

WEBVTT

NOTE duration:"01:02:18"

NOTE recognizability:0.862

NOTE language:en-us

NOTE Confidence: 0.844721467142857

00:00:02.160 --> 00:00:04.036 All right, so it's just about 12:30.

NOTE Confidence: 0.844721467142857

00:00:04.040 --> 00:00:04.908 We'll get things started.

NOTE Confidence: 0.844721467142857

00:00:04.908 --> 00:00:05.993 For those who don't know,

NOTE Confidence: 0.844721467142857

00:00:06.000 --> 00:00:07.060 me, I'm James Elia.

NOTE Confidence: 0.844721467142857

00:00:07.060 --> 00:00:08.385 I'm a graduate student in

NOTE Confidence: 0.844721467142857

00:00:08.385 --> 00:00:09.840 the pathology department,

NOTE Confidence: 0.844721467142857

00:00:09.840 --> 00:00:12.336 and Doctor Caitlin was our choice

NOTE Confidence: 0.844721467142857

00:00:12.336 --> 00:00:14.560 for graduate student grand rounds.

NOTE Confidence: 0.844721467142857

00:00:14.560 --> 00:00:16.300 So each year, the graduate students

NOTE Confidence: 0.844721467142857

00:00:16.300 --> 00:00:17.920 select one Grand round speaker,

NOTE Confidence: 0.844721467142857

00:00:17.920 --> 00:00:19.840 and we're very happy to have him here.

NOTE Confidence: 0.844721467142857

00:00:19.840 --> 00:00:21.490 So I just wanted to give

NOTE Confidence: 0.844721467142857

00:00:21.490 --> 00:00:22.315 a brief introduction.

NOTE Confidence: 0.844721467142857

00:00:22.320 --> 00:00:23.860 So Doctor William G Caitlin
NOTE Confidence: 0.844721467142857

00:00:23.860 --> 00:00:25.400 Junior received his Bachelor of
NOTE Confidence: 0.844721467142857

00:00:25.452 --> 00:00:26.964 Science and Chemistry Mathematics
NOTE Confidence: 0.844721467142857

00:00:26.964 --> 00:00:28.476 from Duke University OR.
NOTE Confidence: 0.844721467142857

00:00:28.480 --> 00:00:30.781 He also began his research career when
NOTE Confidence: 0.844721467142857

00:00:30.781 --> 00:00:32.486 Doctor Kalin questioned his research
NOTE Confidence: 0.844721467142857

00:00:32.486 --> 00:00:34.320 mentors assumptions on a project.
NOTE Confidence: 0.844721467142857

00:00:34.320 --> 00:00:36.300 The mentor wrote that Mister Kalin
NOTE Confidence: 0.844721467142857

00:00:36.300 --> 00:00:39.302 appears to be a bright young man whose
NOTE Confidence: 0.844721467142857

00:00:39.302 --> 00:00:41.720 future lies outside of the laboratory.
NOTE Confidence: 0.844721467142857

00:00:41.720 --> 00:00:42.000 Dr.
NOTE Confidence: 0.844721467142857

00:00:42.000 --> 00:00:43.120 Kalin remained at Duke
NOTE Confidence: 0.844721467142857

00:00:43.120 --> 00:00:44.240 for his medical degree,
NOTE Confidence: 0.844721467142857

00:00:44.240 --> 00:00:45.986 where he first read about tumor
NOTE Confidence: 0.844721467142857

00:00:45.986 --> 00:00:47.150 angiogenesis and the highly
NOTE Confidence: 0.844721467142857

00:00:47.200 --> 00:00:48.680 vascular tumors of von Hippel,

NOTE Confidence: 0.844721467142857
00:00:48.680 --> 00:00:50.292 Lindau, or VHL disease,
NOTE Confidence: 0.844721467142857
00:00:50.292 --> 00:00:52.710 and learn more about the rapidly
NOTE Confidence: 0.844721467142857
00:00:52.789 --> 00:00:55.599 developing field of molecular oncology.
NOTE Confidence: 0.844721467142857
00:00:55.600 --> 00:00:56.964 Doctor Caitlin completed his
NOTE Confidence: 0.844721467142857
00:00:56.964 --> 00:00:58.328 internship and residency in
NOTE Confidence: 0.844721467142857
00:00:58.328 --> 00:00:59.840 internal medicine at Johns Hopkins,
NOTE Confidence: 0.844721467142857
00:00:59.840 --> 00:01:01.496 where he served as an Assistant
NOTE Confidence: 0.844721467142857
00:01:01.496 --> 00:01:02.600 Chief of Service,
NOTE Confidence: 0.844721467142857
00:01:02.600 --> 00:01:04.720 learning more about VHL disease,
NOTE Confidence: 0.844721467142857
00:01:04.720 --> 00:01:06.484 in part so that you could grill
NOTE Confidence: 0.844721467142857
00:01:06.484 --> 00:01:07.760 trainees who questions authority,
NOTE Confidence: 0.844721467142857
00:01:07.760 --> 00:01:09.344 and in part because of the
NOTE Confidence: 0.844721467142857
00:01:09.344 --> 00:01:10.833 budding hypothesis on the VHL
NOTE Confidence: 0.844721467142857
00:01:10.833 --> 00:01:12.998 gene's role in oxygen sensing.
NOTE Confidence: 0.844721467142857
00:01:13.000 --> 00:01:13.284 Dr.
NOTE Confidence: 0.844721467142857

00:01:13.284 --> 00:01:14.704 Caitlin then joined Dana Farber
NOTE Confidence: 0.844721467142857

00:01:14.704 --> 00:01:16.240 as a Medical Oncology Fellow,
NOTE Confidence: 0.844721467142857

00:01:16.240 --> 00:01:18.431 where he determined the T and E1A
NOTE Confidence: 0.844721467142857

00:01:18.431 --> 00:01:20.421 binding site of the RV protein
NOTE Confidence: 0.844721467142857

00:01:20.421 --> 00:01:22.377 and helped identify E2F as a
NOTE Confidence: 0.844721467142857

00:01:22.377 --> 00:01:24.439 binding partner of the RV protein.
NOTE Confidence: 0.844721467142857

00:01:24.440 --> 00:01:25.950 He began his faculty position
NOTE Confidence: 0.844721467142857

00:01:25.950 --> 00:01:26.554 shortly thereafter.
NOTE Confidence: 0.844721467142857

00:01:26.560 --> 00:01:27.808 Just down the hall,
NOTE Confidence: 0.844721467142857

00:01:27.808 --> 00:01:29.680 his research focus turned to VHL,
NOTE Confidence: 0.844721467142857

00:01:29.680 --> 00:01:31.756 the topic of today's grand rounds.
NOTE Confidence: 0.844721467142857

00:01:31.760 --> 00:01:33.410 So on behalf of the pathology
NOTE Confidence: 0.844721467142857

00:01:33.410 --> 00:01:33.960 graduate students,
NOTE Confidence: 0.844721467142857

00:01:33.960 --> 00:01:35.836 our department and Yale School of Medicine,
NOTE Confidence: 0.844721467142857

00:01:35.840 --> 00:01:37.360 please welcome Doctor Bill Kalin.
NOTE Confidence: 0.847872936

00:01:44.520 --> 00:01:45.336 Well, thank you.

NOTE Confidence: 0.847872936

00:01:45.336 --> 00:01:47.235 Thank you, James for the very nice

NOTE Confidence: 0.847872936

00:01:47.235 --> 00:01:49.280 introduction and thank you to all the

NOTE Confidence: 0.847872936

00:01:49.280 --> 00:01:50.925 graduate students who invited me.

NOTE Confidence: 0.847872936

00:01:50.925 --> 00:01:53.716 I was recently I gave a lecture at

NOTE Confidence: 0.847872936

00:01:53.716 --> 00:01:56.299 the Cancer Center in South Dakota and

NOTE Confidence: 0.847872936

00:01:56.299 --> 00:01:58.573 at dinner the faculty confessed that

NOTE Confidence: 0.847872936

00:01:58.573 --> 00:02:02.080 they said we knew if the faculty invited you,

NOTE Confidence: 0.847872936

00:02:02.080 --> 00:02:03.400 you weren't coming to South Dakota.

NOTE Confidence: 0.847872936

00:02:03.400 --> 00:02:05.836 But if the graduate students invited you,

NOTE Confidence: 0.847872936

00:02:05.840 --> 00:02:07.776 you are on the next plane when there's

NOTE Confidence: 0.847872936

00:02:07.776 --> 00:02:09.854 some some element of truth that but I

NOTE Confidence: 0.847872936

00:02:09.854 --> 00:02:11.781 would have come whether the faculty or

NOTE Confidence: 0.847872936

00:02:11.781 --> 00:02:13.755 the graduate students at Yale invited me.

NOTE Confidence: 0.847872936

00:02:13.760 --> 00:02:15.176 So it's it's, it's quite fashionable

NOTE Confidence: 0.847872936

00:02:15.176 --> 00:02:16.959 now to have these disclosure slides,

NOTE Confidence: 0.847872936

00:02:16.960 --> 00:02:18.752 but often I find that people leave
NOTE Confidence: 0.847872936

00:02:18.752 --> 00:02:20.560 them up for literally 2 seconds.
NOTE Confidence: 0.847872936

00:02:20.560 --> 00:02:21.520 So it's like subliminal.
NOTE Confidence: 0.847872936

00:02:21.520 --> 00:02:22.798 So that's why I sort of leave it up.
NOTE Confidence: 0.847872936

00:02:22.800 --> 00:02:25.040 So you all digested this.
NOTE Confidence: 0.847872936

00:02:25.040 --> 00:02:27.314 So here are the people who've
NOTE Confidence: 0.847872936

00:02:27.314 --> 00:02:29.999 worked on Von HIPAA Lindau disease
NOTE Confidence: 0.847872936

00:02:30.000 --> 00:02:31.116 over the years of my laboratory,
NOTE Confidence: 0.847872936

00:02:31.120 --> 00:02:33.958 including your very own Chin Yan.
NOTE Confidence: 0.847872936

00:02:33.960 --> 00:02:36.024 And here's a list of some of our
NOTE Confidence: 0.847872936

00:02:36.024 --> 00:02:37.789 collaborators who have helped us with some
NOTE Confidence: 0.847872936

00:02:37.789 --> 00:02:39.937 of the work I'm going to describe today,
NOTE Confidence: 0.847872936

00:02:39.937 --> 00:02:41.959 including your very own David Brown.
NOTE Confidence: 0.847872936

00:02:41.960 --> 00:02:43.425 I might mention we're also
NOTE Confidence: 0.847872936

00:02:43.425 --> 00:02:44.597 collaborating with Joe Contessa,
NOTE Confidence: 0.847872936

00:02:44.600 --> 00:02:45.476 but in the interest of time,

NOTE Confidence: 0.847872936

00:02:45.480 --> 00:02:50.880 I won't be discussing that work today.

NOTE Confidence: 0.847872936

00:02:50.880 --> 00:02:52.680 So I went to high school at Rodger

NOTE Confidence: 0.847872936

00:02:52.680 --> 00:02:54.720 Ludlow High School at Fairfield, CT.

NOTE Confidence: 0.847872936

00:02:54.720 --> 00:02:59.560 I was rejected from Yale, but I I I did.

NOTE Confidence: 0.847872936

00:02:59.560 --> 00:03:02.352 I did get even because both my children

NOTE Confidence: 0.847872936

00:03:02.352 --> 00:03:03.988 actually attended Yale as undergraduates,

NOTE Confidence: 0.847872936

00:03:03.988 --> 00:03:05.558 including my son Pierre Tripp,

NOTE Confidence: 0.847872936

00:03:05.560 --> 00:03:07.425 who was on your national

NOTE Confidence: 0.847872936

00:03:07.425 --> 00:03:08.522 championship squash team.

NOTE Confidence: 0.847872936

00:03:08.522 --> 00:03:10.688 So obviously he got his athletic

NOTE Confidence: 0.847872936

00:03:10.688 --> 00:03:12.159 ability from his mother.

NOTE Confidence: 0.847872936

00:03:12.160 --> 00:03:15.140 So he was class of 2018, and I'll

NOTE Confidence: 0.847872936

00:03:15.140 --> 00:03:19.730 show you a picture of my daughter later on.

NOTE Confidence: 0.847872936

00:03:19.730 --> 00:03:23.200 Moreover, at the time I won the Nobel Prize,

NOTE Confidence: 0.847872936

00:03:23.200 --> 00:03:24.516 I was dating a very lovely woman,

NOTE Confidence: 0.847872936

00:03:24.520 --> 00:03:28.000 shown here named Karen Cantor,

NOTE Confidence: 0.847872936

00:03:28.000 --> 00:03:30.140 entering the hall at the

NOTE Confidence: 0.847872936

00:03:30.140 --> 00:03:32.280 arm of the Prime Minister.

NOTE Confidence: 0.847872936

00:03:32.280 --> 00:03:33.589 And there may be a handful of

NOTE Confidence: 0.847872936

00:03:33.589 --> 00:03:34.440 you in the room.

NOTE Confidence: 0.847872936

00:03:34.440 --> 00:03:35.140 Actually, no.

NOTE Confidence: 0.847872936

00:03:35.140 --> 00:03:37.240 She's the daughter of Fred Cantor,

NOTE Confidence: 0.847872936

00:03:37.240 --> 00:03:39.490 who was a beloved member of

NOTE Confidence: 0.847872936

00:03:39.490 --> 00:03:41.200 your faculty for many years.

NOTE Confidence: 0.847872936

00:03:41.200 --> 00:03:43.266 So all sorts of Yale connections.

NOTE Confidence: 0.847872936

00:03:43.266 --> 00:03:45.596 So when I was younger,

NOTE Confidence: 0.847872936

00:03:45.600 --> 00:03:46.050 as you heard,

NOTE Confidence: 0.847872936

00:03:46.050 --> 00:03:46.800 I went to medical school.

NOTE Confidence: 0.847872936

00:03:46.800 --> 00:03:47.730 I was so convinced I was

NOTE Confidence: 0.847872936

00:03:47.730 --> 00:03:48.879 going to be a clinical Dr.

NOTE Confidence: 0.847872936

00:03:48.880 --> 00:03:51.274 I spent an extra year at Johns

NOTE Confidence: 0.847872936

00:03:51.274 --> 00:03:54.246 Hopkins as the chief medical resident.

NOTE Confidence: 0.847872936

00:03:54.246 --> 00:03:55.824 But the person who changed my

NOTE Confidence: 0.847872936

00:03:55.824 --> 00:03:57.199 life was David Livingston.

NOTE Confidence: 0.847872936

00:03:57.200 --> 00:03:58.600 So after finishing my residency,

NOTE Confidence: 0.847872936

00:03:58.600 --> 00:04:00.866 I came to the Dana Farber in 1987

NOTE Confidence: 0.847872936

00:04:00.866 --> 00:04:03.796 to be a clinical oncologist.

NOTE Confidence: 0.847872936

00:04:03.800 --> 00:04:05.200 And then I had the good fortune

NOTE Confidence: 0.847872936

00:04:05.200 --> 00:04:07.024 of being a postdoc in his lab at a

NOTE Confidence: 0.847872936

00:04:07.024 --> 00:04:08.720 very good time to be in David's lab.

NOTE Confidence: 0.847872936

00:04:08.720 --> 00:04:10.040 Although frankly any opportunity to

NOTE Confidence: 0.847872936

00:04:10.040 --> 00:04:12.118 train with David would have been a good time.

NOTE Confidence: 0.847872936

00:04:12.120 --> 00:04:14.759 But the field was moving very quickly.

NOTE Confidence: 0.847872936

00:04:14.760 --> 00:04:16.832 The RB gene had just been isolated

NOTE Confidence: 0.847872936

00:04:16.832 --> 00:04:19.510 and I was given the opportunity to

NOTE Confidence: 0.847872936

00:04:19.510 --> 00:04:21.680 work on the RB tumor Spicer gene.

NOTE Confidence: 0.847872936

00:04:21.680 --> 00:04:24.212 So it was really David who sculpted me,
NOTE Confidence: 0.847872936

00:04:24.212 --> 00:04:26.354 crafted me, whatever you want to say,
NOTE Confidence: 0.809395754545454

00:04:26.360 --> 00:04:27.170 into a scientist.
NOTE Confidence: 0.809395754545454

00:04:27.170 --> 00:04:29.440 So I owe my scientific career to David.
NOTE Confidence: 0.809395754545454

00:04:29.440 --> 00:04:32.380 Sadly, we lost him about two years
NOTE Confidence: 0.809395754545454

00:04:32.380 --> 00:04:34.011 ago Now I thought what I would do
NOTE Confidence: 0.809395754545454

00:04:34.011 --> 00:04:35.574 is for the benefit of the young
NOTE Confidence: 0.809395754545454

00:04:35.574 --> 00:04:37.074 people and because you're supposed to
NOTE Confidence: 0.809395754545454

00:04:37.126 --> 00:04:38.638 dance with the one who brought you.
NOTE Confidence: 0.809395754545454

00:04:38.640 --> 00:04:40.656 I do have about 10 or 15
NOTE Confidence: 0.809395754545454

00:04:40.656 --> 00:04:41.706 minutes of historical review,
NOTE Confidence: 0.809395754545454

00:04:41.706 --> 00:04:43.008 so I won't be offended if some
NOTE Confidence: 0.809395754545454

00:04:43.008 --> 00:04:44.273 of my colleagues are checking
NOTE Confidence: 0.809395754545454

00:04:44.273 --> 00:04:45.678 their emails on their phones,
NOTE Confidence: 0.809395754545454

00:04:45.680 --> 00:04:47.794 and then we will move on to
NOTE Confidence: 0.809395754545454

00:04:47.794 --> 00:04:48.671 three unpublished stories.

NOTE Confidence: 0.809395754545454

00:04:48.671 --> 00:04:49.484 So of course,

NOTE Confidence: 0.809395754545454

00:04:49.484 --> 00:04:51.110 one of the most important decisions

NOTE Confidence: 0.809395754545454

00:04:51.160 --> 00:04:53.085 you have to make when you're starting

NOTE Confidence: 0.809395754545454

00:04:53.085 --> 00:04:54.560 your laboratory is what to work on.

NOTE Confidence: 0.809395754545454

00:04:54.560 --> 00:04:56.232 And fortunately for me,

NOTE Confidence: 0.809395754545454

00:04:56.232 --> 00:04:59.680 shortly after I started my own laboratory,

NOTE Confidence: 0.809395754545454

00:04:59.680 --> 00:05:00.880 this paper crossed my desk,

NOTE Confidence: 0.809395754545454

00:05:00.880 --> 00:05:02.800 which was the cloning of the gene that,

NOTE Confidence: 0.809395754545454

00:05:02.800 --> 00:05:03.554 when mutated,

NOTE Confidence: 0.809395754545454

00:05:03.554 --> 00:05:06.193 gives rise to the hereditary cancer syndrome.

NOTE Confidence: 0.809395754545454

00:05:06.200 --> 00:05:07.480 Von Hippel, Lindau disease.

NOTE Confidence: 0.809395754545454

00:05:07.480 --> 00:05:08.440 By the way,

NOTE Confidence: 0.809395754545454

00:05:08.440 --> 00:05:09.840 I left off one more Yale connection.

NOTE Confidence: 0.809395754545454

00:05:09.840 --> 00:05:12.094 So one of the few places that

NOTE Confidence: 0.809395754545454

00:05:12.094 --> 00:05:13.799 recruited me after my postdoc

NOTE Confidence: 0.809395754545454

00:05:13.800 --> 00:05:16.080 with David Livingstone was Yale.
NOTE Confidence: 0.809395754545454

00:05:16.080 --> 00:05:17.608 And I actually saw where my lab was
NOTE Confidence: 0.809395754545454

00:05:17.608 --> 00:05:19.039 going to be in the Boyer Center,
NOTE Confidence: 0.809395754545454

00:05:19.040 --> 00:05:20.960 which I walked past today.
NOTE Confidence: 0.809395754545454

00:05:20.960 --> 00:05:22.878 But the then chairman of medicine at
NOTE Confidence: 0.809395754545454

00:05:22.878 --> 00:05:24.903 Cadman and I didn't exactly have a
NOTE Confidence: 0.809395754545454

00:05:24.903 --> 00:05:27.424 meeting of the minds in terms of how
NOTE Confidence: 0.809395754545454

00:05:27.424 --> 00:05:28.916 you nurture physician scientists.
NOTE Confidence: 0.809395754545454

00:05:28.920 --> 00:05:31.139 So spices say that was a door
NOTE Confidence: 0.809395754545454

00:05:31.139 --> 00:05:32.760 I didn't walk through.
NOTE Confidence: 0.809395754545454

00:05:32.760 --> 00:05:34.677 So I joined the faculty at the Dana Farber.
NOTE Confidence: 0.809395754545454

00:05:34.680 --> 00:05:36.185 This paper crosses my desk and I
NOTE Confidence: 0.809395754545454

00:05:36.185 --> 00:05:37.755 knew from my clinical training this
NOTE Confidence: 0.809395754545454

00:05:37.755 --> 00:05:39.501 would be really be an interesting
NOTE Confidence: 0.809395754545454

00:05:39.501 --> 00:05:40.279 gene to study.
NOTE Confidence: 0.809395754545454

00:05:40.280 --> 00:05:40.560 Moreover,

NOTE Confidence: 0.809395754545454
00:05:40.560 --> 00:05:42.240 I thought from my work on
NOTE Confidence: 0.809395754545454
00:05:42.240 --> 00:05:43.080 the retinoblastoma gene,
NOTE Confidence: 0.809395754545454
00:05:43.080 --> 00:05:45.096 I was well positioned to study
NOTE Confidence: 0.809395754545454
00:05:45.096 --> 00:05:46.440 another tumor suppressor gene,
NOTE Confidence: 0.809395754545454
00:05:46.440 --> 00:05:48.996 namely the VHL tumor suppressor gene.
NOTE Confidence: 0.809395754545454
00:05:49.000 --> 00:05:50.827 So this is a disease that was
NOTE Confidence: 0.809395754545454
00:05:50.827 --> 00:05:52.199 described about 100 years ago.
NOTE Confidence: 0.809395754545454
00:05:52.200 --> 00:05:54.252 It affects about one in 35,000
NOTE Confidence: 0.809395754545454
00:05:54.252 --> 00:05:55.650 people around the world.
NOTE Confidence: 0.809395754545454
00:05:55.650 --> 00:05:57.400 And as you can see,
NOTE Confidence: 0.809395754545454
00:05:57.400 --> 00:05:58.415 these are some kindreds that
NOTE Confidence: 0.809395754545454
00:05:58.415 --> 00:05:59.724 have been followed at the NCI
NOTE Confidence: 0.809395754545454
00:05:59.724 --> 00:06:00.720 with von Hippelindau disease.
NOTE Confidence: 0.809395754545454
00:06:00.720 --> 00:06:03.513 And of course the filled circles and
NOTE Confidence: 0.809395754545454
00:06:03.513 --> 00:06:05.560 squares are affected individuals
NOTE Confidence: 0.809395754545454

00:06:05.560 --> 00:06:07.436 and the classical tumors seen in the
NOTE Confidence: 0.809395754545454

00:06:07.436 --> 00:06:09.560 syndrome are clear cell renal cell carcinoma,
NOTE Confidence: 0.809395754545454

00:06:09.560 --> 00:06:11.464 which is by far the most common
NOTE Confidence: 0.809395754545454

00:06:11.464 --> 00:06:12.760 form of kidney cancer.
NOTE Confidence: 0.809395754545454

00:06:12.760 --> 00:06:14.060 Blood vessel tumors called
NOTE Confidence: 0.809395754545454

00:06:14.060 --> 00:06:15.360 hemangioblastomas of the eye,
NOTE Confidence: 0.809395754545454

00:06:15.360 --> 00:06:17.856 brain and spinal cord and neuro
NOTE Confidence: 0.809395754545454

00:06:17.856 --> 00:06:20.160 Crest tumors called paragangliomas,
NOTE Confidence: 0.809395754545454

00:06:20.160 --> 00:06:22.302 which when they arise in the adrenal
NOTE Confidence: 0.809395754545454

00:06:22.302 --> 00:06:23.854 gland are referred to as pheochromocytomas.
NOTE Confidence: 0.809395754545454

00:06:23.854 --> 00:06:25.912 Now you can see that clinically this
NOTE Confidence: 0.809395754545454

00:06:25.912 --> 00:06:27.958 looks like an autosomal dominant disorder,
NOTE Confidence: 0.809395754545454

00:06:27.960 --> 00:06:29.465 but actually at the molecular
NOTE Confidence: 0.809395754545454

00:06:29.465 --> 00:06:31.346 level this is actually an autosomal
NOTE Confidence: 0.809395754545454

00:06:31.346 --> 00:06:33.242 it's actually caused by a loss
NOTE Confidence: 0.809395754545454

00:06:33.242 --> 00:06:34.062 of function mutation.

NOTE Confidence: 0.809395754545454
00:06:34.062 --> 00:06:34.426 So again,
NOTE Confidence: 0.809395754545454
00:06:34.426 --> 00:06:36.080 just to make sure everyone saw the same page,
NOTE Confidence: 0.809395754545454
00:06:36.080 --> 00:06:37.958 people with about HIPAA Lindow disease
NOTE Confidence: 0.809395754545454
00:06:37.958 --> 00:06:39.789 have have inherited A defective version
NOTE Confidence: 0.809395754545454
00:06:39.789 --> 00:06:41.877 of the VHL gene from mom or dad.
NOTE Confidence: 0.809395754545454
00:06:41.880 --> 00:06:42.822 In this schematic,
NOTE Confidence: 0.809395754545454
00:06:42.822 --> 00:06:44.078 it's the maternal copy.
NOTE Confidence: 0.809395754545454
00:06:44.080 --> 00:06:45.550 But they're initially OK because
NOTE Confidence: 0.809395754545454
00:06:45.550 --> 00:06:47.388 they have the remaining wild type
NOTE Confidence: 0.809395754545454
00:06:47.388 --> 00:06:49.284 allele and there's no evidence for
NOTE Confidence: 0.809395754545454
00:06:49.284 --> 00:06:50.760 HAPLO insufficiency for this gene.
NOTE Confidence: 0.809395754545454
00:06:50.760 --> 00:06:52.080 But unfortunately, if you're born like this,
NOTE Confidence: 0.809395754545454
00:06:52.080 --> 00:06:54.173 you have a 90% chance that one
NOTE Confidence: 0.809395754545454
00:06:54.173 --> 00:06:55.070 or more susceptible
NOTE Confidence: 0.925362958947368
00:06:55.130 --> 00:06:57.545 cells in your body will spontaneously lose
NOTE Confidence: 0.925362958947368

00:06:57.545 --> 00:06:59.440 or mutate the remaining wild type copy.
NOTE Confidence: 0.925362958947368

00:06:59.440 --> 00:07:00.480 And that's the cell that
NOTE Confidence: 0.925362958947368

00:07:00.480 --> 00:07:01.960 will go on to form a tumor.
NOTE Confidence: 0.925362958947368

00:07:01.960 --> 00:07:03.664 And as you would predict from
NOTE Confidence: 0.925362958947368

00:07:03.664 --> 00:07:05.178 the knowledge that germline VHL
NOTE Confidence: 0.925362958947368

00:07:05.178 --> 00:07:06.798 mutations predispose to for example
NOTE Confidence: 0.925362958947368

00:07:06.800 --> 00:07:07.880 clear cell renal cell carcinoma.
NOTE Confidence: 0.925362958947368

00:07:07.880 --> 00:07:09.483 If you now look at non hereditary
NOTE Confidence: 0.925362958947368

00:07:09.483 --> 00:07:10.960 clear cell renal cell carcinomas,
NOTE Confidence: 0.925362958947368

00:07:10.960 --> 00:07:12.836 you again see that both the maternal
NOTE Confidence: 0.925362958947368

00:07:12.836 --> 00:07:14.796 and the paternal copies of the VHL
NOTE Confidence: 0.925362958947368

00:07:14.796 --> 00:07:16.440 gene are frequently mutated or lost.
NOTE Confidence: 0.925362958947368

00:07:16.440 --> 00:07:18.554 But here both mutational events or hits
NOTE Confidence: 0.925362958947368

00:07:18.554 --> 00:07:20.623 if you will have occurred somatically
NOTE Confidence: 0.925362958947368

00:07:20.623 --> 00:07:23.192 in contrast to VHL disease where the
NOTE Confidence: 0.925362958947368

00:07:23.256 --> 00:07:26.918 first hit has occurred in the germline.

