOTE Confidence: 0.9542804

00:31:15.690 --> 00:31:16.650 imagine how it works. It

NOTE Confidence: 0.9542804

00:31:16.650 --> 00:31:17.690 traps the protein in the

NOTE Confidence: 0.9542804

00:31:17.690 --> 00:31:18.970 in the active state. How

NOTE Confidence: 0.9542804

00:31:18.970 --> 00:31:20.250 did the drug work if

NOTE Confidence: 0.9542804

00:31:20.250 --> 00:31:21.210 it binds to the on

NOTE Confidence: 0.9542804

00:31:21.210 --> 00:31:22.225 state? How does that prevent

NOTE Confidence: 0.9542804

00:31:22.225 --> 00:31:22.725 signaling?

NOTE Confidence: 0.9727905

00:31:24.145 --> 00:31:25.024 Well, this shows, first of

NOTE Confidence: 0.9727905

00:31:25.024 --> 00:31:26.385 all, it engages the target

NOTE Confidence: 0.9727905

00:31:26.385 --> 00:31:27.205 much more quickly

NOTE Confidence: 0.8959421

00:31:27.505 --> 00:31:29.105 than the approved drugs. So

NOTE Confidence: 0.8959421

00:31:29.105 --> 00:31:30.065 this is a RAS RAF

NOTE Confidence: 0.8959421

00:31:30.065 --> 00:31:32.145 engagement, target engagement assay. We

NOTE Confidence: 0.8959421

00:31:32.145 --> 00:31:33.585 shut down RAS RAF binding

NOTE Confidence: 0.8959421

00:31:33.585 --> 00:31:35.424 within minutes, whereas the two

NOTE Confidence: 0.8959421

00:31:35.424 --> 00:31:37.284 approved drugs that clinical doses

NOTE Confidence: 0.93848985

00:31:37.720 --> 00:31:39.443 takes, you know, hours. That's

NOTE Confidence: 0.93848985

00:31:39.443 --> 00:31:41.166 because it takes a long

NOTE Confidence: 0.93848985

00:31:41.166 --> 00:31:43.080 time to hydrolyze GTP to,

NOTE Confidence: 0.93848985

00:31:43.480 --> 00:31:44.600 to to the GDP form

NOTE Confidence: 0.93848985

00:31:44.600 --> 00:31:45.639 so the drug can actually

NOTE Confidence: 0.93848985

00:31:45.639 --> 00:31:46.919 interact with the with the

NOTE Confidence: 0.93848985

00:31:46.919 --> 00:31:47.960 with the target. This is

NOTE Confidence: 0.93848985

00:31:47.960 --> 00:31:48.620 well known.

NOTE Confidence: 0.94830656

00:31:49.000 --> 00:31:50.679 So faster and more complete

NOTE Confidence: 0.94830656

00:31:50.679 --> 00:31:52.895 target engagement, we hope, will,

NOTE Confidence: 0.94830656

00:31:53.294 --> 00:31:54.735 translate into better clinical outcome.

NOTE Confidence: 0.94830656

00:31:54.735 --> 00:31:55.715 We don't know yet.

NOTE Confidence: 0.97548354

00:31:56.255 --> 00:31:56.975 But the way that it

NOTE Confidence: 0.97548354

00:31:56.975 --> 00:31:58.495 works is to take advantage

NOTE Confidence: 0.97548354

00:31:58.495 --> 00:31:59.615 of something which we we,

NOTE Confidence: 0.97548354

00:32:00.095 --> 00:32:01.215 noticed when we first started

NOTE Confidence: 0.97548354

00:32:01.215 --> 00:32:02.414 working on structures of RAS

NOTE Confidence: 0.97548354

00:32:02.414 --> 00:32:02.914 proteins,

NOTE Confidence: 0.9989445

00:32:04.575 --> 00:32:05.554 many years ago.

NOTE Confidence: 0.8150769

00:32:05.950 --> 00:32:07.870 So Symantje and Frederick solved,

NOTE Confidence: 0.8150769

00:32:08.190 --> 00:32:10.110 structures of different mutant RAS

NOTE Confidence: 0.8150769

00:32:10.110 --> 00:32:11.710 alleles, and he noticed that

NOTE Confidence: 0.8150769

00:32:11.710 --> 00:32:12.610 in some structures,

NOTE Confidence: 0.8622785

00:32:13.230 --> 00:32:14.670 the switch one region, which

NOTE Confidence: 0.8622785

00:32:14.670 --> 00:32:16.750 is where RAF, interacts, that's

NOTE Confidence: 0.8622785

00:32:16.750 --> 00:32:17.630 the effect of region I

NOTE Confidence: 0.8622785

00:32:17.630 --> 00:32:18.495 showed you earlier,

NOTE Confidence: 0.9430651

00:32:18.895 --> 00:32:19.615 can be in one of

NOTE Confidence: 0.9430651

00:32:19.615 --> 00:32:21.075 two different, configurations,

NOTE Confidence: 0.9900265

00:32:21.455 --> 00:32:23.695 confusingly called state one and

NOTE Confidence: 0.9900265

00:32:23.695 --> 00:32:24.515 state two.

NOTE Confidence: 0.91166735

00:32:25.135 --> 00:32:26.195 So this is state,

NOTE Confidence: 0.9083032

00:32:26.575 --> 00:32:28.015 one in which the switch

NOTE Confidence: 0.9083032

00:32:28.015 --> 00:32:29.375 one region, the effective binding

NOTE Confidence: 0.9083032

00:32:29.375 --> 00:32:30.895 region is away from the

NOTE Confidence: 0.9083032

00:32:30.895 --> 00:32:31.295 main,

NOTE Confidence: 0.9223069

00:32:31.775 --> 00:32:33.075 body of the g domain.

NOTE Confidence: 0.9289133

00:32:33.390 --> 00:32:35.230 Whereas in in, state two,

NOTE Confidence: 0.9289133

00:32:35.230 --> 00:32:36.590 it's tucked down and makes

NOTE Confidence: 0.9289133

00:32:36.590 --> 00:32:37.730 contact with the magnesium,

NOTE Confidence: 0.9424062

00:32:38.270 --> 00:32:40.130 and directly to the, GTP

NOTE Confidence: 0.9424062

00:32:40.270 --> 00:32:41.870 in the GTP molecule in

NOTE Confidence: 0.9424062

00:32:41.870 --> 00:32:43.790 the, active site. So this

NOTE Confidence: 0.9424062

00:32:43.790 --> 00:32:45.070 is the productive state of

NOTE Confidence: 0.9424062

00:32:45.070 --> 00:32:46.350 of RAS that interacts with

NOTE Confidence: 0.9424062

00:32:46.350 --> 00:32:48.325 its effectors. Okay? We know

NOTE Confidence: 0.9424062

00:32:48.325 --> 00:32:49.625 that because we cocrystallize

NOTE Confidence: 0.87661815

00:32:50.405 --> 00:32:52.245 RAS with RAS RBD, and

NOTE Confidence: 0.87661815

00:32:52.245 --> 00:32:53.605 you can see that switch

NOTE Confidence: 0.87661815

00:32:53.605 --> 00:32:54.805 one is in,

NOTE Confidence: 0.91955596

00:32:55.845 --> 00:32:57.465 the state two configuration.

NOTE Confidence: 0.9895985

00:32:57.845 --> 00:32:58.345 Okay?

NOTE Confidence: 0.97048366

00:32:59.205 --> 00:32:59.705 So,

NOTE Confidence: 0.9231478

00:33:00.260 --> 00:33:02.500 this dynamic switch between or

NOTE Confidence: 0.9231478

00:33:02.500 --> 00:33:03.540 or equilibrium, I should say,

NOTE Confidence: 0.9231478

00:33:03.540 --> 00:33:04.740 between state one and state

NOTE Confidence: 0.9231478

00:33:04.740 --> 00:33:05.940 two has been known for

NOTE Confidence: 0.9231478

00:33:05.940 --> 00:33:07.000 many years from,

NOTE Confidence: 0.98510313

00:33:07.620 --> 00:33:08.920 NMR data from,

NOTE Confidence: 0.855331

00:33:09.780 --> 00:33:11.300 Karl Bitzer and Whittinghofer and

NOTE Confidence: 0.855331

00:33:11.300 --> 00:33:12.674 others from way back. Who

NOTE Confidence: 0.855331

00:33:12.674 --> 00:33:13.894 looked at, NMR

NOTE Confidence: 0.9658322

00:33:14.514 --> 00:33:16.115 spectra from emitted from the

NOTE Confidence: 0.9658322

00:33:16.115 --> 00:33:17.554 phosphates in the RAS protein.

NOTE Confidence: 0.9658322

00:33:17.554 --> 00:33:18.595 So these are this is

NOTE Confidence: 0.9658322

00:33:18.595 --> 00:33:20.134 thirty one p NMR

NOTE Confidence: 0.91522104

00:33:20.434 --> 00:33:21.654 where you can see resonances

NOTE Confidence: 0.91522104

00:33:21.875 --> 00:33:23.794 from the alpha, beta, and

NOTE Confidence: 0.91522104

00:33:23.794 --> 00:33:25.554 gamma phosphates in in the

NOTE Confidence: 0.91522104

00:33:25.554 --> 00:33:26.215 g domain.

NOTE Confidence: 0.9519653

00:33:27.150 --> 00:33:28.350 So, the point here is

NOTE Confidence: 0.9519653

00:33:28.350 --> 00:33:29.310 we can tell state two

NOTE Confidence: 0.9519653

00:33:29.310 --> 00:33:30.430 from state one by the

NOTE Confidence: 0.9519653

00:33:30.430 --> 00:33:31.950 resonance of the the gamma

NOTE Confidence: 0.9519653

00:33:31.950 --> 00:33:34.050 phosphate, gamma one, gamma two.

NOTE Confidence: 0.9519653

00:33:34.190 --> 00:33:35.390 And we add our drug

NOTE Confidence: 0.9519653

00:33:35.390 --> 00:33:37.390 to these, g domains, the

NOTE Confidence: 0.9519653

00:33:37.390 --> 00:33:38.990 protein starts to accumulate in

NOTE Confidence: 0.9519653

00:33:38.990 --> 00:33:40.350 state one, which is the

NOTE Confidence: 0.9519653

00:33:40.350 --> 00:33:41.890 form that can't bind RAF.

NOTE Confidence: 0.9519653

00:33:42.184 --> 00:33:42.684 Okay?

NOTE Confidence: 0.99515456

00:33:43.145 --> 00:33:44.525 So we think the drug

NOTE Confidence: 0.8736516

00:33:44.905 --> 00:33:45.785 sort of forces its way

NOTE Confidence: 0.8736516

00:33:45.785 --> 00:33:47.065 into the, into the g

NOTE Confidence: 0.8736516

00:33:47.065 --> 00:33:48.825 domain, this tiny pocket, and

NOTE Confidence: 0.8736516

00:33:48.825 --> 00:33:49.225 then,

NOTE Confidence: 0.95941323

00:33:50.025 --> 00:33:51.785 pops out the switch one

NOTE Confidence: 0.95941323

00:33:51.785 --> 00:33:52.985 region into a state where

NOTE Confidence: 0.95941323

00:33:52.985 --> 00:33:54.025 it can no longer interact

NOTE Confidence: 0.95941323

00:33:54.025 --> 00:33:55.465 with RAF. And then the

NOTE Confidence: 0.95941323

00:33:55.465 --> 00:33:57.304 protein is GTP bound but

NOTE Confidence: 0.95941323

00:33:57.304 --> 00:33:57.804 dead.

NOTE Confidence: 0.8515908

00:33:59.600 --> 00:34:00.320 K? So that's,

NOTE Confidence: 0.9362092

00:34:00.799 --> 00:34:01.860 that's our theory.

NOTE Confidence: 0.872723

00:34:02.880 --> 00:34:04.399 And papers published to support

NOTE Confidence: 0.872723

00:34:04.399 --> 00:34:05.760 that. So that actually should

NOTE Confidence: 0.872723

00:34:05.919 --> 00:34:07.200 that will interfere with all

NOTE Confidence: 0.872723

00:34:07.200 --> 00:34:09.119 effective binding at, let's say,

NOTE Confidence: 0.872723

00:34:09.119 --> 00:34:09.619 at,

NOTE Confidence: 0.9794941

00:34:10.160 --> 00:34:10.560 at,

NOTE Confidence: 0.97814

00:34:11.040 --> 00:34:12.020 switch one.

NOTE Confidence: 0.6224371

00:34:13.065 --> 00:34:13.565 K?

NOTE Confidence: 0.9234466

00:34:14.025 --> 00:34:14.944 So as I said, this

NOTE Confidence: 0.9234466

00:34:15.065 --> 00:34:15.864 the drug has now been

NOTE Confidence: 0.9234466

00:34:15.864 --> 00:34:16.984 through a dose escalation in

NOTE Confidence: 0.9234466

00:34:16.984 --> 00:34:18.185 phase one and, it's now

NOTE Confidence: 0.9234466

00:34:18.185 --> 00:34:19.464 being tested in combination with

NOTE Confidence: 0.9234466

00:34:19.464 --> 00:34:20.445 checkpoint inhibitors,

NOTE Confidence: 0.9739839

00:34:20.905 --> 00:34:21.405 because,

NOTE Confidence: 0.9980402

00:34:22.025 --> 00:34:23.085 in lung cancer,

NOTE Confidence: 0.9769404

00:34:23.625 --> 00:34:25.305 the ideal position to be

NOTE Confidence: 0.9769404

00:34:25.305 --> 00:34:26.265 in to make a real

NOTE Confidence: 0.9769404

00:34:26.265 --> 00:34:27.650 impact on patients is to

NOTE Confidence: 0.9769404

00:34:27.650 --> 00:34:28.310 go to frontline

NOTE Confidence: 0.89228743

00:34:28.690 --> 00:34:29.670 or first line,

NOTE Confidence: 0.8743267

00:34:30.290 --> 00:34:31.969 say, of of, treatment in

NOTE Confidence: 0.8743267

00:34:31.969 --> 00:34:32.370 which,

NOTE Confidence: 0.9352395

00:34:33.090 --> 00:34:34.210 a a drug is combined

NOTE Confidence: 0.9352395

00:34:34.210 --> 00:34:35.969 with a checkpoint inhibitor. Right

NOTE Confidence: 0.9352395

00:34:35.969 --> 00:34:37.489 now, the first line would

NOTE Confidence: 0.9352395

00:34:37.489 --> 00:34:39.030 be checkpoint plus a chemo,

NOTE Confidence: 0.9891146

00:34:39.570 --> 00:34:40.690 but we'd like to replace

NOTE Confidence: 0.9891146

00:34:40.690 --> 00:34:41.190 chemo,

NOTE Confidence: 0.9486468

00:34:41.570 --> 00:34:42.705 with a a a RAS

NOTE Confidence: 0.9486468

00:34:42.705 --> 00:34:44.225 inhibitor. So that's the goal,

NOTE Confidence: 0.9486468

00:34:44.225 --> 00:34:45.345 and that's what every company

NOTE Confidence: 0.9486468

00:34:45.345 --> 00:34:46.725 that has a RAS inhibitor

NOTE Confidence: 0.9486468

00:34:46.945 --> 00:34:48.145 is shooting for. Is that

NOTE Confidence: 0.9486468

00:34:48.145 --> 00:34:48.645 true?

NOTE Confidence: 0.98907655

00:34:50.705 --> 00:34:51.745 Okay. But it hasn't been

NOTE Confidence: 0.98907655

00:34:51.745 --> 00:34:52.245 easy.

NOTE Confidence: 0.9701933

00:34:52.545 --> 00:34:54.065 Well, nothing's easy, but it's

NOTE Confidence: 0.9701933

00:34:54.065 --> 00:34:55.685 been particularly difficult because

NOTE Confidence: 0.90851

00:34:56.840 --> 00:34:58.120 these g twelve c inhibitors

NOTE Confidence: 0.90851

00:34:58.120 --> 00:34:58.860 are covalent,

NOTE Confidence: 0.95890987

00:34:59.719 --> 00:35:00.219 and,

NOTE Confidence: 0.9431703

00:35:00.760 --> 00:35:01.560 the problem is if you

NOTE Confidence: 0.9431703

00:35:01.560 --> 00:35:02.120 if you give a high

NOTE Confidence: 0.9431703

00:35:02.120 --> 00:35:03.660 dose of a covalent compound,

NOTE Confidence: 0.9715826

00:35:03.960 --> 00:35:04.840 the theory is it can

NOTE Confidence: 0.9715826

00:35:04.840 --> 00:35:06.620 haptenize proteins in the liver.

NOTE Confidence: 0.9715826

00:35:06.840 --> 00:35:08.120 It can react with proteins

NOTE Confidence: 0.9715826

00:35:08.120 --> 00:35:09.239 randomly in the liver, and

NOTE Confidence: 0.9715826

00:35:09.239 --> 00:35:11.035 they become antigens. So when

NOTE Confidence: 0.9715826

00:35:11.035 --> 00:35:12.475 you add that effect to

NOTE Confidence: 0.9715826

00:35:12.475 --> 00:35:13.915 a checkpoint inhibitor, now you

NOTE Confidence: 0.9715826

00:35:13.915 --> 00:35:14.875 start to get an immune

NOTE Confidence: 0.9715826

00:35:14.875 --> 00:35:16.335 problem, in the liver.

NOTE Confidence: 0.9878289

00:35:16.635 --> 00:35:17.755 Not sure that's true, but

NOTE Confidence: 0.9878289

00:35:17.755 --> 00:35:18.895 that's, I think, the theory.

NOTE Confidence: 0.8114927

00:35:19.195 --> 00:35:20.075 Yeah. K. So

NOTE Confidence: 0.9120122

00:35:21.114 --> 00:35:21.614 yeah.

