WEBVTT

- NOTE duration:"00:59:38"
- NOTE recognizability:0.858
- NOTE language:en-us
- NOTE Confidence: 0.85961975944444
- $00:00:00.000 \longrightarrow 00:00:02.170$ We have a number of people on
- NOTE Confidence: 0.85961975944444
- $00:00:02.170 \dashrightarrow 00:00:04.080$ the zoom already and I'm sure
- NOTE Confidence: 0.85961975944444
- $00:00:04.080 \longrightarrow 00:00:07.078$ there will be more that the join.
- NOTE Confidence: 0.85961975944444
- $00:00:07.078 \rightarrow 00:00:12.990$ I'm very pleased today to have two speakers.
- NOTE Confidence: 0.85961975944444
- 00:00:12.990 --> 00:00:14.978 Doctors, Hyder and Hanson.
- NOTE Confidence: 0.85961975944444
- $00:00:14.978 \longrightarrow 00:00:18.540$ They will they will go in that
- NOTE Confidence: 0.85961975944444
- 00:00:18.540 --> 00:00:21.886 order and so first is Pharmd Hyder,
- NOTE Confidence: 0.85961975944444
- 00:00:21.890 --> 00:00:24.428 who is a professor of radiology
- NOTE Confidence: 0.85961975944444
- $00:00:24.428 \rightarrow 00:00:26.120$ and biomedical imaging and
- NOTE Confidence: 0.85961975944444
- 00:00:26.193 --> 00:00:27.869 biomedical engineering.
- NOTE Confidence: 0.85961975944444
- 00:00:27.870 --> 00:00:30.180 He received his PhD in
- NOTE Confidence: 0.85961975944444
- 00:00:30.180 --> 00:00:32.028 biophysical chemistry from Yale,
- NOTE Confidence: 0.85961975944444
- $00{:}00{:}32.030 \dashrightarrow 00{:}00{:}34.526$ where he was also an associate
- NOTE Confidence: 0.85961975944444

 $00:00:34.526 \rightarrow 00:00:36.190$ research scientist and postdoctoral

NOTE Confidence: 0.85961975944444

 $00{:}00{:}36.257 \dashrightarrow 00{:}00{:}38.086$ associate with Douglas Rothman.

NOTE Confidence: 0.85961975944444

00:00:38.086 --> 00:00:41.350 He's been in the faculty since 1999,

NOTE Confidence: 0.85961975944444

 $00:00:41.350 \longrightarrow 00:00:43.030$ seems hard to believe.

NOTE Confidence: 0.85961975944444

00:00:43.030 --> 00:00:46.354 You look very young and currently

NOTE Confidence: 0.85961975944444

 $00:00:46.354 \rightarrow 00:00:48.869$ holds dual professor appointments

NOTE Confidence: 0.85961975944444

00:00:48.869 --> 00:00:50.828 in diagnostic radiology

NOTE Confidence: 0.85961975944444

 $00:00:50.828 \rightarrow 00:00:52.787$ and biomedical engineering.

NOTE Confidence: 0.85961975944444

 $00{:}00{:}52.790 \dashrightarrow 00{:}00{:}55.184$ Doctor Hatter is the director of

NOTE Confidence: 0.85961975944444

 $00:00:55.184 \rightarrow 00:00:57.319$ the High field horizontal smallbore

NOTE Confidence: 0.85961975944444

 $00{:}00{:}57{.}319$ --> $00{:}01{:}00{.}145$ systems at Yale's MRI Research Center.

NOTE Confidence: 0.85961975944444

00:01:00.150 --> 00:01:01.227 He uses MRI.

NOTE Confidence: 0.85961975944444

 $00:01:01.227 \longrightarrow 00:01:03.022$ He uses magnetic resonance methods

NOTE Confidence: 0.85961975944444

00:01:03.022 --> 00:01:05.227 to map Physiology and chemistry

NOTE Confidence: 0.85961975944444

 $00{:}01{:}05{.}227 \dashrightarrow 00{:}01{:}07{.}115$ that underlie brain function

NOTE Confidence: 0.85961975944444

 $00:01:07.115 \rightarrow 00:01:09.270$ for early disease detection,

- NOTE Confidence: 0.85961975944444
- $00:01:09.270 \longrightarrow 00:01:10.990$ but also for targeted drug
- NOTE Confidence: 0.85961975944444
- $00:01:10.990 \rightarrow 00:01:12.366$ delivery and monetary treatments.
- NOTE Confidence: 0.85961975944444
- $00:01:12.370 \dashrightarrow 00:01:14.974$ It's also the founder and director
- NOTE Confidence: 0.85961975944444
- $00:01:14.974 \rightarrow 00:01:16.710$ of Yale's quantitative neuroscience
- NOTE Confidence: 0.859619759444444
- $00{:}01{:}16.776 \dashrightarrow 00{:}01{:}19.006$ with magnetic resonance course enter
- NOTE Confidence: 0.85961975944444
- 00:01:19.010 --> 00:01:21.060 the only NIH supported programmatic
- NOTE Confidence: 0.85961975944444
- $00:01:21.060 \rightarrow 00:01:23.110$ effort at Yale on neuroimaging.
- NOTE Confidence: 0.85961975944444
- $00:01:23.110 \longrightarrow 00:01:24.388$ With Mr technologies.
- NOTE Confidence: 0.859619759444444
- 00:01:24.388 --> 00:01:26.944 His work has produced over 100
- NOTE Confidence: 0.85961975944444
- 00:01:26.944 --> 00:01:29.000 peer reviewed publications and
- NOTE Confidence: 0.85961975944444
- $00:01:29.000 \dashrightarrow 00:01:31.580$ he's written and edited books
- NOTE Confidence: 0.85961975944444
- $00{:}01{:}31{.}580 \dashrightarrow 00{:}01{:}33{.}740$ on functional brain imaging.
- NOTE Confidence: 0.85961975944444
- $00{:}01{:}33{.}740 \dashrightarrow 00{:}01{:}36{.}799$ I have to say something that I'm
- NOTE Confidence: 0.85961975944444
- $00:01:36.799 \rightarrow 00:01:38.110$ becoming increasingly interested
- NOTE Confidence: 0.85961975944444
- 00:01:38.182 --> 00:01:41.060 as I age and he has received early
- NOTE Confidence: 0.85961975944444

 $00:01:41.060 \rightarrow 00:01:43.400$ career awards from various scientific

NOTE Confidence: 0.85961975944444

 $00{:}01{:}43{.}474 \dashrightarrow 00{:}01{:}45{.}910$ societies and funding scientific

NOTE Confidence: 0.85961975944444

 $00:01:45.910 \longrightarrow 00:01:47.708$ agencies for me to pleasure.

NOTE Confidence: 0.85961975944444

 $00:01:47.708 \longrightarrow 00:01:48.599$ To have you.

NOTE Confidence: 0.85961975944444

 $00:01:48.600 \longrightarrow 00:01:50.004$ Thanks for being here and we

NOTE Confidence: 0.85961975944444

 $00:01:50.004 \rightarrow 00:01:51.170$ look forward to hearing from

NOTE Confidence: 0.927893886363636

00:01:51.180 --> 00:01:53.854 you. Thank you, thank you very much

NOTE Confidence: 0.927893886363636

 $00:01:53.854 \dashrightarrow 00:01:56.020$ for that generous introduction.

NOTE Confidence: 0.927893886363636

 $00:01:56.020 \rightarrow 00:01:59.845$ I hope I can live up to that introduction.

NOTE Confidence: 0.927893886363636

 $00:01:59.850 \longrightarrow 00:02:02.118$ It's a pleasure to be here.

NOTE Confidence: 0.927893886363636

 $00:02:02.120 \dashrightarrow 00:02:05.228$ So hopefully you can see the slide.

NOTE Confidence: 0.927893886363636

 $00:02:05.230 \longrightarrow 00:02:06.440$ Yep, perfect.

NOTE Confidence: 0.88519594

 $00:02:08.530 \rightarrow 00:02:12.200$ So my topic today is about disregulated

NOTE Confidence: 0.88519594

 $00:02:12.200 \longrightarrow 00:02:14.420$ transmembrane ion gradients.

NOTE Confidence: 0.88519594

 $00{:}02{:}14.420 \dashrightarrow 00{:}02{:}17.216$ I like cancer invasion of liberation.

NOTE Confidence: 0.88519594

 $00:02:17.216 \rightarrow 00:02:19.776$ I believe the latter 4 words are probably

- NOTE Confidence: 0.88519594
- $00:02:19.776 \rightarrow 00:02:22.380$ more akin to a lot of the audience members,

 $00{:}02{:}22{.}380 \dashrightarrow 00{:}02{:}24{.}892$ but I'm going to make the connection or

NOTE Confidence: 0.88519594

 $00:02:24.892 \rightarrow 00:02:27.920$ try to at least before the the initial

NOTE Confidence: 0.88519594

 $00:02:27.920 \longrightarrow 00:02:31.908$ part of this title, which is about.

NOTE Confidence: 0.88519594

 $00{:}02{:}31{.}910 \dashrightarrow 00{:}02{:}34{.}160$ So a little bit of.

NOTE Confidence: 0.88519594

00:02:34.160 --> 00:02:36.230 Preface I guess I'm interested

NOTE Confidence: 0.88519594

 $00:02:36.230 \longrightarrow 00:02:38.750$ in bringing the tablets in why?

NOTE Confidence: 0.88519594

 $00:02:38.750 \rightarrow 00:02:42.350$ Because they tell us about the path weights.

NOTE Confidence: 0.88519594

 $00{:}02{:}42.350 \dashrightarrow 00{:}02{:}44.744$ Which you know end field cells use

NOTE Confidence: 0.88519594

00:02:44.744 --> 00:02:46.830 nutrients to fill their function,

NOTE Confidence: 0.88519594

 $00:02:46.830 \longrightarrow 00:02:49.299$ but also growth.

NOTE Confidence: 0.88519594

 $00{:}02{:}49{.}300 \dashrightarrow 00{:}02{:}52{.}150$ I'm interested in how cells work.

NOTE Confidence: 0.88519594

 $00:02:52.150 \longrightarrow 00:02:53.598$ What their made nutrients

NOTE Confidence: 0.88519594

 $00:02:53.598 \longrightarrow 00:02:55.046$ are in different situations,

NOTE Confidence: 0.88519594

 $00:02:55.050 \rightarrow 00:02:56.602$ different states how they

 $00:02:56.602 \rightarrow 00:02:57.766$ get these nutrients.

NOTE Confidence: 0.88519594

 $00:02:57.770 \longrightarrow 00:03:00.000$ That's actually a very important

NOTE Confidence: 0.88519594

00:03:00.000 --> 00:03:01.860 indicator of disease onset.

NOTE Confidence: 0.88519594

00:03:01.860 --> 00:03:03.740 A lot of fences,

NOTE Confidence: 0.88519594

 $00:03:03.740 \longrightarrow 00:03:05.552$ but also how they use these

NOTE Confidence: 0.88519594

00:03:05.552 --> 00:03:06.760 nutrients to generate energy,

NOTE Confidence: 0.88519594

 $00:03:06.760 \longrightarrow 00:03:08.340$ which is crucial for the

NOTE Confidence: 0.88519594

 $00:03:08.340 \longrightarrow 00:03:10.512$ brain but also to regrow.

NOTE Confidence: 0.88519594

 $00{:}03{:}10.512 \dashrightarrow 00{:}03{:}13.670$ And disease and damage and so on.

NOTE Confidence: 0.88519594

 $00:03:13.670 \rightarrow 00:03:16.712$ And all of these processes happen

NOTE Confidence: 0.88519594

 $00:03:16.712 \rightarrow 00:03:18.165$ naturally for normal situations,

NOTE Confidence: 0.88519594

 $00:03:18.165 \rightarrow 00:03:20.055$ but they also begin to malfunction.

NOTE Confidence: 0.80978602125

 $00:03:22.080 \dashrightarrow 00:03:27.376$ So these questions that I pose for myself,

NOTE Confidence: 0.80978602125

 $00{:}03{:}27{.}380$ --> $00{:}03{:}30{.}184$ as well as my group, my movies and vibrators.

NOTE Confidence: 0.80978602125

 $00:03:30.184 \longrightarrow 00:03:32.589$ These questions are fundamental for

NOTE Confidence: 0.80978602125

 $00:03:32.589 \rightarrow 00:03:34.919$ functional imaging of the brain because

 $00:03:34.919 \longrightarrow 00:03:37.433$ the energy demand for normal brain

NOTE Confidence: 0.80978602125

 $00:03:37.433 \rightarrow 00:03:40.348$ work is extremely high and that still

NOTE Confidence: 0.80978602125

 $00:03:40.348 \rightarrow 00:03:43.400$ is a very unique property of how.

NOTE Confidence: 0.80978602125

 $00:03:43.400 \longrightarrow 00:03:45.507$ This organ varies from a lot of

NOTE Confidence: 0.80978602125

00:03:45.507 --> 00:03:47.019 other buildings in the body,

NOTE Confidence: 0.80978602125

 $00:03:47.020 \longrightarrow 00:03:49.252$ but these questions are also relevant

NOTE Confidence: 0.80978602125

 $00:03:49.252 \rightarrow 00:03:51.085$ in cancer and molecular energy

NOTE Confidence: 0.80978602125

00:03:51.085 - 00:03:53.200 of brain disorders in general,

NOTE Confidence: 0.80978602125

 $00:03:53.200 \rightarrow 00:03:54.580$ but especially concert,

NOTE Confidence: 0.80978602125

 $00:03:54.580 \longrightarrow 00:03:56.348$ because this fundamentally is

NOTE Confidence: 0.80978602125

 $00:03:56.348 \rightarrow 00:03:58.116$ a disease of both,

NOTE Confidence: 0.80978602125

 $00:03:58.120 \longrightarrow 00:04:01.228$ and both requires lots of fuel.

NOTE Confidence: 0.80978602125

 $00:04:01.230 \longrightarrow 00:04:03.240$ Whenever you need to regulate

NOTE Confidence: 0.80978602125

 $00{:}04{:}03.240 \dashrightarrow 00{:}04{:}06.108$ to compete for fuel that is a

NOTE Confidence: 0.80978602125

 $00:04:06.108 \dashrightarrow 00:04:07.940$ medical question that it's tough.

 $00:04:07.940 \longrightarrow 00:04:09.340$ So that's my preference,

NOTE Confidence: 0.80978602125

 $00:04:09.340 \longrightarrow 00:04:12.268$ but my main objective today is to

NOTE Confidence: 0.80978602125

 $00{:}04{:}12.268 \dashrightarrow 00{:}04{:}14.692$ talk to you about the importance

NOTE Confidence: 0.80978602125

 $00:04:14.692 \longrightarrow 00:04:16.040$ of transparent votes.

NOTE Confidence: 0.80978602125

00:04:16.040 --> 00:04:18.324 If they're crucially linked

NOTE Confidence: 0.80978602125

 $00:04:18.324 \longrightarrow 00:04:20.037$ to cellular metabolism,

NOTE Confidence: 0.80978602125

 $00:04:20.040 \rightarrow 00:04:23.210$ and this property differs substantially

NOTE Confidence: 0.80978602125

 $00:04:23.210 \rightarrow 00:04:27.010$ between normal cells and cancer cells.

NOTE Confidence: 0.80978602125

 $00{:}04{:}27.010 \dashrightarrow 00{:}04{:}29.950$ Abnormal transmembrane protein and sodium.

NOTE Confidence: 0.80978602125

00:04:29.950 --> 00:04:30.452 Specifically,

NOTE Confidence: 0.80978602125

 $00{:}04{:}30{.}452 \dashrightarrow 00{:}04{:}33{.}966$ I'll talk about protein and sodium gradient.

NOTE Confidence: 0.80978602125

 $00{:}04{:}33{.}970 \dashrightarrow 00{:}04{:}37{.}260$ Are there consequences of health

NOTE Confidence: 0.80978602125

 $00:04:37.260 \longrightarrow 00:04:38.576$ physiological alterations

NOTE Confidence: 0.80978602125

 $00:04:38.576 \longrightarrow 00:04:41.120$ occurring with cellular level?

