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

 $00:00:04.040 \longrightarrow 00:00:04.908$ 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

 $00:00:07.060 \longrightarrow 00:00:08.385$ 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

 $00:00:09.840 \dashrightarrow 00:00:12.336$ and Doctor Caitlin was our choice

NOTE Confidence: 0.844721467142857

 $00:00:12.336 \rightarrow 00:00:14.560$ for graduate student grand rounds.

NOTE Confidence: 0.844721467142857

 $00:00:14.560 \rightarrow 00:00:16.300$ 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

 $00:00:17.920 \dashrightarrow 00:00:19.840$ and we're very happy to have him here.

NOTE Confidence: 0.844721467142857

 $00:00:19.840 \longrightarrow 00:00:21.490$ So I just wanted to give

NOTE Confidence: 0.844721467142857

 $00:00:21.490 \longrightarrow 00:00:22.315$ a brief introduction.

00:00:22.320 --> 00:00:23.860 So Doctor William G Caitlin

NOTE Confidence: 0.844721467142857

 $00{:}00{:}23.860 \dashrightarrow 00{:}00{:}25.400$ 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 $\operatorname{-->}$ 00:00:30.781 He also began his research career when

NOTE Confidence: 0.844721467142857

 $00{:}00{:}30{.}781 \dashrightarrow 00{:}00{:}32{.}486$ Doctor Kalin questioned his research

NOTE Confidence: 0.844721467142857

 $00:00:32.486 \rightarrow 00:00:34.320$ mentors assumptions on a project.

NOTE Confidence: 0.844721467142857

 $00{:}00{:}34.320 \dashrightarrow 00{:}00{:}36.300$ The mentor wrote that Mister Kalin

NOTE Confidence: 0.844721467142857

 $00{:}00{:}36{.}300 \dashrightarrow 00{:}00{:}39{.}302$ appears to be a bright young man whose

NOTE Confidence: 0.844721467142857

 $00:00:39.302 \rightarrow 00:00:41.720$ future lies outside of the laboratory.

NOTE Confidence: 0.844721467142857

 $00:00:41.720 \longrightarrow 00:00:42.000$ Dr.

NOTE Confidence: 0.844721467142857

00:00:42.000 --> 00:00:43.120 Kalin remained at Duke

NOTE Confidence: 0.844721467142857

 $00:00:43.120 \longrightarrow 00:00:44.240$ for his medical degree,

NOTE Confidence: 0.844721467142857

 $00:00:44.240 \longrightarrow 00:00:45.986$ where he first read about tumor

NOTE Confidence: 0.844721467142857

 $00:00:45.986 \longrightarrow 00:00:47.150$ 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
- $00:00:50.292 \rightarrow 00:00:52.710$ and learn more about the rapidly
- NOTE Confidence: 0.844721467142857
- $00:00:52.789 \rightarrow 00:00:55.599$ 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
- $00{:}00{:}56{.}964 \dashrightarrow 00{:}00{:}58{.}328$ 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
- $00{:}00{:}59{.}840 \dashrightarrow 00{:}01{:}01{.}496$ where he served as an Assistant
- NOTE Confidence: 0.844721467142857
- 00:01:01.496 --> 00:01:02.600 Chief 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
- $00:01:06.484 \rightarrow 00:01:07.760$ trainees who questions authority,
- NOTE Confidence: 0.844721467142857
- $00:01:07.760 \longrightarrow 00:01:09.344$ and in part because of the
- NOTE Confidence: 0.844721467142857
- $00{:}01{:}09{.}344 \dashrightarrow 00{:}01{:}10{.}833$ 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

 $00:01:13.284 \rightarrow 00:01:14.704$ 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

 $00{:}01{:}16{.}240 \dashrightarrow 00{:}01{:}18{.}431$ where he determined the T and E1A

NOTE Confidence: 0.844721467142857

 $00:01:18.431 \longrightarrow 00:01:20.421$ binding site of the RV protein

NOTE Confidence: 0.844721467142857

 $00{:}01{:}20{.}421 \dashrightarrow 00{:}01{:}22{.}377$ and helped identify E2F as a

NOTE Confidence: 0.844721467142857

 $00{:}01{:}22.377 \dashrightarrow 00{:}01{:}24.439$ binding partner of the RV protein.

NOTE Confidence: 0.844721467142857

 $00:01:24.440 \longrightarrow 00:01:25.950$ He began his faculty position

NOTE Confidence: 0.844721467142857

 $00:01:25.950 \rightarrow 00:01:26.554$ shortly thereafter.

NOTE Confidence: 0.844721467142857

 $00{:}01{:}26.560 \dashrightarrow 00{:}01{:}27.808$ Just down the hall,

NOTE Confidence: 0.844721467142857

 $00{:}01{:}27.808 \dashrightarrow 00{:}01{:}29.680$ his research focus turned to VHL,

NOTE Confidence: 0.844721467142857

 $00:01:29.680 \longrightarrow 00:01:31.756$ the topic of today's grand rounds.

NOTE Confidence: 0.844721467142857

 $00:01:31.760 \longrightarrow 00:01:33.410$ 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

 $00{:}01{:}35{.}840 \dashrightarrow 00{:}01{:}37{.}360$ please welcome Doctor Bill Kalin.

NOTE Confidence: 0.847872936

 $00:01:44.520 \longrightarrow 00:01:45.336$ Well, thank you.

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

NOTE Confidence: 0.847872936

 $00:01:47.235 \longrightarrow 00:01:49.280$ introduction and thank you to all the

NOTE Confidence: 0.847872936

 $00{:}01{:}49{.}280 \dashrightarrow 00{:}01{:}50{.}925$ 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

 $00{:}01{:}53.716 \dashrightarrow 00{:}01{:}56.299$ the Cancer Center in South Dakota and

NOTE Confidence: 0.847872936

 $00:01:56.299 \rightarrow 00:01:58.573$ at dinner the faculty confessed that

NOTE Confidence: 0.847872936

 $00:01:58.573 \rightarrow 00:02:02.080$ they said we knew if the faculty invited you,

NOTE Confidence: 0.847872936

 $00:02:02.080 \dashrightarrow 00:02:03.400$ you weren't coming to South Dakota.

NOTE Confidence: 0.847872936

 $00:02:03.400 \dashrightarrow 00:02:05.836$ But if the graduate students invited you,

NOTE Confidence: 0.847872936

 $00{:}02{:}05{.}840 \dashrightarrow 00{:}02{:}07{.}776$ you are on the next plane when there's

NOTE Confidence: 0.847872936

 $00{:}02{:}07{.}776 \dashrightarrow 00{:}02{:}09{.}854$ some some element of truth that but I

NOTE Confidence: 0.847872936

 $00{:}02{:}09.854 \dashrightarrow 00{:}02{:}11.781$ would have come whether the faculty or NOTE Confidence: 0.847872936

 $00:02:11.781 \rightarrow 00:02:13.755$ the graduate students at Yale invited me.

NOTE Confidence: 0.847872936

 $00{:}02{:}13.760 \dashrightarrow 00{:}02{:}15.176$ So it's it's, it's quite fashionable

NOTE Confidence: 0.847872936

 $00:02:15.176 \dashrightarrow 00:02:16.959$ now to have these disclosure slides,

 $00:02:16.960 \longrightarrow 00:02:18.752$ but often I find that people leave

NOTE Confidence: 0.847872936

 $00:02:18.752 \longrightarrow 00:02:20.560$ them up for literally 2 seconds.

NOTE Confidence: 0.847872936

 $00:02:20.560 \longrightarrow 00:02:21.520$ So it's like subliminal.

NOTE Confidence: 0.847872936

 $00:02:21.520 \dashrightarrow 00:02:22.798$ So that's why I sort of leave it up.

NOTE Confidence: 0.847872936

 $00:02:22.800 \longrightarrow 00:02:25.040$ So you all digested this.

NOTE Confidence: 0.847872936

 $00{:}02{:}25{.}040 \dashrightarrow 00{:}02{:}27{.}314$ So here are the people who've

NOTE Confidence: 0.847872936

 $00{:}02{:}27{.}314 \dashrightarrow 00{:}02{:}29{.}999$ worked on Von HIPAA Lindau disease

NOTE Confidence: 0.847872936

 $00:02:30.000 \rightarrow 00:02:31.116$ over the years of my laboratory,

NOTE Confidence: 0.847872936

 $00{:}02{:}31{.}120 \dashrightarrow 00{:}02{:}33{.}958$ including your very own Chin Yan.

NOTE Confidence: 0.847872936

 $00:02:33.960 \longrightarrow 00:02:36.024$ And here's a list of some of our

NOTE Confidence: 0.847872936

 $00{:}02{:}36{.}024 \dashrightarrow 00{:}02{:}37{.}789$ 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

 $00:02:39.937 \dashrightarrow 00:02:41.959$ including your very own David Brown.

NOTE Confidence: 0.847872936

 $00:02:41.960 \longrightarrow 00:02:43.425$ I might mention we're also

NOTE Confidence: 0.847872936

 $00{:}02{:}43.425 \dashrightarrow 00{:}02{:}44.597$ collaborating with Joe Contessa,

NOTE Confidence: 0.847872936

 $00:02:44.600 \rightarrow 00:02:45.476$ but in the interest of time,

- NOTE Confidence: 0.847872936
- $00:02:45.480 \longrightarrow 00:02:50.880$ 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
- $00{:}02{:}59{.}560 \dashrightarrow 00{:}03{:}02{.}352$ 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
- $00:03:05.560 \longrightarrow 00:03:07.425$ who was on your national
- NOTE Confidence: 0.847872936
- $00:03:07.425 \longrightarrow 00:03:08.522$ championship squash team.
- NOTE Confidence: 0.847872936
- $00:03:08.522 \dashrightarrow 00:03:10.688$ So obviously he got his athletic
- NOTE Confidence: 0.847872936
- $00:03:10.688 \longrightarrow 00:03:12.159$ ability from his mother.
- NOTE Confidence: 0.847872936
- $00{:}03{:}12{.}160 \dashrightarrow 00{:}03{:}15{.}140$ So he was class of 2018, and I'll
- NOTE Confidence: 0.847872936
- $00:03:15.140 \longrightarrow 00:03:19.730$ 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
- $00:03:28.000 \longrightarrow 00:03:30.140$ entering the hall at the
- NOTE Confidence: 0.847872936
- $00:03:30.140 \longrightarrow 00:03:32.280$ arm of the Prime Minister.
- NOTE Confidence: 0.847872936
- $00:03:32.280 \longrightarrow 00:03:33.589$ And there may be a handful of
- NOTE Confidence: 0.847872936
- $00{:}03{:}33{.}589 \dashrightarrow 00{:}03{:}34{.}440$ 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
- $00:03:37.240 \longrightarrow 00:03:39.490$ who was a beloved member of
- NOTE Confidence: 0.847872936
- $00{:}03{:}39{.}490 \dashrightarrow 00{:}03{:}41{.}200$ your faculty for many years.
- NOTE Confidence: 0.847872936
- $00{:}03{:}41{.}200 \dashrightarrow 00{:}03{:}43{.}266$ 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
- $00:03:45.600 \rightarrow 00:03:46.050$ as you heard,
- NOTE Confidence: 0.847872936
- $00{:}03{:}46.050 \dashrightarrow 00{:}03{:}46.800$ 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
- $00:03:47.730 \longrightarrow 00:03:48.879$ 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
- $00:03:51.274 \rightarrow 00:03:54.246$ Hopkins as the chief medical resident.

 $00{:}03{:}54.246 \dashrightarrow 00{:}03{:}55.824$ But the person who changed my

NOTE Confidence: 0.847872936

 $00:03:55.824 \rightarrow 00:03:57.199$ 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

 $00{:}03{:}58{.}600 \dashrightarrow 00{:}04{:}00{.}866$ I came to the Dana Farber in 1987

NOTE Confidence: 0.847872936

 $00:04:00.866 \longrightarrow 00:04:03.796$ to be a clinical oncologist.

NOTE Confidence: 0.847872936

 $00{:}04{:}03.800 \dashrightarrow 00{:}04{:}05.200$ And then I had the good for tune

NOTE Confidence: 0.847872936

 $00{:}04{:}05{.}200 \dashrightarrow 00{:}04{:}07{.}024$ of being a postdoc in his lab at a

NOTE Confidence: 0.847872936

 $00:04:07.024 \dashrightarrow 00:04:08.720$ very good time to be in David's lab.

NOTE Confidence: 0.847872936

 $00{:}04{:}08{.}720 \dashrightarrow 00{:}04{:}10{.}040$ Although frankly any opportunity to

NOTE Confidence: 0.847872936

 $00:04:10.040 \longrightarrow 00:04:12.118$ train with David would have been a good time.

NOTE Confidence: 0.847872936

 $00:04:12.120 \dashrightarrow 00:04:14.759$ But the field was moving very quickly.

NOTE Confidence: 0.847872936

 $00:04:14.760 \dashrightarrow 00:04:16.832$ The RB gene had just been isolated

NOTE Confidence: 0.847872936

 $00{:}04{:}16.832 \dashrightarrow 00{:}04{:}19.510$ and I was given the opportunity to

NOTE Confidence: 0.847872936

 $00:04:19.510 \dashrightarrow 00:04:21.680$ work on the RB tumor Spicer gene.

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

NOTE Confidence: 0.847872936

 $00:04:24.212 \rightarrow 00:04:26.354$ crafted me, whatever you want to say,

NOTE Confidence: 0.809395754545454

 $00{:}04{:}26{.}360 \dashrightarrow 00{:}04{:}27{.}170$ into a scientist.

NOTE Confidence: 0.809395754545454

 $00:04:27.170 \longrightarrow 00:04:29.440$ So I owe my scientific career to David.

NOTE Confidence: 0.809395754545454

 $00:04:29.440 \longrightarrow 00:04:32.380$ 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

 $00:04:34.011 \longrightarrow 00:04:35.574$ is for the benefit of the young

NOTE Confidence: 0.809395754545454

 $00{:}04{:}35{.}574 \dashrightarrow 00{:}04{:}37{.}074$ people and because you're supposed to

NOTE Confidence: 0.809395754545454

 $00{:}04{:}37{.}126 \dashrightarrow 00{:}04{:}38{.}638$ 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

 $00:04:41.706 \longrightarrow 00:04:43.008$ 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

 $00:04:44.273 \longrightarrow 00:04:45.678$ their emails on their phones,

NOTE Confidence: 0.809395754545454

 $00{:}04{:}45{.}680 \dashrightarrow 00{:}04{:}47{.}794$ and then we will move on to

NOTE Confidence: 0.809395754545454

 $00:04:47.794 \longrightarrow 00:04:48.671$ three unpublished stories.

- NOTE Confidence: 0.809395754545454
- 00:04:48.671 -> 00:04:49.484 So of course,
- NOTE Confidence: 0.809395754545454
- $00{:}04{:}49{.}484 \dashrightarrow 00{:}04{:}51{.}110$ one of the most important decisions
- NOTE Confidence: 0.809395754545454
- $00:04:51.160 \rightarrow 00:04:53.085$ you have to make when you're starting
- NOTE Confidence: 0.809395754545454
- $00:04:53.085 \rightarrow 00:04:54.560$ your laboratory is what to work on.
- NOTE Confidence: 0.809395754545454
- $00:04:54.560 \longrightarrow 00:04:56.232$ And fortunately for me,
- NOTE Confidence: 0.809395754545454
- $00:04:56.232 \dashrightarrow 00:04:59.680$ 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
- $00:05:00.880 \rightarrow 00:05:02.800$ which was the cloning of the gene that,
- NOTE Confidence: 0.809395754545454
- $00:05:02.800 \longrightarrow 00:05:03.554$ when mutated,
- NOTE Confidence: 0.809395754545454
- $00:05:03.554 \rightarrow 00:05:06.193$ 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
- $00{:}05{:}07{.}480 \dashrightarrow 00{:}05{:}08{.}440$ By the way,
- NOTE Confidence: 0.809395754545454
- $00{:}05{:}08{.}440 \dashrightarrow 00{:}05{:}09{.}840$ I left off one more Yale connection.
- NOTE Confidence: 0.809395754545454
- $00:05:09.840 \longrightarrow 00:05:12.094$ So one of the few places that
- NOTE Confidence: 0.809395754545454
- $00{:}05{:}12.094 \dashrightarrow 00{:}05{:}13.799$ recruited me after my postdoc
- NOTE Confidence: 0.809395754545454

 $00:05:13.800 \rightarrow 00:05:16.080$ 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

 $00:05:19.040 \rightarrow 00:05:20.960$ which I walked past today.

NOTE Confidence: 0.809395754545454

 $00{:}05{:}20{.}960 \dashrightarrow 00{:}05{:}22{.}878$ 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

 $00:05:24.903 \rightarrow 00:05:27.424$ meeting of the minds in terms of how

NOTE Confidence: 0.809395754545454

 $00:05:27.424 \longrightarrow 00:05:28.916$ you nurture physician scientists.

NOTE Confidence: 0.809395754545454

 $00:05:28.920 \longrightarrow 00:05:31.139$ 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

 $00:05:32.760 \dashrightarrow 00:05:34.677$ So I joined the faculty at the Dana Farber.

NOTE Confidence: 0.809395754545454

 $00{:}05{:}34.680 \dashrightarrow 00{:}05{:}36.185$ This paper crosses my desk and I

NOTE Confidence: 0.809395754545454

 $00:05:36.185 \dashrightarrow 00:05:37.755$ knew from my clinical training this

NOTE Confidence: 0.809395754545454

 $00:05:37.755 \rightarrow 00:05:39.501$ would be really be an interesting

NOTE Confidence: 0.809395754545454

 $00:05:39.501 \longrightarrow 00:05:40.279$ gene to study.

NOTE Confidence: 0.809395754545454

 $00:05:40.280 \rightarrow 00:05:40.560$ Moreover,

 $00:05:40.560 \longrightarrow 00:05:42.240$ I thought from my work on

NOTE Confidence: 0.809395754545454

 $00:05:42.240 \rightarrow 00:05:43.080$ 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

 $00:05:45.096 \rightarrow 00:05:46.440$ another tumor suppressor gene,

NOTE Confidence: 0.809395754545454

 $00:05:46.440 \rightarrow 00:05:48.996$ namely the VHL tumor suppressor gene.

NOTE Confidence: 0.809395754545454

 $00:05:49.000 \longrightarrow 00:05:50.827$ So this is a disease that was

NOTE Confidence: 0.809395754545454

 $00:05:50.827 \rightarrow 00:05:52.199$ described about 100 years ago.

NOTE Confidence: 0.809395754545454

 $00{:}05{:}52{.}200 \dashrightarrow 00{:}05{:}54{.}252$ It affects about one in 35,000

NOTE Confidence: 0.809395754545454

 $00:05:54.252 \rightarrow 00:05:55.650$ people around the world.

NOTE Confidence: 0.809395754545454

 $00:05:55.650 \rightarrow 00:05:57.400$ And as you can see,

NOTE Confidence: 0.809395754545454

 $00{:}05{:}57{.}400 \dashrightarrow 00{:}05{:}58{.}415$ these are some kindreds that

NOTE Confidence: 0.809395754545454

 $00{:}05{:}58{.}415 \dashrightarrow 00{:}05{:}59{.}724$ have been followed at the NCI

NOTE Confidence: 0.809395754545454

 $00:05:59.724 \longrightarrow 00:06:00.720$ with von Hippelindau disease.

NOTE Confidence: 0.809395754545454

 $00{:}06{:}00{.}720 \dashrightarrow 00{:}06{:}03{.}513$ And of course the filled circles and

NOTE Confidence: 0.809395754545454

 $00{:}06{:}03.513 \dashrightarrow 00{:}06{:}05.560$ squares are affected individuals

 $00{:}06{:}05{.}560 \dashrightarrow 00{:}06{:}07{.}436$ 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

 $00:06:09.560 \longrightarrow 00:06:11.464$ which is by far the most common

NOTE Confidence: 0.809395754545454

 $00:06:11.464 \rightarrow 00:06:12.760$ form of kidney cancer.

NOTE Confidence: 0.809395754545454

 $00{:}06{:}12.760 \dashrightarrow 00{:}06{:}14.060$ 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

 $00:06:17.856 \rightarrow 00:06:20.160$ Crest tumors called paragen gliomas,

NOTE Confidence: 0.809395754545454

 $00{:}06{:}20{.}160 \dashrightarrow 00{:}06{:}22{.}302$ which when they arise in the adrenal

NOTE Confidence: 0.809395754545454

 $00:06:22.302 \rightarrow 00:06:23.854$ gland are referred to as theocromocytomas.

NOTE Confidence: 0.809395754545454

 $00:06:23.854 \rightarrow 00:06:25.912$ Now you can see that clinically this

NOTE Confidence: 0.809395754545454

 $00:06:25.912 \rightarrow 00:06:27.958$ looks like an autosomal dominant disorder,

NOTE Confidence: 0.809395754545454

 $00{:}06{:}27.960 \dashrightarrow 00{:}06{:}29.465$ but actually at the molecular

NOTE Confidence: 0.809395754545454

 $00:06:29.465 \rightarrow 00:06:31.346$ level this is actually an autosomal

NOTE Confidence: 0.809395754545454

 $00:06:31.346 \longrightarrow 00:06:33.242$ it's actually caused by a loss

NOTE Confidence: 0.809395754545454

 $00:06:33.242 \longrightarrow 00:06:34.062$ of function mutation.

- NOTE Confidence: 0.809395754545454
- 00:06:34.062 --> 00:06:34.426 So again,
- NOTE Confidence: 0.809395754545454
- $00{:}06{:}34{.}426 \dashrightarrow 00{:}06{:}36{.}080$ just to make sure everyone saw the same page,
- NOTE Confidence: 0.809395754545454
- $00:06:36.080 \rightarrow 00:06:37.958$ people with about HIPAA Lindow disease
- NOTE Confidence: 0.809395754545454
- $00{:}06{:}37{.}958 \dashrightarrow 00{:}06{:}39{.}789$ have have inherited A defective version
- NOTE Confidence: 0.809395754545454
- $00:06:39.789 \longrightarrow 00:06:41.877$ of the VHL gene from mom or dad.
- NOTE Confidence: 0.809395754545454
- $00:06:41.880 \rightarrow 00:06:42.822$ In this schematic,
- NOTE Confidence: 0.809395754545454
- $00:06:42.822 \longrightarrow 00:06:44.078$ 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
- $00:06:45.550 \rightarrow 00:06:47.388$ they have the remaining wild type
- NOTE Confidence: 0.809395754545454
- $00{:}06{:}47.388 \dashrightarrow 00{:}06{:}49.284$ 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
- $00:06:52.080 \longrightarrow 00:06:54.173$ 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
- $00{:}06{:}55{.}130 \dashrightarrow 00{:}06{:}57{.}545$ cells in your body will spontaneously lose
- NOTE Confidence: 0.925362958947368

 $00:06:57.545 \rightarrow 00:06:59.440$ or mutate the remaining wild type copy.

NOTE Confidence: 0.925362958947368

 $00{:}06{:}59{.}440 \dashrightarrow 00{:}07{:}00{.}480$ And that's the cell that

NOTE Confidence: 0.925362958947368

 $00:07:00.480 \longrightarrow 00:07:01.960$ 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

 $00:07:03.664 \dashrightarrow 00:07:05.178$ the knowledge that germline VHL

NOTE Confidence: 0.925362958947368

 $00{:}07{:}05{.}178 \dashrightarrow 00{:}07{:}06{.}798$ mutations predispose to for example

NOTE Confidence: 0.925362958947368

 $00{:}07{:}06.800 \dashrightarrow 00{:}07{:}07.880$ 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

 $00{:}07{:}10.960 \dashrightarrow 00{:}07{:}12.836$ you again see that both the maternal

NOTE Confidence: 0.925362958947368

 $00:07:12.836 \dashrightarrow 00:07:14.796$ and the paternal copies of the VHL

NOTE Confidence: 0.925362958947368

 $00:07:14.796 \rightarrow 00:07:16.440$ 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

 $00:07:18.554 \rightarrow 00:07:20.623$ if you will have occurred somatically

NOTE Confidence: 0.925362958947368

 $00{:}07{:}20.623 \dashrightarrow 00{:}07{:}23.192$ in contrast to VHL disease where the

NOTE Confidence: 0.925362958947368

 $00:07:23.256 \rightarrow 00:07:26.918$ first hit has occurred in the germline.

 $00{:}07{:}26.920 \dashrightarrow 00{:}07{:}28.696$ So I knew from my clinical training that

NOTE Confidence: 0.925362958947368

 $00{:}07{:}28.696 \dashrightarrow 00{:}07{:}30.476$ the tumors seen in von Hipolindo disease

NOTE Confidence: 0.925362958947368

 $00:07:30.476 \dashrightarrow 00:07:32.160$ are notoriously rich in blood vessels,

NOTE Confidence: 0.925362958947368

 $00:07:32.160 \longrightarrow 00:07:33.942$ and that's because they frequently over

NOTE Confidence: 0.925362958947368

 $00:07:33.942 \rightarrow 00:07:36.214$ produce BEGF and then they also occasionally

NOTE Confidence: 0.925362958947368

 $00:07:36.214 \dashrightarrow 00:07:38.479$ cause excess red blood cell production,

NOTE Confidence: 0.925362958947368

 $00{:}07{:}38{.}480 \dashrightarrow 00{:}07{:}40{.}450$ and that's because they sometimes

NOTE Confidence: 0.925362958947368

 $00:07:40.450 \longrightarrow 00:07:41.582$ ectopically produce erythropoietin.

NOTE Confidence: 0.925362958947368

 $00:07:41.582 \dashrightarrow 00:07:43.634$ And what VEGF and erythropoiet in have

NOTE Confidence: 0.925362958947368

 $00:07:43.634 \rightarrow 00:07:45.705$ 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

 $00:07:47.360 \longrightarrow 00:07:48.400$ are not getting enough oxygen.

NOTE Confidence: 0.925362958947368

 $00{:}07{:}48{.}400 \dashrightarrow 00{:}07{:}50{.}171$ So that was the clue that by

NOTE Confidence: 0.925362958947368

 $00{:}07{:}50{.}171 \dashrightarrow 00{:}07{:}52{.}302$ studying the VHL gene we might learn

NOTE Confidence: 0.925362958947368

 $00{:}07{:}52{.}302 \dashrightarrow 00{:}07{:}53{.}660$ something about oxygen sensing.

 $00:07:53.660 \rightarrow 00:07:56.460$ Now VEGF and EPO are under the control

NOTE Confidence: 0.925362958947368

 $00:07:56.532 \longrightarrow 00:07:58.524$ of a heterodemeric transcription

NOTE Confidence: 0.925362958947368

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

NOTE Confidence: 0.925362958947368

 $00:08:00.320 \longrightarrow 00:08:02.320$ factor or HIP for short.