NOTE Confidence: 0.92775446

00:35:22.075 --> 00:35:22.395 So,

NOTE Confidence: 0.9180888

00:35:23.035 --> 00:35:24.555 so far, the compound that

NOTE Confidence: 0.9180888

00:35:24.555 --> 00:35:26.500 I mentioned, the the, OnState

NOTE Confidence: 0.9180888

00:35:26.560 --> 00:35:28.739 BB, BBO a five twenty,

NOTE Confidence: 0.9456943

00:35:29.119 --> 00:35:31.140 is so potent. We can,

NOTE Confidence: 0.9013499

00:35:31.680 --> 00:35:33.440 get really good equivalent effects

NOTE Confidence: 0.9013499

00:35:33.440 --> 00:35:34.719 of target engagement at much

NOTE Confidence: 0.9013499

00:35:34.719 --> 00:35:36.400 lower concentration, and we've not

NOTE Confidence: 0.9013499

00:35:36.400 --> 00:35:37.839 seen any liver tox yet,

NOTE Confidence: 0.9013499

00:35:37.839 --> 00:35:38.719 even at the highest dose

NOTE Confidence: 0.9013499

00:35:38.719 --> 00:35:39.680 in combination with,

NOTE Confidence: 0.94359523

00:35:40.960 --> 00:35:43.415 with, checkpoint inhibitors. But that's

NOTE Confidence: 0.94359523

00:35:43.415 --> 00:35:44.935 all, you know, playing out

NOTE Confidence: 0.94359523

00:35:44.935 --> 00:35:45.675 over time.

NOTE Confidence: 0.9216615

00:35:46.375 --> 00:35:47.415 So we will we will

NOTE Confidence: 0.9216615

00:35:47.415 --> 00:35:48.055 see. That one is,

NOTE Confidence: 0.8001691

00:35:49.094 --> 00:35:49.895 in the hands of the

NOTE Confidence: 0.8001691

00:35:49.975 --> 00:35:51.495 of our clinical colleagues. See

NOTE Confidence: 0.8001691

00:35:51.495 --> 00:35:52.715 see what counts out.

NOTE Confidence: 0.97339845

00:35:53.015 --> 00:35:53.495 No. Anyway

NOTE Confidence: 0.97485256

00:35:54.890 --> 00:35:55.950 okay. So the second

NOTE Confidence: 0.85124123

00:35:56.250 --> 00:35:57.370 drug, which entered the clinic

NOTE Confidence: 0.85124123

00:35:57.370 --> 00:35:58.410 a bit little after the

NOTE Confidence: 0.85124123

00:35:58.410 --> 00:35:59.690 the first one, is called

NOTE Confidence: 0.85124123

00:35:59.690 --> 00:36:00.270 the breaker.

NOTE Confidence: 0.57895356

00:36:00.810 --> 00:36:01.310 K?

NOTE Confidence: 0.91371125

00:36:01.690 --> 00:36:03.130 So the breaker, another massive

NOTE Confidence: 0.91371125

00:36:03.130 --> 00:36:05.150 collaboration between the, rash initiative,

NOTE Confidence: 0.8953939

00:36:06.170 --> 00:36:08.330 at Frederick National Lab, headed

NOTE Confidence: 0.8953939

00:36:08.330 --> 00:36:08.989 up by,

NOTE Confidence: 0.35020432

00:36:09.450 --> 00:36:10.190 this manchu,

NOTE Confidence: 0.7618197

00:36:10.974 --> 00:36:12.494 and bridge by bridge by

NOTE Confidence: 0.7618197

00:36:13.135 --> 00:36:14.515 bio oncology therapeutics,

NOTE Confidence: 0.849628

00:36:15.375 --> 00:36:16.175 headed up by,

NOTE Confidence: 0.8965423

00:36:16.655 --> 00:36:17.555 Pedro Beltran.

NOTE Confidence: 0.94768214

00:36:17.855 --> 00:36:19.295 And Eli Wallace is the

NOTE Confidence: 0.94768214

00:36:19.295 --> 00:36:20.655 CEO of this, company we

NOTE Confidence: 0.94768214

00:36:20.655 --> 00:36:21.695 set up really just to

NOTE Confidence: 0.94768214

00:36:21.695 --> 00:36:22.815 develop these three drugs out

NOTE Confidence: 0.94768214

00:36:22.815 --> 00:36:24.275 of the Federal National Lab.

NOTE Confidence: 0.99470407

00:36:24.900 --> 00:36:26.260 Eli is a drug discovery,

NOTE Confidence: 0.8991799

00:36:26.660 --> 00:36:27.880 expert. He developed,

NOTE Confidence: 0.86620945

00:36:29.059 --> 00:36:30.500 selamatinib when he was at

NOTE Confidence: 0.86620945

00:36:30.500 --> 00:36:32.099 Array and the, HIF two

NOTE Confidence: 0.86620945

00:36:32.099 --> 00:36:33.960 alpha inhibitor at at Peloton.

NOTE Confidence: 0.9226202

00:36:35.219 --> 00:36:36.579 So it's a great team,

NOTE Confidence: 0.9226202

00:36:36.579 --> 00:36:37.960 and they developed this compound

NOTE Confidence: 0.9226202

00:36:38.020 --> 00:36:39.480 that we call, the breaker.

NOTE Confidence: 0.9740444

00:36:40.594 --> 00:36:41.714 I should also say that

NOTE Confidence: 0.9740444

00:36:41.714 --> 00:36:43.395 this required a lot of

NOTE Confidence: 0.9740444

00:36:43.395 --> 00:36:43.895 computational,

NOTE Confidence: 0.8971409

00:36:45.075 --> 00:36:46.355 input from group at Lawrence

NOTE Confidence: 0.8971409

00:36:46.355 --> 00:36:47.635 Livermore National Labs that have

NOTE Confidence: 0.8971409

00:36:47.635 --> 00:36:48.295 a supercomputer

NOTE Confidence: 0.9006579

00:36:49.075 --> 00:36:50.355 that until recently was used

NOTE Confidence: 0.9006579

00:36:50.355 --> 00:36:52.454 to, model thermonuclear explosions.

NOTE Confidence: 0.9684692

00:36:53.609 --> 00:36:54.650 When they got fed up

NOTE Confidence: 0.9684692

00:36:54.650 --> 00:36:55.609 with doing that, they came

NOTE Confidence: 0.9684692

00:36:55.609 --> 00:36:56.730 to the NCI and say,

NOTE Confidence: 0.9684692

00:36:56.969 --> 00:36:57.769 so is there a really

NOTE Confidence: 0.9684692

00:36:57.769 --> 00:36:58.890 difficult project you can work

NOTE Confidence: 0.9684692

00:36:58.890 --> 00:36:59.390 on

NOTE Confidence: 0.99102473

00:36:59.690 --> 00:37:00.589 using our supercomputers?

NOTE Confidence: 0.90696836

00:37:00.969 --> 00:37:01.930 So we've been working with

NOTE Confidence: 0.90696836

00:37:01.930 --> 00:37:03.849 them on modeling RAS, RAF

NOTE Confidence: 0.90696836

00:37:03.849 --> 00:37:04.349 interactions,

NOTE Confidence: 0.8827553

00:37:05.049 --> 00:37:06.725 in silico and also on

NOTE Confidence: 0.8827553

00:37:06.725 --> 00:37:08.405 developing, drugs and UA was

NOTE Confidence: 0.8827553

00:37:08.405 --> 00:37:09.385 the head of this group,

NOTE Confidence: 0.91204643

00:37:09.685 --> 00:37:11.465 at Lawrence Livermore Lab.

NOTE Confidence: 0.9675748

00:37:13.125 --> 00:37:14.105 So this drug,

NOTE Confidence: 0.95411736

00:37:14.645 --> 00:37:16.645 prevents RAS activating PI three

NOTE Confidence: 0.95411736

00:37:16.645 --> 00:37:17.145 kinase.

NOTE Confidence: 0.9585684

00:37:18.770 --> 00:37:20.310 People in the RAS world,

NOTE Confidence: 0.98521566

00:37:21.090 --> 00:37:22.450 will know that the relationship

NOTE Confidence: 0.98521566

00:37:22.450 --> 00:37:23.489 between RAS and PI three

NOTE Confidence: 0.98521566

00:37:23.489 --> 00:37:24.770 kinase has been known for

NOTE Confidence: 0.98521566

00:37:24.770 --> 00:37:25.489 a long time in a

NOTE Confidence: 0.98521566

00:37:25.489 --> 00:37:26.469 kind of vague way,

NOTE Confidence: 0.9743927

00:37:26.770 --> 00:37:28.450 because it's not clear whether

NOTE Confidence: 0.9743927

00:37:28.450 --> 00:37:30.130 RAS proteins directly activate PI

NOTE Confidence: 0.9743927

00:37:30.130 --> 00:37:31.410 three kinase or they do

NOTE Confidence: 0.9743927

00:37:31.410 --> 00:37:33.015 it take advantage of PI

NOTE Confidence: 0.9743927

00:37:33.015 --> 00:37:34.395 three kinase from other sources,

NOTE Confidence: 0.9743927

00:37:34.454 --> 00:37:35.575 and it's really, really been

NOTE Confidence: 0.9743927

00:37:35.575 --> 00:37:36.954 very difficult to figure out.

NOTE Confidence: 0.9808337

00:37:37.654 --> 00:37:38.555 We know that,

NOTE Confidence: 0.8864127

00:37:39.255 --> 00:37:41.114 inhibiting MAP kinase pathway,

NOTE Confidence: 0.9320735

00:37:41.494 --> 00:37:42.635 with a RAS inhibitor

NOTE Confidence: 0.9878073

00:37:43.015 --> 00:37:44.454 plus PI three kinase inhibitor

NOTE Confidence: 0.9878073

00:37:44.454 --> 00:37:45.755 has synergistic effects.

NOTE Confidence: 0.978957

00:37:46.469 --> 00:37:46.969 So,

NOTE Confidence: 0.90425205

00:37:47.270 --> 00:37:48.310 this is shown in this

NOTE Confidence: 0.90425205

00:37:48.310 --> 00:37:49.670 mouse model from my colleague,

NOTE Confidence: 0.90425205

00:37:49.670 --> 00:37:51.350 Martin McMahon, who showed that

NOTE Confidence: 0.90425205

00:37:51.350 --> 00:37:52.390 if you activate the MAP

NOTE Confidence: 0.90425205

00:37:52.390 --> 00:37:53.750 kinase pathway with a V

NOTE Confidence: 0.90425205

00:37:53.750 --> 00:37:55.030 six hundred e BRAF, which

NOTE Confidence: 0.90425205

00:37:55.030 --> 00:37:56.390 is just basically RAF is

NOTE Confidence: 0.90425205

00:37:56.390 --> 00:37:58.150 on fire. Okay? There's no

NOTE Confidence: 0.90425205

00:37:58.150 --> 00:37:59.670 BRAF kinase activation. It's just

NOTE Confidence: 0.90425205

00:37:59.670 --> 00:38:00.330 on fire.

NOTE Confidence: 0.9787017

00:38:00.725 --> 00:38:01.844 So in a lung cancer

NOTE Confidence: 0.9787017

00:38:01.844 --> 00:38:03.545 model, this, allele,

NOTE Confidence: 0.96611774

00:38:04.085 --> 00:38:05.765 causes tumors and mice die

NOTE Confidence: 0.96611774

00:38:05.765 --> 00:38:06.965 of the disease. If you

NOTE Confidence: 0.96611774

00:38:06.965 --> 00:38:07.844 add on top of that

NOTE Confidence: 0.96611774

00:38:07.844 --> 00:38:09.844 a PI3 kinase mutation, now,

NOTE Confidence: 0.96611774

00:38:10.085 --> 00:38:11.445 the mice die much more

NOTE Confidence: 0.96611774

00:38:11.445 --> 00:38:12.565 quickly and the tumors are

NOTE Confidence: 0.96611774

00:38:12.565 --> 00:38:13.625 much more aggressive.

NOTE Confidence: 0.9187944

00:38:14.370 --> 00:38:15.250 So that's the sort of

NOTE Confidence: 0.9187944

00:38:15.250 --> 00:38:17.010 gain of function combination, and,

NOTE Confidence: 0.9187944

00:38:17.010 --> 00:38:18.850 reciprocally, if you inhibit these

NOTE Confidence: 0.9187944

00:38:18.850 --> 00:38:20.130 two pathways with,

NOTE Confidence: 0.9218489

00:38:20.770 --> 00:38:21.970 particular inhibitors of these two

NOTE Confidence: 0.9218489

00:38:21.970 --> 00:38:23.010 pathways as shown by Jeff

NOTE Confidence: 0.9218489

00:38:23.010 --> 00:38:24.450 Engelman and colleagues, you can

NOTE Confidence: 0.9218489

00:38:24.450 --> 00:38:24.950 cure

NOTE Confidence: 0.9442935

00:38:25.330 --> 00:38:26.870 KRAS tumors in mice.

NOTE Confidence: 0.94614774

00:38:27.410 --> 00:38:28.375 That was a challenge that

NOTE Confidence: 0.94614774

00:38:28.375 --> 00:38:29.335 Talajax put out a long

NOTE Confidence: 0.94614774

00:38:29.335 --> 00:38:30.135 time ago. We had ten

NOTE Confidence: 0.94614774

00:38:30.135 --> 00:38:31.575 thousand bucks for anybody who

NOTE Confidence: 0.94614774

00:38:31.575 --> 00:38:33.495 could cure a KRAS tumor

NOTE Confidence: 0.94614774

00:38:33.495 --> 00:38:34.295 in mice, and this was,

NOTE Confidence: 0.94614774

00:38:34.295 --> 00:38:35.095 I think, the first time

NOTE Confidence: 0.94614774

00:38:35.095 --> 00:38:36.375 it was done using two

NOTE Confidence: 0.94614774

00:38:36.375 --> 00:38:37.195 different drugs.

NOTE Confidence: 0.8327213

00:38:38.615 --> 00:38:39.115 However,

NOTE Confidence: 0.9992691

00:38:39.895 --> 00:38:41.175 the combination of these drugs

NOTE Confidence: 0.9992691

00:38:41.175 --> 00:38:42.155 is really toxic.

NOTE Confidence: 0.9044184

00:38:43.390 --> 00:38:44.750 Mecanibers, as I mentioned for

NOTE Confidence: 0.9044184

00:38:44.750 --> 00:38:46.210 NF one, are toxic,

NOTE Confidence: 0.916588

00:38:46.510 --> 00:38:47.390 especially if it does high

NOTE Confidence: 0.916588

00:38:47.390 --> 00:38:48.270 enough to have an effect

NOTE Confidence: 0.916588

00:38:48.270 --> 00:38:49.870 on a malignant tumor. And

NOTE Confidence: 0.916588

00:38:49.870 --> 00:38:51.230 PI three kinase inhibitors are

NOTE Confidence: 0.916588

00:38:51.230 --> 00:38:53.489 toxic for multiple reasons, including,

NOTE Confidence: 0.9880112

00:38:54.110 --> 00:38:55.250 generation of hypoglycemia

NOTE Confidence: 0.9636026

00:38:55.895 --> 00:38:57.655 because insulin signaling depends on

NOTE Confidence: 0.9636026

00:38:57.655 --> 00:38:58.555 p I three kinase.

NOTE Confidence: 0.97573495

00:38:59.815 --> 00:39:00.654 So in theory, this is

NOTE Confidence: 0.97573495

00:39:00.654 --> 00:39:01.494 a great idea, but it

NOTE Confidence: 0.97573495

00:39:01.494 --> 00:39:02.614 hasn't been possible to find

NOTE Confidence: 0.97573495

00:39:02.614 --> 00:39:04.375 a combination of drugs which

NOTE Confidence: 0.97573495

00:39:04.375 --> 00:39:05.255 is safe enough,

NOTE Confidence: 0.9902382

00:39:05.575 --> 00:39:06.694 to to test this in

NOTE Confidence: 0.9902382

00:39:06.694 --> 00:39:07.435 in people.

NOTE Confidence: 0.90876514

00:39:08.840 --> 00:39:09.560 So just to show you

NOTE Confidence: 0.90876514

00:39:09.560 --> 00:39:11.000 the complexity of this situation,

NOTE Confidence: 0.90876514

00:39:11.000 --> 00:39:12.120 this is an experiment done

NOTE Confidence: 0.90876514

00:39:12.120 --> 00:39:13.320 by my ex postdoc many

NOTE Confidence: 0.90876514

00:39:13.320 --> 00:39:14.780 years ago where he transfected

NOTE Confidence: 0.90876514

00:39:14.840 --> 00:39:16.280 into cells a whole bunch

NOTE Confidence: 0.90876514

00:39:16.280 --> 00:39:17.400 of different RAS alleles or

NOTE Confidence: 0.90876514

00:39:17.400 --> 00:39:18.700 different RAS family members

NOTE Confidence: 0.8631786

00:39:19.000 --> 00:39:19.960 and and then look for

NOTE Confidence: 0.8631786

00:39:19.960 --> 00:39:21.500 their effect on different isoforms

NOTE Confidence: 0.8631786

00:39:21.560 --> 00:39:22.700 of PI three kinase,

NOTE Confidence: 0.95950615

00:39:23.125 --> 00:39:24.665 alpha, beta, gamma, and delta.

NOTE Confidence: 0.95950615

00:39:24.725 --> 00:39:25.525 And you can see here

NOTE Confidence: 0.95950615

00:39:25.525 --> 00:39:27.785 that six different RAS proteins

NOTE Confidence: 0.95950615

00:39:27.844 --> 00:39:28.985 can activate alpha.

NOTE Confidence: 0.96070516

00:39:29.685 --> 00:39:30.344 The same,

NOTE Confidence: 0.7710579

00:39:30.805 --> 00:39:31.785 SACE can do,

NOTE Confidence: 0.67977536

00:39:32.565 --> 00:39:33.065 delta.

NOTE Confidence: 0.9369053

00:39:33.445 --> 00:39:34.885 Two do sorry, gamma. Two

NOTE Confidence: 0.9369053

00:39:34.885 --> 00:39:36.005 do delta, and none of

NOTE Confidence: 0.9369053

00:39:36.005 --> 00:39:36.825 them do beta.

NOTE Confidence: 0.8127247

00:39:37.430 --> 00:39:38.870 The g proteins can activate

NOTE Confidence: 0.8127247

00:39:38.870 --> 00:39:39.590 the p I three kinase

NOTE Confidence: 0.8127247

00:39:39.590 --> 00:39:40.090 beta.

NOTE Confidence: 0.9581416

00:39:40.630 --> 00:39:41.670 So in a typical cell,

NOTE Confidence: 0.9581416

00:39:41.670 --> 00:39:42.470 you can get inputs to

NOTE Confidence: 0.9581416

00:39:42.470 --> 00:39:43.510 p I three kinase from

NOTE Confidence: 0.9581416

00:39:43.510 --> 00:39:45.030 multiple sources going to different

NOTE Confidence: 0.9581416

00:39:45.030 --> 00:39:45.530 isoforms.