NOTE Confidence: 0.80978602125

 $00:04:41.120 \longrightarrow 00:04:43.202$ And the two primary things I'll

NOTE Confidence: 0.80978602125

 $00:04:43.202 \rightarrow 00:04:46.060$ focus on is the city and salinity

- NOTE Confidence: 0.80978602125
- $00:04:46.060 \longrightarrow 00:04:47.916$ of the interstitial fluid.
- NOTE Confidence: 0.80978602125
- $00:04:47.920 \longrightarrow 00:04:49.654$ These two quantities,
- NOTE Confidence: 0.80978602125
- $00:04:49.654 \rightarrow 00:04:53.700$ reflected as a proton and sodium ions,
- NOTE Confidence: 0.80978602125
- $00:04:53.700 \longrightarrow 00:04:54.192$ respectively.
- NOTE Confidence: 0.80978602125
- $00:04:54.192 \rightarrow 00:04:56.652$ They actually regulate central cellular
- NOTE Confidence: 0.80978602125
- $00:04:56.652 \rightarrow 00:04:59.790$ functions in health as well as improved,
- NOTE Confidence: 0.80978602125
- $00:04:59.790 \longrightarrow 00:05:01.434$ especially cancer under
- NOTE Confidence: 0.80978602125
- $00:05:01.434 \longrightarrow 00:05:03.452$ their bark cancer tomorrow.
- NOTE Confidence: 0.80978602125
- 00:05:03.452 --> 00:05:03.824 Basicness,
- NOTE Confidence: 0.80978602125
- $00:05:03.824 \longrightarrow 00:05:06.056$ which is one of the hallmarks
- NOTE Confidence: 0.80978602125
- $00{:}05{:}06{.}056 \dashrightarrow 00{:}05{:}08{.}259$ and even resistance to the rapy.
- NOTE Confidence: 0.80978602125
- $00:05:08.260 \longrightarrow 00:05:10.384$ This is actually enhanced
- NOTE Confidence: 0.80978602125
- $00:05:10.384 \longrightarrow 00:05:11.977$ by acidic interstitial.
- NOTE Confidence: 0.580223618888889
- 00:05:14.200 --> 00:05:16.265 Which is actually a consequence
- NOTE Confidence: 0.580223618888889
- $00:05:16.265 \rightarrow 00:05:17.917$ of popularity by policies.
- NOTE Confidence: 0.580223618888889

 $00:05:17.920 \longrightarrow 00:05:21.476$ I will talk about this in a few minutes.

NOTE Confidence: 0.580223618888889

 $00{:}05{:}21.476 \dashrightarrow 00{:}05{:}22.912$ But there's also recent

NOTE Confidence: 0.580223618888889

00:05:22.912 --> 00:05:24.259 discoveries from our work,

NOTE Confidence: 0.580223618888889

 $00:05:24.260 \rightarrow 00:05:27.982$ and I work with and related groups

NOTE Confidence: 0.580223618888889

 $00:05:27.982 \longrightarrow 00:05:31.382$ that show that enhance proliferation.

NOTE Confidence: 0.580223618888889

 $00:05:31.382 \dashrightarrow 00:05:35.029$ Which is also a hallmark of cancer

NOTE Confidence: 0.580223618888889

00:05:35.030 - 00:05:38.510 is impacted by interstitial so,

NOTE Confidence: 0.580223618888889

 $00:05:38.510 \longrightarrow 00:05:42.374$ so we both these city and the salinity

NOTE Confidence: 0.580223618888889

 $00:05:42.374 \longrightarrow 00:05:44.900$ of legislation that is crucial.

NOTE Confidence: 0.580223618888889

00:05:44.900 --> 00:05:46.200 A little bit of background,

NOTE Confidence: 0.580223618888889

 $00{:}05{:}46{.}200 \dashrightarrow 00{:}05{:}47{.}635$ I think that's the background

NOTE Confidence: 0.580223618888889

00:05:47.635 - 00:05:48.496 is probably redundant,

NOTE Confidence: 0.580223618888889

 $00:05:48.500 \longrightarrow 00:05:50.817$ but for the sake of being bad

NOTE Confidence: 0.580223618888889

 $00:05:50.820 \longrightarrow 00:05:52.840$ protein and sodium lines are

NOTE Confidence: 0.580223618888889

 $00:05:52.840 \longrightarrow 00:05:54.918$ vital for numerous processes for

NOTE Confidence: 0.580223618888889

 $00:05:54.918 \rightarrow 00:05:58.340$ maintaining blood pressure to fire.

- NOTE Confidence: 0.580223618888889
- $00:05:58.340 \longrightarrow 00:06:00.188$ Only statically we maintain
- NOTE Confidence: 0.580223618888889
- 00:06:00.188 --> 00:06:02.498 a very large sodium gradient.
- NOTE Confidence: 0.580223618888889
- 00:06:02.500 --> 00:06:04.950 Almost two orders of magnitude,
- NOTE Confidence: 0.580223618888889
- $00:06:04.950 \longrightarrow 00:06:06.220$ almost an order of magnitude.
- NOTE Confidence: 0.580223618888889
- $00:06:06.220 \longrightarrow 00:06:08.752$ Sorry. Lending to a very strong
- NOTE Confidence: 0.580223618888889
- $00:06:08.752 \longrightarrow 00:06:10.018$ trance member Radiant.
- NOTE Confidence: 0.580223618888889
- $00:06:10.020 \longrightarrow 00:06:11.468$ Well, certainly, but similarly.
- NOTE Confidence: 0.580223618888889
- 00:06:11.468 --> 00:06:12.916 For for time buildings,
- NOTE Confidence: 0.580223618888889
- $00:06:12.920 \dashrightarrow 00:06:15.000$ which is usually measured in terms of pH,
- NOTE Confidence: 0.580223618888889
- 00:06:15.000 --> 00:06:16.460 which if you know it's
- NOTE Confidence: 0.580223618888889
- $00:06:16.460 \longrightarrow 00:06:17.920$ just a log rhythmic scale.
- NOTE Confidence: 0.580223618888889
- $00:06:17.920 \dashrightarrow 00:06:21.728$ So even though the pH between interstitial
- NOTE Confidence: 0.580223618888889
- $00{:}06{:}21.728 \dashrightarrow 00{:}06{:}23.512$ and intracellular intracellular
- NOTE Confidence: 0.580223618888889
- $00{:}06{:}23.512 \dashrightarrow 00{:}06{:}28.744$ compartments are 7.4 and 7.2 in PS units,
- NOTE Confidence: 0.580223618888889
- $00:06:28.744 \longrightarrow 00:06:29.976$ it's small.
- NOTE Confidence: 0.580223618888889

00:06:29.980 --> 00:06:32.848 But in terms of actual concentration,

NOTE Confidence: 0.580223618888889

 $00:06:32.850 \longrightarrow 00:06:35.350$ it's again very large.

NOTE Confidence: 0.580223618888889

 $00{:}06{:}35{.}350 \dashrightarrow 00{:}06{:}37{.}350$ There are various mechanisms with

NOTE Confidence: 0.580223618888889

 $00:06:37.350 \rightarrow 00:06:38.886$ which are located the cell membrane,

NOTE Confidence: 0.580223618888889

 $00:06:38.890 \longrightarrow 00:06:39.910$ how regularly.

NOTE Confidence: 0.580223618888889

 $00{:}06{:}39{.}910 \dashrightarrow 00{:}06{:}42{.}970$ A proton and certain levels to

NOTE Confidence: 0.580223618888889

 $00:06:42.970 \longrightarrow 00:06:45.488$ avoid these mishaps that are

NOTE Confidence: 0.580223618888889

 $00:06:45.488 \rightarrow 00:06:48.660$ that sells try very hard before.

NOTE Confidence: 0.580223618888889

00:06:48.660 --> 00:06:49.148 First,

NOTE Confidence: 0.580223618888889

 $00{:}06{:}49{.}148 \dashrightarrow 00{:}06{:}51{.}100$ Megan mechanisms that regulate

NOTE Confidence: 0.580223618888889

 $00{:}06{:}51{.}100 \dashrightarrow 00{:}06{:}53{.}052$ transforming what time gradients

NOTE Confidence: 0.580223618888889

 $00:06:53.052 \dashrightarrow 00:06:55.659$ are shown here in the parking form.

NOTE Confidence: 0.580223618888889

 $00:06:55.660 \rightarrow 00:06:58.688$ Let me just go around the cell here first.

NOTE Confidence: 0.580223618888889

 $00{:}06{:}58.688 \dashrightarrow 00{:}07{:}02.228$ Is this mechanism here carbonic

NOTE Confidence: 0.580223618888889

 $00:07:02.230 \rightarrow 00:07:04.081$ anhydrase mine specifically?

NOTE Confidence: 0.580223618888889

 $00:07:04.081 \longrightarrow 00:07:06.549$ But these kinds of.

 $00:07:08.690 \rightarrow 00:07:11.707$ Instruments are used to basically take out

NOTE Confidence: 0.825411373846154

 $00{:}07{:}11.707 \dashrightarrow 00{:}07{:}14.260$ department dioxide and water generated by

NOTE Confidence: 0.828720365714286

 $00{:}07{:}16.350 \dashrightarrow 00{:}07{:}19.129$ oxidation and take them out and it

NOTE Confidence: 0.828720365714286

 $00:07:19.129 \rightarrow 00:07:21.261$ basically takes them out and comes

NOTE Confidence: 0.828720365714286

 $00:07:21.261 \longrightarrow 00:07:24.510$ to bicarbonate and protons and which

NOTE Confidence: 0.828720365714286

 $00:07:24.510 \longrightarrow 00:07:26.878$ signifies the intracellular space.

NOTE Confidence: 0.828720365714286

 $00:07:26.880 \rightarrow 00:07:30.399$ Then there is these channels at BCS and NC.

NOTE Confidence: 0.828720365714286

 $00:07:30.400 \longrightarrow 00:07:33.280$ Is which abbreviations are shown here,

NOTE Confidence: 0.828720365714286

 $00:07:33.280 \longrightarrow 00:07:35.200$ but the second time I'll just

NOTE Confidence: 0.828720365714286

00:07:35.200 -> 00:07:36.480 go through the abbreviations.

NOTE Confidence: 0.828720365714286

00:07:36.480 - > 00:07:38.835 These bring in both bicarbonate

NOTE Confidence: 0.828720365714286

 $00{:}07{:}38.835 \dashrightarrow 00{:}07{:}41.190$ and so dium and this one.

NOTE Confidence: 0.828720365714286

 $00{:}07{:}41.190 \dashrightarrow 00{:}07{:}44.070$ Runs in bicarbonate itself, right islands.

NOTE Confidence: 0.828720365714286

 $00{:}07{:}44.070 \dashrightarrow 00{:}07{:}48.190$ Both of these contributed to a contribute to.

NOTE Confidence: 0.828720365714286

 $00:07:48.190 \rightarrow 00:07:51.890$ Changing of the intracellular field.

 $00:07:51.890 \longrightarrow 00:07:53.822$ Maximo carboxylate transporters

NOTE Confidence: 0.828720365714286

 $00{:}07{:}53.822 \dashrightarrow 00{:}07{:}58.148$ are those kinds and city one and

NOTE Confidence: 0.828720365714286

00:07:58.148 --> 00:08:00.438 NC 3-4 working opposite days.

NOTE Confidence: 0.828720365714286

 $00:08:00.440 \longrightarrow 00:08:03.996$ They bring in assets for NCT one

NOTE Confidence: 0.828720365714286

 $00{:}08{:}03{.}996$ --> $00{:}08{:}08{.}009$ and take out assets for actually 4

NOTE Confidence: 0.828720365714286

 $00:08:08.010 \rightarrow 00:08:12.110$ altering hydrogen ion concentration.

NOTE Confidence: 0.828720365714286

00:08:12.110 --> 00:08:14.729 It's all specifically.

NOTE Confidence: 0.828720365714286

 $00:08:14.730 \longrightarrow 00:08:16.656$ Important one entity,

NOTE Confidence: 0.828720365714286

 $00{:}08{:}16.656 \dashrightarrow 00{:}08{:}19.224$ one sodium proton exchanger,

NOTE Confidence: 0.828720365714286

 $00:08:19.230 \rightarrow 00:08:21.806$ takes like for every proton taken out,

NOTE Confidence: 0.828720365714286

 $00:08:21.810 \rightarrow 00:08:25.154$ brings in every brings in a sodium and

NOTE Confidence: 0.828720365714286

 $00:08:25.154 \rightarrow 00:08:29.918$ that can alter the full time as well.

NOTE Confidence: 0.828720365714286

 $00{:}08{:}29{.}920 \dashrightarrow 00{:}08{:}33{.}520$ These are ATP and ATP dependent,

NOTE Confidence: 0.828720365714286

00:08:33.520 --> 00:08:35.744 vascular full-time ATP ace,

NOTE Confidence: 0.828720365714286

 $00:08:35.744 \rightarrow 00:08:38.310$ where you're bringing in or taking

NOTE Confidence: 0.828720365714286

 $00:08:38.310 \rightarrow 00:08:41.253$ out protons to a city public service

- NOTE Confidence: 0.828720365714286
- $00:08:41.253 \rightarrow 00:08:45.750$ place as well as these acid.
- NOTE Confidence: 0.828720365714286
- $00:08:45.750 \rightarrow 00:08:49.908$ Sensing line channels as well as these
- NOTE Confidence: 0.828720365714286
- $00:08:49.908 \rightarrow 00:08:52.590$ epithelial specific certain channels.
- NOTE Confidence: 0.828720365714286
- $00:08:52.590 \dashrightarrow 00:08:55.615$ They also are known to affect more
- NOTE Confidence: 0.828720365714286
- $00{:}08{:}55{.}615 \dashrightarrow 00{:}08{:}57{.}895$ time but as well as so dium because a
- NOTE Confidence: 0.828720365714286
- $00:08:57.895 \rightarrow 00:09:00.437$ lot of things different channels as
- NOTE Confidence: 0.828720365714286
- $00:09:00.437 \dashrightarrow 00:09:02.545$ sodium gradients and therefore beans
- NOTE Confidence: 0.828720365714286
- $00:09:02.545 \dashrightarrow 00:09:04.675$ won't be repeated because these are
- NOTE Confidence: 0.828720365714286
- $00:09:04.675 \rightarrow 00:09:07.009$ the channels that I just talked about.
- NOTE Confidence: 0.828720365714286
- $00:09:07.010 \rightarrow 00:09:08.660$ But there are other mechanism.
- NOTE Confidence: 0.828720365714286
- $00:09:08.660 \rightarrow 00:09:09.976$ This is a channel that I just
- NOTE Confidence: 0.828720365714286
- $00:09:09.976 \dashrightarrow 00:09:11.250$ showed in the previous slide.
- NOTE Confidence: 0.828720365714286
- $00:09:11.250 \longrightarrow 00:09:14.148$ See energy as well as the
- NOTE Confidence: 0.828720365714286
- $00:09:14.148 \longrightarrow 00:09:16.080$ sort of important change.
- NOTE Confidence: 0.828720365714286
- $00:09:16.080 \rightarrow 00:09:19.329$ Are all of these have a role in altering
- NOTE Confidence: 0.828720365714286

 $00:09:19.329 \rightarrow 00:09:22.900$ the sodium level in the exercise of space?

NOTE Confidence: 0.828720365714286

 $00{:}09{:}22.900 \dashrightarrow 00{:}09{:}25.060$ This particular channel, the NSX,

NOTE Confidence: 0.828720365714286

 $00:09:25.060 \rightarrow 00:09:27.272$ the sodium counseling exchanger,

NOTE Confidence: 0.828720365714286

 $00:09:27.272 \longrightarrow 00:09:29.484$ it's exchanges sodium for

NOTE Confidence: 0.828720365714286

 $00:09:29.484 \dashrightarrow 00:09:31.939$ calcium between the compartments.