NOTE Confidence: 0.925362958947368

 $00{:}08{:}02{.}320 \dashrightarrow 00{:}08{:}03{.}622$ And we knew from the work

NOTE Confidence: 0.925362958947368

 $00:08:03.622 \longrightarrow 00:08:04.273$ of multiple laboratories,

NOTE Confidence: 0.925362958947368

 $00:08:04.280 \longrightarrow 00:08:07.262$ including the work of my fellow

NOTE Confidence: 0.925362958947368

 $00{:}08{:}07{.}262 \dashrightarrow 00{:}08{:}09{.}552$ laureates factors Semenza and Radcliffe

NOTE Confidence: 0.925362958947368

 $00{:}08{:}09{.}552 \dashrightarrow 00{:}08{:}12{.}240$ that the alpha subunit is normally

NOTE Confidence: 0.925362958947368

 $00:08:12.310 \rightarrow 00:08:14.648$ degraded when oxygen is available,

NOTE Confidence: 0.925362958947368

 $00:08:14.648 \dashrightarrow 00:08:17.560$ 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

 $00:08:19.560 \longrightarrow 00:08:21.320$ is constitutively stable and

NOTE Confidence: 0.925362958947368

 $00:08:21.320 \longrightarrow 00:08:23.520$ over the course of time,

NOTE Confidence: 0.925362958947368

 $00:08:23.520 \dashrightarrow 00:08:25.256$ 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
- $00:08:27.127 \longrightarrow 00:08:28.768$ 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
- $00{:}08{:}30{.}496 \dashrightarrow 00{:}08{:}32{.}400$ targets it for proteasomal degradation
- NOTE Confidence: 0.925362958947368
- $00:08:32.400 \longrightarrow 00:08:34.360$ provided oxidant is present.
- NOTE Confidence: 0.925362958947368
- $00:08:34.360 \rightarrow 00:08:35.896$ 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
- $00{:}08{:}47.185 \dashrightarrow 00{:}08{:}48.327$ on occasion erythropoiet in.
- NOTE Confidence: 0.925362958947368
- $00{:}08{:}48{.}327 \dashrightarrow 00{:}08{:}50{.}616$ And also point out that there are
- NOTE Confidence: 0.925362958947368
- $00:08:50.616 \rightarrow 00:08:52.421$ 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

 $00{:}08{:}54{.}080 \dashrightarrow 00{:}08{:}55{.}550$ 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

 $00:08:57.056 \rightarrow 00:08:58.936$ and ligase and the other is the beta

NOTE Confidence: 0.925362958947368

 $00{:}08{:}58{.}993 \dashrightarrow 00{:}09{:}00{.}862$ domain which we showed is the actual

NOTE Confidence: 0.925362958947368

 $00:09:00.862 \dashrightarrow 00:09:02.264$ docking site for the substrate.

NOTE Confidence: 0.925362958947368

 $00:09:02.264 \rightarrow 00:09:04.280$ Now this of course begs the question,

NOTE Confidence: 0.925362958947368

 $00:09:04.280 \rightarrow 00:09:05.516$ how does the VHL protein know,

NOTE Confidence: 0.925362958947368

 $00:09:05.520 \longrightarrow 00:09:07.263$ if you will whether oxygen is or

NOTE Confidence: 0.925362958947368

 $00{:}09{:}07{.}263 \dashrightarrow 00{:}09{:}08{.}896$ is not available and hence whether

NOTE Confidence: 0.925362958947368

 $00:09:08.896 \dashrightarrow 00:09:10.558$ it should or should not destroy

NOTE Confidence: 0.925362958947368

 $00{:}09{:}10.560 \dashrightarrow 00{:}09{:}12.720$ HIP or mark HIP for destruction.

NOTE Confidence: 0.925362958947368

 $00:09:12.720 \longrightarrow 00:09:13.960$ 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

 $00:09:15.920 \longrightarrow 00:09:16.940$ independently in parallel,

NOTE Confidence: 0.925362958947368

 $00:09:16.940 \longrightarrow 00:09:18.980$ showed that in the presence of

- NOTE Confidence: 0.925362958947368
- $00:09:18.980 \rightarrow 00:09:21.405$ oxygen one of two conserve prolial
- NOTE Confidence: 0.925362958947368
- 00:09:21.405 --> 00:09:23.490 residues gets hydroxylated in hip
- NOTE Confidence: 0.925362958947368
- $00{:}09{:}23.561 \dashrightarrow 00{:}09{:}25.865$ 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
- $00:09:27.954 \dashrightarrow 00:09:31.020$ The the enzymes that do the work
- NOTE Confidence: 0.925362958947368
- $00:09:31.115 \rightarrow 00:09:33.875$ here are variably called the Egolan
- 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
- $00{:}09{:}37{.}978 \dashrightarrow 00{:}09{:}39{.}340$ use one of
- NOTE Confidence: 0.8205883146666667
- $00:09:39.417 \rightarrow 00:09:43.400$ 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: 0.8205883146666667
- $00:09:45.080 \dashrightarrow 00:09:46.625$ which explains an old observation
- NOTE Confidence: 0.8205883146666667
- $00{:}09{:}46.625 \dashrightarrow 00{:}09{:}48.471$ that iron chelators when given to
- NOTE Confidence: 0.8205883146666667
- $00{:}09{:}48{.}471 \dashrightarrow 00{:}09{:}50{.}160$ cells and culture will mimic or
- NOTE Confidence: 0.820588314666667
- $00:09:50.160 \rightarrow 00:09:52.360$ stimulate A hypoxic like response.
- NOTE Confidence: 0.8205883146666667

 $00:09:52.360 \rightarrow 00:09:54.652$ They also require a cofactor which

NOTE Confidence: 0.8205883146666667

 $00:09:54.652 \dashrightarrow 00:09:56.925$ is variably called 2 oxygood rate or

NOTE Confidence: 0.8205883146666667

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

NOTE Confidence: 0.8205883146666667

 $00:09:58.800 \rightarrow 00:10:01.680$ which gets decarboxylated to succinate.

NOTE Confidence: 0.820588314666667

 $00:10:01.680 \longrightarrow 00:10:02.612$ Not shown here, however,

NOTE Confidence: 0.8205883146666667

 $00:10:02.612 \rightarrow 00:10:04.520$ is one other critical piece of the puzzle,

NOTE Confidence: 0.820588314666667

 $00:10:04.520 \rightarrow 00:10:06.812$ which is These enzymes have very

NOTE Confidence: 0.8205883146666667

 $00{:}10{:}06.812 \dashrightarrow 00{:}10{:}08.676$ low oxygen affinities and hence

NOTE Confidence: 0.8205883146666667

 $00:10:08.676 \rightarrow 00:10:10.890$ they're poised to sense oxygen in

NOTE Confidence: 0.8205883146666667

 $00:10:10.959 \rightarrow 00:10:12.959$ a physiologically relevant range.

NOTE Confidence: 0.8205883146666667

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

NOTE Confidence: 0.8205883146666667

 $00:10:14.480 \longrightarrow 00:10:16.260$ the collagen pro hydroxylases you

NOTE Confidence: 0.8205883146666667

 $00:10:16.260 \longrightarrow 00:10:18.040$ might have studied in college

NOTE Confidence: 0.8205883146666667

00:10:18.104 --> 00:10:19.520 and college biochemistry.

NOTE Confidence: 0.8205883146666667

 $00:10:19.520 \rightarrow 00:10:21.605$ The collagen pro hydroxylases have

NOTE Confidence: 0.8205883146666667

 $00:10:21.605 \rightarrow 00:10:23.273$ extremely high oxygen affinities.

- NOTE Confidence: 0.8205883146666667
- $00:10:23.280 \rightarrow 00:10:25.272$ You'd have to be virtually anoxic
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}25.272 \dashrightarrow 00{:}10{:}27.148$ before the collagen pro hydroxylases
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}27.148 \dashrightarrow 00{:}10{:}28.502$ would become inactive.
- NOTE Confidence: 0.8205883146666667
- $00:10:28.502 \rightarrow 00:10:31.558$ So these enzymes I just introduced to you,
- NOTE Confidence: 0.8205883146666667
- $00:10:31.560 \rightarrow 00:10:33.205$ which I'll stick with the original and
- NOTE Confidence: 0.820588314666667
- $00{:}10{:}33.205 \dashrightarrow 00{:}10{:}35.268$ the meclids, are the EGELEN enzymes.
- NOTE Confidence: 0.8205883146666667
- $00:10:35.268 \rightarrow 00:10:37.650$ So these are the pro hydroxylases
- NOTE Confidence: 0.820588314666667
- $00:10:37.724 \longrightarrow 00:10:38.840$ that modify hip.
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}38{.}840 \dashrightarrow 00{:}10{:}40{.}730$ But you can see these enzymes are
- NOTE Confidence: 0.8205883146666667
- 00:10:40.730 --> 00:10:43.118 part of a much larger superfamily,
- NOTE Confidence: 0.8205883146666667
- 00:10:43.120 --> 00:10:45.450 so-called 2 oxyglate dependent de
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}45{.}450 \dashrightarrow 00{:}10{:}48{.}870$ oxygenases which includes many of the
- NOTE Confidence: 0.8205883146666667
- 00:10:48.870 --> 00:10:51.600 so-called Jumanji C histone demethylases
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}51{.}600 \dashrightarrow 00{:}10{:}55{.}440$ as well as the Ted enzymes that are
- NOTE Confidence: 0.8205883146666667
- $00{:}10{:}55{.}533 \dashrightarrow 00{:}10{:}58{.}277$ implicated in DNA demethylation.
- NOTE Confidence: 0.820588314666667

 $00:10:58.280 \dashrightarrow 00:11:01.232$ So let's go back to the Jumanji C proteins.

NOTE Confidence: 0.8205883146666667

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: 0.8205883146666667

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

NOTE Confidence: 0.8205883146666667

 $00:11:08.760 \longrightarrow 00:11:11.105$ but what they do is they hydroxylate

NOTE Confidence: 0.8205883146666667

00:11:11.105 --> 00:11:13.851 the histone methyl group which is then NOTE Confidence: 0.8205883146666667

 $00:11:13.851 \rightarrow 00:11:16.408$ unstable and given off as formaldehyde.

NOTE Confidence: 0.820588314666667

 $00{:}11{:}16{.}408 \dashrightarrow 00{:}11{:}18{.}956$ Now this raised the question in our

NOTE Confidence: 0.820588314666667

 $00{:}11{:}18.956 \dashrightarrow 00{:}11{:}20.957$ minds and other people's minds,

NOTE Confidence: 0.8205883146666667

 $00:11:20.960 \rightarrow 00:11:22.780$ are these enzymes more like

NOTE Confidence: 0.8205883146666667

 $00:11:22.780 \longrightarrow 00:11:24.600$ the enzymes that modify HIP?

NOTE Confidence: 0.8205883146666667

 $00:11:24.600 \rightarrow 00:11:26.904$ Meaning are they going to be very oxygen

NOTE Confidence: 0.8205883146666667

 $00:11:26.904 \rightarrow 00:11:28.691$ sensitive or are they going to be more

NOTE Confidence: 0.8205883146666667

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

NOTE Confidence: 0.8205883146666667

 $00:11:30.314 \rightarrow 00:11:31.874$ and be relatively oxygen insensitive?

NOTE Confidence: 0.8205883146666667

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

- NOTE Confidence: 0.8205883146666667
- $00:11:33.840 \longrightarrow 00:11:35.245$ many examples of both.
- NOTE Confidence: 0.8205883146666667
- $00:11:35.245 \rightarrow 00:11:37.120$ Some of the histamine methylases
- NOTE Confidence: 0.8205883146666667
- $00:11:37.120 \rightarrow 00:11:39.545$ actually turn out to be exquisitely
- NOTE Confidence: 0.8205883146666667
- $00:11:39.545 \rightarrow 00:11:41.157$ sensitive to oxygen availability.
- NOTE Confidence: 0.8205883146666667
- 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: 0.8205883146666667
- $00{:}11{:}46.560 \dashrightarrow 00{:}11{:}48.928$ So this enzyme is every bit as oxygen
- NOTE Confidence: 0.8205883146666667
- $00:11:48.928 \rightarrow 00:11:51.236$ sensitive as the enzymes that modify HIP,
- NOTE Confidence: 0.8205883146666667
- $00{:}11{:}51{.}240 \dashrightarrow 00{:}11{:}53{.}830$ and so this provides A surprisingly direct
- NOTE Confidence: 0.8205883146666667
- $00:11:53.830 \rightarrow 00:11:55.483$ linkage between oxygen availability
- NOTE Confidence: 0.8205883146666667
- $00{:}11{:}55{.}483 \dashrightarrow 00{:}11{:}57{.}399$ and certain epigenetic marks.
- NOTE Confidence: 0.8205883146666667
- $00{:}11{:}57{.}400 \dashrightarrow 00{:}11{:}59{.}178$ And we think this has relevance to
- NOTE Confidence: 0.8205883146666667
- $00:11:59.178 \rightarrow 00:12:01.528$ the role of hypoxia, for example,
- NOTE Confidence: 0.8205883146666667
- $00{:}12{:}01{.}528 \dashrightarrow 00{:}12{:}03{.}640$ during embryologic development in
- NOTE Confidence: 0.820588314666667
- $00:12:03.640 \longrightarrow 00:12:06.520$ certain stem cell niches as well
- NOTE Confidence: 0.820588314666667

- $00:12:06.520 \longrightarrow 00:12:07.829$ as within tumors.
- NOTE Confidence: 0.8205883146666667
- 00:12:07.829 --> 00:12:10.272 Now the other reason I showed you
- NOTE Confidence: 0.8205883146666667
- $00:12:10.272 \rightarrow 00:12:11.879$ this superfamily of enzymes is,
- NOTE Confidence: 0.820588314666667
- $00:12:11.880 \longrightarrow 00:12:13.833$ I must say I'm a bit of what we
- NOTE Confidence: 0.820588314666667
- $00:12:13.833 \longrightarrow 00:12:14.920$ say on the wards.
- NOTE Confidence: 0.8205883146666667
- $00:12:14.920 \rightarrow 00:12:16.838$ I'm a lumper rather than a splitter.
- NOTE Confidence: 0.8205883146666667
- $00:12:16.840 \longrightarrow 00:12:18.688$ I'm always looking for sort of
- NOTE Confidence: 0.820588314666667
- $00{:}12{:}18.688 \dashrightarrow 00{:}12{:}19.920$ common themes and commonalities.
- NOTE Confidence: 0.8205883146666667
- 00:12:19.920 --> 00:12:21.840 So I'm always looking for sort
- NOTE Confidence: 0.8205883146666667
- $00:12:21.840 \longrightarrow 00:12:22.800$ 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: 0.8205883146666667
- $00:12:25.440 \longrightarrow 00:12:27.544$ who you may know in the middle of
- NOTE Confidence: 0.8205883146666667
- $00:12:27.544 \rightarrow 00:12:30.041$ the last century argued that altered
- NOTE Confidence: 0.8205883146666667
- 00:12:30.041 --> 00:12:31.640 metabolism was a cause of cancer.
- NOTE Confidence: 0.8205883146666667
- $00:12:31.640 \rightarrow 00:12:33.600$ But then over the decades the debate was,
- NOTE Confidence: 0.8205883146666667
- $00:12:33.600 \longrightarrow 00:12:34.065$ well,

- NOTE Confidence: 0.8205883146666667
- $00:12:34.065 \rightarrow 00:12:36.855$ is ultimate metabolism A cause of
- NOTE Confidence: 0.8205883146666667
- 00:12:36.855 --> 00:12:38.600 cancer a consequence of cancer,
- NOTE Confidence: 0.8205883146666667
- $00:12:38.600 \rightarrow 00:12:39.560$ both or neither?
- NOTE Confidence: 0.8205883146666667
- $00:12:39.560 \longrightarrow 00:12:41.726$ And what what Warburg lacked was
- NOTE Confidence: 0.8205883146666667
- 00:12:41.726 --> 00:12:43.170 sort of a genetic
- NOTE Confidence: 0.8479819066666667
- $00:12:43.245 \longrightarrow 00:12:44.680$ smoking gun that alter
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}44.680 \dashrightarrow 00{:}12{:}45.960$ metabolism could cause cancer.
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}45{.}960 \dashrightarrow 00{:}12{:}48{.}904$ But we now know that some cancers have
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}48{.}904 \dashrightarrow 00{:}12{:}50{.}554$ inactivating mutations and succinate
- NOTE Confidence: 0.8479819066666667
- $00:12:50.554 \rightarrow 00:12:52.564$ to hydrogenase or fumarate hydratase,
- NOTE Confidence: 0.8479819066666667
- $00:12:52.564 \rightarrow 00:12:54.892$ which lead to the accumulation of
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}54.892 \dashrightarrow 00{:}12{:}56.516$ succinate and fumarate respectively.
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}56{.}516$ --> $00{:}12{:}59{.}400$ And it's clear these chemicals can inhibit
- NOTE Confidence: 0.8479819066666667
- $00{:}12{:}59{.}463 \dashrightarrow 00{:}13{:}01{.}268$ these various two OG dependent enzymes.
- NOTE Confidence: 0.8479819066666667
- 00:13:01.268 --> 00:13:03.136 In fact you might have noticed that
- NOTE Confidence: 0.8479819066666667

 $00{:}13{:}03{.}136 \dashrightarrow 00{:}13{:}05{.}227$ succinate was the product of the reaction.

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}05{.}227 \dashrightarrow 00{:}13{:}07{.}530$ And then we learned from Burt Vogelstein

NOTE Confidence: 0.8479819066666667

 $00:13:07.589 \rightarrow 00:13:09.563$ and Haiyan and others that certain

NOTE Confidence: 0.8479819066666667

 $00:13:09.563 \rightarrow 00:13:12.064$ tumors such as certain brain tumors and

NOTE Confidence: 0.8479819066666667

 $00:13:12.064 \rightarrow 00:13:13.919$ leukemias have neomorphic mutations

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}13{.}919 \dashrightarrow 00{:}13{:}16{.}384$ and isositrate dehydrogenase one or

NOTE Confidence: 0.8479819066666667

 $00:13:16.384 \rightarrow 00:13:18.992$ two which allow these enzymes to make

NOTE Confidence: 0.8479819066666667

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

NOTE Confidence: 0.8479819066666667

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

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}23{.}360 \dashrightarrow 00{:}13{:}26{.}160$ which also can inhibit these various enzymes.

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}26.160 \dashrightarrow 00{:}13{:}27.276$ So we could actually do it.

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}27{.}280 \dashrightarrow 00{:}13{:}29{.}116$ Now an entire research seminar about,

NOTE Confidence: 0.8479819066666667

 $00:13:29.120 \longrightarrow 00:13:30.602$ well, which of the enzymes are

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}30{.}602 \dashrightarrow 00{:}13{:}31{.}915$ critical in which setting with

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}31{.}915 \dashrightarrow 00{:}13{:}33{.}275$ which mutation and which cancer.

NOTE Confidence: 0.8479819066666667

 $00{:}13{:}33{.}280 \dashrightarrow 00{:}13{:}34{.}690$ But I'm not going to do that to you again

- NOTE Confidence: 0.8479819066666667
- $00:13:34.726 \rightarrow 00:13:36.238$ because I'm a lumper rather than a splitter.
- NOTE Confidence: 0.8479819066666667
- $00:13:36.240 \rightarrow 00:13:38.650$ So this is my lumpers view of how we get
- NOTE Confidence: 0.8479819066666667
- $00{:}13{:}38{.}711 \dashrightarrow 00{:}13{:}40{.}876$ cancer from these various mutations.
- NOTE Confidence: 0.8479819066666667
- $00:13:40.880 \longrightarrow 00:13:43.504$ But I will say that early on the
- NOTE Confidence: 0.8479819066666667
- $00:13:43.504 \rightarrow 00:13:45.024$ naysayers and for the students
- NOTE Confidence: 0.8479819066666667
- $00:13:45.024 \rightarrow 00:13:46.240$ always beware of naysayers.
- NOTE Confidence: 0.8479819066666667
- $00:13:46.240 \longrightarrow 00:13:47.458$ You can always think of a reason
- NOTE Confidence: 0.8479819066666667
- 00:13:47.458 --> 00:13:48.279 why something's going to fail.
- NOTE Confidence: 0.8479819066666667
- 00:13:48.280 --> 00:13:49.520 It's not going to work.
- NOTE Confidence: 0.8479819066666667
- $00{:}13{:}49{.}520 \dashrightarrow 00{:}13{:}51{.}476$ So the naysayers argue that even
- NOTE Confidence: 0.8479819066666667
- $00:13:51.476 \rightarrow 00:13:54.152$ if you could make a drug that would
- NOTE Confidence: 0.8479819066666667
- $00:13:54.152 \longrightarrow 00:13:56.640$ prevent the production of two HG,
- NOTE Confidence: 0.8479819066666667
- $00{:}13{:}56{.}640 \dashrightarrow 00{:}13{:}58{.}348$ it would not be helpful because many
- NOTE Confidence: 0.8479819066666667
- $00{:}13{:}58{.}348 \dashrightarrow 00{:}13{:}59{.}840$ of these enzymes, as I just told you,
- NOTE Confidence: 0.8479819066666667
- $00{:}13{:}59{.}840 \dashrightarrow 00{:}14{:}02{.}680$ are involved in epigenetic reprogramming.
- NOTE Confidence: 0.8479819066666667

 $00:14:02.680 \rightarrow 00:14:04.714$ And the argument was those epigenetic

NOTE Confidence: 0.8479819066666667

 $00:14:04.714 \rightarrow 00:14:06.734$ marks would be relatively stable and

NOTE Confidence: 0.8479819066666667

 $00:14:06.734 \longrightarrow 00:14:08.459$ would not reverse in a clinically

NOTE Confidence: 0.8479819066666667

 $00:14:08.459 \longrightarrow 00:14:09.278$ useful time scale.

NOTE Confidence: 0.8479819066666667

 $00:14:09.280 \longrightarrow 00:14:11.116$ So to sort of tackle that,

NOTE Confidence: 0.8479819066666667

 $00:14:11.120 \rightarrow 00:14:13.200$ Julie Lostman, when she was in my lab,

NOTE Confidence: 0.8479819066666667

 $00{:}14{:}13.200 \dashrightarrow 00{:}14{:}15.708$ decided to test whether there was

NOTE Confidence: 0.8479819066666667

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

NOTE Confidence: 0.8479819066666667

 $00{:}14{:}18{.}192 \dashrightarrow 00{:}14{:}19{.}676$ and IDH mutant leukemias.

NOTE Confidence: 0.8479819066666667

 $00{:}14{:}19.680 \dashrightarrow 00{:}14{:}21.675$ And so she created a model based

NOTE Confidence: 0.8479819066666667

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

NOTE Confidence: 0.8479819066666667

 $00:14:23.840 \rightarrow 00:14:25.665$ where she created isogenic cells

NOTE Confidence: 0.8479819066666667

 $00:14:25.665 \rightarrow 00:14:28.522$ that were wild type for IDH one or

NOTE Confidence: 0.8479819066666667

 $00{:}14{:}28{.}522 \dashrightarrow 00{:}14{:}30{.}436$ had this canonical IDH 1 mutants.

NOTE Confidence: 0.8479819066666667

 $00{:}14{:}30{.}440 \dashrightarrow 00{:}14{:}32{.}272$ She then measured 2 HG levels and as

NOTE Confidence: 0.8479819066666667

 $00:14:32.272 \rightarrow 00:14:34.154$ expected when she put in the IDH one mutant,

- NOTE Confidence: 0.8479819066666667
- 00:14:34.160 --> 00:14:37.112 now you had milli molar amounts of two HG.
- NOTE Confidence: 0.8479819066666667
- $00{:}14{:}37{.}120 \dashrightarrow 00{:}14{:}39{.}052$ And then she treated these cells
- NOTE Confidence: 0.8479819066666667
- $00{:}14{:}39.052 \dashrightarrow 00{:}14{:}41.083$ with a tool compound developed by
- NOTE Confidence: 0.8479819066666667
- $00{:}14{:}41.083 \dashrightarrow 00{:}14{:}43.123$ Agios that blocks two HG production
- NOTE Confidence: 0.8479819066666667
- 00:14:43.123 --> 00:14:46.360 and you see the two HG go down.
- NOTE Confidence: 0.8479819066666667
- 00:14:46.360 --> 00:14:47.713 More importantly, perhaps,
- NOTE Confidence: 0.8479819066666667
- $00:14:47.713 \longrightarrow 00:14:50.419$ she'd also shown that the cells
- NOTE Confidence: 0.8479819066666667
- $00:14:50.419 \rightarrow 00:14:53.128$ with the wild type IDH One,
- NOTE Confidence: 0.8479819066666667
- 00:14:53.128 --> 00:14:55.000 despite being leukemic,
- NOTE Confidence: 0.8479819066666667
- 00:14:55.000 00:14:56.710 can't proliferate in the absence
- NOTE Confidence: 0.8479819066666667
- $00:14:56.710 \longrightarrow 00:14:57.394$ of cytokines.
- NOTE Confidence: 0.8479819066666667
- $00{:}14{:}57{.}400 \dashrightarrow 00{:}14{:}59{.}356$ So that's what's shown in red.
- NOTE Confidence: 0.8479819066666667
- 00:14:59.360 --> 00:14:59.653 However,
- NOTE Confidence: 0.8479819066666667
- $00{:}14{:}59{.}653 \dashrightarrow 00{:}15{:}01{.}704$ she found that if the cells had
- NOTE Confidence: 0.8479819066666667
- $00{:}15{:}01{.}704 \dashrightarrow 00{:}15{:}03{.}359$ this canonical IDH One mutant now,
- NOTE Confidence: 0.8479819066666667

 $00:15:03.360 \rightarrow 00:15:05.840$ these cells could proliferate well,

NOTE Confidence: 0.8479819066666667

 $00:15:05.840 \longrightarrow 00:15:06.848$ even without cytokines.

NOTE Confidence: 0.8479819066666667

 $00{:}15{:}06.848 \dashrightarrow 00{:}15{:}09.200$ It's sort of a hallmark of transformation.

NOTE Confidence: 0.8479819066666667

 $00:15:09.200 \longrightarrow 00:15:11.258$ And now she's ready to treat the

NOTE Confidence: 0.8479819066666667

 $00{:}15{:}11{.}258 \dashrightarrow 00{:}15{:}13{.}362$ cells with the inhibitor and the

NOTE Confidence: 0.8479819066666667

 $00:15:13.362 \rightarrow 00:15:14.520$ cells stop growing.

NOTE Confidence: 0.8479819066666667

 $00:15:14.520 \longrightarrow 00:15:15.160$ So for the students,

NOTE Confidence: 0.8479819066666667

 $00{:}15{:}15{.}160 \dashrightarrow 00{:}15{:}16{.}379$ this is one of the most dangerous

NOTE Confidence: 0.8479819066666667

 $00:15:16.379 \dashrightarrow 00:15:17.717$ results you're ever going to get.

NOTE Confidence: 0.8479819066666667

 $00{:}15{:}17.720 \dashrightarrow 00{:}15{:}19.295$ Because this is Exactly what

NOTE Confidence: 0.8479819066666667

 $00:15:19.295 \longrightarrow 00:15:20.555$ you were hoping for.

NOTE Confidence: 0.8479819066666667

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

NOTE Confidence: 0.8479819066666667

 $00:15:22.260 \longrightarrow 00:15:23.800$ So you want to call the editor.

NOTE Confidence: 0.895037921428572

 $00:15:23.800 \longrightarrow 00:15:25.704$ This is figure six. Look at me

NOTE Confidence: 0.895037921428572

 $00:15:25.704 \rightarrow 00:15:27.878$ high fives up and down the hallway.