NOTE Confidence: 0.925362958947368

00:07:26.920 --> 00:07:28.696 So I knew from my clinical training that

NOTE Confidence: 0.925362958947368

00:07:28.696 --> 00:07:30.476 the tumors seen in von Hippel-Lindau disease

NOTE Confidence: 0.925362958947368

00:07:30.476 --> 00:07:32.160 are notoriously rich in blood vessels,

NOTE Confidence: 0.925362958947368

00:07:32.160 --> 00:07:33.942 and that's because they frequently over

NOTE Confidence: 0.925362958947368

00:07:33.942 --> 00:07:36.214 produce BEGF and then they also occasionally

NOTE Confidence: 0.925362958947368

00:07:36.214 --> 00:07:38.479 cause excess red blood cell production,

NOTE Confidence: 0.925362958947368

00:07:38.480 --> 00:07:40.450 and that's because they sometimes

NOTE Confidence: 0.925362958947368

00:07:40.450 --> 00:07:41.582 ectopically produce erythropoietin.

NOTE Confidence: 0.925362958947368

00:07:41.582 --> 00:07:43.634 And what VEGF and erythropoietin have

NOTE Confidence: 0.925362958947368

00:07:43.634 --> 00:07:45.705 in common is that they're normally

NOTE Confidence: 0.925362958947368

00:07:45.705 --> 00:07:47.355 induced when cells or tissues

NOTE Confidence: 0.925362958947368

00:07:47.360 --> 00:07:48.400 are not getting enough oxygen.

NOTE Confidence: 0.925362958947368

00:07:48.400 --> 00:07:50.171 So that was the clue that by

NOTE Confidence: 0.925362958947368

00:07:50.171 --> 00:07:52.302 studying the VHL gene we might learn

NOTE Confidence: 0.925362958947368

00:07:52.302 --> 00:07:53.660 something about oxygen sensing.

NOTE Confidence: 0.925362958947368

00:07:53.660 --> 00:07:56.460 Now VEGF and EPO are under the control

NOTE Confidence: 0.925362958947368

00:07:56.532 --> 00:07:58.524 of a heterodimeric transcription

NOTE Confidence: 0.925362958947368

00:07:58.524 --> 00:08:00.320 factor called hypoxia decibal

NOTE Confidence: 0.925362958947368

00:08:00.320 --> 00:08:02.320 factor or HIP for short.

NOTE Confidence: 0.925362958947368

00:08:02.320 --> 00:08:03.622 And we knew from the work

NOTE Confidence: 0.925362958947368

00:08:03.622 --> 00:08:04.273 of multiple laboratories,

NOTE Confidence: 0.925362958947368

00:08:04.280 --> 00:08:07.262 including the work of my fellow

NOTE Confidence: 0.925362958947368

00:08:07.262 --> 00:08:09.552 laureates factors Semenza and Radcliffe

NOTE Confidence: 0.925362958947368

00:08:09.552 --> 00:08:12.240 that the alpha subunit is normally

NOTE Confidence: 0.925362958947368

00:08:12.310 --> 00:08:14.648 degraded when oxygen is available,

NOTE Confidence: 0.925362958947368

00:08:14.648 --> 00:08:17.560 hence hypoxia inducible factor.

NOTE Confidence: 0.925362958947368

00:08:17.560 --> 00:08:18.226 Whereas HIP beta,

NOTE Confidence: 0.925362958947368

00:08:18.226 --> 00:08:19.558 which is also known as RNT,

NOTE Confidence: 0.925362958947368

00:08:19.560 --> 00:08:21.320 is constitutively stable and

NOTE Confidence: 0.925362958947368

00:08:21.320 --> 00:08:23.520 over the course of time,

NOTE Confidence: 0.925362958947368

00:08:23.520 --> 00:08:25.256 our lab and others showed that the

NOTE Confidence: 0.925362958947368

00:08:25.256 --> 00:08:27.127 VHL protein is part of a so-called

NOTE Confidence: 0.925362958947368

00:08:27.127 --> 00:08:28.768 GABIC one and ligase complex that

NOTE Confidence: 0.925362958947368

00:08:28.768 --> 00:08:30.496 binds directly to hip alpha and

NOTE Confidence: 0.925362958947368

00:08:30.496 --> 00:08:32.400 targets it for proteasomal degradation

NOTE Confidence: 0.925362958947368

00:08:32.400 --> 00:08:34.360 provided oxidant is present.

NOTE Confidence: 0.925362958947368

00:08:34.360 --> 00:08:35.896 Whereas when oxygen levels are low

NOTE Confidence: 0.925362958947368

00:08:35.896 --> 00:08:37.599 or the VHL protein is defective,

NOTE Confidence: 0.925362958947368

00:08:37.600 --> 00:08:39.560 such as in kidney cancer,

NOTE Confidence: 0.925362958947368

00:08:39.560 --> 00:08:41.360 now HIP alpha can accumulate,

NOTE Confidence: 0.925362958947368

00:08:41.360 --> 00:08:42.800 dimerize with its partner protein,

NOTE Confidence: 0.925362958947368

00:08:42.800 --> 00:08:44.765 Orient and activate various and

NOTE Confidence: 0.925362958947368

00:08:44.765 --> 00:08:47.185 sundry genes such as VEGF and

NOTE Confidence: 0.925362958947368

00:08:47.185 --> 00:08:48.327 on occasion erythropoietin.

NOTE Confidence: 0.925362958947368

00:08:48.327 --> 00:08:50.616 And also point out that there are

NOTE Confidence: 0.925362958947368

00:08:50.616 --> 00:08:52.421 two mutational hotspots if you look

NOTE Confidence: 0.925362958947368

00:08:52.421 --> 00:08:54.071 at BHL families around the world,
NOTE Confidence: 0.925362958947368

00:08:54.080 --> 00:08:55.550 one is the alpha domain which
NOTE Confidence: 0.925362958947368

00:08:55.550 --> 00:08:57.056 recruits the rest of the ubiquin
NOTE Confidence: 0.925362958947368

00:08:57.056 --> 00:08:58.936 and ligase and the other is the beta
NOTE Confidence: 0.925362958947368

00:08:58.993 --> 00:09:00.862 domain which we showed is the actual
NOTE Confidence: 0.925362958947368

00:09:00.862 --> 00:09:02.264 docking site for the substrate.
NOTE Confidence: 0.925362958947368

00:09:02.264 --> 00:09:04.280 Now this of course begs the question,
NOTE Confidence: 0.925362958947368

00:09:04.280 --> 00:09:05.516 how does the VHL protein know,
NOTE Confidence: 0.925362958947368

00:09:05.520 --> 00:09:07.263 if you will whether oxygen is or
NOTE Confidence: 0.925362958947368

00:09:07.263 --> 00:09:08.896 is not available and hence whether
NOTE Confidence: 0.925362958947368

00:09:08.896 --> 00:09:10.558 it should or should not destroy
NOTE Confidence: 0.925362958947368

00:09:10.560 --> 00:09:12.720 HIP or mark HIP for destruction.
NOTE Confidence: 0.925362958947368

00:09:12.720 --> 00:09:13.960 And work That we did,
NOTE Confidence: 0.925362958947368

00:09:13.960 --> 00:09:15.916 and Sir Peter Ratcliff did working
NOTE Confidence: 0.925362958947368

00:09:15.920 --> 00:09:16.940 independently in parallel,
NOTE Confidence: 0.925362958947368

00:09:16.940 --> 00:09:18.980 showed that in the presence of

NOTE Confidence: 0.925362958947368

00:09:18.980 --> 00:09:21.405 oxygen one of two conserve prolia

NOTE Confidence: 0.925362958947368

00:09:21.405 --> 00:09:23.490 residues gets hydroxylated in hip

NOTE Confidence: 0.925362958947368

00:09:23.561 --> 00:09:25.865 alpha and this then generates a

NOTE Confidence: 0.925362958947368

00:09:25.865 --> 00:09:27.954 high affinity VHL binding site.

NOTE Confidence: 0.925362958947368

00:09:27.954 --> 00:09:31.020 The the enzymes that do the work

NOTE Confidence: 0.925362958947368

00:09:31.115 --> 00:09:33.875 here are variably called the Ego

NOTE Confidence: 0.925362958947368

00:09:33.875 --> 00:09:35.708 or PhD Prol hydroxylases.

NOTE Confidence: 0.925362958947368

00:09:35.708 --> 00:09:37.978 They split molecular oxygen and

NOTE Confidence: 0.925362958947368

00:09:37.978 --> 00:09:39.340 use one of

NOTE Confidence: 0.820588314666667

00:09:39.417 --> 00:09:43.400 the oxidant atoms to hydroxylate the hip.

NOTE Confidence: 0.820588314666667

00:09:43.400 --> 00:09:45.080 They also require reduced iron,

NOTE Confidence: 0.820588314666667

00:09:45.080 --> 00:09:46.625 which explains an old observation

NOTE Confidence: 0.820588314666667

00:09:46.625 --> 00:09:48.471 that iron chelators when given to

NOTE Confidence: 0.820588314666667

00:09:48.471 --> 00:09:50.160 cells and culture will mimic or

NOTE Confidence: 0.820588314666667

00:09:50.160 --> 00:09:52.360 stimulate A hypoxic like response.

NOTE Confidence: 0.820588314666667

00:09:52.360 --> 00:09:54.652 They also require a cofactor which
NOTE Confidence: 0.820588314666667

00:09:54.652 --> 00:09:56.925 is variably called 2 oxygoodrate or
NOTE Confidence: 0.820588314666667

00:09:56.925 --> 00:09:58.800 alpha ketoglydrate if you prefer,
NOTE Confidence: 0.820588314666667

00:09:58.800 --> 00:10:01.680 which gets decarboxylated to succinate.
NOTE Confidence: 0.820588314666667

00:10:01.680 --> 00:10:02.612 Not shown here, however,
NOTE Confidence: 0.820588314666667

00:10:02.612 --> 00:10:04.520 is one other critical piece of the puzzle,
NOTE Confidence: 0.820588314666667

00:10:04.520 --> 00:10:06.812 which is These enzymes have very
NOTE Confidence: 0.820588314666667

00:10:06.812 --> 00:10:08.676 low oxygen affinities and hence
NOTE Confidence: 0.820588314666667

00:10:08.676 --> 00:10:10.890 they're poised to sense oxygen in
NOTE Confidence: 0.820588314666667

00:10:10.959 --> 00:10:12.959 a physiologically relevant range.
NOTE Confidence: 0.820588314666667

00:10:12.960 --> 00:10:14.478 That's in contrast to, for example,
NOTE Confidence: 0.820588314666667

00:10:14.480 --> 00:10:16.260 the collagen pro hydroxylases you
NOTE Confidence: 0.820588314666667

00:10:16.260 --> 00:10:18.040 might have studied in college
NOTE Confidence: 0.820588314666667

00:10:18.104 --> 00:10:19.520 and college biochemistry.
NOTE Confidence: 0.820588314666667

00:10:19.520 --> 00:10:21.605 The collagen pro hydroxylases have
NOTE Confidence: 0.820588314666667

00:10:21.605 --> 00:10:23.273 extremely high oxygen affinities.

NOTE Confidence: 0.820588314666667
00:10:23.280 --> 00:10:25.272 You'd have to be virtually anoxic
NOTE Confidence: 0.820588314666667
00:10:25.272 --> 00:10:27.148 before the collagen pro hydroxylases
NOTE Confidence: 0.820588314666667
00:10:27.148 --> 00:10:28.502 would become inactive.
NOTE Confidence: 0.820588314666667
00:10:28.502 --> 00:10:31.558 So these enzymes I just introduced to you,
NOTE Confidence: 0.820588314666667
00:10:31.560 --> 00:10:33.205 which I'll stick with the original and
NOTE Confidence: 0.820588314666667
00:10:33.205 --> 00:10:35.268 the meclids, are the EGELIN enzymes.
NOTE Confidence: 0.820588314666667
00:10:35.268 --> 00:10:37.650 So these are the pro hydroxylases
NOTE Confidence: 0.820588314666667
00:10:37.724 --> 00:10:38.840 that modify hip.
NOTE Confidence: 0.820588314666667
00:10:38.840 --> 00:10:40.730 But you can see these enzymes are
NOTE Confidence: 0.820588314666667
00:10:40.730 --> 00:10:43.118 part of a much larger superfamily,
NOTE Confidence: 0.820588314666667
00:10:43.120 --> 00:10:45.450 so-called 2 oxyglate dependent de
NOTE Confidence: 0.820588314666667
00:10:45.450 --> 00:10:48.870 oxygenases which includes many of the
NOTE Confidence: 0.820588314666667
00:10:48.870 --> 00:10:51.600 so-called Jumanji C histone demethylases
NOTE Confidence: 0.820588314666667
00:10:51.600 --> 00:10:55.440 as well as the Ted enzymes that are
NOTE Confidence: 0.820588314666667
00:10:55.533 --> 00:10:58.277 implicated in DNA demethylation.
NOTE Confidence: 0.820588314666667

00:10:58.280 --> 00:11:01.232 So let's go back to the Jumanji C proteins.

NOTE Confidence: 0.820588314666667

00:11:01.240 --> 00:11:04.354 So the Jumanji C histone methylases

NOTE Confidence: 0.820588314666667

00:11:04.354 --> 00:11:07.608 as first shown by Yi Zhang use

NOTE Confidence: 0.820588314666667

00:11:07.608 --> 00:11:08.760 a fairly similar chemistry,

NOTE Confidence: 0.820588314666667

00:11:08.760 --> 00:11:11.105 but what they do is they hydroxylate

NOTE Confidence: 0.820588314666667

00:11:11.105 --> 00:11:13.851 the histone methyl group which is then

NOTE Confidence: 0.820588314666667

00:11:13.851 --> 00:11:16.408 unstable and given off as formaldehyde.

NOTE Confidence: 0.820588314666667

00:11:16.408 --> 00:11:18.956 Now this raised the question in our

NOTE Confidence: 0.820588314666667

00:11:18.956 --> 00:11:20.957 minds and other people's minds,

NOTE Confidence: 0.820588314666667

00:11:20.960 --> 00:11:22.780 are these enzymes more like

NOTE Confidence: 0.820588314666667

00:11:22.780 --> 00:11:24.600 the enzymes that modify HIP?

NOTE Confidence: 0.820588314666667

00:11:24.600 --> 00:11:26.904 Meaning are they going to be very oxygen

NOTE Confidence: 0.820588314666667

00:11:26.904 --> 00:11:28.691 sensitive or are they going to be more

NOTE Confidence: 0.820588314666667

00:11:28.691 --> 00:11:30.314 like the collagen pro hydroxy ACES

NOTE Confidence: 0.820588314666667

00:11:30.314 --> 00:11:31.874 and be relatively oxygen insensitive?

NOTE Confidence: 0.820588314666667

00:11:31.880 --> 00:11:33.840 And it turns out you can find

NOTE Confidence: 0.820588314666667
00:11:33.840 --> 00:11:35.245 many examples of both.
NOTE Confidence: 0.820588314666667
00:11:35.245 --> 00:11:37.120 Some of the histamine methylases
NOTE Confidence: 0.820588314666667
00:11:37.120 --> 00:11:39.545 actually turn out to be exquisitely
NOTE Confidence: 0.820588314666667
00:11:39.545 --> 00:11:41.157 sensitive to oxygen availability.
NOTE Confidence: 0.820588314666667
00:11:41.160 --> 00:11:43.519 One example is the one shown here,
NOTE Confidence: 0.820588314666667
00:11:43.520 --> 00:11:46.556 KDM 6A, otherwise known as UTX.
NOTE Confidence: 0.820588314666667
00:11:46.560 --> 00:11:48.928 So this enzyme is every bit as oxygen
NOTE Confidence: 0.820588314666667
00:11:48.928 --> 00:11:51.236 sensitive as the enzymes that modify HIP,
NOTE Confidence: 0.820588314666667
00:11:51.240 --> 00:11:53.830 and so this provides A surprisingly direct
NOTE Confidence: 0.820588314666667
00:11:53.830 --> 00:11:55.483 linkage between oxygen availability
NOTE Confidence: 0.820588314666667
00:11:55.483 --> 00:11:57.399 and certain epigenetic marks.
NOTE Confidence: 0.820588314666667
00:11:57.400 --> 00:11:59.178 And we think this has relevance to
NOTE Confidence: 0.820588314666667
00:11:59.178 --> 00:12:01.528 the role of hypoxia, for example,
NOTE Confidence: 0.820588314666667
00:12:01.528 --> 00:12:03.640 during embryologic development in
NOTE Confidence: 0.820588314666667
00:12:03.640 --> 00:12:06.520 certain stem cell niches as well
NOTE Confidence: 0.820588314666667

00:12:06.520 --> 00:12:07.829 as within tumors.
NOTE Confidence: 0.820588314666667

00:12:07.829 --> 00:12:10.272 Now the other reason I showed you
NOTE Confidence: 0.820588314666667

00:12:10.272 --> 00:12:11.879 this superfamily of enzymes is,
NOTE Confidence: 0.820588314666667

00:12:11.880 --> 00:12:13.833 I must say I'm a bit of what we
NOTE Confidence: 0.820588314666667

00:12:13.833 --> 00:12:14.920 say on the wards.
NOTE Confidence: 0.820588314666667

00:12:14.920 --> 00:12:16.838 I'm a lumper rather than a splitter.
NOTE Confidence: 0.820588314666667

00:12:16.840 --> 00:12:18.688 I'm always looking for sort of
NOTE Confidence: 0.820588314666667

00:12:18.688 --> 00:12:19.920 common themes and commonalities.
NOTE Confidence: 0.820588314666667

00:12:19.920 --> 00:12:21.840 So I'm always looking for sort
NOTE Confidence: 0.820588314666667

00:12:21.840 --> 00:12:22.800 of unifying hypothesis.
NOTE Confidence: 0.820588314666667

00:12:22.800 --> 00:12:25.440 So now I want to introduce Otto Warburg,
NOTE Confidence: 0.820588314666667

00:12:25.440 --> 00:12:27.544 who you may know in the middle of
NOTE Confidence: 0.820588314666667

00:12:27.544 --> 00:12:30.041 the last century argued that altered
NOTE Confidence: 0.820588314666667

00:12:30.041 --> 00:12:31.640 metabolism was a cause of cancer.
NOTE Confidence: 0.820588314666667

00:12:31.640 --> 00:12:33.600 But then over the decades the debate was,
NOTE Confidence: 0.820588314666667

00:12:33.600 --> 00:12:34.065 well,

NOTE Confidence: 0.820588314666667
00:12:34.065 --> 00:12:36.855 is ultimate metabolism A cause of
NOTE Confidence: 0.820588314666667
00:12:36.855 --> 00:12:38.600 cancer a consequence of cancer,
NOTE Confidence: 0.820588314666667
00:12:38.600 --> 00:12:39.560 both or neither?
NOTE Confidence: 0.820588314666667
00:12:39.560 --> 00:12:41.726 And what what Warburg lacked was
NOTE Confidence: 0.820588314666667
00:12:41.726 --> 00:12:43.170 sort of a genetic
NOTE Confidence: 0.847981906666667
00:12:43.245 --> 00:12:44.680 smoking gun that alter
NOTE Confidence: 0.847981906666667
00:12:44.680 --> 00:12:45.960 metabolism could cause cancer.
NOTE Confidence: 0.847981906666667
00:12:45.960 --> 00:12:48.904 But we now know that some cancers have
NOTE Confidence: 0.847981906666667
00:12:48.904 --> 00:12:50.554 inactivating mutations and succinate
NOTE Confidence: 0.847981906666667
00:12:50.554 --> 00:12:52.564 to hydrogenase or fumarate hydratase,
NOTE Confidence: 0.847981906666667
00:12:52.564 --> 00:12:54.892 which lead to the accumulation of
NOTE Confidence: 0.847981906666667
00:12:54.892 --> 00:12:56.516 succinate and fumarate respectively.
NOTE Confidence: 0.847981906666667
00:12:56.516 --> 00:12:59.400 And it's clear these chemicals can inhibit
NOTE Confidence: 0.847981906666667
00:12:59.463 --> 00:13:01.268 these various two OG dependent enzymes.
NOTE Confidence: 0.847981906666667
00:13:01.268 --> 00:13:03.136 In fact you might have noticed that
NOTE Confidence: 0.847981906666667

00:13:03.136 --> 00:13:05.227 succinate was the product of the reaction.
NOTE Confidence: 0.847981906666667

00:13:05.227 --> 00:13:07.530 And then we learned from Burt Vogelstein
NOTE Confidence: 0.847981906666667

00:13:07.589 --> 00:13:09.563 and Haiyan and others that certain
NOTE Confidence: 0.847981906666667

00:13:09.563 --> 00:13:12.064 tumors such as certain brain tumors and
NOTE Confidence: 0.847981906666667

00:13:12.064 --> 00:13:13.919 leukemias have neomorphic mutations
NOTE Confidence: 0.847981906666667

00:13:13.919 --> 00:13:16.384 and isocitrate dehydrogenase one or
NOTE Confidence: 0.847981906666667

00:13:16.384 --> 00:13:18.992 two which allow these enzymes to make
NOTE Confidence: 0.847981906666667

00:13:18.992 --> 00:13:21.430 milli molar amounts of a so-called
NOTE Confidence: 0.847981906666667

00:13:21.430 --> 00:13:23.358 onco metabolite 2 hydroxychlorate,
NOTE Confidence: 0.847981906666667

00:13:23.360 --> 00:13:26.160 which also can inhibit these various enzymes.
NOTE Confidence: 0.847981906666667

00:13:26.160 --> 00:13:27.276 So we could actually do it.
NOTE Confidence: 0.847981906666667

00:13:27.280 --> 00:13:29.116 Now an entire research seminar about,
NOTE Confidence: 0.847981906666667

00:13:29.120 --> 00:13:30.602 well, which of the enzymes are
NOTE Confidence: 0.847981906666667

00:13:30.602 --> 00:13:31.915 critical in which setting with
NOTE Confidence: 0.847981906666667

00:13:31.915 --> 00:13:33.275 which mutation and which cancer.
NOTE Confidence: 0.847981906666667

00:13:33.280 --> 00:13:34.690 But I'm not going to do that to you again

NOTE Confidence: 0.847981906666667

00:13:34.726 --> 00:13:36.238 because I'm a lumpers rather than a splitter.

NOTE Confidence: 0.847981906666667

00:13:36.240 --> 00:13:38.650 So this is my lumpers view of how we get

NOTE Confidence: 0.847981906666667

00:13:38.711 --> 00:13:40.876 cancer from these various mutations.

NOTE Confidence: 0.847981906666667

00:13:40.880 --> 00:13:43.504 But I will say that early on the

NOTE Confidence: 0.847981906666667

00:13:43.504 --> 00:13:45.024 naysayers and for the students

NOTE Confidence: 0.847981906666667

00:13:45.024 --> 00:13:46.240 always beware of naysayers.

NOTE Confidence: 0.847981906666667

00:13:46.240 --> 00:13:47.458 You can always think of a reason

NOTE Confidence: 0.847981906666667

00:13:47.458 --> 00:13:48.279 why something's going to fail.

NOTE Confidence: 0.847981906666667

00:13:48.280 --> 00:13:49.520 It's not going to work.

NOTE Confidence: 0.847981906666667

00:13:49.520 --> 00:13:51.476 So the naysayers argue that even

NOTE Confidence: 0.847981906666667

00:13:51.476 --> 00:13:54.152 if you could make a drug that would

NOTE Confidence: 0.847981906666667

00:13:54.152 --> 00:13:56.640 prevent the production of two HG,

NOTE Confidence: 0.847981906666667

00:13:56.640 --> 00:13:58.348 it would not be helpful because many

NOTE Confidence: 0.847981906666667

00:13:58.348 --> 00:13:59.840 of these enzymes, as I just told you,

NOTE Confidence: 0.847981906666667

00:13:59.840 --> 00:14:02.680 are involved in epigenetic reprogramming.

NOTE Confidence: 0.847981906666667

00:14:02.680 --> 00:14:04.714 And the argument was those epigenetic
NOTE Confidence: 0.847981906666667

00:14:04.714 --> 00:14:06.734 marks would be relatively stable and
NOTE Confidence: 0.847981906666667

00:14:06.734 --> 00:14:08.459 would not reverse in a clinically
NOTE Confidence: 0.847981906666667

00:14:08.459 --> 00:14:09.278 useful time scale.
NOTE Confidence: 0.847981906666667

00:14:09.280 --> 00:14:11.116 So to sort of tackle that,
NOTE Confidence: 0.847981906666667

00:14:11.120 --> 00:14:13.200 Julie Lostman, when she was in my lab,
NOTE Confidence: 0.847981906666667

00:14:13.200 --> 00:14:15.708 decided to test whether there was
NOTE Confidence: 0.847981906666667

00:14:15.708 --> 00:14:18.192 an ongoing requirement for two HG
NOTE Confidence: 0.847981906666667

00:14:18.192 --> 00:14:19.676 and IDH mutant leukemias.
NOTE Confidence: 0.847981906666667

00:14:19.680 --> 00:14:21.675 And so she created a model based
NOTE Confidence: 0.847981906666667

00:14:21.675 --> 00:14:23.838 on a leukemic cell line called TF1
NOTE Confidence: 0.847981906666667

00:14:23.840 --> 00:14:25.665 where she created isogenic cells
NOTE Confidence: 0.847981906666667

00:14:25.665 --> 00:14:28.522 that were wild type for IDH one or
NOTE Confidence: 0.847981906666667

00:14:28.522 --> 00:14:30.436 had this canonical IDH 1 mutants.
NOTE Confidence: 0.847981906666667

00:14:30.440 --> 00:14:32.272 She then measured 2 HG levels and as
NOTE Confidence: 0.847981906666667

00:14:32.272 --> 00:14:34.154 expected when she put in the IDH one mutant,

NOTE Confidence: 0.847981906666667

00:14:34.160 --> 00:14:37.112 now you had milli molar amounts of two HG.

NOTE Confidence: 0.847981906666667

00:14:37.120 --> 00:14:39.052 And then she treated these cells

NOTE Confidence: 0.847981906666667

00:14:39.052 --> 00:14:41.083 with a tool compound developed by

NOTE Confidence: 0.847981906666667

00:14:41.083 --> 00:14:43.123 Agios that blocks two HG production

NOTE Confidence: 0.847981906666667

00:14:43.123 --> 00:14:46.360 and you see the two HG go down.

NOTE Confidence: 0.847981906666667

00:14:46.360 --> 00:14:47.713 More importantly, perhaps,

NOTE Confidence: 0.847981906666667

00:14:47.713 --> 00:14:50.419 she'd also shown that the cells

NOTE Confidence: 0.847981906666667

00:14:50.419 --> 00:14:53.128 with the wild type IDH One,

NOTE Confidence: 0.847981906666667

00:14:53.128 --> 00:14:55.000 despite being leukemic,

NOTE Confidence: 0.847981906666667

00:14:55.000 --> 00:14:56.710 can't proliferate in the absence

NOTE Confidence: 0.847981906666667

00:14:56.710 --> 00:14:57.394 of cytokines.

NOTE Confidence: 0.847981906666667

00:14:57.400 --> 00:14:59.356 So that's what's shown in red.

NOTE Confidence: 0.847981906666667

00:14:59.360 --> 00:14:59.653 However,

NOTE Confidence: 0.847981906666667

00:14:59.653 --> 00:15:01.704 she found that if the cells had

NOTE Confidence: 0.847981906666667

00:15:01.704 --> 00:15:03.359 this canonical IDH One mutant now,

NOTE Confidence: 0.847981906666667

00:15:03.360 --> 00:15:05.840 these cells could proliferate well,
NOTE Confidence: 0.847981906666667

00:15:05.840 --> 00:15:06.848 even without cytokines.
NOTE Confidence: 0.847981906666667

00:15:06.848 --> 00:15:09.200 It's sort of a hallmark of transformation.
NOTE Confidence: 0.847981906666667

00:15:09.200 --> 00:15:11.258 And now she's ready to treat the
NOTE Confidence: 0.847981906666667

00:15:11.258 --> 00:15:13.362 cells with the inhibitor and the
NOTE Confidence: 0.847981906666667

00:15:13.362 --> 00:15:14.520 cells stop growing.
NOTE Confidence: 0.847981906666667

00:15:14.520 --> 00:15:15.160 So for the students,
NOTE Confidence: 0.847981906666667

00:15:15.160 --> 00:15:16.379 this is one of the most dangerous
NOTE Confidence: 0.847981906666667

00:15:16.379 --> 00:15:17.717 results you're ever going to get.
NOTE Confidence: 0.847981906666667

00:15:17.720 --> 00:15:19.295 Because this is Exactly what
NOTE Confidence: 0.847981906666667

00:15:19.295 --> 00:15:20.555 you were hoping for.
NOTE Confidence: 0.847981906666667

00:15:20.560 --> 00:15:22.260 And that's when you get really lazy, right?
NOTE Confidence: 0.847981906666667

00:15:22.260 --> 00:15:23.800 So you want to call the editor.
NOTE Confidence: 0.895037921428572

00:15:23.800 --> 00:15:25.704 This is figure six. Look at me
NOTE Confidence: 0.895037921428572

00:15:25.704 --> 00:15:27.878 high fives up and down the hallway.
NOTE Confidence: 0.895037921428572

00:15:27.880 --> 00:15:31.156 But this is a dangerous experiment.