NOTE Confidence: 0.977998

00:39:45.989 --> 00:39:47.110 That makes life, you know,

NOTE Confidence: 0.977998

00:39:47.110 --> 00:39:48.310 really complicated to figure out

NOTE Confidence: 0.977998

00:39:48.310 --> 00:39:49.670 what RAS is adding to

NOTE Confidence: 0.977998

00:39:49.670 --> 00:39:51.050 that, that picnic.

NOTE Confidence: 0.93942785

00:39:51.835 --> 00:39:53.435 Well, this was, solved at

NOTE Confidence: 0.93942785

00:39:53.435 --> 00:39:53.935 least,

NOTE Confidence: 0.92524874

00:39:54.875 --> 00:39:55.835 in a sort of very

NOTE Confidence: 0.92524874

00:39:55.835 --> 00:39:56.955 specific way by a really

NOTE Confidence: 0.92524874

00:39:56.955 --> 00:39:58.575 brilliant experiment by,

NOTE Confidence: 0.92663383

00:39:59.035 --> 00:39:59.935 Julian Downwood,

NOTE Confidence: 0.92305034

00:40:01.035 --> 00:40:02.395 who showed, many years ago

NOTE Confidence: 0.92305034

00:40:02.395 --> 00:40:03.755 back in two thousand seven

NOTE Confidence: 0.92305034

00:40:03.755 --> 00:40:05.855 that if you, engineer mice

NOTE Confidence: 0.918865

00:40:06.410 --> 00:40:07.770 so that, I I got

NOTE Confidence: 0.918865

00:40:07.770 --> 00:40:09.210 goosebumps thinking about this experiment.

NOTE Confidence: 0.918865

00:40:09.210 --> 00:40:10.510 It's, you know, really awesome.

NOTE Confidence: 0.9074278

00:40:11.850 --> 00:40:13.530 He engineered mice in which,

NOTE Confidence: 0.9074278

00:40:13.850 --> 00:40:15.050 he took a mutant allele

NOTE Confidence: 0.9074278

00:40:15.050 --> 00:40:16.250 of p p I kinase

NOTE Confidence: 0.9074278

00:40:16.250 --> 00:40:17.550 alpha, p one ten alpha,

NOTE Confidence: 0.9074278

00:40:17.610 --> 00:40:19.770 mutated the, the RAS binding

NOTE Confidence: 0.9074278

00:40:19.770 --> 00:40:21.070 domain with these two mutations

NOTE Confidence: 0.9074278

00:40:21.275 --> 00:40:22.094 so that this

NOTE Confidence: 0.8575074

00:40:23.195 --> 00:40:24.795 domain can't interact with any

NOTE Confidence: 0.8575074

00:40:24.795 --> 00:40:26.715 RAS protein. Okay. RAS, MRAS,

NOTE Confidence: 0.8575074

00:40:26.715 --> 00:40:28.715 whatever cannot bind. That site

NOTE Confidence: 0.8575074

00:40:28.715 --> 00:40:29.455 is dead.

NOTE Confidence: 0.923944

00:40:29.755 --> 00:40:31.775 So he in several experiments,

NOTE Confidence: 0.923944

00:40:31.835 --> 00:40:33.114 but the most important one,

NOTE Confidence: 0.923944

00:40:33.114 --> 00:40:34.715 he'd knocked this allele into

NOTE Confidence: 0.923944

00:40:34.715 --> 00:40:36.255 mice, which already had established

NOTE Confidence: 0.923944

00:40:36.315 --> 00:40:36.815 tumors,

NOTE Confidence: 0.9372096

00:40:37.329 --> 00:40:39.329 okay, in adult mice. And

NOTE Confidence: 0.9372096

00:40:39.329 --> 00:40:40.369 the effect was that the,

NOTE Confidence: 0.9372096

00:40:40.849 --> 00:40:42.630 it this is systemic disruption.

NOTE Confidence: 0.9372096

00:40:42.770 --> 00:40:44.549 Systemic disruption was well tolerated.

NOTE Confidence: 0.96632755

00:40:45.010 --> 00:40:45.969 They didn't have any any

NOTE Confidence: 0.96632755

00:40:45.969 --> 00:40:47.089 serious problems. They went on

NOTE Confidence: 0.96632755

00:40:47.089 --> 00:40:48.130 to live, you know, full

NOTE Confidence: 0.96632755

00:40:48.130 --> 00:40:49.890 and productive lives. So that

NOTE Confidence: 0.96632755

00:40:49.890 --> 00:40:51.349 says that in normal adult

NOTE Confidence: 0.96632755

00:40:51.410 --> 00:40:53.165 mice, at least, this interaction

NOTE Confidence: 0.96632755

00:40:53.165 --> 00:40:54.145 is not essential.

NOTE Confidence: 0.974129

00:40:54.525 --> 00:40:55.025 Okay?

NOTE Confidence: 0.9143739

00:40:56.605 --> 00:40:57.105 However,

NOTE Confidence: 0.70768064

00:40:57.405 --> 00:40:58.545 and and and,

NOTE Confidence: 0.9644229

00:40:58.844 --> 00:40:59.344 importantly,

NOTE Confidence: 0.9479914

00:40:59.725 --> 00:41:00.525 no you didn't see any

NOTE Confidence: 0.9479914

00:41:00.525 --> 00:41:01.825 effect on insulin homeostasis.

NOTE Confidence: 0.9926301

00:41:02.205 --> 00:41:04.385 So this shows that, insulin

NOTE Confidence: 0.8918937

00:41:04.844 --> 00:41:06.605 activation of PFK kinase doesn't

NOTE Confidence: 0.8918937

00:41:06.605 --> 00:41:07.984 need input from RAS.

NOTE Confidence: 0.8883045

00:41:08.980 --> 00:41:10.020 But he did see tumor

NOTE Confidence: 0.8883045

00:41:10.020 --> 00:41:11.620 stasis or regression in different,

NOTE Confidence: 0.8883045

00:41:11.860 --> 00:41:13.620 mass models, including each activated

NOTE Confidence: 0.8883045

00:41:13.620 --> 00:41:15.640 EGFR or activated RAS.

NOTE Confidence: 0.9266469

00:41:16.580 --> 00:41:17.780 So from a drug discovery

NOTE Confidence: 0.9266469

00:41:17.780 --> 00:41:18.660 point of view, this is

NOTE Confidence: 0.9266469

00:41:18.660 --> 00:41:19.460 a green light. You know,

NOTE Confidence: 0.9266469

00:41:19.460 --> 00:41:20.835 it's a target which is

NOTE Confidence: 0.9266469

00:41:20.835 --> 00:41:22.114 safe, apparently, in mice at

NOTE Confidence: 0.9266469

00:41:22.114 --> 00:41:23.974 least, doesn't cause the expected

NOTE Confidence: 0.8205194

00:41:24.275 --> 00:41:25.955 talks of an, PI3 kinase

NOTE Confidence: 0.8205194

00:41:25.955 --> 00:41:26.455 inhibitor,

NOTE Confidence: 0.9554158

00:41:26.835 --> 00:41:28.614 and actually has clinical benefit,

NOTE Confidence: 0.9554158

00:41:28.755 --> 00:41:30.114 particularly in combination as he

NOTE Confidence: 0.9554158

00:41:30.114 --> 00:41:30.614 showed.

NOTE Confidence: 0.9413935

00:41:31.155 --> 00:41:32.755 So, this was a, you

NOTE Confidence: 0.9413935

00:41:32.755 --> 00:41:33.974 know, a really good start.

NOTE Confidence: 0.9413935

00:41:34.230 --> 00:41:35.690 And then, in parallel,

NOTE Confidence: 0.68097544

00:41:36.710 --> 00:41:37.830 Sally Levers at,

NOTE Confidence: 0.95817375

00:41:38.230 --> 00:41:39.270 his colleague in in the

NOTE Confidence: 0.95817375

00:41:39.270 --> 00:41:39.770 UK,

NOTE Confidence: 0.998053

00:41:40.550 --> 00:41:41.830 made the same mutations in

NOTE Confidence: 0.998053

00:41:41.830 --> 00:41:42.330 flies.

NOTE Confidence: 0.8252061

00:41:42.790 --> 00:41:44.070 So fly and flies, the

NOTE Confidence: 0.8252061

00:41:44.070 --> 00:41:45.910 whole pathway, RAS pathway is

NOTE Confidence: 0.8252061

00:41:45.910 --> 00:41:47.850 identical really to humans.

NOTE Confidence: 0.92034304

00:41:48.474 --> 00:41:49.675 But in so in flies,

NOTE Confidence: 0.92034304

00:41:49.675 --> 00:41:51.194 she made my flies in

NOTE Confidence: 0.92034304

00:41:51.194 --> 00:41:52.395 which this interaction is also

NOTE Confidence: 0.92034304

00:41:52.395 --> 00:41:53.855 disrupted by the same mutations.

NOTE Confidence: 0.90835005

00:41:54.395 --> 00:41:55.515 And these flies that have

NOTE Confidence: 0.90835005

00:41:55.515 --> 00:41:56.714 no interaction between RAS and

NOTE Confidence: 0.90835005

00:41:56.714 --> 00:41:58.315 PI three kinase go on

NOTE Confidence: 0.90835005

00:41:58.315 --> 00:41:59.515 to leave normal, happy, and

NOTE Confidence: 0.90835005

00:41:59.515 --> 00:42:00.575 productive lives.

NOTE Confidence: 0.9831488

00:42:01.170 --> 00:42:01.670 So,

NOTE Confidence: 0.96602225

00:42:02.770 --> 00:42:04.210 except when it comes to

NOTE Confidence: 0.96602225

00:42:04.210 --> 00:42:05.589 tie time to lay eggs

NOTE Confidence: 0.96602225

00:42:05.809 --> 00:42:07.250 so that they are defective

NOTE Confidence: 0.96602225

00:42:07.250 --> 00:42:07.989 at egg laying.

NOTE Confidence: 0.9423233

00:42:08.609 --> 00:42:10.130 So in this paper, Sally

NOTE Confidence: 0.9423233

00:42:10.130 --> 00:42:11.730 concluded that the interaction between

NOTE Confidence: 0.9423233

00:42:11.730 --> 00:42:13.030 RAS and PI three kinase

NOTE Confidence: 0.9423233

00:42:13.170 --> 00:42:14.930 is only necessary in certain

NOTE Confidence: 0.9423233

00:42:14.930 --> 00:42:16.515 situations, which which in flies

NOTE Confidence: 0.9423233

00:42:16.515 --> 00:42:17.635 requires a ton of protein

NOTE Confidence: 0.9423233

00:42:17.635 --> 00:42:19.174 synthesis to make eggs,

NOTE Confidence: 0.8822984

00:42:19.555 --> 00:42:21.075 and in, mice or probably

NOTE Confidence: 0.8822984

00:42:21.075 --> 00:42:21.815 in humans,

NOTE Confidence: 0.97619617

00:42:22.114 --> 00:42:22.855 during development,

NOTE Confidence: 0.98700356

00:42:23.315 --> 00:42:24.135 during angiogenesis,

NOTE Confidence: 0.9987038

00:42:24.594 --> 00:42:25.734 and during malignancy.

NOTE Confidence: 0.9081153

00:42:26.194 --> 00:42:26.994 That's where you need to

NOTE Confidence: 0.9081153

00:42:26.994 --> 00:42:27.494 turbocharge

NOTE Confidence: 0.9326865

00:42:28.130 --> 00:42:29.489 the system to get a

NOTE Confidence: 0.9326865

00:42:29.489 --> 00:42:31.250 sustained activation of PI3 kinase

NOTE Confidence: 0.9326865

00:42:31.250 --> 00:42:33.230 or stronger activation in these,

NOTE Confidence: 0.92074144

00:42:33.730 --> 00:42:35.989 none, in these pathogenic situations.

NOTE Confidence: 0.9180976

00:42:38.130 --> 00:42:39.010 And this is kind of

NOTE Confidence: 0.9180976

00:42:39.010 --> 00:42:40.070 sort of a

NOTE Confidence: 0.8296642

00:42:40.535 --> 00:42:41.255 maybe a dumber way of

NOTE Confidence: 0.8296642

00:42:41.255 --> 00:42:42.215 doing the same experiment in

NOTE Confidence: 0.8296642

00:42:42.215 --> 00:42:43.895 which, we took, cells in

NOTE Confidence: 0.8296642

00:42:43.895 --> 00:42:44.935 which we knocked out all

NOTE Confidence: 0.8296642

00:42:44.935 --> 00:42:46.135 the RAS genes, h n

NOTE Confidence: 0.8296642

00:42:46.135 --> 00:42:47.015 and k and r r

NOTE Confidence: 0.8296642

00:42:47.015 --> 00:42:47.815 s, r r s two,

NOTE Confidence: 0.8296642

00:42:47.815 --> 00:42:48.935 and m r s by

NOTE Confidence: 0.8296642

00:42:48.935 --> 00:42:49.835 adding to cells

NOTE Confidence: 0.8701427

00:42:50.135 --> 00:42:51.175 in which k ras is

NOTE Confidence: 0.8701427

00:42:51.175 --> 00:42:51.675 under

NOTE Confidence: 0.776146

00:42:51.975 --> 00:42:53.495 a a usable promoter. Get

NOTE Confidence: 0.776146

00:42:53.495 --> 00:42:54.695 rid of k ras, MAP

NOTE Confidence: 0.776146

00:42:54.695 --> 00:42:56.075 kinase signaling stops,

NOTE Confidence: 0.91165334

00:42:56.670 --> 00:42:57.790 but p h three kinase

NOTE Confidence: 0.91165334

00:42:57.790 --> 00:42:59.150 signaling does not in in

NOTE Confidence: 0.91165334

00:42:59.150 --> 00:43:00.989 response to multiple different growth

NOTE Confidence: 0.91165334

00:43:00.989 --> 00:43:01.489 factors.

NOTE Confidence: 0.94450337

00:43:02.030 --> 00:43:03.869 So EGF, for example, does

NOTE Confidence: 0.94450337

00:43:03.869 --> 00:43:05.630 not need any RAS protein

NOTE Confidence: 0.94450337

00:43:05.630 --> 00:43:06.849 to act as a AKT,

NOTE Confidence: 0.94450337

00:43:06.989 --> 00:43:08.290 not as IGF one.

NOTE Confidence: 0.93478787

00:43:09.085 --> 00:43:09.585 PDGF

NOTE Confidence: 0.93839306

00:43:09.965 --> 00:43:10.844 actually is better than the

NOTE Confidence: 0.93839306

00:43:10.844 --> 00:43:12.045 absence of RAS proteins because

NOTE Confidence: 0.93839306

00:43:12.045 --> 00:43:12.925 when you knock out RAS

NOTE Confidence: 0.93839306

00:43:12.925 --> 00:43:15.005 proteins, PDGF receptor levels go

NOTE Confidence: 0.93839306

00:43:15.005 --> 00:43:15.965 through the roof, by the

NOTE Confidence: 0.93839306

00:43:15.965 --> 00:43:17.805 way. But, certainly, you don't

NOTE Confidence: 0.93839306

00:43:17.805 --> 00:43:19.725 need any RAS proteins to

NOTE Confidence: 0.93839306

00:43:19.725 --> 00:43:21.325 activate PI three kinase in

NOTE Confidence: 0.93839306

00:43:21.325 --> 00:43:23.025 response to RTKs. Okay?

NOTE Confidence: 0.89751065

00:43:24.200 --> 00:43:25.640 Which is the reciprocal same

NOTE Confidence: 0.89751065

00:43:25.640 --> 00:43:27.660 conclusion that, Julian did.

NOTE Confidence: 0.9798948

00:43:28.920 --> 00:43:30.140 Okay. So, again,

NOTE Confidence: 0.9125757

00:43:30.440 --> 00:43:32.200 verifying this interaction is being

NOTE Confidence: 0.9125757

00:43:32.200 --> 00:43:34.700 really, potentially valuable drug target.

NOTE Confidence: 0.9906315

00:43:35.400 --> 00:43:36.779 So why didn't Julian,

NOTE Confidence: 0.967329

00:43:37.160 --> 00:43:38.200 or anybody actually,

NOTE Confidence: 0.9314662

00:43:38.925 --> 00:43:39.885 find a drug when they

NOTE Confidence: 0.9314662

00:43:39.965 --> 00:43:40.844 this paper was published in

NOTE Confidence: 0.9314662

00:43:40.844 --> 00:43:41.825 two thousand seven?

NOTE Confidence: 0.8755854

00:43:42.605 --> 00:43:43.565 When we started the RAS

NOTE Confidence: 0.8755854

00:43:43.565 --> 00:43:44.844 list, I called up Julian

NOTE Confidence: 0.8755854

00:43:44.844 --> 00:43:46.364 and said, okay. Well, how

NOTE Confidence: 0.8755854

00:43:46.364 --> 00:43:47.245 are you doing on finding

NOTE Confidence: 0.8755854

00:43:47.245 --> 00:43:48.605 a breaker for this interaction?

NOTE Confidence: 0.8755854

00:43:48.605 --> 00:43:50.045 The phenocop is your mutant

NOTE Confidence: 0.8755854

00:43:50.045 --> 00:43:51.565 mice. And he said, he

NOTE Confidence: 0.8755854

00:43:51.565 --> 00:43:52.980 tried. I collaborated with a

NOTE Confidence: 0.8755854

00:43:52.980 --> 00:43:54.180 company in the UK, a

NOTE Confidence: 0.8755854

00:43:54.180 --> 00:43:55.400 screen for inhibitors.

NOTE Confidence: 0.9890978

00:43:55.700 --> 00:43:56.680 The problem is

NOTE Confidence: 0.87879604

00:43:57.060 --> 00:43:58.820 the binding constant between RAS

NOTE Confidence: 0.87879604

00:43:58.820 --> 00:44:00.420 and kinase is about twenty

NOTE Confidence: 0.87879604

00:44:00.420 --> 00:44:00.920 micromolar.

NOTE Confidence: 0.9502261

00:44:01.620 --> 00:44:02.820 That's really too weak to

NOTE Confidence: 0.9502261

00:44:02.820 --> 00:44:04.260 do a robust screen for

NOTE Confidence: 0.9502261

00:44:04.260 --> 00:44:05.775 interaction, so they barely bind

NOTE Confidence: 0.9502261

00:44:05.775 --> 00:44:06.815 really in the test tube,

NOTE Confidence: 0.9502261

00:44:06.815 --> 00:44:07.775 and there were no crystal

NOTE Confidence: 0.9502261

00:44:07.775 --> 00:44:09.954 structures available to model compounds.