NOTE Confidence: 0.895037921428572

 $00:15:27.880 \rightarrow 00:15:31.156$ But this is a dangerous experiment.

00:15:31.160 --> 00:15:32.432 A because I just said it's

NOTE Confidence: 0.895037921428572

 $00:15:32.432 \rightarrow 00:15:33.520$ one we were looking for.

NOTE Confidence: 0.895037921428572

 $00{:}15{:}33{.}520 \dashrightarrow 00{:}15{:}35{.}417$ But it's also dangerous because these are

NOTE Confidence: 0.895037921428572

 $00:15:35.417 \rightarrow 00:15:37.359$ what some people would call down assays.

NOTE Confidence: 0.895037921428572

 $00{:}15{:}37{.}360 \dashrightarrow 00{:}15{:}38{.}560$ 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

 $00:15:41.000 \rightarrow 00:15:44.276$ 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

 $00{:}15{:}45{.}880 \dashrightarrow 00{:}15{:}47{.}606$ say this is just another poison that

NOTE Confidence: 0.895037921428572

 $00{:}15{:}47.606 \dashrightarrow 00{:}15{:}49.635$ they sent you after that MTA that you

NOTE Confidence: 0.895037921428572

 $00:15:49.635 \rightarrow 00:15:51.588$ negotiated for a year and it's just kill.

NOTE Confidence: 0.895037921428572

 $00:15:51.588 \rightarrow 00:15:53.436$ The cells are just really sick.

NOTE Confidence: 0.895037921428572

 $00{:}15{:}53{.}440 \dashrightarrow 00{:}15{:}54{.}880$ And since and this you could

NOTE Confidence: 0.895037921428572

 $00{:}15{:}54{.}880 \dashrightarrow 00{:}15{:}55{.}840$ have measured any metabolite,

NOTE Confidence: 0.895037921428572

 $00{:}15{:}55{.}840 \dashrightarrow 00{:}15{:}58{.}378$ but you just measure 2 HG and Gee you

 $00:15:58.378 \rightarrow 00:16:00.440$ know this is true, true and unrelated.

NOTE Confidence: 0.895037921428572

 $00{:}16{:}00{.}440 \dashrightarrow 00{:}16{:}02{.}400$ These cells are just dying, who cares?

NOTE Confidence: 0.895037921428572

 $00:16:02.400 \dashrightarrow 00:16:04.080$ 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

 $00:16:04.956 \longrightarrow 00:16:05.960$ to do a better experiment.

NOTE Confidence: 0.895037921428572

 $00{:}16{:}05{.}960 \dashrightarrow 00{:}16{:}07{.}856$ So the better experiment was rather

NOTE Confidence: 0.895037921428572

 $00{:}16{:}07.856 \dashrightarrow 00{:}16{:}10.020$ than give these cells the IDH mutant,

NOTE Confidence: 0.895037921428572

 $00{:}16{:}10.020 \dashrightarrow 00{:}16{:}12.120$ 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

 $00{:}16{:}14.059 \dashrightarrow 00{:}16{:}16.687$ enters the cells and then gets trapped

NOTE Confidence: 0.895037921428572

 $00{:}16{:}16{.}687 \dashrightarrow 00{:}16{:}18{.}439$ 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

 $00:16:20.720 \longrightarrow 00:16:22.565$ 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

 $00:16:25.160 \longrightarrow 00:16:26.497$ And that's shown here is if you

NOTE Confidence: 0.895037921428572

 $00:16:26.497 \rightarrow 00:16:27.719$ give this Ester to these cells,

- NOTE Confidence: 0.895037921428572
- $00:16:27.720 \longrightarrow 00:16:28.612$ 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
- $00:16:30.400 \rightarrow 00:16:32.800$ which is really, really important.
- NOTE Confidence: 0.895037921428572
- 00:16:32.800 --> 00:16:33.310 So thankfully,
- NOTE Confidence: 0.895037921428572
- $00:16:33.310 \longrightarrow 00:16:34.840$ because for this and other reasons,
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}34{.}840 \dashrightarrow 00{:}16{:}36{.}835$ these drugs move forward and I'm happy
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}36{.}835 \dashrightarrow 00{:}16{:}39{.}319$ to report we now have an inhibitor of
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}39{.}319 \dashrightarrow 00{:}16{:}41{.}936$ both mutinite H1 and mutinite H2 for
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}41.936 \dashrightarrow 00{:}16{:}44.080$ 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
- $00:16:46.320 \rightarrow 00:16:47.208$ although some patients certainly
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}47.208 \dashrightarrow 00{:}16{:}48.318$ get a lot of benefit.
- NOTE Confidence: 0.895037921428572
- $00:16:48.320 \rightarrow 00:16:49.604$ But clearly there's heterogeneity
- NOTE Confidence: 0.895037921428572
- $00{:}16{:}49{.}604 \dashrightarrow 00{:}16{:}51{.}209$ and we have to understand
- NOTE Confidence: 0.895037921428572
- $00:16:51.209 \rightarrow 00:16:52.590$ 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

 $00:16:57.080 \rightarrow 00:16:59.000$ it was certainly plausible that the

NOTE Confidence: 0.895037921428572

 $00{:}16{:}59{.}000 \dashrightarrow 00{:}17{:}01{.}479$ tumors seen in VHL disease were all about

NOTE Confidence: 0.895037921428572

 $00:17:01.479 \rightarrow 00:17:04.079$ hip and were all about an excessive hip.

NOTE Confidence: 0.895037921428572

 $00{:}17{:}04.080 \dashrightarrow 00{:}17{:}06.936$ But another take home for the students

NOTE Confidence: 0.895037921428572

 $00:17:06.936 \rightarrow 00:17:08.662$ is correlation plus plausibility

NOTE Confidence: 0.895037921428572

 $00{:}17{:}08.662 \dashrightarrow 00{:}17{:}10.917$ is not proof of causation.

NOTE Confidence: 0.895037921428572

 $00:17:10.920 \dashrightarrow 00:17:13.040$ 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

 $00:17:14.760 \longrightarrow 00:17:16.038$ hip does a lot of things.

NOTE Confidence: 0.895037921428572

 $00{:}17{:}16.040 \dashrightarrow 00{:}17{:}17.160$ Maybe that promotes tumor growth,

NOTE Confidence: 0.895037921428572

 $00:17:17.160 \longrightarrow 00:17:19.500$ but you have to do sort of the killer

NOTE Confidence: 0.895037921428572

 $00:17:19.500 \longrightarrow 00:17:21.000$ experiments, if you, if you can,

NOTE Confidence: 0.895037921428572

 $00:17:21.000 \longrightarrow 00:17:22.626$ just try to establish what you
$00:17:22.626 \rightarrow 00:17:24.159$ know what's really going on here.

NOTE Confidence: 0.895037921428572

 $00:17:24.160 \longrightarrow 00:17:24.914$ And again,

NOTE Confidence: 0.895037921428572

 $00{:}17{:}24{.}914 \dashrightarrow 00{:}17{:}26{.}799$ that often requires sort of

NOTE Confidence: 0.895037921428572

 $00:17:26.799 \longrightarrow 00:17:27.553$ genetic paradigms.

NOTE Confidence: 0.895037921428572

 $00{:}17{:}27.560 \dashrightarrow 00{:}17{:}29.486$ So we had shown some time ago that if

NOTE Confidence: 0.895037921428572

 $00{:}17{:}29{.}486 \dashrightarrow 00{:}17{:}31{.}687$ 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

 $00:17:33.360 \longrightarrow 00:17:35.826$ they lose the ability to form

NOTE Confidence: 0.895037921428572

 $00:17:35.826 \longrightarrow 00:17:37.440$ tumors and nude mice.

NOTE Confidence: 0.895037921428572

 $00{:}17{:}37{.}440 \dashrightarrow 00{:}17{:}40{.}240$ So Kichi Kondo took these cells and

NOTE Confidence: 0.895037921428572

 $00{:}17{:}40.320 \dashrightarrow 00{:}17{:}42.822$ 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

 $00:17:45.240 \rightarrow 00:17:47.325$ by BHL because the Prolil sites have

NOTE Confidence: 0.895037921428572

 $00{:}17{:}47{.}325 \dashrightarrow 00{:}17{:}49{.}035$ been converted to a lanine 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

 $00:17:51.108 \rightarrow 00:17:52.872$ a reciprocal set of experiments he

NOTE Confidence: 0.895037921428572

 $00{:}17{:}52.872 \dashrightarrow 00{:}17{:}54.828$ took these cells and eliminated HIP

NOTE Confidence: 0.895037921428572

 $00{:}17{:}54.828 \dashrightarrow 00{:}17{:}56.790$ 2A then with hairpin technology we NOTE Confidence: 0.856356112

 $00{:}17{:}56.853 \dashrightarrow 00{:}17{:}58.715$ now do this with CRISPR and these

NOTE Confidence: 0.856356112

 $00{:}17{:}58.715 \dashrightarrow 00{:}18{:}00.656$ cells lose the ability to form tumors.

NOTE Confidence: 0.856356112

 $00{:}18{:}00{.}656 \dashrightarrow 00{:}18{:}02{.}076$ And I will tell you,

NOTE Confidence: 0.856356112

 $00{:}18{:}02{.}080 \dashrightarrow 00{:}18{:}03{.}809$ when we did the same experiments with

NOTE Confidence: 0.856356112

 $00:18:03.809 \rightarrow 00:18:05.199$ the canonical member of the family,

NOTE Confidence: 0.856356112

 $00:18:05.200 \dashrightarrow 00:18:07.636$ HIP One, we got the opposite result.

NOTE Confidence: 0.856356112

 $00:18:07.640 \longrightarrow 00:18:09.400$ 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

 $00{:}18{:}10.360 \dashrightarrow 00{:}18{:}13.664$ but it's really hip to the less

NOTE Confidence: 0.856356112

 $00{:}18{:}13.664 \dashrightarrow 00{:}18{:}16.310$ well studied member of the family.

NOTE Confidence: 0.856356112

 $00:18:16.310 \longrightarrow 00:18:19.180$ Now, not shown here are the kind

NOTE Confidence: 0.856356112

 $00:18:19.271 \longrightarrow 00:18:21.815$ of controls I learned about at

NOTE Confidence: 0.856356112

 $00:18:21.815 \longrightarrow 00:18:23.036$ the knee of David Livingston,

- NOTE Confidence: 0.856356112
- $00:18:23.036 \dashrightarrow 00:18:24.760$ who taught me how to be a scientist.
- NOTE Confidence: 0.856356112
- $00:18:24.760 \longrightarrow 00:18:26.080$ So for the students,
- NOTE Confidence: 0.856356112
- $00:18:26.080 \rightarrow 00:18:27.560$ this is your required reading.
- NOTE Confidence: 0.856356112
- $00:18:27.560 \rightarrow 00:18:29.200$ I'm going to come back to that one more time.
- NOTE Confidence: 0.856356112
- $00:18:29.200 \longrightarrow 00:18:30.532$ But this is the required reading
- NOTE Confidence: 0.856356112
- $00{:}18{:}30{.}532 \dashrightarrow 00{:}18{:}31{.}900$ 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
- $00{:}18{:}33{.}419 \dashrightarrow 00{:}18{:}34{.}998$ 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
- $00:18:36.400 \rightarrow 00:18:38.440$ our colleagues in industry have
- NOTE Confidence: 0.856356112
- $00:18:38.440 \longrightarrow 00:18:41.251$ reported that 50 to 90% of the time
- NOTE Confidence: 0.856356112
- $00:18:41.251 \rightarrow 00:18:43.050$ when they go to replicate results from
- NOTE Confidence: 0.856356112
- $00:18:43.106 \rightarrow 00:18:45.320$ academic labs related to target validation,
- NOTE Confidence: 0.856356112
- $00{:}18{:}45{.}320 \dashrightarrow 00{:}18{:}47{.}240$ either the results are not
- NOTE Confidence: 0.856356112
- $00:18:47.240 \rightarrow 00:18:49.160$ reproducible or they're not robust,
- NOTE Confidence: 0.856356112

 $00:18:49.160 \longrightarrow 00:18:50.730$ 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

 $00:18:51.930 \longrightarrow 00:18:53.505$ OK. So I think we have to all

NOTE Confidence: 0.856356112

 $00{:}18{:}53{.}505 \dashrightarrow 00{:}18{:}54{.}480$ do a little bit better.

NOTE Confidence: 0.856356112

 $00{:}18{:}54{.}480 \dashrightarrow 00{:}18{:}57{.}000$ 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

 $00:18:58.240 \longrightarrow 00:19:00.543$ Well, we certainly knew by the 90s

NOTE Confidence: 0.856356112

 $00:19:00.543 \dashrightarrow 00:19:02.840$ that VEGF was under hip control.

NOTE Confidence: 0.856356112

 $00{:}19{:}02.840 \dashrightarrow 00{:}19{:}03.472$ And thank fully,

NOTE Confidence: 0.856356112

 $00:19:03.472 \longrightarrow 00:19:05.052$ a number of companies were

NOTE Confidence: 0.856356112

 $00{:}19{:}05{.}052 \dashrightarrow 00{:}19{:}06{.}000$ making VEGF inhibitors.

NOTE Confidence: 0.856356112

 $00:19:06.000 \longrightarrow 00:19:07.491$ 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

 $00:19:08.960 \rightarrow 00:19:10.160$ they should work in VHL,

NOTE Confidence: 0.856356112

 $00:19:10.160 \dashrightarrow 00:19:12.520$ defective kidney tumors, for example.

NOTE Confidence: 0.856356112

 $00:19:12.520 \longrightarrow 00:19:14.319$ 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
- $00:19:16.422 \longrightarrow 00:19:17.666$ VEGF inhibitors approved for
- NOTE Confidence: 0.856356112
- $00:19:17.666 \rightarrow 00:19:19.320$ the treatment of kidney cancer.
- NOTE Confidence: 0.856356112
- $00{:}19{:}19{.}320 \dashrightarrow 00{:}19{:}20{.}120$ 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
- $00:19:23.400 \longrightarrow 00:19:25.020$ and even those that do will
- NOTE Confidence: 0.856356112
- $00:19:25.020 \rightarrow 00:19:25.560$ eventually progress,
- NOTE Confidence: 0.856356112
- $00:19:25.560 \rightarrow 00:19:26.760$ although thankfully sometimes
- NOTE Confidence: 0.856356112
- $00:19:26.760 \longrightarrow 00:19:28.050$ it takes many years.
- NOTE Confidence: 0.856356112
- $00:19:28.050 \longrightarrow 00:19:29.520$ So how can we do better?
- NOTE Confidence: 0.856356112
- $00:19:29.520 \longrightarrow 00:19:31.032$ Well, I hope some of the students
- NOTE Confidence: 0.856356112
- $00:19:31.032 \rightarrow 00:19:32.240$ are saying to themselves,
- NOTE Confidence: 0.856356112
- $00{:}19{:}32{.}240 \dashrightarrow 00{:}19{:}34{.}352$ kale and you dummy, rather than
- NOTE Confidence: 0.856356112
- $00:19:34.352 \rightarrow 00:19:36.120$ target anyone hip responsive gene,
- NOTE Confidence: 0.856356112

- $00:19:36.120 \longrightarrow 00:19:37.260$ 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
- $00:19:39.320 \longrightarrow 00:19:40.280$ you should target hip too.
- NOTE Confidence: 0.856356112
- $00:19:40.280 \longrightarrow 00:19:41.264$ Wouldn't that be nice?
- NOTE Confidence: 0.856356112
- 00:19:41.264 --> 00:19:41.756 But again,
- NOTE Confidence: 0.856356112
- $00{:}19{:}41.760 \dashrightarrow 00{:}19{:}43.468$ the naysayers come out of the woodwork
- NOTE Confidence: 0.856356112
- $00{:}19{:}43.468 \dashrightarrow 00{:}19{:}45.136$ and they start saying you can't do
- NOTE Confidence: 0.856356112
- $00:19:45.136 \rightarrow 00:19:47.904$ 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
- $00:19:51.028 \rightarrow 00:19:51.640$ hormone receptor family.
- NOTE Confidence: 0.856356112
- $00{:}19{:}51{.}640 \dashrightarrow 00{:}19{:}53{.}383$ So it doesn't have a natural pocket
- NOTE Confidence: 0.856356112
- $00:19:53.383 \longrightarrow 00:19:55.279$ for a drug like small molecule.
- NOTE Confidence: 0.856356112
- $00:19:55.280 \longrightarrow 00:19:57.492$ So forget about it.
- NOTE Confidence: 0.856356112
- 00:19:57.492 --> 00:19:58.598 But fortunately,
- NOTE Confidence: 0.856356112
- $00:19:58.600 \rightarrow 00:20:00.412$ 2 very talented scientists,

00:20:00.412 --> 00:20:02.226 Rick Bruick and Kevin Gardner,

NOTE Confidence: 0.856356112

 $00{:}20{:}02{.}226 \dashrightarrow 00{:}20{:}04.038$ who were then at UT Southwestern,

NOTE Confidence: 0.856356112

 $00{:}20{:}04.040 \dashrightarrow 00{:}20{:}06.150$ identified a potentially druggable pocket

NOTE Confidence: 0.856356112

 $00{:}20{:}06{.}150 \dashrightarrow 00{:}20{:}09{.}611$ in the so-called Pass B domain of HIP 2A.

NOTE Confidence: 0.856356112

 $00:20:09.611 \rightarrow 00:20:11.393$ And they did high throughput screens

NOTE Confidence: 0.856356112

 $00{:}20{:}11.393 \dashrightarrow 00{:}20{:}13.275$ at UT Southwestern and identified

NOTE Confidence: 0.856356112

 $00:20:13.275 \rightarrow 00:20:16.040$ chemicals that could bind to this pocket.

NOTE Confidence: 0.856356112

 $00:20:16.040 \longrightarrow 00:20:17.848$ And in so doing and do some allosteric

NOTE Confidence: 0.856356112

 $00{:}20{:}17.848 \dashrightarrow 00{:}20{:}19.429$ change in HIF to alpha such that

NOTE Confidence: 0.856356112

 $00{:}20{:}19{.}429 \dashrightarrow 00{:}20{:}21{.}009$ it could no longer bind to aren't

NOTE Confidence: 0.856356112

 $00:20:21.009 \rightarrow 00:20:24.680$ and hits no longer bind to DNA.

NOTE Confidence: 0.856356112

 $00{:}20{:}24.680 \dashrightarrow 00{:}20{:}26.670$ Now these chemicals are what

NOTE Confidence: 0.856356112

 $00:20:26.670 \longrightarrow 00:20:28.660$ some of my drug hunter

NOTE Confidence: 0.945157414166667

 $00{:}20{:}28{.}745 \dashrightarrow 00{:}20{:}30{.}626$ friends called publication grade

NOTE Confidence: 0.945157414166667

 $00{:}20{:}30.626 \dashrightarrow 00{:}20{:}32.198$ but not pharmaceutical grade.

NOTE Confidence: 0.945157414166667

 $00:20:32.200 \rightarrow 00:20:34.366$ They had too many blemishes and

NOTE Confidence: 0.945157414166667

 $00{:}20{:}34{.}366 \dashrightarrow 00{:}20{:}37{.}120$ warts to really be drugs for people.

NOTE Confidence: 0.945157414166667

 $00:20:37.120 \longrightarrow 00:20:38.492$ But fortunately these chemicals

NOTE Confidence: 0.945157414166667

 $00:20:38.492 \longrightarrow 00:20:40.550$ were out licensed to a biotech

NOTE Confidence: 0.945157414166667

 $00:20:40.612 \longrightarrow 00:20:43.532$ company in Dallas or that was in

NOTE Confidence: 0.945157414166667

 $00:20:43.532 \rightarrow 00:20:45.013$ Dallas called Peloton Therapeutics.

NOTE Confidence: 0.945157414166667

 $00{:}20{:}45.013 \dashrightarrow 00{:}20{:}47.119$ And the chemist at Peloton improved

NOTE Confidence: 0.945157414166667

 $00:20:47.119 \longrightarrow 00:20:48.479$ these chemicals substantially in

NOTE Confidence: 0.945157414166667

 $00{:}20{:}48.479 \dashrightarrow 00{:}20{:}50.340$ terms of their drug like properties.

NOTE Confidence: 0.945157414166667

 $00{:}20{:}50{.}340 \dashrightarrow 00{:}20{:}52{.}420$ And they were kind enough to share with

NOTE Confidence: 0.945157414166667

 $00:20:52.420 \longrightarrow 00:20:55.690$ us a tool compound called PT2399 which

NOTE Confidence: 0.945157414166667

 $00{:}20{:}55{.}690 \dashrightarrow 00{:}20{:}58{.}077$ at the time was only one or two atoms

NOTE Confidence: 0.945157414166667

 $00{:}20{:}58.077 \dashrightarrow 00{:}21{:}01.400$ removed from the then lead compound.

NOTE Confidence: 0.945157414166667

 $00:21:01.400 \longrightarrow 00:21:03.240$ And so we had early access to this

NOTE Confidence: 0.945157414166667

 $00:21:03.240 \rightarrow 00:21:05.147$ compound and we could show that this

NOTE Confidence: 0.945157414166667

 $00:21:05.147 \rightarrow 00:21:06.840$ 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
- $00{:}21{:}13.080 \dashrightarrow 00{:}21{:}15.960$ Jim Brogarolis in his own laboratory.
- NOTE Confidence: 0.945157414166667
- $00:21:15.960 \longrightarrow 00:21:17.374$ And so now it looks like maybe
- NOTE Confidence: 0.945157414166667
- $00:21:17.374 \longrightarrow 00:21:18.520$ we're on to something,
- NOTE Confidence: 0.945157414166667
- $00:21:18.520 \longrightarrow 00:21:20.032$ but I'll point out the assays
- NOTE Confidence: 0.945157414166667
- $00:21:20.032 \rightarrow 00:21:21.832$ 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
- $00:21:24.180 \rightarrow 00:21:26.645$ decreased soft dog growth decrease,
- NOTE Confidence: 0.945157414166667
- 00:21:26.645 --> 00:21:27.615 proliferation decrease,
- NOTE Confidence: 0.945157414166667
- $00:21:27.615 \rightarrow 00:21:29.555$ 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

 $00:21:34.280 \longrightarrow 00:21:36.596$ here's a lovely soft dagger essay

NOTE Confidence: 0.945157414166667

 $00:21:36.600 \rightarrow 00:21:38.360$ that was done by Chincho in my lab.

NOTE Confidence: 0.945157414166667

 $00:21:38.360 \longrightarrow 00:21:40.691$ So you had 0.2 or two micromolar of the

NOTE Confidence: 0.945157414166667

 $00{:}21{:}40.691 \dashrightarrow 00{:}21{:}43.268$ HIP 2 inhibitor and these renal carcinoma

NOTE Confidence: 0.945157414166667

 $00{:}21{:}43.268 \dashrightarrow 00{:}21{:}45.660$ 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

 $00:21:52.780 \longrightarrow 00:21:54.080$ cancer cell we've ever looked at,

NOTE Confidence: 0.945157414166667

 $00:21:54.080 \rightarrow 00:21:56.159$ whether it expresses if to or not.

NOTE Confidence: 0.945157414166667

 $00:21:56.160 \longrightarrow 00:21:57.480$ So by definition,

NOTE Confidence: 0.945157414166667

 $00:21:57.480 \longrightarrow 00:21:58.800$ 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,

 $00{:}22{:}01{.}282 \dashrightarrow 00{:}22{:}03{.}538$ I've said this is the kind of experiment

NOTE Confidence: 0.945157414166667

 $00:22:03.538 \rightarrow 00:22:05.915$ 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

 $00{:}22{:}09{.}332 \dashrightarrow 00{:}22{:}11.888$ to as sprinklers because they simply

NOTE Confidence: 0.945157414166667

 $00{:}22{:}11.888 \dashrightarrow 00{:}22{:}13.304$ sprinkled noxious chemicals on

NOTE Confidence: 0.945157414166667

 $00{:}22{:}13{.}304 \dashrightarrow 00{:}22{:}15{.}272$ cancer cells and watch them die.

NOTE Confidence: 0.945157414166667

 $00:22:15.280 \rightarrow 00:22:15.489$ So,

NOTE Confidence: 0.945157414166667

00:22:15.489 --> 00:22:15.907 you know,

NOTE Confidence: 0.945157414166667

 $00{:}22{:}15{.}907 \dashrightarrow 00{:}22{:}17{.}720$ I could have done this with Clorox bleach.

NOTE Confidence: 0.945157414166667

 $00{:}22{:}17.720 \dashrightarrow 00{:}22{:}19.960$ I could have done this with formal in.

NOTE Confidence: 0.945157414166667

 $00:22:19.960 \longrightarrow 00:22:21.320$ You know what's what's really?

NOTE Confidence: 0.945157414166667

 $00:22:21.320 \longrightarrow 00:22:22.560$ Is this just another poison?

NOTE Confidence: 0.945157414166667

 $00{:}22{:}22{.}560 \dashrightarrow 00{:}22{:}26.618$ But CHIN used CRISPR to make is agenic

NOTE Confidence: 0.945157414166667

 $00{:}22{:}26.618 \dashrightarrow 00{:}22{:}29.910$ cells that had wild type HIP 2A or had

NOTE Confidence: 0.945157414166667

 $00:22:29.910 \rightarrow 00:22:31.950$ hip 2A with a single amino acid change

NOTE Confidence: 0.945157414166667

 $00{:}22{:}32.009 \dashrightarrow 00{:}22{:}33.878$ in that pocket that I showed you.

NOTE Confidence: 0.945157414166667

 $00{:}22{:}33{.}880 \dashrightarrow 00{:}22{:}36{.}112$ That prevents the drug from binding to the

NOTE Confidence: 0.945157414166667

 $00:22:36.112 \rightarrow 00:22:38.356$ pocket but otherwise leaves hip 2A intact.

NOTE Confidence: 0.945157414166667

 $00{:}22{:}38{.}360 \dashrightarrow 00{:}22{:}41{.}070$ And now you can see we rescue the phenotype.

NOTE Confidence: 0.945157414166667

 $00:22:41.070 \longrightarrow 00:22:42.840$ Now eventually an approved version of

NOTE Confidence: 0.945157414166667

 $00:22:42.840 \longrightarrow 00:22:44.748$ this HIP 2 inhibitor which is called

NOTE Confidence: 0.945157414166667

 $00{:}22{:}44.748 \dashrightarrow 00{:}22{:}46.563$ Bel Sudafan and I should declare I

NOTE Confidence: 0.945157414166667

 $00{:}22{:}46.563 \dashrightarrow 00{:}22{:}48.388$ have a financial conflict of interest

NOTE Confidence: 0.945157414166667

 $00{:}22{:}48{.}388 \dashrightarrow 00{:}22{:}50{.}168$ with Balsedifan went into testing

NOTE Confidence: 0.945157414166667

 $00{:}22{:}50{.}168 \dashrightarrow 00{:}22{:}51{.}984$ for patients with advanced kidney

NOTE Confidence: 0.945157414166667

 $00{:}22{:}51{.}984 \dashrightarrow 00{:}22{:}54{.}072$ 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

 $00{:}22{:}55{.}680 \dashrightarrow 00{:}22{:}56{.}480$ etcetera etcetera.

NOTE Confidence: 0.945157414166667

 $00{:}22{:}56{.}480 \dashrightarrow 00{:}22{:}58{.}680$ These are so-called swimmers plots.