NOTE Confidence: 0.895037921428572
00:15:31.160 --> 00:15:32.432 A because I just said it's
NOTE Confidence: 0.895037921428572
00:15:32.432 --> 00:15:33.520 one we were looking for.
NOTE Confidence: 0.895037921428572
00:15:33.520 --> 00:15:35.417 But it's also dangerous because these are
NOTE Confidence: 0.895037921428572
00:15:35.417 --> 00:15:37.359 what some people would call down assays.
NOTE Confidence: 0.895037921428572
00:15:37.360 --> 00:15:38.560 So you add a chemical,
NOTE Confidence: 0.895037921428572
00:15:38.560 --> 00:15:41.000 two HG goes down, You add a chemical.
NOTE Confidence: 0.895037921428572
00:15:41.000 --> 00:15:44.276 The cells stop proliferating down and down.
NOTE Confidence: 0.895037921428572
00:15:44.280 --> 00:15:45.880 So if you were a cynic you would
NOTE Confidence: 0.895037921428572
00:15:45.880 --> 00:15:47.606 say this is just another poison that
NOTE Confidence: 0.895037921428572
00:15:47.606 --> 00:15:49.635 they sent you after that MTA that you
NOTE Confidence: 0.895037921428572
00:15:49.635 --> 00:15:51.588 negotiated for a year and it's just kill.
NOTE Confidence: 0.895037921428572
00:15:51.588 --> 00:15:53.436 The cells are just really sick.
NOTE Confidence: 0.895037921428572
00:15:53.440 --> 00:15:54.880 And since and this you could
NOTE Confidence: 0.895037921428572
00:15:54.880 --> 00:15:55.840 have measured any metabolite,
NOTE Confidence: 0.895037921428572
00:15:55.840 --> 00:15:58.378 but you just measure 2 HG and Gee you
NOTE Confidence: 0.895037921428572

00:15:58.378 --> 00:16:00.440 know this is true, true and unrelated.
NOTE Confidence: 0.895037921428572

00:16:00.440 --> 00:16:02.400 These cells are just dying, who cares?
NOTE Confidence: 0.895037921428572

00:16:02.400 --> 00:16:04.080 So you need a better experiment.
NOTE Confidence: 0.895037921428572

00:16:04.080 --> 00:16:04.956 So you got to push yourself
NOTE Confidence: 0.895037921428572

00:16:04.956 --> 00:16:05.960 to do a better experiment.
NOTE Confidence: 0.895037921428572

00:16:05.960 --> 00:16:07.856 So the better experiment was rather
NOTE Confidence: 0.895037921428572

00:16:07.856 --> 00:16:10.020 than give these cells the IDH mutant,
NOTE Confidence: 0.895037921428572

00:16:10.020 --> 00:16:12.120 she gave the cells a cell membrane
NOTE Confidence: 0.895037921428572

00:16:12.187 --> 00:16:14.059 permeable version of R2 HG that
NOTE Confidence: 0.895037921428572

00:16:14.059 --> 00:16:16.687 enters the cells and then gets trapped
NOTE Confidence: 0.895037921428572

00:16:16.687 --> 00:16:18.439 at tumor relevant concentrations.
NOTE Confidence: 0.895037921428572

00:16:18.440 --> 00:16:20.717 So now if you give the cells two HG,
NOTE Confidence: 0.895037921428572

00:16:20.720 --> 00:16:22.565 they're completely insensitive to a
NOTE Confidence: 0.895037921428572

00:16:22.565 --> 00:16:25.160 drug that prevents 2 HG production.
NOTE Confidence: 0.895037921428572

00:16:25.160 --> 00:16:26.497 And that's shown here is if you
NOTE Confidence: 0.895037921428572

00:16:26.497 --> 00:16:27.719 give this Ester to these cells,

NOTE Confidence: 0.895037921428572
00:16:27.720 --> 00:16:28.612 they start growing again.
NOTE Confidence: 0.895037921428572
00:16:28.612 --> 00:16:30.400 So now you really know you're on target,
NOTE Confidence: 0.895037921428572
00:16:30.400 --> 00:16:32.800 which is really, really important.
NOTE Confidence: 0.895037921428572
00:16:32.800 --> 00:16:33.310 So thankfully,
NOTE Confidence: 0.895037921428572
00:16:33.310 --> 00:16:34.840 because for this and other reasons,
NOTE Confidence: 0.895037921428572
00:16:34.840 --> 00:16:36.835 these drugs move forward and I'm happy
NOTE Confidence: 0.895037921428572
00:16:36.835 --> 00:16:39.319 to report we now have an inhibitor of
NOTE Confidence: 0.895037921428572
00:16:39.319 --> 00:16:41.936 both mutinone H1 and mutinone H2 for
NOTE Confidence: 0.895037921428572
00:16:41.936 --> 00:16:44.080 the treatment of IDH mutant leukemias.
NOTE Confidence: 0.895037921428572
00:16:44.080 --> 00:16:46.320 I wouldn't say these are home runs,
NOTE Confidence: 0.895037921428572
00:16:46.320 --> 00:16:47.208 although some patients certainly
NOTE Confidence: 0.895037921428572
00:16:47.208 --> 00:16:48.318 get a lot of benefit.
NOTE Confidence: 0.895037921428572
00:16:48.320 --> 00:16:49.604 But clearly there's heterogeneity
NOTE Confidence: 0.895037921428572
00:16:49.604 --> 00:16:51.209 and we have to understand
NOTE Confidence: 0.895037921428572
00:16:51.209 --> 00:16:52.590 that heterogeneity further.
NOTE Confidence: 0.895037921428572

00:16:52.590 --> 00:16:52.940 OK.
NOTE Confidence: 0.895037921428572
00:16:52.940 --> 00:16:55.040 So now returning to this slide,
NOTE Confidence: 0.895037921428572
00:16:55.040 --> 00:16:57.080 I already showed you again,
NOTE Confidence: 0.895037921428572
00:16:57.080 --> 00:16:59.000 it was certainly plausible that the
NOTE Confidence: 0.895037921428572
00:16:59.000 --> 00:17:01.479 tumors seen in VHL disease were all about
NOTE Confidence: 0.895037921428572
00:17:01.479 --> 00:17:04.079 hip and were all about an excessive hip.
NOTE Confidence: 0.895037921428572
00:17:04.080 --> 00:17:06.936 But another take home for the students
NOTE Confidence: 0.895037921428572
00:17:06.936 --> 00:17:08.662 is correlation plus plausibility
NOTE Confidence: 0.895037921428572
00:17:08.662 --> 00:17:10.917 is not proof of causation.
NOTE Confidence: 0.895037921428572
00:17:10.920 --> 00:17:13.040 We often get kind of lazy at that last step.
NOTE Confidence: 0.895037921428572
00:17:13.040 --> 00:17:14.760 OK, I can imagine it's all about hip,
NOTE Confidence: 0.895037921428572
00:17:14.760 --> 00:17:16.038 hip does a lot of things.
NOTE Confidence: 0.895037921428572
00:17:16.040 --> 00:17:17.160 Maybe that promotes tumor growth,
NOTE Confidence: 0.895037921428572
00:17:17.160 --> 00:17:19.500 but you have to do sort of the killer
NOTE Confidence: 0.895037921428572
00:17:19.500 --> 00:17:21.000 experiments, if you, if you can,
NOTE Confidence: 0.895037921428572
00:17:21.000 --> 00:17:22.626 just try to establish what you

NOTE Confidence: 0.895037921428572

00:17:22.626 --> 00:17:24.159 know what's really going on here.

NOTE Confidence: 0.895037921428572

00:17:24.160 --> 00:17:24.914 And again,

NOTE Confidence: 0.895037921428572

00:17:24.914 --> 00:17:26.799 that often requires sort of

NOTE Confidence: 0.895037921428572

00:17:26.799 --> 00:17:27.553 genetic paradigms.

NOTE Confidence: 0.895037921428572

00:17:27.560 --> 00:17:29.486 So we had shown some time ago that if

NOTE Confidence: 0.895037921428572

00:17:29.486 --> 00:17:31.687 you restore the function of VHL and a

NOTE Confidence: 0.895037921428572

00:17:31.687 --> 00:17:33.360 VHL defective wieno cell carcinoma,

NOTE Confidence: 0.895037921428572

00:17:33.360 --> 00:17:35.826 they lose the ability to form

NOTE Confidence: 0.895037921428572

00:17:35.826 --> 00:17:37.440 tumors and nude mice.

NOTE Confidence: 0.895037921428572

00:17:37.440 --> 00:17:40.240 So Kichi Kondo took these cells and

NOTE Confidence: 0.895037921428572

00:17:40.320 --> 00:17:42.822 introduced into these cells a version

NOTE Confidence: 0.895037921428572

00:17:42.822 --> 00:17:45.240 of HIP 2A that can't be recognized

NOTE Confidence: 0.895037921428572

00:17:45.240 --> 00:17:47.325 by BHL because the Prolil sites have

NOTE Confidence: 0.895037921428572

00:17:47.325 --> 00:17:49.035 been converted to alanine and these

NOTE Confidence: 0.895037921428572

00:17:49.035 --> 00:17:51.108 now once again form tumors and and

NOTE Confidence: 0.895037921428572

00:17:51.108 --> 00:17:52.872 a reciprocal set of experiments he
NOTE Confidence: 0.895037921428572

00:17:52.872 --> 00:17:54.828 took these cells and eliminated HIP
NOTE Confidence: 0.895037921428572

00:17:54.828 --> 00:17:56.790 2A then with hairpin technology we
NOTE Confidence: 0.856356112

00:17:56.853 --> 00:17:58.715 now do this with CRISPR and these
NOTE Confidence: 0.856356112

00:17:58.715 --> 00:18:00.656 cells lose the ability to form tumors.
NOTE Confidence: 0.856356112

00:18:00.656 --> 00:18:02.076 And I will tell you,
NOTE Confidence: 0.856356112

00:18:02.080 --> 00:18:03.809 when we did the same experiments with
NOTE Confidence: 0.856356112

00:18:03.809 --> 00:18:05.199 the canonical member of the family,
NOTE Confidence: 0.856356112

00:18:05.200 --> 00:18:07.636 HIP One, we got the opposite result.
NOTE Confidence: 0.856356112

00:18:07.640 --> 00:18:09.400 So much to our surprise.
NOTE Confidence: 0.856356112

00:18:09.400 --> 00:18:10.360 On one level it is hip,
NOTE Confidence: 0.856356112

00:18:10.360 --> 00:18:13.664 but it's really hip to the less
NOTE Confidence: 0.856356112

00:18:13.664 --> 00:18:16.310 well studied member of the family.
NOTE Confidence: 0.856356112

00:18:16.310 --> 00:18:19.180 Now, not shown here are the kind
NOTE Confidence: 0.856356112

00:18:19.271 --> 00:18:21.815 of controls I learned about at
NOTE Confidence: 0.856356112

00:18:21.815 --> 00:18:23.036 the knee of David Livingston,

NOTE Confidence: 0.856356112

00:18:23.036 --> 00:18:24.760 who taught me how to be a scientist.

NOTE Confidence: 0.856356112

00:18:24.760 --> 00:18:26.080 So for the students,

NOTE Confidence: 0.856356112

00:18:26.080 --> 00:18:27.560 this is your required reading.

NOTE Confidence: 0.856356112

00:18:27.560 --> 00:18:29.200 I'm going to come back to that one more time.

NOTE Confidence: 0.856356112

00:18:29.200 --> 00:18:30.532 But this is the required reading

NOTE Confidence: 0.856356112

00:18:30.532 --> 00:18:31.900 for the kinds of controls you

NOTE Confidence: 0.856356112

00:18:31.900 --> 00:18:33.419 might want to do if you're going

NOTE Confidence: 0.856356112

00:18:33.419 --> 00:18:34.998 to do Target validation studies.

NOTE Confidence: 0.856356112

00:18:35.000 --> 00:18:36.400 Because I can tell you,

NOTE Confidence: 0.856356112

00:18:36.400 --> 00:18:38.440 our colleagues in industry have

NOTE Confidence: 0.856356112

00:18:38.440 --> 00:18:41.251 reported that 50 to 90% of the time

NOTE Confidence: 0.856356112

00:18:41.251 --> 00:18:43.050 when they go to replicate results from

NOTE Confidence: 0.856356112

00:18:43.106 --> 00:18:45.320 academic labs related to target validation,

NOTE Confidence: 0.856356112

00:18:45.320 --> 00:18:47.240 either the results are not

NOTE Confidence: 0.856356112

00:18:47.240 --> 00:18:49.160 reproducible or they're not robust,

NOTE Confidence: 0.856356112

00:18:49.160 --> 00:18:50.730 meaning they're only true under
NOTE Confidence: 0.856356112

00:18:50.730 --> 00:18:51.930 very narrow set of conditions.
NOTE Confidence: 0.856356112

00:18:51.930 --> 00:18:53.505 OK. So I think we have to all
NOTE Confidence: 0.856356112

00:18:53.505 --> 00:18:54.480 do a little bit better.
NOTE Confidence: 0.856356112

00:18:54.480 --> 00:18:57.000 I'll come back to that at the end.
NOTE Confidence: 0.856356112

00:18:57.000 --> 00:18:58.240 OK. So what can we do about this?
NOTE Confidence: 0.856356112

00:18:58.240 --> 00:19:00.543 Well, we certainly knew by the 90s
NOTE Confidence: 0.856356112

00:19:00.543 --> 00:19:02.840 that VEGF was under hip control.
NOTE Confidence: 0.856356112

00:19:02.840 --> 00:19:03.472 And thankfully,
NOTE Confidence: 0.856356112

00:19:03.472 --> 00:19:05.052 a number of companies were
NOTE Confidence: 0.856356112

00:19:05.052 --> 00:19:06.000 making VEGF inhibitors.
NOTE Confidence: 0.856356112

00:19:06.000 --> 00:19:07.491 And we argued if these inhibitors were
NOTE Confidence: 0.856356112

00:19:07.491 --> 00:19:08.959 going to work in any solid tumor,
NOTE Confidence: 0.856356112

00:19:08.960 --> 00:19:10.160 they should work in VHL,
NOTE Confidence: 0.856356112

00:19:10.160 --> 00:19:12.520 defective kidney tumors, for example.
NOTE Confidence: 0.856356112

00:19:12.520 --> 00:19:14.319 And that turned out to be true.

NOTE Confidence: 0.856356112
00:19:14.320 --> 00:19:16.422 So we're now up to 8 or 9, I think,
NOTE Confidence: 0.856356112
00:19:16.422 --> 00:19:17.666 VEGF inhibitors approved for
NOTE Confidence: 0.856356112
00:19:17.666 --> 00:19:19.320 the treatment of kidney cancer.
NOTE Confidence: 0.856356112
00:19:19.320 --> 00:19:20.120 So that's the good news.
NOTE Confidence: 0.856356112
00:19:20.120 --> 00:19:21.716 But not every patient with kidney
NOTE Confidence: 0.856356112
00:19:21.716 --> 00:19:23.400 cancer will respond to these drugs,
NOTE Confidence: 0.856356112
00:19:23.400 --> 00:19:25.020 and even those that do will
NOTE Confidence: 0.856356112
00:19:25.020 --> 00:19:25.560 eventually progress,
NOTE Confidence: 0.856356112
00:19:25.560 --> 00:19:26.760 although thankfully sometimes
NOTE Confidence: 0.856356112
00:19:26.760 --> 00:19:28.050 it takes many years.
NOTE Confidence: 0.856356112
00:19:28.050 --> 00:19:29.520 So how can we do better?
NOTE Confidence: 0.856356112
00:19:29.520 --> 00:19:31.032 Well, I hope some of the students
NOTE Confidence: 0.856356112
00:19:31.032 --> 00:19:32.240 are saying to themselves,
NOTE Confidence: 0.856356112
00:19:32.240 --> 00:19:34.352 kale and you dummy, rather than
NOTE Confidence: 0.856356112
00:19:34.352 --> 00:19:36.120 target anyone hip responsive gene,
NOTE Confidence: 0.856356112

00:19:36.120 --> 00:19:37.260 you should target HIP.
NOTE Confidence: 0.856356112

00:19:37.260 --> 00:19:39.320 And if you believe your own data,
NOTE Confidence: 0.856356112

00:19:39.320 --> 00:19:40.280 you should target hip too.
NOTE Confidence: 0.856356112

00:19:40.280 --> 00:19:41.264 Wouldn't that be nice?
NOTE Confidence: 0.856356112

00:19:41.264 --> 00:19:41.756 But again,
NOTE Confidence: 0.856356112

00:19:41.760 --> 00:19:43.468 the naysayers come out of the woodwork
NOTE Confidence: 0.856356112

00:19:43.468 --> 00:19:45.136 and they start saying you can't do
NOTE Confidence: 0.856356112

00:19:45.136 --> 00:19:47.904 that because HIP too is adna binding
NOTE Confidence: 0.856356112

00:19:47.904 --> 00:19:49.600 sequence specific transcription factor.
NOTE Confidence: 0.856356112

00:19:49.600 --> 00:19:51.028 It's not a member of the steroid
NOTE Confidence: 0.856356112

00:19:51.028 --> 00:19:51.640 hormone receptor family.
NOTE Confidence: 0.856356112

00:19:51.640 --> 00:19:53.383 So it doesn't have a natural pocket
NOTE Confidence: 0.856356112

00:19:53.383 --> 00:19:55.279 for a drug like small molecule.
NOTE Confidence: 0.856356112

00:19:55.280 --> 00:19:57.492 So forget about it.
NOTE Confidence: 0.856356112

00:19:57.492 --> 00:19:58.598 But fortunately,
NOTE Confidence: 0.856356112

00:19:58.600 --> 00:20:00.412 2 very talented scientists,

NOTE Confidence: 0.856356112
00:20:00.412 --> 00:20:02.226 Rick Bruick and Kevin Gardner,
NOTE Confidence: 0.856356112
00:20:02.226 --> 00:20:04.038 who were then at UT Southwestern,
NOTE Confidence: 0.856356112
00:20:04.040 --> 00:20:06.150 identified a potentially druggable pocket
NOTE Confidence: 0.856356112
00:20:06.150 --> 00:20:09.611 in the so-called Pass B domain of HIP 2A.
NOTE Confidence: 0.856356112
00:20:09.611 --> 00:20:11.393 And they did high throughput screens
NOTE Confidence: 0.856356112
00:20:11.393 --> 00:20:13.275 at UT Southwestern and identified
NOTE Confidence: 0.856356112
00:20:13.275 --> 00:20:16.040 chemicals that could bind to this pocket.
NOTE Confidence: 0.856356112
00:20:16.040 --> 00:20:17.848 And in so doing and do some allosteric
NOTE Confidence: 0.856356112
00:20:17.848 --> 00:20:19.429 change in HIF to alpha such that
NOTE Confidence: 0.856356112
00:20:19.429 --> 00:20:21.009 it could no longer bind to aren't
NOTE Confidence: 0.856356112
00:20:21.009 --> 00:20:24.680 and hits no longer bind to DNA.
NOTE Confidence: 0.856356112
00:20:24.680 --> 00:20:26.670 Now these chemicals are what
NOTE Confidence: 0.856356112
00:20:26.670 --> 00:20:28.660 some of my drug hunter
NOTE Confidence: 0.945157414166667
00:20:28.745 --> 00:20:30.626 friends called publication grade
NOTE Confidence: 0.945157414166667
00:20:30.626 --> 00:20:32.198 but not pharmaceutical grade.
NOTE Confidence: 0.945157414166667

00:20:32.200 --> 00:20:34.366 They had too many blemishes and
NOTE Confidence: 0.945157414166667

00:20:34.366 --> 00:20:37.120 wants to really be drugs for people.
NOTE Confidence: 0.945157414166667

00:20:37.120 --> 00:20:38.492 But fortunately these chemicals
NOTE Confidence: 0.945157414166667

00:20:38.492 --> 00:20:40.550 were out licensed to a biotech
NOTE Confidence: 0.945157414166667

00:20:40.612 --> 00:20:43.532 company in Dallas or that was in
NOTE Confidence: 0.945157414166667

00:20:43.532 --> 00:20:45.013 Dallas called Peloton Therapeutics.
NOTE Confidence: 0.945157414166667

00:20:45.013 --> 00:20:47.119 And the chemist at Peloton improved
NOTE Confidence: 0.945157414166667

00:20:47.119 --> 00:20:48.479 these chemicals substantially in
NOTE Confidence: 0.945157414166667

00:20:48.479 --> 00:20:50.340 terms of their drug like properties.
NOTE Confidence: 0.945157414166667

00:20:50.340 --> 00:20:52.420 And they were kind enough to share with
NOTE Confidence: 0.945157414166667

00:20:52.420 --> 00:20:55.690 us a tool compound called PT2399 which
NOTE Confidence: 0.945157414166667

00:20:55.690 --> 00:20:58.077 at the time was only one or two atoms
NOTE Confidence: 0.945157414166667

00:20:58.077 --> 00:21:01.400 removed from the then lead compound.
NOTE Confidence: 0.945157414166667

00:21:01.400 --> 00:21:03.240 And so we had early access to this
NOTE Confidence: 0.945157414166667

00:21:03.240 --> 00:21:05.147 compound and we could show that this
NOTE Confidence: 0.945157414166667

00:21:05.147 --> 00:21:06.840 compound did everything you would want.

NOTE Confidence: 0.945157414166667
00:21:06.840 --> 00:21:09.396 And preclinical models of VHL mutant
NOTE Confidence: 0.945157414166667
00:21:09.400 --> 00:21:10.985 kidney cancer and similar findings
NOTE Confidence: 0.945157414166667
00:21:10.985 --> 00:21:13.080 were made by my former postdoc,
NOTE Confidence: 0.945157414166667
00:21:13.080 --> 00:21:15.960 Jim Brogarolis in his own laboratory.
NOTE Confidence: 0.945157414166667
00:21:15.960 --> 00:21:17.374 And so now it looks like maybe
NOTE Confidence: 0.945157414166667
00:21:17.374 --> 00:21:18.520 we're on to something,
NOTE Confidence: 0.945157414166667
00:21:18.520 --> 00:21:20.032 but I'll point out the assays
NOTE Confidence: 0.945157414166667
00:21:20.032 --> 00:21:21.832 in this paper were things like
NOTE Confidence: 0.945157414166667
00:21:21.832 --> 00:21:24.180 decreased HIF target gene expression
NOTE Confidence: 0.945157414166667
00:21:24.180 --> 00:21:26.645 decreased soft dog growth decrease,
NOTE Confidence: 0.945157414166667
00:21:26.645 --> 00:21:27.615 proliferation decrease,
NOTE Confidence: 0.945157414166667
00:21:27.615 --> 00:21:29.555 orthotopic tumor formation decrease,
NOTE Confidence: 0.945157414166667
00:21:29.560 --> 00:21:29.829 decrease.
NOTE Confidence: 0.945157414166667
00:21:29.829 --> 00:21:30.636 So once again,
NOTE Confidence: 0.945157414166667
00:21:30.636 --> 00:21:32.720 down SA after down SA after down SA.
NOTE Confidence: 0.945157414166667

00:21:32.720 --> 00:21:34.274 So just to give you an example,
NOTE Confidence: 0.945157414166667

00:21:34.280 --> 00:21:36.596 here's a lovely soft dagger essay
NOTE Confidence: 0.945157414166667

00:21:36.600 --> 00:21:38.360 that was done by Chincho in my lab.
NOTE Confidence: 0.945157414166667

00:21:38.360 --> 00:21:40.691 So you had 0.2 or two micromolar of the
NOTE Confidence: 0.945157414166667

00:21:40.691 --> 00:21:43.268 HIP 2 inhibitor and these renal carcinoma
NOTE Confidence: 0.945157414166667

00:21:43.268 --> 00:21:45.660 cells stop forming soft dagger colonies.
NOTE Confidence: 0.945157414166667

00:21:45.660 --> 00:21:47.880 So you get OK pretty good.
NOTE Confidence: 0.945157414166667

00:21:47.880 --> 00:21:50.290 But not shown here is, first of all,
NOTE Confidence: 0.945157414166667

00:21:50.290 --> 00:21:51.640 at 10 to 20 micromolar,
NOTE Confidence: 0.945157414166667

00:21:51.640 --> 00:21:52.780 This compound will kill every
NOTE Confidence: 0.945157414166667

00:21:52.780 --> 00:21:54.080 cancer cell we've ever looked at,
NOTE Confidence: 0.945157414166667

00:21:54.080 --> 00:21:56.159 whether it expresses if to or not.
NOTE Confidence: 0.945157414166667

00:21:56.160 --> 00:21:57.480 So by definition,
NOTE Confidence: 0.945157414166667

00:21:57.480 --> 00:21:58.800 that's off target.
NOTE Confidence: 0.945157414166667

00:21:58.800 --> 00:22:01.000 How would you know this is on target?
NOTE Confidence: 0.945157414166667

00:22:01.000 --> 00:22:01.282 Again,

NOTE Confidence: 0.945157414166667
00:22:01.282 --> 00:22:03.538 I've said this is the kind of experiment
NOTE Confidence: 0.945157414166667
00:22:03.538 --> 00:22:05.915 that gives cancer pharmacology a bad name.
NOTE Confidence: 0.945157414166667
00:22:05.915 --> 00:22:08.013 I used to hear people who did these
NOTE Confidence: 0.945157414166667
00:22:08.013 --> 00:22:09.332 experiments disparagingly referred
NOTE Confidence: 0.945157414166667
00:22:09.332 --> 00:22:11.888 to as sprinklers because they simply
NOTE Confidence: 0.945157414166667
00:22:11.888 --> 00:22:13.304 sprinkled noxious chemicals on
NOTE Confidence: 0.945157414166667
00:22:13.304 --> 00:22:15.272 cancer cells and watch them die.
NOTE Confidence: 0.945157414166667
00:22:15.280 --> 00:22:15.489 So,
NOTE Confidence: 0.945157414166667
00:22:15.489 --> 00:22:15.907 you know,
NOTE Confidence: 0.945157414166667
00:22:15.907 --> 00:22:17.720 I could have done this with Clorox bleach.
NOTE Confidence: 0.945157414166667
00:22:17.720 --> 00:22:19.960 I could have done this with formalin.
NOTE Confidence: 0.945157414166667
00:22:19.960 --> 00:22:21.320 You know what's what's really?
NOTE Confidence: 0.945157414166667
00:22:21.320 --> 00:22:22.560 Is this just another poison?
NOTE Confidence: 0.945157414166667
00:22:22.560 --> 00:22:26.618 But CHIN used CRISPR to make isagenic
NOTE Confidence: 0.945157414166667
00:22:26.618 --> 00:22:29.910 cells that had wild type HIP 2A or had
NOTE Confidence: 0.945157414166667

00:22:29.910 --> 00:22:31.950 hip 2A with a single amino acid change
NOTE Confidence: 0.945157414166667

00:22:32.009 --> 00:22:33.878 in that pocket that I showed you.
NOTE Confidence: 0.945157414166667

00:22:33.880 --> 00:22:36.112 That prevents the drug from binding to the
NOTE Confidence: 0.945157414166667

00:22:36.112 --> 00:22:38.356 pocket but otherwise leaves hip 2A intact.
NOTE Confidence: 0.945157414166667

00:22:38.360 --> 00:22:41.070 And now you can see we rescue the phenotype.
NOTE Confidence: 0.945157414166667

00:22:41.070 --> 00:22:42.840 Now eventually an approved version of
NOTE Confidence: 0.945157414166667

00:22:42.840 --> 00:22:44.748 this HIP 2 inhibitor which is called
NOTE Confidence: 0.945157414166667

00:22:44.748 --> 00:22:46.563 Bel Sudafan and I should declare I
NOTE Confidence: 0.945157414166667

00:22:46.563 --> 00:22:48.388 have a financial conflict of interest
NOTE Confidence: 0.945157414166667

00:22:48.388 --> 00:22:50.168 with Balsedifan went into testing
NOTE Confidence: 0.945157414166667

00:22:50.168 --> 00:22:51.984 for patients with advanced kidney
NOTE Confidence: 0.945157414166667

00:22:51.984 --> 00:22:54.072 cancer who had failed VEGF inhibitors,
NOTE Confidence: 0.945157414166667

00:22:54.080 --> 00:22:55.680 failed immune checkpoint inhibitors,
NOTE Confidence: 0.945157414166667

00:22:55.680 --> 00:22:56.480 etcetera etcetera.
NOTE Confidence: 0.945157414166667

00:22:56.480 --> 00:22:58.680 These are so-called swimmers plots.
NOTE Confidence: 0.945157414166667

00:22:58.680 --> 00:23:00.440 So you may know that each of these

NOTE Confidence: 0.945157414166667

00:23:00.440 --> 00:23:01.680 horizontal bars is a patient on

NOTE Confidence: 0.945157414166667

00:23:01.680 --> 00:23:03.080 the trial and how long they were

NOTE Confidence: 0.945157414166667

00:23:03.080 --> 00:23:04.695 on therapy at the time of this

NOTE Confidence: 0.945157414166667

00:23:04.695 --> 00:23:05.400 analysis of orientation.