NOTE Confidence: 0.828720365714286

 $00:09:31.940 \longrightarrow 00:09:33.956$ It's interesting, it was recently discovered,

NOTE Confidence: 0.828720365714286

 $00:09:33.960 \longrightarrow 00:09:36.348$ but in cancer specifically,

NOTE Confidence: 0.828720365714286

 $00:09:36.348 \rightarrow 00:09:39.333$ this is actually need to.

NOTE Confidence: 0.828720365714286

 $00:09:39.340 \longrightarrow 00:09:40.244$ In addition,

NOTE Confidence: 0.828720365714286

 $00:09:40.244 \rightarrow 00:09:42.956$ there is this additional new channels

NOTE Confidence: 0.828720365714286

 $00{:}09{:}42.960 \dashrightarrow 00{:}09{:}45.522$ mentioned here that are specific to

NOTE Confidence: 0.828720365714286

 $00:09:45.522 \rightarrow 00:09:48.040$ sodium regulation across the department.

NOTE Confidence: 0.828720365714286

 $00:09:48.040 \longrightarrow 00:09:49.979$ The most important one of this is

NOTE Confidence: 0.828720365714286

 $00:09:49.979 \longrightarrow 00:09:52.059$ probably a well known as the support.

NOTE Confidence: 0.828720365714286

 $00:09:52.060 \rightarrow 00:09:55.990$ The sodium proton switches exchanging

NOTE Confidence: 0.828720365714286

 $00:09:55.990 \longrightarrow 00:10:00.272$ of sodium and potent potassium at the

 $00:10:00.272 \rightarrow 00:10:06.072$ cost of ATP to basically maintain a balance.

NOTE Confidence: 0.828720365714286

00:10:06.072 --> 00:10:09.960 To keep resting potential.

NOTE Confidence: 0.828720365714286

 $00:10:09.960 \longrightarrow 00:10:12.025$ The same so that the cell can

NOTE Confidence: 0.828720365714286

 $00:10:12.025 \rightarrow 00:10:13.680$ actually keep on doing that.

NOTE Confidence: 0.828720365714286

 $00:10:13.680 \longrightarrow 00:10:15.440$ It's designed to do so.

NOTE Confidence: 0.828720365714286

 $00:10:15.440 \longrightarrow 00:10:19.144$ These are the mechanisms that are in play.

NOTE Confidence: 0.828720365714286

 $00{:}10{:}19{.}150 \dashrightarrow 00{:}10{:}21{.}574$ Glucose metabolism is key to all

NOTE Confidence: 0.828720365714286

 $00:10:21.574 \longrightarrow 00:10:24.204$ of these processes and the healthy

NOTE Confidence: 0.828720365714286

 $00:10:24.204 \longrightarrow 00:10:27.125$ miracle as blood drains in both

NOTE Confidence: 0.828720365714286

 $00:10:27.125 \longrightarrow 00:10:30.416$ glucose and oxygen in the form of

NOTE Confidence: 0.828720365714286

 $00:10:30.416 \rightarrow 00:10:32.642$ oxyhemoglobin glucose is its transport

NOTE Confidence: 0.828720365714286

 $00{:}10{:}32.642 \dashrightarrow 00{:}10{:}34.857$ is expedited by these transporters,

NOTE Confidence: 0.828720365714286

00:10:34.860 -> 00:10:37.170 but oxygen goes through just

NOTE Confidence: 0.828720365714286

 $00{:}10{:}37{.}170 \dashrightarrow 00{:}10{:}40{.}540$ passive diffusion into the cell.

NOTE Confidence: 0.828720365714286

 $00:10:40.540 \longrightarrow 00:10:42.056$ Just breakdown appointments through

 $00:10:42.056 \rightarrow 00:10:44.787$ the bike clinic steps and then further

NOTE Confidence: 0.828720365714286

00:10:44.787 --> 00:10:47.986 breakdown in in in the prep cycle

NOTE Confidence: 0.828720365714286

00:10:47.986 --> 00:10:50.740 of generating large amounts of ATP.

NOTE Confidence: 0.828720365714286

 $00:10:50.740 \longrightarrow 00:10:52.404$ All of these processes,

NOTE Confidence: 0.828720365714286

 $00:10:52.404 \rightarrow 00:10:54.484$ generally small amounts of protons

NOTE Confidence: 0.828720365714286

 $00{:}10{:}54.484 \dashrightarrow 00{:}10{:}57.025$ but also carbon dioxide water which

NOTE Confidence: 0.828720365714286

00:10:57.025 --> 00:10:58.258 I just mentioned.

NOTE Confidence: 0.828720365714286

 $00:10:58.260 \rightarrow 00:11:01.768$ Carbonic anhydrase has a has a role in in,

NOTE Confidence: 0.828720365714286

 $00{:}11{:}01.768 \dashrightarrow 00{:}11{:}04.960$ in, in taking out these these products.

NOTE Confidence: 0.828720365714286

 $00{:}11{:}04{.}960 \dashrightarrow 00{:}11{:}06{.}476$ So this is a.

NOTE Confidence: 0.828720365714286

00:11:06.476 --> 00:11:09.210 Complete oxidation of glucose if you will,

NOTE Confidence: 0.828720365714286

 $00{:}11{:}09{.}210 \dashrightarrow 00{:}11{:}11{.}580$ but even under normal conditions

NOTE Confidence: 0.911633533333333

 $00:11:11.580 \longrightarrow 00:11:12.720$ there is some.

NOTE Confidence: 0.786814948333333

 $00{:}11{:}16.200 \dashrightarrow 00{:}11{:}20.376$ Less oxidation than expected from theory,

NOTE Confidence: 0.786814948333333

 $00:11:20.380 \rightarrow 00:11:23.075$ where some of the glucose is actually

NOTE Confidence: 0.786814948333333

00:11:23.075 --> 00:11:24.880 shunted towards biosynthetic processes,

- NOTE Confidence: 0.786814948333333
- $00:11:24.880 \rightarrow 00:11:29.446$ but some of the invoices actually.
- NOTE Confidence: 0.786814948333333
- $00:11:29.450 \longrightarrow 00:11:32.650$ Excluded in terms of lactate by the public.
- NOTE Confidence: 0.786814948333333
- $00{:}11{:}32.650 \dashrightarrow 00{:}11{:}35.585$ Feeds on CTV's that you
- NOTE Confidence: 0.786814948333333
- 00:11:35.585 --> 00:11:37.346 have mentioned earlier.
- NOTE Confidence: 0.786814948333333
- $00:11:37.350 \rightarrow 00:11:40.380$ A lot of the protons generated are removed.
- NOTE Confidence: 0.786814948333333
- $00:11:40.380 \longrightarrow 00:11:42.930$ As I said from these different
- NOTE Confidence: 0.786814948333333
- $00{:}11{:}42{.}930 \dashrightarrow 00{:}11{:}45{.}013$ mechanisms which I mentioned me
- NOTE Confidence: 0.786814948333333
- $00{:}11{:}45{.}013 \dashrightarrow 00{:}11{:}47{.}329$ cheese also about the heart races.
- NOTE Confidence: 0.786814948333333
- $00:11:47.330 \longrightarrow 00:11:51.200$ But if cancer and the unhealthy durable the.
- NOTE Confidence: 0.786814948333333
- $00:11:51.200 \longrightarrow 00:11:53.660$ A lot of dysfunction happens in
- NOTE Confidence: 0.786814948333333
- 00:11:53.660 --> 00:11:56.318 terms of amount of bike policies,
- NOTE Confidence: 0.786814948333333
- $00{:}11{:}56{.}320 \dashrightarrow 00{:}11{:}58{.}550$ which is the amount of
- NOTE Confidence: 0.786814948333333
- $00:11:58.550 \longrightarrow 00:11:59.888$ oxidation that happens.
- NOTE Confidence: 0.786814948333333
- $00{:}11{:}59{.}890 \dashrightarrow 00{:}12{:}02{.}210$ And therefore some of these
- NOTE Confidence: 0.786814948333333
- $00:12:02.210 \longrightarrow 00:12:03.882$ there will be glycolytic.
- NOTE Confidence: 0.786814948333333

 $00:12:03.882 \rightarrow 00:12:06.390$ Steps are augmented to the point.

NOTE Confidence: 0.786814948333333

00:12:06.390 --> 00:12:09.348 Where these machinery's that I speak

NOTE Confidence: 0.786814948333333

 $00:12:09.348 \rightarrow 00:12:11.830$ just mentioned with carbonic and

NOTE Confidence: 0.786814948333333

 $00:12:11.830 \rightarrow 00:12:14.558$ hybrid sister upregulated in NCT 4?

NOTE Confidence: 0.786814948333333

 $00:12:14.558 \longrightarrow 00:12:17.360$ Is that up regulated to handle

NOTE Confidence: 0.786814948333333

 $00:12:17.454 \rightarrow 00:12:20.869$ exclusion of lactate more efficiently,

NOTE Confidence: 0.786814948333333

00:12:20.870 --> 00:12:24.566 but also in terms of the NET,

NOTE Confidence: 0.786814948333333

 $00:12:24.570 \rightarrow 00:12:27.814$ which is also up regulated to alter the

NOTE Confidence: 0.786814948333333

 $00{:}12{:}27.814 \dashrightarrow 00{:}12{:}31.083$ whole time in the access center space.

NOTE Confidence: 0.786814948333333

 $00:12:31.090 \longrightarrow 00:12:31.760$ We vacuumed.

NOTE Confidence: 0.896359014285714

 $00{:}12{:}34.850 \dashrightarrow 00{:}12{:}36.908$ Along with some of the same mechanism,

NOTE Confidence: 0.896359014285714

00:12:36.910 --> 00:12:39.766 the same machinery or additional machinery,

NOTE Confidence: 0.896359014285714

00:12:39.770 --> 00:12:43.151 you can also experience a lot of

NOTE Confidence: 0.896359014285714

 $00:12:43.151 \rightarrow 00:12:44.932$ imbalances in a certain environment,

NOTE Confidence: 0.896359014285714

 $00{:}12{:}44{.}932 \dashrightarrow 00{:}12{:}47{.}279$ but key player as I just mentioned

NOTE Confidence: 0.896359014285714

 $00:12:47.279 \longrightarrow 00:12:49.325$ is the mutation of the NSX,

- NOTE Confidence: 0.896359014285714
- $00:12:49.330 \longrightarrow 00:12:51.430$ which happens which is most
- NOTE Confidence: 0.896359014285714
- 00:12:51.430 --> 00:12:53.110 recently discovered in cancer,
- NOTE Confidence: 0.896359014285714
- $00{:}12{:}53{.}110 \dashrightarrow 00{:}12{:}56{.}426$ but also the fact that there
- NOTE Confidence: 0.896359014285714
- $00:12:56.426 \rightarrow 00:12:59.530$ is actually downregulation of
- NOTE Confidence: 0.896359014285714
- $00{:}12{:}59{.}530 \dashrightarrow 00{:}13{:}03{.}920$ oxidation within a cancer cells.
- NOTE Confidence: 0.896359014285714
- $00{:}13{:}03{.}920 \dashrightarrow 00{:}13{:}11{.}036$ Reduce potassium sodium is also an important
- NOTE Confidence: 0.896359014285714
- $00:13:11.036 \rightarrow 00:13:14.970$ role of causing these sodium imbalances as.
- NOTE Confidence: 0.896359014285714
- $00:13:14.970 \longrightarrow 00:13:16.617$ And it's culture.
- NOTE Confidence: 0.896359014285714
- $00:13:16.617 \rightarrow 00:13:20.970$ So this is the unhealthy miracle and our.
- NOTE Confidence: 0.896359014285714
- $00{:}13{:}20{.}970 \dashrightarrow 00{:}13{:}24{.}323$ Our role is to understand and observe
- NOTE Confidence: 0.896359014285714
- $00:13:24.323 \rightarrow 00:13:27.392$ these the impact of the altered proton
- NOTE Confidence: 0.896359014285714
- $00{:}13{:}27{.}392 \dashrightarrow 00{:}13{:}29{.}006$ as well as transgender, Ingrid.
- NOTE Confidence: 0.896359014285714
- $00{:}13{:}29.006 \dashrightarrow 00{:}13{:}31.442$ So tumors are highly like little
- NOTE Confidence: 0.896359014285714
- $00:13:31.442 \longrightarrow 00:13:34.134$ even when off, well oxygenated,
- NOTE Confidence: 0.896359014285714
- $00:13:34.134 \rightarrow 00:13:37.819$ and this aerobic glycolysis phenotype.
- NOTE Confidence: 0.896359014285714

 $00:13:37.820 \longrightarrow 00:13:39.772$ Enables enabled by metabolism.

NOTE Confidence: 0.896359014285714

00:13:39.772 --> 00:13:41.236 Different nutrients generates

NOTE Confidence: 0.896359014285714

00:13:41.236 --> 00:13:43.733 lots of their civic products

NOTE Confidence: 0.896359014285714

 $00:13:43.733 \rightarrow 00:13:45.665$ that are extremely deficient.

NOTE Confidence: 0.896359014285714

00:13:45.670 --> 00:13:46.444 For example,

NOTE Confidence: 0.896359014285714

 $00{:}13{:}46{.}444 \dashrightarrow 00{:}13{:}48{.}766$ even carbon dioxide and water generated

NOTE Confidence: 0.896359014285714

00:13:48.766 -> 00:13:50.469 from oxidative metabolism are,

NOTE Confidence: 0.896359014285714

00:13:50.470 --> 00:13:51.334 you know,

NOTE Confidence: 0.896359014285714

 $00{:}13{:}51{.}334 \dashrightarrow 00{:}13{:}53{.}062$ they contribute to certification

NOTE Confidence: 0.896359014285714

 $00{:}13{:}53.062 \dashrightarrow 00{:}13{:}55.369$ of the interstitial space by these

NOTE Confidence: 0.896359014285714

 $00{:}13{:}55{.}370 \dashrightarrow 00{:}14{:}00{.}078$ these anionic exchangers like.

NOTE Confidence: 0.896359014285714

00:14:00.080 --> 00:14:00.450 Invite.

NOTE Confidence: 0.60703224325

00:14:02.680 --> 00:14:04.315 Interstitial acidosis actually

NOTE Confidence: 0.60703224325

 $00:14:04.315 \longrightarrow 00:14:07.040$ helps with tumor cell invasion.

NOTE Confidence: 0.60703224325

 $00:14:07.040 \longrightarrow 00:14:09.250$ They they actually did break

NOTE Confidence: 0.60703224325

 $00:14:09.250 \longrightarrow 00:14:10.576$ the interstitial matrix,

 $00:14:10.580 \rightarrow 00:14:14.360$ and they also promote angiogenesis

NOTE Confidence: 0.60703224325

00:14:14.360 --> 00:14:18.308 while suppressing entry. Sense.

NOTE Confidence: 0.60703224325

 $00{:}14{:}18{.}308 \dashrightarrow 00{:}14{:}21{.}727$ So this is an example from Bob

NOTE Confidence: 0.60703224325

 $00:14:21.727 \longrightarrow 00:14:25.976$ Giles work where it is shown that

NOTE Confidence: 0.60703224325

 $00:14:25.976 \longrightarrow 00:14:28.442$ whenever there is use acidification,

NOTE Confidence: 0.60703224325

 $00:14:28.442 \longrightarrow 00:14:31.988$ this is done in a culture system

NOTE Confidence: 0.60703224325

 $00:14:31.988 \rightarrow 00:14:35.060$ where there's reduce acidification,

NOTE Confidence: 0.60703224325

 $00:14:35.060 \longrightarrow 00:14:37.915$ there is enhanced invasion of

NOTE Confidence: 0.60703224325

 $00{:}14{:}37{.}915 \dashrightarrow 00{:}14{:}40{.}660$ cells in terms of timber growth.