NOTE Confidence: 0.945157414166667

 $00:22:58.680 \rightarrow 00:23:00.440$ So you may know that each of these

- NOTE Confidence: 0.945157414166667
- $00:23:00.440 \longrightarrow 00:23:01.680$ horizontal bars is a patient on
- NOTE Confidence: 0.945157414166667
- $00:23:01.680 \rightarrow 00:23:03.080$ the trial and how long they were
- NOTE Confidence: 0.945157414166667
- $00:23:03.080 \longrightarrow 00:23:04.695$ 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
- $00:23:05.400 \longrightarrow 00:23:07.440$ Here's one year on the rapy.
- NOTE Confidence: 0.945157414166667
- $00{:}23{:}07{.}440 \dashrightarrow 00{:}23{:}09{.}125$ The black arrows were patients
- NOTE Confidence: 0.945157414166667
- $00:23:09.125 \longrightarrow 00:23:10.810$ who were still doing well
- NOTE Confidence: 0.916370030833333
- $00:23:10.877 \longrightarrow 00:23:12.794$ on the rapy at the time of this analysis
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}12.794 \dashrightarrow 00{:}23{:}14.680$ and the yellow star patients were patients
- NOTE Confidence: 0.916370030833333
- $00:23:14.680 \longrightarrow 00:23:17.120$ who achieved a resist partial response.
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}17.120 \dashrightarrow 00{:}23{:}20.635$ And I'll come back to the development
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}20.635 \dashrightarrow 00{:}23{:}23.358$ of belsitovan at the end of the talk.
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}23{.}360 \dashrightarrow 00{:}23{:}24{.}920$ So now I want to move to some newer data.
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}24{.}920 \dashrightarrow 00{:}23{:}27{.}395$ So this is the first story is work of
- NOTE Confidence: 0.916370030833333
- $00{:}23{:}27{.}395 \dashrightarrow 00{:}23{:}29{.}520$ 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

 $00{:}23{:}31{.}188 \dashrightarrow 00{:}23{:}33{.}276$ we have this if two inhibitor,

NOTE Confidence: 0.916370030833333

 $00:23:33.280 \longrightarrow 00:23:34.610$ it's inhibiting the growth of

NOTE Confidence: 0.916370030833333

 $00:23:34.610 \longrightarrow 00:23:35.674$ these kidney cancer cells.

NOTE Confidence: 0.916370030833333

 $00{:}23{:}35{.}680 \dashrightarrow 00{:}23{:}37{.}846$ But are all hip to target

NOTE Confidence: 0.916370030833333

 $00{:}23{:}37{.}846 \dashrightarrow 00{:}23{:}39{.}640$ genes equally important or not.

NOTE Confidence: 0.916370030833333

 $00:23:39.640 \longrightarrow 00:23:41.838$ So the simple idea is you have

NOTE Confidence: 0.916370030833333

 $00:23:41.838 \longrightarrow 00:23:43.600$ 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

 $00:23:44.720 \longrightarrow 00:23:47.240$ but for this illustration let's pick 4.

NOTE Confidence: 0.916370030833333

 $00{:}23{:}47{.}240 \dashrightarrow 00{:}23{:}49{.}656$ You come in with your inhibitor and now

NOTE Confidence: 0.916370030833333

 $00{:}23{:}49{.}656 \dashrightarrow 00{:}23{:}51{.}960$ 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

 $00:23:59.080 \longrightarrow 00:24:01.796$ even in the face of the inhibitor,

- NOTE Confidence: 0.916370030833333
- $00:24:01.800 \rightarrow 00:24:04.026$ And to do this systematically go through
- NOTE Confidence: 0.916370030833333
- $00:24:04.026 \rightarrow 00:24:06.360$ all of the HIP two target genes.
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}06{.}360 \dashrightarrow 00{:}24{:}06{.}912$ And in fact,
- NOTE Confidence: 0.916370030833333
- $00:24:06.912 \longrightarrow 00:24:08.200$ as I'll show you in a moment
- NOTE Confidence: 0.916370030833333
- $00:24:08.200 \longrightarrow 00:24:09.061$ 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
- $00:24:11.447 \longrightarrow 00:24:13.360$ scale and then in silico looked
- NOTE Confidence: 0.916370030833333
- $00:24:13.360 \longrightarrow 00:24:15.084$ for HIP two target genes.
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}15.084 \dashrightarrow 00{:}24{:}17.376$ 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
- $00:24:19.592 \rightarrow 00:24:21.317$ colleagues at the Broad Institute
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}21{.}317 \dashrightarrow 00{:}24{:}23{.}040$ and this was the the preferred
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}23.040 \dashrightarrow 00{:}24{:}24.440$ technology about two years ago.
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}24{.}440 \dashrightarrow 00{:}24{:}25{.}928$ I can tell you they've improved upon it
- NOTE Confidence: 0.916370030833333
- $00:24:25.928 \rightarrow 00:24:28.200$ further, but this worked quite well.
- NOTE Confidence: 0.916370030833333

 $00:24:28.200 \rightarrow 00:24:30.040$ 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

 $00{:}24{:}31.050 \dashrightarrow 00{:}24{:}33.070$ that recruits A transitional

NOTE Confidence: 0.916370030833333

 $00:24:33.070 \longrightarrow 00:24:34.782$ activation domain BP 64.

NOTE Confidence: 0.916370030833333

 $00{:}24{:}34{.}782 \dashrightarrow 00{:}24{:}37{.}239$ And then you you have some additional

NOTE Confidence: 0.916370030833333

 $00:24:37.239 \longrightarrow 00:24:39.190$ engineering of the CRISPR guides to

NOTE Confidence: 0.916370030833333

 $00:24:39.190 \longrightarrow 00:24:41.919$ 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

 $00{:}24{:}42.688 \dashrightarrow 00{:}24{:}44.480$ this is kind of complicated and baroque,

NOTE Confidence: 0.916370030833333

 $00:24:44.480 \longrightarrow 00:24:46.160$ but it actually turns out to

NOTE Confidence: 0.916370030833333

 $00:24:46.160 \longrightarrow 00:24:46.995$ 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

 $00:24:49.200 \longrightarrow 00:24:51.216$ 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

 $00:24:54.416 \longrightarrow 00:24:57.020$ a guide library in cells that

- NOTE Confidence: 0.916370030833333
- $00{:}24{:}57{.}020 \dashrightarrow 00{:}24{:}59{.}160$ express that specialized CAS 9.
- NOTE Confidence: 0.916370030833333
- $00{:}24{:}59{.}160 \dashrightarrow 00{:}25{:}01{.}392$ And then he treats the cells with DMSO or
- NOTE Confidence: 0.916370030833333
- $00:25:01.392 \rightarrow 00:25:03.676$ the tool compound that inhibits hip two.
- NOTE Confidence: 0.916370030833333
- $00:25:03.680 \rightarrow 00:25:05.455$ And then he monitors guide
- NOTE Confidence: 0.916370030833333
- $00{:}25{:}05{.}455 \dashrightarrow 00{:}25{:}07{.}560$ abundance over time by next Gen.
- NOTE Confidence: 0.916370030833333
- $00:25:07.560 \rightarrow 00:25:07.820$ sequencing.
- NOTE Confidence: 0.916370030833333
- $00{:}25{:}07{.}820 \dashrightarrow 00{:}25{:}09{.}640$ 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
- $00{:}25{:}11.000 \dashrightarrow 00{:}25{:}13.056$ So these this is the data from the
- NOTE Confidence: 0.916370030833333
- $00{:}25{:}13.056 \dashrightarrow 00{:}25{:}15.172$ cells treated with PT2399 and it turns
- NOTE Confidence: 0.916370030833333
- $00:25:15.172 \rightarrow 00:25:17.680$ out one of the top scoring genes.
- NOTE Confidence: 0.916370030833333
- $00{:}25{:}17.680 \dashrightarrow 00{:}25{:}19.255$ 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
- $00:25:21.067 \rightarrow 00:25:23.712$ 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

 $00:25:25.928 \rightarrow 00:25:27.916$ already known to be a hip two

NOTE Confidence: 0.916370030833333

 $00{:}25{:}27{.}916 \dashrightarrow 00{:}25{:}29{.}334$ target in kidney cancer,

NOTE Confidence: 0.916370030833333

 $00:25:29.334 \rightarrow 00:25:31.224$ but interestingly and every other

NOTE Confidence: 0.916370030833333

 $00:25:31.224 \rightarrow 00:25:33.767$ cancer that's been examined to date if

NOTE Confidence: 0.916370030833333

 $00:25:33.767 \rightarrow 00:25:35.720$ if anything down regulates Cyclone D1.

NOTE Confidence: 0.916370030833333

 $00:25:35.720 \longrightarrow 00:25:37.694$ So this is probably part of the

NOTE Confidence: 0.916370030833333

 $00:25:37.694 \longrightarrow 00:25:39.629$ puzzle of why VHL loss causes

NOTE Confidence: 0.916370030833333

 $00:25:39.629 \rightarrow 00:25:41.675$ kidney cancer but not for example

NOTE Confidence: 0.916370030833333

 $00{:}25{:}41.680 \dashrightarrow 00{:}25{:}43.600$ lung cancer or colon cancer.

NOTE Confidence: 0.916370030833333

 $00:25:43.600 \rightarrow 00:25:45.376$ So just to show you how

NOTE Confidence: 0.916370030833333

 $00:25:45.376 \rightarrow 00:25:46.560$ beautifully this technology works,

NOTE Confidence: 0.916370030833333

 $00:25:46.560 \longrightarrow 00:25:48.625$ what I have here is a control

NOTE Confidence: 0.916370030833333

 $00:25:48.625 \rightarrow 00:25:50.412$ guide or two different CRISPR

NOTE Confidence: 0.916370030833333

 $00:25:50.412 \rightarrow 00:25:52.277$ activation guides from Cyclone D1.

NOTE Confidence: 0.881593069230769

 $00:25:52.280 \longrightarrow 00:25:54.240$ So now we either don't or do

NOTE Confidence: 0.881593069230769

 $00:25:54.240 \longrightarrow 00:25:56.199$ treat with the Hip 2 inhibitor.

- NOTE Confidence: 0.881593069230769
- $00:25:56.200 \rightarrow 00:25:58.118$ So now let's look at Cyclone D1.
- NOTE Confidence: 0.881593069230769
- $00{:}25{:}58{.}120 \dashrightarrow 00{:}26{:}00{.}960$ So if you down regulate hip two activity,
- NOTE Confidence: 0.881593069230769
- $00:26:00.960 \longrightarrow 00:26:02.760$ you down regulate second D1.
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}02{.}760 \dashrightarrow 00{:}26{:}05{.}064$ But now with the CRISPR A guides we can
- NOTE Confidence: 0.881593069230769
- $00:26:05.064 \rightarrow 00:26:06.999$ maintain the expression of Cyclone D1.
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}06{.}999 \dashrightarrow 00{:}26{:}08{.}757$ This is specific because NDRG one
- NOTE Confidence: 0.881593069230769
- $00:26:08.757 \rightarrow 00:26:10.720$ is another hip two target gene.
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}10.720 \dashrightarrow 00{:}26{:}12.448$ So you can see the CRISPR A guides
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}12.448 \dashrightarrow 00{:}26{:}14.600$ are really specific or second D1 and
- NOTE Confidence: 0.881593069230769
- $00:26:14.600 \longrightarrow 00:26:16.520$ now we can do validation assays.
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}16{.}520 \dashrightarrow 00{:}26{:}18{.}956$ And I apologize that by my
- NOTE Confidence: 0.881593069230769
- $00:26:18.956 \longrightarrow 00:26:21.720$ counts this is a busy slide,
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}21.720 \dashrightarrow 00{:}26{:}23.729$ although what counts for a busy slide
- NOTE Confidence: 0.881593069230769
- $00{:}26{:}23.729 \dashrightarrow 00{:}26{:}25.720$ these days is certainly changing.
- NOTE Confidence: 0.881593069230769
- $00:26:25.720 \longrightarrow 00:26:28.216$ So here I have cell number on the
- NOTE Confidence: 0.881593069230769

 $00:26:28.216 \longrightarrow 00:26:30.717$ Y axis and days on the X axis.

NOTE Confidence: 0.881593069230769

 $00{:}26{:}30{.}720 \dashrightarrow 00{:}26{:}32{.}164$ So now for orientation,

NOTE Confidence: 0.881593069230769

 $00:26:32.164 \rightarrow 00:26:34.760$ here are the cells grown in DMSO.

NOTE Confidence: 0.881593069230769

 $00:26:34.760 \longrightarrow 00:26:36.224$ Here are the cells now treated

NOTE Confidence: 0.881593069230769

 $00:26:36.224 \longrightarrow 00:26:37.800$ 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

 $00:26:40.840 \rightarrow 00:26:43.228$ the cells are completely resistant,

NOTE Confidence: 0.881593069230769

 $00{:}26{:}43.228 \dashrightarrow 00{:}26{:}45.796$ at least in this preclinical model.

NOTE Confidence: 0.881593069230769

 $00:26:45.800 \longrightarrow 00:26:47.192$ So we think there's an analogy

NOTE Confidence: 0.881593069230769

 $00:26:47.192 \longrightarrow 00:26:48.917$ to be made here potentially with

NOTE Confidence: 0.881593069230769

 $00:26:48.917 \rightarrow 00:26:50.393$ hormone responsive breast cancer

NOTE Confidence: 0.881593069230769

 $00{:}26{:}50{.}393 \dashrightarrow 00{:}26{:}52{.}530$ because the standard of care for

NOTE Confidence: 0.881593069230769

 $00:26:52.530 \rightarrow 00:26:54.045$ many women with hormone responsive

NOTE Confidence: 0.881593069230769

 $00{:}26{:}54.045 \dashrightarrow 00{:}26{:}56.336$ 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
- $00:27:04.160 \longrightarrow 00:27:06.192$ And so you can imagine you get some
- NOTE Confidence: 0.881593069230769
- $00{:}27{:}06.192 \dashrightarrow 00{:}27{:}07.635$ synergy there because ER drives
- NOTE Confidence: 0.881593069230769
- $00{:}27{:}07.635 \dashrightarrow 00{:}27{:}09.381$ the expression of cyclin D1 in
- NOTE Confidence: 0.881593069230769
- $00:27:09.381 \rightarrow 00:27:11.079$ 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
- $00{:}27{:}12.706 \dashrightarrow 00{:}27{:}14.799$ 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
- $00:27:16.298 \rightarrow 00:27:17.893$ and we have some preclinical data
- NOTE Confidence: 0.881593069230769
- $00{:}27{:}17.893 \dashrightarrow 00{:}27{:}18.796$ to support this.
- NOTE Confidence: 0.881593069230769
- $00{:}27{:}18.800 \dashrightarrow 00{:}27{:}20.432$ It would be a good idea to combine
- NOTE Confidence: 0.881593069230769
- $00{:}27{:}20{.}432 \dashrightarrow 00{:}27{:}22{.}620$ a HEF 2 inhibitor with the CDK 46
- NOTE Confidence: 0.881593069230769
- $00:27:22.620 \rightarrow 00:27:24.370$ inhibitor and kidney cancer and
- NOTE Confidence: 0.881593069230769

 $00:27:24.370 \rightarrow 00:27:27.680$ such clinical trials have now begun

NOTE Confidence: 0.881593069230769

 $00{:}27{:}27{.}680 \dashrightarrow 00{:}27{:}30{.}259$ now as often happens in experiments

NOTE Confidence: 0.881593069230769

 $00{:}27{:}30{.}259 \dashrightarrow 00{:}27{:}32{.}053$ and another reason to do controls

NOTE Confidence: 0.881593069230769

 $00:27:32.053 \rightarrow 00:27:34.081$ is it's I've been amazed over the

NOTE Confidence: 0.881593069230769

 $00{:}27{:}34.081 \dashrightarrow 00{:}27{:}35.689$ years how often there's gold in

NOTE Confidence: 0.881593069230769

 $00{:}27{:}35{.}748 \dashrightarrow 00{:}27{:}37{.}519$ 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

 $00{:}27{:}38{.}882 \dashrightarrow 00{:}27{:}40{.}989$ So now let's look at the cells

NOTE Confidence: 0.881593069230769

 $00{:}27{:}40.989 \dashrightarrow 00{:}27{:}42.120$ that got the DMSO,

NOTE Confidence: 0.881593069230769

 $00:27:42.120 \rightarrow 00:27:44.600$ 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

 $00{:}27{:}45{.}288 \dashrightarrow 00{:}27{:}47{.}008$ these data caught our attention

NOTE Confidence: 0.881593069230769

 $00{:}27{:}47.008 \dashrightarrow 00{:}27{:}48.800$ as well because here's MEC,

NOTE Confidence: 0.881593069230769

 $00{:}27{:}48.800 \dashrightarrow 00{:}27{:}50.475$ which had already been implicated

NOTE Confidence: 0.881593069230769

 $00:27:50.475 \longrightarrow 00:27:52.600$ in kidney cancer growth by others.

NOTE Confidence: 0.881593069230769

 $00:27:52.600 \longrightarrow 00:27:54.862$ 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
- $00:27:56.084 \rightarrow 00:27:59.038$ which among other things activates NRF 2,
- NOTE Confidence: 0.881593069230769
- $00:27:59.040 \longrightarrow 00:28:01.633$ which the gene name is NFE 2L2.
- NOTE Confidence: 0.881593069230769
- $00{:}28{:}01{.}633 \dashrightarrow 00{:}28{:}03{.}544$ So the reason we were excited about
- NOTE Confidence: 0.881593069230769
- $00:28:03.544 \rightarrow 00:28:05.785$ this is I have to say the most
- NOTE Confidence: 0.881593069230769
- $00{:}28{:}05{.}785 \dashrightarrow 00{:}28{:}07{.}218$ 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
- $00{:}28{:}08{.}640 \dashrightarrow 00{:}28{:}11{.}046$ I mean a carcinoma is amplification
- NOTE Confidence: 0.881593069230769
- $00:28:11.046 \longrightarrow 00:28:13.523$ OF5Q And using horse and buggy
- NOTE Confidence: 0.881593069230769
- $00:28:13.523 \rightarrow 00:28:15.822$ technology about 10 years ago we
- NOTE Confidence: 0.881593069230769
- $00{:}28{:}15.822 \dashrightarrow 00{:}28{:}17.936$ deduced that the most likely target of
- NOTE Confidence: 0.881593069230769
- $00{:}28{:}17{.}936 \dashrightarrow 00{:}28{:}20{.}500$ 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
- $00:28:22.000 \rightarrow 00:28:24.200$ maybe even somewhat orthogonal evidence
- NOTE Confidence: 0.881593069230769
- $00{:}28{:}24{.}200 \dashrightarrow 00{:}28{:}26{.}742$ that maybe we were even correct.
- NOTE Confidence: 0.881593069230769

 $00:28:26.742 \longrightarrow 00:28:28.794$ The other reason we like this

NOTE Confidence: 0.881593069230769

 $00{:}28{:}28{.}794 \dashrightarrow 00{:}28{:}30{.}758$ is now let's go over here.

NOTE Confidence: 0.881593069230769

 $00:28:30.760 \rightarrow 00:28:35.313$ 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

 $00:28:38.240 \longrightarrow 00:28:40.040$ to the kidney cancer cells.

NOTE Confidence: 0.966137331428571

 $00:28:40.040 \longrightarrow 00:28:42.994$ 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

 $00:28:44.764 \longrightarrow 00:28:47.332$ a lot of examples in cancer where

NOTE Confidence: 0.966137331428571

 $00{:}28{:}47{.}332 \dashrightarrow 00{:}28{:}49{.}522$ chromosomal arms or sometimes entire

NOTE Confidence: 0.966137331428571

 $00:28:49.522 \rightarrow 00:28:53.520$ chromosomes are missing. Excuse me.

NOTE Confidence: 0.966137331428571

 $00:28:53.520 \longrightarrow 00:28:55.081$ And the thought is that in many

NOTE Confidence: 0.966137331428571

 $00:28:55.081 \rightarrow 00:28:56.516$ cases you're dealing with HAPLO

NOTE Confidence: 0.966137331428571

 $00{:}28{:}56{.}516 \dashrightarrow 00{:}28{:}57{.}596$ 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

 $00{:}28{:}59{.}720 \dashrightarrow 00{:}29{:}01{.}084$ you've lowered the expression.

NOTE Confidence: 0.966137331428571

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

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

NOTE Confidence: 0.966137331428571

 $00{:}29{:}04.080 \dashrightarrow 00{:}29{:}06.144$ we don't have the smoking gun of a

NOTE Confidence: 0.966137331428571

 $00:29:06.144 \rightarrow 00:29:08.232$ mutation in the remaining allele as you

NOTE Confidence: 0.966137331428571

 $00:29:08.232 \rightarrow 00:29:09.800$ would with a Knutson 2 hit tumor suppressor.

NOTE Confidence: 0.966137331428571

 $00:29:09.800 \longrightarrow 00:29:12.072$ But now we think we have a very

NOTE Confidence: 0.966137331428571

 $00:29:12.072 \rightarrow 00:29:13.830$ powerful technology for reactivating

NOTE Confidence: 0.966137331428571

 $00:29:13.830 \rightarrow 00:29:16.805$ these putative PAPLO insufficient tumor

NOTE Confidence: 0.966137331428571

 $00:29:16.805 \longrightarrow 00:29:18.760$ suppressors that are lost in cancer.

NOTE Confidence: 0.966137331428571

 $00:29:18.760 \longrightarrow 00:29:21.280$ 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

 $00:29:22.800 \rightarrow 00:29:25.110$ a library for chromosome 1P which is

NOTE Confidence: 0.966137331428571

 $00:29:25.110 \rightarrow 00:29:27.359$ frequently deleted in a variety of cancers,

NOTE Confidence: 0.966137331428571

 $00:29:27.360 \longrightarrow 00:29:28.884$ including famously neuroblastomas

NOTE Confidence: 0.966137331428571

 $00:29:28.884 \rightarrow 00:29:30.916$ and are using CRISPR,

NOTE Confidence: 0.966137331428571

 $00{:}29{:}30{.}920 \dashrightarrow 00{:}29{:}33{.}165$ a technology with focused chromosome

NOTE Confidence: 0.966137331428571

 $00:29:33.165 \rightarrow 00:29:35.410$ or chromosome arm CRISPR guide

NOTE Confidence: 0.966137331428571

 $00{:}29{:}35{.}480 \dashrightarrow 00{:}29{:}38{.}216$ libraries to look for the relevant

NOTE Confidence: 0.966137331428571

 $00{:}29{:}38{.}216 \dashrightarrow 00{:}29{:}40{.}040$ HAPLO insufficient tumor express.

NOTE Confidence: 0.966137331428571

00:29:40.040 --> 00:29:40.240 OK,

NOTE Confidence: 0.966137331428571

 $00:29:40.240 \longrightarrow 00:29:41.840$ so now I'm going to completely switch gears.

NOTE Confidence: 0.966137331428571

 $00:29:41.840 \longrightarrow 00:29:42.918$ So if you didn't like that story,

NOTE Confidence: 0.966137331428571

 $00:29:42.920 \longrightarrow 00:29:43.880$ thank you for bearing with me.

NOTE Confidence: 0.966137331428571

 $00:29:43.880 \rightarrow 00:29:45.800$ We have a completely different type of story.

NOTE Confidence: 0.966137331428571

 $00{:}29{:}45{.}800 \dashrightarrow 00{:}29{:}47{.}150$ So it's been known for decades

NOTE Confidence: 0.966137331428571

 $00{:}29{:}47.150 \dashrightarrow 00{:}29{:}48.431$ that clear cell Weiner cell

NOTE Confidence: 0.966137331428571

 $00{:}29{:}48.431 \dashrightarrow 00{:}29{:}49.759$ carcinomas are highly immunogenic.

NOTE Confidence: 0.966137331428571

 $00:29:49.760 \longrightarrow 00:29:51.416$ They occasionally undergo

NOTE Confidence: 0.966137331428571

 $00:29:51.416 \longrightarrow 00:29:52.520$ spontaneous progressions.

NOTE Confidence: 0.966137331428571

 $00:29:52.520 \longrightarrow 00:29:54.095$ 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

 $00:29:55.360 \longrightarrow 00:29:56.368$ In the old days,

- NOTE Confidence: 0.966137331428571
- $00{:}29{:}56{.}368 \dashrightarrow 00{:}29{:}57{.}628$ 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
- $00{:}29{:}59{.}120 \dashrightarrow 00{:}30{:}00{.}260$ but some of those patients
- NOTE Confidence: 0.966137331428571
- $00:30:00.260 \longrightarrow 00:30:01.400$ wound up in the ICU.
- NOTE Confidence: 0.966137331428571
- $00{:}30{:}01{.}400 \dashrightarrow 00{:}30{:}03{.}514$ The treatment was so toxic and
- NOTE Confidence: 0.966137331428571
- $00:30:03.514 \rightarrow 00:30:05.878$ many of these patients will respond
- NOTE Confidence: 0.966137331428571
- $00:30:05.878 \dashrightarrow 00:30:07.720$ to immune checkpoint blockade.
- NOTE Confidence: 0.966137331428571
- $00:30:07.720 \longrightarrow 00:30:09.477$ So why do I tell you that?
- NOTE Confidence: 0.966137331428571
- 00:30:09.480 --> 00:30:09.779 Well,
- NOTE Confidence: 0.966137331428571
- $00{:}30{:}09{.}779 \dashrightarrow 00{:}30{:}12{.}470$ 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
- $00:30:15.400 \longrightarrow 00:30:16.765$ we think they're immunogenic because
- NOTE Confidence: 0.966137331428571
- $00:30:16.765 \longrightarrow 00:30:18.480$ they have a high mutational burden,
- NOTE Confidence: 0.966137331428571
- $00{:}30{:}18{.}480 \dashrightarrow 00{:}30{:}20{.}517$ which is what I'm showing you here
- NOTE Confidence: 0.966137331428571
- $00{:}30{:}20{.}520 \dashrightarrow 00{:}30{:}22{.}608$ on the Y axis compared to the names
- NOTE Confidence: 0.966137331428571

 $00:30:22.608 \rightarrow 00:30:24.900$ 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

 $00:30:26.175 \dashrightarrow 00:30:27.680$ carcinomas smack dab in the middle,

NOTE Confidence: 0.966137331428571

 $00:30:27.680 \rightarrow 00:30:29.080$ 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

 $00:30:31.226 \rightarrow 00:30:33.201$ Why should it be immunogenic?

NOTE Confidence: 0.966137331428571

 $00:30:33.201 \rightarrow 00:30:36.087$ So I think some widely underappreciated

NOTE Confidence: 0.966137331428571

 $00{:}30{:}36{.}087 \dashrightarrow 00{:}30{:}39{.}415$ work was the work of Richard Childs

NOTE Confidence: 0.966137331428571

 $00{:}30{:}39{.}415 \dashrightarrow 00{:}30{:}41.675$ at the National Cancer Institute

NOTE Confidence: 0.966137331428571

 $00:30:41.680 \longrightarrow 00:30:43.720$ dating back more than 15 years.