NOTE Confidence: 0.945157414166667

00:23:05.400 --> 00:23:07.440 Here's one year on therapy.

NOTE Confidence: 0.945157414166667

00:23:07.440 --> 00:23:09.125 The black arrows were patients

NOTE Confidence: 0.945157414166667

00:23:09.125 --> 00:23:10.810 who were still doing well

NOTE Confidence: 0.916370030833333

00:23:10.877 --> 00:23:12.794 on therapy at the time of this analysis

NOTE Confidence: 0.916370030833333

00:23:12.794 --> 00:23:14.680 and the yellow star patients were patients

NOTE Confidence: 0.916370030833333

00:23:14.680 --> 00:23:17.120 who achieved a resist partial response.

NOTE Confidence: 0.916370030833333

00:23:17.120 --> 00:23:20.635 And I'll come back to the development

NOTE Confidence: 0.916370030833333

00:23:20.635 --> 00:23:23.358 of belsitovan at the end of the talk.

NOTE Confidence: 0.916370030833333

00:23:23.360 --> 00:23:24.920 So now I want to move to some newer data.

NOTE Confidence: 0.916370030833333

00:23:24.920 --> 00:23:27.395 So this is the first story is work of

NOTE Confidence: 0.916370030833333

00:23:27.395 --> 00:23:29.520 Nathan Chiroli, a postdoc in the lab.

NOTE Confidence: 0.916370030833333

00:23:29.520 --> 00:23:31.188 And he wanted to know, OK,
NOTE Confidence: 0.916370030833333

00:23:31.188 --> 00:23:33.276 we have this if two inhibitor,
NOTE Confidence: 0.916370030833333

00:23:33.280 --> 00:23:34.610 it's inhibiting the growth of
NOTE Confidence: 0.916370030833333

00:23:34.610 --> 00:23:35.674 these kidney cancer cells.
NOTE Confidence: 0.916370030833333

00:23:35.680 --> 00:23:37.846 But are all hip to target
NOTE Confidence: 0.916370030833333

00:23:37.846 --> 00:23:39.640 genes equally important or not.
NOTE Confidence: 0.916370030833333

00:23:39.640 --> 00:23:41.838 So the simple idea is you have
NOTE Confidence: 0.916370030833333

00:23:41.838 --> 00:23:43.600 hip two driving expression.
NOTE Confidence: 0.916370030833333

00:23:43.600 --> 00:23:44.716 We know it's hundreds of genes,
NOTE Confidence: 0.916370030833333

00:23:44.720 --> 00:23:47.240 but for this illustration let's pick 4.
NOTE Confidence: 0.916370030833333

00:23:47.240 --> 00:23:49.656 You come in with your inhibitor and now
NOTE Confidence: 0.916370030833333

00:23:49.656 --> 00:23:51.960 you down regulate these four genes.
NOTE Confidence: 0.916370030833333

00:23:51.960 --> 00:23:54.795 And so Nathan's idea was to now use CRISPR,
NOTE Confidence: 0.916370030833333

00:23:54.800 --> 00:23:57.175 a technology to activate HIP
NOTE Confidence: 0.916370030833333

00:23:57.175 --> 00:23:59.075 two target genes artificially,
NOTE Confidence: 0.916370030833333

00:23:59.080 --> 00:24:01.796 even in the face of the inhibitor,

NOTE Confidence: 0.916370030833333
00:24:01.800 --> 00:24:04.026 And to do this systematically go through
NOTE Confidence: 0.916370030833333
00:24:04.026 --> 00:24:06.360 all of the HIP two target genes.
NOTE Confidence: 0.916370030833333
00:24:06.360 --> 00:24:06.912 And in fact,
NOTE Confidence: 0.916370030833333
00:24:06.912 --> 00:24:08.200 as I'll show you in a moment
NOTE Confidence: 0.916370030833333
00:24:08.200 --> 00:24:09.061 for good measure,
NOTE Confidence: 0.916370030833333
00:24:09.061 --> 00:24:11.447 he just did this on a genome wide
NOTE Confidence: 0.916370030833333
00:24:11.447 --> 00:24:13.360 scale and then in silico looked
NOTE Confidence: 0.916370030833333
00:24:13.360 --> 00:24:15.084 for HIP two target genes.
NOTE Confidence: 0.916370030833333
00:24:15.084 --> 00:24:17.376 Now we're using a technology that
NOTE Confidence: 0.916370030833333
00:24:17.376 --> 00:24:19.592 was developed by John Dench and
NOTE Confidence: 0.916370030833333
00:24:19.592 --> 00:24:21.317 colleagues at the Broad Institute
NOTE Confidence: 0.916370030833333
00:24:21.317 --> 00:24:23.040 and this was the the preferred
NOTE Confidence: 0.916370030833333
00:24:23.040 --> 00:24:24.440 technology about two years ago.
NOTE Confidence: 0.916370030833333
00:24:24.440 --> 00:24:25.928 I can tell you they've improved upon it
NOTE Confidence: 0.916370030833333
00:24:25.928 --> 00:24:28.200 further, but this worked quite well.
NOTE Confidence: 0.916370030833333

00:24:28.200 --> 00:24:30.040 So the idea here is you have a nucleus state,
NOTE Confidence: 0.916370030833333
00:24:30.040 --> 00:24:31.050 CAS nine,
NOTE Confidence: 0.916370030833333
00:24:31.050 --> 00:24:33.070 that recruits A transitional
NOTE Confidence: 0.916370030833333
00:24:33.070 --> 00:24:34.782 activation domain BP 64.
NOTE Confidence: 0.916370030833333
00:24:34.782 --> 00:24:37.239 And then you you have some additional
NOTE Confidence: 0.916370030833333
00:24:37.239 --> 00:24:39.190 engineering of the CRISPR guides to
NOTE Confidence: 0.916370030833333
00:24:39.190 --> 00:24:41.919 bring in some other trans activation domain.
NOTE Confidence: 0.916370030833333
00:24:41.920 --> 00:24:42.688 So I'm sorry,
NOTE Confidence: 0.916370030833333
00:24:42.688 --> 00:24:44.480 this is kind of complicated and baroque,
NOTE Confidence: 0.916370030833333
00:24:44.480 --> 00:24:46.160 but it actually turns out to
NOTE Confidence: 0.916370030833333
00:24:46.160 --> 00:24:46.995 be incredibly robust.
NOTE Confidence: 0.916370030833333
00:24:46.995 --> 00:24:49.195 So now Nathan's ready to do his screen.
NOTE Confidence: 0.916370030833333
00:24:49.200 --> 00:24:51.216 He takes a HIF 2 dependent
NOTE Confidence: 0.916370030833333
00:24:51.216 --> 00:24:52.560 renal carcinoma cell line.
NOTE Confidence: 0.916370030833333
00:24:52.560 --> 00:24:54.416 He introduces the CRISPR,
NOTE Confidence: 0.916370030833333
00:24:54.416 --> 00:24:57.020 a guide library in cells that

NOTE Confidence: 0.916370030833333
00:24:57.020 --> 00:24:59.160 express that specialized CAS 9.
NOTE Confidence: 0.916370030833333
00:24:59.160 --> 00:25:01.392 And then he treats the cells with DMSO or
NOTE Confidence: 0.916370030833333
00:25:01.392 --> 00:25:03.676 the tool compound that inhibits hip two.
NOTE Confidence: 0.916370030833333
00:25:03.680 --> 00:25:05.455 And then he monitors guide
NOTE Confidence: 0.916370030833333
00:25:05.455 --> 00:25:07.560 abundance over time by next Gen.
NOTE Confidence: 0.916370030833333
00:25:07.560 --> 00:25:07.820 sequencing.
NOTE Confidence: 0.916370030833333
00:25:07.820 --> 00:25:09.640 So here's what the data looks like.
NOTE Confidence: 0.916370030833333
00:25:09.640 --> 00:25:11.000 Now I have to put up my glasses.
NOTE Confidence: 0.916370030833333
00:25:11.000 --> 00:25:13.056 So these this is the data from the
NOTE Confidence: 0.916370030833333
00:25:13.056 --> 00:25:15.172 cells treated with PT2399 and it turns
NOTE Confidence: 0.916370030833333
00:25:15.172 --> 00:25:17.680 out one of the top scoring genes.
NOTE Confidence: 0.916370030833333
00:25:17.680 --> 00:25:19.255 Let's see if I have an animation
NOTE Confidence: 0.916370030833333
00:25:19.255 --> 00:25:21.067 here is Cyclin D1.
NOTE Confidence: 0.916370030833333
00:25:21.067 --> 00:25:23.712 Now this immediately caught our
NOTE Confidence: 0.916370030833333
00:25:23.712 --> 00:25:25.928 attention because Cyclin D1 was
NOTE Confidence: 0.916370030833333

00:25:25.928 --> 00:25:27.916 already known to be a hip two
NOTE Confidence: 0.916370030833333

00:25:27.916 --> 00:25:29.334 target in kidney cancer,
NOTE Confidence: 0.916370030833333

00:25:29.334 --> 00:25:31.224 but interestingly and every other
NOTE Confidence: 0.916370030833333

00:25:31.224 --> 00:25:33.767 cancer that's been examined to date if
NOTE Confidence: 0.916370030833333

00:25:33.767 --> 00:25:35.720 if anything down regulates Cyclone D1.
NOTE Confidence: 0.916370030833333

00:25:35.720 --> 00:25:37.694 So this is probably part of the
NOTE Confidence: 0.916370030833333

00:25:37.694 --> 00:25:39.629 puzzle of why VHL loss causes
NOTE Confidence: 0.916370030833333

00:25:39.629 --> 00:25:41.675 kidney cancer but not for example
NOTE Confidence: 0.916370030833333

00:25:41.680 --> 00:25:43.600 lung cancer or colon cancer.
NOTE Confidence: 0.916370030833333

00:25:43.600 --> 00:25:45.376 So just to show you how
NOTE Confidence: 0.916370030833333

00:25:45.376 --> 00:25:46.560 beautifully this technology works,
NOTE Confidence: 0.916370030833333

00:25:46.560 --> 00:25:48.625 what I have here is a control
NOTE Confidence: 0.916370030833333

00:25:48.625 --> 00:25:50.412 guide or two different CRISPR
NOTE Confidence: 0.916370030833333

00:25:50.412 --> 00:25:52.277 activation guides from Cyclone D1.
NOTE Confidence: 0.881593069230769

00:25:52.280 --> 00:25:54.240 So now we either don't or do
NOTE Confidence: 0.881593069230769

00:25:54.240 --> 00:25:56.199 treat with the Hip 2 inhibitor.

NOTE Confidence: 0.881593069230769

00:25:56.200 --> 00:25:58.118 So now let's look at Cyclone D1.

NOTE Confidence: 0.881593069230769

00:25:58.120 --> 00:26:00.960 So if you down regulate hip two activity,

NOTE Confidence: 0.881593069230769

00:26:00.960 --> 00:26:02.760 you down regulate second D1.

NOTE Confidence: 0.881593069230769

00:26:02.760 --> 00:26:05.064 But now with the CRISPR A guides we can

NOTE Confidence: 0.881593069230769

00:26:05.064 --> 00:26:06.999 maintain the expression of Cyclone D1.

NOTE Confidence: 0.881593069230769

00:26:06.999 --> 00:26:08.757 This is specific because NDRG one

NOTE Confidence: 0.881593069230769

00:26:08.757 --> 00:26:10.720 is another hip two target gene.

NOTE Confidence: 0.881593069230769

00:26:10.720 --> 00:26:12.448 So you can see the CRISPR A guides

NOTE Confidence: 0.881593069230769

00:26:12.448 --> 00:26:14.600 are really specific or second D1 and

NOTE Confidence: 0.881593069230769

00:26:14.600 --> 00:26:16.520 now we can do validation assays.

NOTE Confidence: 0.881593069230769

00:26:16.520 --> 00:26:18.956 And I apologize that by my

NOTE Confidence: 0.881593069230769

00:26:18.956 --> 00:26:21.720 counts this is a busy slide,

NOTE Confidence: 0.881593069230769

00:26:21.720 --> 00:26:23.729 although what counts for a busy slide

NOTE Confidence: 0.881593069230769

00:26:23.729 --> 00:26:25.720 these days is certainly changing.

NOTE Confidence: 0.881593069230769

00:26:25.720 --> 00:26:28.216 So here I have cell number on the

NOTE Confidence: 0.881593069230769

00:26:28.216 --> 00:26:30.717 Y axis and days on the X axis.
NOTE Confidence: 0.881593069230769

00:26:30.720 --> 00:26:32.164 So now for orientation,
NOTE Confidence: 0.881593069230769

00:26:32.164 --> 00:26:34.760 here are the cells grown in DMSO.
NOTE Confidence: 0.881593069230769

00:26:34.760 --> 00:26:36.224 Here are the cells now treated
NOTE Confidence: 0.881593069230769

00:26:36.224 --> 00:26:37.800 with the Hip 2 inhibitor.
NOTE Confidence: 0.881593069230769

00:26:37.800 --> 00:26:39.485 But now if you artificially
NOTE Confidence: 0.881593069230769

00:26:39.485 --> 00:26:40.833 maintain second D1 expression,
NOTE Confidence: 0.881593069230769

00:26:40.840 --> 00:26:43.228 the cells are completely resistant,
NOTE Confidence: 0.881593069230769

00:26:43.228 --> 00:26:45.796 at least in this preclinical model.
NOTE Confidence: 0.881593069230769

00:26:45.800 --> 00:26:47.192 So we think there's an analogy
NOTE Confidence: 0.881593069230769

00:26:47.192 --> 00:26:48.917 to be made here potentially with
NOTE Confidence: 0.881593069230769

00:26:48.917 --> 00:26:50.393 hormone responsive breast cancer
NOTE Confidence: 0.881593069230769

00:26:50.393 --> 00:26:52.530 because the standard of care for
NOTE Confidence: 0.881593069230769

00:26:52.530 --> 00:26:54.045 many women with hormone responsive
NOTE Confidence: 0.881593069230769

00:26:54.045 --> 00:26:56.336 breast cancer is to be treated with
NOTE Confidence: 0.881593069230769

00:26:56.336 --> 00:26:58.400 an ER antagonist such as Tamoxifen

NOTE Confidence: 0.881593069230769
00:26:58.400 --> 00:27:01.436 together with a C DK46 inhibitor,
NOTE Confidence: 0.881593069230769
00:27:01.440 --> 00:27:02.950 CDK 46 being the catalytic
NOTE Confidence: 0.881593069230769
00:27:02.950 --> 00:27:04.158 partner for cyclin D1.
NOTE Confidence: 0.881593069230769
00:27:04.160 --> 00:27:06.192 And so you can imagine you get some
NOTE Confidence: 0.881593069230769
00:27:06.192 --> 00:27:07.635 synergy there because ER drives
NOTE Confidence: 0.881593069230769
00:27:07.635 --> 00:27:09.381 the expression of cyclin D1 in
NOTE Confidence: 0.881593069230769
00:27:09.381 --> 00:27:11.079 hormone response to breast cancer.
NOTE Confidence: 0.881593069230769
00:27:11.080 --> 00:27:12.706 And so now you're down regulating
NOTE Confidence: 0.881593069230769
00:27:12.706 --> 00:27:14.799 second D1 and you're hitting the kinase.
NOTE Confidence: 0.881593069230769
00:27:14.800 --> 00:27:16.298 So we think based on this analogy
NOTE Confidence: 0.881593069230769
00:27:16.298 --> 00:27:17.893 and we have some preclinical data
NOTE Confidence: 0.881593069230769
00:27:17.893 --> 00:27:18.796 to support this.
NOTE Confidence: 0.881593069230769
00:27:18.800 --> 00:27:20.432 It would be a good idea to combine
NOTE Confidence: 0.881593069230769
00:27:20.432 --> 00:27:22.620 a HEF 2 inhibitor with the CDK 46
NOTE Confidence: 0.881593069230769
00:27:22.620 --> 00:27:24.370 inhibitor and kidney cancer and
NOTE Confidence: 0.881593069230769

00:27:24.370 --> 00:27:27.680 such clinical trials have now begun
NOTE Confidence: 0.881593069230769

00:27:27.680 --> 00:27:30.259 now as often happens in experiments
NOTE Confidence: 0.881593069230769

00:27:30.259 --> 00:27:32.053 and another reason to do controls
NOTE Confidence: 0.881593069230769

00:27:32.053 --> 00:27:34.081 is it's I've been amazed over the
NOTE Confidence: 0.881593069230769

00:27:34.081 --> 00:27:35.689 years how often there's gold in
NOTE Confidence: 0.881593069230769

00:27:35.748 --> 00:27:37.519 the quote UN quote control arm or
NOTE Confidence: 0.881593069230769

00:27:37.519 --> 00:27:38.882 the control set of experiments.
NOTE Confidence: 0.881593069230769

00:27:38.882 --> 00:27:40.989 So now let's look at the cells
NOTE Confidence: 0.881593069230769

00:27:40.989 --> 00:27:42.120 that got the DMSO,
NOTE Confidence: 0.881593069230769

00:27:42.120 --> 00:27:44.600 not the Hip 2 inhibitor subjected to CRISPR.
NOTE Confidence: 0.881593069230769

00:27:44.600 --> 00:27:45.288 A Well,
NOTE Confidence: 0.881593069230769

00:27:45.288 --> 00:27:47.008 these data caught our attention
NOTE Confidence: 0.881593069230769

00:27:47.008 --> 00:27:48.800 as well because here's MEC,
NOTE Confidence: 0.881593069230769

00:27:48.800 --> 00:27:50.475 which had already been implicated
NOTE Confidence: 0.881593069230769

00:27:50.475 --> 00:27:52.600 in kidney cancer growth by others.
NOTE Confidence: 0.881593069230769

00:27:52.600 --> 00:27:54.862 Here's a gene that's less famous

NOTE Confidence: 0.881593069230769
00:27:54.862 --> 00:27:56.084 called SQST M1,
NOTE Confidence: 0.881593069230769
00:27:56.084 --> 00:27:59.038 which among other things activates NRF 2,
NOTE Confidence: 0.881593069230769
00:27:59.040 --> 00:28:01.633 which the gene name is NFE 2L2.
NOTE Confidence: 0.881593069230769
00:28:01.633 --> 00:28:03.544 So the reason we were excited about
NOTE Confidence: 0.881593069230769
00:28:03.544 --> 00:28:05.785 this is I have to say the most
NOTE Confidence: 0.881593069230769
00:28:05.785 --> 00:28:07.218 common implicon in kidney cancer
NOTE Confidence: 0.881593069230769
00:28:07.218 --> 00:28:08.638 or at least clear cell,
NOTE Confidence: 0.881593069230769
00:28:08.640 --> 00:28:11.046 I mean a carcinoma is amplification
NOTE Confidence: 0.881593069230769
00:28:11.046 --> 00:28:13.523 OF5Q And using horse and buggy
NOTE Confidence: 0.881593069230769
00:28:13.523 --> 00:28:15.822 technology about 10 years ago we
NOTE Confidence: 0.881593069230769
00:28:15.822 --> 00:28:17.936 deduced that the most likely target of
NOTE Confidence: 0.881593069230769
00:28:17.936 --> 00:28:20.500 the five Q applicon was probably SQST M1.
NOTE Confidence: 0.881593069230769
00:28:20.500 --> 00:28:22.000 So this provides some now additional,
NOTE Confidence: 0.881593069230769
00:28:22.000 --> 00:28:24.200 maybe even somewhat orthogonal evidence
NOTE Confidence: 0.881593069230769
00:28:24.200 --> 00:28:26.742 that maybe we were even correct.
NOTE Confidence: 0.881593069230769

00:28:26.742 --> 00:28:28.794 The other reason we like this
NOTE Confidence: 0.881593069230769

00:28:28.794 --> 00:28:30.758 is now let's go over here.
NOTE Confidence: 0.881593069230769

00:28:30.760 --> 00:28:35.313 So these are genes that when activated,
NOTE Confidence: 0.881593069230769

00:28:35.313 --> 00:28:38.237 confer a fitness disadvantage
NOTE Confidence: 0.881593069230769

00:28:38.240 --> 00:28:40.040 to the kidney cancer cells.
NOTE Confidence: 0.966137331428571

00:28:40.040 --> 00:28:42.994 So why might we care about that?
NOTE Confidence: 0.966137331428571

00:28:43.000 --> 00:28:44.764 Well, you may know that there are
NOTE Confidence: 0.966137331428571

00:28:44.764 --> 00:28:47.332 a lot of examples in cancer where
NOTE Confidence: 0.966137331428571

00:28:47.332 --> 00:28:49.522 chromosomal arms or sometimes entire
NOTE Confidence: 0.966137331428571

00:28:49.522 --> 00:28:53.520 chromosomes are missing. Excuse me.
NOTE Confidence: 0.966137331428571

00:28:53.520 --> 00:28:55.081 And the thought is that in many
NOTE Confidence: 0.966137331428571

00:28:55.081 --> 00:28:56.516 cases you're dealing with HAPLO
NOTE Confidence: 0.966137331428571

00:28:56.516 --> 00:28:57.596 insufficient tumor suppressors,
NOTE Confidence: 0.966137331428571

00:28:57.600 --> 00:28:59.718 where by reducing the copy number,
NOTE Confidence: 0.966137331428571

00:28:59.720 --> 00:29:01.084 you've lowered the expression.
NOTE Confidence: 0.966137331428571

00:29:01.084 --> 00:29:02.789 But since these are HAPLO

NOTE Confidence: 0.966137331428571

00:29:02.789 --> 00:29:04.080 insufficient tumor suppressors,

NOTE Confidence: 0.966137331428571

00:29:04.080 --> 00:29:06.144 we don't have the smoking gun of a

NOTE Confidence: 0.966137331428571

00:29:06.144 --> 00:29:08.232 mutation in the remaining allele as you

NOTE Confidence: 0.966137331428571

00:29:08.232 --> 00:29:09.800 would with a Knutson 2 hit tumor suppressor.

NOTE Confidence: 0.966137331428571

00:29:09.800 --> 00:29:12.072 But now we think we have a very

NOTE Confidence: 0.966137331428571

00:29:12.072 --> 00:29:13.830 powerful technology for reactivating

NOTE Confidence: 0.966137331428571

00:29:13.830 --> 00:29:16.805 these putative PAPLO insufficient tumor

NOTE Confidence: 0.966137331428571

00:29:16.805 --> 00:29:18.760 suppressors that are lost in cancer.

NOTE Confidence: 0.966137331428571

00:29:18.760 --> 00:29:21.280 And so we've now just as an example,

NOTE Confidence: 0.966137331428571

00:29:21.280 --> 00:29:22.800 we've made a custom CRISPR,

NOTE Confidence: 0.966137331428571

00:29:22.800 --> 00:29:25.110 a library for chromosome 1P which is

NOTE Confidence: 0.966137331428571

00:29:25.110 --> 00:29:27.359 frequently deleted in a variety of cancers,

NOTE Confidence: 0.966137331428571

00:29:27.360 --> 00:29:28.884 including famously neuroblastomas

NOTE Confidence: 0.966137331428571

00:29:28.884 --> 00:29:30.916 and are using CRISPR,

NOTE Confidence: 0.966137331428571

00:29:30.920 --> 00:29:33.165 a technology with focused chromosome

NOTE Confidence: 0.966137331428571

00:29:33.165 --> 00:29:35.410 or chromosome arm CRISPR guide
NOTE Confidence: 0.966137331428571

00:29:35.480 --> 00:29:38.216 libraries to look for the relevant
NOTE Confidence: 0.966137331428571

00:29:38.216 --> 00:29:40.040 HAPLO insufficient tumor express.
NOTE Confidence: 0.966137331428571

00:29:40.040 --> 00:29:40.240 OK,
NOTE Confidence: 0.966137331428571

00:29:40.240 --> 00:29:41.840 so now I'm going to completely switch gears.
NOTE Confidence: 0.966137331428571

00:29:41.840 --> 00:29:42.918 So if you didn't like that story,
NOTE Confidence: 0.966137331428571

00:29:42.920 --> 00:29:43.880 thank you for bearing with me.
NOTE Confidence: 0.966137331428571

00:29:43.880 --> 00:29:45.800 We have a completely different type of story.
NOTE Confidence: 0.966137331428571

00:29:45.800 --> 00:29:47.150 So it's been known for decades
NOTE Confidence: 0.966137331428571

00:29:47.150 --> 00:29:48.431 that clear cell Weiner cell
NOTE Confidence: 0.966137331428571

00:29:48.431 --> 00:29:49.759 carcinomas are highly immunogenic.
NOTE Confidence: 0.966137331428571

00:29:49.760 --> 00:29:51.416 They occasionally undergo
NOTE Confidence: 0.966137331428571

00:29:51.416 --> 00:29:52.520 spontaneous progressions.
NOTE Confidence: 0.966137331428571

00:29:52.520 --> 00:29:54.095 They have a high level
NOTE Confidence: 0.966137331428571

00:29:54.095 --> 00:29:55.355 of T cell infiltration.
NOTE Confidence: 0.966137331428571

00:29:55.360 --> 00:29:56.368 In the old days,

NOTE Confidence: 0.966137331428571

00:29:56.368 --> 00:29:57.628 they were occasionally cured with

NOTE Confidence: 0.966137331428571

00:29:57.628 --> 00:29:59.117 treatments like high dose interleukin 2,

NOTE Confidence: 0.966137331428571

00:29:59.120 --> 00:30:00.260 but some of those patients

NOTE Confidence: 0.966137331428571

00:30:00.260 --> 00:30:01.400 wound up in the ICU.

NOTE Confidence: 0.966137331428571

00:30:01.400 --> 00:30:03.514 The treatment was so toxic and

NOTE Confidence: 0.966137331428571

00:30:03.514 --> 00:30:05.878 many of these patients will respond

NOTE Confidence: 0.966137331428571

00:30:05.878 --> 00:30:07.720 to immune checkpoint blockade.

NOTE Confidence: 0.966137331428571

00:30:07.720 --> 00:30:09.477 So why do I tell you that?