NOTE Confidence: 0.9002536

00:44:10.335 --> 00:44:11.375 So the whole field, they

NOTE Confidence: 0.9002536

00:44:11.375 --> 00:44:12.114 got stuck.

NOTE Confidence: 0.8578454

00:44:12.734 --> 00:44:13.935 And then, quite honestly, the

NOTE Confidence: 0.8578454

00:44:13.935 --> 00:44:15.295 whole field got fixated on

NOTE Confidence: 0.8578454

00:44:15.295 --> 00:44:16.515 RAF and MAP kinase inhibitors

NOTE Confidence: 0.8578454

00:44:16.655 --> 00:44:17.795 and ignored the pathway

NOTE Confidence: 0.8770299

00:44:18.789 --> 00:44:19.529 for years,

NOTE Confidence: 0.9459972

00:44:19.910 --> 00:44:20.809 but it's back.

NOTE Confidence: 0.7526871

00:44:21.989 --> 00:44:23.289 Not just for the stuff.

NOTE Confidence: 0.82746935

00:44:23.589 --> 00:44:25.029 Everybody else is now realizing

NOTE Confidence: 0.82746935

00:44:25.029 --> 00:44:25.930 that PI preconews,

NOTE Confidence: 0.8571666

00:44:26.309 --> 00:44:27.829 is a resistance mechanism to

NOTE Confidence: 0.8571666

00:44:27.829 --> 00:44:28.730 RAF inhibition.

NOTE Confidence: 0.9250882

00:44:30.069 --> 00:44:31.430 Anyway, so that stole the

NOTE Confidence: 0.9250882

00:44:31.430 --> 00:44:33.049 whole field. K?

NOTE Confidence: 0.999843

00:44:34.015 --> 00:44:34.515 However,

NOTE Confidence: 0.99696994

00:44:35.215 --> 00:44:36.275 by sheer luck,

NOTE Confidence: 0.96658254

00:44:36.895 --> 00:44:38.494 I was, in in Tokyo

NOTE Confidence: 0.96658254

00:44:38.494 --> 00:44:39.775 a while ago. I have

NOTE Confidence: 0.96658254

00:44:39.775 --> 00:44:41.295 a long standing collaboration with,

NOTE Confidence: 0.92961985

00:44:41.855 --> 00:44:43.935 Daichi Sankyo, now oncology group

NOTE Confidence: 0.92961985

00:44:43.935 --> 00:44:44.755 in in Shinagawa

NOTE Confidence: 0.9337746

00:44:45.055 --> 00:44:46.275 in the suburb of Tokyo,

NOTE Confidence: 0.9844777

00:44:46.655 --> 00:44:47.695 where I've been going every

NOTE Confidence: 0.9844777

00:44:47.695 --> 00:44:48.655 year for the last twenty

NOTE Confidence: 0.9844777

00:44:48.655 --> 00:44:50.010 five years. And I was

NOTE Confidence: 0.9844777

00:44:50.010 --> 00:44:51.230 there a few years ago,

NOTE Confidence: 0.9415232

00:44:51.530 --> 00:44:52.810 one of the the people

NOTE Confidence: 0.9415232

00:44:52.810 --> 00:44:53.370 in the in the group

NOTE Confidence: 0.9415232

00:44:53.370 --> 00:44:55.210 there, Kazu, said, hey. The

NOTE Confidence: 0.9415232

00:44:55.210 --> 00:44:57.469 diabetes group at, Daishankyo

NOTE Confidence: 0.9219345

00:44:57.850 --> 00:44:58.989 have found a compound

NOTE Confidence: 0.9089674

00:44:59.370 --> 00:45:00.410 that they were trying to

NOTE Confidence: 0.9089674

00:45:00.410 --> 00:45:01.070 find an

NOTE Confidence: 0.917842

00:45:02.184 --> 00:45:04.525 orally available insulin memetic compound,

NOTE Confidence: 0.917842

00:45:04.744 --> 00:45:05.785 and they found a compound

NOTE Confidence: 0.917842

00:45:05.785 --> 00:45:07.464 that glues RAS to PI

NOTE Confidence: 0.917842

00:45:07.464 --> 00:45:08.125 three kinase.

NOTE Confidence: 0.9927462

00:45:08.665 --> 00:45:09.165 So

NOTE Confidence: 0.5572426

00:45:09.545 --> 00:45:10.285 so, okay,

NOTE Confidence: 0.96380544

00:45:10.585 --> 00:45:11.785 we'll take it. So,

NOTE Confidence: 0.95572007

00:45:12.665 --> 00:45:13.964 they offered me the compound

NOTE Confidence: 0.95572007

00:45:14.025 --> 00:45:15.944 to, to to test, and

NOTE Confidence: 0.95572007

00:45:15.944 --> 00:45:17.020 then use that for for

NOTE Confidence: 0.95572007

00:45:17.020 --> 00:45:17.820 the reason I'll just show

NOTE Confidence: 0.95572007

00:45:17.820 --> 00:45:18.320 you.

NOTE Confidence: 0.937557

00:45:18.700 --> 00:45:19.739 So here's the deal. So

NOTE Confidence: 0.937557

00:45:19.739 --> 00:45:21.100 they would this is insulin

NOTE Confidence: 0.937557

00:45:21.100 --> 00:45:23.340 signaling. Okay? Insulin activates, insulin

NOTE Confidence: 0.937557

00:45:23.340 --> 00:45:25.420 receptor, obviously. IRS one recruits

NOTE Confidence: 0.937557

00:45:25.420 --> 00:45:27.180 PI three kinase here, and

NOTE Confidence: 0.937557

00:45:27.180 --> 00:45:27.920 then activates,

NOTE Confidence: 0.9603337

00:45:28.620 --> 00:45:30.880 AKT. This promotes GLUT4 translocation,

NOTE Confidence: 0.99440247

00:45:31.180 --> 00:45:32.994 which causes glucose uptake. This

NOTE Confidence: 0.99440247

00:45:32.994 --> 00:45:34.035 is what you need when

NOTE Confidence: 0.99440247

00:45:34.035 --> 00:45:35.635 you need to, take take

NOTE Confidence: 0.99440247

00:45:35.635 --> 00:45:36.935 up glucose. Right?

NOTE Confidence: 0.9525684

00:45:38.915 --> 00:45:40.035 So they wanted to find

NOTE Confidence: 0.9525684

00:45:40.035 --> 00:45:41.075 a drug which would replace

NOTE Confidence: 0.9525684

00:45:41.075 --> 00:45:42.515 insulin so that a diabetic

NOTE Confidence: 0.9525684

00:45:42.515 --> 00:45:43.734 could just take a pill

NOTE Confidence: 0.9525684

00:45:43.875 --> 00:45:44.535 and then

NOTE Confidence: 0.9260824

00:45:45.075 --> 00:45:46.355 take up glucose without having

NOTE Confidence: 0.9260824

00:45:46.355 --> 00:45:47.255 to have an injection.

NOTE Confidence: 0.919228

00:45:47.829 --> 00:45:48.890 So we get a phenotypic

NOTE Confidence: 0.919228

00:45:49.030 --> 00:45:50.630 screen for compounds that would

NOTE Confidence: 0.919228

00:45:50.630 --> 00:45:51.989 do just that, and the

NOTE Confidence: 0.919228

00:45:51.989 --> 00:45:53.190 screen bait was based on

NOTE Confidence: 0.919228

00:45:53.190 --> 00:45:55.270 translocation of GLUT four, to

NOTE Confidence: 0.919228

00:45:55.270 --> 00:45:56.950 the plasma membrane in response

NOTE Confidence: 0.919228

00:45:56.950 --> 00:45:58.329 to a library of compounds.

NOTE Confidence: 0.94606465

00:45:58.950 --> 00:46:00.309 And amazingly enough, they found

NOTE Confidence: 0.94606465

00:46:00.309 --> 00:46:01.829 compounds which do exactly what

NOTE Confidence: 0.94606465

00:46:01.829 --> 00:46:02.489 they wanted.

NOTE Confidence: 0.95455337

00:46:02.855 --> 00:46:03.674 But these compounds

NOTE Confidence: 0.9186652

00:46:03.974 --> 00:46:05.674 promote, glucose uptake

NOTE Confidence: 0.89436686

00:46:06.135 --> 00:46:07.515 in the absence of insulin

NOTE Confidence: 0.89436686

00:46:07.575 --> 00:46:09.015 with a with a, sort

NOTE Confidence: 0.89436686

00:46:09.015 --> 00:46:10.214 of kinetic curve or those

NOTE Confidence: 0.89436686

00:46:10.214 --> 00:46:11.755 curve very similar to insulin

NOTE Confidence: 0.89436686

00:46:11.974 --> 00:46:12.474 itself.

NOTE Confidence: 0.9679295

00:46:13.174 --> 00:46:14.214 So that looked that looked

NOTE Confidence: 0.9679295

00:46:14.214 --> 00:46:14.875 pretty good.

NOTE Confidence: 0.9562926

00:46:15.410 --> 00:46:16.370 And then they spent years

NOTE Confidence: 0.9562926

00:46:16.370 --> 00:46:17.410 trying to figure out which

NOTE Confidence: 0.9562926

00:46:17.410 --> 00:46:18.930 part of this complicated pathway

NOTE Confidence: 0.9562926

00:46:18.930 --> 00:46:20.150 does the drug act on.

NOTE Confidence: 0.9562926

00:46:20.370 --> 00:46:21.170 And they narrowed it down

NOTE Confidence: 0.9562926

00:46:21.170 --> 00:46:22.550 to PI three kinase alpha,

NOTE Confidence: 0.9562926

00:46:22.770 --> 00:46:23.650 and then they did mass

NOTE Confidence: 0.9562926

00:46:23.650 --> 00:46:24.770 spec on PI three kinase

NOTE Confidence: 0.9562926

00:46:24.770 --> 00:46:26.550 alpha plus or minus compound,

NOTE Confidence: 0.9562926

00:46:26.770 --> 00:46:27.670 and they found,

NOTE Confidence: 0.782037

00:46:28.290 --> 00:46:30.310 our old friend, ras two,

NOTE Confidence: 0.81277233

00:46:31.235 --> 00:46:32.995 found to, PI two kinase

NOTE Confidence: 0.81277233

00:46:32.995 --> 00:46:33.975 alpha in the IP.

NOTE Confidence: 0.900727

00:46:34.675 --> 00:46:35.715 And then mass spec also

NOTE Confidence: 0.900727

00:46:35.715 --> 00:46:36.915 shows some KRAS, but this

NOTE Confidence: 0.900727

00:46:36.915 --> 00:46:38.295 was a major RAS isoform.

NOTE Confidence: 0.90596193

00:46:39.395 --> 00:46:40.355 So we now know that

NOTE Confidence: 0.90596193

00:46:40.355 --> 00:46:41.555 this compound, t nine two

NOTE Confidence: 0.90596193

00:46:41.555 --> 00:46:42.055 seven,

NOTE Confidence: 0.9537365

00:46:42.835 --> 00:46:44.195 is a molecular glue which

NOTE Confidence: 0.9537365

00:46:44.195 --> 00:46:45.975 sticks RAS proteins in general

NOTE Confidence: 0.91880685

00:46:46.310 --> 00:46:47.850 to PI three kinase alpha

NOTE Confidence: 0.91880685

00:46:48.150 --> 00:46:49.750 and then just jams on,

NOTE Confidence: 0.89072233

00:46:50.230 --> 00:46:52.090 GLUT four translocation and glucose

NOTE Confidence: 0.89072233

00:46:52.150 --> 00:46:53.130 uptake. Okay?

NOTE Confidence: 0.9339495

00:46:54.390 --> 00:46:54.890 So,

NOTE Confidence: 0.9021409

00:46:55.670 --> 00:46:57.030 that's, that's a good start.

NOTE Confidence: 0.9021409

00:46:57.030 --> 00:46:57.989 So we we've working on

NOTE Confidence: 0.9021409

00:46:57.989 --> 00:46:58.950 this compound for a while.

NOTE Confidence: 0.9021409

00:46:58.950 --> 00:47:00.150 And, Frederick, we got all

NOTE Confidence: 0.9021409

00:47:00.150 --> 00:47:01.275 of the compound to test

NOTE Confidence: 0.9021409

00:47:01.434 --> 00:47:02.954 which RAS isoforms that lice

NOTE Confidence: 0.9021409

00:47:02.954 --> 00:47:04.395 best. So we went back

NOTE Confidence: 0.9021409

00:47:04.395 --> 00:47:05.434 to our panel of single

NOTE Confidence: 0.9021409

00:47:05.434 --> 00:47:06.795 isoform mesh that only have

NOTE Confidence: 0.9021409

00:47:06.795 --> 00:47:07.775 one RAS protein,

NOTE Confidence: 0.9385634

00:47:08.635 --> 00:47:09.914 each of these, and then

NOTE Confidence: 0.9385634

00:47:09.914 --> 00:47:11.594 dump the glue onto this,

NOTE Confidence: 0.9385634

00:47:11.835 --> 00:47:12.875 this panel. And you see

NOTE Confidence: 0.9385634

00:47:12.875 --> 00:47:14.430 that each of them activate

NOTE Confidence: 0.9385634

00:47:14.489 --> 00:47:15.770 AKT in response to the

NOTE Confidence: 0.9385634

00:47:15.770 --> 00:47:17.050 glue, but ras two is

NOTE Confidence: 0.9385634

00:47:17.050 --> 00:47:18.110 by far the strongest,

NOTE Confidence: 0.919121

00:47:18.730 --> 00:47:19.230 interaction.

NOTE Confidence: 0.8481667

00:47:19.690 --> 00:47:20.570 And that correlates with the

NOTE Confidence: 0.8481667

00:47:20.570 --> 00:47:22.330 fact that ras two, is

NOTE Confidence: 0.8481667

00:47:22.330 --> 00:47:23.130 the one of the better

NOTE Confidence: 0.8481667

00:47:23.130 --> 00:47:24.270 binders to the ad glucanase

NOTE Confidence: 0.8481667

00:47:24.330 --> 00:47:25.070 alpha, actually.

NOTE Confidence: 0.9298458

00:47:25.530 --> 00:47:26.355 And if you just dump

NOTE Confidence: 0.9298458

00:47:26.355 --> 00:47:27.475 the compound on the cells,

NOTE Confidence: 0.9298458

00:47:27.475 --> 00:47:28.114 you activate,

NOTE Confidence: 0.9772192

00:47:28.435 --> 00:47:29.335 AKT signaling

NOTE Confidence: 0.9903713

00:47:29.635 --> 00:47:30.375 without affecting

NOTE Confidence: 0.89244896

00:47:30.675 --> 00:47:32.355 phospho ERK, okay, as you'd

NOTE Confidence: 0.89244896

00:47:32.355 --> 00:47:33.175 expect probably.

NOTE Confidence: 0.85212034

00:47:34.114 --> 00:47:35.735 Okay. So it's a glue

NOTE Confidence: 0.85212034

00:47:35.875 --> 00:47:37.475 that activates map kinase p

NOTE Confidence: 0.85212034

00:47:37.475 --> 00:47:38.675 I three kinase signaling through,

NOTE Confidence: 0.85212034

00:47:38.915 --> 00:47:40.035 pretty much any any RAS

NOTE Confidence: 0.85212034

00:47:40.035 --> 00:47:40.535 protein.

NOTE Confidence: 0.91199714

00:47:41.850 --> 00:47:42.650 So we were able to

NOTE Confidence: 0.91199714

00:47:42.650 --> 00:47:43.770 use this compound to solve

NOTE Confidence: 0.91199714

00:47:43.770 --> 00:47:45.550 a structure of KRAS alpha

NOTE Confidence: 0.91506743

00:47:46.330 --> 00:47:47.690 for the first time, and

NOTE Confidence: 0.91506743

00:47:47.690 --> 00:47:49.370 this is published, just a

NOTE Confidence: 0.91506743

00:47:49.370 --> 00:47:50.570 few months ago. So this

NOTE Confidence: 0.91506743

00:47:50.570 --> 00:47:51.530 is KRAS. This is the

NOTE Confidence: 0.91506743

00:47:51.530 --> 00:47:52.970 RAS spani domain where Julian's

NOTE Confidence: 0.91506743

00:47:52.970 --> 00:47:54.250 mutants were made. This is

NOTE Confidence: 0.91506743

00:47:54.250 --> 00:47:54.970 the kind this is the

NOTE Confidence: 0.91506743

00:47:54.970 --> 00:47:56.424 kinase domain, which is distinct

NOTE Confidence: 0.91506743

00:47:56.424 --> 00:47:57.704 from the RAS binding domain,

NOTE Confidence: 0.91506743

00:47:57.704 --> 00:47:58.744 and these are other structural

NOTE Confidence: 0.91506743

00:47:58.744 --> 00:47:59.864 protein parts of the of

NOTE Confidence: 0.91506743

00:47:59.864 --> 00:48:00.525 the protein.

NOTE Confidence: 0.8438375

00:48:01.625 --> 00:48:02.505 So these are the RAS

NOTE Confidence: 0.8438375

00:48:02.505 --> 00:48:03.864 proteins that that bind to

NOTE Confidence: 0.8438375

00:48:03.864 --> 00:48:05.224 PI three kinase alpha. K

NOTE Confidence: 0.8438375

00:48:05.224 --> 00:48:06.265 RAS, as I said, has

NOTE Confidence: 0.8438375

00:48:06.265 --> 00:48:07.464 a IC fifty about twenty

NOTE Confidence: 0.8438375

00:48:07.464 --> 00:48:07.964 micromolar,

NOTE Confidence: 0.8468406

00:48:08.344 --> 00:48:09.785 but our glue is dropped

NOTE Confidence: 0.8468406

00:48:09.785 --> 00:48:10.684 to six nanomolar.

NOTE Confidence: 0.93434846

00:48:11.305 --> 00:48:12.420 So So just that compound

NOTE Confidence: 0.93434846

00:48:12.420 --> 00:48:13.700 alone adds three orders of

NOTE Confidence: 0.93434846

00:48:13.700 --> 00:48:14.680 magnitude in binding.