NOTE Confidence: 0.966137331428571

 $00{:}30{:}43.720 \dashrightarrow 00{:}30{:}45.250$ So out of sheer desperation and

NOTE Confidence: 0.966137331428571

 $00{:}30{:}45{.}250 \dashrightarrow 00{:}30{:}46{.}857$ 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

 $00:30:47.920 \longrightarrow 00:30:49.834$ he took 74 patients with metastatic

NOTE Confidence: 0.966137331428571

 $00{:}30{:}49{.}834 \dashrightarrow 00{:}30{:}51{.}930$ clear cell Reno cell carcinoma and

NOTE Confidence: 0.966137331428571

 $00{:}30{:}51{.}930 \dashrightarrow 00{:}30{:}53{.}835$ treated them with all ogeneic stem

- NOTE Confidence: 0.966137331428571
- $00{:}30{:}53.835 \dashrightarrow 00{:}30{:}56.188$ cell transplants as a source of
- NOTE Confidence: 0.966137331428571
- $00:30:56.188 \rightarrow 00:30:57.716$ potentially immunoreactive T cells.
- NOTE Confidence: 0.966137331428571
- 00:30:57.720 --> 00:30:58.280 And remarkably,
- NOTE Confidence: 0.966137331428571
- $00:30:58.280 \rightarrow 00:30:59.960$ about half of the patients responded,
- NOTE Confidence: 0.966137331428571
- $00:30:59.960 \rightarrow 00:31:02.276$ including some who were durable responders.
- NOTE Confidence: 0.966137331428571
- $00:31:02.280 \longrightarrow 00:31:04.728$ So about 10 to 12% of the patients
- NOTE Confidence: 0.966137331428571
- $00:31:04.728 \rightarrow 00:31:06.004$ 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
- $00:31:07.560 \rightarrow 00:31:09.120$ one of the complete responders,
- NOTE Confidence: 0.966137331428571
- $00:31:09.120 \dashrightarrow 00:31:12.355$ he found donor derived T cells that
- NOTE Confidence: 0.966137331428571
- $00:31:12.355 \rightarrow 00:31:14.245$ were recognizing on the surface of
- NOTE Confidence: 0.966137331428571
- $00{:}31{:}14{.}245 \dashrightarrow 00{:}31{:}16{.}428$ the tumor cells a tenmor peptide
- NOTE Confidence: 0.966137331428571
- $00{:}31{:}16.428 \dashrightarrow 00{:}31{:}18.393$ derived from an endogenous retrovirus.
- NOTE Confidence: 0.966137331428571
- 00:31:18.400 $\operatorname{-->}$ 00:31:19.737 And they were able to show that
- NOTE Confidence: 0.966137331428571
- $00:31:19.737 \rightarrow 00:31:20.119$ this retrovirus,
- NOTE Confidence: 0.966137331428571

 $00:31:20.120 \longrightarrow 00:31:22.276$ 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

 $00:31:25.520 \longrightarrow 00:31:27.710$ and it was not detectable in

NOTE Confidence: 0.90966450125

 $00:31:27.710 \dashrightarrow 00:31:30.000$ 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

 $00:31:32.868 \longrightarrow 00:31:35.232$ have have reported that the expression

NOTE Confidence: 0.90966450125

 $00:31:35.232 \rightarrow 00:31:37.346$ of endogenous retroviruses at least

NOTE Confidence: 0.90966450125

 $00{:}31{:}37{.}346 \dashrightarrow 00{:}31{:}39{.}441$ correlates with the probability that

NOTE Confidence: 0.90966450125

 $00{:}31{:}39{.}441 \dashrightarrow 00{:}31{:}42{.}037$ a kidney cancer patient will respond

NOTE Confidence: 0.90966450125

 $00:31:42.040 \dashrightarrow 00:31:43.444$ 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

 $00:31:46.756 \rightarrow 00:31:49.122$ they were able to show that this

NOTE Confidence: 0.90966450125

 $00{:}31{:}49{.}122 \dashrightarrow 00{:}31{:}51{.}322$ ERB was directly regulated by HIF

NOTE Confidence: 0.90966450125

 $00:31:51.322 \longrightarrow 00:31:53.040$ 2 at the transcriptional level,

NOTE Confidence: 0.90966450125

 $00:31:53.040 \rightarrow 00:31:55.080$ which would very satisfyingly explain why

- NOTE Confidence: 0.90966450125
- $00:31:55.130 \rightarrow 00:31:57.090$ it would be up regulated in kidney cancer.
- NOTE Confidence: 0.90966450125
- $00{:}31{:}57{.}090 \dashrightarrow 00{:}31{:}59{.}575$ 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
- $00:32:01.582 \rightarrow 00:32:02.838$ She wanted to know,
- NOTE Confidence: 0.90966450125
- $00{:}32{:}02{.}840 \dashrightarrow 00{:}32{:}06{.}400$ 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
- $00:32:08.320 \longrightarrow 00:32:09.670$ I mean great for this patient
- NOTE Confidence: 0.90966450125
- $00:32:09.670 \longrightarrow 00:32:10.920$ never to be seen again?
- NOTE Confidence: 0.90966450125
- $00{:}32{:}10{.}920 \dashrightarrow 00{:}32{:}12{.}594$ Or was it the tip of the ice berg and
- NOTE Confidence: 0.90966450125
- 00:32:12.594 --> 00:32:14.279 was it trying to tell us something?
- NOTE Confidence: 0.90966450125
- $00:32:14.280 \longrightarrow 00:32:17.000$ So that's what she set out to do.
- NOTE Confidence: 0.90966450125
- $00:32:17.000 \dashrightarrow 00:32:19.716$ So her hypothesis were that hip drives
- NOTE Confidence: 0.90966450125
- $00{:}32{:}19.716 \dashrightarrow 00{:}32{:}21.920$ the expression of multiple Ervs,
- NOTE Confidence: 0.90966450125
- $00:32:21.920 \longrightarrow 00:32:22.522$ with erve,
- NOTE Confidence: 0.90966450125
- $00:32:22.522 \dashrightarrow 00:32:24.328$ which has now been renamed ERV
- NOTE Confidence: 0.90966450125

 $00:32:24.328 \longrightarrow 00:32:26.078$ 4 simply being one example.

NOTE Confidence: 0.90966450125

 $00:32:26.080 \dashrightarrow 00:32:28.040$ So this being the Richard Childs ERV.

NOTE Confidence: 0.90966450125

 $00{:}32{:}28{.}040 \dashrightarrow 00{:}32{:}29{.}774$ And then she hypothesized that may be

NOTE Confidence: 0.90966450125

 $00{:}32{:}29{.}774 \dashrightarrow 00{:}32{:}31{.}811$ some of these other Ervs like the

NOTE Confidence: 0.90966450125

 $00{:}32{:}31{.}811 \dashrightarrow 00{:}32{:}34{.}284$ Richard Childs ERV are transcribed and

NOTE Confidence: 0.90966450125

 $00:32:34.284 \rightarrow 00:32:36.695$ translated into MHC bound peptides.

NOTE Confidence: 0.90966450125

 $00{:}32{:}36.695 \dashrightarrow 00{:}32{:}37.985$ And I should point out we're

NOTE Confidence: 0.90966450125

 $00:32:37.985 \longrightarrow 00:32:39.080$ not looking at every ERV,

NOTE Confidence: 0.90966450125

 $00:32:39.080 \rightarrow 00:32:40.952$ 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

 $00{:}32{:}43.187 \dashrightarrow 00{:}32{:}44.921$ We're looking at about 3000 Ervs

NOTE Confidence: 0.90966450125

 $00{:}32{:}44{.}921 \dashrightarrow 00{:}32{:}46{.}856$ 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

 $00:32:48.501 \rightarrow 00:32:50.306$ can imagine them being transcribed

NOTE Confidence: 0.90966450125

 $00:32:50.306 \longrightarrow 00:32:52.111$ and translated to some degree.

NOTE Confidence: 0.90966450125

 $00:32:52.120 \dashrightarrow 00:32:53.552$ And I should also point out that this

- NOTE Confidence: 0.90966450125
- $00:32:53.552 \rightarrow 00:32:55.280$ is a collaboration with David Brown,

00:32:55.280 --> 00:32:56.204 who's sitting here,

NOTE Confidence: 0.90966450125

 $00:32:56.204 \rightarrow 00:32:58.022$ as well as with Kathy Wu,

NOTE Confidence: 0.90966450125

 $00:32:58.022 \rightarrow 00:33:00.059$ and we could not have done this

NOTE Confidence: 0.90966450125

 $00{:}33{:}00{.}059 \dashrightarrow 00{:}33{:}01{.}239$ work without them.

NOTE Confidence: 0.90966450125

 $00:33:01.240 \dashrightarrow 00:33:03.080$ 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

 $00{:}33{:}04{.}900 \dashrightarrow 00{:}33{:}06{.}915$ that lacks VHL and then she generated

NOTE Confidence: 0.90966450125

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

 $00:33:12.240 \rightarrow 00:33:14.556$ multiple technologies, that's a good thing.

NOTE Confidence: 0.90966450125

 $00{:}33{:}14.560 \dashrightarrow 00{:}33{:}16.768$ So she either infected these cells

NOTE Confidence: 0.90966450125

 $00:33:16.768 \rightarrow 00:33:19.003$ with an empty expression vector or

NOTE Confidence: 0.90966450125

 $00:33:19.003 \rightarrow 00:33:21.097$ 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

 $00{:}33{:}23{.}360 \dashrightarrow 00{:}33{:}25{.}621$ or she used CRISPR to eliminate HIP

NOTE Confidence: 0.90966450125

 $00:33:25.621 \dashrightarrow 00:33:28.040$ 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

 $00{:}33{:}28.836 \dashrightarrow 00{:}33{:}30.336$ I should point out that at least

NOTE Confidence: 0.90966450125

 $00{:}33{:}30{.}336 \dashrightarrow 00{:}33{:}31{.}848$ in the short term these cells

NOTE Confidence: 0.90966450125

 $00:33:31.848 \longrightarrow 00:33:33.310$ will tolerate loss of hip two if

NOTE Confidence: 0.90966450125

 $00:33:33.310 \longrightarrow 00:33:34.600$ you keep them in high serum.

NOTE Confidence: 0.90966450125

 $00{:}33{:}34{.}600 \dashrightarrow 00{:}33{:}36{.}644$ And then with the help of David

NOTE Confidence: 0.90966450125

 $00:33:36.644 \longrightarrow 00:33:37.520$ and his colleagues,

NOTE Confidence: 0.90966450125

 $00{:}33{:}37{.}520 \dashrightarrow 00{:}33{:}41{.}480$ we looked for Ervs and RNA seek data.

NOTE Confidence: 0.90966450125

 $00{:}33{:}41{.}480 \dashrightarrow 00{:}33{:}43{.}262$ So here are the Venn diagrams

NOTE Confidence: 0.90966450125

 $00:33:43.262 \dashrightarrow 00:33:45.160$ with with those three conditions.

NOTE Confidence: 0.90966450125

00:33:45.160 --> 00:33:46.678 But again I'm a lumper rather

NOTE Confidence: 0.90966450125

 $00:33:46.678 \longrightarrow 00:33:47.437$ than a splitter.

- NOTE Confidence: 0.90966450125
- $00:33:47.440 \longrightarrow 00:33:49.456$ 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
- $00:33:51.360 \longrightarrow 00:33:54.198$ There were 15 Ervs that scored
- NOTE Confidence: 0.90966450125
- $00:33:54.200 \longrightarrow 00:33:55.692$ in all three comparisons.
- NOTE Confidence: 0.90966450125
- 00:33:55.692 --> 00:33:56.438 And I'm,
- NOTE Confidence: 0.90966450125
- $00:33:56.440 \longrightarrow 00:33:58.090$ I apologize for the kind
- NOTE Confidence: 0.90966450125
- 00:33:58.090 --> 00:33:59.080 of crazy nomenclature,
- NOTE Confidence: 0.90966450125
- $00:33:59.080 \rightarrow 00:34:00.920$ 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
- $00:34:04.680 \longrightarrow 00:34:05.400$ had an internal control.
- NOTE Confidence: 0.848833221428571
- $00{:}34{:}05{.}400 \dashrightarrow 00{:}34{:}07{.}794$ SO1 internal control was we did rediscover
- NOTE Confidence: 0.848833221428571
- $00:34:07.800 \dashrightarrow 00:34:10.038$ the Richard Childs ERB, that's good.
- NOTE Confidence: 0.848833221428571

 $00:34:10.040 \rightarrow 00:34:12.042$ And we also rediscovered in the ERB

NOTE Confidence: 0.848833221428571

 $00:34:12.042 \longrightarrow 00:34:14.093$ 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

 $00:34:16.490 \rightarrow 00:34:18.630$ a potential predictive biomarker for

NOTE Confidence: 0.848833221428571

 $00:34:18.630 \rightarrow 00:34:20.604$ response to immune checkpoint blockade.

NOTE Confidence: 0.848833221428571

 $00{:}34{:}20.604 \dashrightarrow 00{:}34{:}22.998$ So then the question was well are

NOTE Confidence: 0.848833221428571

 $00:34:22.998 \longrightarrow 00:34:24.771$ are these things really under

NOTE Confidence: 0.848833221428571

 $00:34:24.771 \longrightarrow 00:34:26.476$ direct hip control or not.

NOTE Confidence: 0.848833221428571

 $00:34:26.480 \rightarrow 00:34:30.155$ 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

 $00{:}34{:}33.056 \dashrightarrow 00{:}34{:}35.448$ in using CRISPR combined with

NOTE Confidence: 0.848833221428571

 $00:34:35.448 \longrightarrow 00:34:36.456$ homologous recombination.

NOTE Confidence: 0.848833221428571

 $00:34:36.456 \rightarrow 00:34:39.480$ We knocked an an endogenous flag

NOTE Confidence: 0.848833221428571

 $00:34:39.550 \rightarrow 00:34:41.614$ tag into the endogenous HIP 2 locus

NOTE Confidence: 0.848833221428571

 $00{:}34{:}41{.}614 \dashrightarrow 00{:}34{:}43{.}415$ and a renal carcinoma cell line

NOTE Confidence: 0.848833221428571

 $00{:}34{:}43{.}415 \dashrightarrow 00{:}34{:}45{.}423$ that that allowed us to do a chip
- NOTE Confidence: 0.848833221428571
- $00{:}34{:}45{.}482 \dashrightarrow 00{:}34{:}46{.}997$ seek with a flag antibody.
- NOTE Confidence: 0.848833221428571
- $00:34:47.000 \longrightarrow 00:34:49.360$ 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
- $00:34:52.480 \longrightarrow 00:34:55.640$ did or did not eliminate hip 2A.
- NOTE Confidence: 0.848833221428571
- $00{:}34{:}55{.}640 \dashrightarrow 00{:}34{:}57{.}327$ And again getting to you know corroboration
- NOTE Confidence: 0.848833221428571
- $00{:}34{:}57{.}327 \dashrightarrow 00{:}34{:}58{.}559$ and multiple lines of evidence.
- NOTE Confidence: 0.848833221428571
- $00{:}34{:}58{.}560 \dashrightarrow 00{:}35{:}01{.}053$ 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
- $00:35:03.127 \longrightarrow 00:35:05.520$ 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
- $00:35:07.120 \longrightarrow 00:35:08.720$ 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
- $00:35:10.480 \dashrightarrow 00:35:12.265$ there's a there's a hip to binding
- NOTE Confidence: 0.848833221428571
- $00{:}35{:}12.265 \dashrightarrow 00{:}35{:}14.131$ site parent hetically for for
- NOTE Confidence: 0.848833221428571
- $00{:}35{:}14{.}131 \dashrightarrow 00{:}35{:}16{.}279$ 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

 $00:35:18.324 \rightarrow 00:35:20.556$ to hip binding site on the shoulder here.

NOTE Confidence: 0.848833221428571

 $00:35:20.560 \longrightarrow 00:35:21.598$ I think he probably missed it,

NOTE Confidence: 0.848833221428571

 $00:35:21.600 \rightarrow 00:35:23.640$ not that it really mattered.

NOTE Confidence: 0.848833221428571

 $00{:}35{:}23.640 \dashrightarrow 00{:}35{:}24.960$ So there clearly is a hip

NOTE Confidence: 0.848833221428571

 $00{:}35{:}24{.}960 \dashrightarrow 00{:}35{:}25{.}840$ to binding site here.

NOTE Confidence: 0.848833221428571

 $00{:}35{:}25{.}840 \dashrightarrow 00{:}35{:}27{.}520$ 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

 $00:35:31.080 \longrightarrow 00:35:32.310$ for whatever reason,

NOTE Confidence: 0.848833221428571

 $00{:}35{:}32{.}310 \dashrightarrow 00{:}35{:}34{.}360$ they are actually precisely bookended

NOTE Confidence: 0.848833221428571

 $00:35:34.360 \longrightarrow 00:35:35.200$ by hip 2 binding sites.

NOTE Confidence: 0.848833221428571

 $00{:}35{:}35{.}200 \dashrightarrow 00{:}35{:}37{.}020$ So here's one called 5875 and you

NOTE Confidence: 0.848833221428571

 $00:35:37.020 \dashrightarrow 00:35:39.199$ can see the hip binding sites here.

NOTE Confidence: 0.848833221428571

 $00:35:39.200 \longrightarrow 00:35:41.065$ 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.

 $00{:}35{:}43{.}480 \dashrightarrow 00{:}35{:}45{.}860$ And all these and all these validated

NOTE Confidence: 0.848833221428571

 $00{:}35{:}45{.}860 \dashrightarrow 00{:}35{:}47{.}183$ secondary experiments I'm not

NOTE Confidence: 0.848833221428571

 $00:35:47.183 \rightarrow 00:35:48.682$ going to share with you today.

NOTE Confidence: 0.848833221428571

 $00:35:48.682 \rightarrow 00:35:50.656$ So now could it really be that

NOTE Confidence: 0.848833221428571

 $00{:}35{:}50.656 \dashrightarrow 00{:}35{:}53.099$ 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

 $00:35:54.920 \longrightarrow 00:35:56.288$ transcribed and translated?

NOTE Confidence: 0.848833221428571

 $00:35:56.288 \dashrightarrow 00:35:58.568$ So we collaborated with Sterling

NOTE Confidence: 0.848833221428571

 $00{:}35{:}58{.}568 \dashrightarrow 00{:}36{:}00{.}838$ 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

 $00:36:02.928 \rightarrow 00:36:04.677$ criteria where now we'll overlap

NOTE Confidence: 0.848833221428571

 $00{:}36{:}04.677 \dashrightarrow 00{:}36{:}06.832$ the RNA seek data with the chip seek

NOTE Confidence: 0.848833221428571

 $00:36:06.832 \rightarrow 00:36:08.320$ data and the Polysome seek data,

NOTE Confidence: 0.848833221428571

 $00{:}36{:}08{.}320 \dashrightarrow 00{:}36{:}10{.}144$ again probably using overly

NOTE Confidence: 0.848833221428571

 $00:36:10.144 \rightarrow 00:36:11.144$ stringent cut offs.

- $00{:}36{:}11.144 \dashrightarrow 00{:}36{:}12.232$ But again we rediscovered
- NOTE Confidence: 0.848833221428571
- 00:36:12.232 --> 00:36:13.320 the Richard Childs ERB.
- NOTE Confidence: 0.848833221428571
- $00{:}36{:}13{.}320 \dashrightarrow 00{:}36{:}16{.}460$ We also discovered those two Ervs I
- NOTE Confidence: 0.848833221428571
- $00:36:16.460 \rightarrow 00:36:18.460$ just showed you a moment ago that are
- NOTE Confidence: 0.848833221428571
- $00:36:18.525 \longrightarrow 00:36:20.517$ bookended with hip 2 binding sites.
- NOTE Confidence: 0.848833221428571
- $00:36:20.520 \longrightarrow 00:36:21.840$ So now we're ready to ask,
- NOTE Confidence: 0.848833221428571
- $00{:}36{:}21.840 \dashrightarrow 00{:}36{:}25.266$ are these some of these Ervs also
- NOTE Confidence: 0.848833221428571
- $00{:}36{:}25.266 \dashrightarrow 00{:}36{:}26.970$ transcribed and translated into
- NOTE Confidence: 0.848833221428571
- $00{:}36{:}26{.}970 \dashrightarrow 00{:}36{:}28{.}674$ peptides that are displayed.
- NOTE Confidence: 0.848833221428571
- $00:36:28.680 \rightarrow 00:36:31.320$ 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
- $00{:}36{:}34{.}639 \dashrightarrow 00{:}36{:}36{.}640$ Carr at the Broad Institute.
- NOTE Confidence: 0.848833221428571
- $00:36:36.640 \longrightarrow 00:36:37.564$ Suffice it to say,
- NOTE Confidence: 0.848833221428571
- $00:36:37.564 \rightarrow 00:36:39.560$ we can find these things in cell lines,
- NOTE Confidence: 0.848833221428571
- $00:36:39.560 \longrightarrow 00:36:40.499$ but more importantly,

- NOTE Confidence: 0.848833221428571
- $00:36:40.499 \longrightarrow 00:36:42.377$ we find some of these peptides
- NOTE Confidence: 0.848833221428571
- $00:36:42.377 \longrightarrow 00:36:43.839$ in real kidney tumors.
- NOTE Confidence: 0.848833221428571
- $00:36:43.840 \longrightarrow 00:36:45.751$ So here we have the data from
- NOTE Confidence: 0.848833221428571
- $00:36:45.751 \longrightarrow 00:36:48.127$ 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
- $00{:}36{:}49{.}240 \dashrightarrow 00{:}36{:}51{.}956$ samples. For six of these 11 patients,
- NOTE Confidence: 0.953299821428571
- $00{:}36{:}51{.}960 \dashrightarrow 00{:}36{:}54{.}800$ we had normal controlled tissue
- NOTE Confidence: 0.953299821428571
- $00:36:54.800 \rightarrow 00:36:56.594$ 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
- $00:37:06.280 \rightarrow 00:37:07.840$ they were not detected in the normal tissue,
- NOTE Confidence: 0.953299821428571
- $00{:}37{:}07{.}840 \dashrightarrow 00{:}37{:}09{.}848$ they were exclusively present
- NOTE Confidence: 0.953299821428571
- $00{:}37{:}09{.}848 \dashrightarrow 00{:}37{:}12.671$ in the in the tumor tissue.
- NOTE Confidence: 0.953299821428571

 $00:37:12.671 \rightarrow 00:37:14.537$ So we're excited that by continuing

NOTE Confidence: 0.953299821428571

 $00{:}37{:}14{.}537{\:}{\dashrightarrow}>00{:}37{:}16{.}585$ these sorts of studies we can start

NOTE Confidence: 0.953299821428571

 $00{:}37{:}16.585 \dashrightarrow 00{:}37{:}18.491$ to learn more and more about which

NOTE Confidence: 0.953299821428571

 $00:37:18.491 \rightarrow 00:37:20.540$ Ervs can be transcribed and translated

NOTE Confidence: 0.953299821428571

 $00:37:20.540 \longrightarrow 00:37:22.320$ and which maybe potentially could

NOTE Confidence: 0.953299821428571

 $00{:}37{:}22{.}374 \dashrightarrow 00{:}37{:}24{.}556$ be the basis for various types of

NOTE Confidence: 0.953299821428571

 $00:37:24.556 \rightarrow 00:37:25.971$ passive or active immunotherapy.

NOTE Confidence: 0.953299821428571

 $00:37:25.971 \dashrightarrow 00:37:28.939$ 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

 $00:37:31.573 \rightarrow 00:37:33.453$ grade hip stabilizer and treat other

NOTE Confidence: 0.953299821428571

 $00:37:33.453 \rightarrow 00:37:35.319$ 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

 $00:37:45.610 \dashrightarrow 00:37:48.340$ Now, I think you probably know there's

 $00:37:48.404 \rightarrow 00:37:50.599$ 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

 $00:37:52.126 \rightarrow 00:37:53.741$ although there's been enough progress

NOTE Confidence: 0.953299821428571

 $00{:}37{:}53{.}741 \dashrightarrow 00{:}37{:}56{.}048$ on Ras in the past year that may be

NOTE Confidence: 0.953299821428571

 $00:37:56.048 \dashrightarrow 00:37:57.698$ RASP will leave this list shortly.

NOTE Confidence: 0.953299821428571

 $00{:}37{:}57{.}698 \dashrightarrow 00{:}37{:}59{.}243$ But certainly there's no shortage

NOTE Confidence: 0.953299821428571

 $00:37:59.243 \longrightarrow 00:38:00.729$ of undruggables that we might

NOTE Confidence: 0.953299821428571

 $00:38:00.729 \dashrightarrow 00:38:01.994$ want to think about accessing.

NOTE Confidence: 0.953299821428571

 $00{:}38{:}02.000 \dashrightarrow 00{:}38{:}03.512$ I think generically there are a number

NOTE Confidence: 0.953299821428571

 $00:38:03.512 \rightarrow 00:38:05.437$ of ways to go after these undruggables.

NOTE Confidence: 0.953299821428571

 $00{:}38{:}05{.}440 \dashrightarrow 00{:}38{:}06{.}418$ In some cases,

NOTE Confidence: 0.953299821428571

 $00{:}38{:}06{.}418 \dashrightarrow 00{:}38{:}08{.}736$ 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

 $00{:}38{:}10.072 \dashrightarrow 00{:}38{:}11.438$ did with loss of VHL.

NOTE Confidence: 0.953299821428571

 $00{:}38{:}11{.}440 \dashrightarrow 00{:}38{:}13{.}918$ We went downstream and targeted a hip,

 $00:38:13.920 \longrightarrow 00:38:15.888$ effectively exploiting an

NOTE Confidence: 0.953299821428571

00:38:15.888 --> 00:38:17.200 epistatic relationship.

NOTE Confidence: 0.953299821428571

 $00:38:17.200 \longrightarrow 00:38:18.640$ There's renewed interest in

NOTE Confidence: 0.953299821428571

 $00:38:18.640 \rightarrow 00:38:19.720$ developing allosteric inhibitors.

NOTE Confidence: 0.953299821428571

 $00{:}38{:}19.720 \dashrightarrow 00{:}38{:}20.740$ That's effectively what

NOTE Confidence: 0.953299821428571

 $00{:}38{:}20{.}740 \dashrightarrow 00{:}38{:}22{.}440$ the HIP 2 inhibitor was.

NOTE Confidence: 0.953299821428571

 $00:38:22.440 \longrightarrow 00:38:24.300$ I've had a long standing

NOTE Confidence: 0.953299821428571

 $00:38:24.300 \rightarrow 00:38:25.788$ interest in exploiting synthetic

NOTE Confidence: 0.953299821428571

 $00:38:25.788 \longrightarrow 00:38:27.360$ 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

 $00:38:28.680 \longrightarrow 00:38:29.819$ 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

 $00:38:31.504 \longrightarrow 00:38:32.800$ small molecule degraders,

NOTE Confidence: 0.953299821428571

 $00{:}38{:}32{.}800 \dashrightarrow 00{:}38{:}34{.}368$ which I I deal with some trepidation

NOTE Confidence: 0.953299821428571

 $00:38:34.368 \longrightarrow 00:38:36.117$ with Craig Cruz in the in the front row.