NOTE Confidence: 0.60703224325

 $00{:}14{:}40.660 \dashrightarrow 00{:}14{:}42.335$ This is an example where

NOTE Confidence: 0.60703224325

00:14:42.335 --> 00:14:43.888 you study shown in situ,

NOTE Confidence: 0.60703224325

 $00:14:43.888 \longrightarrow 00:14:45.532$ but in people evidence for this

NOTE Confidence: 0.60703224325

 $00{:}14{:}45{.}532 \dashrightarrow 00{:}14{:}47{.}197$ from our lab and other labs,

NOTE Confidence: 0.60703224325

 $00{:}14{:}47{.}200 \dashrightarrow 00{:}14{:}50{.}628$ so security is absolute.

NOTE Confidence: 0.60703224325

 $00{:}14{:}50{.}630 \dashrightarrow 00{:}14{:}53{.}126$ Impact with the altered transplant in

 $00:14:53.126 \rightarrow 00:14:55.430$ sodium gradient normal cells maintain.

NOTE Confidence: 0.60703224325

 $00:14:55.430 \rightarrow 00:14:58.340$ Hyperpolarized membrane potential.

NOTE Confidence: 0.60703224325

 $00{:}14{:}58{.}340 \dashrightarrow 00{:}15{:}01{.}358$ But before I see member interventional NOTE Confidence: 0.60703224325

 $00{:}15{:}01{.}358 \dashrightarrow 00{:}15{:}05{.}776$ and non excitable cells is linked to

NOTE Confidence: 0.60703224325

 $00{:}15{:}05{.}776 \dashrightarrow 00{:}15{:}09{.}662$ their proliferation of point to this in

NOTE Confidence: 0.60703224325

 $00{:}15{:}09.662 \dashrightarrow 00{:}15{:}11.770$ in the next slide a little bit more.

NOTE Confidence: 0.60703224325

 $00{:}15{:}11.770 \dashrightarrow 00{:}15{:}14.962$ In fact, even in mean cells consensus

NOTE Confidence: 0.60703224325

 $00:15:14.962 \longrightarrow 00:15:17.370$ in the interstitial in the loop.

NOTE Confidence: 0.60703224325

 $00:15:17.370 \longrightarrow 00:15:17.848$ Therefore,

NOTE Confidence: 0.60703224325

 $00:15:17.848 \longrightarrow 00:15:20.238$ salinity of the interstitial and

NOTE Confidence: 0.60703224325

 $00{:}15{:}20{.}238 \dashrightarrow 00{:}15{:}22{.}710$ intracellular compartments may be crucial.

NOTE Confidence: 0.60703224325

 $00:15:22.710 \rightarrow 00:15:26.448$ As has been pointed out by recent.

NOTE Confidence: 0.60703224325

 $00:15:26.450 \rightarrow 00:15:28.622$ Work that may be important for

NOTE Confidence: 0.60703224325

00:15:28.622 --> 00:15:30.070 early diagnosis of cancer,

NOTE Confidence: 0.60703224325

 $00:15:30.070 \longrightarrow 00:15:32.314$ but also maybe contracting

NOTE Confidence: 0.60703224325

 $00:15:32.314 \rightarrow 00:15:33.997$ in cancer treatments.

- NOTE Confidence: 0.60703224325
- $00:15:34.000 \rightarrow 00:15:35.816$ So this point, this light points this out.
- NOTE Confidence: 0.60703224325
- $00{:}15{:}35{.}820 \dashrightarrow 00{:}15{:}38{.}277$ This is the scale of membrane potential.
- NOTE Confidence: 0.60703224325
- $00:15:38.280 \longrightarrow 00:15:40.630$ On the bottom are these
- NOTE Confidence: 0.60703224325
- $00:15:40.630 \rightarrow 00:15:42.040$ non proliferating cells?
- NOTE Confidence: 0.60703224325
- $00:15:42.040 \rightarrow 00:15:43.672$ These are real cells,
- NOTE Confidence: 0.60703224325
- $00{:}15{:}43.672 \dashrightarrow 00{:}15{:}44.488$ neuronal cells.
- NOTE Confidence: 0.60703224325
- 00:15:44.490 --> 00:15:47.980 They have a very hyperpolarized
- NOTE Confidence: 0.60703224325
- $00:15:47.980 \longrightarrow 00:15:50.046$ membrane potential equation which
- NOTE Confidence: 0.60703224325
- $00{:}15{:}50{.}046 \dashrightarrow 00{:}15{:}51{.}711$ takes into account so dium and
- NOTE Confidence: 0.60703224325
- $00:15:51.711 \longrightarrow 00:15:53.840$ the poor at concentrations up.
- NOTE Confidence: 0.60703224325
- $00:15:53.840 \longrightarrow 00:15:55.176$ Here are the perfect.
- NOTE Confidence: 0.60703224325
- $00:15:55.176 \longrightarrow 00:15:57.180$ Or looks writing cells which are
- NOTE Confidence: 0.60703224325
- $00{:}15{:}57{.}248 \dashrightarrow 00{:}15{:}59{.}438$ non tumor cells but the membrane
- NOTE Confidence: 0.60703224325
- $00:15:59.438 \rightarrow 00:16:01.301$ potential measure of tumor cells
- NOTE Confidence: 0.60703224325
- $00:16:01.301 \longrightarrow 00:16:03.317$ in the rieti of different kinds.
- NOTE Confidence: 0.60703224325

00:16:03.320 --> 00:16:06.848 You see they right up here in the

NOTE Confidence: 0.60703224325

 $00{:}16{:}06{.}848 \dashrightarrow 00{:}16{:}09{.}596$ depolarized level. So in essence.

NOTE Confidence: 0.60703224325

 $00:16:09.596 \rightarrow 00:16:13.328$ What a lot about solutions from NOTE Confidence: 0.60703224325

 $00{:}16{:}13.328 \dashrightarrow 00{:}16{:}17.500$ various groups have shown is that.

NOTE Confidence: 0.60703224325

00:16:17.500 --> 00:16:19.752 The week transmembrane sodium

NOTE Confidence: 0.60703224325

 $00{:}16{:}19.752 \dashrightarrow 00{:}16{:}22.004$ gradient maintaining a depolarized NOTE Confidence: 0.60703224325

00:16:22.004 --> 00:16:23.973 membrane potential is actually

NOTE Confidence: 0.60703224325

 $00:16:23.973 \longrightarrow 00:16:26.289$ necessary for these cells to survive

NOTE Confidence: 0.60703224325

 $00{:}16{:}26.289 \dashrightarrow 00{:}16{:}28.476$ in their altered environment that

NOTE Confidence: 0.60703224325

 $00:16:28.476 \rightarrow 00:16:30.745$ they create for their survival.

NOTE Confidence: 0.60703224325

 $00{:}16{:}30{.}745 \dashrightarrow 00{:}16{:}32{.}200$ Update at the.

NOTE Confidence: 0.60703224325

 $00:16:32.200 \rightarrow 00:16:36.030$ Cost of normal cells that they're replacing.

NOTE Confidence: 0.60703224325

 $00{:}16{:}36{.}030 \dashrightarrow 00{:}16{:}38{.}970$ Whereas you know these normal cells,

NOTE Confidence: 0.60703224325

 $00:16:38.970 \longrightarrow 00:16:40.394$ especially in the brain,

NOTE Confidence: 0.60703224325

00:16:40.394 --> 00:16:41.106 maintain strong,

NOTE Confidence: 0.60703224325

 $00:16:41.110 \rightarrow 00:16:42.226$ transmembrane certain buildings

00:16:42.226 --> 00:16:44.830 and they may do so by maintaining

NOTE Confidence: 0.60703224325

00:16:44.896 --> 00:16:46.100 their hyperpolarized.

NOTE Confidence: 0.908159307142857

 $00:16:48.640 \rightarrow 00:16:51.937$ So these are the hallmarks of cancer,

NOTE Confidence: 0.908159307142857

 $00:16:51.940 \longrightarrow 00:16:54.847$ our goal, and my goal in the next few

NOTE Confidence: 0.908159307142857

 $00:16:54.847 \rightarrow 00:16:57.446$ minutes is to show that you can employ

NOTE Confidence: 0.908159307142857

 $00{:}16{:}57{.}446 \dashrightarrow 00{:}17{:}00{.}176$ sodium and proton imaging methods

NOTE Confidence: 0.908159307142857

 $00:17:00.176 \rightarrow 00:17:04.219$ to actually observe 2 properties,

NOTE Confidence: 0.908159307142857

 $00:17:04.220 \rightarrow 00:17:07.358$ invasion and proliferation of cancer cells

NOTE Confidence: 0.908159307142857

 $00:17:07.360 \rightarrow 00:17:11.380$ by using proton and imaging perspective.

NOTE Confidence: 0.908159307142857

 $00:17:11.380 \longrightarrow 00:17:13.235$ We talked a little bit about that.

NOTE Confidence: 0.908159307142857

00:17:13.240 --> 00:17:14.908 I'm sure this method is quite

NOTE Confidence: 0.908159307142857

 $00{:}17{:}14.908 \dashrightarrow 00{:}17{:}15.742$ familiar with most.

NOTE Confidence: 0.2881721566666667

 $00:17:21.120 \longrightarrow 00:17:22.128$ Slash house light.

NOTE Confidence: 0.417400417333333

 $00{:}17{:}38{.}200 \dashrightarrow 00{:}17{:}39{.}049$ Turns out that.

NOTE Confidence: 0.2631551125

 $00{:}17{:}44.990 \dashrightarrow 00{:}17{:}49.358$ In like one step. Slide disappeared, yeah.

 $00:17:49.360 \longrightarrow 00:17:51.862$ I realized that it just didn't like 1 slide.

NOTE Confidence: 0.846737995714286

00:17:54.920 --> 00:17:56.159 Do you wanna stop sharing and start

NOTE Confidence: 0.846737995714286

 $00:17:56.159 \rightarrow 00:17:57.600$ again or is that what you're doing?

NOTE Confidence: 0.81298438125

00:17:57.900 --> 00:17:59.790 Yeah, I'm trying to do that right now, OK?

NOTE Confidence: 0.10258365

00:18:01.270 --> 00:18:03.860 OK, so I'll skip that slide.

NOTE Confidence: 0.29788578

 $00:18:10.250 \longrightarrow 00:18:12.447$ And see if I can get from that.

NOTE Confidence: 0.9386621

 $00{:}18{:}15{.}450 \dashrightarrow 00{:}18{:}20{.}790$ So the slide that I unfortunately had that.

NOTE Confidence: 0.9386621

 $00:18:20.790 \rightarrow 00:18:23.934$ You know it bounced me out of PowerPoint.

NOTE Confidence: 0.9386621

 $00{:}18{:}23{.}940 \dashrightarrow 00{:}18{:}27{.}360$ Basically this describes a key late.

NOTE Confidence: 0.9386621

 $00:18:27.360 \rightarrow 00:18:30.112$ That is the design structure of most contrast

NOTE Confidence: 0.9386621

 $00:18:30.112 \longrightarrow 00:18:32.266$ agents that is used in the preferable

NOTE Confidence: 0.9386621

 $00{:}18{:}32.266 \dashrightarrow 00{:}18{:}35.052$ design is where you take a gadolinium.

NOTE Confidence: 0.9386621

00:18:35.060 --> 00:18:38.228 Mine is very car magnetic and you

NOTE Confidence: 0.9386621

 $00:18:38.228 \rightarrow 00:18:41.522$ use that to reduce its toxicity

NOTE Confidence: 0.9386621

00:18:41.522 --> 00:18:44.240 Yuzuki late with donating.

NOTE Confidence: 0.9386621

 $00:18:44.240 \rightarrow 00:18:47.000$ Components like oxygen atoms that would

- NOTE Confidence: 0.9386621
- $00:18:47.000 \rightarrow 00:18:49.770$ provide the stability for conjugation,

00:18:49.770 --> 00:18:51.591 reducing discovery toxicity

NOTE Confidence: 0.9386621

 $00{:}18{:}51{.}591 \dashrightarrow 00{:}18{:}54{.}019$ of the metal iron.

NOTE Confidence: 0.9386621

 $00:18:54.020 \longrightarrow 00:18:56.799$ But discriminating iron is some of the

NOTE Confidence: 0.9386621

 $00:18:56.799 \rightarrow 00:18:59.430$ key of the types of imaging observations

NOTE Confidence: 0.9386621

00:18:59.430 --> 00:19:01.915 that I'm going to show you about.

NOTE Confidence: 0.9386621

 $00{:}19{:}01{.}920 \dashrightarrow 00{:}19{:}03{.}852$ So this is essentially a proton

NOTE Confidence: 0.9386621

 $00:19:03.852 \rightarrow 00:19:06.199$ spectrum of a key late like this.

NOTE Confidence: 0.9386621

 $00:19:06.200 \rightarrow 00:19:09.336$ This is a it's called appear TP molecule.

NOTE Confidence: 0.9386621

 $00:19:09.340 \longrightarrow 00:19:11.670$ It's basically a molecule that

NOTE Confidence: 0.9386621

 $00:19:11.670 \longrightarrow 00:19:13.534$ contains multiple phosphinate groups,

NOTE Confidence: 0.9386621

00:19:13.540 --> 00:19:15.570 much like phosphonates that exist

NOTE Confidence: 0.9386621

 $00:19:15.570 \longrightarrow 00:19:17.950$ in molecules like ATP and ADP.

NOTE Confidence: 0.81158357

 $00:19:18.480 \longrightarrow 00:19:19.650$ So this is a very

NOTE Confidence: 0.860093169166667

 $00:19:20.020 \rightarrow 00:19:22.306$ common diamagnetic range of signals that

 $00:19:22.306 \rightarrow 00:19:24.729$ you would see emanating for different.

NOTE Confidence: 0.860093169166667

 $00{:}19{:}24.730 \dashrightarrow 00{:}19{:}27.586$ Protons, the non exchangeable protons that

NOTE Confidence: 0.860093169166667

 $00{:}19{:}27.586 \dashrightarrow 00{:}19{:}31.154$ exist in these carbons as well as the

NOTE Confidence: 0.860093169166667

 $00:19:31.154 \rightarrow 00:19:33.530$ carbons existing in these pendant arms.

NOTE Confidence: 0.9649444675

 $00:19:35.700 \longrightarrow 00:19:37.340$ By the way, I point out that these

NOTE Confidence: 0.9649444675

 $00{:}19{:}37{.}340 \dashrightarrow 00{:}19{:}40{.}036$ phosphates on this on a molecule like this.

NOTE Confidence: 0.9649444675

 $00:19:40.040 \rightarrow 00:19:42.290$ These protons exchange with protons

NOTE Confidence: 0.9649444675

 $00:19:42.290 \rightarrow 00:19:45.321$ of water and that kind of exchange

NOTE Confidence: 0.9649444675

 $00{:}19{:}45{.}321 \dashrightarrow 00{:}19{:}48{.}400$ is actually a a pH mediated

NOTE Confidence: 0.9649444675

 $00:19:48.400 \rightarrow 00:19:51.840$ and and and therefore they are.

NOTE Confidence: 0.9649444675

 $00{:}19{:}51{.}840 \dashrightarrow 00{:}19{:}54{.}240$ These molecules are essentially

NOTE Confidence: 0.9649444675

 $00{:}19{:}54{.}240 \dashrightarrow 00{:}19{:}57{.}692$ create sensor much like ATP and

NOTE Confidence: 0.9649444675

 $00:19:57.692 \rightarrow 00:20:00.067$ ADP is using phosphorus and.

NOTE Confidence: 0.9649444675

 $00:20:00.070 \longrightarrow 00:20:02.728$ So if you now collate this,

NOTE Confidence: 0.9649444675

 $00:20:02.730 \longrightarrow 00:20:05.046$ take this molecule and and complexes

NOTE Confidence: 0.9649444675

 $00:20:05.046 \longrightarrow 00:20:06.590$ with the paramagnetic metal.