NOTE Confidence: 0.9161167

00:48:15.619 --> 00:48:17.140 RRAS two binds at four

NOTE Confidence: 0.9161167

00:48:17.140 --> 00:48:19.300 micromolar without glue as MRAS

NOTE Confidence: 0.9161167

00:48:19.300 --> 00:48:20.900 is similar. So Symantje was

NOTE Confidence: 0.9161167

00:48:20.900 --> 00:48:21.940 able to solve the structure

NOTE Confidence: 0.9161167

00:48:21.940 --> 00:48:23.780 of these, these proteins bound

NOTE Confidence: 0.9161167

00:48:23.780 --> 00:48:24.820 to PI two kinase alpha

NOTE Confidence: 0.9161167

00:48:24.820 --> 00:48:26.214 without any glue to help

NOTE Confidence: 0.9161167

00:48:26.214 --> 00:48:27.255 verify that the glue wasn't

NOTE Confidence: 0.9161167

00:48:27.255 --> 00:48:28.474 doing something really weird,

NOTE Confidence: 0.96237266

00:48:28.855 --> 00:48:30.075 and this is not published.

NOTE Confidence: 0.9769626

00:48:30.535 --> 00:48:31.734 And just to come back

NOTE Confidence: 0.9769626

00:48:31.734 --> 00:48:32.795 to the cancer context,

NOTE Confidence: 0.8727338

00:48:33.655 --> 00:48:35.255 the mutant alleles in in

NOTE Confidence: 0.8727338

00:48:35.255 --> 00:48:36.135 in the KRAS are the

NOTE Confidence: 0.8727338

00:48:36.135 --> 00:48:36.875 most common,

NOTE Confidence: 0.92494655

00:48:37.175 --> 00:48:38.214 g twelve d and d

NOTE Confidence: 0.92494655

00:48:38.214 --> 00:48:39.575 twelve v. These are the

NOTE Confidence: 0.92494655

00:48:39.575 --> 00:48:41.219 two RAS isoforms that have

NOTE Confidence: 0.92494655

00:48:41.219 --> 00:48:42.260 the highest affinity for p

NOTE Confidence: 0.92494655

00:48:42.260 --> 00:48:43.480 I three kinase alpha.

NOTE Confidence: 0.8117094

00:48:44.180 --> 00:48:45.380 D and v, the lowest

NOTE Confidence: 0.8117094

00:48:45.380 --> 00:48:46.840 I c lowest k m,

NOTE Confidence: 0.7889762

00:48:47.460 --> 00:48:48.280 k d,

NOTE Confidence: 0.88338774

00:48:48.580 --> 00:48:50.500 compared with, wild type or

NOTE Confidence: 0.88338774

00:48:50.500 --> 00:48:51.300 d twelve c and so

NOTE Confidence: 0.88338774

00:48:51.300 --> 00:48:51.800 on.

NOTE Confidence: 0.9390441

00:48:52.340 --> 00:48:53.940 So it could be coincidence,

NOTE Confidence: 0.9390441

00:48:53.940 --> 00:48:54.900 but it seems likely to

NOTE Confidence: 0.9390441

00:48:54.900 --> 00:48:55.780 me that the reason that

NOTE Confidence: 0.9390441

00:48:55.780 --> 00:48:57.080 d twelve d and v

NOTE Confidence: 0.9390441

00:48:57.245 --> 00:48:58.765 are so prominent in human

NOTE Confidence: 0.9390441

00:48:58.765 --> 00:48:59.965 cancer is because they can

NOTE Confidence: 0.9390441

00:48:59.965 --> 00:49:01.725 activate PI3 kinase as well

NOTE Confidence: 0.9390441

00:49:01.725 --> 00:49:02.765 as MAP kinase, and that

NOTE Confidence: 0.9390441

00:49:02.765 --> 00:49:04.445 combination together is, you know,

NOTE Confidence: 0.9390441

00:49:04.445 --> 00:49:05.645 a very bad combination for

NOTE Confidence: 0.9390441

00:49:05.645 --> 00:49:06.305 the tumor.

NOTE Confidence: 0.8871908

00:49:07.645 --> 00:49:08.945 Anyway, so now we've

NOTE Confidence: 0.92004293

00:49:09.320 --> 00:49:10.200 saw the structure of the

NOTE Confidence: 0.92004293

00:49:10.200 --> 00:49:11.080 of the complex for the

NOTE Confidence: 0.92004293

00:49:11.080 --> 00:49:12.920 first time, and, the moment

NOTE Confidence: 0.92004293

00:49:12.920 --> 00:49:14.040 we saw it, saw the

NOTE Confidence: 0.92004293

00:49:14.040 --> 00:49:16.200 structure, it's obvious that we

NOTE Confidence: 0.92004293

00:49:16.200 --> 00:49:17.560 could convert the glue to

NOTE Confidence: 0.92004293

00:49:17.560 --> 00:49:19.260 a breaker. And that's because

NOTE Confidence: 0.92004293

00:49:19.320 --> 00:49:20.920 the crystal structure of, PI

NOTE Confidence: 0.92004293

00:49:20.920 --> 00:49:21.960 three kinase bound to the

NOTE Confidence: 0.92004293

00:49:21.960 --> 00:49:23.239 blue so is that most

NOTE Confidence: 0.92004293

00:49:23.239 --> 00:49:24.540 of the contact is actually,

NOTE Confidence: 0.92457134

00:49:25.175 --> 00:49:26.295 with the blue compound is

NOTE Confidence: 0.92457134

00:49:26.295 --> 00:49:27.094 is with p I three

NOTE Confidence: 0.92457134

00:49:27.094 --> 00:49:27.915 kinase alpha.

NOTE Confidence: 0.9566982

00:49:28.535 --> 00:49:30.055 So this stabilizes p I

NOTE Confidence: 0.9566982

00:49:30.055 --> 00:49:31.175 three kinase alpha into a

NOTE Confidence: 0.9566982

00:49:31.175 --> 00:49:32.775 RAS binding structure, which takes

NOTE Confidence: 0.9566982

00:49:32.775 --> 00:49:33.735 out a ton of energy

NOTE Confidence: 0.9566982

00:49:33.735 --> 00:49:35.094 of binding and also makes

NOTE Confidence: 0.9566982

00:49:35.094 --> 00:49:36.455 contact with the RAS protein

NOTE Confidence: 0.9566982

00:49:36.455 --> 00:49:38.075 directly. It has more energy

NOTE Confidence: 0.9566982

00:49:38.135 --> 00:49:39.094 that gives you three orders

NOTE Confidence: 0.9566982

00:49:39.094 --> 00:49:40.555 of magnitude in in binding.

NOTE Confidence: 0.9334164

00:49:41.520 --> 00:49:42.560 So this is the blue

NOTE Confidence: 0.9334164

00:49:42.560 --> 00:49:43.060 compound,

NOTE Confidence: 0.9635688

00:49:43.360 --> 00:49:45.280 and so I naively thought

NOTE Confidence: 0.9635688

00:49:45.280 --> 00:49:46.080 it wouldn't take long to

NOTE Confidence: 0.9635688

00:49:46.080 --> 00:49:47.760 make this blue compound into

NOTE Confidence: 0.9635688

00:49:47.760 --> 00:49:48.880 a compound that binds to

NOTE Confidence: 0.9635688

00:49:48.880 --> 00:49:50.080 the same site but now

NOTE Confidence: 0.9635688

00:49:50.080 --> 00:49:50.580 repels

NOTE Confidence: 0.88390857

00:49:51.040 --> 00:49:52.400 KRAS. Okay? So now it's

NOTE Confidence: 0.88390857

00:49:52.400 --> 00:49:53.380 now it's a breaker.

NOTE Confidence: 0.9393992

00:49:54.675 --> 00:49:56.114 Well, the the chemistry group

NOTE Confidence: 0.9393992

00:49:56.114 --> 00:49:58.035 at BridgeBio Oncology with the

NOTE Confidence: 0.9393992

00:49:58.035 --> 00:49:59.635 group of Frederick succeeded in

NOTE Confidence: 0.9393992

00:49:59.635 --> 00:50:00.515 doing this, but it took

NOTE Confidence: 0.9393992

00:50:00.515 --> 00:50:01.875 about two or three years

NOTE Confidence: 0.9393992

00:50:01.875 --> 00:50:03.235 of very heavy med chem

NOTE Confidence: 0.9393992

00:50:03.235 --> 00:50:04.215 and structural biology

NOTE Confidence: 0.90202224

00:50:04.675 --> 00:50:06.195 because the glue does cause

NOTE Confidence: 0.90202224

00:50:06.195 --> 00:50:07.235 a conformational change in the

NOTE Confidence: 0.90202224

00:50:07.235 --> 00:50:08.435 protein, which is basically more

NOTE Confidence: 0.90202224

00:50:08.435 --> 00:50:08.935 complicated,

NOTE Confidence: 0.8986866

00:50:09.270 --> 00:50:10.150 And we had to find

NOTE Confidence: 0.8986866

00:50:10.150 --> 00:50:11.430 a compound that didn't just

NOTE Confidence: 0.8986866

00:50:11.430 --> 00:50:12.730 serve as a a breaker,

NOTE Confidence: 0.8986866

00:50:12.870 --> 00:50:13.910 was also gonna be a

NOTE Confidence: 0.8986866

00:50:13.910 --> 00:50:15.270 good drug that with great

NOTE Confidence: 0.8986866

00:50:15.270 --> 00:50:16.090 PK properties,

NOTE Confidence: 0.896892

00:50:16.390 --> 00:50:17.130 good biodistribution,

NOTE Confidence: 0.9652034

00:50:17.750 --> 00:50:19.030 etcetera, all the things which

NOTE Confidence: 0.9652034

00:50:19.030 --> 00:50:20.310 academics don't like to think

NOTE Confidence: 0.9652034

00:50:20.310 --> 00:50:21.510 about that really make or

NOTE Confidence: 0.9652034

00:50:21.510 --> 00:50:22.390 break a drug in the

NOTE Confidence: 0.9652034

00:50:22.390 --> 00:50:22.890 clinic.

NOTE Confidence: 0.94928896

00:50:23.405 --> 00:50:24.605 So it took all that

NOTE Confidence: 0.94928896

00:50:24.605 --> 00:50:25.825 time to make this compound.

NOTE Confidence: 0.94928896

00:50:25.964 --> 00:50:27.005 And it turns out when

NOTE Confidence: 0.94928896

00:50:27.005 --> 00:50:28.925 we got the, first structures

NOTE Confidence: 0.94928896

00:50:28.925 --> 00:50:30.525 of our first candidates, we

NOTE Confidence: 0.94928896

00:50:30.525 --> 00:50:31.585 saw it was a cystine

NOTE Confidence: 0.94928896

00:50:31.724 --> 00:50:33.244 close by the compound, so

NOTE Confidence: 0.94928896

00:50:33.244 --> 00:50:33.964 we made it into a

NOTE Confidence: 0.94928896

00:50:33.964 --> 00:50:35.244 covalent compound just to add

NOTE Confidence: 0.94928896

00:50:35.244 --> 00:50:35.905 to binding,

NOTE Confidence: 0.78045195

00:50:36.285 --> 00:50:38.065 just a little linkage here.

NOTE Confidence: 0.8543328

00:50:38.559 --> 00:50:40.239 So this compound binds to

NOTE Confidence: 0.8543328

00:50:40.239 --> 00:50:41.279 p ad hoc kinase alpha

NOTE Confidence: 0.8543328

00:50:41.279 --> 00:50:42.660 covalently and prevents

NOTE Confidence: 0.9507351

00:50:42.960 --> 00:50:44.559 KRAS and other RAS proteins

NOTE Confidence: 0.9507351

00:50:44.559 --> 00:50:45.059 binding.

NOTE Confidence: 0.9831947

00:50:46.480 --> 00:50:46.880 And,

NOTE Confidence: 0.90670764

00:50:47.359 --> 00:50:49.119 this shows inhibition of binding

NOTE Confidence: 0.90670764

00:50:49.119 --> 00:50:50.980 of of g twelve d

NOTE Confidence: 0.90670764

00:50:51.039 --> 00:50:51.995 to p one ten alpha

NOTE Confidence: 0.90670764

00:50:51.995 --> 00:50:52.875 in a pull down assay.

NOTE Confidence: 0.90670764

00:50:52.875 --> 00:50:53.915 It binds tightly enough to

NOTE Confidence: 0.90670764

00:50:53.915 --> 00:50:54.875 do a pull down, and

NOTE Confidence: 0.90670764

00:50:54.875 --> 00:50:55.835 the IC fit is about

NOTE Confidence: 0.90670764

00:50:55.835 --> 00:50:56.735 six nanomolar.

NOTE Confidence: 0.9497717

00:50:58.075 --> 00:50:58.575 And

NOTE Confidence: 0.88847697

00:50:58.955 --> 00:50:59.695 very importantly,

NOTE Confidence: 0.94822675

00:51:00.395 --> 00:51:02.235 this compound, the, the breaker

NOTE Confidence: 0.94822675

00:51:02.235 --> 00:51:02.735 compound,

NOTE Confidence: 0.84600896

00:51:03.035 --> 00:51:04.555 doesn't affect the kinase activity

NOTE Confidence: 0.84600896

00:51:04.555 --> 00:51:05.594 of of PIAT three kinase

NOTE Confidence: 0.84600896

00:51:05.594 --> 00:51:07.070 alpha. Unlike alpelosib,

NOTE Confidence: 0.9700522

00:51:07.370 --> 00:51:08.410 which is the drug approved

NOTE Confidence: 0.9700522

00:51:08.410 --> 00:51:09.070 for treating,

NOTE Confidence: 0.9759673

00:51:09.610 --> 00:51:10.410 patients with p ad free

NOTE Confidence: 0.9759673

00:51:10.410 --> 00:51:11.390 kinase mutations.

NOTE Confidence: 0.92715466

00:51:12.090 --> 00:51:13.690 This directly inhibits the kinase,

NOTE Confidence: 0.98610663

00:51:14.170 --> 00:51:16.670 domain. This prevents RAS activation

NOTE Confidence: 0.98610663

00:51:16.810 --> 00:51:18.090 of the kinase, but doesn't

NOTE Confidence: 0.98610663

00:51:18.090 --> 00:51:19.870 affect the kinase directly. Okay?

NOTE Confidence: 0.99933016

00:51:20.484 --> 00:51:20.984 So

NOTE Confidence: 0.92193156

00:51:21.285 --> 00:51:22.805 the the compound breaks this

NOTE Confidence: 0.92193156

00:51:22.805 --> 00:51:24.484 interaction. It doesn't affect the

NOTE Confidence: 0.92193156

00:51:24.484 --> 00:51:25.305 kinase activity.

NOTE Confidence: 0.9090291

00:51:26.484 --> 00:51:28.005 That's that's really important because

NOTE Confidence: 0.9090291

00:51:28.005 --> 00:51:29.925 it allows, insulin homeostasis to

NOTE Confidence: 0.9090291

00:51:29.925 --> 00:51:31.145 continue as we'll see.

NOTE Confidence: 0.9438092

00:51:31.844 --> 00:51:32.724 So for the first time,

NOTE Confidence: 0.9438092

00:51:32.724 --> 00:51:33.525 we could then ask, well,

NOTE Confidence: 0.9438092

00:51:33.525 --> 00:51:34.724 how many RAS driven cancers

NOTE Confidence: 0.9438092

00:51:34.724 --> 00:51:35.830 or other cancers depend on

NOTE Confidence: 0.9438092

00:51:35.830 --> 00:51:37.690 the RAS PI3 kinase interaction?

NOTE Confidence: 0.96214217

00:51:37.989 --> 00:51:39.609 Previously, it was totally unknown.

NOTE Confidence: 0.9827079

00:51:40.790 --> 00:51:41.290 So,

NOTE Confidence: 0.92458344

00:51:41.829 --> 00:51:42.550 turns out to be a

NOTE Confidence: 0.92458344

00:51:42.550 --> 00:51:43.050 lot.

NOTE Confidence: 0.72996783

00:51:43.910 --> 00:51:45.430 Once they don't care are

NOTE Confidence: 0.72996783

00:51:45.430 --> 00:51:46.550 p ten null cells as

NOTE Confidence: 0.72996783

00:51:46.550 --> 00:51:47.369 you might expect,

NOTE Confidence: 0.81658804

00:51:47.675 --> 00:51:49.035 but tumor cells of mutant

NOTE Confidence: 0.81658804

00:51:49.035 --> 00:51:50.795 KRAS or mutations in PI3

NOTE Confidence: 0.81658804

00:51:50.795 --> 00:51:52.815 kinase alpha, helical, or

NOTE Confidence: 0.9053912

00:51:53.114 --> 00:51:54.255 kinase domain mutations,

NOTE Confidence: 0.97389966

00:51:55.195 --> 00:51:56.415 show pretty good effects,

NOTE Confidence: 0.936752

00:51:56.795 --> 00:51:58.094 not down to zero.

NOTE Confidence: 0.9378799

00:51:58.395 --> 00:51:59.915 But by far, the most

NOTE Confidence: 0.9378799

00:51:59.915 --> 00:52:00.974 responsive subset

NOTE Confidence: 0.73816913

00:52:01.920 --> 00:52:02.600 of those tumors would amplify

NOTE Confidence: 0.73816913

00:52:02.600 --> 00:52:02.960 H02,

NOTE Confidence: 0.8483299

00:52:03.760 --> 00:52:04.660 H02 new.

NOTE Confidence: 0.80092466

00:52:04.960 --> 00:52:05.460 Okay?

NOTE Confidence: 0.9098358

00:52:06.000 --> 00:52:06.960 That was a shock to

NOTE Confidence: 0.9098358

00:52:06.960 --> 00:52:08.260 us because in the literature,

NOTE Confidence: 0.9451989

00:52:08.560 --> 00:52:10.000 H02 new is definitely known

NOTE Confidence: 0.9451989

00:52:10.000 --> 00:52:11.599 to activate PI3 kinase, like,

NOTE Confidence: 0.9451989

00:52:11.599 --> 00:52:13.119 you know, on fire, but

NOTE Confidence: 0.9451989

00:52:13.119 --> 00:52:14.480 it's been shown previously not

NOTE Confidence: 0.9451989

00:52:14.480 --> 00:52:16.020 to use canonical Ras proteins.