NOTE Confidence: 0.966137331428571

00:30:09.480 --> 00:30:09.779 Well,

NOTE Confidence: 0.966137331428571

00:30:09.779 --> 00:30:12.470 you may know that in the case of some

NOTE Confidence: 0.966137331428571

00:30:12.544 --> 00:30:15.399 highly immunogenic tumors like melanomas,

NOTE Confidence: 0.966137331428571

00:30:15.400 --> 00:30:16.765 we think they're immunogenic because

NOTE Confidence: 0.966137331428571

00:30:16.765 --> 00:30:18.480 they have a high mutational burden,

NOTE Confidence: 0.966137331428571

00:30:18.480 --> 00:30:20.517 which is what I'm showing you here

NOTE Confidence: 0.966137331428571

00:30:20.520 --> 00:30:22.608 on the Y axis compared to the names

NOTE Confidence: 0.966137331428571

00:30:22.608 --> 00:30:24.900 of the tumor types on the X axis.
NOTE Confidence: 0.966137331428571

00:30:24.900 --> 00:30:26.175 But clear cell renal cell
NOTE Confidence: 0.966137331428571

00:30:26.175 --> 00:30:27.680 carcinomas smack dab in the middle,
NOTE Confidence: 0.966137331428571

00:30:27.680 --> 00:30:29.080 there's nothing conspicuous about
NOTE Confidence: 0.966137331428571

00:30:29.080 --> 00:30:31.226 clear cell renal cell, carcinoma cell.
NOTE Confidence: 0.966137331428571

00:30:31.226 --> 00:30:33.201 Why should it be immunogenic?
NOTE Confidence: 0.966137331428571

00:30:33.201 --> 00:30:36.087 So I think some widely underappreciated
NOTE Confidence: 0.966137331428571

00:30:36.087 --> 00:30:39.415 work was the work of Richard Childs
NOTE Confidence: 0.966137331428571

00:30:39.415 --> 00:30:41.675 at the National Cancer Institute
NOTE Confidence: 0.966137331428571

00:30:41.680 --> 00:30:43.720 dating back more than 15 years.
NOTE Confidence: 0.966137331428571

00:30:43.720 --> 00:30:45.250 So out of sheer desperation and
NOTE Confidence: 0.966137331428571

00:30:45.250 --> 00:30:46.857 I discussed this with him and
NOTE Confidence: 0.966137331428571

00:30:46.857 --> 00:30:47.917 it was sheer desperation,
NOTE Confidence: 0.966137331428571

00:30:47.920 --> 00:30:49.834 he took 74 patients with metastatic
NOTE Confidence: 0.966137331428571

00:30:49.834 --> 00:30:51.930 clear cell Reno cell carcinoma and
NOTE Confidence: 0.966137331428571

00:30:51.930 --> 00:30:53.835 treated them with allogeneic stem

NOTE Confidence: 0.966137331428571
00:30:53.835 --> 00:30:56.188 cell transplants as a source of
NOTE Confidence: 0.966137331428571
00:30:56.188 --> 00:30:57.716 potentially immunoreactive T cells.
NOTE Confidence: 0.966137331428571
00:30:57.720 --> 00:30:58.280 And remarkably,
NOTE Confidence: 0.966137331428571
00:30:58.280 --> 00:30:59.960 about half of the patients responded,
NOTE Confidence: 0.966137331428571
00:30:59.960 --> 00:31:02.276 including some who were durable responders.
NOTE Confidence: 0.966137331428571
00:31:02.280 --> 00:31:04.728 So about 10 to 12% of the patients
NOTE Confidence: 0.966137331428571
00:31:04.728 --> 00:31:06.004 were durable complete responders.
NOTE Confidence: 0.966137331428571
00:31:06.004 --> 00:31:07.558 And in one of the CR patients,
NOTE Confidence: 0.966137331428571
00:31:07.560 --> 00:31:09.120 one of the complete responders,
NOTE Confidence: 0.966137331428571
00:31:09.120 --> 00:31:12.355 he found donor derived T cells that
NOTE Confidence: 0.966137331428571
00:31:12.355 --> 00:31:14.245 were recognizing on the surface of
NOTE Confidence: 0.966137331428571
00:31:14.245 --> 00:31:16.428 the tumor cells a tenmor peptide
NOTE Confidence: 0.966137331428571
00:31:16.428 --> 00:31:18.393 derived from an endogenous retrovirus.
NOTE Confidence: 0.966137331428571
00:31:18.400 --> 00:31:19.737 And they were able to show that
NOTE Confidence: 0.966137331428571
00:31:19.737 --> 00:31:20.119 this retrovirus,
NOTE Confidence: 0.966137331428571

00:31:20.120 --> 00:31:22.276 which at the time was called Erbe,
NOTE Confidence: 0.966137331428571

00:31:22.280 --> 00:31:23.900 its expression was restricted to
NOTE Confidence: 0.966137331428571

00:31:23.900 --> 00:31:25.520 clear cell renal cell carcinoma,
NOTE Confidence: 0.90966450125

00:31:25.520 --> 00:31:27.710 and it was not detectable in
NOTE Confidence: 0.90966450125

00:31:27.710 --> 00:31:30.000 normal tissues or other cancers.
NOTE Confidence: 0.90966450125

00:31:30.000 --> 00:31:32.868 Moreover, some but not all groups
NOTE Confidence: 0.90966450125

00:31:32.868 --> 00:31:35.232 have have reported that the expression
NOTE Confidence: 0.90966450125

00:31:35.232 --> 00:31:37.346 of endogenous retroviruses at least
NOTE Confidence: 0.90966450125

00:31:37.346 --> 00:31:39.441 correlates with the probability that
NOTE Confidence: 0.90966450125

00:31:39.441 --> 00:31:42.037 a kidney cancer patient will respond
NOTE Confidence: 0.90966450125

00:31:42.040 --> 00:31:43.444 to immune checkpoint blockade.
NOTE Confidence: 0.90966450125

00:31:43.444 --> 00:31:46.756 Now in the case of the Richard Child's ERB,
NOTE Confidence: 0.90966450125

00:31:46.756 --> 00:31:49.122 they were able to show that this
NOTE Confidence: 0.90966450125

00:31:49.122 --> 00:31:51.322 ERB was directly regulated by HIF
NOTE Confidence: 0.90966450125

00:31:51.322 --> 00:31:53.040 2 at the transcriptional level,
NOTE Confidence: 0.90966450125

00:31:53.040 --> 00:31:55.080 which would very satisfyingly explain why

NOTE Confidence: 0.90966450125

00:31:55.130 --> 00:31:57.090 it would be up regulated in kidney cancer.

NOTE Confidence: 0.90966450125

00:31:57.090 --> 00:31:59.575 And so at this point I can introduce

NOTE Confidence: 0.90966450125

00:31:59.575 --> 00:32:01.582 another postdoc, Chin Chin Chiang.

NOTE Confidence: 0.90966450125

00:32:01.582 --> 00:32:02.838 She wanted to know,

NOTE Confidence: 0.90966450125

00:32:02.840 --> 00:32:06.400 was this Richard child's Erba

NOTE Confidence: 0.90966450125

00:32:06.400 --> 00:32:08.320 one off like a Unicorn?

NOTE Confidence: 0.90966450125

00:32:08.320 --> 00:32:09.670 I mean great for this patient

NOTE Confidence: 0.90966450125

00:32:09.670 --> 00:32:10.920 never to be seen again?

NOTE Confidence: 0.90966450125

00:32:10.920 --> 00:32:12.594 Or was it the tip of the iceberg and

NOTE Confidence: 0.90966450125

00:32:12.594 --> 00:32:14.279 was it trying to tell us something?

NOTE Confidence: 0.90966450125

00:32:14.280 --> 00:32:17.000 So that's what she set out to do.

NOTE Confidence: 0.90966450125

00:32:17.000 --> 00:32:19.716 So her hypothesis were that hip drives

NOTE Confidence: 0.90966450125

00:32:19.716 --> 00:32:21.920 the expression of multiple Ervs,

NOTE Confidence: 0.90966450125

00:32:21.920 --> 00:32:22.522 with erve,

NOTE Confidence: 0.90966450125

00:32:22.522 --> 00:32:24.328 which has now been renamed ERV

NOTE Confidence: 0.90966450125

00:32:24.328 --> 00:32:26.078 4 simply being one example.
NOTE Confidence: 0.90966450125

00:32:26.080 --> 00:32:28.040 So this being the Richard Childs ERV.
NOTE Confidence: 0.90966450125

00:32:28.040 --> 00:32:29.774 And then she hypothesized that maybe
NOTE Confidence: 0.90966450125

00:32:29.774 --> 00:32:31.811 some of these other Ervs like the
NOTE Confidence: 0.90966450125

00:32:31.811 --> 00:32:34.284 Richard Childs ERV are transcribed and
NOTE Confidence: 0.90966450125

00:32:34.284 --> 00:32:36.695 translated into MHC bound peptides.
NOTE Confidence: 0.90966450125

00:32:36.695 --> 00:32:37.985 And I should point out we're
NOTE Confidence: 0.90966450125

00:32:37.985 --> 00:32:39.080 not looking at every ERV,
NOTE Confidence: 0.90966450125

00:32:39.080 --> 00:32:40.952 we're not looking at every remnant of an ERV.
NOTE Confidence: 0.90966450125

00:32:40.960 --> 00:32:43.187 Excuse me, I'm sorry.
NOTE Confidence: 0.90966450125

00:32:43.187 --> 00:32:44.921 We're looking at about 3000 Ervs
NOTE Confidence: 0.90966450125

00:32:44.921 --> 00:32:46.856 that have been annotated to be
NOTE Confidence: 0.90966450125

00:32:46.856 --> 00:32:48.441 relatively intact and where you
NOTE Confidence: 0.90966450125

00:32:48.501 --> 00:32:50.306 can imagine them being transcribed
NOTE Confidence: 0.90966450125

00:32:50.306 --> 00:32:52.111 and translated to some degree.
NOTE Confidence: 0.90966450125

00:32:52.120 --> 00:32:53.552 And I should also point out that this

NOTE Confidence: 0.90966450125
00:32:53.552 --> 00:32:55.280 is a collaboration with David Brown,
NOTE Confidence: 0.90966450125
00:32:55.280 --> 00:32:56.204 who's sitting here,
NOTE Confidence: 0.90966450125
00:32:56.204 --> 00:32:58.022 as well as with Kathy Wu,
NOTE Confidence: 0.90966450125
00:32:58.022 --> 00:33:00.059 and we could not have done this
NOTE Confidence: 0.90966450125
00:33:00.059 --> 00:33:01.239 work without them.
NOTE Confidence: 0.90966450125
00:33:01.240 --> 00:33:03.080 So the first thing Chin Chin did was
NOTE Confidence: 0.90966450125
00:33:03.080 --> 00:33:04.900 she took a rhino carcinoma cell line
NOTE Confidence: 0.90966450125
00:33:04.900 --> 00:33:06.915 that lacks VHL and then she generated
NOTE Confidence: 0.90966450125
00:33:06.915 --> 00:33:08.560 3 isagenic pairs because again,
NOTE Confidence: 0.90966450125
00:33:08.560 --> 00:33:09.320 for the students, you know,
NOTE Confidence: 0.90966450125
00:33:09.320 --> 00:33:10.616 corroboration is your friend.
NOTE Confidence: 0.90966450125
00:33:10.616 --> 00:33:12.236 So corroborating across multiple systems,
NOTE Confidence: 0.90966450125
00:33:12.240 --> 00:33:14.556 multiple technologies, that's a good thing.
NOTE Confidence: 0.90966450125
00:33:14.560 --> 00:33:16.768 So she either infected these cells
NOTE Confidence: 0.90966450125
00:33:16.768 --> 00:33:19.003 with an empty expression vector or
NOTE Confidence: 0.90966450125

00:33:19.003 --> 00:33:21.097 a vector encoding VHL she treated
NOTE Confidence: 0.90966450125

00:33:21.097 --> 00:33:23.357 with vehicle or that HIP 2 inhibitor,
NOTE Confidence: 0.90966450125

00:33:23.360 --> 00:33:25.621 or she used CRISPR to eliminate HIP
NOTE Confidence: 0.90966450125

00:33:25.621 --> 00:33:28.040 2A or treated with a control guide.
NOTE Confidence: 0.90966450125

00:33:28.040 --> 00:33:28.836 I can point out,
NOTE Confidence: 0.90966450125

00:33:28.836 --> 00:33:30.336 I should point out that at least
NOTE Confidence: 0.90966450125

00:33:30.336 --> 00:33:31.848 in the short term these cells
NOTE Confidence: 0.90966450125

00:33:31.848 --> 00:33:33.310 will tolerate loss of hip two if
NOTE Confidence: 0.90966450125

00:33:33.310 --> 00:33:34.600 you keep them in high serum.
NOTE Confidence: 0.90966450125

00:33:34.600 --> 00:33:36.644 And then with the help of David
NOTE Confidence: 0.90966450125

00:33:36.644 --> 00:33:37.520 and his colleagues,
NOTE Confidence: 0.90966450125

00:33:37.520 --> 00:33:41.480 we looked for Ervs and RNA seek data.
NOTE Confidence: 0.90966450125

00:33:41.480 --> 00:33:43.262 So here are the Venn diagrams
NOTE Confidence: 0.90966450125

00:33:43.262 --> 00:33:45.160 with with those three conditions.
NOTE Confidence: 0.90966450125

00:33:45.160 --> 00:33:46.678 But again I'm a lumpner rather
NOTE Confidence: 0.90966450125

00:33:46.678 --> 00:33:47.437 than a splitter.

NOTE Confidence: 0.90966450125
00:33:47.440 --> 00:33:49.456 So let's be maybe even overly stringent
NOTE Confidence: 0.90966450125
00:33:49.456 --> 00:33:51.358 here with fairly stringent cut offs.
NOTE Confidence: 0.90966450125
00:33:51.360 --> 00:33:54.198 There were 15 Ervs that scored
NOTE Confidence: 0.90966450125
00:33:54.200 --> 00:33:55.692 in all three comparisons.
NOTE Confidence: 0.90966450125
00:33:55.692 --> 00:33:56.438 And I'm,
NOTE Confidence: 0.90966450125
00:33:56.440 --> 00:33:58.090 I apologize for the kind
NOTE Confidence: 0.90966450125
00:33:58.090 --> 00:33:59.080 of crazy nomenclature,
NOTE Confidence: 0.90966450125
00:33:59.080 --> 00:34:00.920 but that's where we are in the world of ER,
NOTE Confidence: 0.90966450125
00:34:00.920 --> 00:34:01.188 BS.
NOTE Confidence: 0.90966450125
00:34:01.188 --> 00:34:02.796 But it's always nice to have
NOTE Confidence: 0.90966450125
00:34:02.796 --> 00:34:03.600 an internal control,
NOTE Confidence: 0.90966450125
00:34:03.600 --> 00:34:04.680 even if you didn't know you
NOTE Confidence: 0.90966450125
00:34:04.680 --> 00:34:05.400 had an internal control.
NOTE Confidence: 0.848833221428571
00:34:05.400 --> 00:34:07.794 SO1 internal control was we did rediscover
NOTE Confidence: 0.848833221428571
00:34:07.800 --> 00:34:10.038 the Richard Childs ERB, that's good.
NOTE Confidence: 0.848833221428571

00:34:10.040 --> 00:34:12.042 And we also rediscovered in the ERB
NOTE Confidence: 0.848833221428571

00:34:12.042 --> 00:34:14.093 which is sometimes called 3.2 which was
NOTE Confidence: 0.848833221428571

00:34:14.093 --> 00:34:16.490 in one of those JCI papers as being
NOTE Confidence: 0.848833221428571

00:34:16.490 --> 00:34:18.630 a potential predictive biomarker for
NOTE Confidence: 0.848833221428571

00:34:18.630 --> 00:34:20.604 response to immune checkpoint blockade.
NOTE Confidence: 0.848833221428571

00:34:20.604 --> 00:34:22.998 So then the question was well are
NOTE Confidence: 0.848833221428571

00:34:22.998 --> 00:34:24.771 are these things really under
NOTE Confidence: 0.848833221428571

00:34:24.771 --> 00:34:26.476 direct hip control or not.
NOTE Confidence: 0.848833221428571

00:34:26.480 --> 00:34:30.155 So we did chip seek multiple ways.
NOTE Confidence: 0.848833221428571

00:34:30.160 --> 00:34:33.056 One way we did it was to knock
NOTE Confidence: 0.848833221428571

00:34:33.056 --> 00:34:35.448 in using CRISPR combined with
NOTE Confidence: 0.848833221428571

00:34:35.448 --> 00:34:36.456 homologous recombination.
NOTE Confidence: 0.848833221428571

00:34:36.456 --> 00:34:39.480 We knocked an an endogenous flag
NOTE Confidence: 0.848833221428571

00:34:39.550 --> 00:34:41.614 tag into the endogenous HIP 2 locus
NOTE Confidence: 0.848833221428571

00:34:41.614 --> 00:34:43.415 and a renal carcinoma cell line
NOTE Confidence: 0.848833221428571

00:34:43.415 --> 00:34:45.423 that that allowed us to do a chip

NOTE Confidence: 0.848833221428571

00:34:45.482 --> 00:34:46.997 seek with a flag antibody.

NOTE Confidence: 0.848833221428571

00:34:47.000 --> 00:34:49.360 Or we did chip seek with an anti

NOTE Confidence: 0.848833221428571

00:34:49.360 --> 00:34:52.480 HIP 2A antibody in cells where we

NOTE Confidence: 0.848833221428571

00:34:52.480 --> 00:34:55.640 did or did not eliminate hip 2A.

NOTE Confidence: 0.848833221428571

00:34:55.640 --> 00:34:57.327 And again getting to you know corroboration

NOTE Confidence: 0.848833221428571

00:34:57.327 --> 00:34:58.559 and multiple lines of evidence.

NOTE Confidence: 0.848833221428571

00:34:58.560 --> 00:35:01.053 If I only had these two tracks and I

NOTE Confidence: 0.848833221428571

00:35:01.053 --> 00:35:03.127 squinted I guess I could convince myself

NOTE Confidence: 0.848833221428571

00:35:03.127 --> 00:35:05.520 there's a hip 2 binding site there.

NOTE Confidence: 0.848833221428571

00:35:05.520 --> 00:35:07.120 But now if I bring in the flag

NOTE Confidence: 0.848833221428571

00:35:07.120 --> 00:35:08.720 chip seek and the knock in cells,

NOTE Confidence: 0.848833221428571

00:35:08.720 --> 00:35:10.478 I think you can convince yourself

NOTE Confidence: 0.848833221428571

00:35:10.480 --> 00:35:12.265 there's a there's a hip to binding

NOTE Confidence: 0.848833221428571

00:35:12.265 --> 00:35:14.131 site parenthetically for for

NOTE Confidence: 0.848833221428571

00:35:14.131 --> 00:35:16.279 splitters rather than lumpers.

NOTE Confidence: 0.848833221428571

00:35:16.280 --> 00:35:18.324 Richard Childs had identified up with Peter
NOTE Confidence: 0.848833221428571

00:35:18.324 --> 00:35:20.556 to hip binding site on the shoulder here.
NOTE Confidence: 0.848833221428571

00:35:20.560 --> 00:35:21.598 I think he probably missed it,
NOTE Confidence: 0.848833221428571

00:35:21.600 --> 00:35:23.640 not that it really mattered.
NOTE Confidence: 0.848833221428571

00:35:23.640 --> 00:35:24.960 So there clearly is a hip
NOTE Confidence: 0.848833221428571

00:35:24.960 --> 00:35:25.840 to binding site here.
NOTE Confidence: 0.848833221428571

00:35:25.840 --> 00:35:27.520 But now let's look at some of our new Ervs.
NOTE Confidence: 0.848833221428571

00:35:27.520 --> 00:35:29.416 I picked 2 examples I like
NOTE Confidence: 0.848833221428571

00:35:29.416 --> 00:35:31.080 because for these two Ervs,
NOTE Confidence: 0.848833221428571

00:35:31.080 --> 00:35:32.310 for whatever reason,
NOTE Confidence: 0.848833221428571

00:35:32.310 --> 00:35:34.360 they are actually precisely bookended
NOTE Confidence: 0.848833221428571

00:35:34.360 --> 00:35:35.200 by hip 2 binding sites.
NOTE Confidence: 0.848833221428571

00:35:35.200 --> 00:35:37.020 So here's one called 5875 and you
NOTE Confidence: 0.848833221428571

00:35:37.020 --> 00:35:39.199 can see the hip binding sites here.
NOTE Confidence: 0.848833221428571

00:35:39.200 --> 00:35:41.065 And here's another one called 4818.
NOTE Confidence: 0.848833221428571

00:35:41.065 --> 00:35:43.480 Nice Hip 2 binding sites shown here.

NOTE Confidence: 0.848833221428571
00:35:43.480 --> 00:35:45.860 And all these and all these validated
NOTE Confidence: 0.848833221428571
00:35:45.860 --> 00:35:47.183 secondary experiments I'm not
NOTE Confidence: 0.848833221428571
00:35:47.183 --> 00:35:48.682 going to share with you today.
NOTE Confidence: 0.848833221428571
00:35:48.682 --> 00:35:50.656 So now could it really be that
NOTE Confidence: 0.848833221428571
00:35:50.656 --> 00:35:53.099 some of these other Ervs like the
NOTE Confidence: 0.848833221428571
00:35:53.099 --> 00:35:54.914 Richard Child's ERV are actually
NOTE Confidence: 0.848833221428571
00:35:54.920 --> 00:35:56.288 transcribed and translated?
NOTE Confidence: 0.848833221428571
00:35:56.288 --> 00:35:58.568 So we collaborated with Sterling
NOTE Confidence: 0.848833221428571
00:35:58.568 --> 00:36:00.838 Churchmen who helped doing Polysome
NOTE Confidence: 0.848833221428571
00:36:00.840 --> 00:36:02.928 Seek and again using very stringent
NOTE Confidence: 0.848833221428571
00:36:02.928 --> 00:36:04.677 criteria where now we'll overlap
NOTE Confidence: 0.848833221428571
00:36:04.677 --> 00:36:06.832 the RNA seek data with the chip seek
NOTE Confidence: 0.848833221428571
00:36:06.832 --> 00:36:08.320 data and the Polysome seek data,
NOTE Confidence: 0.848833221428571
00:36:08.320 --> 00:36:10.144 again probably using overly
NOTE Confidence: 0.848833221428571
00:36:10.144 --> 00:36:11.144 stringent cut offs.
NOTE Confidence: 0.848833221428571

00:36:11.144 --> 00:36:12.232 But again we rediscovered
NOTE Confidence: 0.848833221428571

00:36:12.232 --> 00:36:13.320 the Richard Childs ERB.
NOTE Confidence: 0.848833221428571

00:36:13.320 --> 00:36:16.460 We also discovered those two Ervs I
NOTE Confidence: 0.848833221428571

00:36:16.460 --> 00:36:18.460 just showed you a moment ago that are
NOTE Confidence: 0.848833221428571

00:36:18.525 --> 00:36:20.517 bookended with hip 2 binding sites.
NOTE Confidence: 0.848833221428571

00:36:20.520 --> 00:36:21.840 So now we're ready to ask,
NOTE Confidence: 0.848833221428571

00:36:21.840 --> 00:36:25.266 are these some of these Ervs also
NOTE Confidence: 0.848833221428571

00:36:25.266 --> 00:36:26.970 transcribed and translated into
NOTE Confidence: 0.848833221428571

00:36:26.970 --> 00:36:28.674 peptides that are displayed.
NOTE Confidence: 0.848833221428571

00:36:28.680 --> 00:36:31.320 And here we were helped immeasurably
NOTE Confidence: 0.848833221428571

00:36:31.320 --> 00:36:32.556 not only by David and Kathy,
NOTE Confidence: 0.848833221428571

00:36:32.560 --> 00:36:34.639 but also by Carl Klauser and Steve
NOTE Confidence: 0.848833221428571

00:36:34.639 --> 00:36:36.640 Carr at the Broad Institute.
NOTE Confidence: 0.848833221428571

00:36:36.640 --> 00:36:37.564 Suffice it to say,
NOTE Confidence: 0.848833221428571

00:36:37.564 --> 00:36:39.560 we can find these things in cell lines,
NOTE Confidence: 0.848833221428571

00:36:39.560 --> 00:36:40.499 but more importantly,

NOTE Confidence: 0.848833221428571
00:36:40.499 --> 00:36:42.377 we find some of these peptides
NOTE Confidence: 0.848833221428571
00:36:42.377 --> 00:36:43.839 in real kidney tumors.
NOTE Confidence: 0.848833221428571
00:36:43.840 --> 00:36:45.751 So here we have the data from
NOTE Confidence: 0.848833221428571
00:36:45.751 --> 00:36:48.127 the 1st 11 patients for whom we
NOTE Confidence: 0.848833221428571
00:36:48.127 --> 00:36:49.240 had kidney tumors
NOTE Confidence: 0.953299821428571
00:36:49.240 --> 00:36:51.956 samples. For six of these 11 patients,
NOTE Confidence: 0.953299821428571
00:36:51.960 --> 00:36:54.800 we had normal controlled tissue
NOTE Confidence: 0.953299821428571
00:36:54.800 --> 00:36:56.594 and we've identified again this is
NOTE Confidence: 0.953299821428571
00:36:56.594 --> 00:36:58.599 primarily the work of called Kauser,
NOTE Confidence: 0.953299821428571
00:36:58.600 --> 00:37:02.360 about 30 Ervs peptides,
NOTE Confidence: 0.953299821428571
00:37:02.360 --> 00:37:05.056 ERV derived peptides and in every
NOTE Confidence: 0.953299821428571
00:37:05.056 --> 00:37:06.280 case where we had normal tissue,
NOTE Confidence: 0.953299821428571
00:37:06.280 --> 00:37:07.840 they were not detected in the normal tissue,
NOTE Confidence: 0.953299821428571
00:37:07.840 --> 00:37:09.848 they were exclusively present
NOTE Confidence: 0.953299821428571
00:37:09.848 --> 00:37:12.671 in the in the tumor tissue.
NOTE Confidence: 0.953299821428571

00:37:12.671 --> 00:37:14.537 So we're excited that by continuing
NOTE Confidence: 0.953299821428571

00:37:14.537 --> 00:37:16.585 these sorts of studies we can start
NOTE Confidence: 0.953299821428571

00:37:16.585 --> 00:37:18.491 to learn more and more about which
NOTE Confidence: 0.953299821428571

00:37:18.491 --> 00:37:20.540 Ervs can be transcribed and translated
NOTE Confidence: 0.953299821428571

00:37:20.540 --> 00:37:22.320 and which maybe potentially could
NOTE Confidence: 0.953299821428571

00:37:22.374 --> 00:37:24.556 be the basis for various types of
NOTE Confidence: 0.953299821428571

00:37:24.556 --> 00:37:25.971 passive or active immunotherapy.
NOTE Confidence: 0.953299821428571

00:37:25.971 --> 00:37:28.939 I will also tell you although not shown
NOTE Confidence: 0.953299821428571

00:37:28.939 --> 00:37:31.573 here is if you now take a clinical
NOTE Confidence: 0.953299821428571

00:37:31.573 --> 00:37:33.453 grade hip stabilizer and treat other
NOTE Confidence: 0.953299821428571

00:37:33.453 --> 00:37:35.319 types of cancers such as melanomas,
NOTE Confidence: 0.953299821428571

00:37:35.320 --> 00:37:36.888 brain tumors, colon cancers,
NOTE Confidence: 0.953299821428571

00:37:36.888 --> 00:37:38.456 you dramatically up regulate
NOTE Confidence: 0.953299821428571

00:37:38.456 --> 00:37:41.838 the expression of various Erbs.
NOTE Confidence: 0.953299821428571

00:37:41.838 --> 00:37:45.610 OK, Story 3 undruggable cancer targets.
NOTE Confidence: 0.953299821428571

00:37:45.610 --> 00:37:48.340 Now, I think you probably know there's

NOTE Confidence: 0.953299821428571
00:37:48.404 --> 00:37:50.599 no shortage of genetically validated
NOTE Confidence: 0.953299821428571
00:37:50.599 --> 00:37:52.126 but undruggable cancer targets,
NOTE Confidence: 0.953299821428571
00:37:52.126 --> 00:37:53.741 although there's been enough progress
NOTE Confidence: 0.953299821428571
00:37:53.741 --> 00:37:56.048 on Ras in the past year that maybe
NOTE Confidence: 0.953299821428571
00:37:56.048 --> 00:37:57.698 RASP will leave this list shortly.
NOTE Confidence: 0.953299821428571
00:37:57.698 --> 00:37:59.243 But certainly there's no shortage
NOTE Confidence: 0.953299821428571
00:37:59.243 --> 00:38:00.729 of undruggables that we might
NOTE Confidence: 0.953299821428571
00:38:00.729 --> 00:38:01.994 want to think about accessing.
NOTE Confidence: 0.953299821428571
00:38:02.000 --> 00:38:03.512 I think generically there are a number
NOTE Confidence: 0.953299821428571
00:38:03.512 --> 00:38:05.437 of ways to go after these undruggables.
NOTE Confidence: 0.953299821428571
00:38:05.440 --> 00:38:06.418 In some cases,
NOTE Confidence: 0.953299821428571
00:38:06.418 --> 00:38:08.736 you can go downstream of the mutation.
NOTE Confidence: 0.953299821428571
00:38:08.736 --> 00:38:10.072 Effectively that's what we
NOTE Confidence: 0.953299821428571
00:38:10.072 --> 00:38:11.438 did with loss of VHL.
NOTE Confidence: 0.953299821428571
00:38:11.440 --> 00:38:13.918 We went downstream and targeted a hip,
NOTE Confidence: 0.953299821428571

00:38:13.920 --> 00:38:15.888 effectively exploiting an
NOTE Confidence: 0.953299821428571
00:38:15.888 --> 00:38:17.200 epistatic relationship.
NOTE Confidence: 0.953299821428571
00:38:17.200 --> 00:38:18.640 There's renewed interest in
NOTE Confidence: 0.953299821428571
00:38:18.640 --> 00:38:19.720 developing allosteric inhibitors.
NOTE Confidence: 0.953299821428571
00:38:19.720 --> 00:38:20.740 That's effectively what
NOTE Confidence: 0.953299821428571
00:38:20.740 --> 00:38:22.440 the HIP 2 inhibitor was.
NOTE Confidence: 0.953299821428571
00:38:22.440 --> 00:38:24.300 I've had a long standing
NOTE Confidence: 0.953299821428571
00:38:24.300 --> 00:38:25.788 interest in exploiting synthetic
NOTE Confidence: 0.953299821428571
00:38:25.788 --> 00:38:27.360 lethal interactions in cancer,
NOTE Confidence: 0.953299821428571
00:38:27.360 --> 00:38:28.680 but I'm not going to talk
NOTE Confidence: 0.953299821428571
00:38:28.680 --> 00:38:29.819 about the about that today.
NOTE Confidence: 0.953299821428571
00:38:29.819 --> 00:38:31.450 But I do want to talk about
NOTE Confidence: 0.953299821428571
00:38:31.504 --> 00:38:32.800 small molecule degraders,
NOTE Confidence: 0.953299821428571
00:38:32.800 --> 00:38:34.368 which I I deal with some trepidation
NOTE Confidence: 0.953299821428571
00:38:34.368 --> 00:38:36.117 with Craig Cruz in the in the front row.
NOTE Confidence: 0.953299821428571
00:38:36.120 --> 00:38:38.112 So he he's going to keep me honest

NOTE Confidence: 0.953299821428571

00:38:38.112 --> 00:38:39.823 through this section of the talk.