- NOTE Confidence: 0.9649444675
- $00:20:06.590 \longrightarrow 00:20:07.343$ In this case,
- NOTE Confidence: 0.9649444675
- 00:20:07.343 --> 00:20:08.347 I'm not using gadolinium,
- NOTE Confidence: 0.9649444675
- 00:20:08.350 --> 00:20:11.942 but a fully am I and you essentially
- NOTE Confidence: 0.9649444675
- $00:20:11.942 \rightarrow 00:20:14.108$ caused this large expansion of the
- NOTE Confidence: 0.9649444675
- 00:20:14.108 --> 00:20:16.385 same chemical shift that you see here
- NOTE Confidence: 0.9649444675
- $00{:}20{:}16.385 \dashrightarrow 00{:}20{:}18.760$ within a few partner million and that's
- NOTE Confidence: 0.9649444675
- $00:20:18.760 \dashrightarrow 00:20:20.735$ expanded by hundreds across people.
- NOTE Confidence: 0.9649444675
- $00:20:20.740 \longrightarrow 00:20:23.728$ So these signals have no potential
- NOTE Confidence: 0.9649444675
- $00:20:23.728 \rightarrow 00:20:26.650$ overlap with other types of signals
- NOTE Confidence: 0.9649444675
- $00:20:26.650 \longrightarrow 00:20:28.870$ that you may observe in vivo.
- NOTE Confidence: 0.9649444675
- $00:20:28.870 \longrightarrow 00:20:31.228$ And this is the water signal.
- NOTE Confidence: 0.9649444675
- $00{:}20{:}31{.}230 \dashrightarrow 00{:}20{:}33{.}396$ And so this hyperfine shifted
- NOTE Confidence: 0.9649444675
- $00:20:33.396 \rightarrow 00:20:36.026$ signal has very unusual properties.
- NOTE Confidence: 0.9649444675
- $00{:}20{:}36{.}030 \dashrightarrow 00{:}20{:}37{.}800$ Basically, all it means is that
- NOTE Confidence: 0.9649444675
- $00:20:37.800 \longrightarrow 00:20:39.490$ you can observe them quickly.
- NOTE Confidence: 0.9649444675

 $00:20:39.490 \longrightarrow 00:20:42.670$ You can observe them under very

NOTE Confidence: 0.9649444675

 $00{:}20{:}42.670 \dashrightarrow 00{:}20{:}45.841$ precarious in vivo situations that we

NOTE Confidence: 0.9649444675

 $00{:}20{:}45{.}841$ --> $00{:}20{:}48{.}552$ may experience the relaxation times are NOTE Confidence: 0.9649444675

 $00{:}20{:}48.552 \dashrightarrow 00{:}20{:}51.180$ so short because of the paramagnetic

NOTE Confidence: 0.9649444675

 $00{:}20{:}51{.}261 \dashrightarrow 00{:}20{:}53{.}276$ environment that these photons

NOTE Confidence: 0.9649444675

 $00:20:53.276 \rightarrow 00:20:56.729$ are in create a very sensitive scenario.

NOTE Confidence: 0.9649444675

00:20:56.730 --> 00:20:57.714 That's most, importantly,

NOTE Confidence: 0.9649444675

 $00:20:57.714 \rightarrow 00:21:00.010$ that the chemical shift of these signals,

NOTE Confidence: 0.9649444675

 $00{:}21{:}00{.}010 \dashrightarrow 00{:}21{:}01{.}150$ not the amplitude,

NOTE Confidence: 0.9649444675

 $00:21:01.150 \longrightarrow 00:21:02.290$ of these signals.

NOTE Confidence: 0.9649444675

 $00:21:02.290 \longrightarrow 00:21:05.175$ But how these signals are

NOTE Confidence: 0.9649444675

 $00:21:05.175 \longrightarrow 00:21:07.500$ located and how they shift?

NOTE Confidence: 0.9649444675

 $00:21:07.500 \rightarrow 00:21:10.356$ Is the readout that we observe again,

NOTE Confidence: 0.9649444675

 $00:21:10.360 \rightarrow 00:21:13.177$ so this is a molecule which is the sensor.

NOTE Confidence: 0.9649444675

 $00:21:13.180 \longrightarrow 00:21:15.130$ So if you change the

NOTE Confidence: 0.9649444675

 $00:21:15.130 \longrightarrow 00:21:16.690$ environment of the sensor.

- NOTE Confidence: 0.9649444675
- $00:21:16.690 \rightarrow 00:21:19.070$ The structure of the molecule will change
- NOTE Confidence: 0.9649444675
- $00{:}21{:}19{.}070 \dashrightarrow 00{:}21{:}22{.}387$ and as the structure of the molecule changes.
- NOTE Confidence: 0.9649444675
- $00{:}21{:}22{.}390 \dashrightarrow 00{:}21{:}25{.}204$ What you then read out that structural
- NOTE Confidence: 0.9649444675
- $00:21:25.204 \rightarrow 00:21:27.659$ changes from the chemical change.
- NOTE Confidence: 0.9649444675
- $00{:}21{:}27.660 \dashrightarrow 00{:}21{:}29.880$ And so this is encapsulated here.
- NOTE Confidence: 0.9649444675
- $00{:}21{:}29{.}880 \dashrightarrow 00{:}21{:}31{.}698$ This is a molecule that we
- NOTE Confidence: 0.9649444675
- $00:21:31.698 \longrightarrow 00:21:33.480$ are using as our sensor.
- NOTE Confidence: 0.9649444675
- $00:21:33.480 \longrightarrow 00:21:36.640$ These are the types of signals that we
- NOTE Confidence: 0.9649444675
- $00:21:36.640 \rightarrow 00:21:39.715$ observe using this as an example 86 proton.
- NOTE Confidence: 0.9649444675
- 00:21:39.720 --> 00:21:41.520 It has a pH sensitivity,
- NOTE Confidence: 0.9649444675
- 00:21:41.520 --> 00:21:43.185 but obviously any molecule reports
- NOTE Confidence: 0.9649444675
- $00{:}21{:}43.185 \dashrightarrow 00{:}21{:}44.850$ environment by changes like these
- NOTE Confidence: 0.9649444675
- $00{:}21{:}44{.}908 \dashrightarrow 00{:}21{:}46{.}612$ molecules have or molecules like this
- NOTE Confidence: 0.9649444675
- $00{:}21{:}46.612 \dashrightarrow 00{:}21{:}48.639$ have very very short relaxation times.
- NOTE Confidence: 0.9649444675
- $00:21:48.640 \rightarrow 00:21:50.932$ So you can observe them quickly
- NOTE Confidence: 0.9649444675

 $00:21:50.932 \rightarrow 00:21:52.921$ and therefore imaging these have

NOTE Confidence: 0.9649444675

 $00{:}21{:}52{.}921 \dashrightarrow 00{:}21{:}55{.}508$ been possible and the readout from

NOTE Confidence: 0.9649444675

 $00{:}21{:}55{.}508 \dashrightarrow 00{:}21{:}58{.}060$ them in terms of chemical shift is.

NOTE Confidence: 0.9649444675

00:21:58.060 --> 00:22:01.708 Not confounded by other overlapping signals.

NOTE Confidence: 0.9649444675

 $00{:}22{:}01{.}710 \dashrightarrow 00{:}22{:}04{.}572$ So this is an in vitro example of this

NOTE Confidence: 0.9649444675

 $00{:}22{:}04{.}572 \dashrightarrow 00{:}22{:}07{.}506$ kind of work from my colleague Dan

NOTE Confidence: 0.9649444675

 $00{:}22{:}07.506 \dashrightarrow 00{:}22{:}10.950$ Employment and then this method is.

NOTE Confidence: 0.9649444675

 $00:22:10.950 \longrightarrow 00:22:12.698$ Paul by sensor imaging,

NOTE Confidence: 0.9649444675

 $00{:}22{:}12.698 \dashrightarrow 00{:}22{:}15.273$ redundant deviation shifts, birds for short.

NOTE Confidence: 0.9649444675

 $00:22:15.273 \rightarrow 00:22:17.799$ Essentially showing you that in these

NOTE Confidence: 0.9649444675

 $00:22:17.799 \rightarrow 00:22:21.058$ two phantoms which have very different pH,

NOTE Confidence: 0.9649444675

 $00:22:21.060 \rightarrow 00:22:23.400$ you can read out the pH with high confidence

NOTE Confidence: 0.9649444675

 $00:22:23.400 \rightarrow 00:22:25.317$ even if you change the temperature.

NOTE Confidence: 0.9649444675

00:22:25.320 --> 00:22:27.168 So you can essentially

NOTE Confidence: 0.9649444675

 $00{:}22{:}27.168 \dashrightarrow 00{:}22{:}29.478$ give these two things out.

NOTE Confidence: 0.9649444675

 $00:22:29.480 \longrightarrow 00:22:30.420$ Simultaneously,

- NOTE Confidence: 0.9649444675
- $00:22:30.420 \longrightarrow 00:22:33.261$ the key thing is is that this is

00:22:33.261 - > 00:22:36.059 not like most imaging contrast.

NOTE Confidence: 0.9649444675

 $00:22:36.060 \longrightarrow 00:22:38.670$ This contrast is not based on

NOTE Confidence: 0.9649444675

 $00:22:38.670 \longrightarrow 00:22:41.659$ the amount of agent that you have

NOTE Confidence: 0.9649444675

00:22:41.660 --> 00:22:43.500 in in the given compartment,

NOTE Confidence: 0.9649444675

00:22:43.500 - 00:22:44.980 but really their chemical shift.

NOTE Confidence: 0.9649444675

 $00:22:44.980 \longrightarrow 00:22:47.140$ So it's it's a readout that's

NOTE Confidence: 0.9649444675

00:22:47.140 --> 00:22:48.220 independent of concentration,

NOTE Confidence: 0.9649444675

 $00:22:48.220 \longrightarrow 00:22:50.324$ and so using this method we've

NOTE Confidence: 0.9649444675

 $00:22:50.324 \longrightarrow 00:22:52.836$ been able to apply it to look at

NOTE Confidence: 0.9649444675

 $00:22:52.840 \longrightarrow 00:22:54.154$ the cancer environment,

NOTE Confidence: 0.9649444675

 $00{:}22{:}54{.}154 \dashrightarrow 00{:}22{:}57{.}220$ specifically the the pH in the extracellular

NOTE Confidence: 0.734225631818182

 $00{:}22{:}57{.}293 \dashrightarrow 00{:}22{:}59{.}430$ space, and a variety of different.

NOTE Confidence: 0.734225631818182

 $00{:}22{:}59{.}430 \dashrightarrow 00{:}23{:}02{.}255$ Scenarios these these are examples

NOTE Confidence: 0.734225631818182

 $00:23:02.255 \rightarrow 00:23:04.554$ from breaking specifically shown for

 $00:23:04.554 \rightarrow 00:23:06.366$ two different types of tumors here,

NOTE Confidence: 0.734225631818182

 $00{:}23{:}06{.}370 \dashrightarrow 00{:}23{:}09{.}370$ but you can note and appreciate the acidity.

NOTE Confidence: 0.734225631818182

 $00:23:09.370 \longrightarrow 00:23:13.306$ Acidity within the tumor poor as shown here.

NOTE Confidence: 0.734225631818182

00:23:13.310 - > 00:23:17.786 Core being identified by the line

NOTE Confidence: 0.734225631818182

 $00{:}23{:}17.790 \dashrightarrow 00{:}23{:}20.954$ that shows up in the MRI contrast.

NOTE Confidence: 0.734225631818182

 $00{:}23{:}20{.}960 \dashrightarrow 00{:}23{:}22{.}748$ But you can also appreciate this

NOTE Confidence: 0.734225631818182

 $00{:}23{:}22{.}748 \dashrightarrow 00{:}23{:}24{.}358$ extended area of a certification

NOTE Confidence: 0.734225631818182

 $00:23:24.358 \longrightarrow 00:23:26.815$ for this tumor and not that tumor,

NOTE Confidence: 0.734225631818182

 $00{:}23{:}26.820 \dashrightarrow 00{:}23{:}29.004$ and that has to do with the

NOTE Confidence: 0.734225631818182

 $00:23:29.004 \rightarrow 00:23:30.660$ how evasive this tumor is,

NOTE Confidence: 0.734225631818182

00:23:30.660 --> 00:23:32.500 and using cellular markers,

NOTE Confidence: 0.734225631818182

 $00{:}23{:}32{.}500 \dashrightarrow 00{:}23{:}34{.}800$ you can corroborate that funding,

NOTE Confidence: 0.734225631818182

 $00:23:34.800 \longrightarrow 00:23:36.762$ so this goes back to the

NOTE Confidence: 0.734225631818182

 $00:23:36.762 \longrightarrow 00:23:38.780$ point that our pH readout,

NOTE Confidence: 0.734225631818182

 $00{:}23{:}38{.}780 \dashrightarrow 00{:}23{:}40{.}716$ so this is a case of a a

NOTE Confidence: 0.734225631818182

00:23:40.716 --> 00:23:42.380 very non invasive tumor,
$00:23:42.380 \rightarrow 00:23:47.364$ versus this one is tumors invade and this.

NOTE Confidence: 0.734225631818182

 $00:23:47.370 \rightarrow 00:23:49.462$ Invasion if you will.

NOTE Confidence: 0.734225631818182

 $00:23:49.462 \rightarrow 00:23:52.600$ I we believe is essentially preconditioning

NOTE Confidence: 0.734225631818182

 $00:23:52.686 \rightarrow 00:23:56.230$ for the expansion of this tumor within time.

NOTE Confidence: 0.734225631818182

 $00{:}23{:}56{.}230 \dashrightarrow 00{:}23{:}58{.}030$ For these two specific cases,

NOTE Confidence: 0.734225631818182

 $00:23:58.030 \rightarrow 00:24:02.958$ here in the 2nd and R2, but not the help.

NOTE Confidence: 0.734225631818182

 $00{:}24{:}02{.}960 \dashrightarrow 00{:}24{:}05{.}632$ So talked about a little bit about what

NOTE Confidence: 0.734225631818182

 $00:24:05.632 \longrightarrow 00:24:08.466$ we do with the Proton imaging part to

NOTE Confidence: 0.734225631818182

00:24:08.466 --> 00:24:11.676 read up pH and that uses the proton nucleus,

NOTE Confidence: 0.734225631818182

00:24:11.680 --> 00:24:12.145 right?

NOTE Confidence: 0.734225631818182

 $00:24:12.145 \longrightarrow 00:24:14.935$ This is a very highly sensitive

NOTE Confidence: 0.734225631818182

 $00{:}24{:}14{.}940 \dashrightarrow 00{:}24{:}17{.}124$ nucleus to observe because with the

NOTE Confidence: 0.734225631818182

 $00{:}24{:}17.124 \dashrightarrow 00{:}24{:}18.580$ hygiene gentlemen medical issue.

NOTE Confidence: 0.734225631818182

00:24:18.580 --> 00:24:21.316 But what I'm going to talk about next

NOTE Confidence: 0.734225631818182

 $00{:}24{:}21{.}316 \dashrightarrow 00{:}24{:}24{.}506$ is the sodium imaging part which has

 $00:24:24.506 \rightarrow 00:24:27.224$ a lower gyromagnetic ratio but aided

NOTE Confidence: 0.734225631818182

 $00{:}24{:}27{.}224 \dashrightarrow 00{:}24{:}30{.}320$ by the fact that we are looking at.

NOTE Confidence: 0.734225631818182

 $00{:}24{:}30{.}320 \dashrightarrow 00{:}24{:}33{.}176$ You know our product nucleus we are.

NOTE Confidence: 0.734225631818182

 $00:24:33.180 \longrightarrow 00:24:36.312$ So we can benefit a little bit from the

NOTE Confidence: 0.734225631818182

 $00{:}24{:}36{.}312 \dashrightarrow 00{:}24{:}39{.}126$ certain relaxation times of this nucleus.

NOTE Confidence: 0.734225631818182

 $00{:}24{:}39{.}126 \dashrightarrow 00{:}24{:}41{.}940$ So that's kind of where we are.