NOTE Confidence: 0.953299821428571

 $00:38:36.120 \rightarrow 00:38:38.112$ So he he's going to keep me honest

- NOTE Confidence: 0.953299821428571
- $00:38:38.112 \rightarrow 00:38:39.823$ through this section of the talk.
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}39{.}823 \dashrightarrow 00{:}38{:}42{.}037$ So our group and Ben Ebers group working
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}42.037 \dashrightarrow 00{:}38{:}43.987$ in parallel showed about five years
- NOTE Confidence: 0.953299821428571
- $00:38:43.987 \rightarrow 00:38:46.359$ ago that the thalidomide like drugs,
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}46{.}360 \dashrightarrow 00{:}38{:}47{.}842$ the so-called image,
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}47.842 \dashrightarrow 00{:}38{:}50.312$ 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
- $00:38:52.840 \longrightarrow 00:38:54.440$ not the VHL Ubiquin ligase,
- NOTE Confidence: 0.953299821428571
- $00:38:54.440 \longrightarrow 00:38:56.440$ but in fact the cereblond,
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}56{.}440 \dashrightarrow 00{:}38{:}59{.}408$ the ubiquit in ligase to now target for
- NOTE Confidence: 0.953299821428571
- $00{:}38{:}59{.}408 \dashrightarrow 00{:}39{:}01{.}108$ degradation to transcription factors
- NOTE Confidence: 0.953299821428571
- 00:39:01.108 --> 00:39:03.152 called IKZF one and IKZF 3 which
- NOTE Confidence: 0.953299821428571
- $00{:}39{:}03{.}152 \dashrightarrow 00{:}39{:}05{.}258$ turned out to be near and dear to
- NOTE Confidence: 0.953299821428571
- $00{:}39{:}05{.}258 \dashrightarrow 00{:}39{:}07{.}204$ the hearts of multiple myeloma cells.
- NOTE Confidence: 0.953299821428571
- $00:39:07.204 \rightarrow 00:39:09.224$ Now in fairness this really
- NOTE Confidence: 0.953299821428571

- $00{:}39{:}09{.}224 \dashrightarrow 00{:}39{:}10{.}840$ kind of Harkins back.
- NOTE Confidence: 0.953299821428571
- 00:39:10.840 --> 00:39:11.234 Oh,
- NOTE Confidence: 0.953299821428571
- $00:39:11.234 \rightarrow 00:39:13.598$ 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
- $00:39:15.790 \longrightarrow 00:39:17.680$ Brenner showed that you could
- NOTE Confidence: 0.953299821428571
- $00{:}39{:}17.680 \dashrightarrow 00{:}39{:}19.828$ chemically modify an image so that
- NOTE Confidence: 0.953299821428571
- $00:39:19.828 \longrightarrow 00:39:22.600$ 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
- $00:39:23.760 \longrightarrow 00:39:24.442$ in fairness,
- NOTE Confidence: 0.953299821428571
- $00:39:24.442 \rightarrow 00:39:26.488$ this general idea of having a
- NOTE Confidence: 0.953299821428571
- $00{:}39{:}26{.}488 \dashrightarrow 00{:}39{:}28{.}379$ chemical that acts as a match maker
- NOTE Confidence: 0.953299821428571
- 00:39:28.379 $\operatorname{-->}$ 00:39:30.451 between an E3 ligase and a target
- NOTE Confidence: 0.953299821428571
- $00:39:30.451 \rightarrow 00:39:32.352$ 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
- $00:39:34.400 \rightarrow 00:39:37.198$ And just to introduce some nomenclature here,
- NOTE Confidence: 0.953299821428571
- $00:39:37.198 \rightarrow 00:39:39.151$ 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
- $00:39:40.760 \longrightarrow 00:39:42.410$ I realize this is bringing
- NOTE Confidence: 0.953299821428571
- $00{:}39{:}42{.}410 \dashrightarrow 00{:}39{:}43{.}400$ Coles to Newcastle.
- NOTE Confidence: 0.9487915625
- $00:39:43.400 \rightarrow 00:39:44.900$ These are sometimes referred
- NOTE Confidence: 0.9487915625
- $00:39:44.900 \longrightarrow 00:39:46.400$ 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
- $00:39:47.939 \rightarrow 00:39:49.277$ tried to call these degronomists.
- NOTE Confidence: 0.9487915625
- $00:39:49.280 \longrightarrow 00:39:50.318$ I think you need a publicist.
- NOTE Confidence: 0.9487915625
- $00:39:50.320 \longrightarrow 00:39:51.741$ 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
- $00{:}39{:}53{.}320 \dashrightarrow 00{:}39{:}56{.}280$ molecular glues or the protax.
- NOTE Confidence: 0.9487915625
- $00{:}39{:}56{.}280 \dashrightarrow 00{:}39{:}58{.}760$ 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
- $00:40:00.770 \longrightarrow 00:40:02.640$ 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

- $00:40:04.480 \rightarrow 00:40:06.160$ your favorite undruggable protein.
- NOTE Confidence: 0.9487915625
- 00:40:06.160 --> 00:40:07.420 Because protein stability
- NOTE Confidence: 0.9487915625
- $00:40:07.420 \longrightarrow 00:40:08.680$ is highly regulated.
- NOTE Confidence: 0.9487915625
- 00:40:08.680 00:40:11.040 There are about 500 Ubiquitoligases.
- NOTE Confidence: 0.9487915625
- $00:40:11.040 \longrightarrow 00:40:13.278$ They're opposed by about 100 Dubs.
- NOTE Confidence: 0.9487915625
- $00{:}40{:}13.280 \dashrightarrow 00{:}40{:}15.500$ Whether these ligases and dubs will
- NOTE Confidence: 0.9487915625
- $00:40:15.500 \rightarrow 00:40:17.541$ recognize their targets are often
- NOTE Confidence: 0.9487915625
- $00:40:17.541 \rightarrow 00:40:20.036$ influenced by post translation modifications,
- NOTE Confidence: 0.9487915625
- $00:40:20.040 \longrightarrow 00:40:21.272$ protein folding,
- NOTE Confidence: 0.9487915625
- $00:40:21.272 \longrightarrow 00:40:23.120$ protein protein interaction,
- NOTE Confidence: 0.9487915625
- $00:40:23.120 \longrightarrow 00:40:24.128$ sub cellular localization,
- NOTE Confidence: 0.9487915625
- $00{:}40{:}24.128 \dashrightarrow 00{:}40{:}25.856$ et cetera, et cetera, et cetera.
- NOTE Confidence: 0.9487915625
- $00:40:25.856 \longrightarrow 00:40:27.440$ So we wanted to develop an
- NOTE Confidence: 0.9487915625
- $00:40:27.495 \longrightarrow 00:40:29.340$ as say for degraders that was
- NOTE Confidence: 0.9487915625
- $00{:}40{:}29{.}340 \dashrightarrow 00{:}40{:}30{.}382$ actually mechanism agnostic.
- NOTE Confidence: 0.9487915625
- 00:40:30.382 --> 00:40:30.684 Now,

- NOTE Confidence: 0.9487915625
- $00:40:30.684 \longrightarrow 00:40:32.496$ we've talked a lot today about
- NOTE Confidence: 0.9487915625
- $00:40:32.496 \longrightarrow 00:40:34.200$ up assays versus down assays.
- NOTE Confidence: 0.9487915625
- $00:40:34.200 \longrightarrow 00:40:35.526$ And that's because 20 plus years
- NOTE Confidence: 0.9487915625
- $00{:}40{:}35{.}526 \dashrightarrow 00{:}40{:}37{.}201$ ago some of my colleagues in pharma
- NOTE Confidence: 0.9487915625
- $00:40:37.201 \longrightarrow 00:40:38.916$ tried to beat into my head why?
- NOTE Confidence: 0.9487915625
- $00{:}40{:}38{.}920 \dashrightarrow 00{:}40{:}40{.}100$ If we're doing a chemical
- NOTE Confidence: 0.9487915625
- $00:40:40.100 \rightarrow 00:40:41.280$ screen or a genetic screen,
- NOTE Confidence: 0.9487915625
- $00:40:41.280 \longrightarrow 00:40:42.635$ you'd almost always rather do
- NOTE Confidence: 0.9487915625
- $00:40:42.635 \longrightarrow 00:40:44.621$ an up as say than a down essay
- NOTE Confidence: 0.9487915625
- $00:40:44.621 \longrightarrow 00:40:46.319$ 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
- $00:40:47.172 \longrightarrow 00:40:48.876$ up assays tend to have better
- NOTE Confidence: 0.9487915625
- $00{:}40{:}48.876 \dashrightarrow 00{:}40{:}50.638$ 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
- $00:40:52.626 \rightarrow 00:40:54.106$ positive and a sea of negative than
- NOTE Confidence: 0.9487915625

 $00{:}40{:}54.106 \dashrightarrow 00{:}40{:}55.678$ a negative and a sea of positives.

NOTE Confidence: 0.9487915625

 $00{:}40{:}55{.}680 \dashrightarrow 00{:}40{:}56{.}320$ If you think about it,

NOTE Confidence: 0.9487915625

 $00{:}40{:}56{.}320 \dashrightarrow 00{:}40{:}58{.}600$ 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

 $00:41:00.275 \longrightarrow 00:41:01.280$ us as biologists,

NOTE Confidence: 0.9487915625

 $00:41:01.280 \longrightarrow 00:41:02.505$ they're just lots of trivial

NOTE Confidence: 0.9487915625

 $00:41:02.505 \rightarrow 00:41:04.120$ ways to make a complex system,

NOTE Confidence: 0.9487915625

 $00:41:04.120 \rightarrow 00:41:06.440$ including a complex biological system,

NOTE Confidence: 0.9487915625

 $00{:}41{:}06{.}440 \dashrightarrow 00{:}41{:}09{.}116$ work worse rather than work better.

NOTE Confidence: 0.9487915625

 $00:41:09.120 \rightarrow 00:41:10.674$ So my thought experiment for the students,

NOTE Confidence: 0.9487915625

 $00:41:10.680 \longrightarrow 00:41:11.920$ 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

 $00:41:13.320 \longrightarrow 00:41:14.976$ is you go out to your car one

NOTE Confidence: 0.9487915625

 $00:41:14.976 \longrightarrow 00:41:16.503$ evening and start randomly removing

NOTE Confidence: 0.9487915625

 $00:41:16.503 \rightarrow 00:41:18.268$ parts from your internal combustion

NOTE Confidence: 0.9487915625

 $00:41:18.268 \rightarrow 00:41:20.426$ engine and tell me how often it goes

- NOTE Confidence: 0.9487915625
- $00:41:20.426 \rightarrow 00:41:22.065$ faster and how often it goes slower.
- NOTE Confidence: 0.9487915625
- $00:41:22.065 \rightarrow 00:41:23.240$ 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
- $00{:}41{:}24.505 \dashrightarrow 00{:}41{:}25.817$ should be a thought experiment.
- NOTE Confidence: 0.9487915625
- $00{:}41{:}25{.}817 \dashrightarrow 00{:}41{:}28{.}193$ So we wanted to develop an up as say.
- NOTE Confidence: 0.9487915625
- 00:41:28.200 --> 00:41:30.125 So Sagar Kaduri when he was in
- NOTE Confidence: 0.9487915625
- $00:41:30.125 \rightarrow 00:41:32.248$ my lab a very talented physician
- NOTE Confidence: 0.9487915625
- $00:41:32.248 \rightarrow 00:41:33.816$ 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
- $00{:}41{:}35{.}889 \dashrightarrow 00{:}41{:}37{.}918$ fused to a modified cited in kinase
- NOTE Confidence: 0.9487915625
- $00{:}41{:}37{.}918 \dashrightarrow 00{:}41{:}39{.}514$ that was developed by Jeff Medin
- NOTE Confidence: 0.9487915625
- $00{:}41{:}39{.}514 \dashrightarrow 00{:}41{:}41{.}323$ that will accept the non natural
- NOTE Confidence: 0.9487915625
- $00{:}41{:}41{.}323 \dashrightarrow 00{:}41{:}43{.}160$ nucleoside and converted into a toxin.
- NOTE Confidence: 0.9487915625
- $00{:}41{:}43.160 \dashrightarrow 00{:}41{:}44.308$ There's a little spacer,
- NOTE Confidence: 0.9487915625
- $00{:}41{:}44{.}308 \dashrightarrow 00{:}41{:}46{.}307$ there's AV5 tag and then importantly off
- NOTE Confidence: 0.9487915625

- $00{:}41{:}46{.}307 \dashrightarrow 00{:}41{:}48{.}230$ 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
- $00{:}41{:}48{.}505 \dashrightarrow 00{:}41{:}51{.}015$ so the idea is you can add a
- NOTE Confidence: 0.9487915625
- $00:41:51.015 \rightarrow 00:41:53.039$ chemical or genetic perturbance,
- NOTE Confidence: 0.9487915625
- $00{:}41{:}53.040 \dashrightarrow 00{:}41{:}55.994$ add BBDU and look for green survivors.
- NOTE Confidence: 0.9487915625
- $00{:}41{:}56{.}000 \dashrightarrow 00{:}41{:}57{.}660$ And as this is an up assay this can be
- NOTE Confidence: 0.9487915625
- $00:41:57.712 \longrightarrow 00:41:59.595$ 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
- $00{:}42{:}01{.}189 \dashrightarrow 00{:}42{:}02{.}400$ form at with CRISPR libraries.
- NOTE Confidence: 0.9487915625
- $00:42:02.400 \longrightarrow 00:42:03.972$ Just to show you a proof
- NOTE Confidence: 0.9487915625
- $00:42:03.972 \longrightarrow 00:42:04.758$ of concept experiment,
- NOTE Confidence: 0.9487915625
- $00:42:04.760 \longrightarrow 00:42:06.559$ here's a 384 well plate as say where
- NOTE Confidence: 0.9487915625
- $00{:}42{:}06.559 \dashrightarrow 00{:}42{:}08.714$ the cells have the Imid target IKZ F1.
- NOTE Confidence: 0.9487915625
- $00:42:08.714 \longrightarrow 00:42:10.653$ I hope you can see there are
- NOTE Confidence: 0.9487915625
- $00:42:10.653 \rightarrow 00:42:12.319$ three positive wells here.
- NOTE Confidence: 0.9487915625
- $00:42:12.320 \longrightarrow 00:42:14.426$ 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
- $00:42:15.926 \rightarrow 00:42:19.940$ whereas this well had a chemical that we now
- NOTE Confidence: 0.780078463
- $00:42:20.017 \rightarrow 00:42:23.083$ know is an assay positive that interferes
- NOTE Confidence: 0.780078463
- $00:42:23.083 \rightarrow 00:42:25.532$ with BVD uptake by themselves,
- NOTE Confidence: 0.780078463
- $00:42:25.532 \longrightarrow 00:42:27.796$ 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
- $00:42:30.560 \rightarrow 00:42:32.040$ Sagar did the following experiment.
- NOTE Confidence: 0.780078463
- $00{:}42{:}32{.}040 \dashrightarrow 00{:}42{:}33{.}845$ So again, the top plate
- NOTE Confidence: 0.780078463
- $00{:}42{:}33{.}845 \dashrightarrow 00{:}42{:}36{.}400$ is the IKZ of 1 fusion.
- NOTE Confidence: 0.780078463
- $00:42:36.400 \rightarrow 00:42:39.074$ The bottom plate is the counter screen
- NOTE Confidence: 0.780078463
- $00:42:39.074 \rightarrow 00:42:40.860$ 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
- $00{:}42{:}43{.}309 \dashrightarrow 00{:}42{:}45{.}556$ 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
- $00{:}42{:}47.504 \dashrightarrow 00{:}42{:}49.640$ 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

 $00:42:51.760 \longrightarrow 00:42:53.363$ so we don't care about that we're

NOTE Confidence: 0.780078463

 $00:42:53.363 \longrightarrow 00:42:54.519$ at the highest concentration

NOTE Confidence: 0.780078463

 $00:42:54.519 \longrightarrow 00:42:56.199$ somehow promotes the survival.

NOTE Confidence: 0.780078463

 $00{:}42{:}56{.}200 \dashrightarrow 00{:}42{:}58{.}464$ 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

 $00:42:59.840 \longrightarrow 00:43:01.562$ 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

 $00{:}43{:}03{.}400 \dashrightarrow 00{:}43{:}05{.}705$ 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

 $00{:}43{:}07{.}280 \dashrightarrow 00{:}43{:}09{.}032$ 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

 $00{:}43{:}11.800 \dashrightarrow 00{:}43{:}13.837$ but secondly in contrast to the image.

NOTE Confidence: 0.780078463

 $00:43:13.840 \longrightarrow 00:43:16.640$ This doesn't require Cerebon

NOTE Confidence: 0.780078463

 $00:43:16.640 \rightarrow 00:43:19.560$ to degrade IKZ F1.

 $00:43:19.560 \rightarrow 00:43:23.042$ Now we thought our UP assay might

NOTE Confidence: 0.780078463

 $00:43:23.042 \rightarrow 00:43:24.932$ allow us to revisit screening

NOTE Confidence: 0.780078463

 $00:43:24.932 \longrightarrow 00:43:26.720$ natural product collections.

NOTE Confidence: 0.780078463

 $00:43:26.720 \longrightarrow 00:43:29.597$ Now for those of you who are

NOTE Confidence: 0.780078463

 $00:43:29.600 \rightarrow 00:43:31.400$ who haven't lived through this,

NOTE Confidence: 0.780078463

 $00{:}43{:}31{.}400 \dashrightarrow 00{:}43{:}33{.}143$ there was a time back in the

NOTE Confidence: 0.780078463

 $00:43:33.143 \rightarrow 00:43:34.660$ days of dinosaurs where screening

NOTE Confidence: 0.780078463

 $00{:}43{:}34{.}660 \dashrightarrow 00{:}43{:}36{.}088$ natural product collections was

NOTE Confidence: 0.780078463

 $00:43:36.088 \rightarrow 00:43:38.280$ a preferred way of finding drugs

NOTE Confidence: 0.780078463

 $00{:}43{:}38{.}280 \dashrightarrow 00{:}43{:}41{.}200$ 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

 $00{:}43{:}47{.}120 \dashrightarrow 00{:}43{:}49{.}040$ has ever been able to make.

NOTE Confidence: 0.780078463

 $00{:}43{:}49{.}040 \dashrightarrow 00{:}43{:}50{.}708$ And natural product hits often have

 $00:43:50.708 \rightarrow 00:43:52.089$ drug like product properties right

NOTE Confidence: 0.780078463

 $00{:}43{:}52.089 \dashrightarrow 00{:}43{:}53.825$ out of the gate because in many cases

NOTE Confidence: 0.780078463

 $00{:}43{:}53.825 \dashrightarrow 00{:}43{:}55.395$ 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

 $00{:}43{:}56{.}480 \dashrightarrow 00{:}43{:}58{.}384$ to cross cell membranes.

NOTE Confidence: 0.780078463

 $00:43:58.384 \rightarrow 00:44:01.240$ The cons are that contaminating toxins

NOTE Confidence: 0.780078463

00:44:01.321 --> 00:44:04.117 cause false positives and down as says

NOTE Confidence: 0.780078463

 $00:44:04.120 \longrightarrow 00:44:05.560$ and false negatives and up assays.

NOTE Confidence: 0.780078463

 $00{:}44{:}05{.}560 \dashrightarrow 00{:}44{:}08{.}278$ And again we're doing up as says.

NOTE Confidence: 0.780078463

 $00{:}44{:}08{.}280 \dashrightarrow 00{:}44{:}10{.}120$ It's historically difficult to isolate

NOTE Confidence: 0.780078463

 $00:44:10.120 \longrightarrow 00:44:11.960$ and identify the active chemicals

NOTE Confidence: 0.780078463

 $00:44:12.014 \longrightarrow 00:44:13.598$ 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

 $00:44:15.960 \longrightarrow 00:44:17.112$ decades to Infinity.

NOTE Confidence: 0.780078463

 $00:44:17.112 \rightarrow 00:44:19.800$ And then sometimes it's not very frequently.

NOTE Confidence: 0.780078463

 $00{:}44{:}19{.}800 \dashrightarrow 00{:}44{:}22{.}362$ It's difficult to identify the direct

- NOTE Confidence: 0.780078463
- $00{:}44{:}22.362 \dashrightarrow 00{:}44{:}24.720$ protein target for the chemical
- NOTE Confidence: 0.780078463
- $00{:}44{:}24{.}720 \dashrightarrow 00{:}44{:}26{.}316$ coming out of the phenotypic screens.
- NOTE Confidence: 0.780078463
- $00:44:26.320 \rightarrow 00:44:28.161$ Although I have to say there's some
- NOTE Confidence: 0.780078463
- $00:44:28.161 \rightarrow 00:44:30.127$ very clever and powerful genetic and
- NOTE Confidence: 0.780078463
- $00:44:30.127 \rightarrow 00:44:32.384$ 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
- $00:44:33.920 \longrightarrow 00:44:36.032$ that's how they should say so this is
- NOTE Confidence: 0.780078463
- $00{:}44{:}36{.}032 \dashrightarrow 00{:}44{:}37{.}757$ the unpublished work of Matt Boudreaux.
- NOTE Confidence: 0.780078463
- $00{:}44{:}37{.}760 \dashrightarrow 00{:}44{:}40{.}056$ 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
- $00{:}44{:}42.200 \dashrightarrow 00{:}44{:}45.548$ 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
- $00:44:48.886 \rightarrow 00:44:51.238$ that all of us paid for with our tax money.
- NOTE Confidence: 0.780078463

- $00:44:51.240 \rightarrow 00:44:52.824$ So you might as well ask for this
- NOTE Confidence: 0.780078463
- $00:44:52.824 \rightarrow 00:44:54.568$ collection at some point because you paid
- NOTE Confidence: 0.780078463
- $00:44:54.568 \rightarrow 00:44:57.880$ 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
- $00:44:58.264 \rightarrow 00:44:58.840$ for the students,
- NOTE Confidence: 0.780078463
- $00:44:58.840 \longrightarrow 00:45:00.420$ 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
- $00:45:02.321 \longrightarrow 00:45:04.568$ OK, so I think we're drawn to
- NOTE Confidence: 0.780078463
- $00{:}45{:}04{.}568 \dashrightarrow 00{:}45{:}06{.}039$ the complicated fancy ideas.
- NOTE Confidence: 0.780078463
- $00:45:06.040 \longrightarrow 00:45:07.265$ It's often the simple things
- NOTE Confidence: 0.780078463
- $00{:}45{:}07{.}265 \dashrightarrow 00{:}45{:}08{.}000$ that moves for th.
- NOTE Confidence: 0.780078463
- $00:45:08.000 \rightarrow 00:45:10.688$ So his embarrassingly simple but very
- NOTE Confidence: 0.780078463
- $00{:}45{:}10.688 \dashrightarrow 00{:}45{:}13.599$ powerful idea was what if I took this
- NOTE Confidence: 0.727035305
- $00{:}45{:}13.600 \dashrightarrow 00{:}45{:}15.196$ 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.

 $00:45:19.760 \rightarrow 00:45:22.757$ And suppose we run them over a single column.

NOTE Confidence: 0.727035305

 $00:45:22.760 \longrightarrow 00:45:25.088$ So now each mixture is now

NOTE Confidence: 0.727035305

 $00:45:25.088 \longrightarrow 00:45:26.640$ represented by 7 fractions.

NOTE Confidence: 0.727035305

 $00:45:26.640 \rightarrow 00:45:28.840$ And I apologize for all the verbage here,

NOTE Confidence: 0.727035305

 $00:45:28.840 \rightarrow 00:45:31.477$ but suffice it to say let's pick the column.

NOTE Confidence: 0.727035305

 $00{:}45{:}31{.}480 \dashrightarrow 00{:}45{:}34{.}423$ So it removes a lot of the nuisance compounds

NOTE Confidence: 0.727035305

 $00:45:34.423 \rightarrow 00:45:37.520$ that plagues many phenotypic screens and in

NOTE Confidence: 0.727035305

 $00:45:37.520 \rightarrow 00:45:39.520$ particular the so-called pain compounds,

NOTE Confidence: 0.727035305

 $00{:}45{:}39{.}520 \dashrightarrow 00{:}45{:}40{.}753$ Pan interference compounds.

NOTE Confidence: 0.727035305

 $00{:}45{:}40.753 \dashrightarrow 00{:}45{:}42.808$ And because we now have

NOTE Confidence: 0.727035305

 $00:45:42.808 \longrightarrow 00:45:44.439$ separated into 7 fractions,

NOTE Confidence: 0.727035305

 $00{:}45{:}44{.}440 \dashrightarrow 00{:}45{:}46{.}240$ we've simplified the mixtures and

NOTE Confidence: 0.727035305

 $00{:}45{:}46{.}240 \dashrightarrow 00{:}45{:}47{.}880$ that increases the probability that

NOTE Confidence: 0.727035305

 $00{:}45{:}47.880 \dashrightarrow 00{:}45{:}49.080$ you'll get to the active chemical.

NOTE Confidence: 0.727035305

 $00:45:49.080 \rightarrow 00:45:52.077$ They tell me their success rate is about 80%.

 $00:45:52.080 \longrightarrow 00:45:53.744$ If you get a hit from one of

NOTE Confidence: 0.727035305

 $00:45:53.744 \longrightarrow 00:45:55.244$ these single fraction comes,

NOTE Confidence: 0.727035305

 $00:45:55.244 \rightarrow 00:45:56.956$ it helps with reproducibility,

NOTE Confidence: 0.727035305

 $00:45:56.960 \rightarrow 00:45:57.560$ yada, yada yada.

NOTE Confidence: 0.727035305

 $00:45:57.560 \longrightarrow 00:45:58.960$ So for those of you are interested,

NOTE Confidence: 0.727035305

 $00:45:58.960 \rightarrow 00:46:02.428$ this nice summary of this platform.

NOTE Confidence: 0.727035305

 $00{:}46{:}02{.}428 \dashrightarrow 00{:}46{:}05{.}200$ 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

 $00{:}46{:}07{.}649 \dashrightarrow 00{:}46{:}10{.}039$ well with some overall up as says.

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

 $00{:}46{:}15.640 \dashrightarrow 00{:}46{:}16.810$ another classically undruggable.

NOTE Confidence: 0.727035305

 $00{:}46{:}16.810 \dashrightarrow 00{:}46{:}18.760$ 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

 $00:46:20.460 \rightarrow 00:46:22.160$ through the entire collection.