NOTE Confidence: 0.8357465

00:52:16.815 --> 00:52:18.335 Okay? So it's assumed that

NOTE Confidence: 0.8357465

00:52:18.335 --> 00:52:20.094 that interaction is straight binding

NOTE Confidence: 0.8357465

00:52:20.094 --> 00:52:21.535 of p eighty five p

NOTE Confidence: 0.8357465

00:52:21.535 --> 00:52:22.350 eighty five p eighty five

NOTE Confidence: 0.8357465

00:52:22.399 --> 00:52:22.974 you have to kind of

NOTE Confidence: 0.8357465

00:52:22.974 --> 00:52:23.614 straight to,

NOTE Confidence: 0.9346311

00:52:24.015 --> 00:52:25.295 HER2 new or to HER3,

NOTE Confidence: 0.9346311

00:52:25.295 --> 00:52:27.135 its partner, and activation without

NOTE Confidence: 0.9346311

00:52:27.135 --> 00:52:28.335 any need for any Ras

NOTE Confidence: 0.9346311

00:52:28.335 --> 00:52:30.260 proteins. But this shows that

NOTE Confidence: 0.9346311

00:52:30.260 --> 00:52:32.119 this interaction is completely dependent

NOTE Confidence: 0.9346311

00:52:32.339 --> 00:52:34.099 on a RAS protein interacting

NOTE Confidence: 0.9346311

00:52:34.099 --> 00:52:35.640 with PI3 kinase alpha.

NOTE Confidence: 0.89141417

00:52:36.980 --> 00:52:38.040 So that was a shock,

NOTE Confidence: 0.8427282

00:52:38.739 --> 00:52:39.859 and this shows basically a

NOTE Confidence: 0.8427282

00:52:39.859 --> 00:52:40.980 dispatch of that with multiple

NOTE Confidence: 0.8427282

00:52:40.980 --> 00:52:41.940 cell lines to show this

NOTE Confidence: 0.8427282

00:52:41.940 --> 00:52:42.819 is the sort of the

NOTE Confidence: 0.8427282

00:52:42.819 --> 00:52:44.579 breadth of the cell lines

NOTE Confidence: 0.8427282

00:52:44.579 --> 00:52:45.239 we studied.

NOTE Confidence: 0.8011439

00:52:46.475 --> 00:52:47.755 So in cells with looking

NOTE Confidence: 0.8011439

00:52:47.755 --> 00:52:48.255 KRAS,

NOTE Confidence: 0.9191624

00:52:48.955 --> 00:52:50.795 most of the activity does

NOTE Confidence: 0.9191624

00:52:50.795 --> 00:52:51.935 actually come from,

NOTE Confidence: 0.9767615

00:52:52.395 --> 00:52:53.614 from KRAS itself.

NOTE Confidence: 0.95821935

00:52:54.315 --> 00:52:55.675 So we believe that's true.

NOTE Confidence: 0.95821935

00:52:55.675 --> 00:52:56.715 So this is the g

NOTE Confidence: 0.95821935

00:52:56.715 --> 00:52:58.075 twelve c cell line, but

NOTE Confidence: 0.95821935

00:52:58.075 --> 00:52:59.250 we add either the

NOTE Confidence: 0.8695187

00:52:59.730 --> 00:53:01.570 breaker, which is, ten two

NOTE Confidence: 0.8695187

00:53:01.570 --> 00:53:03.510 zero three in red or

NOTE Confidence: 0.8695187

00:53:03.730 --> 00:53:05.250 a pan KRAS compound, the

NOTE Confidence: 0.8695187

00:53:05.250 --> 00:53:06.530 red MET g, six two

NOTE Confidence: 0.8695187

00:53:06.530 --> 00:53:07.810 thirty six, which hits HN

NOTE Confidence: 0.8695187

00:53:07.810 --> 00:53:09.250 and KRAS. So they look

NOTE Confidence: 0.8695187

00:53:09.250 --> 00:53:10.530 the same in response to,

NOTE Confidence: 0.8695187

00:53:11.010 --> 00:53:12.224 AKT. Alpelosib

NOTE Confidence: 0.9160893

00:53:12.605 --> 00:53:13.964 also slams it, but it's

NOTE Confidence: 0.9160893

00:53:13.964 --> 00:53:15.565 much less potent, same in

NOTE Confidence: 0.9160893

00:53:15.565 --> 00:53:16.464 this cell line.

NOTE Confidence: 0.8972845

00:53:16.925 --> 00:53:17.805 So here we see we

NOTE Confidence: 0.8972845

00:53:17.805 --> 00:53:18.765 don't not not all the

NOTE Confidence: 0.8972845

00:53:18.765 --> 00:53:19.964 PI three kinase activity is

NOTE Confidence: 0.8972845

00:53:19.964 --> 00:53:20.785 coming through,

NOTE Confidence: 0.9418065

00:53:21.244 --> 00:53:22.844 k through RAS. Some must

NOTE Confidence: 0.9418065

00:53:22.844 --> 00:53:24.420 be coming from other other

NOTE Confidence: 0.9418065

00:53:24.420 --> 00:53:26.020 sources directly from receptors or

NOTE Confidence: 0.9418065

00:53:26.020 --> 00:53:27.140 from g proteins, but, you

NOTE Confidence: 0.9418065

00:53:27.140 --> 00:53:28.359 know, most of it does.

NOTE Confidence: 0.9613177

00:53:29.300 --> 00:53:30.579 But in in HER2 new

NOTE Confidence: 0.9613177

00:53:30.579 --> 00:53:31.700 cells, most of it comes

NOTE Confidence: 0.9613177

00:53:31.700 --> 00:53:32.680 from something else.

NOTE Confidence: 0.8542701

00:53:33.219 --> 00:53:34.020 So here we do the

NOTE Confidence: 0.8542701

00:53:34.020 --> 00:53:35.060 same experiment. We add the

NOTE Confidence: 0.8542701

00:53:35.060 --> 00:53:36.535 RevMed compounds, and it does

NOTE Confidence: 0.8542701

00:53:36.535 --> 00:53:37.495 have it has no effect

NOTE Confidence: 0.8542701

00:53:37.495 --> 00:53:39.755 on PAKT in this, amplified

NOTE Confidence: 0.8542701

00:53:40.055 --> 00:53:41.575 new cell line, but the

NOTE Confidence: 0.8542701

00:53:41.575 --> 00:53:42.075 breaker

NOTE Confidence: 0.99443126

00:53:42.375 --> 00:53:43.515 really shuts down

NOTE Confidence: 0.99363106

00:53:43.815 --> 00:53:45.195 PAKT very effectively,

NOTE Confidence: 0.9966484

00:53:45.815 --> 00:53:46.875 as well as

NOTE Confidence: 0.85769117

00:53:47.255 --> 00:53:48.455 pretty much. And then b

NOTE Confidence: 0.85769117

00:53:48.455 --> 00:53:49.590 t four seven four,

NOTE Confidence: 0.9316278

00:53:50.070 --> 00:53:50.710 same. There's a bit of

NOTE Confidence: 0.9316278

00:53:50.710 --> 00:53:51.510 a bit of an effect

NOTE Confidence: 0.9316278

00:53:51.510 --> 00:53:53.030 here from wild type HN

NOTE Confidence: 0.9316278

00:53:53.030 --> 00:53:54.090 and KRAS proteins,

NOTE Confidence: 0.8556943

00:53:54.550 --> 00:53:54.790 from,

NOTE Confidence: 0.9983061

00:53:55.350 --> 00:53:56.630 this analysis, but most of

NOTE Confidence: 0.9983061

00:53:56.630 --> 00:53:58.010 it comes from something else.

NOTE Confidence: 0.82584876

00:53:58.950 --> 00:54:00.070 And before you all ask,

NOTE Confidence: 0.82584876

00:54:00.070 --> 00:54:01.450 what is it, RS two?

NOTE Confidence: 0.8714764

00:54:02.710 --> 00:54:04.075 We think it's not. So,

NOTE Confidence: 0.8714764

00:54:04.155 --> 00:54:05.675 we've knocked out ras two,

NOTE Confidence: 0.8714764

00:54:05.675 --> 00:54:07.355 best we can, and ras

NOTE Confidence: 0.8714764

00:54:07.355 --> 00:54:08.175 and mras,

NOTE Confidence: 0.99335134

00:54:08.555 --> 00:54:09.755 and none of those account

NOTE Confidence: 0.99335134

00:54:09.755 --> 00:54:10.575 for this effect.

NOTE Confidence: 0.94593656

00:54:11.355 --> 00:54:12.655 But now we're stuck with

NOTE Confidence: 0.94593656

00:54:12.795 --> 00:54:14.955 another another protein, presumably, not

NOTE Confidence: 0.94593656

00:54:14.955 --> 00:54:16.094 necessarily, but, presumably,

NOTE Confidence: 0.93330526

00:54:16.395 --> 00:54:18.320 binding at that RAS binding

NOTE Confidence: 0.93330526

00:54:18.320 --> 00:54:20.080 domain, which is essential for

NOTE Confidence: 0.93330526

00:54:20.080 --> 00:54:21.360 HER2 new signaling, but we

NOTE Confidence: 0.93330526

00:54:21.360 --> 00:54:22.080 just don't know what the

NOTE Confidence: 0.93330526

00:54:22.080 --> 00:54:22.900 hell it is.

NOTE Confidence: 0.9203611

00:54:23.680 --> 00:54:24.820 So, any suggestions?

NOTE Confidence: 0.93619347

00:54:26.000 --> 00:54:26.739 I'll be delighted.

NOTE Confidence: 0.89728755

00:54:27.200 --> 00:54:28.560 We have a mass spec

NOTE Confidence: 0.89728755

00:54:28.560 --> 00:54:29.760 analysis going on right now

NOTE Confidence: 0.89728755

00:54:29.760 --> 00:54:30.960 with, t I p kinase

NOTE Confidence: 0.89728755

00:54:30.960 --> 00:54:32.535 alpha with Julian's mutants and

NOTE Confidence: 0.89728755

00:54:32.614 --> 00:54:33.895 blue and breaker, etcetera. It

NOTE Confidence: 0.89728755

00:54:33.895 --> 00:54:35.655 might sort of reveal it

NOTE Confidence: 0.89728755

00:54:35.655 --> 00:54:37.094 for the, the last resort

NOTE Confidence: 0.89728755

00:54:37.094 --> 00:54:39.035 of the intellectually bankrupt just

NOTE Confidence: 0.9235082

00:54:39.575 --> 00:54:40.295 to just to a mass

NOTE Confidence: 0.9235082

00:54:40.295 --> 00:54:41.414 spec and hope it solves

NOTE Confidence: 0.9235082

00:54:41.414 --> 00:54:42.375 the problem for us, but

NOTE Confidence: 0.9235082

00:54:42.375 --> 00:54:43.414 we we haven't gotten any

NOTE Confidence: 0.9235082

00:54:43.414 --> 00:54:44.295 good ideas as to what

NOTE Confidence: 0.9235082

00:54:44.295 --> 00:54:45.114 this could be.

NOTE Confidence: 0.7913389

00:54:46.730 --> 00:54:47.130 Anyway,

NOTE Confidence: 0.959116

00:54:47.849 --> 00:54:48.569 this drug is now in

NOTE Confidence: 0.959116

00:54:48.569 --> 00:54:49.530 the clinic, so you might

NOTE Confidence: 0.959116

00:54:49.530 --> 00:54:50.650 say, well, who cares? But,

NOTE Confidence: 0.9597875

00:54:51.290 --> 00:54:51.950 I do.

NOTE Confidence: 0.78173786

00:54:54.089 --> 00:54:54.589 Anyway,

NOTE Confidence: 0.8758285

00:54:55.930 --> 00:54:57.050 so important feature of this

NOTE Confidence: 0.8758285

00:54:57.050 --> 00:54:58.329 drug is that it shuts

NOTE Confidence: 0.8758285

00:54:58.329 --> 00:54:59.150 down signaling

NOTE Confidence: 0.8043051

00:54:59.770 --> 00:55:01.844 in these genotypes that doesn't

NOTE Confidence: 0.8043051

00:55:01.844 --> 00:55:02.325 affect,

NOTE Confidence: 0.9956012

00:55:02.645 --> 00:55:03.625 insulin signaling.

NOTE Confidence: 0.9198671

00:55:04.325 --> 00:55:06.005 So, in a mouse model,

NOTE Confidence: 0.9198671

00:55:06.005 --> 00:55:07.045 we can shut down AKT

NOTE Confidence: 0.9198671

00:55:07.045 --> 00:55:08.505 in tumors just like alpettosib,

NOTE Confidence: 0.84747

00:55:08.885 --> 00:55:10.344 but in contrast to alpettosib,

NOTE Confidence: 0.9639467

00:55:10.645 --> 00:55:12.245 we don't provoke accumulation of

NOTE Confidence: 0.9639467

00:55:12.245 --> 00:55:13.525 glucose and we don't cause

NOTE Confidence: 0.9639467

00:55:13.525 --> 00:55:14.025 hypoglycemia.

NOTE Confidence: 0.8235226

00:55:15.570 --> 00:55:17.330 For clinical people here will

NOTE Confidence: 0.8235226

00:55:17.330 --> 00:55:19.010 know that patients being treated

NOTE Confidence: 0.8235226

00:55:19.010 --> 00:55:20.950 with alpolis for, eight

NOTE Confidence: 0.6594295

00:55:21.330 --> 00:55:21.989 of the mutant

NOTE Confidence: 0.9522203

00:55:22.770 --> 00:55:23.590 breast cancers,

NOTE Confidence: 0.913893

00:55:24.530 --> 00:55:25.030 often,

NOTE Confidence: 0.98217684

00:55:25.410 --> 00:55:26.370 go off drug because of

NOTE Confidence: 0.98217684

00:55:26.370 --> 00:55:27.489 the side effects caused by

NOTE Confidence: 0.98217684

00:55:27.489 --> 00:55:27.989 hypoglycemia.

NOTE Confidence: 0.9623883

00:55:28.770 --> 00:55:29.945 So So this compound does

NOTE Confidence: 0.9623883

00:55:29.945 --> 00:55:30.925 not cause hypoglycemia,

NOTE Confidence: 0.91668844

00:55:31.625 --> 00:55:33.065 okay, in the mouse models,

NOTE Confidence: 0.91668844

00:55:33.065 --> 00:55:33.785 even though it can be

NOTE Confidence: 0.91668844

00:55:33.785 --> 00:55:34.525 as effective.

NOTE Confidence: 0.8963118

00:55:35.145 --> 00:55:36.105 So we hope it will

NOTE Confidence: 0.8963118

00:55:36.105 --> 00:55:37.465 be at a better version,

NOTE Confidence: 0.8963118

00:55:37.465 --> 00:55:38.765 a safer version of alpelacib

NOTE Confidence: 0.8963118

00:55:38.985 --> 00:55:40.605 with the same potency, hopefully,

NOTE Confidence: 0.8963118

00:55:40.825 --> 00:55:41.325 and

NOTE Confidence: 0.45087695

00:55:41.625 --> 00:55:42.765 and we have a tox.

NOTE Confidence: 0.85640657

00:55:45.380 --> 00:55:46.980 You also know probably that

NOTE Confidence: 0.85640657

00:55:46.980 --> 00:55:47.940 activation of p I three

NOTE Confidence: 0.85640657

00:55:47.940 --> 00:55:49.400 kinase makes many,

NOTE Confidence: 0.9305165

00:55:49.940 --> 00:55:50.440 drugs,

NOTE Confidence: 0.9110767

00:55:51.300 --> 00:55:53.140 fail to, work effectively in

NOTE Confidence: 0.9110767

00:55:53.140 --> 00:55:54.500 different contexts in in cancer

NOTE Confidence: 0.9110767

00:55:54.500 --> 00:55:56.020 cells. So here, looking at

NOTE Confidence: 0.9110767

00:55:56.020 --> 00:55:57.540 combination of the breaker with

NOTE Confidence: 0.9110767

00:55:57.540 --> 00:55:59.320 actually g twelve c inhibition.

NOTE Confidence: 0.9110767

00:55:59.540 --> 00:56:00.325 And this is I draw

NOTE Confidence: 0.9110767

00:56:00.325 --> 00:56:01.285 attention to this one. This

NOTE Confidence: 0.9110767

00:56:01.285 --> 00:56:02.005 is a model in which

NOTE Confidence: 0.9110767

00:56:02.005 --> 00:56:02.965 we have mutations in PIP

NOTE Confidence: 0.9110767

00:56:02.965 --> 00:56:04.805 one and STK eleven, which

NOTE Confidence: 0.9110767

00:56:04.805 --> 00:56:06.805 make lung cancer cells relatively

NOTE Confidence: 0.9110767

00:56:06.805 --> 00:56:07.305 resistant

NOTE Confidence: 0.9794402

00:56:07.685 --> 00:56:08.905 to G12C inhibitors.

NOTE Confidence: 0.92230624

00:56:10.245 --> 00:56:11.605 So, this is the p

NOTE Confidence: 0.92230624

00:56:11.605 --> 00:56:12.165 I three this is the

NOTE Confidence: 0.92230624

00:56:12.165 --> 00:56:13.445 G12C inhibitor. This is the

NOTE Confidence: 0.92230624

00:56:13.445 --> 00:56:14.940 breaker. Together, we see really

NOTE Confidence: 0.92230624

00:56:14.940 --> 00:56:15.920 nice responses.

NOTE Confidence: 0.9898027

00:56:16.300 --> 00:56:17.020 The same is true in

NOTE Confidence: 0.9898027

00:56:17.020 --> 00:56:18.160 these other models.

NOTE Confidence: 0.8493124

00:56:18.940 --> 00:56:20.460 So that kinda makes sense,

NOTE Confidence: 0.914311

00:56:20.940 --> 00:56:22.219 but we see that kind

NOTE Confidence: 0.914311

00:56:22.219 --> 00:56:23.739 of additive or super additive

NOTE Confidence: 0.914311

00:56:23.739 --> 00:56:25.180 effects in all the models

NOTE Confidence: 0.914311

00:56:25.180 --> 00:56:26.300 we've tested so far, which

NOTE Confidence: 0.914311

00:56:26.300 --> 00:56:27.839 include the follistrant, palvaciclib,

NOTE Confidence: 0.97569793

00:56:29.915 --> 00:56:30.415 trastuzumab,

NOTE Confidence: 0.9991126

00:56:31.594 --> 00:56:32.655 and even chemotherapy

NOTE Confidence: 0.83443373

00:56:32.955 --> 00:56:33.455 where

NOTE Confidence: 0.8894967

00:56:33.835 --> 00:56:35.755 breaker alone, has an effect,

NOTE Confidence: 0.8894967

00:56:35.755 --> 00:56:37.614 but in combination with irinotecan,

NOTE Confidence: 0.98697674

00:56:37.995 --> 00:56:39.695 we see really substantial effects.