NOTE Confidence: 0.734225631818182

 $00:24:41.940 \longrightarrow 00:24:44.614$ Our basic rationale for this type of

NOTE Confidence: 0.734225631818182

 $00:24:44.614 \rightarrow 00:24:46.584$ experiment is that the problem that

NOTE Confidence: 0.734225631818182

 $00:24:46.584 \rightarrow 00:24:48.900$ we face is that the sodium signal,

NOTE Confidence: 0.734225631818182

 $00:24:48.900 \longrightarrow 00:24:52.952$ whether looking at the the interstitial

NOTE Confidence: 0.734225631818182

 $00:24:52.952 \longrightarrow 00:24:55.000$ or the intercellular pool,

NOTE Confidence: 0.734225631818182

 $00:24:55.000 \rightarrow 00:24:56.602$ signals they overlap.

NOTE Confidence: 0.734225631818182

00:24:56.602 --> 00:24:58.738 They're not chemically different,

NOTE Confidence: 0.734225631818182

 $00:24:58.740 \longrightarrow 00:25:00.440$ and therefore the total signal

NOTE Confidence: 0.734225631818182

 $00{:}25{:}00{.}440 \dashrightarrow 00{:}25{:}02{.}677$ you observe is is a representative

NOTE Confidence: 0.734225631818182

 $00:25:02.677 \rightarrow 00:25:04.958$ of these two types, etc.

 $00{:}25{:}04{.}958 \dashrightarrow 00{:}25{:}07{.}954$ Our expectation is that somehow we can

NOTE Confidence: 0.734225631818182

 $00{:}25{:}07{.}954 \dashrightarrow 00{:}25{:}10{.}729$ separate the two and that separation.

NOTE Confidence: 0.734225631818182

 $00{:}25{:}10.730 \dashrightarrow 00{:}25{:}13.260$ Will allow us to look at things

NOTE Confidence: 0.734225631818182

 $00:25:13.260 \longrightarrow 00:25:15.540$ like the transmembrane great.

NOTE Confidence: 0.734225631818182

 $00{:}25{:}15{.}540 \dashrightarrow 00{:}25{:}17{.}268$ So the idea stemmed from work

NOTE Confidence: 0.734225631818182

 $00:25:17.268 \longrightarrow 00:25:18.840$ that existed in the field,

NOTE Confidence: 0.734225631818182

 $00{:}25{:}18.840 \dashrightarrow 00{:}25{:}21.736$ but the advanced it in the last few

NOTE Confidence: 0.734225631818182

 $00:25:21.736 \rightarrow 00:25:25.817$ years is that if we have a polyanionic.

NOTE Confidence: 0.734225631818182

 $00:25:25.820 \longrightarrow 00:25:26.921$ Our magnetic agent,

NOTE Confidence: 0.734225631818182

 $00:25:26.921 \rightarrow 00:25:29.950$ much like pet agents that I've talked about.

NOTE Confidence: 0.734225631818182

00:25:29.950 --> 00:25:32.794 And we take a sodium ion because

NOTE Confidence: 0.734225631818182

 $00{:}25{:}32{.}794 \dashrightarrow 00{:}25{:}34{.}250$ of its negative charge.

NOTE Confidence: 0.734225631818182

 $00{:}25{:}34{.}250 \dashrightarrow 00{:}25{:}37{.}430$ It's attracted to it and there

NOTE Confidence: 0.734225631818182

 $00{:}25{:}37{.}430 \dashrightarrow 00{:}25{:}40.666$ is superbound bounding of some of

NOTE Confidence: 0.734225631818182

 $00{:}25{:}40.666 \dashrightarrow 00{:}25{:}43.720$ these ions because of the negative.

 $00:25:43.720 \longrightarrow 00:25:46.492$ Target of this agents and we have

NOTE Confidence: 0.734225631818182

 $00{:}25{:}46.492 \dashrightarrow 00{:}25{:}49.045$ some exchange of free sodium with

NOTE Confidence: 0.734225631818182

00:25:49.045 --> 00:25:51.175 this sort of bound sodium,

NOTE Confidence: 0.734225631818182

 $00:25:51.180 \longrightarrow 00:25:54.880$ and if that exchange happens.

NOTE Confidence: 0.734225631818182

 $00{:}25{:}54{.}880 \dashrightarrow 00{:}25{:}58{.}169$ Fast enough that we can reflect the

NOTE Confidence: 0.734225631818182

 $00{:}25{:}58.169 \dashrightarrow 00{:}26{:}00.863$ shifting of the sodium signal from

NOTE Confidence: 0.734225631818182

 $00{:}26{:}00{.}863 \dashrightarrow 00{:}26{:}04{.}279$ a from this process to reflect the

NOTE Confidence: 0.734225631818182

 $00:26:04.280 \longrightarrow 00:26:06.370$ true 2 compartments of service.

NOTE Confidence: 0.734225631818182

 $00:26:06.370 \longrightarrow 00:26:07.423$ So in essence,

NOTE Confidence: 0.734225631818182

 $00:26:07.423 \rightarrow 00:26:11.250$ what we do and this is our rationale take.

NOTE Confidence: 0.734225631818182

00:26:11.250 --> 00:26:13.378 Before we add an agent like this,

NOTE Confidence: 0.734225631818182

 $00:26:13.380 \longrightarrow 00:26:15.828$ this is the total signal we will look here.

NOTE Confidence: 0.734225631818182

00:26:15.830 --> 00:26:18.734 And when we inject or introduce

NOTE Confidence: 0.734225631818182

 $00{:}26{:}18.734 \dashrightarrow 00{:}26{:}21.768$ an agent like this because it's so

NOTE Confidence: 0.734225631818182

 $00{:}26{:}21.768 \dashrightarrow 00{:}26{:}23.964$ negative and it can attract positive

NOTE Confidence: 0.734225631818182

 $00:26:23.964 \rightarrow 00:26:25.770$ recharge sodium ions towards it,

 $00:26:25.770 \longrightarrow 00:26:29.922$ we can separate these two sodium

NOTE Confidence: 0.734225631818182

 $00:26:29.922 \rightarrow 00:26:30.614$ compartments.

NOTE Confidence: 0.788664675555556

 $00:26:30.620 \longrightarrow 00:26:32.671$ And this is a theory which we've

NOTE Confidence: 0.788664675555556

 $00:26:32.671 \longrightarrow 00:26:34.343$ contributed to, and a key.

NOTE Confidence: 0.788664675555556

 $00:26:34.343 \rightarrow 00:26:37.506$ Two key factors that we point out in in

NOTE Confidence: 0.788664675555556

 $00{:}26{:}37{.}506 \dashrightarrow 00{:}26{:}39{.}568$ this theoretical and practical demonstration

NOTE Confidence: 0.788664675555556

 $00:26:39.568 \rightarrow 00:26:43.010$ of pages like this is the fact that.

NOTE Confidence: 0.788664675555556

 $00:26:43.010 \longrightarrow 00:26:45.610$ There is a certain bound fraction of sodium

NOTE Confidence: 0.788664675555556

 $00{:}26{:}45.610 \dashrightarrow 00{:}26{:}47.688$ towards these agents that's important,

NOTE Confidence: 0.788664675555556

 $00{:}26{:}47.690 \dashrightarrow 00{:}26{:}50.938$ but also their exchange and these two

NOTE Confidence: 0.788664675555556

 $00:26:50.938 \rightarrow 00:26:53.811$ mechanisms have NKX actually contribute to

NOTE Confidence: 0.788664675555556

 $00{:}26{:}53.811 \dashrightarrow 00{:}26{:}57.800$ how much the sodium signal will be shifted.

NOTE Confidence: 0.788664675555556

 $00{:}26{:}57{.}800 \dashrightarrow 00{:}26{:}59{.}700$ So the shift ability factor,

NOTE Confidence: 0.788664675555556

 $00{:}26{:}59{.}700 \dashrightarrow 00{:}27{:}02{.}916$ but also how these signals could be broadened

NOTE Confidence: 0.788664675555556

 $00{:}27{:}02{.}916 \dashrightarrow 00{:}27{:}05{.}670$ because of their kind of like nature.

 $00{:}27{:}05.670 \dashrightarrow 00{:}27{:}08.294$ So, uh, another key thing that we point

NOTE Confidence: 0.788664675555556

 $00{:}27{:}08{.}294 \dashrightarrow 00{:}27{:}10{.}562$ out is that these shifted signals

NOTE Confidence: 0.788664675555556

 $00{:}27{:}10.562 \dashrightarrow 00{:}27{:}13.329$ brought in signals of of sodium

NOTE Confidence: 0.788664675555556

 $00:27:13.329 \rightarrow 00:27:15.812$ that we will observe is dependent

NOTE Confidence: 0.788664675555556

 $00{:}27{:}15.812 \dashrightarrow 00{:}27{:}18.570$ on the sodium concentration on the

NOTE Confidence: 0.788664675555556

 $00{:}27{:}18.570 \dashrightarrow 00{:}27{:}20.310$ on the agent concentration.

NOTE Confidence: 0.788664675555556

 $00:27:20.310 \longrightarrow 00:27:22.750$ And here we are limited by the fact

NOTE Confidence: 0.788664675555556

 $00{:}27{:}22.750 \dashrightarrow 00{:}27{:}25.232$ that we need sufficient amount of

NOTE Confidence: 0.788664675555556

 $00{:}27{:}25{.}232 \dashrightarrow 00{:}27{:}27{.}920$ this agent present to process certain

NOTE Confidence: 0.788664675555556

 $00{:}27{:}27{.}993 \dashrightarrow 00{:}27{:}30{.}268$ for the broadening and therefore

NOTE Confidence: 0.788664675555556

 $00:27:30.270 \longrightarrow 00:27:33.476$ this is something that will act as

NOTE Confidence: 0.788664675555556

 $00{:}27{:}33.476 \dashrightarrow 00{:}27{:}35.609$ a benefit for certain sensor.

NOTE Confidence: 0.788664675555556

 $00:27:35.609 \rightarrow 00:27:38.027$ But it was not necessary for

NOTE Confidence: 0.788664675555556

 $00:27:38.027 \longrightarrow 00:27:40.179$ them for the poor concepts.

NOTE Confidence: 0.788664675555556

 $00:27:40.180 \longrightarrow 00:27:42.430$ So our expected idea for these

NOTE Confidence: 0.788664675555556

 $00:27:42.430 \longrightarrow 00:27:44.516$ experimentation is that before we add

 $00:27:44.516 \rightarrow 00:27:46.240$ the agent, we're seeing one single,

NOTE Confidence: 0.788664675555556

 $00:27:46.240 \longrightarrow 00:27:48.040$ and after we add this agent,

NOTE Confidence: 0.788664675555556

 $00:27:48.040 \rightarrow 00:27:49.880$ we're gonna separate the signal.

NOTE Confidence: 0.788664675555556

 $00:27:49.880 \rightarrow 00:27:52.624$ Now you see three and I point out

NOTE Confidence: 0.788664675555556

 $00:27:52.624 \rightarrow 00:27:54.918$ three because you also have sodium.

NOTE Confidence: 0.788664675555556

 $00{:}27{:}54{.}920 \dashrightarrow 00{:}27{:}56{.}942$ Plenty of sodium also in the

NOTE Confidence: 0.788664675555556

 $00:27:56.942 \longrightarrow 00:27:57.616$ blood department.

NOTE Confidence: 0.788664675555556

 $00{:}27{:}57{.}620 \dashrightarrow 00{:}28{:}00{.}548$ But because the the blood department is much

NOTE Confidence: 0.788664675555556

 $00{:}28{:}00{.}548 \dashrightarrow 00{:}28{:}03{.}219$ smaller than the interstitial compartment,

NOTE Confidence: 0.788664675555556

 $00:28:03.220 \longrightarrow 00:28:05.494$ these representative amplitudes

NOTE Confidence: 0.788664675555556

 $00:28:05.494 \longrightarrow 00:28:08.634$ of these beats are depicted.

NOTE Confidence: 0.788664675555556

 $00:28:08.634 \longrightarrow 00:28:11.658$ So in vivo inside a tumor voxel.

NOTE Confidence: 0.788664675555556

 $00{:}28{:}11.660 \dashrightarrow 00{:}28{:}13.240$ This is what we see.

NOTE Confidence: 0.788664675555556

 $00{:}28{:}13{.}240 \dashrightarrow 00{:}28{:}15{.}030$ This is before the agent.

NOTE Confidence: 0.788664675555556

 $00:28:15.030 \longrightarrow 00:28:16.730$ It's been separated here.

00:28:16.730 --> 00:28:18.855 And outside of the tumor,

NOTE Confidence: 0.788664675555556

 $00:28:18.860 \rightarrow 00:28:20.948$ we see something that's similar but

NOTE Confidence: 0.788664675555556

 $00:28:20.948 \rightarrow 00:28:23.370$ to the shifting and the broadening

NOTE Confidence: 0.788664675555556

 $00:28:23.370 \longrightarrow 00:28:25.440$ is to some lesser extent.

NOTE Confidence: 0.788664675555556

 $00:28:25.440 \longrightarrow 00:28:27.316$ So this is kind of what we

NOTE Confidence: 0.788664675555556

 $00:28:27.316 \longrightarrow 00:28:28.120$ typically do nowadays,

NOTE Confidence: 0.788664675555556

 $00{:}28{:}28{.}120 \dashrightarrow 00{:}28{:}30{.}088$ and this is work by Mohammad Khan who

NOTE Confidence: 0.788664675555556

 $00:28:30.088 \rightarrow 00:28:32.179$ did his thesis work on this project.

NOTE Confidence: 0.788664675555556

 $00{:}28{:}32{.}180 \dashrightarrow 00{:}28{:}34{.}088$ Is is this is the conventional

NOTE Confidence: 0.788664675555556

 $00:28:34.088 \longrightarrow 00:28:35.360$ location of the tumor.

NOTE Confidence: 0.788664675555556

 $00:28:35.360 \longrightarrow 00:28:36.945$ We inject the agent to

NOTE Confidence: 0.788664675555556

00:28:36.945 -> 00:28:38.213 identify the blood compartment,

NOTE Confidence: 0.788664675555556

00:28:38.220 --> 00:28:39.544 interstitial compartment,

NOTE Confidence: 0.788664675555556

00:28:39.544 --> 00:28:41.530 interstitial intracellular compartment

NOTE Confidence: 0.788664675555556

 $00{:}28{:}41{.}530 \dashrightarrow 00{:}28{:}44{.}178$ in terms of so dium.

NOTE Confidence: 0.788664675555556

 $00:28:44.180 \longrightarrow 00:28:45.800$ We integrate these signals to

- NOTE Confidence: 0.788664675555556
- 00:28:45.800 --> 00:28:47.096 get maps like this,
- NOTE Confidence: 0.788664675555556
- 00:28:47.100 --> 00:28:48.920 and using a combination of these two,
- NOTE Confidence: 0.788664675555556
- $00:28:48.920 \longrightarrow 00:28:50.680$ we can get what's called
- NOTE Confidence: 0.788664675555556
- $00:28:50.680 \longrightarrow 00:28:51.736$ an endothelial gradient.
- NOTE Confidence: 0.788664675555556
- $00:28:51.740 \longrightarrow 00:28:53.655$ This is asserting gradient representing
- NOTE Confidence: 0.788664675555556
- $00{:}28{:}53.655 \dashrightarrow 00{:}28{:}55.570$ the and the feeling department.
- NOTE Confidence: 0.788664675555556
- $00:28:55.570 \longrightarrow 00:28:57.100$ And this is the critical one
- NOTE Confidence: 0.788664675555556
- $00:28:57.100 \longrightarrow 00:28:58.510$ that we will talk about,
- NOTE Confidence: 0.788664675555556
- $00:28:58.510 \longrightarrow 00:29:00.725$ which is the transmembrane gradient
- NOTE Confidence: 0.788664675555556
- $00{:}29{:}00{.}725 \dashrightarrow 00{:}29{:}03{.}588$ which is obtained from the intracellular
- NOTE Confidence: 0.788664675555556
- $00:29:03.588 \rightarrow 00:29:06.448$ and the interstitial signals also.
- NOTE Confidence: 0.788664675555556
- $00{:}29{:}06{.}450 \dashrightarrow 00{:}29{:}08{.}952$ And we we can now map this into ID
- NOTE Confidence: 0.788664675555556
- $00{:}29{:}08{.}952 \dashrightarrow 00{:}29{:}11{.}239$ to get the transmembrane gradient
- NOTE Confidence: 0.788664675555556
- $00{:}29{:}11{.}239 \dashrightarrow 00{:}29{:}13.863$ how it appears within the tumor.
- NOTE Confidence: 0.788664675555556
- $00{:}29{:}13.863 \dashrightarrow 00{:}29{:}17.261$ I point out there's these blobs of high
- NOTE Confidence: 0.788664675555556

 $00:29:17.261 \longrightarrow 00:29:20.146$ intense signal represents the ventricles.