NOTE Confidence: 0.953299821428571

00:38:39.823 --> 00:38:42.037 So our group and Ben Ebers group working

NOTE Confidence: 0.953299821428571

00:38:42.037 --> 00:38:43.987 in parallel showed about five years

NOTE Confidence: 0.953299821428571

00:38:43.987 --> 00:38:46.359 ago that the thalidomide like drugs,

NOTE Confidence: 0.953299821428571

00:38:46.360 --> 00:38:47.842 the so-called image,

NOTE Confidence: 0.953299821428571

00:38:47.842 --> 00:38:50.312 act as molecular glues that

NOTE Confidence: 0.953299821428571

00:38:50.312 --> 00:38:52.839 recruit A ubiquitin ligase,

NOTE Confidence: 0.953299821428571

00:38:52.840 --> 00:38:54.440 not the VHL Ubiquitin ligase,

NOTE Confidence: 0.953299821428571

00:38:54.440 --> 00:38:56.440 but in fact the cereblon,

NOTE Confidence: 0.953299821428571

00:38:56.440 --> 00:38:59.408 the ubiquitin ligase to now target for

NOTE Confidence: 0.953299821428571

00:38:59.408 --> 00:39:01.108 degradation to transcription factors

NOTE Confidence: 0.953299821428571

00:39:01.108 --> 00:39:03.152 called IKZF 1 and IKZF 3 which

NOTE Confidence: 0.953299821428571

00:39:03.152 --> 00:39:05.258 turned out to be near and dear to

NOTE Confidence: 0.953299821428571

00:39:05.258 --> 00:39:07.204 the hearts of multiple myeloma cells.

NOTE Confidence: 0.953299821428571

00:39:07.204 --> 00:39:09.224 Now in fairness this really

NOTE Confidence: 0.953299821428571

00:39:09.224 --> 00:39:10.840 kind of Harkins back.
NOTE Confidence: 0.953299821428571

00:39:10.840 --> 00:39:11.234 Oh,
NOTE Confidence: 0.953299821428571

00:39:11.234 --> 00:39:13.598 I should also say almost immediately
NOTE Confidence: 0.953299821428571

00:39:13.600 --> 00:39:15.790 people like Craig Cruz and Jay
NOTE Confidence: 0.953299821428571

00:39:15.790 --> 00:39:17.680 Brenner showed that you could
NOTE Confidence: 0.953299821428571

00:39:17.680 --> 00:39:19.828 chemically modify an image so that
NOTE Confidence: 0.953299821428571

00:39:19.828 --> 00:39:22.600 it would now go after another target.
NOTE Confidence: 0.953299821428571

00:39:22.600 --> 00:39:23.758 But I was about to say,
NOTE Confidence: 0.953299821428571

00:39:23.760 --> 00:39:24.442 in fairness,
NOTE Confidence: 0.953299821428571

00:39:24.442 --> 00:39:26.488 this general idea of having a
NOTE Confidence: 0.953299821428571

00:39:26.488 --> 00:39:28.379 chemical that acts as a matchmaker
NOTE Confidence: 0.953299821428571

00:39:28.379 --> 00:39:30.451 between an E3 ligase and a target
NOTE Confidence: 0.953299821428571

00:39:30.451 --> 00:39:32.352 goes back to the Seminole work of
NOTE Confidence: 0.953299821428571

00:39:32.352 --> 00:39:34.400 Craig Cruz as well as Raid Deshays.
NOTE Confidence: 0.953299821428571

00:39:34.400 --> 00:39:37.198 And just to introduce some nomenclature here,
NOTE Confidence: 0.953299821428571

00:39:37.198 --> 00:39:39.151 these molecules on the left are sometimes

NOTE Confidence: 0.953299821428571
00:39:39.151 --> 00:39:40.760 of course referred to as protax.
NOTE Confidence: 0.953299821428571
00:39:40.760 --> 00:39:42.410 I realize this is bringing
NOTE Confidence: 0.953299821428571
00:39:42.410 --> 00:39:43.400 Coles to Newcastle.
NOTE Confidence: 0.9487915625
00:39:43.400 --> 00:39:44.900 These are sometimes referred
NOTE Confidence: 0.9487915625
00:39:44.900 --> 00:39:46.400 to as molecular glues,
NOTE Confidence: 0.9487915625
00:39:46.400 --> 00:39:47.939 and I and I think either you or Jay
NOTE Confidence: 0.9487915625
00:39:47.939 --> 00:39:49.277 tried to call these degonomists.
NOTE Confidence: 0.9487915625
00:39:49.280 --> 00:39:50.318 I think you need a publicist.
NOTE Confidence: 0.9487915625
00:39:50.320 --> 00:39:51.741 I'm not sure that one caught on
NOTE Confidence: 0.9487915625
00:39:51.741 --> 00:39:53.319 as well as the molecular glue,
NOTE Confidence: 0.9487915625
00:39:53.320 --> 00:39:56.280 molecular glues or the protax.
NOTE Confidence: 0.9487915625
00:39:56.280 --> 00:39:58.760 So when you think about it,
NOTE Confidence: 0.9487915625
00:39:58.760 --> 00:40:00.770 however, there are lots of other
NOTE Confidence: 0.9487915625
00:40:00.770 --> 00:40:02.640 ways a small molecule could
NOTE Confidence: 0.9487915625
00:40:02.640 --> 00:40:04.480 degrade directly or indirectly,
NOTE Confidence: 0.9487915625

00:40:04.480 --> 00:40:06.160 your favorite undruggable protein.
NOTE Confidence: 0.9487915625

00:40:06.160 --> 00:40:07.420 Because protein stability
NOTE Confidence: 0.9487915625

00:40:07.420 --> 00:40:08.680 is highly regulated.
NOTE Confidence: 0.9487915625

00:40:08.680 --> 00:40:11.040 There are about 500 Ubiquitin ligases.
NOTE Confidence: 0.9487915625

00:40:11.040 --> 00:40:13.278 They're opposed by about 100 Dubs.
NOTE Confidence: 0.9487915625

00:40:13.280 --> 00:40:15.500 Whether these ligases and dubs will
NOTE Confidence: 0.9487915625

00:40:15.500 --> 00:40:17.541 recognize their targets are often
NOTE Confidence: 0.9487915625

00:40:17.541 --> 00:40:20.036 influenced by post translation modifications,
NOTE Confidence: 0.9487915625

00:40:20.040 --> 00:40:21.272 protein folding,
NOTE Confidence: 0.9487915625

00:40:21.272 --> 00:40:23.120 protein protein interaction,
NOTE Confidence: 0.9487915625

00:40:23.120 --> 00:40:24.128 sub cellular localization,
NOTE Confidence: 0.9487915625

00:40:24.128 --> 00:40:25.856 et cetera, et cetera, et cetera.
NOTE Confidence: 0.9487915625

00:40:25.856 --> 00:40:27.440 So we wanted to develop an
NOTE Confidence: 0.9487915625

00:40:27.495 --> 00:40:29.340 assay for degraders that was
NOTE Confidence: 0.9487915625

00:40:29.340 --> 00:40:30.382 actually mechanism agnostic.
NOTE Confidence: 0.9487915625

00:40:30.382 --> 00:40:30.684 Now,

NOTE Confidence: 0.9487915625

00:40:30.684 --> 00:40:32.496 we've talked a lot today about

NOTE Confidence: 0.9487915625

00:40:32.496 --> 00:40:34.200 up assays versus down assays.

NOTE Confidence: 0.9487915625

00:40:34.200 --> 00:40:35.526 And that's because 20 plus years

NOTE Confidence: 0.9487915625

00:40:35.526 --> 00:40:37.201 ago some of my colleagues in pharma

NOTE Confidence: 0.9487915625

00:40:37.201 --> 00:40:38.916 tried to beat into my head why?

NOTE Confidence: 0.9487915625

00:40:38.920 --> 00:40:40.100 If we're doing a chemical

NOTE Confidence: 0.9487915625

00:40:40.100 --> 00:40:41.280 screen or a genetic screen,

NOTE Confidence: 0.9487915625

00:40:41.280 --> 00:40:42.635 you'd almost always rather do

NOTE Confidence: 0.9487915625

00:40:42.635 --> 00:40:44.621 an up assay than a down essay

NOTE Confidence: 0.9487915625

00:40:44.621 --> 00:40:46.319 for for at least two reasons.

NOTE Confidence: 0.9487915625

00:40:46.320 --> 00:40:47.172 First of all,

NOTE Confidence: 0.9487915625

00:40:47.172 --> 00:40:48.876 up assays tend to have better

NOTE Confidence: 0.9487915625

00:40:48.876 --> 00:40:50.638 signal to noise characteristics.

NOTE Confidence: 0.9487915625

00:40:50.640 --> 00:40:52.626 It's usually easier to see a

NOTE Confidence: 0.9487915625

00:40:52.626 --> 00:40:54.106 positive and a sea of negative than

NOTE Confidence: 0.9487915625

00:40:54.106 --> 00:40:55.678 a negative and a sea of positives.
NOTE Confidence: 0.9487915625

00:40:55.680 --> 00:40:56.320 If you think about it,
NOTE Confidence: 0.9487915625

00:40:56.320 --> 00:40:58.600 that's what makes astronomy work.
NOTE Confidence: 0.9487915625

00:40:58.600 --> 00:41:00.275 But maybe more important for
NOTE Confidence: 0.9487915625

00:41:00.275 --> 00:41:01.280 us as biologists,
NOTE Confidence: 0.9487915625

00:41:01.280 --> 00:41:02.505 they're just lots of trivial
NOTE Confidence: 0.9487915625

00:41:02.505 --> 00:41:04.120 ways to make a complex system,
NOTE Confidence: 0.9487915625

00:41:04.120 --> 00:41:06.440 including a complex biological system,
NOTE Confidence: 0.9487915625

00:41:06.440 --> 00:41:09.116 work worse rather than work better.
NOTE Confidence: 0.9487915625

00:41:09.120 --> 00:41:10.674 So my thought experiment for the students,
NOTE Confidence: 0.9487915625

00:41:10.680 --> 00:41:11.920 if you don't believe me,
NOTE Confidence: 0.9487915625

00:41:11.920 --> 00:41:13.320 I hope it's just a thought experiment,
NOTE Confidence: 0.9487915625

00:41:13.320 --> 00:41:14.976 is you go out to your car one
NOTE Confidence: 0.9487915625

00:41:14.976 --> 00:41:16.503 evening and start randomly removing
NOTE Confidence: 0.9487915625

00:41:16.503 --> 00:41:18.268 parts from your internal combustion
NOTE Confidence: 0.9487915625

00:41:18.268 --> 00:41:20.426 engine and tell me how often it goes

NOTE Confidence: 0.9487915625

00:41:20.426 --> 00:41:22.065 faster and how often it goes slower.

NOTE Confidence: 0.9487915625

00:41:22.065 --> 00:41:23.240 So that's your that's your.

NOTE Confidence: 0.9487915625

00:41:23.240 --> 00:41:24.505 Again I emphasize this probably

NOTE Confidence: 0.9487915625

00:41:24.505 --> 00:41:25.817 should be a thought experiment.

NOTE Confidence: 0.9487915625

00:41:25.817 --> 00:41:28.193 So we wanted to develop an up assay.

NOTE Confidence: 0.9487915625

00:41:28.200 --> 00:41:30.125 So Sagar Kaduri when he was in

NOTE Confidence: 0.9487915625

00:41:30.125 --> 00:41:32.248 my lab a very talented physician

NOTE Confidence: 0.9487915625

00:41:32.248 --> 00:41:33.816 scientist developed this assay

NOTE Confidence: 0.9487915625

00:41:33.816 --> 00:41:35.889 where your protein of interest is

NOTE Confidence: 0.9487915625

00:41:35.889 --> 00:41:37.918 fused to a modified cited in kinase

NOTE Confidence: 0.9487915625

00:41:37.918 --> 00:41:39.514 that was developed by Jeff Medin

NOTE Confidence: 0.9487915625

00:41:39.514 --> 00:41:41.323 that will accept the non natural

NOTE Confidence: 0.9487915625

00:41:41.323 --> 00:41:43.160 nucleoside and converted into a toxin.

NOTE Confidence: 0.9487915625

00:41:43.160 --> 00:41:44.308 There's a little spacer,

NOTE Confidence: 0.9487915625

00:41:44.308 --> 00:41:46.307 there's AV5 tag and then importantly off

NOTE Confidence: 0.9487915625

00:41:46.307 --> 00:41:48.230 the same transcript you have a a GFP.
NOTE Confidence: 0.9487915625

00:41:48.230 --> 00:41:48.505 So,
NOTE Confidence: 0.9487915625

00:41:48.505 --> 00:41:51.015 so the idea is you can add a
NOTE Confidence: 0.9487915625

00:41:51.015 --> 00:41:53.039 chemical or genetic perturbation,
NOTE Confidence: 0.9487915625

00:41:53.040 --> 00:41:55.994 add BBDU and look for green survivors.
NOTE Confidence: 0.9487915625

00:41:56.000 --> 00:41:57.660 And as this is an up assay this can be
NOTE Confidence: 0.9487915625

00:41:57.712 --> 00:41:59.595 done in both arrayed format with chemicals.
NOTE Confidence: 0.9487915625

00:41:59.600 --> 00:42:01.189 It can also be done in pooled
NOTE Confidence: 0.9487915625

00:42:01.189 --> 00:42:02.400 format with CRISPR libraries.
NOTE Confidence: 0.9487915625

00:42:02.400 --> 00:42:03.972 Just to show you a proof
NOTE Confidence: 0.9487915625

00:42:03.972 --> 00:42:04.758 of concept experiment,
NOTE Confidence: 0.9487915625

00:42:04.760 --> 00:42:06.559 here's a 384 well plate assay where
NOTE Confidence: 0.9487915625

00:42:06.559 --> 00:42:08.714 the cells have the Imid target IKZ F1.
NOTE Confidence: 0.9487915625

00:42:08.714 --> 00:42:10.653 I hope you can see there are
NOTE Confidence: 0.9487915625

00:42:10.653 --> 00:42:12.319 three positive wells here.
NOTE Confidence: 0.9487915625

00:42:12.320 --> 00:42:14.426 It turns out these two wells

NOTE Confidence: 0.9487915625

00:42:14.426 --> 00:42:15.926 had an Imid pomalidomide,

NOTE Confidence: 0.9487915625

00:42:15.926 --> 00:42:19.940 whereas this well had a chemical that we now

NOTE Confidence: 0.780078463

00:42:20.017 --> 00:42:23.083 know is an assay positive that interferes

NOTE Confidence: 0.780078463

00:42:23.083 --> 00:42:25.532 with BVD uptake by themselves,

NOTE Confidence: 0.780078463

00:42:25.532 --> 00:42:27.796 but that's easily detected.

NOTE Confidence: 0.780078463

00:42:27.800 --> 00:42:30.560 Then again, for proof of concept,

NOTE Confidence: 0.780078463

00:42:30.560 --> 00:42:32.040 Sagar did the following experiment.

NOTE Confidence: 0.780078463

00:42:32.040 --> 00:42:33.845 So again, the top plate

NOTE Confidence: 0.780078463

00:42:33.845 --> 00:42:36.400 is the IKZ of 1 fusion.

NOTE Confidence: 0.780078463

00:42:36.400 --> 00:42:39.074 The bottom plate is the counter screen

NOTE Confidence: 0.780078463

00:42:39.074 --> 00:42:40.860 counter screen with unfused CK.

NOTE Confidence: 0.780078463

00:42:40.860 --> 00:42:43.240 There are various controls in the outer

NOTE Confidence: 0.780078463

00:42:43.309 --> 00:42:45.556 columns which you can ignore for now.

NOTE Confidence: 0.780078463

00:42:45.560 --> 00:42:47.504 Otherwise each row has two different

NOTE Confidence: 0.780078463

00:42:47.504 --> 00:42:49.640 chemicals at 10 different concentrations.

NOTE Confidence: 0.780078463

00:42:49.640 --> 00:42:51.760 So here's an assay positive,
NOTE Confidence: 0.780078463

00:42:51.760 --> 00:42:53.363 so we don't care about that we're
NOTE Confidence: 0.780078463

00:42:53.363 --> 00:42:54.519 at the highest concentration
NOTE Confidence: 0.780078463

00:42:54.519 --> 00:42:56.199 somehow promotes the survival.
NOTE Confidence: 0.780078463

00:42:56.200 --> 00:42:58.464 But here's a true positive which
NOTE Confidence: 0.780078463

00:42:58.464 --> 00:42:59.840 was originally named Spout,
NOTE Confidence: 0.780078463

00:42:59.840 --> 00:43:01.562 and one it's been reported to
NOTE Confidence: 0.780078463

00:43:01.562 --> 00:43:03.400 be a modifier of autophagy,
NOTE Confidence: 0.780078463

00:43:03.400 --> 00:43:05.705 but that turns out to be a red herring here.
NOTE Confidence: 0.780078463

00:43:05.705 --> 00:43:07.280 But this turns out to be true,
NOTE Confidence: 0.780078463

00:43:07.280 --> 00:43:09.032 positive and and we know it's
NOTE Confidence: 0.780078463

00:43:09.032 --> 00:43:10.200 not just another image,
NOTE Confidence: 0.780078463

00:43:10.200 --> 00:43:11.800 first of all by looking at the structure,
NOTE Confidence: 0.780078463

00:43:11.800 --> 00:43:13.837 but secondly in contrast to the image.
NOTE Confidence: 0.780078463

00:43:13.840 --> 00:43:16.640 This doesn't require Cerebon
NOTE Confidence: 0.780078463

00:43:16.640 --> 00:43:19.560 to degrade IKZ F1.

NOTE Confidence: 0.780078463

00:43:19.560 --> 00:43:23.042 Now we thought our UP assay might

NOTE Confidence: 0.780078463

00:43:23.042 --> 00:43:24.932 allow us to revisit screening

NOTE Confidence: 0.780078463

00:43:24.932 --> 00:43:26.720 natural product collections.

NOTE Confidence: 0.780078463

00:43:26.720 --> 00:43:29.597 Now for those of you who are

NOTE Confidence: 0.780078463

00:43:29.600 --> 00:43:31.400 who haven't lived through this,

NOTE Confidence: 0.780078463

00:43:31.400 --> 00:43:33.143 there was a time back in the

NOTE Confidence: 0.780078463

00:43:33.143 --> 00:43:34.660 days of dinosaurs where screening

NOTE Confidence: 0.780078463

00:43:34.660 --> 00:43:36.088 natural product collections was

NOTE Confidence: 0.780078463

00:43:36.088 --> 00:43:38.280 a preferred way of finding drugs

NOTE Confidence: 0.780078463

00:43:38.280 --> 00:43:41.200 and the and the and the pros are

NOTE Confidence: 0.780078463

00:43:41.200 --> 00:43:42.703 enhanced chemical diversity.

NOTE Confidence: 0.780078463

00:43:42.703 --> 00:43:44.707 Nature's produced chemicals that

NOTE Confidence: 0.780078463

00:43:44.707 --> 00:43:47.120 I don't think any human chemist

NOTE Confidence: 0.780078463

00:43:47.120 --> 00:43:49.040 has ever been able to make.

NOTE Confidence: 0.780078463

00:43:49.040 --> 00:43:50.708 And natural product hits often have

NOTE Confidence: 0.780078463

00:43:50.708 --> 00:43:52.089 drug like product properties right
NOTE Confidence: 0.780078463

00:43:52.089 --> 00:43:53.825 out of the gate because in many cases
NOTE Confidence: 0.780078463

00:43:53.825 --> 00:43:55.395 that's what they were designed to do.
NOTE Confidence: 0.780078463

00:43:55.400 --> 00:43:56.480 They were designed, for example,
NOTE Confidence: 0.780078463

00:43:56.480 --> 00:43:58.384 to cross cell membranes.
NOTE Confidence: 0.780078463

00:43:58.384 --> 00:44:01.240 The cons are that contaminating toxins
NOTE Confidence: 0.780078463

00:44:01.321 --> 00:44:04.117 cause false positives and down assays
NOTE Confidence: 0.780078463

00:44:04.120 --> 00:44:05.560 and false negatives and up assays.
NOTE Confidence: 0.780078463

00:44:05.560 --> 00:44:08.278 And again we're doing up assays.
NOTE Confidence: 0.780078463

00:44:08.280 --> 00:44:10.120 It's historically difficult to isolate
NOTE Confidence: 0.780078463

00:44:10.120 --> 00:44:11.960 and identify the active chemicals
NOTE Confidence: 0.780078463

00:44:12.014 --> 00:44:13.598 in the mixtures of scores hits.
NOTE Confidence: 0.780078463

00:44:13.600 --> 00:44:15.958 This can take anywhere from years,
NOTE Confidence: 0.780078463

00:44:15.960 --> 00:44:17.112 decades to Infinity.
NOTE Confidence: 0.780078463

00:44:17.112 --> 00:44:19.800 And then sometimes it's not very frequently.
NOTE Confidence: 0.780078463

00:44:19.800 --> 00:44:22.362 It's difficult to identify the direct

NOTE Confidence: 0.780078463

00:44:22.362 --> 00:44:24.720 protein target for the chemical

NOTE Confidence: 0.780078463

00:44:24.720 --> 00:44:26.316 coming out of the phenotypic screens.

NOTE Confidence: 0.780078463

00:44:26.320 --> 00:44:28.161 Although I have to say there's some

NOTE Confidence: 0.780078463

00:44:28.161 --> 00:44:30.127 very clever and powerful genetic and

NOTE Confidence: 0.780078463

00:44:30.127 --> 00:44:32.384 biochemical techniques for doing this now.

NOTE Confidence: 0.780078463

00:44:32.384 --> 00:44:33.536 So we became,

NOTE Confidence: 0.780078463

00:44:33.536 --> 00:44:33.920 oh,

NOTE Confidence: 0.780078463

00:44:33.920 --> 00:44:36.032 that's how they should say so this is

NOTE Confidence: 0.780078463

00:44:36.032 --> 00:44:37.757 the unpublished work of Matt Boudreaux.

NOTE Confidence: 0.780078463

00:44:37.760 --> 00:44:40.056 So how can we leverage natural products

NOTE Confidence: 0.780078463

00:44:40.056 --> 00:44:42.197 and do screens with our UP assay?

NOTE Confidence: 0.780078463

00:44:42.200 --> 00:44:45.548 So we became aware of the work of Barry

NOTE Confidence: 0.780078463

00:44:45.548 --> 00:44:47.320 O'Keefe at the National Cancer Institute,

NOTE Confidence: 0.780078463

00:44:47.320 --> 00:44:48.886 who overseas the natural product collection

NOTE Confidence: 0.780078463

00:44:48.886 --> 00:44:51.238 that all of us paid for with our tax money.

NOTE Confidence: 0.780078463

00:44:51.240 --> 00:44:52.824 So you might as well ask for this
NOTE Confidence: 0.780078463

00:44:52.824 --> 00:44:54.568 collection at some point because you paid
NOTE Confidence: 0.780078463

00:44:54.568 --> 00:44:57.880 for it and his very simple but powerful idea.
NOTE Confidence: 0.780078463

00:44:57.880 --> 00:44:58.264 And again,
NOTE Confidence: 0.780078463

00:44:58.264 --> 00:44:58.840 for the students,
NOTE Confidence: 0.780078463

00:44:58.840 --> 00:45:00.420 simple is not bad.
NOTE Confidence: 0.780078463

00:45:00.420 --> 00:45:02.321 Simple is often like, good.
NOTE Confidence: 0.780078463

00:45:02.321 --> 00:45:04.568 OK, so I think we're drawn to
NOTE Confidence: 0.780078463

00:45:04.568 --> 00:45:06.039 the complicated fancy ideas.
NOTE Confidence: 0.780078463

00:45:06.040 --> 00:45:07.265 It's often the simple things
NOTE Confidence: 0.780078463

00:45:07.265 --> 00:45:08.000 that moves forth.
NOTE Confidence: 0.780078463

00:45:08.000 --> 00:45:10.688 So his embarrassingly simple but very
NOTE Confidence: 0.780078463

00:45:10.688 --> 00:45:13.599 powerful idea was what if I took this
NOTE Confidence: 0.727035305

00:45:13.600 --> 00:45:15.196 compound collection and there are over
NOTE Confidence: 0.727035305

00:45:15.200 --> 00:45:16.838 200,000 of these very complicated broths,
NOTE Confidence: 0.727035305

00:45:16.840 --> 00:45:19.756 extracts, mixtures housed at the NCI.

NOTE Confidence: 0.727035305

00:45:19.760 --> 00:45:22.757 And suppose we run them over a single column.

NOTE Confidence: 0.727035305

00:45:22.760 --> 00:45:25.088 So now each mixture is now

NOTE Confidence: 0.727035305

00:45:25.088 --> 00:45:26.640 represented by 7 fractions.

NOTE Confidence: 0.727035305

00:45:26.640 --> 00:45:28.840 And I apologize for all the verbage here,

NOTE Confidence: 0.727035305

00:45:28.840 --> 00:45:31.477 but suffice it to say let's pick the column.

NOTE Confidence: 0.727035305

00:45:31.480 --> 00:45:34.423 So it removes a lot of the nuisance compounds

NOTE Confidence: 0.727035305

00:45:34.423 --> 00:45:37.520 that plagues many phenotypic screens and in

NOTE Confidence: 0.727035305

00:45:37.520 --> 00:45:39.520 particular the so-called pain compounds,

NOTE Confidence: 0.727035305

00:45:39.520 --> 00:45:40.753 Pan interference compounds.

NOTE Confidence: 0.727035305

00:45:40.753 --> 00:45:42.808 And because we now have

NOTE Confidence: 0.727035305

00:45:42.808 --> 00:45:44.439 separated into 7 fractions,

NOTE Confidence: 0.727035305

00:45:44.440 --> 00:45:46.240 we've simplified the mixtures and

NOTE Confidence: 0.727035305

00:45:46.240 --> 00:45:47.880 that increases the probability that

NOTE Confidence: 0.727035305

00:45:47.880 --> 00:45:49.080 you'll get to the active chemical.

NOTE Confidence: 0.727035305

00:45:49.080 --> 00:45:52.077 They tell me their success rate is about 80%.