NOTE Confidence: 0.84097934

00:56:40.555 --> 00:56:42.335 So we don't really understand

NOTE Confidence: 0.84097934

00:56:42.555 --> 00:56:43.710 why this would be. We

NOTE Confidence: 0.84097934

00:56:43.710 --> 00:56:45.550 know, generally, the PIAT mechanics

NOTE Confidence: 0.84097934

00:56:45.550 --> 00:56:46.670 makes cells more difficult to

NOTE Confidence: 0.84097934

00:56:46.670 --> 00:56:47.170 kill.

NOTE Confidence: 0.9618382

00:56:47.630 --> 00:56:48.830 That's been known forever. We

NOTE Confidence: 0.9618382

00:56:48.830 --> 00:56:49.630 don't really know what the

NOTE Confidence: 0.9618382

00:56:49.630 --> 00:56:51.070 molecular mechanism is, and we

NOTE Confidence: 0.9618382

00:56:51.070 --> 00:56:51.790 don't know that this will

NOTE Confidence: 0.9618382

00:56:51.790 --> 00:56:53.230 translate in the clinic. Obviously,

NOTE Confidence: 0.9618382

00:56:53.230 --> 00:56:54.050 this is all,

NOTE Confidence: 0.92704946

00:56:54.910 --> 00:56:56.145 in vitro model. So,

NOTE Confidence: 0.97426844

00:56:56.705 --> 00:56:57.585 but we will see because

NOTE Confidence: 0.97426844

00:56:57.585 --> 00:56:58.705 this compound is now moving

NOTE Confidence: 0.97426844

00:56:58.705 --> 00:57:00.305 through dose escalation in phase

NOTE Confidence: 0.97426844

00:57:00.305 --> 00:57:01.905 one clinical trials. And once

NOTE Confidence: 0.97426844

00:57:01.905 --> 00:57:03.025 we reach a certain dose,

NOTE Confidence: 0.97426844

00:57:03.025 --> 00:57:03.905 we can then test it

NOTE Confidence: 0.97426844

00:57:03.905 --> 00:57:04.565 in combination,

NOTE Confidence: 0.9437152

00:57:04.864 --> 00:57:05.985 and we'll definitely test it

NOTE Confidence: 0.9437152

00:57:05.985 --> 00:57:07.344 in combination with t twelve

NOTE Confidence: 0.9437152

00:57:07.344 --> 00:57:09.125 c and other KRAS drugs

NOTE Confidence: 0.9437152

00:57:09.185 --> 00:57:09.685 plus,

NOTE Confidence: 0.89969426

00:57:10.145 --> 00:57:11.265 these other drugs, which I've

NOTE Confidence: 0.89969426

00:57:11.265 --> 00:57:11.925 just mentioned.

NOTE Confidence: 0.9305944

00:57:12.760 --> 00:57:14.280 So, you know, fingers crossed

NOTE Confidence: 0.9305944

00:57:14.280 --> 00:57:15.240 for us at least. We'll

NOTE Confidence: 0.9305944

00:57:15.240 --> 00:57:16.680 see on the patients, see

NOTE Confidence: 0.9305944

00:57:16.680 --> 00:57:17.420 what happens.

NOTE Confidence: 0.78063476

00:57:18.200 --> 00:57:19.340 So this kind of summarizes

NOTE Confidence: 0.9370869

00:57:19.640 --> 00:57:21.320 the very complicated story of

NOTE Confidence: 0.9370869

00:57:21.320 --> 00:57:23.240 PI three kinase. So insulin

NOTE Confidence: 0.9370869

00:57:23.240 --> 00:57:24.380 receptor activates,

NOTE Confidence: 0.9899371

00:57:24.760 --> 00:57:26.440 glucose uptake without any RAS

NOTE Confidence: 0.9899371

00:57:26.440 --> 00:57:27.615 involvement that we know of.

NOTE Confidence: 0.9899371

00:57:27.775 --> 00:57:28.595 Okay? So,

NOTE Confidence: 0.9900087

00:57:29.295 --> 00:57:30.515 breaker doesn't affect that.

NOTE Confidence: 0.93025184

00:57:30.895 --> 00:57:32.895 Most normal signaling doesn't need

NOTE Confidence: 0.93025184

00:57:32.895 --> 00:57:33.855 RAS either as I showed

NOTE Confidence: 0.93025184

00:57:33.855 --> 00:57:35.295 you, so it don't affect

NOTE Confidence: 0.93025184

00:57:35.295 --> 00:57:37.295 normal RTK signaling. But under

NOTE Confidence: 0.93025184

00:57:37.295 --> 00:57:38.115 these circumstances,

NOTE Confidence: 0.99475676

00:57:38.575 --> 00:57:39.935 we do need a RAS

NOTE Confidence: 0.99475676

00:57:39.935 --> 00:57:40.435 protein

NOTE Confidence: 0.9040122

00:57:40.960 --> 00:57:41.780 either to turbocharge

NOTE Confidence: 0.9828616

00:57:42.240 --> 00:57:43.600 the reaction, as I said,

NOTE Confidence: 0.9828616

00:57:43.600 --> 00:57:44.960 or some other mechanism yet

NOTE Confidence: 0.9828616

00:57:44.960 --> 00:57:45.700 to be determined.

NOTE Confidence: 0.9833269

00:57:46.320 --> 00:57:46.820 But,

NOTE Confidence: 0.9197148

00:57:47.920 --> 00:57:49.040 we're we are working on

NOTE Confidence: 0.9197148

00:57:49.040 --> 00:57:50.240 this mechanism, but this is

NOTE Confidence: 0.9197148

00:57:50.240 --> 00:57:51.940 where the the breaker compound

NOTE Confidence: 0.9197148

00:57:52.000 --> 00:57:53.680 could work or directly on

NOTE Confidence: 0.9197148

00:57:53.680 --> 00:57:54.960 tumors driven by KRAS where

NOTE Confidence: 0.9197148

00:57:54.960 --> 00:57:56.020 the mutant alleles

NOTE Confidence: 0.94683754

00:57:56.365 --> 00:57:57.245 enable them to bind to

NOTE Confidence: 0.94683754

00:57:57.245 --> 00:57:58.445 PI3 kinase alpha, which they

NOTE Confidence: 0.94683754

00:57:58.445 --> 00:57:59.725 don't normally do, and we

NOTE Confidence: 0.94683754

00:57:59.725 --> 00:58:01.245 can interrupt that with the

NOTE Confidence: 0.94683754

00:58:01.245 --> 00:58:01.745 breaker.

NOTE Confidence: 0.91279453

00:58:02.765 --> 00:58:04.625 And with that, I will

NOTE Confidence: 0.91279453

00:58:04.765 --> 00:58:05.725 thank the people of the

NOTE Confidence: 0.91279453

00:58:05.725 --> 00:58:07.805 team from National Lab, and

NOTE Confidence: 0.91279453

00:58:07.805 --> 00:58:09.325 Lawrence Livermore National Lab. And

NOTE Confidence: 0.91279453

00:58:09.325 --> 00:58:10.569 my lab, part of work

NOTE Confidence: 0.91279453

00:58:10.569 --> 00:58:11.630 here in California.

NOTE Confidence: 0.96655875

00:58:12.890 --> 00:58:13.849 So, and with that, I'll

NOTE Confidence: 0.96655875

00:58:13.849 --> 00:58:14.650 I'll stop and be happy

NOTE Confidence: 0.96655875

00:58:14.650 --> 00:58:15.530 to take questions. Thank you

NOTE Confidence: 0.96655875

00:58:15.530 --> 00:58:16.589 very much. Thank you.

NOTE Confidence: 0.79833114

00:58:26.245 --> 00:58:26.745 Yes.

NOTE Confidence: 0.8824444

00:58:53.505 --> 00:58:54.865 Who's that? Yeah. That's that's

NOTE Confidence: 0.8824444

00:58:54.865 --> 00:58:55.924 a great question. Yeah.

NOTE Confidence: 0.9032029

00:58:58.065 --> 00:58:58.565 Sorry?

NOTE Confidence: 0.7432397

00:58:59.105 --> 00:59:00.785 May not be the direct

NOTE Confidence: 0.7432397

00:59:00.785 --> 00:59:01.285 one.

NOTE Confidence: 0.9475769

00:59:03.105 --> 00:59:04.464 Yeah. Correct. Yeah. We we

NOTE Confidence: 0.9475769

00:59:04.464 --> 00:59:05.265 we don't really know how

NOTE Confidence: 0.9475769

00:59:05.265 --> 00:59:06.224 it's working. We don't see

NOTE Confidence: 0.9475769

00:59:06.305 --> 00:59:07.184 we we do see that

NOTE Confidence: 0.9475769

00:59:07.184 --> 00:59:07.684 the,

NOTE Confidence: 0.8450944

00:59:09.140 --> 00:59:10.760 ras two, you know, binds

NOTE Confidence: 0.9764157

00:59:11.140 --> 00:59:11.380 to,

NOTE Confidence: 0.9119669

00:59:12.420 --> 00:59:13.300 p one ten in those

NOTE Confidence: 0.9119669

00:59:13.300 --> 00:59:14.580 cells and are most likely

NOTE Confidence: 0.9119669

00:59:14.580 --> 00:59:15.800 still engaged with the receptor.

NOTE Confidence: 0.98101306

00:59:17.380 --> 00:59:18.840 The drug interrupts that.

NOTE Confidence: 0.77735984

00:59:19.540 --> 00:59:21.300 Drugs that inhibit HOTO new

NOTE Confidence: 0.77735984

00:59:21.300 --> 00:59:22.260 make that all fall apart,

NOTE Confidence: 0.77735984

00:59:22.260 --> 00:59:23.560 so it's RTK dependent

NOTE Confidence: 0.94526756

00:59:23.915 --> 00:59:25.035 binding. But beyond that, we

NOTE Confidence: 0.94526756

00:59:25.035 --> 00:59:25.755 haven't got a handle on

NOTE Confidence: 0.94526756

00:59:25.755 --> 00:59:26.795 the mechanism. But, you know,

NOTE Confidence: 0.94526756

00:59:26.795 --> 00:59:27.295 obviously,

NOTE Confidence: 0.9679525

00:59:27.595 --> 00:59:28.555 you might have much better

NOTE Confidence: 0.9679525

00:59:28.555 --> 00:59:29.675 ideas than I do about

NOTE Confidence: 0.9679525

00:59:29.675 --> 00:59:30.895 how to deal with that.

NOTE Confidence: 0.92570275

00:59:31.435 --> 00:59:32.875 So it's, it's very, very

NOTE Confidence: 0.92570275

00:59:32.875 --> 00:59:33.994 strange. And and we only

NOTE Confidence: 0.92570275

00:59:33.994 --> 00:59:35.515 see the really dramatic effect

NOTE Confidence: 0.92570275

00:59:35.515 --> 00:59:36.795 of dependence on cells that

NOTE Confidence: 0.92570275

00:59:36.795 --> 00:59:37.295 amplified,

NOTE Confidence: 0.7264175

00:59:38.060 --> 00:59:39.340 HOTA new and or her

NOTE Confidence: 0.7264175

00:59:39.340 --> 00:59:39.840 three.

NOTE Confidence: 0.9827835

00:59:40.220 --> 00:59:41.260 But don't think it happens

NOTE Confidence: 0.9827835

00:59:41.260 --> 00:59:42.540 during normal signaling. It's a

NOTE Confidence: 0.9827835

00:59:42.540 --> 00:59:44.060 gain of function, but what

NOTE Confidence: 0.9827835

00:59:44.060 --> 00:59:45.280 it is, we don't know.

NOTE Confidence: 0.9209835

00:59:46.460 --> 00:59:47.420 Yeah. And we haven't we

NOTE Confidence: 0.9209835

00:59:47.420 --> 00:59:48.620 haven't really gone through all

NOTE Confidence: 0.9209835

00:59:48.620 --> 00:59:50.060 RTKs either really, but, honestly,

NOTE Confidence: 0.9209835

00:59:50.060 --> 00:59:50.860 just in that panel of

NOTE Confidence: 0.9209835

00:59:50.860 --> 00:59:51.900 cancer cells that I showed

NOTE Confidence: 0.9209835

00:59:51.900 --> 00:59:53.585 you where Houton new jumps

NOTE Confidence: 0.86703175

00:59:53.965 --> 00:59:55.405 out. But, it simulates that

NOTE Confidence: 0.86703175

00:59:55.405 --> 00:59:56.925 the EGFR mutations also do

NOTE Confidence: 0.86703175

00:59:56.925 --> 00:59:57.885 respond, but not as well

NOTE Confidence: 0.86703175

00:59:57.885 --> 00:59:58.785 as the Houton.

NOTE Confidence: 0.9486082

01:00:10.200 --> 01:00:11.240 Yeah. Very good very good

NOTE Confidence: 0.9486082

01:00:11.240 --> 01:00:12.200 thought. Yeah. Yeah. We should

NOTE Confidence: 0.9486082

01:00:12.200 --> 01:00:12.780 do that.

NOTE Confidence: 0.89404637

01:00:13.720 --> 01:00:15.000 Yeah. Maybe we should what

NOTE Confidence: 0.89404637

01:00:15.000 --> 01:00:15.720 I'd like to have is

NOTE Confidence: 0.89404637

01:00:15.720 --> 01:00:17.240 a simple system with, you

NOTE Confidence: 0.89404637

01:00:17.240 --> 01:00:17.880 know, like a like a

NOTE Confidence: 0.89404637

01:00:17.880 --> 01:00:18.760 math where you put things

NOTE Confidence: 0.89404637

01:00:18.760 --> 01:00:19.480 back in again and you

NOTE Confidence: 0.89404637

01:00:19.480 --> 01:00:20.280 can take them away again.

NOTE Confidence: 0.89404637

01:00:20.280 --> 01:00:20.715 But this

NOTE Confidence: 0.9162846

01:00:22.155 --> 01:00:22.208 is now we're working in

NOTE Confidence: 0.9162846

01:00:22.208 --> 01:00:22.555 cancer cell lines. It just

NOTE Confidence: 0.9162846

01:00:22.555 --> 01:00:23.835 makes it more complicated. But

NOTE Confidence: 0.9162846

01:00:23.915 --> 01:00:24.415 yeah.

NOTE Confidence: 0.9390062

01:00:27.115 --> 01:00:27.615 Yeah.

NOTE Confidence: 0.78861856

01:00:28.475 --> 01:00:29.675 I will we'll talk about

NOTE Confidence: 0.78861856

01:00:29.675 --> 01:00:30.575 it later maybe.

NOTE Confidence: 0.9974072

01:00:31.115 --> 01:00:31.855 Thank you.

NOTE Confidence: 0.61426157

01:00:33.355 --> 01:00:33.855 Hi.

NOTE Confidence: 0.77511287

01:00:35.120 --> 01:00:36.560 Some cancers don't have obvious

NOTE Confidence: 0.77511287

01:00:36.560 --> 01:00:38.080 genetic drivers of PI three

NOTE Confidence: 0.77511287

01:00:38.080 --> 01:00:39.280 kinase, you know, in the

NOTE Confidence: 0.77511287

01:00:39.280 --> 01:00:40.880 pathway. I was wondering if

NOTE Confidence: 0.77511287

01:00:40.880 --> 01:00:41.920 this with the screening of

NOTE Confidence: 0.77511287

01:00:41.920 --> 01:00:43.200 cell lines, like, suffer or

NOTE Confidence: 0.77511287

01:00:43.200 --> 01:00:44.020 to do that,

NOTE Confidence: 0.9101453

01:00:44.400 --> 01:00:46.020 you probably find some surprises

NOTE Confidence: 0.9101453

01:00:46.160 --> 01:00:47.840 where the breakers have really

NOTE Confidence: 0.9101453

01:00:47.840 --> 01:00:49.060 substantial effects,

NOTE Confidence: 0.96173865

01:00:50.095 --> 01:00:50.915 in the lines

NOTE Confidence: 0.9090106

01:00:51.215 --> 01:00:52.415 that don't have an obvious

NOTE Confidence: 0.9090106

01:00:52.415 --> 01:00:52.915 driver.

NOTE Confidence: 0.7656266

01:00:54.655 --> 01:00:56.495 Second really is, other RAS

NOTE Confidence: 0.7656266

01:00:56.495 --> 01:00:57.615 and deals that's not on

NOTE Confidence: 0.7656266

01:00:57.615 --> 01:00:59.295 person. NRAS put on sixty

NOTE Confidence: 0.7656266

01:00:59.295 --> 01:01:00.575 one. Are you seeing any

NOTE Confidence: 0.7656266

01:01:00.575 --> 01:01:02.015 activity with this drug? There's

NOTE Confidence: 0.7656266

01:01:02.015 --> 01:01:03.235 needs in

NOTE Confidence: 0.8856104

01:01:04.660 --> 01:01:05.960 cancers that don't have.

NOTE Confidence: 0.9616238

01:01:07.460 --> 01:01:07.960 Right.

NOTE Confidence: 0.9121299

01:01:09.140 --> 01:01:10.020 Well, second part of the

NOTE Confidence: 0.9121299

01:01:10.020 --> 01:01:11.060 question, yeah, we do see

NOTE Confidence: 0.9121299

01:01:11.060 --> 01:01:11.780 effects on,

NOTE Confidence: 0.83370125

01:01:12.260 --> 01:01:13.780 cell lines with h mutant

NOTE Confidence: 0.83370125

01:01:13.780 --> 01:01:15.540 or mutant. Same it's the

NOTE Confidence: 0.83370125

01:01:15.540 --> 01:01:16.900 same binding site version. There

NOTE Confidence: 0.83370125

01:01:16.900 --> 01:01:17.940 are actually cell lines with

NOTE Confidence: 0.83370125

01:01:17.940 --> 01:01:19.515 mutant two also, which it

NOTE Confidence: 0.83370125

01:01:19.515 --> 01:01:21.194 also blocks. But here's here's

NOTE Confidence: 0.83370125

01:01:21.194 --> 01:01:21.934 all of those.