NOTE Confidence: 0.788664675555556

00:29:20.150 --> 00:29:22.050 V
entricles hasn't has a

NOTE Confidence: 0.788664675555556

 $00:29:22.050 \longrightarrow 00:29:24.425$ lot of sodium in them,

NOTE Confidence: 0.788664675555556

 $00:29:24.430 \rightarrow 00:29:28.315$ and that has variety of them applications.

NOTE Confidence: 0.788664675555556

00:29:28.320 --> 00:29:31.200 Or other disease disorders as well,

NOTE Confidence: 0.788664675555556

 $00:29:31.200 \longrightarrow 00:29:33.448$ but the key thing is that we can

NOTE Confidence: 0.788664675555556

 $00{:}29{:}33{.}448 \dashrightarrow 00{:}29{:}35{.}918$ obtain a clear readout of the

NOTE Confidence: 0.788664675555556

 $00:29:35.918 \rightarrow 00:29:38.213$ transmembrane gradient shown for two

NOTE Confidence: 0.788664675555556

 $00:29:38.213 \rightarrow 00:29:40.028$ different three different tumor types,

NOTE Confidence: 0.788664675555556

 $00:29:40.028 \rightarrow 00:29:42.896$ and so this is a pretty uniform and

NOTE Confidence: 0.788664675555556

 $00:29:42.896 \rightarrow 00:29:45.619$ vigorous observation that we can now make.

NOTE Confidence: 0.788664675555556

 $00:29:45.620 \longrightarrow 00:29:48.044$ We even began to employ these

NOTE Confidence: 0.788664675555556

 $00:29:48.044 \longrightarrow 00:29:49.660$ methods for variety of

NOTE Confidence: 0.565210293181818

 $00:29:49.740 \longrightarrow 00:29:51.070$ different treatments.

NOTE Confidence: 0.88799386

 $00:29:53.140 \longrightarrow 00:29:56.940$ And and so this is a very unique entry.

NOTE Confidence: 0.88799386

 $00:29:56.940 \rightarrow 00:29:58.571$ Genic antiangiogenic treatment and

- NOTE Confidence: 0.88799386
- $00:29:58.571 \rightarrow 00:30:01.420$ what is shown here is a comparison
- NOTE Confidence: 0.88799386
- $00:30:01.485 \longrightarrow 00:30:03.900$ of what's your afternoon, does it?
- NOTE Confidence: 0.88799386
- $00{:}30{:}03{.}900 \dashrightarrow 00{:}30{:}05{.}500$ It it blunts it.
- NOTE Confidence: 0.88799386
- $00:30:05.500 \dashrightarrow 00:30:08.028$ It sort of impedes that's in the growth
- NOTE Confidence: 0.88799386
- $00:30:08.028 \rightarrow 00:30:10.969$ which is most significant within two weeks.
- NOTE Confidence: 0.88799386
- $00{:}30{:}10.970 \dashrightarrow 00{:}30{:}12.972$ And this kind of effect can be
- NOTE Confidence: 0.88799386
- $00:30:12.972 \longrightarrow 00:30:15.605$ read out by the teenage as well
- NOTE Confidence: 0.88799386
- 00:30:15.605 00:30:17.309 as the transmembrane gradient.
- NOTE Confidence: 0.88799386
- $00{:}30{:}17{.}310 \dashrightarrow 00{:}30{:}20{.}187$ As you can see the sorafenib against
- NOTE Confidence: 0.88799386
- $00:30:20.187 \dashrightarrow 00:30:24.340$ renormalize the pH with treatment and.
- NOTE Confidence: 0.88799386
- $00:30:24.340 \longrightarrow 00:30:27.526$ As well as normal, you know.
- NOTE Confidence: 0.88799386
- $00:30:27.530 \longrightarrow 00:30:29.734$ Strengthening the sodium transmembrane
- NOTE Confidence: 0.88799386
- $00{:}30{:}29{.}734 \dashrightarrow 00{:}30{:}31{.}938$ gradient upon treatment even
- NOTE Confidence: 0.88799386
- $00:30:31.938 \longrightarrow 00:30:34.253$ the Chamber making it similar
- NOTE Confidence: 0.88799386
- $00:30:34.253 \longrightarrow 00:30:36.448$ to the normal tissue as well,
- NOTE Confidence: 0.88799386

 $00:30:36.448 \longrightarrow 00:30:39.160$ so I hope that's been able to show

NOTE Confidence: 0.88799386

 $00{:}30{:}39{.}241 \dashrightarrow 00{:}30{:}41{.}162$ within the last few minutes is

NOTE Confidence: 0.88799386

 $00{:}30{:}41.162 \dashrightarrow 00{:}30{:}43.654$ that we now have a quote which can

NOTE Confidence: 0.88799386

 $00:30:43.654 \rightarrow 00:30:45.826$ sense both quote photon and sodium.

NOTE Confidence: 0.88799386

 $00{:}30{:}45{.}830 \dashrightarrow 00{:}30{:}49{.}178$ A lot of credit to both.

NOTE Confidence: 0.88799386

00:30:49.180 --> 00:30:51.890 I'm sharing design quotes of

NOTE Confidence: 0.88799386

 $00:30:51.890 \longrightarrow 00:30:53.516$ this particular quote,

NOTE Confidence: 0.88799386

 $00:30:53.520 \longrightarrow 00:30:54.924$ and quotes like this,

NOTE Confidence: 0.88799386

 $00:30:54.924 \rightarrow 00:30:57.849$ which with proton imaging can be a very

NOTE Confidence: 0.88799386

 $00:30:57.849 \rightarrow 00:31:00.519$ powerful proton sensor for pH imaging,

NOTE Confidence: 0.88799386

 $00{:}31{:}00{.}519 \dashrightarrow 00{:}31{:}03{.}678$ but also a sodium sensor in terms

NOTE Confidence: 0.88799386

 $00:31:03.678 \longrightarrow 00:31:05.148$ of its its signal shifted.

NOTE Confidence: 0.679780554285714

 $00:31:07.400 \longrightarrow 00:31:10.515$ It it can be also used simultaneously.

NOTE Confidence: 0.679780554285714

 $00:31:10.520 \longrightarrow 00:31:12.008$ So I hope I've what I've

NOTE Confidence: 0.679780554285714

 $00:31:12.008 \rightarrow 00:31:13.420$ shown is that all cells,

NOTE Confidence: 0.679780554285714

 $00:31:13.420 \rightarrow 00:31:16.396$ not just excitable neurons and muscle,

- NOTE Confidence: 0.679780554285714
- $00:31:16.400 \rightarrow 00:31:18.715$ generate and receive by electrical
- NOTE Confidence: 0.679780554285714
- $00:31:18.715 \longrightarrow 00:31:21.169$ signals that are encoded.
- NOTE Confidence: 0.679780554285714
- $00:31:21.170 \longrightarrow 00:31:24.135$ Within changes in the transmembrane
- NOTE Confidence: 0.679780554285714
- $00:31:24.135 \longrightarrow 00:31:26.360$ potential and the iron fluxes that
- NOTE Confidence: 0.679780554285714
- $00{:}31{:}26{.}360 \dashrightarrow 00{:}31{:}28{.}426$ occur at the cell membrane and
- NOTE Confidence: 0.679780554285714
- $00:31:28.426 \longrightarrow 00:31:29.872$ these things happen regularly,
- NOTE Confidence: 0.679780554285714
- $00:31:29.872 \rightarrow 00:31:31.924$ you know on timescales of milliseconds,
- NOTE Confidence: 0.679780554285714
- $00:31:31.930 \longrightarrow 00:31:34.270$ seconds to even days.
- NOTE Confidence: 0.679780554285714
- $00:31:34.270 \longrightarrow 00:31:36.610$ But these are inextricably
- NOTE Confidence: 0.679780554285714
- $00:31:36.610 \rightarrow 00:31:38.940$ regulated by catabolism,
- NOTE Confidence: 0.679780554285714
- $00:31:38.940 \longrightarrow 00:31:44.318$ and that is the connection that it is is.
- NOTE Confidence: 0.679780554285714
- $00:31:44.320 \rightarrow 00:31:48.128$ This is needed to find the proper readouts
- NOTE Confidence: 0.679780554285714
- $00{:}31{:}48.128 \dashrightarrow 00{:}31{:}51.237$ of various treatments that we see.
- NOTE Confidence: 0.679780554285714
- $00{:}31{:}51{.}240 \dashrightarrow 00{:}31{:}53{.}544$ And I, I think this is another way of
- NOTE Confidence: 0.679780554285714
- $00:31:53.544 \rightarrow 00:31:55.820$ saying this is that we need advancing
- NOTE Confidence: 0.679780554285714

 $00:31:55.820 \longrightarrow 00:31:57.827$ before imaging methods to assess the

NOTE Confidence: 0.679780554285714

00:31:57.827 --> 00:32:00.206 non genetic by physical aspects of

NOTE Confidence: 0.679780554285714

00:32:00.206 --> 00:32:01.942 tumor microenvironment that regulates

NOTE Confidence: 0.679780554285714

 $00{:}32{:}01{.}942 \dashrightarrow 00{:}32{:}03{.}610$ balance between normal growth

NOTE Confidence: 0.679780554285714

 $00{:}32{:}03.610 \dashrightarrow 00{:}32{:}06.245$ but also the disorganization that

NOTE Confidence: 0.679780554285714

 $00:32:06.245 \rightarrow 00:32:10.800$ happened with most solid solid cancer.

NOTE Confidence: 0.679780554285714

00:32:10.800 --> 00:32:12.250 But importantly,

NOTE Confidence: 0.679780554285714

 $00{:}32{:}12.250 \dashrightarrow 00{:}32{:}15.150$ simultaneous imaging invasion and

NOTE Confidence: 0.679780554285714

 $00{:}32{:}15{.}150 \dashrightarrow 00{:}32{:}18{.}250$ qualification can hold a promise for

NOTE Confidence: 0.679780554285714

 $00:32:18.250 \rightarrow 00:32:20.620$ early cancer diagnosis and tracking

NOTE Confidence: 0.679780554285714

 $00:32:20.711 \rightarrow 00:32:24.978$ therapies. From chemotherapy to two.

NOTE Confidence: 0.679780554285714

 $00:32:24.980 \longrightarrow 00:32:26.668$ There's always grateful for

NOTE Confidence: 0.679780554285714

 $00{:}32{:}26.668 \dashrightarrow 00{:}32{:}29.200$ to night support and this work is

NOTE Confidence: 0.679780554285714

 $00:32:29.277 \rightarrow 00:32:31.457$ unique collaboration among many

NOTE Confidence: 0.679780554285714

 $00:32:31.460 \longrightarrow 00:32:34.760$ colleagues within our group.

NOTE Confidence: 0.679780554285714

00:32:34.760 --> 00:32:38.040 Khan and John Walsh,

- NOTE Confidence: 0.679780554285714
- 00:32:38.040 --> 00:32:38.826 PhD and MD,
- NOTE Confidence: 0.679780554285714
- $00{:}32{:}38{.}826 \dashrightarrow 00{:}32{:}40{.}398$ PhD students are involved in a
- NOTE Confidence: 0.679780554285714
- $00:32:40.398 \longrightarrow 00:32:41.460$ lot of this work,
- NOTE Confidence: 0.679780554285714
- $00:32:41.460 \longrightarrow 00:32:43.135$ but also by colleagues in
- NOTE Confidence: 0.679780554285714
- $00{:}32{:}43.135 \dashrightarrow 00{:}32{:}44.475$ terms of post starts.
- NOTE Confidence: 0.679780554285714
- 00:32:44.480 --> 00:32:45.880 You're still present Doctor
- NOTE Confidence: 0.679780554285714
- $00:32:45.880 \longrightarrow 00:32:47.980$ Kumar Mishra and the high
- NOTE Confidence: 0.679780554285714
- $00:32:48.044 \rightarrow 00:32:50.009$ leverage but also my colleagues.
- NOTE Confidence: 0.599430574285714
- $00:32:52.120 \longrightarrow 00:32:54.205$ Within radiology and
- NOTE Confidence: 0.599430574285714
- $00:32:54.205 \longrightarrow 00:32:56.985$ surgery that department so.
- NOTE Confidence: 0.599430574285714
- 00:32:56.990 --> 00:33:00.770 And I thank you for your.
- NOTE Confidence: 0.599430574285714
- $00{:}33{:}00{.}770 \dashrightarrow 00{:}33{:}01{.}340$ Your attention.
- NOTE Confidence: 0.753175349
- $00:33:02.520 \longrightarrow 00:33:04.820$ Thanks, thanks very much it.
- NOTE Confidence: 0.753175349
- $00{:}33{:}04.820 \dashrightarrow 00{:}33{:}06.480$ I think that was great.
- NOTE Confidence: 0.753175349
- $00:33:06.480 \dashrightarrow 00:33:08.560$ You mentioned chemotherapy and
- NOTE Confidence: 0.753175349

 $00:33:08.560 \rightarrow 00:33:10.013$ immunotherapy, and you know,

NOTE Confidence: 0.753175349

 $00{:}33{:}10.013 \dashrightarrow 00{:}33{:}12.190$ our next talk is from a radiation

NOTE Confidence: 0.753175349

00:33:12.258 --> 00:33:14.796 on cologist and one wonders whether this

NOTE Confidence: 0.753175349

 $00:33:14.796 \rightarrow 00:33:17.425$ might also help identify tumors and

NOTE Confidence: 0.753175349

 $00:33:17.425 \rightarrow 00:33:20.215$ tract tumors that are being irradiated.

NOTE Confidence: 0.753175349

 $00:33:20.220 \longrightarrow 00:33:23.220$ Since, as he well knows,

NOTE Confidence: 0.753175349

 $00:33:23.220 \longrightarrow 00:33:25.638$ it is that his doctor Hanson.

NOTE Confidence: 0.753175349

00:33:25.640 --> 00:33:26.908 It is sometimes confusing

NOTE Confidence: 0.753175349

 $00{:}33{:}26{.}908$ --> $00{:}33{:}28{.}176$ after some one's been treated,

NOTE Confidence: 0.753175349

 $00{:}33{:}28.180 \dashrightarrow 00{:}33{:}31.474$ whether there's active tumor or or not.

NOTE Confidence: 0.753175349

 $00:33:31.474 \longrightarrow 00:33:33.330$ So without further ado.

NOTE Confidence: 0.753175349

00:33:33.330 $\operatorname{-->}$ 00:33:35.880 Guy James Hansen is an associate

NOTE Confidence: 0.753175349

 $00:33:35.880 \rightarrow 00:33:37.580$ professor of the rapeutic radiology

NOTE Confidence: 0.753175349

00:33:37.651 --> 00:33:40.009 and chief of the Gamma Knife

NOTE Confidence: 0.753175349

 $00{:}33{:}40.009 \dashrightarrow 00{:}33{:}41.581$ program in the rapeutic radiology.

NOTE Confidence: 0.753175349

00:33:41.590 - > 00:33:43.780 He received his medical degree

- NOTE Confidence: 0.753175349
- $00{:}33{:}43.780 \dashrightarrow 00{:}33{:}46.522$ from UCLA School of Medicine and

 $00{:}33{:}46{.}522 \dashrightarrow 00{:}33{:}48{.}897$ Masters degree in biochemistry and

NOTE Confidence: 0.753175349

00:33:48.897 --> 00:33:51.470 Molecular Biology at UCLA as well.