- NOTE Confidence: 0.727035305
- $00:46:22.160 \longrightarrow 00:46:23.315$ For those of you who do screens,
- NOTE Confidence: 0.727035305
- $00{:}46{:}23.320 \dashrightarrow 00{:}46{:}25.036$ the screen had very good statistics.
- NOTE Confidence: 0.727035305
- $00{:}46{:}25.040 \dashrightarrow 00{:}46{:}26.810$ But I want to kind of give you a sense
- NOTE Confidence: 0.727035305
- $00:46:26.864 \rightarrow 00:46:28.358$ of the power of this technology.
- NOTE Confidence: 0.727035305
- $00:46:28.360 \longrightarrow 00:46:32.079$ 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
- $00:46:37.328 \longrightarrow 00:46:39.720$ measure of the number of viable
- NOTE Confidence: 0.727035305
- $00:46:39.720 \longrightarrow 00:46:42.120 ***$ 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 may
be there's a little bit of a
- NOTE Confidence: 0.727035305
- $00:46:46.704 \longrightarrow 00:46:48.317$ blip here with the master mix,
- NOTE Confidence: 0.727035305
- $00{:}46{:}48.320 \dashrightarrow 00{:}46{:}50.672$ but this doesn't come close to our
- NOTE Confidence: 0.727035305
- $00{:}46{:}50.672 \dashrightarrow 00{:}46{:}52.340$ threshold for calling a positive
- NOTE Confidence: 0.727035305

- $00:46:52.340 \longrightarrow 00:46:53.240$ in the screen.
- NOTE Confidence: 0.727035305
- $00:46:53.240 \longrightarrow 00:46:54.020$ 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
- $00:46:55.840 \longrightarrow 00:46:57.712$ we just have thousands and thousands
- NOTE Confidence: 0.727035305
- $00{:}46{:}57{.}712 \dashrightarrow 00{:}46{:}59{.}400$ 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
- $00:47:02.400 \longrightarrow 00:47:04.432$ you can see that F5 and F6 are
- NOTE Confidence: 0.727035305
- $00{:}47{:}04{.}432 \dashrightarrow 00{:}47{:}06{.}119$ a winner and we like this.
- NOTE Confidence: 0.727035305
- $00{:}47{:}06{.}120 \dashrightarrow 00{:}47{:}08{.}682$ We take great comfort if two adjacent
- NOTE Confidence: 0.727035305
- $00{:}47{:}08.682 \dashrightarrow 00{:}47{:}10.452$ fractions score because again this
- NOTE Confidence: 0.727035305
- $00:47:10.452 \rightarrow 00:47:12.594$ is a single column so it's unlikely
- NOTE Confidence: 0.727035305
- $00:47:12.594 \rightarrow 00:47:14.760$ that anyone chemical is going to
- NOTE Confidence: 0.727035305
- $00:47:14.760 \longrightarrow 00:47:16.760$ 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
- $00:47:18.756 \rightarrow 00:47:20.160$ in secondary screens.

- NOTE Confidence: 0.727035305
- $00:47:20.160 \longrightarrow 00:47:21.792$ 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
- $00:47:23.400 \longrightarrow 00:47:25.792$ Here is an example of a fraction that
- NOTE Confidence: 0.727035305
- $00{:}47{:}25.792 \dashrightarrow 00{:}47{:}28.024$ 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
- $00:47:30.866 \longrightarrow 00:47:31.159$ well,
- NOTE Confidence: 0.727035305
- $00:47:31.159 \longrightarrow 00:47:33.896$ it's called dash 5 and here's fraction 7.
- NOTE Confidence: 0.727035305
- $00{:}47{:}33.896 \dashrightarrow 00{:}47{:}35.360$ Here's an adjacent.
- NOTE Confidence: 0.727035305
- 00:47:35.360 --> 00:47:36.034 But anyway,
- NOTE Confidence: 0.727035305
- $00:47:36.034 \rightarrow 00:47:38.834$ you can see we're degrading not only or
- NOTE Confidence: 0.727035305
- $00{:}47{:}38{.}834 \dashrightarrow 00{:}47{:}41{.}438$ down regulating the beta catena fusion,
- NOTE Confidence: 0.727035305
- $00{:}47{:}41{.}440 \dashrightarrow 00{:}47{:}43{.}820$ but more importantly we're down
- NOTE Confidence: 0.727035305
- $00{:}47{:}43.820 \dashrightarrow 00{:}47{:}45.724$ regulating endogenous beta catena
- NOTE Confidence: 0.727035305
- $00{:}47{:}45.724 \dashrightarrow 00{:}47{:}48.178$ and we're turning off beta catena
- NOTE Confidence: 0.727035305
- $00:47:48.178 \longrightarrow 00:47:50.375$ target genes such as Axon 2.
- NOTE Confidence: 0.727035305

 $00:47:50.375 \rightarrow 00:47:52.440$ And for those of you who care,

NOTE Confidence: 0.727035305

 $00{:}47{:}52{.}440 \dashrightarrow 00{:}47{:}54{.}972$ this extract is from a plant

NOTE Confidence: 0.727035305

 $00:47:54.972 \rightarrow 00:47:58.320$ that's living somewhere in Belize,

NOTE Confidence: 0.727035305

 $00:47:58.320 \rightarrow 00:47:59.678$ 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

 $00:48:01.480 \longrightarrow 00:48:03.693$ we may wind up going down to

NOTE Confidence: 0.898606856666667

 $00:48:03.693 \dashrightarrow 00:48:05.958$ Belize and harvesting this plant.

NOTE Confidence: 0.8986068566666667

 $00{:}48{:}05{.}960 \dashrightarrow 00{:}48{:}06{.}952$ But another truism is,

NOTE Confidence: 0.8986068566666667

 $00:48:06.952 \rightarrow 00:48:08.192$ I've learned over the years,

NOTE Confidence: 0.8986068566666667

 $00:48:08.200 \rightarrow 00:48:09.118$ 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

 $00:48:10.380 \rightarrow 00:48:13.280$ you get the things you were hoping to get,

NOTE Confidence: 0.8986068566666667

 $00:48:13.280 \longrightarrow 00:48:14.393$ 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: 0.8986068566666667

 $00:48:15.560 \longrightarrow 00:48:16.780$ but in fact you were

- NOTE Confidence: 0.8986068566666667
- $00:48:16.780 \longrightarrow 00:48:18.000$ screening for them all along.
- NOTE Confidence: 0.8986068566666667
- $00:48:18.000 \longrightarrow 00:48:20.448$ So here's another robust positive that
- NOTE Confidence: 0.8986068566666667
- $00{:}48{:}20{.}448 \dashrightarrow 00{:}48{:}23{.}684$ scored as a pro survival chemical in
- NOTE Confidence: 0.8986068566666667
- $00:48:23.684 \rightarrow 00:48:26.918$ that reporter system I described to you.
- NOTE Confidence: 0.898606856666667
- $00:48:26.920 \rightarrow 00:48:29.560$ So somehow we're inactivating Beta Catena.
- NOTE Confidence: 0.898606856666667
- $00:48:29.560 \longrightarrow 00:48:31.233$ But now to our surprise when we
- NOTE Confidence: 0.898606856666667
- $00:48:31.233 \longrightarrow 00:48:32.890$ did the western blots and here
- NOTE Confidence: 0.8986068566666667
- $00:48:32.890 \rightarrow 00:48:34.365$ multiple fractions of this extract
- NOTE Confidence: 0.8986068566666667
- $00{:}48{:}34{.}365 \dashrightarrow 00{:}48{:}36{.}680$ which is from a plant in Tanzania,
- NOTE Confidence: 0.8986068566666667
- $00{:}48{:}36{.}680 \dashrightarrow 00{:}48{:}38{.}924$ you can see that actually the
- NOTE Confidence: 0.898606856666667
- $00:48:38.924 \longrightarrow 00:48:40.420$ reporter and endogenous beta
- NOTE Confidence: 0.8986068566666667
- 00:48:40.490 --> 00:48:42.768 Catena abundance goes up not down.
- NOTE Confidence: 0.8986068566666667
- $00:48:42.768 \longrightarrow 00:48:44.952$ But it is apparently inactive because
- NOTE Confidence: 0.8986068566666667
- $00{:}48{:}44{.}952 \dashrightarrow 00{:}48{:}47{.}213$ here is X and two which again
- NOTE Confidence: 0.898606856666667
- $00{:}48{:}47{.}213 \dashrightarrow 00{:}48{:}48{.}604$ reads out beta catena in activity.
- NOTE Confidence: 0.898606856666667

 $00:48:48.604 \rightarrow 00:48:50.280$ And when you look under the microscope,

NOTE Confidence: 0.8986068566666667

 $00:48:50.280 \rightarrow 00:48:52.786$ you can see that this chemicals inducing

NOTE Confidence: 0.898606856666667

 $00:48:52.786 \rightarrow 00:48:55.120$ beta catena into go into aggregates.

NOTE Confidence: 0.898606856666667

 $00:48:55.120 \rightarrow 00:48:56.560$ So maybe that's not such a bad thing.

NOTE Confidence: 0.898606856666667

 $00{:}48{:}56{.}560 \dashrightarrow 00{:}48{:}58{.}000$ Maybe that's another way

NOTE Confidence: 0.8986068566666667

 $00:48:58.000 \longrightarrow 00:48:59.428$ 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: 0.8986068566666667

 $00:49:01.552 \rightarrow 00:49:02.846$ as opposed to destabilizing.

NOTE Confidence: 0.898606856666667

 $00{:}49{:}02{.}846 \dashrightarrow 00{:}49{:}05{.}440$ Now I should point out for this

NOTE Confidence: 0.8986068566666667

 $00:49:05.440 \longrightarrow 00:49:07.120$ chemical and I can't even say

NOTE Confidence: 0.8986068566666667

 $00:49:07.120 \longrightarrow 00:49:08.394$ chemical singular now because

NOTE Confidence: 0.898606856666667

 $00:49:08.394 \rightarrow 00:49:10.039$ these are only partially purified.

NOTE Confidence: 0.8986068566666667

 $00{:}49{:}10.040 \dashrightarrow 00{:}49{:}13.059$ I don't know whether this extract or the

NOTE Confidence: 0.8986068566666667

 $00{:}49{:}13.059 \dashrightarrow 00{:}49{:}15.520$ previous extract are going to hit a dead end.

NOTE Confidence: 0.898606856666667

 $00:49:15.520 \longrightarrow 00:49:16.695$ I can't tell you anything

NOTE Confidence: 0.8986068566666667

00:49:16.695 - 00:49:17.635 yet about true specificity.

- NOTE Confidence: 0.8986068566666667
- $00:49:17.640 \longrightarrow 00:49:19.273$ What I can tell you is
- NOTE Confidence: 0.8986068566666667
- 00:49:19.273 --> 00:49:20.238 because it's an up assay,
- NOTE Confidence: 0.8986068566666667
- $00:49:20.240 \rightarrow 00:49:22.838$ they're presumably not just rat poison,
- NOTE Confidence: 0.898606856666667
- $00:49:22.840 \longrightarrow 00:49:24.730$ but maybe they are affecting dozens
- NOTE Confidence: 0.898606856666667
- $00{:}49{:}24.730 \dashrightarrow 00{:}49{:}26.581$ if not hundreds of other proteins
- NOTE Confidence: 0.898606856666667
- $00{:}49{:}26{.}581 \dashrightarrow 00{:}49{:}28{.}613$ 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
- $00{:}49{:}33.120 \dashrightarrow 00{:}49{:}37.760$ I I wrote this paper in 2017 and
- NOTE Confidence: 0.898606856666667
- $00:49:37.760 \longrightarrow 00:49:41.372$ it was my attempt to summarize in
- NOTE Confidence: 0.8986068566666667
- 00:49:41.372 --> 00:49:45.056 about 8 pages every common mistake
- NOTE Confidence: 0.8986068566666667
- 00:49:45.056 --> 00:49:47.820 pitfall artifact I had seen in
- NOTE Confidence: 0.8986068566666667
- $00{:}49{:}47{.}820 \dashrightarrow 00{:}49{:}49{.}495$ the literature related to target
- NOTE Confidence: 0.8986068566666667
- $00{:}49{:}49{.}495 \dashrightarrow 00{:}49{:}50{.}720$ identification and validation,
- NOTE Confidence: 0.8986068566666667
- $00{:}49{:}50{.}720 \dashrightarrow 00{:}49{:}52{.}052$ including by the way some mistakes
- NOTE Confidence: 0.898606856666667

 $00:49:52.052 \rightarrow 00:49:53.160$ we made along the way.

NOTE Confidence: 0.8986068566666667

00:49:53.160 --> 00:49:53.940 We all make mistakes.

NOTE Confidence: 0.898606856666667

 $00:49:53.940 \longrightarrow 00:49:55.559$ So this may be partially A mea culpa,

NOTE Confidence: 0.898606856666667

 $00:49:55.560 \rightarrow 00:49:57.200$ but this was my attempt to

NOTE Confidence: 0.8986068566666667

 $00:49:57.200 \longrightarrow 00:49:58.160$ say we have to do better.

NOTE Confidence: 0.8986068566666667

 $00{:}49{:}58.160 \dashrightarrow 00{:}50{:}00.029$ We can't have our friends in industry

NOTE Confidence: 0.898606856666667

 $00:50:00.029 \rightarrow 00:50:02.145$ saying that 50 to 90% of the time

NOTE Confidence: 0.8986068566666667

00:50:02.145 --> 00:50:03.720 they can't replicate our findings.

NOTE Confidence: 0.898606856666667

 $00{:}50{:}03.720 \dashrightarrow 00{:}50{:}05.152$ And so these are some of the controls

NOTE Confidence: 0.8986068566666667

 $00{:}50{:}05{.}152 \dashrightarrow 00{:}50{:}06{.}694$ you might want to think about if you're

NOTE Confidence: 0.8986068566666667

 $00:50:06.694 \rightarrow 00:50:07.960$ 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: 0.8986068566666667

 $00:50:10.291 \rightarrow 00:50:13.079$ was a breast cancer surgeon at the Brigham.

NOTE Confidence: 0.8986068566666667

 $00:50:13.080 \longrightarrow 00:50:14.540$ She developed breast cancer.

NOTE Confidence: 0.898606856666667

00:50:14.540 --> 00:50:16.000 She actually self diagnosed

NOTE Confidence: 0.8986068566666667

 $00:50:16.000 \rightarrow 00:50:17.960$ herself with breast cancer in 2003.

- NOTE Confidence: 0.8986068566666667
- 00:50:17.960 --> 00:50:20.101 In fact, Dara Weiner, who's now here,
- NOTE Confidence: 0.8986068566666667
- $00{:}50{:}20{.}101 \dashrightarrow 00{:}50{:}21{.}536$ was her medical on cologist and
- NOTE Confidence: 0.8986068566666667
- $00{:}50{:}21{.}536 \dashrightarrow 00{:}50{:}23{.}039$ she survived her breast cancer,
- NOTE Confidence: 0.8986068566666667
- $00:50:23.040 \dashrightarrow 00:50:25.365$ but she developed an unrelated
- NOTE Confidence: 0.898606856666667
- $00:50:25.365 \longrightarrow 00:50:26.760$ glioblastoma in 2010,
- NOTE Confidence: 0.898606856666667
- $00:50:26.760 \longrightarrow 00:50:29.105$ 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: 0.8986068566666667
- 00:50:33.960 --> 00:50:35.280 if you're wondering.
- NOTE Confidence: 0.898606856666667
- $00{:}50{:}35{.}280 \dashrightarrow 00{:}50{:}38{.}617$ 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: 0.8986068566666667
- $00:50:40.696 \rightarrow 00:50:42.840$ or has a you all have mothers.
- NOTE Confidence: 0.8986068566666667
- 00:50:42.840 --> 00:50:43.390 You know,
- NOTE Confidence: 0.898606856666667
- $00:50:43.390 \rightarrow 00:50:43.940$ I was.
- NOTE Confidence: 0.8986068566666667

 $00:50:43.940 \longrightarrow 00:50:45.590$ I was sure if there was

NOTE Confidence: 0.89679579

 $00:50:45.662 \rightarrow 00:50:48.070$ any way Carolyn could live to see

NOTE Confidence: 0.89679579

 $00{:}50{:}48.070 \dashrightarrow 00{:}50{:}50{.}480$ her eldest child graduate from Yale,

NOTE Confidence: 0.89679579

 $00:50:50.480 \longrightarrow 00:50:51.642$ she was going to figure out a

NOTE Confidence: 0.89679579

 $00:50:51.642 \rightarrow 00:50:53.520$ way to do it, and she didn't.

NOTE Confidence: 0.89679579

 $00{:}50{:}53{.}520 \dashrightarrow 00{:}50{:}56{.}198$ So I wrote this because if you think NOTE Confidence: 0.89679579

 $00{:}50{:}56{.}198 \dashrightarrow 00{:}50{:}57{.}780$ 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

 $00{:}50{:}59{.}452 \dashrightarrow 00{:}51{:}01{.}156$ you think it's all about whether

NOTE Confidence: 0.89679579

 $00:51:01.156 \dashrightarrow 00:51:03.203$ you fooled Reviewer 3 one more time NOTE Confidence: 0.89679579

 $00:51:03.203 \rightarrow 00:51:04.760$ and you slipped another one in,

NOTE Confidence: 0.89679579

 $00{:}51{:}04.760 \dashrightarrow 00{:}51{:}06.248$ and it's all about what societies

NOTE Confidence: 0.89679579

 $00:51:06.248 \rightarrow 00:51:07.648$ 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

 $00{:}51{:}09{.}688 \dashrightarrow 00{:}51{:}11{.}320$ becoming a dominant negative.

NOTE Confidence: 0.89679579

 $00:51:11.320 \rightarrow 00:51:13.624$ The only thing you should care about is

- NOTE Confidence: 0.89679579
- $00:51:13.624 \rightarrow 00:51:16.060$ whether what I've discovered is so true,
- NOTE Confidence: 0.89679579
- $00:51:16.060 \rightarrow 00:51:18.035$ so reproducible and so robust,
- NOTE Confidence: 0.89679579
- $00:51:18.040 \longrightarrow 00:51:19.768$ the next group of people can
- NOTE Confidence: 0.89679579
- $00:51:19.768 \longrightarrow 00:51:21.280$ come and build upon that.
- NOTE Confidence: 0.89679579
- $00:51:21.280 \rightarrow 00:51:23.000$ 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
- $00:51:24.240 \rightarrow 00:51:26.816$ Because I can tell you everything we had
- NOTE Confidence: 0.89679579
- $00{:}51{:}26.816 \dashrightarrow 00{:}51{:}29.247$ available to treat my wife was based on
- NOTE Confidence: 0.89679579
- $00{:}51{:}29{.}247 \dashrightarrow 00{:}51{:}32{.}199$ 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
- $00{:}51{:}33{.}915 \dashrightarrow 00{:}51{:}35{.}357$ or grandchildren gets this disease
- NOTE Confidence: 0.89679579
- $00{:}51{:}35{.}357 \dashrightarrow 00{:}51{:}36{.}350$ and statistically unfortunately
- NOTE Confidence: 0.89679579
- $00{:}51{:}36{.}350 \dashrightarrow 00{:}51{:}37{.}674$ it's likely to happen,
- NOTE Confidence: 0.89679579
- $00{:}51{:}37{.}680 \dashrightarrow 00{:}51{:}39{.}264$ they're going to be counting on
- NOTE Confidence: 0.89679579

 $00:51:39.264 \rightarrow 00:51:40.560$ the science we're doing now.

NOTE Confidence: 0.89679579

 $00{:}51{:}40{.}560 \dashrightarrow 00{:}51{:}42{.}555$ So we have to do much better.

NOTE Confidence: 0.89679579

 $00:51:42.560 \longrightarrow 00:51:43.638$ 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

 $00{:}51{:}45{.}200 \dashrightarrow 00{:}51{:}46{.}200$ I showed you these data,

NOTE Confidence: 0.89679579

 $00{:}51{:}46{.}200 \dashrightarrow 00{:}51{:}47{.}760$ these were the data from the

NOTE Confidence: 0.89679579

 $00:51:47.760 \longrightarrow 00:51:48.800$ phase one two trial.

NOTE Confidence: 0.89679579

 $00:51:48.800 \rightarrow 00:51:51.206$ The phase three data were positive

NOTE Confidence: 0.89679579

 $00{:}51{:}51{.}206 \dashrightarrow 00{:}51{:}53{.}741$ 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

 $00{:}51{:}56{.}212 \dashrightarrow 00{:}51{:}58{.}536$ cancer just about a month ago in

NOTE Confidence: 0.89679579

 $00{:}51{:}58{.}536 \dashrightarrow 00{:}52{:}00{.}988$ patients who have failed VEGF inhibitor

NOTE Confidence: 0.89679579

 $00{:}52{:}00{.}988 \dashrightarrow 00{:}52{:}02{.}732$ or immune checkpoint inhibitor.

NOTE Confidence: 0.89679579

 $00{:}52{:}02.732 \dashrightarrow 00{:}52{:}05.444$ But another truism in medical on cology

NOTE Confidence: 0.89679579

 $00:52:05.444 \rightarrow 00:52:08.093$ is most drugs and medical oncology

NOTE Confidence: 0.89679579

 $00:52:08.093 \rightarrow 00:52:10.679$ work better in front line settings
$00:52:10.680 \rightarrow 00:52:12.087$ 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

 $00{:}52{:}13.283 \dashrightarrow 00{:}52{:}14.564$ and treated them with all sorts of

NOTE Confidence: 0.89679579

 $00{:}52{:}14.605 \dashrightarrow 00{:}52{:}15.967$ noxious things and you've selected for

NOTE Confidence: 0.89679579

 $00{:}52{:}15{.}967 \dashrightarrow 00{:}52{:}17{.}142$ all sorts of resistance mechanisms.

NOTE Confidence: 0.89679579

 $00:52:17.142 \longrightarrow 00:52:18.976$ 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

 $00:52:20.360 \rightarrow 00:52:22.040$ So these patients developed so many tumors,

NOTE Confidence: 0.89679579

 $00:52:22.040 \longrightarrow 00:52:23.790$ they're often in careful surveillance

NOTE Confidence: 0.89679579

 $00:52:23.790 \dashrightarrow 00:52:25.540$ programs where they'll get Mris

NOTE Confidence: 0.89679579

 $00{:}52{:}25{.}598 \dashrightarrow 00{:}52{:}27{.}348$ every three to four months in an

NOTE Confidence: 0.89679579

 $00{:}52{:}27{.}348 \dashrightarrow 00{:}52{:}28{.}632$ attempt to delay or prevent the

NOTE Confidence: 0.89679579

 $00:52:28.632 \rightarrow 00:52:29.999$ need for repeated surgeries,

NOTE Confidence: 0.89679579

 $00{:}52{:}30{.}000 \dashrightarrow 00{:}52{:}32{.}320$ such as repeated partial nephrectomies,

NOTE Confidence: 0.89679579

 $00{:}52{:}32{.}320 \dashrightarrow 00{:}52{:}34{.}120$ which in the case of partial

 $00:52:34.120 \rightarrow 00:52:35.320$ nephrectomies would leave them

NOTE Confidence: 0.89679579

 $00:52:35.320 \longrightarrow 00:52:36.445$ eventually functionally an ephic.

NOTE Confidence: 0.89679579

 $00{:}52{:}36{.}445 \dashrightarrow 00{:}52{:}39{.}070$ So we were able to convince Peloton NOTE Confidence: 0.89679579

 $00{:}52{:}39{.}127 \dashrightarrow 00{:}52{:}41{.}248$ and then Merck to treat 61 patients

NOTE Confidence: 0.89679579

 $00{:}52{:}41{.}248 \dashrightarrow 00{:}52{:}42{.}972$ with von Hippelinda disease that

NOTE Confidence: 0.89679579

 $00{:}52{:}42{.}972 \dashrightarrow 00{:}52{:}44{.}813$ had measurable kidney tumors that NOTE Confidence: 0.89679579

 $00:52:44.813 \longrightarrow 00:52:46.478$ had never been treated before.

NOTE Confidence: 0.89679579

 $00:52:46.480 \rightarrow 00:52:48.226$ They were just in these surveillance

NOTE Confidence: 0.89679579

 $00{:}52{:}48.226 \dashrightarrow 00{:}52{:}48.517$ programs.

NOTE Confidence: 0.89679579

 $00:52:48.520 \longrightarrow 00:52:50.263$ So now you can see the the

NOTE Confidence: 0.89679579

 $00{:}52{:}50{.}263 \dashrightarrow 00{:}52{:}51{.}719$ swimmers plots look even better.

NOTE Confidence: 0.89679579

 $00:52:51.720 \longrightarrow 00:52:54.753$ So once again the dotted line is one year,

NOTE Confidence: 0.89679579

 $00:52:54.760 \longrightarrow 00:52:56.584$ but now I think you can see that

NOTE Confidence: 0.89679579

 $00:52:56.584 \rightarrow 00:52:58.331$ most of the patients are doing

NOTE Confidence: 0.89679579

 $00{:}52{:}58{.}331 \dashrightarrow 00{:}53{:}00{.}010$ well and many of these patients

NOTE Confidence: 0.89679579

 $00:53:00.010 \rightarrow 00:53:02.413$ went on to have a partial response.

- NOTE Confidence: 0.89679579
- $00:53:02.413 \longrightarrow 00:53:05.078$ If you prefer waterfall plots

00:53:05.078 - 00:53:06.677 then swimmers plots.

NOTE Confidence: 0.89679579

 $00{:}53{:}06{.}680 \dashrightarrow 00{:}53{:}09{.}488$ Here are the changes in the size of

NOTE Confidence: 0.89679579

 $00:53:09.488 \longrightarrow 00:53:11.496$ the indicator kidney tumors that

NOTE Confidence: 0.89679579

 $00{:}53{:}11{.}496 \dashrightarrow 00{:}53{:}13{.}272$ were the basis of these patients

NOTE Confidence: 0.89679579

 $00:53:13.272 \rightarrow 00:53:14.160$ 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

 $00:53:15.680 \dashrightarrow 00:53:16.877$ I'm a lumper rather than a splitter.

NOTE Confidence: 0.89679579

 $00{:}53{:}16.880 \dashrightarrow 00{:}53{:}19.076$ So I would say these are all going down.

NOTE Confidence: 0.812062645

 $00:53:19.080 \longrightarrow 00:53:21.280$ 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

 $00{:}53{:}24{.}504 \dashrightarrow 00{:}53{:}26{.}137$ the patient as long as the tumor

NOTE Confidence: 0.812062645

 $00{:}53{:}26.137 \dashrightarrow 00{:}53{:}27.452$ is getting smaller, that's good.

NOTE Confidence: 0.812062645

 $00{:}53{:}27{.}452 \dashrightarrow 00{:}53{:}29{.}408$ We had also done some preclinical

 $00:53:29.408 \rightarrow 00:53:31.331$ modeling that suggested that hip two

NOTE Confidence: 0.812062645

 $00:53:31.331 \rightarrow 00:53:33.583$ was important in the blood vessel tumors

NOTE Confidence: 0.812062645

 $00{:}53{:}33{.}583 \dashrightarrow 00{:}53{:}35{.}438$ and here are the hemangiobla stoma.

NOTE Confidence: 0.812062645

 $00:53:35.440 \longrightarrow 00:53:36.512$ So again to be on the trial you

NOTE Confidence: 0.812062645

 $00:53:36.512 \rightarrow 00:53:37.519$ had to have a kidney tumor,

NOTE Confidence: 0.812062645

 $00:53:37.520 \longrightarrow 00:53:39.164$ but you could have other tumors

NOTE Confidence: 0.812062645

 $00{:}53{:}39{.}164 \dashrightarrow 00{:}53{:}40{.}680$ associated with VHL disease as well.

NOTE Confidence: 0.812062645

 $00:53:40.680 \rightarrow 00:53:43.320$ So here are the hemangioblastoma shrinking.

NOTE Confidence: 0.812062645

 $00{:}53{:}43{.}320 \dashrightarrow 00{:}53{:}45{.}160$ These patients also develop an

NOTE Confidence: 0.812062645

 $00{:}53{:}45{.}160 \dashrightarrow 00{:}53{:}46{.}632$ unusual neuroendocrine tumor of

NOTE Confidence: 0.812062645

 $00:53:46.632 \longrightarrow 00:53:48.398$ the pancreas called peanuts.