NOTE Confidence: 0.727035305

00:45:52.080 --> 00:45:53.744 If you get a hit from one of
NOTE Confidence: 0.727035305

00:45:53.744 --> 00:45:55.244 these single fraction comes,
NOTE Confidence: 0.727035305

00:45:55.244 --> 00:45:56.956 it helps with reproducibility,
NOTE Confidence: 0.727035305

00:45:56.960 --> 00:45:57.560 yada, yada yada.
NOTE Confidence: 0.727035305

00:45:57.560 --> 00:45:58.960 So for those of you are interested,
NOTE Confidence: 0.727035305

00:45:58.960 --> 00:46:02.428 this nice summary of this platform.
NOTE Confidence: 0.727035305

00:46:02.428 --> 00:46:05.200 So we moved this platform to Harvard
NOTE Confidence: 0.727035305

00:46:05.273 --> 00:46:07.649 and we decided this would marry
NOTE Confidence: 0.727035305

00:46:07.649 --> 00:46:10.039 well with some overall up assays.
NOTE Confidence: 0.727035305

00:46:10.040 --> 00:46:10.892 So Matt Boudreaux,
NOTE Confidence: 0.727035305

00:46:10.892 --> 00:46:12.596 whose picture I just showed you,
NOTE Confidence: 0.727035305

00:46:12.600 --> 00:46:15.640 he decided to take on mutated beta catenin,
NOTE Confidence: 0.727035305

00:46:15.640 --> 00:46:16.810 another classically undruggable.
NOTE Confidence: 0.727035305

00:46:16.810 --> 00:46:18.760 This could be updated now,
NOTE Confidence: 0.727035305

00:46:18.760 --> 00:46:20.460 but he's effectively gone
NOTE Confidence: 0.727035305

00:46:20.460 --> 00:46:22.160 through the entire collection.

NOTE Confidence: 0.727035305

00:46:22.160 --> 00:46:23.315 For those of you who do screens,

NOTE Confidence: 0.727035305

00:46:23.320 --> 00:46:25.036 the screen had very good statistics.

NOTE Confidence: 0.727035305

00:46:25.040 --> 00:46:26.810 But I want to kind of give you a sense

NOTE Confidence: 0.727035305

00:46:26.864 --> 00:46:28.358 of the power of this technology.

NOTE Confidence: 0.727035305

00:46:28.360 --> 00:46:32.079 So for all 7 fractions we get the

NOTE Confidence: 0.727035305

00:46:32.079 --> 00:46:34.797 unfractionated master mix if you will,

NOTE Confidence: 0.727035305

00:46:34.800 --> 00:46:37.328 as F0 and Z score here is a

NOTE Confidence: 0.727035305

00:46:37.328 --> 00:46:39.720 measure of the number of viable

NOTE Confidence: 0.727035305

00:46:39.720 --> 00:46:42.120 *** positive cells in the well.

NOTE Confidence: 0.727035305

00:46:42.120 --> 00:46:44.717 So in hindsight you could see that,

NOTE Confidence: 0.727035305

00:46:44.720 --> 00:46:44.968 yeah,

NOTE Confidence: 0.727035305

00:46:44.968 --> 00:46:46.704 maybe there's a little bit of a

NOTE Confidence: 0.727035305

00:46:46.704 --> 00:46:48.317 blip here with the master mix,

NOTE Confidence: 0.727035305

00:46:48.320 --> 00:46:50.672 but this doesn't come close to our

NOTE Confidence: 0.727035305

00:46:50.672 --> 00:46:52.340 threshold for calling a positive

NOTE Confidence: 0.727035305

00:46:52.340 --> 00:46:53.240 in the screen.
NOTE Confidence: 0.727035305

00:46:53.240 --> 00:46:54.020 If we had,
NOTE Confidence: 0.727035305

00:46:54.020 --> 00:46:55.840 if we moved our threshold down here,
NOTE Confidence: 0.727035305

00:46:55.840 --> 00:46:57.712 we just have thousands and thousands
NOTE Confidence: 0.727035305

00:46:57.712 --> 00:46:59.400 and thousands and thousands of hits.
NOTE Confidence: 0.727035305

00:46:59.400 --> 00:47:01.800 But now if you look at the seven
NOTE Confidence: 0.727035305

00:47:01.800 --> 00:47:02.400 sub fractions,
NOTE Confidence: 0.727035305

00:47:02.400 --> 00:47:04.432 you can see that F5 and F6 are
NOTE Confidence: 0.727035305

00:47:04.432 --> 00:47:06.119 a winner and we like this.
NOTE Confidence: 0.727035305

00:47:06.120 --> 00:47:08.682 We take great comfort if two adjacent
NOTE Confidence: 0.727035305

00:47:08.682 --> 00:47:10.452 fractions score because again this
NOTE Confidence: 0.727035305

00:47:10.452 --> 00:47:12.594 is a single column so it's unlikely
NOTE Confidence: 0.727035305

00:47:12.594 --> 00:47:14.760 that anyone chemical is going to
NOTE Confidence: 0.727035305

00:47:14.760 --> 00:47:16.760 be exclusively in in one fraction.
NOTE Confidence: 0.727035305

00:47:16.760 --> 00:47:18.680 So some of these do validate
NOTE Confidence: 0.727035305

00:47:18.756 --> 00:47:20.160 in secondary screens.

NOTE Confidence: 0.727035305

00:47:20.160 --> 00:47:21.792 This is a work in progress and it's

NOTE Confidence: 0.727035305

00:47:21.792 --> 00:47:23.400 unpublished, but I'll just show you.

NOTE Confidence: 0.727035305

00:47:23.400 --> 00:47:25.792 Here is an example of a fraction that

NOTE Confidence: 0.727035305

00:47:25.792 --> 00:47:28.024 where the Master was called 15 O 9

NOTE Confidence: 0.727035305

00:47:28.024 --> 00:47:30.866 and here are two adjacent fractions I think,

NOTE Confidence: 0.727035305

00:47:30.866 --> 00:47:31.159 well,

NOTE Confidence: 0.727035305

00:47:31.159 --> 00:47:33.896 it's called dash 5 and here's fraction 7.

NOTE Confidence: 0.727035305

00:47:33.896 --> 00:47:35.360 Here's an adjacent.

NOTE Confidence: 0.727035305

00:47:35.360 --> 00:47:36.034 But anyway,

NOTE Confidence: 0.727035305

00:47:36.034 --> 00:47:38.834 you can see we're degrading not only or

NOTE Confidence: 0.727035305

00:47:38.834 --> 00:47:41.438 down regulating the beta catena fusion,

NOTE Confidence: 0.727035305

00:47:41.440 --> 00:47:43.820 but more importantly we're down

NOTE Confidence: 0.727035305

00:47:43.820 --> 00:47:45.724 regulating endogenous beta catena

NOTE Confidence: 0.727035305

00:47:45.724 --> 00:47:48.178 and we're turning off beta catena

NOTE Confidence: 0.727035305

00:47:48.178 --> 00:47:50.375 target genes such as Axon 2.

NOTE Confidence: 0.727035305

00:47:50.375 --> 00:47:52.440 And for those of you who care,
NOTE Confidence: 0.727035305

00:47:52.440 --> 00:47:54.972 this extract is from a plant
NOTE Confidence: 0.727035305

00:47:54.972 --> 00:47:58.320 that's living somewhere in Belize,
NOTE Confidence: 0.727035305

00:47:58.320 --> 00:47:59.678 which brings up a whole other issue.
NOTE Confidence: 0.727035305

00:47:59.680 --> 00:48:00.805 If some smart chemists can't
NOTE Confidence: 0.727035305

00:48:00.805 --> 00:48:01.480 make this chemical,
NOTE Confidence: 0.898606856666667

00:48:01.480 --> 00:48:03.693 we may wind up going down to
NOTE Confidence: 0.898606856666667

00:48:03.693 --> 00:48:05.958 Belize and harvesting this plant.
NOTE Confidence: 0.898606856666667

00:48:05.960 --> 00:48:06.952 But another truism is,
NOTE Confidence: 0.898606856666667

00:48:06.952 --> 00:48:08.192 I've learned over the years,
NOTE Confidence: 0.898606856666667

00:48:08.200 --> 00:48:09.118 when you set up a screen,
NOTE Confidence: 0.898606856666667

00:48:09.120 --> 00:48:10.380 even a good screen,
NOTE Confidence: 0.898606856666667

00:48:10.380 --> 00:48:13.280 you get the things you were hoping to get,
NOTE Confidence: 0.898606856666667

00:48:13.280 --> 00:48:14.393 and then you get the things you
NOTE Confidence: 0.898606856666667

00:48:14.393 --> 00:48:15.558 didn't know you were screening for,
NOTE Confidence: 0.898606856666667

00:48:15.560 --> 00:48:16.780 but in fact you were

NOTE Confidence: 0.898606856666667
00:48:16.780 --> 00:48:18.000 screening for them all along.
NOTE Confidence: 0.898606856666667
00:48:18.000 --> 00:48:20.448 So here's another robust positive that
NOTE Confidence: 0.898606856666667
00:48:20.448 --> 00:48:23.684 scored as a pro survival chemical in
NOTE Confidence: 0.898606856666667
00:48:23.684 --> 00:48:26.918 that reporter system I described to you.
NOTE Confidence: 0.898606856666667
00:48:26.920 --> 00:48:29.560 So somehow we're inactivating Beta Catena.
NOTE Confidence: 0.898606856666667
00:48:29.560 --> 00:48:31.233 But now to our surprise when we
NOTE Confidence: 0.898606856666667
00:48:31.233 --> 00:48:32.890 did the western blots and here
NOTE Confidence: 0.898606856666667
00:48:32.890 --> 00:48:34.365 multiple fractions of this extract
NOTE Confidence: 0.898606856666667
00:48:34.365 --> 00:48:36.680 which is from a plant in Tanzania,
NOTE Confidence: 0.898606856666667
00:48:36.680 --> 00:48:38.924 you can see that actually the
NOTE Confidence: 0.898606856666667
00:48:38.924 --> 00:48:40.420 reporter and endogenous beta
NOTE Confidence: 0.898606856666667
00:48:40.490 --> 00:48:42.768 Catena abundance goes up not down.
NOTE Confidence: 0.898606856666667
00:48:42.768 --> 00:48:44.952 But it is apparently inactive because
NOTE Confidence: 0.898606856666667
00:48:44.952 --> 00:48:47.213 here is X and two which again
NOTE Confidence: 0.898606856666667
00:48:47.213 --> 00:48:48.604 reads out beta catena in activity.
NOTE Confidence: 0.898606856666667

00:48:48.604 --> 00:48:50.280 And when you look under the microscope,
NOTE Confidence: 0.898606856666667

00:48:50.280 --> 00:48:52.786 you can see that this chemicals inducing
NOTE Confidence: 0.898606856666667

00:48:52.786 --> 00:48:55.120 beta catena into go into aggregates.
NOTE Confidence: 0.898606856666667

00:48:55.120 --> 00:48:56.560 So maybe that's not such a bad thing.
NOTE Confidence: 0.898606856666667

00:48:56.560 --> 00:48:58.000 Maybe that's another way
NOTE Confidence: 0.898606856666667

00:48:58.000 --> 00:48:59.428 to inactivate beta catena,
NOTE Confidence: 0.898606856666667

00:48:59.428 --> 00:49:01.552 we'll just drive it into aggregates
NOTE Confidence: 0.898606856666667

00:49:01.552 --> 00:49:02.846 as opposed to destabilizing.
NOTE Confidence: 0.898606856666667

00:49:02.846 --> 00:49:05.440 Now I should point out for this
NOTE Confidence: 0.898606856666667

00:49:05.440 --> 00:49:07.120 chemical and I can't even say
NOTE Confidence: 0.898606856666667

00:49:07.120 --> 00:49:08.394 chemical singular now because
NOTE Confidence: 0.898606856666667

00:49:08.394 --> 00:49:10.039 these are only partially purified.
NOTE Confidence: 0.898606856666667

00:49:10.040 --> 00:49:13.059 I don't know whether this extract or the
NOTE Confidence: 0.898606856666667

00:49:13.059 --> 00:49:15.520 previous extract are going to hit a dead end.
NOTE Confidence: 0.898606856666667

00:49:15.520 --> 00:49:16.695 I can't tell you anything
NOTE Confidence: 0.898606856666667

00:49:16.695 --> 00:49:17.635 yet about true specificity.

NOTE Confidence: 0.898606856666667
00:49:17.640 --> 00:49:19.273 What I can tell you is
NOTE Confidence: 0.898606856666667
00:49:19.273 --> 00:49:20.238 because it's an up assay,
NOTE Confidence: 0.898606856666667
00:49:20.240 --> 00:49:22.838 they're presumably not just rat poison,
NOTE Confidence: 0.898606856666667
00:49:22.840 --> 00:49:24.730 but maybe they are affecting dozens
NOTE Confidence: 0.898606856666667
00:49:24.730 --> 00:49:26.581 if not hundreds of other proteins
NOTE Confidence: 0.898606856666667
00:49:26.581 --> 00:49:28.613 and so that has to be determined.
NOTE Confidence: 0.898606856666667
00:49:28.613 --> 00:49:29.972 So in closing,
NOTE Confidence: 0.898606856666667
00:49:29.972 --> 00:49:33.120 I showed you this a moment ago.
NOTE Confidence: 0.898606856666667
00:49:33.120 --> 00:49:37.760 I I wrote this paper in 2017 and
NOTE Confidence: 0.898606856666667
00:49:37.760 --> 00:49:41.372 it was my attempt to summarize in
NOTE Confidence: 0.898606856666667
00:49:41.372 --> 00:49:45.056 about 8 pages every common mistake
NOTE Confidence: 0.898606856666667
00:49:45.056 --> 00:49:47.820 pitfall artifact I had seen in
NOTE Confidence: 0.898606856666667
00:49:47.820 --> 00:49:49.495 the literature related to target
NOTE Confidence: 0.898606856666667
00:49:49.495 --> 00:49:50.720 identification and validation,
NOTE Confidence: 0.898606856666667
00:49:50.720 --> 00:49:52.052 including by the way some mistakes
NOTE Confidence: 0.898606856666667

00:49:52.052 --> 00:49:53.160 we made along the way.
NOTE Confidence: 0.898606856666667

00:49:53.160 --> 00:49:53.940 We all make mistakes.
NOTE Confidence: 0.898606856666667

00:49:53.940 --> 00:49:55.559 So this may be partially A mea culpa,
NOTE Confidence: 0.898606856666667

00:49:55.560 --> 00:49:57.200 but this was my attempt to
NOTE Confidence: 0.898606856666667

00:49:57.200 --> 00:49:58.160 say we have to do better.
NOTE Confidence: 0.898606856666667

00:49:58.160 --> 00:50:00.029 We can't have our friends in industry
NOTE Confidence: 0.898606856666667

00:50:00.029 --> 00:50:02.145 saying that 50 to 90% of the time
NOTE Confidence: 0.898606856666667

00:50:02.145 --> 00:50:03.720 they can't replicate our findings.
NOTE Confidence: 0.898606856666667

00:50:03.720 --> 00:50:05.152 And so these are some of the controls
NOTE Confidence: 0.898606856666667

00:50:05.152 --> 00:50:06.694 you might want to think about if you're
NOTE Confidence: 0.898606856666667

00:50:06.694 --> 00:50:07.960 doing these types of experiments.
NOTE Confidence: 0.898606856666667

00:50:07.960 --> 00:50:10.291 So the reason I wrote this is my wife
NOTE Confidence: 0.898606856666667

00:50:10.291 --> 00:50:13.079 was a breast cancer surgeon at the Brigham.
NOTE Confidence: 0.898606856666667

00:50:13.080 --> 00:50:14.540 She developed breast cancer.
NOTE Confidence: 0.898606856666667

00:50:14.540 --> 00:50:16.000 She actually self diagnosed
NOTE Confidence: 0.898606856666667

00:50:16.000 --> 00:50:17.960 herself with breast cancer in 2003.

NOTE Confidence: 0.898606856666667
00:50:17.960 --> 00:50:20.101 In fact, Dara Weiner, who's now here,
NOTE Confidence: 0.898606856666667
00:50:20.101 --> 00:50:21.536 was her medical oncologist and
NOTE Confidence: 0.898606856666667
00:50:21.536 --> 00:50:23.039 she survived her breast cancer,
NOTE Confidence: 0.898606856666667
00:50:23.040 --> 00:50:25.365 but she developed an unrelated
NOTE Confidence: 0.898606856666667
00:50:25.365 --> 00:50:26.760 glioblastoma in 2010,
NOTE Confidence: 0.898606856666667
00:50:26.760 --> 00:50:29.105 which took her life in 2015.
NOTE Confidence: 0.898606856666667
00:50:29.105 --> 00:50:30.115 In fact,
NOTE Confidence: 0.898606856666667
00:50:30.115 --> 00:50:32.640 here she is with Catherine
NOTE Confidence: 0.898606856666667
00:50:32.640 --> 00:50:33.960 graduating from Saybrook,
NOTE Confidence: 0.898606856666667
00:50:33.960 --> 00:50:35.280 if you're wondering.
NOTE Confidence: 0.898606856666667
00:50:35.280 --> 00:50:38.617 And Carolyn died about a month or two later.
NOTE Confidence: 0.898606856666667
00:50:38.617 --> 00:50:40.696 In fact, anyone here is a mother
NOTE Confidence: 0.898606856666667
00:50:40.696 --> 00:50:42.840 or has a you all have mothers.
NOTE Confidence: 0.898606856666667
00:50:42.840 --> 00:50:43.390 You know,
NOTE Confidence: 0.898606856666667
00:50:43.390 --> 00:50:43.940 I was.
NOTE Confidence: 0.898606856666667

00:50:43.940 --> 00:50:45.590 I was sure if there was
NOTE Confidence: 0.89679579

00:50:45.662 --> 00:50:48.070 any way Carolyn could live to see
NOTE Confidence: 0.89679579

00:50:48.070 --> 00:50:50.480 her eldest child graduate from Yale,
NOTE Confidence: 0.89679579

00:50:50.480 --> 00:50:51.642 she was going to figure out a
NOTE Confidence: 0.89679579

00:50:51.642 --> 00:50:53.520 way to do it, and she didn't.
NOTE Confidence: 0.89679579

00:50:53.520 --> 00:50:56.198 So I wrote this because if you think
NOTE Confidence: 0.89679579

00:50:56.198 --> 00:50:57.780 it's all about how many papers you
NOTE Confidence: 0.89679579

00:50:57.830 --> 00:50:59.452 publish in Cell, Science or Nature,
NOTE Confidence: 0.89679579

00:50:59.452 --> 00:51:01.156 you think it's all about whether
NOTE Confidence: 0.89679579

00:51:01.156 --> 00:51:03.203 you fooled Reviewer 3 one more time
NOTE Confidence: 0.89679579

00:51:03.203 --> 00:51:04.760 and you slipped another one in,
NOTE Confidence: 0.89679579

00:51:04.760 --> 00:51:06.248 and it's all about what societies
NOTE Confidence: 0.89679579

00:51:06.248 --> 00:51:07.648 you've been elected to, etcetera,
NOTE Confidence: 0.89679579

00:51:07.648 --> 00:51:09.688 please stop, because you're just
NOTE Confidence: 0.89679579

00:51:09.688 --> 00:51:11.320 becoming a dominant negative.
NOTE Confidence: 0.89679579

00:51:11.320 --> 00:51:13.624 The only thing you should care about is

NOTE Confidence: 0.89679579

00:51:13.624 --> 00:51:16.060 whether what I've discovered is so true,

NOTE Confidence: 0.89679579

00:51:16.060 --> 00:51:18.035 so reproducible and so robust,

NOTE Confidence: 0.89679579

00:51:18.040 --> 00:51:19.768 the next group of people can

NOTE Confidence: 0.89679579

00:51:19.768 --> 00:51:21.280 come and build upon that.

NOTE Confidence: 0.89679579

00:51:21.280 --> 00:51:23.000 So if this is all about ego gratification,

NOTE Confidence: 0.89679579

00:51:23.000 --> 00:51:23.496 please, please,

NOTE Confidence: 0.89679579

00:51:23.496 --> 00:51:24.240 please just stop.

NOTE Confidence: 0.89679579

00:51:24.240 --> 00:51:26.816 Because I can tell you everything we had

NOTE Confidence: 0.89679579

00:51:26.816 --> 00:51:29.247 available to treat my wife was based on

NOTE Confidence: 0.89679579

00:51:29.247 --> 00:51:32.199 science that was done 10 or 20 years ago.

NOTE Confidence: 0.89679579

00:51:32.200 --> 00:51:33.915 If God forbid one of our children

NOTE Confidence: 0.89679579

00:51:33.915 --> 00:51:35.357 or grandchildren gets this disease

NOTE Confidence: 0.89679579

00:51:35.357 --> 00:51:36.350 and statistically unfortunately

NOTE Confidence: 0.89679579

00:51:36.350 --> 00:51:37.674 it's likely to happen,

NOTE Confidence: 0.89679579

00:51:37.680 --> 00:51:39.264 they're going to be counting on

NOTE Confidence: 0.89679579

00:51:39.264 --> 00:51:40.560 the science we're doing now.
NOTE Confidence: 0.89679579

00:51:40.560 --> 00:51:42.555 So we have to do much better.
NOTE Confidence: 0.89679579

00:51:42.560 --> 00:51:43.638 So to end on a happy note,
NOTE Confidence: 0.89679579

00:51:43.640 --> 00:51:45.197 because I don't want to end on that note,
NOTE Confidence: 0.89679579

00:51:45.200 --> 00:51:46.200 I showed you these data,
NOTE Confidence: 0.89679579

00:51:46.200 --> 00:51:47.760 these were the data from the
NOTE Confidence: 0.89679579

00:51:47.760 --> 00:51:48.800 phase one two trial.
NOTE Confidence: 0.89679579

00:51:48.800 --> 00:51:51.206 The phase three data were positive
NOTE Confidence: 0.89679579

00:51:51.206 --> 00:51:53.741 and the FDA approved Bel Sudafan
NOTE Confidence: 0.89679579

00:51:53.741 --> 00:51:56.212 for the treatment of sporadic kidney
NOTE Confidence: 0.89679579

00:51:56.212 --> 00:51:58.536 cancer just about a month ago in
NOTE Confidence: 0.89679579

00:51:58.536 --> 00:52:00.988 patients who have failed VEGF inhibitor
NOTE Confidence: 0.89679579

00:52:00.988 --> 00:52:02.732 or immune checkpoint inhibitor.
NOTE Confidence: 0.89679579

00:52:02.732 --> 00:52:05.444 But another truism in medical oncology
NOTE Confidence: 0.89679579

00:52:05.444 --> 00:52:08.093 is most drugs and medical oncology
NOTE Confidence: 0.89679579

00:52:08.093 --> 00:52:10.679 work better in front line settings

NOTE Confidence: 0.89679579

00:52:10.680 --> 00:52:12.087 than in very late lines of settings

NOTE Confidence: 0.89679579

00:52:12.087 --> 00:52:13.283 where you've beaten the patients up

NOTE Confidence: 0.89679579

00:52:13.283 --> 00:52:14.564 and treated them with all sorts of

NOTE Confidence: 0.89679579

00:52:14.605 --> 00:52:15.967 noxious things and you've selected for

NOTE Confidence: 0.89679579

00:52:15.967 --> 00:52:17.142 all sorts of resistance mechanisms.

NOTE Confidence: 0.89679579

00:52:17.142 --> 00:52:18.976 So let's go back to those Von

NOTE Confidence: 0.89679579

00:52:18.976 --> 00:52:20.360 Hippel Lindau disease patients.

NOTE Confidence: 0.89679579

00:52:20.360 --> 00:52:22.040 So these patients developed so many tumors,

NOTE Confidence: 0.89679579

00:52:22.040 --> 00:52:23.790 they're often in careful surveillance

NOTE Confidence: 0.89679579

00:52:23.790 --> 00:52:25.540 programs where they'll get Mris

NOTE Confidence: 0.89679579

00:52:25.598 --> 00:52:27.348 every three to four months in an

NOTE Confidence: 0.89679579

00:52:27.348 --> 00:52:28.632 attempt to delay or prevent the

NOTE Confidence: 0.89679579

00:52:28.632 --> 00:52:29.999 need for repeated surgeries,

NOTE Confidence: 0.89679579

00:52:30.000 --> 00:52:32.320 such as repeated partial nephrectomies,

NOTE Confidence: 0.89679579

00:52:32.320 --> 00:52:34.120 which in the case of partial

NOTE Confidence: 0.89679579

00:52:34.120 --> 00:52:35.320 nephrectomies would leave them

NOTE Confidence: 0.89679579

00:52:35.320 --> 00:52:36.445 eventually functionally anephic.

NOTE Confidence: 0.89679579

00:52:36.445 --> 00:52:39.070 So we were able to convince Peloton

NOTE Confidence: 0.89679579

00:52:39.127 --> 00:52:41.248 and then Merck to treat 61 patients

NOTE Confidence: 0.89679579

00:52:41.248 --> 00:52:42.972 with von Hippelinda disease that

NOTE Confidence: 0.89679579

00:52:42.972 --> 00:52:44.813 had measurable kidney tumors that

NOTE Confidence: 0.89679579

00:52:44.813 --> 00:52:46.478 had never been treated before.

NOTE Confidence: 0.89679579

00:52:46.480 --> 00:52:48.226 They were just in these surveillance

NOTE Confidence: 0.89679579

00:52:48.226 --> 00:52:48.517 programs.

NOTE Confidence: 0.89679579

00:52:48.520 --> 00:52:50.263 So now you can see the the

NOTE Confidence: 0.89679579

00:52:50.263 --> 00:52:51.719 swimmers plots look even better.

NOTE Confidence: 0.89679579

00:52:51.720 --> 00:52:54.753 So once again the dotted line is one year,

NOTE Confidence: 0.89679579

00:52:54.760 --> 00:52:56.584 but now I think you can see that

NOTE Confidence: 0.89679579

00:52:56.584 --> 00:52:58.331 most of the patients are doing

NOTE Confidence: 0.89679579

00:52:58.331 --> 00:53:00.010 well and many of these patients

NOTE Confidence: 0.89679579

00:53:00.010 --> 00:53:02.413 went on to have a partial response.

NOTE Confidence: 0.89679579

00:53:02.413 --> 00:53:05.078 If you prefer waterfall plots

NOTE Confidence: 0.89679579

00:53:05.078 --> 00:53:06.677 then swimmers plots.

NOTE Confidence: 0.89679579

00:53:06.680 --> 00:53:09.488 Here are the changes in the size of

NOTE Confidence: 0.89679579

00:53:09.488 --> 00:53:11.496 the indicator kidney tumors that

NOTE Confidence: 0.89679579

00:53:11.496 --> 00:53:13.272 were the basis of these patients

NOTE Confidence: 0.89679579

00:53:13.272 --> 00:53:14.160 entering the trial.

NOTE Confidence: 0.89679579

00:53:14.160 --> 00:53:15.679 So again, I'm as you now know,

NOTE Confidence: 0.89679579

00:53:15.680 --> 00:53:16.877 I'm a lumpier rather than a splitter.

NOTE Confidence: 0.89679579

00:53:16.880 --> 00:53:19.076 So I would say these are all going down.

NOTE Confidence: 0.812062645

00:53:19.080 --> 00:53:21.280 Some officially meet the criteria

NOTE Confidence: 0.812062645

00:53:21.280 --> 00:53:23.076 for resist response, some don't,

NOTE Confidence: 0.812062645

00:53:23.076 --> 00:53:24.504 but you know frankly if you're

NOTE Confidence: 0.812062645

00:53:24.504 --> 00:53:26.137 the patient as long as the tumor

NOTE Confidence: 0.812062645

00:53:26.137 --> 00:53:27.452 is getting smaller, that's good.