NOTE Confidence: 0.9635179

01:01:22.474 --> 01:01:22.974 Okay.

NOTE Confidence: 0.8624612

01:01:23.515 --> 01:01:24.335 First question,

NOTE Confidence: 0.96970856

01:01:24.875 --> 01:01:25.755 there's a lot of cell

NOTE Confidence: 0.96970856

01:01:25.755 --> 01:01:26.315 lines that,

NOTE Confidence: 0.9428186

01:01:26.954 --> 01:01:28.154 that we see responses that

NOTE Confidence: 0.9428186

01:01:28.154 --> 01:01:28.954 have wild type p I

NOTE Confidence: 0.9428186

01:01:28.954 --> 01:01:30.154 three kinase for sure. Right?

NOTE Confidence: 0.9428186

01:01:30.154 --> 01:01:31.775 That's we know that.

NOTE Confidence: 0.9511133

01:01:32.510 --> 01:01:33.950 How many of those don't

NOTE Confidence: 0.9511133

01:01:33.950 --> 01:01:35.950 have known drivers that could

NOTE Confidence: 0.9511133

01:01:35.950 --> 01:01:37.250 affect p I three kinase?

NOTE Confidence: 0.9666944

01:01:37.950 --> 01:01:39.150 I'm not so sure because

NOTE Confidence: 0.9666944

01:01:39.150 --> 01:01:40.670 RTKs definitely can activate p

NOTE Confidence: 0.9666944

01:01:40.670 --> 01:01:42.290 I three kinase directly. Right?

NOTE Confidence: 0.6048174

01:01:42.670 --> 01:01:43.810 So, Like,

NOTE Confidence: 0.8894478

01:01:44.349 --> 01:01:45.494 blocks and things like that.

NOTE Confidence: 0.8894478

01:01:45.494 --> 01:01:46.694 I mean, that wouldn't be

NOTE Confidence: 0.8894478

01:01:46.694 --> 01:01:47.994 expected, but Yeah.

NOTE Confidence: 0.80876774

01:01:48.694 --> 01:01:49.194 Surprises.

NOTE Confidence: 0.9968916

01:01:49.494 --> 01:01:49.994 Right.

NOTE Confidence: 0.97801703

01:01:50.615 --> 01:01:51.194 I think

NOTE Confidence: 0.920295

01:01:51.974 --> 01:01:53.414 lines are completely resistant, but

NOTE Confidence: 0.920295

01:01:53.414 --> 01:01:54.535 I'm not hundred percent sure

NOTE Confidence: 0.920295

01:01:54.535 --> 01:01:55.654 about that. Very good, very

NOTE Confidence: 0.920295

01:01:55.654 --> 01:01:56.375 good point. I need to

NOTE Confidence: 0.920295

01:01:56.375 --> 01:01:57.355 come back and check.

NOTE Confidence: 0.72554284

01:02:05.710 --> 01:02:06.210 Okay.

NOTE Confidence: 0.90998256

01:02:07.950 --> 01:02:08.610 Any questions

NOTE Confidence: 0.8522295

01:02:09.550 --> 01:02:10.770 from an AI component?

NOTE Confidence: 0.63887036

01:02:12.030 --> 01:02:13.310 Does the greater change of

NOTE Confidence: 0.63887036

01:02:13.310 --> 01:02:14.369 the PI distribution

NOTE Confidence: 0.9120565

01:02:14.830 --> 01:02:15.570 on the memory

NOTE Confidence: 0.49653265

01:02:16.335 --> 01:02:17.795 ever yet created

NOTE Confidence: 0.48212898

01:02:18.255 --> 01:02:18.755 products?

NOTE Confidence: 0.6712479

01:02:19.695 --> 01:02:20.595 Their their localization

NOTE Confidence: 0.73703367

01:02:20.895 --> 01:02:22.675 is not their localization signal.

NOTE Confidence: 0.98915625

01:02:24.095 --> 01:02:24.595 Yes.

NOTE Confidence: 0.9943331

01:02:25.935 --> 01:02:26.974 That's one of the that's

NOTE Confidence: 0.9943331

01:02:26.974 --> 01:02:27.935 one of the possibilities on

NOTE Confidence: 0.9943331

01:02:27.935 --> 01:02:28.895 our list. We haven't been

NOTE Confidence: 0.9943331

01:02:28.895 --> 01:02:30.195 able to address that yet.

NOTE Confidence: 0.9943331

01:02:30.494 --> 01:02:31.234 In fact,

NOTE Confidence: 0.88629454

01:02:32.200 --> 01:02:33.820 don't really know how RAS

NOTE Confidence: 0.88629454

01:02:33.880 --> 01:02:34.860 cooperates with,

NOTE Confidence: 0.8777413

01:02:35.160 --> 01:02:36.520 PIP kinase anyway, but one

NOTE Confidence: 0.8777413

01:02:36.520 --> 01:02:37.240 model is that,

NOTE Confidence: 0.92351395

01:02:37.880 --> 01:02:40.280 KRAS particularly pluses PIP two

NOTE Confidence: 0.92351395

01:02:40.280 --> 01:02:41.720 around itself in the membrane.

NOTE Confidence: 0.92351395

01:02:41.720 --> 01:02:42.560 It's like a it's like

NOTE Confidence: 0.92351395

01:02:42.560 --> 01:02:43.640 a little puddle of PIP

NOTE Confidence: 0.92351395

01:02:43.640 --> 01:02:45.260 two induced by RAS itself.

NOTE Confidence: 0.92351395

01:02:45.455 --> 01:02:46.415 PIP two obviously is a

NOTE Confidence: 0.92351395

01:02:46.415 --> 01:02:47.295 substrate for p I three

NOTE Confidence: 0.92351395

01:02:47.295 --> 01:02:47.795 kinase.

NOTE Confidence: 0.9946426

01:02:48.095 --> 01:02:49.055 So it could actually be

NOTE Confidence: 0.9946426

01:02:49.055 --> 01:02:50.655 redistribution of lipids in the

NOTE Confidence: 0.9946426

01:02:50.655 --> 01:02:51.855 membrane to give the kinase

NOTE Confidence: 0.9946426

01:02:51.855 --> 01:02:52.675 more substrate.

NOTE Confidence: 0.5738503

01:02:53.215 --> 01:02:54.595 A change in signaling today.

NOTE Confidence: 0.9107593

01:02:55.695 --> 01:02:57.215 Yeah. Yeah. Yeah. All these

NOTE Confidence: 0.9107593

01:02:57.215 --> 01:02:58.730 signaling proteins have multiple c

NOTE Confidence: 0.9107593

01:02:58.730 --> 01:03:00.089 two domains and second and

NOTE Confidence: 0.9107593

01:03:00.089 --> 01:03:01.550 so on. Yeah. Yeah. Those

NOTE Confidence: 0.9107593

01:03:01.609 --> 01:03:02.970 are questions which might well

NOTE Confidence: 0.9107593

01:03:02.970 --> 01:03:03.770 be true, but it kinda

NOTE Confidence: 0.9107593

01:03:03.770 --> 01:03:04.730 makes me nauseous to think

NOTE Confidence: 0.9107593

01:03:04.730 --> 01:03:05.930 about. It's so difficult to

NOTE Confidence: 0.9107593

01:03:05.930 --> 01:03:06.750 do the experiment,

NOTE Confidence: 0.95765424

01:03:07.210 --> 01:03:08.250 but that might well be

NOTE Confidence: 0.95765424

01:03:08.250 --> 01:03:09.369 the case. Yeah. We don't

NOTE Confidence: 0.95765424

01:03:09.369 --> 01:03:10.650 really understand what the complex

NOTE Confidence: 0.95765424

01:03:10.650 --> 01:03:11.690 looks like, you know, before

NOTE Confidence: 0.95765424

01:03:11.690 --> 01:03:12.910 or after drug yet,

NOTE Confidence: 0.92848456

01:03:13.255 --> 01:03:14.135 but we hope to solve

NOTE Confidence: 0.92848456

01:03:14.135 --> 01:03:15.515 that out. Great great point.

NOTE Confidence: 0.9973676

01:03:17.815 --> 01:03:18.555 Yeah. Alright.

NOTE Confidence: 0.85202366

01:03:18.855 --> 01:03:19.974 No. We haven't used AI

NOTE Confidence: 0.85202366

01:03:19.974 --> 01:03:21.095 yet. Actually, we have to

NOTE Confidence: 0.85202366

01:03:21.095 --> 01:03:21.994 develop a drug.

NOTE Confidence: 0.71922004

01:03:22.295 --> 01:03:22.795 So,

NOTE Confidence: 0.8749182

01:03:23.575 --> 01:03:24.615 you said it took two

NOTE Confidence: 0.8749182

01:03:24.615 --> 01:03:25.895 or three years to figure

NOTE Confidence: 0.8749182

01:03:25.895 --> 01:03:27.675 out, structure for the breaker.

NOTE Confidence: 0.9032864

01:03:28.030 --> 01:03:28.850 Could you share,

NOTE Confidence: 0.8362021

01:03:29.230 --> 01:03:30.690 what were maybe some surprises

NOTE Confidence: 0.8362021

01:03:30.830 --> 01:03:33.310 in that process that may

NOTE Confidence: 0.8362021

01:03:33.310 --> 01:03:34.210 have led to it.

NOTE Confidence: 0.962836

01:03:37.630 --> 01:03:38.910 Yeah. Well, actually, that's kinda

NOTE Confidence: 0.962836

01:03:38.910 --> 01:03:40.110 short in a way. I

NOTE Confidence: 0.962836

01:03:40.110 --> 01:03:40.270 mean

NOTE Confidence: 0.9326038

01:03:41.565 --> 01:03:42.605 so getting a hit is

NOTE Confidence: 0.9326038

01:03:42.605 --> 01:03:43.645 easy, but getting a drug

NOTE Confidence: 0.9326038

01:03:43.645 --> 01:03:44.605 that's that has a PK

NOTE Confidence: 0.9326038

01:03:44.605 --> 01:03:45.964 properties that are compatible with

NOTE Confidence: 0.9326038

01:03:45.964 --> 01:03:46.865 orally available

NOTE Confidence: 0.9325893

01:03:47.405 --> 01:03:48.525 drug binding and not, you

NOTE Confidence: 0.9325893

01:03:48.525 --> 01:03:50.125 know, getting good target exposure

NOTE Confidence: 0.9325893

01:03:50.125 --> 01:03:51.165 and so on. That just

NOTE Confidence: 0.9325893

01:03:51.165 --> 01:03:52.305 takes a lot of empirical

NOTE Confidence: 0.9325893

01:03:52.365 --> 01:03:54.365 testing in mice, essentially. A

NOTE Confidence: 0.9325893

01:03:54.365 --> 01:03:55.165 lot of those stuff you

NOTE Confidence: 0.9325893

01:03:55.165 --> 01:03:56.865 can't do you can't predict,

NOTE Confidence: 0.9325893

01:03:57.119 --> 01:03:57.920 you know, a lot of

NOTE Confidence: 0.9325893

01:03:57.920 --> 01:03:58.880 those factors. Yes. A lot

NOTE Confidence: 0.9325893

01:03:58.880 --> 01:03:59.759 of it is just plowing

NOTE Confidence: 0.9325893

01:03:59.759 --> 01:04:01.039 through mice looking for things

NOTE Confidence: 0.9325893

01:04:01.039 --> 01:04:02.500 that have the right absorption,

NOTE Confidence: 0.9325893

01:04:02.720 --> 01:04:04.640 serum binding, distribution in tissues,

NOTE Confidence: 0.9325893

01:04:04.640 --> 01:04:05.279 and so on. A lot

NOTE Confidence: 0.9325893

01:04:05.279 --> 01:04:06.240 of it's just grunt work

NOTE Confidence: 0.9325893

01:04:06.240 --> 01:04:07.220 really, but honestly.

NOTE Confidence: 0.93827605

01:04:07.599 --> 01:04:08.160 And we do have a

NOTE Confidence: 0.93827605

01:04:08.160 --> 01:04:09.200 few surprises which are more

NOTE Confidence: 0.93827605

01:04:09.200 --> 01:04:10.160 interesting, and that is there

NOTE Confidence: 0.93827605

01:04:10.160 --> 01:04:10.980 are some compounds

NOTE Confidence: 0.88611007

01:04:11.495 --> 01:04:12.775 that affect our RAS two

NOTE Confidence: 0.88611007

01:04:12.775 --> 01:04:14.455 binding, but don't affect,

NOTE Confidence: 0.87764704

01:04:15.175 --> 01:04:16.535 the and other drugs that

NOTE Confidence: 0.87764704

01:04:16.535 --> 01:04:17.495 don't. And even though they

NOTE Confidence: 0.87764704

01:04:17.495 --> 01:04:18.775 all bind, they all affect

NOTE Confidence: 0.87764704

01:04:18.775 --> 01:04:19.895 KRAS, but only some of

NOTE Confidence: 0.87764704

01:04:19.895 --> 01:04:21.415 them affect RAS two even

NOTE Confidence: 0.87764704

01:04:21.415 --> 01:04:22.455 though the sequence is almost

NOTE Confidence: 0.87764704

01:04:22.455 --> 01:04:22.955 identical.

NOTE Confidence: 0.974431

01:04:23.335 --> 01:04:24.390 So So the compounds do

NOTE Confidence: 0.974431

01:04:24.390 --> 01:04:25.910 have different spectra of activity

NOTE Confidence: 0.974431

01:04:25.910 --> 01:04:27.510 against different RAS proteins despite

NOTE Confidence: 0.974431

01:04:27.510 --> 01:04:28.950 being so similar, which I

NOTE Confidence: 0.974431

01:04:28.950 --> 01:04:30.550 didn't really expect, but that's

NOTE Confidence: 0.974431

01:04:30.550 --> 01:04:31.349 become a bit of an

NOTE Confidence: 0.974431

01:04:31.349 --> 01:04:31.829 issue. But,

NOTE Confidence: 0.8305584

01:04:32.869 --> 01:04:34.170 yeah, mostly it was just

NOTE Confidence: 0.90784

01:04:34.630 --> 01:04:35.670 getting a compound that have

NOTE Confidence: 0.90784

01:04:35.670 --> 01:04:36.975 the right affinity, the right

NOTE Confidence: 0.90784

01:04:37.135 --> 01:04:38.435 PK properties, binding,

NOTE Confidence: 0.9861734

01:04:38.975 --> 01:04:40.675 safe, clean, high potency.

NOTE Confidence: 0.8610966

01:04:41.215 --> 01:04:42.035 That's hard.

NOTE Confidence: 0.9214849

01:04:42.895 --> 01:04:44.015 That's where AI may will

NOTE Confidence: 0.9214849

01:04:44.015 --> 01:04:44.655 make a difference in the

NOTE Confidence: 0.9214849

01:04:44.655 --> 01:04:45.695 future. If we can predict

NOTE Confidence: 0.9214849

01:04:45.695 --> 01:04:47.135 how to make drugs where

NOTE Confidence: 0.9214849

01:04:47.135 --> 01:04:47.615 I wish,

NOTE Confidence: 0.9012909

01:04:48.015 --> 01:04:49.615 a better add new properties,

NOTE Confidence: 0.9012909

01:04:49.615 --> 01:04:50.415 that would be a huge

NOTE Confidence: 0.9012909

01:04:50.415 --> 01:04:51.155 step forward.

NOTE Confidence: 0.79467374

01:05:40.095 --> 01:05:41.635 Directly possible. Yes.

NOTE Confidence: 0.8262633

01:05:42.095 --> 01:05:43.215 Yeah. I'm quite I'm a

NOTE Confidence: 0.8262633

01:05:43.215 --> 01:05:44.435 bit worried about that.

NOTE Confidence: 0.74787307

01:05:45.770 --> 01:05:47.130 Yeah. We think in some

NOTE Confidence: 0.74787307

01:05:47.130 --> 01:05:48.890 context that the blue compound

NOTE Confidence: 0.74787307

01:05:48.890 --> 01:05:49.849 on, yeah, the bridge top

NOTE Confidence: 0.74787307

01:05:49.849 --> 01:05:50.670 out, for example,

NOTE Confidence: 0.9297587

01:05:51.130 --> 01:05:53.130 combines RS two, cause a

NOTE Confidence: 0.9297587

01:05:53.130 --> 01:05:54.569 conformational change in p one

NOTE Confidence: 0.9297587

01:05:54.569 --> 01:05:55.930 ten, which could recruit other

NOTE Confidence: 0.9297587

01:05:55.930 --> 01:05:58.170 proteins, even chaperone proteins, and

NOTE Confidence: 0.9297587

01:05:58.170 --> 01:05:58.810 that could get in the

NOTE Confidence: 0.9297587

01:05:58.810 --> 01:05:59.690 way of the complex. So

NOTE Confidence: 0.9297587

01:05:59.690 --> 01:06:00.569 there there could be other

NOTE Confidence: 0.9297587

01:06:00.569 --> 01:06:02.145 players involved that we haven't

NOTE Confidence: 0.9297587

01:06:02.145 --> 01:06:03.825 yet seen. That's definitely a

NOTE Confidence: 0.9297587

01:06:03.825 --> 01:06:04.325 concern.

NOTE Confidence: 0.9406519

01:06:04.785 --> 01:06:05.985 And glue compound, though, works

NOTE Confidence: 0.9406519

01:06:05.985 --> 01:06:06.705 in in the test tube

NOTE Confidence: 0.9406519

01:06:06.705 --> 01:06:07.985 with recombinant proteins. So the

NOTE Confidence: 0.9406519

01:06:07.985 --> 01:06:09.285 glue, I think, is clean,

NOTE Confidence: 0.9406519

01:06:09.345 --> 01:06:10.385 but the breaker is not

NOTE Confidence: 0.9406519

01:06:10.385 --> 01:06:11.505 quite so clear what's going

NOTE Confidence: 0.9406519

01:06:11.505 --> 01:06:12.325 on. You know?

NOTE Confidence: 0.92094344

01:06:14.621 --> 01:06:15.361 Thank you.

NOTE Confidence: 0.82048744

01:06:15.981 --> 01:06:16.481 Okay.

NOTE Confidence: 0.9097285

01:06:18.701 --> 01:06:19.661 Thank you for your attention.

NOTE Confidence: 0.9097285

01:06:19.661 --> 01:06:20.401 Thank you.