NOTE Confidence: 0.812062645

 $00:53:48.400 \rightarrow 00:53:52.045$ They responded very nicely and

NOTE Confidence: 0.812062645

 $00:53:52.045 \longrightarrow 00:53:53.020$ perhaps as importantly,

NOTE Confidence: 0.812062645

 $00:53:53.020 \longrightarrow 00:53:54.645$ I I mentioned these patients

NOTE Confidence: 0.812062645

 $00:53:54.645 \dashrightarrow 00:53:56.359$ were in surveillance programs.

NOTE Confidence: 0.812062645

 $00:53:56.360 \longrightarrow 00:53:58.628$ So in Gray are the four years

- NOTE Confidence: 0.812062645
- $00{:}53{:}58{.}628 \dashrightarrow 00{:}54{:}00{.}317$ of surveillance before going on
- NOTE Confidence: 0.812062645
- $00:54:00.317 \longrightarrow 00:54:02.585$ 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
- $00:54:05.600 \rightarrow 00:54:07.644$ that patient's going back to the operating
- NOTE Confidence: 0.812062645
- $00{:}54{:}07{.}644 \dashrightarrow 00{:}54{:}10{.}037$ 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
- $00:54:10.980 \longrightarrow 00:54:12.610$ the spinal cord removed, tumor removed.
- NOTE Confidence: 0.812062645
- $00:54:12.610 \longrightarrow 00:54:14.680$ And you can see that the,
- NOTE Confidence: 0.812062645
- $00:54:14.680 \rightarrow 00:54:17.760$ the frequency of the surgery goes way down,
- NOTE Confidence: 0.812062645
- $00:54:17.760 \longrightarrow 00:54:18.860$ doesn't go to 0,
- NOTE Confidence: 0.812062645
- $00{:}54{:}18{.}860 \dashrightarrow 00{:}54{:}20{.}610$ but it does go way down.
- NOTE Confidence: 0.812062645
- $00:54:20.610 \longrightarrow 00:54:22.235$ And so based on that,
- NOTE Confidence: 0.812062645
- 00:54:22.240 --> 00:54:23.047 several years ago,
- NOTE Confidence: 0.812062645
- $00{:}54{:}23.047 \dashrightarrow 00{:}54{:}25.311$ the FDA just on the phase two data
- NOTE Confidence: 0.812062645

 $00:54:25.311 \longrightarrow 00:54:28.012$ approved this drug for the treatment of

NOTE Confidence: 0.812062645

 $00:54:28.012 \rightarrow 00:54:31.545$ Von Hippel Lindau disease just about 100

NOTE Confidence: 0.812062645

 $00:54:31.545 \rightarrow 00:54:34.025$ years after Lindau's initial report.

NOTE Confidence: 0.812062645

 $00{:}54{:}34{.}025 \dashrightarrow 00{:}54{:}35{.}750$ But just because statistics can

NOTE Confidence: 0.812062645

 $00:54:35.750 \longrightarrow 00:54:37.639$ sometimes be a little bit dry,

NOTE Confidence: 0.812062645

 $00:54:37.640 \rightarrow 00:54:39.960$ to put a bit of a human face on this, NOTE Confidence: 0.812062645

 $00{:}54{:}39{.}960 \dashrightarrow 00{:}54{:}41{.}948$ we actually knew the trial was going

NOTE Confidence: 0.812062645

 $00{:}54{:}41{.}948 \dashrightarrow 00{:}54{:}44{.}175$ 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

 $00{:}54{:}45{.}820 \dashrightarrow 00{:}54{:}47{.}845$ the VHL patients were posting on

NOTE Confidence: 0.812062645

 $00:54:47.845 \rightarrow 00:54:49.814$ their social media pages They were doing.

NOTE Confidence: 0.812062645

 $00{:}54{:}49{.}814 \dashrightarrow 00{:}54{:}51{.}122$ And you can imagine these patients

NOTE Confidence: 0.812062645

 $00{:}54{:}51{.}122 \dashrightarrow 00{:}54{:}52{.}369$ have lived with the Sword of

NOTE Confidence: 0.812062645

 $00:54:52.369 \rightarrow 00:54:53.560$ Damocles over their neck or hey,

NOTE Confidence: 0.812062645

 $00{:}54{:}53{.}560 \dashrightarrow 00{:}54{:}54{.}816$ whatever the expression is,

NOTE Confidence: 0.812062645

 $00:54:54.816 \rightarrow 00:54:56.386$ because they've watched this disease

- NOTE Confidence: 0.812062645
- $00:54:56.386 \rightarrow 00:54:57.882$ ravage their families generation
- NOTE Confidence: 0.812062645
- 00:54:57.882 --> 00:54:59.398 after generation after generation.
- NOTE Confidence: 0.812062645
- $00:54:59.400 \rightarrow 00:55:00.816$ And they just assume they're going
- NOTE Confidence: 0.812062645
- $00:55:00.816 \rightarrow 00:55:02.240$ 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
- $00:55:03.840 \longrightarrow 00:55:05.478$ I never thought I'd see this day.
- NOTE Confidence: 0.812062645
- $00:55:05.480 \rightarrow 00:55:07.080$ 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
- $00:55:08.520 \rightarrow 00:55:10.834$ 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
- $00:55:12.720 \longrightarrow 00:55:13.680$ 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
- $00:55:15.374 \rightarrow 00:55:16.758$ until this was sent to me,
- NOTE Confidence: 0.812062645
- $00{:}55{:}16.760 \dashrightarrow 00{:}55{:}18.710$ but I do have permission to
- NOTE Confidence: 0.812062645
- $00:55:18.710 \longrightarrow 00:55:19.890$ show this patient's face.
- NOTE Confidence: 0.812062645

- $00:55:19.890 \longrightarrow 00:55:21.215$ But this is another patient
- NOTE Confidence: 0.812062645
- $00{:}55{:}21{.}215 \dashrightarrow 00{:}55{:}22{.}600$ who was on that trial.
- NOTE Confidence: 0.812062645
- $00:55:22.600 \longrightarrow 00:55:23.052$ Hey everybody,
- NOTE Confidence: 0.812062645
- 00:55:23.052 --> 00:55:23.504 it's Justin,
- NOTE Confidence: 0.812062645
- $00{:}55{:}23.504 \dashrightarrow 00{:}55{:}25.720$ And I just wanted to give you a quick update.
- NOTE Confidence: 0.812062645
- $00{:}55{:}25{.}720 \dashrightarrow 00{:}55{:}29{.}262$ I am in a gondola right now in Taiwan.
- NOTE Confidence: 0.812062645
- $00:55:29.262 \longrightarrow 00:55:33.399$ 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
- $00{:}55{:}37{.}320 \dashrightarrow 00{:}55{:}39{.}056$ 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
- $00:55:40.680 \longrightarrow 00:55:42.492$ 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
- $00{:}55{:}45.636 \dashrightarrow 00{:}55{:}48.284$ I would have never been able to come out
- NOTE Confidence: 0.812062645
- $00:55:48.284 \rightarrow 00:55:50.436$ here and do what I'm doing right now.
- NOTE Confidence: 0.812062645
- $00:55:50.440 \dashrightarrow 00:55:52.799$ So I just wanted to thank Peloton

- NOTE Confidence: 0.812062645
- $00{:}55{:}52{.}799 \dashrightarrow 00{:}55{:}55{.}454$ and I hope Mark will fast track
- NOTE Confidence: 0.812062645
- $00:55:55.454 \dashrightarrow 00:55:57.800$ this drug for a VHL treatment.
- NOTE Confidence: 0.763883952857143
- $00:55:57.800 \rightarrow 00:55:59.914$ So if you guys are listed in,
- NOTE Confidence: 0.763883952857143
- $00:55:59.920 \longrightarrow 00:56:01.312$ hopefully you guys will
- NOTE Confidence: 0.763883952857143
- $00:56:01.312 \longrightarrow 00:56:03.400$ put on market to help VHL.
- NOTE Confidence: 0.763883952857143
- $00:56:03.400 \dashrightarrow 00:56:06.735$ But yeah, keep watching these videos.
- NOTE Confidence: 0.763883952857143
- $00:56:06.735 \longrightarrow 00:56:07.960$ I'll be making more and
- NOTE Confidence: 0.763883952857143
- $00{:}56{:}07{.}960 \dashrightarrow 00{:}56{:}09{.}079$ I'll get better at it.
- NOTE Confidence: 0.763883952857143
- $00{:}56{:}09{.}080 \dashrightarrow 00{:}56{:}10{.}488$ 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
- $00{:}56{:}13.740 \dashrightarrow 00{:}56{:}15.624$ 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
- $00{:}56{:}17{.}440 \dashrightarrow 00{:}56{:}18{.}680$ Because at that age,
- NOTE Confidence: 0.763883952857143
- $00{:}56{:}18.680 \dashrightarrow 00{:}56{:}20.540$ your biggest concern should be whether
- NOTE Confidence: 0.763883952857143

 $00{:}56{:}20{.}594 \dashrightarrow 00{:}56{:}22{.}314$ you look fat on your blog and not

NOTE Confidence: 0.763883952857143

 $00{:}56{:}22.314 \dashrightarrow 00{:}56{:}24.069$ how bad your MRI might look next

NOTE Confidence: 0.763883952857143

 $00:56:24.069 \rightarrow 00:56:25.683$ time around and your doctor telling

NOTE Confidence: 0.763883952857143

 $00:56:25.683 \rightarrow 00:56:27.540$ you to get your affairs in order.

NOTE Confidence: 0.763883952857143

 $00{:}56{:}27{.}540 \dashrightarrow 00{:}56{:}28{.}320$ So with that,

NOTE Confidence: 0.763883952857143

 $00:56:28.320 \rightarrow 00:56:29.600$ I thank you very much for your attention.

NOTE Confidence: 0.763883952857143

 $00:56:29.600 \rightarrow 00:56:30.800$ I'm happy to take questions.

NOTE Confidence: 0.3983846

 $00:56:43.440 \longrightarrow 00:56:43.720$ Yes.

NOTE Confidence: 0.840521202

 $00{:}56{:}54{.}280 \dashrightarrow 00{:}56{:}55{.}440$ Yeah, that's a great question.

NOTE Confidence: 0.840521202

 $00{:}56{:}55{.}440 \dashrightarrow 00{:}56{:}56{.}595$ So we talk about this a lot.

NOTE Confidence: 0.840521202

 $00{:}56{:}56{.}600 \dashrightarrow 00{:}56{:}57{.}600$ So the question relates to,

NOTE Confidence: 0.840521202

 $00:56:57.600 \rightarrow 00:56:58.620$ 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

 $00{:}57{:}01{.}000 \dashrightarrow 00{:}57{:}02{.}602$ you would down regulate the expression

NOTE Confidence: 0.840521202

 $00{:}57{:}02.602 \dashrightarrow 00{:}57{:}05.482$ of the ZR VS and that might make immune

NOTE Confidence: 0.840521202

 $00:57:05.482 \rightarrow 00:57:07.237$ checkpoint inhibitor therapy work worse.

- NOTE Confidence: 0.840521202
- $00:57:07.240 \longrightarrow 00:57:09.240$ And so maybe the combination
- NOTE Confidence: 0.840521202
- $00:57:09.240 \longrightarrow 00:57:10.840$ would actually be antagonistic.
- NOTE Confidence: 0.840521202
- $00:57:10.840 \longrightarrow 00:57:12.343$ I think we just have to do the clinical
- NOTE Confidence: 0.840521202
- $00:57:12.343 \longrightarrow 00:57:13.517$ 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
- $00{:}57{:}14.978 \dashrightarrow 00{:}57{:}16.319$ surprised if that's what we see.
- NOTE Confidence: 0.840521202
- $00:57:16.320 \longrightarrow 00:57:17.488$ 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
- $00{:}57{:}19{.}240 \dashrightarrow 00{:}57{:}21{.}170$ there's so many benefits from
- NOTE Confidence: 0.840521202
- $00:57:21.170 \longrightarrow 00:57:23.100$ combining 2 drugs that have
- NOTE Confidence: 0.840521202
- $00:57:23.177 \longrightarrow 00:57:25.162$ distinct mechanisms of action in
- NOTE Confidence: 0.840521202
- $00:57:25.162 \rightarrow 00:57:26.896$ terms of treating or preventing
- NOTE Confidence: 0.840521202
- $00:57:26.896 \dashrightarrow 00:57:28.456$ 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
- $00{:}57{:}30{.}305 \dashrightarrow 00{:}57{:}31{.}770$ drugs with very distinct mechanisms
- NOTE Confidence: 0.840521202

 $00:57:31.770 \longrightarrow 00:57:33.363$ of action would outweigh this

NOTE Confidence: 0.840521202

 $00{:}57{:}33{.}363 \dashrightarrow 00{:}57{:}34{.}923$ theoretical concern that in some

NOTE Confidence: 0.840521202

 $00:57:34.923 \dashrightarrow 00:57:36.448$ cases they would be antagonistic.

NOTE Confidence: 0.840521202

 $00{:}57{:}36{.}448 \dashrightarrow 00{:}57{:}38{.}549$ I can also imagine there might be

NOTE Confidence: 0.840521202

 $00{:}57{:}38{.}549 \dashrightarrow 00{:}57{:}40{.}421$ some games you could do in terms of

NOTE Confidence: 0.840521202

 $00:57:40.421 \rightarrow 00:57:42.118$ timing that might also be helpful.

NOTE Confidence: 0.840521202

 $00:57:42.120 \longrightarrow 00:57:42.400$ There

NOTE Confidence: 0.501148141666667

 $00:57:45.720 \longrightarrow 00:57:47.118$ is. There is that a student?

NOTE Confidence: 0.501148141666667

00:57:47.120 --> 00:57:47.800 Well, students should always

NOTE Confidence: 0.5011481416666667

 $00{:}57{:}47.800 \dashrightarrow 00{:}57{:}48.936$ go first if that. I can't,

NOTE Confidence: 0.501148141666667

 $00{:}57{:}48{.}936 \dashrightarrow 00{:}57{:}50{.}760$ 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: 0.5011481416666667

 $00{:}57{:}52{.}000 \dashrightarrow 00{:}57{:}53{.}840$ but I this no, it's not the Dean.

NOTE Confidence: 0.5011481416666667

 $00{:}57{:}53{.}840 \dashrightarrow 00{:}57{:}55{.}478$ I'm quite sure now that I see the beard,

NOTE Confidence: 0.5011481416666667

 $00:57:55.480 \longrightarrow 00:57:57.040$ it's not the Dean, but anyway

NOTE Confidence: 0.757077424117647

 $00{:}58{:}09{.}560 \dashrightarrow 00{:}58{:}11{.}936$ yeah so. So let me do a medical student

 $00:58:11.936 \rightarrow 00:58:14.185$ trick and answer a related question

NOTE Confidence: 0.757077424117647

 $00:58:14.185 \rightarrow 00:58:15.604$ before answering your question.

NOTE Confidence: 0.757077424117647

 $00:58:15.604 \longrightarrow 00:58:18.758$ So one is I I I do think hip and

NOTE Confidence: 0.757077424117647

 $00{:}58{:}18.758 \dashrightarrow 00{:}58{:}20.424$ and in particular hip too is part

NOTE Confidence: 0.757077424117647

 $00{:}58{:}20{.}424 \dashrightarrow 00{:}58{:}22{.}477$ 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

 $00{:}58{:}25{.}280 \dashrightarrow 00{:}58{:}28{.}885$ So I also think there are wides pread

NOTE Confidence: 0.757077424117647

 $00{:}58{:}28{.}885 \ldots > 00{:}58{:}31{.}030$ 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

 $00{:}58{:}32{.}880 \dashrightarrow 00{:}58{:}35{.}679$ that I think is creating a permissive

NOTE Confidence: 0.757077424117647

 $00:58:35.680 \dashrightarrow 00:58:37.248$ environment for the expression.

NOTE Confidence: 0.757077424117647

 $00{:}58{:}37{.}248 \dashrightarrow 00{:}58{:}40{.}004$ 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

 $00{:}58{:}42.084 \dashrightarrow 00{:}58{:}43.638$ regulates them if we add a DNA

 $00:58:43.638 \rightarrow 00:58:44.784$ methyl transferase inhibitor and

NOTE Confidence: 0.757077424117647

 $00{:}58{:}44{.}784 \dashrightarrow 00{:}58{:}46{.}814$ then you could see the creation of

NOTE Confidence: 0.757077424117647

 $00:58:46.866 \longrightarrow 00:58:48.554$ a hip binding site next to the ERB.

NOTE Confidence: 0.757077424117647

 $00{:}58{:}48{.}560 \dashrightarrow 00{:}58{:}50{.}864$ So I think it's an interplay of HIP and

NOTE Confidence: 0.757077424117647

 $00:58:50.864 \rightarrow 00:58:52.560$ 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

 $00:58:54.000 \rightarrow 00:58:55.200$ but if these things aren't regulated,

NOTE Confidence: 0.757077424117647

 $00:58:55.200 \rightarrow 00:58:57.996$ why doesn't the endogenous immune system,

NOTE Confidence: 0.757077424117647

 $00{:}58{:}58{.}000 \dashrightarrow 00{:}58{:}59{.}640$ oh and it's one other thing so far

NOTE Confidence: 0.757077424117647

 $00{:}58{:}59{.}640 \dashrightarrow 00{:}59{:}01{.}083$ every time we've looked with these

NOTE Confidence: 0.757077424117647

 $00{:}59{:}01{.}083 \dashrightarrow 00{:}59{:}02{.}559$ do seem to be tumor restricted

NOTE Confidence: 0.757077424117647

 $00:59:02.608 \longrightarrow 00:59:03.838$ 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

 $00{:}59{:}04{.}278 \dashrightarrow 00{:}59{:}05{.}154$ I think you're asking the question,

NOTE Confidence: 0.757077424117647

 $00:59:05.160 \longrightarrow 00:59:05.865$ well that's fine,

 $00{:}59{:}05{.}865 \dashrightarrow 00{:}59{:}07{.}275$ but why doesn't the immune system

NOTE Confidence: 0.757077424117647

 $00:59:07.280 \longrightarrow 00:59:08.540$ recognize these kidney tumors

NOTE Confidence: 0.757077424117647

 $00:59:08.540 \longrightarrow 00:59:10.115$ that already have the Erbs?

NOTE Confidence: 0.757077424117647

 $00:59:10.120 \rightarrow 00:59:12.560$ So that's a question for people like David.

NOTE Confidence: 0.757077424117647

 $00{:}59{:}12{.}560 \dashrightarrow 00{:}59{:}15{.}315$ I walk around thinking that the

NOTE Confidence: 0.757077424117647

 $00{:}59{:}15{.}315 \dashrightarrow 00{:}59{:}17{.}800$ T cells that we needed or wanted

NOTE Confidence: 0.757077424117647

 $00:59:17.800 \rightarrow 00:59:19.718$ eventually lost that they became

NOTE Confidence: 0.757077424117647

 $00{:}59{:}19{.}718 \dashrightarrow 00{:}59{:}21{.}964$ exhausted and that the tumor use

NOTE Confidence: 0.757077424117647

 $00{:}59{:}21{.}964 \dashrightarrow 00{:}59{:}23{.}774$ various molecular signals and tricks

NOTE Confidence: 0.757077424117647

 $00:59:23.774 \rightarrow 00:59:26.188$ to either obey the immune system or

NOTE Confidence: 0.757077424117647

 $00:59:26.188 \rightarrow 00:59:28.078$ or to cripple the immune system.

NOTE Confidence: 0.757077424117647

 $00:59:28.080 \longrightarrow 00:59:29.280$ So I'm hoping that,

NOTE Confidence: 0.757077424117647

00:59:29.280 --> 00:59:29.880 you know,

NOTE Confidence: 0.757077424117647

 $00{:}59{:}29{.}880 \dashrightarrow 00{:}59{:}30{.}932$ the immune checkpoint inhibitors

NOTE Confidence: 0.757077424117647

 $00{:}59{:}30{.}932 \dashrightarrow 00{:}59{:}32{.}803$ are just the foot in the door

 $00:59:32.803 \longrightarrow 00:59:34.267$ to having better and better and

NOTE Confidence: 0.757077424117647

 $00{:}59{:}34{.}267 \dashrightarrow 00{:}59{:}35{.}827$ 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

 $00:59:37.375 \rightarrow 00:59:39.160$ kind of things that they probably

NOTE Confidence: 0.757077424117647

 $00:59:39.160 \longrightarrow 00:59:41.320$ should have been able to recognize.

NOTE Confidence: 0.757077424117647

 $00:59:41.320 \longrightarrow 00:59:41.920$ Is that, is that OK,

NOTE Confidence: 0.757077424117647

 $00:59:41.920 \longrightarrow 00:59:45.340$ 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

 $00{:}59{:}46{.}840 \dashrightarrow 00{:}59{:}47{.}200$ He said good

NOTE Confidence: 0.4781626516666667

 $00{:}59{:}49{.}240 \dashrightarrow 00{:}59{:}51{.}076$ question about the other, the secondary.

NOTE Confidence: 0.526713168333333

 $00{:}59{:}53{.}240 \dashrightarrow 00{:}59{:}55{.}740$ Yeah. So how about the

NOTE Confidence: 0.526713168333333

 $00:59:55.740 \rightarrow 00:59:59.012$ occupation in bad competition?

NOTE Confidence: 0.526713168333333

 $00:59:59.012 \longrightarrow 01:00:00.476$ 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

 $01:00:02.118 \rightarrow 01:00:03.520$ make this point that VHL loss,

NOTE Confidence: 0.526713168333333

 $01:00:03.520 \longrightarrow 01:00:04.532$ although it's a critical

- NOTE Confidence: 0.526713168333333
- $01:00:04.532 \longrightarrow 01:00:05.797$ first step in kidney cancer,
- NOTE Confidence: 0.526713168333333
- $01:00:05.800 \rightarrow 01:00:07.756$ is not sufficient for kidney cancer.
- NOTE Confidence: 0.526713168333333
- $01{:}00{:}07.760 \dashrightarrow 01{:}00{:}09.100$ You need other cooperating.
- NOTE Confidence: 0.526713168333333
- $01{:}00{:}09{.}100 \dashrightarrow 01{:}00{:}11{.}416$ Mutations such as in genes like PBRM
- NOTE Confidence: 0.526713168333333
- $01:00:11.416 \rightarrow 01:00:13.600$ One and BAP One and other other genes,
- NOTE Confidence: 0.526713168333333
- $01:00:13.600 \longrightarrow 01:00:15.400$ many of which are involved
- NOTE Confidence: 0.526713168333333
- $01:00:15.400 \longrightarrow 01:00:16.480$ 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
- $01:00:18.200 \rightarrow 01:00:20.513$ 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
- $01:00:21.340 \rightarrow 01:00:23.800$ 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
- $01{:}00{:}25{.}150 \dashrightarrow 01{:}00{:}27{.}518$ 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
- $01:00:28.798 \longrightarrow 01:00:30.750$ of the other gene products that
- NOTE Confidence: 0.526713168333333

- $01:00:30.750 \longrightarrow 01:00:32.026$ 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
- $01:00:33.600 \longrightarrow 01:00:35.154$ it is partly about amping up
- NOTE Confidence: 0.526713168333333
- $01:00:35.154 \longrightarrow 01:00:36.720$ 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
- $01:01:08.385 \rightarrow 01:01:10.378$ occasionally see and this is another
- NOTE Confidence: 0.848982355909091
- $01:01:10.378 \rightarrow 01:01:12.639$ old idea that's coming back in vogue.
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}12.640 \dashrightarrow 01{:}01{:}14.456$ You know there are a lot of examples
- NOTE Confidence: 0.848982355909091
- $01:01:14.456 \longrightarrow 01:01:16.298$ 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
- $01:01:18.640 \longrightarrow 01:01:19.696$ we'll call it E2F.
- NOTE Confidence: 0.848982355909091
- $01:01:19.696 \rightarrow 01:01:21.626$ And so the knee jerk response usually

- NOTE Confidence: 0.848982355909091
- $01:01:21.626 \rightarrow 01:01:23.914$ when we see an oncogenic signal very high
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}23.914 \dashrightarrow 01{:}01{:}26.077$ is to try to inhibit it with a drug.
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}26.080 \dashrightarrow 01{:}01{:}28.128$ But there's their data that go back 20
- NOTE Confidence: 0.848982355909091
- $01:01:28.128 \longrightarrow 01:01:30.771$ or 30 years ago that show in some cases
- NOTE Confidence: 0.848982355909091
- $01:01:30.771 \longrightarrow 01:01:32.842$ these cancers are just at the brink
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}32.842 \dashrightarrow 01{:}01{:}34.866$ 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
- $01:01:37.640 \longrightarrow 01:01:39.024$ the cells would die.
- NOTE Confidence: 0.848982355909091
- $01:01:39.024 \rightarrow 01:01:40.754$ So paradoxically in some cases,
- NOTE Confidence: 0.848982355909091
- $01:01:40.760 \rightarrow 01:01:42.794$ 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
- $01:01:43.904 \rightarrow 01:01:44.640$ much of this oncogene,
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}44.640 \dashrightarrow 01{:}01{:}45.756$ you're going to choke on it.
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}45.760 \dashrightarrow 01{:}01{:}47.916$ So we have seen in certain settings
- NOTE Confidence: 0.848982355909091
- $01{:}01{:}47.916 \dashrightarrow 01{:}01{:}49.719$ using CRISPR A where further
- NOTE Confidence: 0.848982355909091

 $01:01:49.719 \longrightarrow 01:01:51.754$ activation of a professional oncogene

NOTE Confidence: 0.848982355909091

 $01{:}01{:}51{.}754 \dashrightarrow 01{:}01{:}54{.}063$ in that cancer causes cell death

NOTE Confidence: 0.848982355909091

 $01:01:54.063 \dashrightarrow 01:01:56.115$ and you delete the CRISPR guide.

NOTE Confidence: 0.848982355909091

 $01{:}01{:}56{.}120 \dashrightarrow 01{:}01{:}58{.}040$ So I think that's And so now

NOTE Confidence: 0.848982355909091

 $01:01:58.040 \longrightarrow 01:01:58.840$ 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

 $01:02:00.040 \longrightarrow 01:02:00.640$ of synthetic lethality.

NOTE Confidence: 0.848982355909091

 $01{:}02{:}00.640 \dashrightarrow 01{:}02{:}02{.}474$ If you knew there was a target

NOTE Confidence: 0.848982355909091

 $01{:}02{:}02{.}480 \dashrightarrow 01{:}02{:}04{.}220$ that when inhibited further

NOTE Confidence: 0.848982355909091

 $01{:}02{:}04{.}220 \dashrightarrow 01{:}02{:}05{.}960$ activated the Aqua gene.

NOTE Confidence: 0.946145264

 $01:02:13.260 \longrightarrow 01:02:14.660$ People have work to do,

NOTE Confidence: 0.946145264

 $01:02:14.660 \longrightarrow 01:02:15.192$ We should let them.

NOTE Confidence: 0.946145264

 $01{:}02{:}15{.}192 \dashrightarrow 01{:}02{:}15{.}857$ We should let them go.

NOTE Confidence: 0.946145264

01:02:15.860 --> 01:02:17.996 All right. Thank you very much.