NOTE Confidence: 0.812062645

00:53:27.452 --> 00:53:29.408 We had also done some preclinical

NOTE Confidence: 0.812062645

00:53:29.408 --> 00:53:31.331 modeling that suggested that hip two
NOTE Confidence: 0.812062645

00:53:31.331 --> 00:53:33.583 was important in the blood vessel tumors
NOTE Confidence: 0.812062645

00:53:33.583 --> 00:53:35.438 and here are the hemangioblastoma.
NOTE Confidence: 0.812062645

00:53:35.440 --> 00:53:36.512 So again to be on the trial you
NOTE Confidence: 0.812062645

00:53:36.512 --> 00:53:37.519 had to have a kidney tumor,
NOTE Confidence: 0.812062645

00:53:37.520 --> 00:53:39.164 but you could have other tumors
NOTE Confidence: 0.812062645

00:53:39.164 --> 00:53:40.680 associated with VHL disease as well.
NOTE Confidence: 0.812062645

00:53:40.680 --> 00:53:43.320 So here are the hemangioblastoma shrinking.
NOTE Confidence: 0.812062645

00:53:43.320 --> 00:53:45.160 These patients also develop an
NOTE Confidence: 0.812062645

00:53:45.160 --> 00:53:46.632 unusual neuroendocrine tumor of
NOTE Confidence: 0.812062645

00:53:46.632 --> 00:53:48.398 the pancreas called peanuts.
NOTE Confidence: 0.812062645

00:53:48.400 --> 00:53:52.045 They responded very nicely and
NOTE Confidence: 0.812062645

00:53:52.045 --> 00:53:53.020 perhaps as importantly,
NOTE Confidence: 0.812062645

00:53:53.020 --> 00:53:54.645 I I mentioned these patients
NOTE Confidence: 0.812062645

00:53:54.645 --> 00:53:56.359 were in surveillance programs.
NOTE Confidence: 0.812062645

00:53:56.360 --> 00:53:58.628 So in Gray are the four years

NOTE Confidence: 0.812062645
00:53:58.628 --> 00:54:00.317 of surveillance before going on
NOTE Confidence: 0.812062645
00:54:00.317 --> 00:54:02.585 the HIP 2 inhibitor in green and
NOTE Confidence: 0.812062645
00:54:02.585 --> 00:54:04.039 everywhere you see a circle,
NOTE Confidence: 0.812062645
00:54:04.040 --> 00:54:05.600 a square, a diamond, whatever,
NOTE Confidence: 0.812062645
00:54:05.600 --> 00:54:07.644 that patient's going back to the operating
NOTE Confidence: 0.812062645
00:54:07.644 --> 00:54:10.037 room again to have a kidney tumor removed,
NOTE Confidence: 0.812062645
00:54:10.040 --> 00:54:10.980 an eye tumor removed,
NOTE Confidence: 0.812062645
00:54:10.980 --> 00:54:12.610 the spinal cord removed, tumor removed.
NOTE Confidence: 0.812062645
00:54:12.610 --> 00:54:14.680 And you can see that the,
NOTE Confidence: 0.812062645
00:54:14.680 --> 00:54:17.760 the frequency of the surgery goes way down,
NOTE Confidence: 0.812062645
00:54:17.760 --> 00:54:18.860 doesn't go to 0,
NOTE Confidence: 0.812062645
00:54:18.860 --> 00:54:20.610 but it does go way down.
NOTE Confidence: 0.812062645
00:54:20.610 --> 00:54:22.235 And so based on that,
NOTE Confidence: 0.812062645
00:54:22.240 --> 00:54:23.047 several years ago,
NOTE Confidence: 0.812062645
00:54:23.047 --> 00:54:25.311 the FDA just on the phase two data
NOTE Confidence: 0.812062645

00:54:25.311 --> 00:54:28.012 approved this drug for the treatment of
NOTE Confidence: 0.812062645

00:54:28.012 --> 00:54:31.545 Von Hippel Lindau disease just about 100
NOTE Confidence: 0.812062645

00:54:31.545 --> 00:54:34.025 years after Lindau's initial report.
NOTE Confidence: 0.812062645

00:54:34.025 --> 00:54:35.750 But just because statistics can
NOTE Confidence: 0.812062645

00:54:35.750 --> 00:54:37.639 sometimes be a little bit dry,
NOTE Confidence: 0.812062645

00:54:37.640 --> 00:54:39.960 to put a bit of a human face on this,
NOTE Confidence: 0.812062645

00:54:39.960 --> 00:54:41.948 we actually knew the trial was going
NOTE Confidence: 0.812062645

00:54:41.948 --> 00:54:44.175 to be positive long before any public
NOTE Confidence: 0.812062645

00:54:44.175 --> 00:54:45.820 presentation of the data because
NOTE Confidence: 0.812062645

00:54:45.820 --> 00:54:47.845 the VHL patients were posting on
NOTE Confidence: 0.812062645

00:54:47.845 --> 00:54:49.814 their social media pages They were doing.
NOTE Confidence: 0.812062645

00:54:49.814 --> 00:54:51.122 And you can imagine these patients
NOTE Confidence: 0.812062645

00:54:51.122 --> 00:54:52.369 have lived with the Sword of
NOTE Confidence: 0.812062645

00:54:52.369 --> 00:54:53.560 Damocles over their neck or hey,
NOTE Confidence: 0.812062645

00:54:53.560 --> 00:54:54.816 whatever the expression is,
NOTE Confidence: 0.812062645

00:54:54.816 --> 00:54:56.386 because they've watched this disease

NOTE Confidence: 0.812062645

00:54:56.386 --> 00:54:57.882 ravage their families generation

NOTE Confidence: 0.812062645

00:54:57.882 --> 00:54:59.398 after generation after generation.

NOTE Confidence: 0.812062645

00:54:59.400 --> 00:55:00.816 And they just assume they're going

NOTE Confidence: 0.812062645

00:55:00.816 --> 00:55:02.240 to probably die sometime in midlife.

NOTE Confidence: 0.812062645

00:55:02.240 --> 00:55:03.836 So here's a VHL patient saying,

NOTE Confidence: 0.812062645

00:55:03.840 --> 00:55:05.478 I never thought I'd see this day.

NOTE Confidence: 0.812062645

00:55:05.480 --> 00:55:07.080 And they're describing their tumors

NOTE Confidence: 0.812062645

00:55:07.080 --> 00:55:08.520 getting smaller, being stable,

NOTE Confidence: 0.812062645

00:55:08.520 --> 00:55:10.834 or in some cases disappearing entirely.

NOTE Confidence: 0.812062645

00:55:10.834 --> 00:55:12.718 And since everyone likes a movie,

NOTE Confidence: 0.812062645

00:55:12.720 --> 00:55:13.680 I was sent a vlog.

NOTE Confidence: 0.812062645

00:55:13.680 --> 00:55:15.374 I didn't know what a vlog was

NOTE Confidence: 0.812062645

00:55:15.374 --> 00:55:16.758 until this was sent to me,

NOTE Confidence: 0.812062645

00:55:16.760 --> 00:55:18.710 but I do have permission to

NOTE Confidence: 0.812062645

00:55:18.710 --> 00:55:19.890 show this patient's face.

NOTE Confidence: 0.812062645

00:55:19.890 --> 00:55:21.215 But this is another patient
NOTE Confidence: 0.812062645

00:55:21.215 --> 00:55:22.600 who was on that trial.
NOTE Confidence: 0.812062645

00:55:22.600 --> 00:55:23.052 Hey everybody,
NOTE Confidence: 0.812062645

00:55:23.052 --> 00:55:23.504 it's Justin,
NOTE Confidence: 0.812062645

00:55:23.504 --> 00:55:25.720 And I just wanted to give you a quick update.
NOTE Confidence: 0.812062645

00:55:25.720 --> 00:55:29.262 I am in a gondola right now in Taiwan.
NOTE Confidence: 0.812062645

00:55:29.262 --> 00:55:33.399 Over there is Taipei One O 1.
NOTE Confidence: 0.812062645

00:55:33.400 --> 00:55:35.575 The gondola is actually right
NOTE Confidence: 0.812062645

00:55:35.575 --> 00:55:37.315 by the Taipei Zoo,
NOTE Confidence: 0.812062645

00:55:37.320 --> 00:55:39.056 but I just wanted to give you a
NOTE Confidence: 0.812062645

00:55:39.056 --> 00:55:40.679 quick update and say I'm doing well.
NOTE Confidence: 0.812062645

00:55:40.680 --> 00:55:42.492 I'm enjoying my trip.
NOTE Confidence: 0.812062645

00:55:42.492 --> 00:55:45.636 If it wasn't for the PT2977 drug trial,
NOTE Confidence: 0.812062645

00:55:45.636 --> 00:55:48.284 I would have never been able to come out
NOTE Confidence: 0.812062645

00:55:48.284 --> 00:55:50.436 here and do what I'm doing right now.
NOTE Confidence: 0.812062645

00:55:50.440 --> 00:55:52.799 So I just wanted to thank Peloton

NOTE Confidence: 0.812062645

00:55:52.799 --> 00:55:55.454 and I hope Mark will fast track

NOTE Confidence: 0.812062645

00:55:55.454 --> 00:55:57.800 this drug for a VHL treatment.

NOTE Confidence: 0.763883952857143

00:55:57.800 --> 00:55:59.914 So if you guys are listed in,

NOTE Confidence: 0.763883952857143

00:55:59.920 --> 00:56:01.312 hopefully you guys will

NOTE Confidence: 0.763883952857143

00:56:01.312 --> 00:56:03.400 put on market to help VHL.

NOTE Confidence: 0.763883952857143

00:56:03.400 --> 00:56:06.735 But yeah, keep watching these videos.

NOTE Confidence: 0.763883952857143

00:56:06.735 --> 00:56:07.960 I'll be making more and

NOTE Confidence: 0.763883952857143

00:56:07.960 --> 00:56:09.079 I'll get better at it.

NOTE Confidence: 0.763883952857143

00:56:09.080 --> 00:56:10.488 And I have to get the angles right

NOTE Confidence: 0.763883952857143

00:56:10.488 --> 00:56:12.920 because they kind of look fat, you know?

NOTE Confidence: 0.763883952857143

00:56:12.920 --> 00:56:13.740 Anyway, so, so I.

NOTE Confidence: 0.763883952857143

00:56:13.740 --> 00:56:15.624 So I love that because that tells me

NOTE Confidence: 0.763883952857143

00:56:15.624 --> 00:56:17.436 he's back through his premorbid personality.

NOTE Confidence: 0.763883952857143

00:56:17.440 --> 00:56:18.680 Because at that age,

NOTE Confidence: 0.763883952857143

00:56:18.680 --> 00:56:20.540 your biggest concern should be whether

NOTE Confidence: 0.763883952857143

00:56:20.594 --> 00:56:22.314 you look fat on your blog and not
NOTE Confidence: 0.763883952857143

00:56:22.314 --> 00:56:24.069 how bad your MRI might look next
NOTE Confidence: 0.763883952857143

00:56:24.069 --> 00:56:25.683 time around and your doctor telling
NOTE Confidence: 0.763883952857143

00:56:25.683 --> 00:56:27.540 you to get your affairs in order.
NOTE Confidence: 0.763883952857143

00:56:27.540 --> 00:56:28.320 So with that,
NOTE Confidence: 0.763883952857143

00:56:28.320 --> 00:56:29.600 I thank you very much for your attention.
NOTE Confidence: 0.763883952857143

00:56:29.600 --> 00:56:30.800 I'm happy to take questions.
NOTE Confidence: 0.3983846

00:56:43.440 --> 00:56:43.720 Yes.
NOTE Confidence: 0.840521202

00:56:54.280 --> 00:56:55.440 Yeah, that's a great question.
NOTE Confidence: 0.840521202

00:56:55.440 --> 00:56:56.595 So we talk about this a lot.
NOTE Confidence: 0.840521202

00:56:56.600 --> 00:56:57.600 So the question relates to,
NOTE Confidence: 0.840521202

00:56:57.600 --> 00:56:58.620 in principle then,
NOTE Confidence: 0.840521202

00:56:58.620 --> 00:57:01.000 if you had a Hip 2 inhibitor,
NOTE Confidence: 0.840521202

00:57:01.000 --> 00:57:02.602 you would down regulate the expression
NOTE Confidence: 0.840521202

00:57:02.602 --> 00:57:05.482 of the ZR VS and that might make immune
NOTE Confidence: 0.840521202

00:57:05.482 --> 00:57:07.237 checkpoint inhibitor therapy work worse.

NOTE Confidence: 0.840521202

00:57:07.240 --> 00:57:09.240 And so maybe the combination

NOTE Confidence: 0.840521202

00:57:09.240 --> 00:57:10.840 would actually be antagonistic.

NOTE Confidence: 0.840521202

00:57:10.840 --> 00:57:12.343 I think we just have to do the clinical

NOTE Confidence: 0.840521202

00:57:12.343 --> 00:57:13.517 trial that that is a prediction.

NOTE Confidence: 0.840521202

00:57:13.520 --> 00:57:14.978 And so I won't be completely

NOTE Confidence: 0.840521202

00:57:14.978 --> 00:57:16.319 surprised if that's what we see.

NOTE Confidence: 0.840521202

00:57:16.320 --> 00:57:17.488 On the other hand,

NOTE Confidence: 0.840521202

00:57:17.488 --> 00:57:19.240 as I'm sure you well appreciate,

NOTE Confidence: 0.840521202

00:57:19.240 --> 00:57:21.170 there's so many benefits from

NOTE Confidence: 0.840521202

00:57:21.170 --> 00:57:23.100 combining 2 drugs that have

NOTE Confidence: 0.840521202

00:57:23.177 --> 00:57:25.162 distinct mechanisms of action in

NOTE Confidence: 0.840521202

00:57:25.162 --> 00:57:26.896 terms of treating or preventing

NOTE Confidence: 0.840521202

00:57:26.896 --> 00:57:28.456 resistance that I still wonder

NOTE Confidence: 0.840521202

00:57:28.456 --> 00:57:30.305 whether the benefits of having two

NOTE Confidence: 0.840521202

00:57:30.305 --> 00:57:31.770 drugs with very distinct mechanisms

NOTE Confidence: 0.840521202

00:57:31.770 --> 00:57:33.363 of action would outweigh this
NOTE Confidence: 0.840521202

00:57:33.363 --> 00:57:34.923 theoretical concern that in some
NOTE Confidence: 0.840521202

00:57:34.923 --> 00:57:36.448 cases they would be antagonistic.
NOTE Confidence: 0.840521202

00:57:36.448 --> 00:57:38.549 I can also imagine there might be
NOTE Confidence: 0.840521202

00:57:38.549 --> 00:57:40.421 some games you could do in terms of
NOTE Confidence: 0.840521202

00:57:40.421 --> 00:57:42.118 timing that might also be helpful.
NOTE Confidence: 0.840521202

00:57:42.120 --> 00:57:42.400 There
NOTE Confidence: 0.501148141666667

00:57:45.720 --> 00:57:47.118 is. There is that a student?
NOTE Confidence: 0.501148141666667

00:57:47.120 --> 00:57:47.800 Well, students should always
NOTE Confidence: 0.501148141666667

00:57:47.800 --> 00:57:48.936 go first if that. I can't,
NOTE Confidence: 0.501148141666667

00:57:48.936 --> 00:57:50.760 It's so dark back there I can't tell.
NOTE Confidence: 0.501148141666667

00:57:50.760 --> 00:57:51.993 This could be the Dean for all I know,
NOTE Confidence: 0.501148141666667

00:57:52.000 --> 00:57:53.840 but I this no, it's not the Dean.
NOTE Confidence: 0.501148141666667

00:57:53.840 --> 00:57:55.478 I'm quite sure now that I see the beard,
NOTE Confidence: 0.501148141666667

00:57:55.480 --> 00:57:57.040 it's not the Dean, but anyway
NOTE Confidence: 0.757077424117647

00:58:09.560 --> 00:58:11.936 yeah so. So let me do a medical student

NOTE Confidence: 0.757077424117647

00:58:11.936 --> 00:58:14.185 trick and answer a related question

NOTE Confidence: 0.757077424117647

00:58:14.185 --> 00:58:15.604 before answering your question.

NOTE Confidence: 0.757077424117647

00:58:15.604 --> 00:58:18.758 So one is I I I do think hip and

NOTE Confidence: 0.757077424117647

00:58:18.758 --> 00:58:20.424 and in particular hip too is part

NOTE Confidence: 0.757077424117647

00:58:20.424 --> 00:58:22.477 of the reason these Ervs are up

NOTE Confidence: 0.757077424117647

00:58:22.477 --> 00:58:23.992 regulated in the kidney tumors,

NOTE Confidence: 0.757077424117647

00:58:24.000 --> 00:58:25.280 but I don't think it's the only reason.

NOTE Confidence: 0.757077424117647

00:58:25.280 --> 00:58:28.885 So I also think there are widespread

NOTE Confidence: 0.757077424117647

00:58:28.885 --> 00:58:31.030 abnormalities and DNA and histone

NOTE Confidence: 0.757077424117647

00:58:31.030 --> 00:58:32.880 methylation and the kidney tumors

NOTE Confidence: 0.757077424117647

00:58:32.880 --> 00:58:35.679 that I think is creating a permissive

NOTE Confidence: 0.757077424117647

00:58:35.680 --> 00:58:37.248 environment for the expression.

NOTE Confidence: 0.757077424117647

00:58:37.248 --> 00:58:40.004 And we know this is true because

NOTE Confidence: 0.757077424117647

00:58:40.004 --> 00:58:42.084 for some of the Ervs HIP only

NOTE Confidence: 0.757077424117647

00:58:42.084 --> 00:58:43.638 regulates them if we add a DNA

NOTE Confidence: 0.757077424117647

00:58:43.638 --> 00:58:44.784 methyl transferase inhibitor and
NOTE Confidence: 0.757077424117647

00:58:44.784 --> 00:58:46.814 then you could see the creation of
NOTE Confidence: 0.757077424117647

00:58:46.866 --> 00:58:48.554 a hip binding site next to the ERB.
NOTE Confidence: 0.757077424117647

00:58:48.560 --> 00:58:50.864 So I think it's an interplay of HIP and
NOTE Confidence: 0.757077424117647

00:58:50.864 --> 00:58:52.560 a permissive epigenetic environment.
NOTE Confidence: 0.757077424117647

00:58:52.560 --> 00:58:53.400 Now I think you're asking,
NOTE Confidence: 0.757077424117647

00:58:53.400 --> 00:58:54.000 OK, that's fine,
NOTE Confidence: 0.757077424117647

00:58:54.000 --> 00:58:55.200 but if these things aren't regulated,
NOTE Confidence: 0.757077424117647

00:58:55.200 --> 00:58:57.996 why doesn't the endogenous immune system,
NOTE Confidence: 0.757077424117647

00:58:58.000 --> 00:58:59.640 oh and it's one other thing so far
NOTE Confidence: 0.757077424117647

00:58:59.640 --> 00:59:01.083 every time we've looked with these
NOTE Confidence: 0.757077424117647

00:59:01.083 --> 00:59:02.559 do seem to be tumor restricted
NOTE Confidence: 0.757077424117647

00:59:02.608 --> 00:59:03.838 and not seen in the normal.
NOTE Confidence: 0.757077424117647

00:59:03.840 --> 00:59:04.278 But you still,
NOTE Confidence: 0.757077424117647

00:59:04.278 --> 00:59:05.154 I think you're asking the question,
NOTE Confidence: 0.757077424117647

00:59:05.160 --> 00:59:05.865 well that's fine,

NOTE Confidence: 0.757077424117647
00:59:05.865 --> 00:59:07.275 but why doesn't the immune system
NOTE Confidence: 0.757077424117647
00:59:07.280 --> 00:59:08.540 recognize these kidney tumors
NOTE Confidence: 0.757077424117647
00:59:08.540 --> 00:59:10.115 that already have the Erbs?
NOTE Confidence: 0.757077424117647
00:59:10.120 --> 00:59:12.560 So that's a question for people like David.
NOTE Confidence: 0.757077424117647
00:59:12.560 --> 00:59:15.315 I walk around thinking that the
NOTE Confidence: 0.757077424117647
00:59:15.315 --> 00:59:17.800 T cells that we needed or wanted
NOTE Confidence: 0.757077424117647
00:59:17.800 --> 00:59:19.718 eventually lost that they became
NOTE Confidence: 0.757077424117647
00:59:19.718 --> 00:59:21.964 exhausted and that the tumor use
NOTE Confidence: 0.757077424117647
00:59:21.964 --> 00:59:23.774 various molecular signals and tricks
NOTE Confidence: 0.757077424117647
00:59:23.774 --> 00:59:26.188 to either obey the immune system or
NOTE Confidence: 0.757077424117647
00:59:26.188 --> 00:59:28.078 or to cripple the immune system.
NOTE Confidence: 0.757077424117647
00:59:28.080 --> 00:59:29.280 So I'm hoping that,
NOTE Confidence: 0.757077424117647
00:59:29.280 --> 00:59:29.880 you know,
NOTE Confidence: 0.757077424117647
00:59:29.880 --> 00:59:30.932 the immune checkpoint inhibitors
NOTE Confidence: 0.757077424117647
00:59:30.932 --> 00:59:32.803 are just the foot in the door
NOTE Confidence: 0.757077424117647

00:59:32.803 --> 00:59:34.267 to having better and better and
NOTE Confidence: 0.757077424117647

00:59:34.267 --> 00:59:35.827 better agents to allow the immune
NOTE Confidence: 0.757077424117647

00:59:35.827 --> 00:59:37.375 system to once again recognize the
NOTE Confidence: 0.757077424117647

00:59:37.375 --> 00:59:39.160 kind of things that they probably
NOTE Confidence: 0.757077424117647

00:59:39.160 --> 00:59:41.320 should have been able to recognize.
NOTE Confidence: 0.757077424117647

00:59:41.320 --> 00:59:41.920 Is that, is that OK,
NOTE Confidence: 0.757077424117647

00:59:41.920 --> 00:59:45.340 David, That is all right.
NOTE Confidence: 0.757077424117647

00:59:45.340 --> 00:59:46.840 Yeah, Yeah, yeah. Acceptable answer.
NOTE Confidence: 0.757077424117647

00:59:46.840 --> 00:59:47.200 He said good
NOTE Confidence: 0.478162651666667

00:59:49.240 --> 00:59:51.076 question about the other, the secondary.
NOTE Confidence: 0.526713168333333

00:59:53.240 --> 00:59:55.740 Yeah. So how about the
NOTE Confidence: 0.526713168333333

00:59:55.740 --> 00:59:59.012 occupation in bad competition?
NOTE Confidence: 0.526713168333333

00:59:59.012 --> 01:00:00.476 How does that practice?
NOTE Confidence: 0.526713168333333

01:00:00.480 --> 01:00:02.118 Yeah, so Chin's asking and I didn't
NOTE Confidence: 0.526713168333333

01:00:02.118 --> 01:00:03.520 make this point that VHL loss,
NOTE Confidence: 0.526713168333333

01:00:03.520 --> 01:00:04.532 although it's a critical

NOTE Confidence: 0.526713168333333

01:00:04.532 --> 01:00:05.797 first step in kidney cancer,

NOTE Confidence: 0.526713168333333

01:00:05.800 --> 01:00:07.756 is not sufficient for kidney cancer.

NOTE Confidence: 0.526713168333333

01:00:07.760 --> 01:00:09.100 You need other cooperating.

NOTE Confidence: 0.526713168333333

01:00:09.100 --> 01:00:11.416 Mutations such as in genes like PBRM

NOTE Confidence: 0.526713168333333

01:00:11.416 --> 01:00:13.600 One and BAP One and other other genes,

NOTE Confidence: 0.526713168333333

01:00:13.600 --> 01:00:15.400 many of which are involved

NOTE Confidence: 0.526713168333333

01:00:15.400 --> 01:00:16.480 in epigenetic regulation.

NOTE Confidence: 0.526713168333333

01:00:16.480 --> 01:00:18.195 In the case of PBRM One loss,

NOTE Confidence: 0.526713168333333

01:00:18.200 --> 01:00:20.513 we and others have shown that PBRM One loss,

NOTE Confidence: 0.526713168333333

01:00:20.520 --> 01:00:21.340 if anything,

NOTE Confidence: 0.526713168333333

01:00:21.340 --> 01:00:23.800 amplifies the hip activity even further.

NOTE Confidence: 0.526713168333333

01:00:23.800 --> 01:00:25.150 I'm not convinced that's true

NOTE Confidence: 0.526713168333333

01:00:25.150 --> 01:00:27.518 for BAP One and so we are trying

NOTE Confidence: 0.526713168333333

01:00:27.518 --> 01:00:28.798 to understand the biochemistry

NOTE Confidence: 0.526713168333333

01:00:28.798 --> 01:00:30.750 of the other gene products that

NOTE Confidence: 0.526713168333333

01:00:30.750 --> 01:00:32.026 are altered in kidney cancer.
NOTE Confidence: 0.526713168333333

01:00:32.026 --> 01:00:33.600 But I think in the case of PBRM One,
NOTE Confidence: 0.526713168333333

01:00:33.600 --> 01:00:35.154 it is partly about amping up
NOTE Confidence: 0.526713168333333

01:00:35.154 --> 01:00:36.720 even further the hip response.
NOTE Confidence: 0.38754156

01:00:38.920 --> 01:00:39.240 Yes,
NOTE Confidence: 0.44978255

01:00:42.920 --> 01:00:44.480 yes. So
NOTE Confidence: 0.640448085

01:00:54.440 --> 01:00:54.840 I'm wondering,
NOTE Confidence: 0.848982355909091

01:01:05.640 --> 01:01:08.385 I, I, I do in fact another thing we
NOTE Confidence: 0.848982355909091

01:01:08.385 --> 01:01:10.378 occasionally see and this is another
NOTE Confidence: 0.848982355909091

01:01:10.378 --> 01:01:12.639 old idea that's coming back in vogue.
NOTE Confidence: 0.848982355909091

01:01:12.640 --> 01:01:14.456 You know there are a lot of examples
NOTE Confidence: 0.848982355909091

01:01:14.456 --> 01:01:16.298 where we know in the cancer a
NOTE Confidence: 0.848982355909091

01:01:16.298 --> 01:01:17.633 certain oncogene signal is high.
NOTE Confidence: 0.848982355909091

01:01:17.640 --> 01:01:18.636 You know, we'll call it MIC,
NOTE Confidence: 0.848982355909091

01:01:18.640 --> 01:01:19.696 we'll call it E2F.
NOTE Confidence: 0.848982355909091

01:01:19.696 --> 01:01:21.626 And so the knee jerk response usually

NOTE Confidence: 0.848982355909091

01:01:21.626 --> 01:01:23.914 when we see an oncogenic signal very high

NOTE Confidence: 0.848982355909091

01:01:23.914 --> 01:01:26.077 is to try to inhibit it with a drug.

NOTE Confidence: 0.848982355909091

01:01:26.080 --> 01:01:28.128 But there's their data that go back 20

NOTE Confidence: 0.848982355909091

01:01:28.128 --> 01:01:30.771 or 30 years ago that show in some cases

NOTE Confidence: 0.848982355909091

01:01:30.771 --> 01:01:32.842 these cancers are just at the brink

NOTE Confidence: 0.848982355909091

01:01:32.842 --> 01:01:34.866 of apoptosis that if you could drive

NOTE Confidence: 0.848982355909091

01:01:34.866 --> 01:01:37.634 the oncogenic signal up even a little higher,

NOTE Confidence: 0.848982355909091

01:01:37.640 --> 01:01:39.024 the cells would die.

NOTE Confidence: 0.848982355909091

01:01:39.024 --> 01:01:40.754 So paradoxically in some cases,

NOTE Confidence: 0.848982355909091

01:01:40.760 --> 01:01:42.794 the answer I think is you want this oncogene,

NOTE Confidence: 0.848982355909091

01:01:42.800 --> 01:01:43.904 I'm going to give you so

NOTE Confidence: 0.848982355909091

01:01:43.904 --> 01:01:44.640 much of this oncogene,

NOTE Confidence: 0.848982355909091

01:01:44.640 --> 01:01:45.756 you're going to choke on it.

NOTE Confidence: 0.848982355909091

01:01:45.760 --> 01:01:47.916 So we have seen in certain settings

NOTE Confidence: 0.848982355909091

01:01:47.916 --> 01:01:49.719 using CRISPR A where further

NOTE Confidence: 0.848982355909091

01:01:49.719 --> 01:01:51.754 activation of a professional oncogene

NOTE Confidence: 0.848982355909091

01:01:51.754 --> 01:01:54.063 in that cancer causes cell death

NOTE Confidence: 0.848982355909091

01:01:54.063 --> 01:01:56.115 and you delete the CRISPR guide.

NOTE Confidence: 0.848982355909091

01:01:56.120 --> 01:01:58.040 So I think that's And so now

NOTE Confidence: 0.848982355909091

01:01:58.040 --> 01:01:58.840 we get into semantics.

NOTE Confidence: 0.848982355909091

01:01:58.840 --> 01:02:00.040 I think that is a form

NOTE Confidence: 0.848982355909091

01:02:00.040 --> 01:02:00.640 of synthetic lethality.

NOTE Confidence: 0.848982355909091

01:02:00.640 --> 01:02:02.474 If you knew there was a target

NOTE Confidence: 0.848982355909091

01:02:02.480 --> 01:02:04.220 that when inhibited further

NOTE Confidence: 0.848982355909091

01:02:04.220 --> 01:02:05.960 activated the Aqua gene.

NOTE Confidence: 0.946145264

01:02:13.260 --> 01:02:14.660 People have work to do,

NOTE Confidence: 0.946145264

01:02:14.660 --> 01:02:15.192 We should let them.

NOTE Confidence: 0.946145264

01:02:15.192 --> 01:02:15.857 We should let them go.

NOTE Confidence: 0.946145264

01:02:15.860 --> 01:02:17.996 All right. Thank you very much.