NOTE Confidence: 0.753175349

00:33:51.470 --> 00:33:52.192 Doctor Hanson,

NOTE Confidence: 0.753175349

 $00{:}33{:}52{.}192 \dashrightarrow 00{:}33{:}54{.}358$ Clinical area of expertise is gamma

NOTE Confidence: 0.753175349

 $00:33:54.358 \rightarrow 00:33:56.065$ knife stereotactic radio surgery for the

NOTE Confidence: 0.753175349

00:33:56.065 --> 00:33:58.228 premium of CNS tumors had neck tumors,

NOTE Confidence: 0.753175349

00:33:58.230 --> 00:34:00.330 lung cancer as well as lymphoma,

NOTE Confidence: 0.753175349

00:34:00.330 --> 00:34:00.604 skin,

NOTE Confidence: 0.753175349

 $00{:}34{:}00{.}604 \dashrightarrow 00{:}34{:}03{.}070$ GI and GUI will bet that he spends more

NOTE Confidence: 0.753175349

 $00:34:03.132 \longrightarrow 00:34:05.739$ time on CNS disease than other things.

NOTE Confidence: 0.753175349

 $00{:}34{:}05{.}740 \dashrightarrow 00{:}34{:}07{.}948$ But he can tell us his research focus

NOTE Confidence: 0.753175349

 $00:34:07.948 \rightarrow 00:34:09.831$ is studying the interplay between

NOTE Confidence: 0.753175349

 $00{:}34{:}09{.}831 \dashrightarrow 00{:}34{:}11{.}523$ autoimmunity and malignancy and

NOTE Confidence: 0.753175349

 $00{:}34{:}11{.}523$ --> $00{:}34{:}14{.}058$ attempting to harness and optimize select

- $00:34:14.058 \longrightarrow 00:34:16.068$ autoantibodies to use against cancer.
- NOTE Confidence: 0.753175349
- $00{:}34{:}16.070 \dashrightarrow 00{:}34{:}17.642$ James, thanks for.
- NOTE Confidence: 0.753175349
- 00:34:17.642 --> 00:34:18.690 Joining us.
- NOTE Confidence: 0.93134971625
- 00:34:19.310 --> 00:34:20.620 Thank you and thank you
- NOTE Confidence: 0.93134971625
- $00{:}34{:}20.620 \dashrightarrow 00{:}34{:}21.406$ for that introduction.
- NOTE Confidence: 0.93134971625
- $00:34:21.410 \longrightarrow 00:34:23.356$ And yes, if if you can explain
- NOTE Confidence: 0.93134971625
- $00:34:23.356 \longrightarrow 00:34:24.589$ my clinical career to me,
- NOTE Confidence: 0.93134971625
- $00:34:24.590 \longrightarrow 00:34:26.058$ that would be great.
- NOTE Confidence: 0.93134971625
- $00{:}34{:}26.058 \dashrightarrow 00{:}34{:}29.950$ I would love to. But it's hot.
- NOTE Confidence: 0.93134971625
- 00:34:29.950 --> 00:34:31.186 Alright, so let's see,
- NOTE Confidence: 0.93134971625
- 00:34:31.186 --> 00:34:33.630 can you see my slides and hear me?
- NOTE Confidence: 0.75257992375
- $00{:}34{:}33{.}640 \dashrightarrow 00{:}34{:}35{.}090$ Yeah, it's in that presentation
- NOTE Confidence: 0.75257992375
- $00{:}34{:}35{.}090 \dashrightarrow 00{:}34{:}36{.}250$ now that's great. Yeah
- NOTE Confidence: 0.95649372
- $00{:}34{:}36{.}300 \dashrightarrow 00{:}34{:}37{.}724$ alright. Here we go.
- NOTE Confidence: 0.95649372
- 00:34:37.724 --> 00:34:40.180 So I'm gonna be talking today about
- NOTE Confidence: 0.95649372
- 00:34:40.180 --> 00:34:42.900 my particular interest in using

- NOTE Confidence: 0.95649372
- 00:34:42.900 --> 00:34:45.076 lupus antibodies against cancer,
- NOTE Confidence: 0.95649372
- $00{:}34{:}45{.}080 \dashrightarrow 00{:}34{:}48{.}370$ and in this case, how we can may be use lupus
- NOTE Confidence: 0.95649372
- $00{:}34{:}48{.}444 \dashrightarrow 00{:}34{:}51{.}360$ antibodies against brain tumors and so.
- NOTE Confidence: 0.95649372
- 00:34:51.360 --> 00:34:52.752 Already, I probably have lost half
- NOTE Confidence: 0.95649372
- 00:34:52.752 --> 00:34:54.259 of youth that are just saying,
- NOTE Confidence: 0.95649372
- $00:34:54.260 \longrightarrow 00:34:55.616$ well, that's impossible.
- NOTE Confidence: 0.95649372
- $00{:}34{:}55{.}616 \dashrightarrow 00{:}34{:}57{.}424$ Antibodies can't do that.
- NOTE Confidence: 0.95649372
- 00:34:57.430 --> 00:34:58.950 But just give me 20 minutes or so,
- NOTE Confidence: 0.95649372
- $00:34:58.950 \longrightarrow 00:34:59.918$ give me a chance.
- NOTE Confidence: 0.95649372
- 00:34:59.918 --> 00:35:01.370 I I think that there's something
- NOTE Confidence: 0.95649372
- $00:35:01.420 \longrightarrow 00:35:02.970$ here that's worth talking about.
- NOTE Confidence: 0.95649372
- $00:35:02.970 \longrightarrow 00:35:04.150$ Do you have some disclosures?
- NOTE Confidence: 0.95649372
- 00:35:04.150 --> 00:35:05.176 I'm a consultant.
- NOTE Confidence: 0.95649372
- $00{:}35{:}05{.}176 \dashrightarrow 00{:}35{:}06{.}940$ I have grants from inventor
- NOTE Confidence: 0.95649372
- $00:35:06.940 \longrightarrow 00:35:09.280$ on a patent licensed by this
- NOTE Confidence: 0.95649372

00:35:09.280 --> 00:35:11.050 company called Patrys Limited,

NOTE Confidence: 0.95649372

 $00:35:11.050 \rightarrow 00:35:14.067$ who has licensed the DEOXY mab technology.

NOTE Confidence: 0.95649372

 $00:35:14.070 \longrightarrow 00:35:17.166$ So with that said, let's jump head first in.

NOTE Confidence: 0.95649372

 $00:35:17.170 \longrightarrow 00:35:19.165$ I don't think there's any

NOTE Confidence: 0.95649372

00:35:19.165 --> 00:35:20.761 secret that antibodies have

NOTE Confidence: 0.95649372

 $00{:}35{:}20.761 \dashrightarrow 00{:}35{:}22.110$ revolutionized our approaches.

NOTE Confidence: 0.95649372

 $00{:}35{:}22.110 \dashrightarrow 00{:}35{:}24.777$ In modern day two treatment of cancer.

NOTE Confidence: 0.95649372

 $00:35:24.780 \longrightarrow 00:35:26.677$ But I think it's important to recognize

NOTE Confidence: 0.95649372

 $00{:}35{:}26.677 \dashrightarrow 00{:}35{:}28.650$ that all the antibodies that we really

NOTE Confidence: 0.95649372

 $00:35:28.650 \rightarrow 00:35:31.084$ rely on in the clinic right now are

NOTE Confidence: 0.95649372

 $00:35:31.084 \rightarrow 00:35:33.340$ targeted towards extracellular targets.

NOTE Confidence: 0.95649372

 $00{:}35{:}33{.}340 \dashrightarrow 00{:}35{:}35{.}945$ So things like surface receptors

NOTE Confidence: 0.95649372

00:35:35.945 --> 00:35:38.029 or circulating growth factors.

NOTE Confidence: 0.95649372

 $00:35:38.030 \rightarrow 00:35:39.842$ But doggone it seems like there

NOTE Confidence: 0.95649372

 $00:35:39.842 \rightarrow 00:35:41.362$ are so many intracellular antigens

NOTE Confidence: 0.95649372

 $00:35:41.362 \longrightarrow 00:35:43.175$ that if we could just get an

- NOTE Confidence: 0.95649372
- 00:35:43.175 00:35:44.598 antibody in there to engage,

 $00{:}35{:}44.600 \dashrightarrow 00{:}35{:}46.922$ we could add an entire new

NOTE Confidence: 0.95649372

00:35:46.922 --> 00:35:48.083 dimension to immunotherapy.

NOTE Confidence: 0.95649372

 $00:35:48.090 \rightarrow 00:35:50.305$ But the dogma has always

NOTE Confidence: 0.95649372

 $00:35:50.305 \longrightarrow 00:35:52.077$ been that that's impossible.

NOTE Confidence: 0.95649372

 $00:35:52.080 \rightarrow 00:35:55.520$ Antibodies don't penetrate live cells.

NOTE Confidence: 0.95649372

 $00{:}35{:}55{.}520 \dashrightarrow 00{:}35{:}57{.}466$ Now this is where critics will often

NOTE Confidence: 0.95649372

 $00:35:57.466 \dashrightarrow 00:35:59.407$ interrupt me and say that's not true.

NOTE Confidence: 0.95649372

 $00{:}35{:}59{.}410 \dashrightarrow 00{:}36{:}01{.}370$ We have antibodies that are already in

NOTE Confidence: 0.95649372

 $00:36:01.370 \dashrightarrow 00:36:03.120$ clinical use that are internalized.

NOTE Confidence: 0.95649372

 $00:36:03.120 \longrightarrow 00:36:04.095$ What about cats?

NOTE Confidence: 0.95649372

 $00{:}36{:}04.095 \dashrightarrow 00{:}36{:}06.980$ I love the TDM ones and I I would

NOTE Confidence: 0.95649372

00:36:06.980 --> 00:36:08.240 say I say DNA.

NOTE Confidence: 0.95649372

 $00{:}36{:}08{.}240 \dashrightarrow 00{:}36{:}09{.}698$ That's not what I'm talking about.

NOTE Confidence: 0.95649372

 $00{:}36{:}09{.}700 \dashrightarrow 00{:}36{:}12{.}244$ I'm talking about an antibody that can get

 $00:36:12.244 \rightarrow 00:36:15.098$ in and engage its actual native antigen.

NOTE Confidence: 0.95649372

00:36:15.100 --> 00:36:16.584 In these ADC constructs,

NOTE Confidence: 0.95649372

 $00:36:16.584 \longrightarrow 00:36:18.439$ these antibodies are still looking

NOTE Confidence: 0.95649372

 $00{:}36{:}18{.}439 \dashrightarrow 00{:}36{:}20{.}222$ for surface receptors like her

NOTE Confidence: 0.95649372

 $00{:}36{:}20{.}222 \dashrightarrow 00{:}36{:}22{.}462$ two in this example and then the

NOTE Confidence: 0.95649372

 $00{:}36{:}22.462 \dashrightarrow 00{:}36{:}24.226$ antibody gets eaten up and destroyed NOTE Confidence: 0.95649372

 $00{:}36{:}24.226 \dashrightarrow 00{:}36{:}26.222$ in the endosome and lysosome which

NOTE Confidence: 0.95649372

 $00:36:26.222 \rightarrow 00:36:27.554$ is great for this mechanism because

NOTE Confidence: 0.95649372

 $00:36:27.554 \rightarrow 00:36:28.460$ that's what we want,

NOTE Confidence: 0.95649372

 $00:36:28.460 \rightarrow 00:36:30.294$ we want that drug to be released,

NOTE Confidence: 0.95649372

00:36:30.300 --> 00:36:32.508 but that doesn't utilize the exquisite

NOTE Confidence: 0.95649372

 $00:36:32.508 \rightarrow 00:36:34.605$ binding specificity of an antibody

NOTE Confidence: 0.95649372

 $00{:}36{:}34.605 \dashrightarrow 00{:}36{:}36.288$ against intracellular targets.

NOTE Confidence: 0.95649372

 $00:36:36.290 \longrightarrow 00:36:37.844$ So I think we need an antibody

NOTE Confidence: 0.95649372

 $00:36:37.844 \rightarrow 00:36:39.865$ that can get into cells and not get

NOTE Confidence: 0.95649372

 $00:36:39.865 \longrightarrow 00:36:41.571$ stuck in those Endo celebs, but.

- NOTE Confidence: 0.95649372
- $00:36:41.571 \rightarrow 00:36:44.859$ How are we going to do that well?

 $00{:}36{:}44.860 \dashrightarrow 00{:}36{:}46.340$ I guess we could try to invent one.

NOTE Confidence: 0.95649372

 $00:36:46.340 \longrightarrow 00:36:48.746$ We could stick things like cell

NOTE Confidence: 0.95649372

 $00:36:48.746 \rightarrow 00:36:50.350$ penetrating peptides onto antibodies

NOTE Confidence: 0.95649372

 $00:36:50.411 \rightarrow 00:36:52.235$ like that at peptides and such,

NOTE Confidence: 0.95649372

 $00:36:52.240 \longrightarrow 00:36:53.508$ and that's been tried,

NOTE Confidence: 0.95649372

 $00{:}36{:}53{.}508 \dashrightarrow 00{:}36{:}55{.}844$ but those tend to still get stuck

NOTE Confidence: 0.95649372

 $00:36:55.844 \rightarrow 00:36:56.939$ in the endosomes.

NOTE Confidence: 0.95649372

 $00:36:56.940 \dashrightarrow 00:36:59.350$ I guess we could try gene therapy, but boy,

NOTE Confidence: 0.95649372

 $00:36:59.350 \dashrightarrow 00:37:00.880$ that's got all kinds of challenges.

NOTE Confidence: 0.95649372

 $00:37:00.880 \rightarrow 00:37:04.256$ I'm going to leave that to other people.

NOTE Confidence: 0.95649372

 $00{:}37{:}04.260 \dashrightarrow 00{:}37{:}06.332$ Maybe if we can just find a naturally

NOTE Confidence: 0.95649372

 $00:37:06.332 \rightarrow 00:37:07.366$ occurring antibody that penetrates

NOTE Confidence: 0.95649372

 $00{:}37{:}07{.}366 \dashrightarrow 00{:}37{:}09{.}246$ cells and use that as a platform to

NOTE Confidence: 0.95649372

 $00:37:09.300 \dashrightarrow 00:37:11.148$ teach us how to invent these antibodies,

 $00:37:11.150 \longrightarrow 00:37:14.055$ that seems the most appealing to me.

NOTE Confidence: 0.95649372

00:37:14.060 --> 00:37:16.860 But any
body have any idea where we're

NOTE Confidence: 0.95649372

 $00:37:16.860 \dashrightarrow 00:37:20.256$ going to find an antibody like that well? NOTE Confidence: 0.95649372

10112 Confidence: 0.55045512

 $00{:}37{:}20.260 \dashrightarrow 00{:}37{:}22.488$ How about in lupus?

NOTE Confidence: 0.95649372

 $00:37:22.488 \rightarrow 00:37:24.159$ Systemic lupus erythematous?

NOTE Confidence: 0.95649372

 $00{:}37{:}24.160 \dashrightarrow 00{:}37{:}26.620$ It is the prototype autoimmune disease.

NOTE Confidence: 0.95649372

00:37:26.620 --> 00:37:28.684 Patients suffer wides
pread tissue

NOTE Confidence: 0.95649372

 $00{:}37{:}28.684 \dashrightarrow 00{:}37{:}30.232$ destruction and inflammation

NOTE Confidence: 0.95649372

 $00{:}37{:}30{.}232 \dashrightarrow 00{:}37{:}31{.}780$ as their immune

NOTE Confidence: 0.936914994705882

00:37:31.847 - 00:37:33.149 systems recognize their

NOTE Confidence: 0.936914994705882

 $00{:}37{:}33.149 \dashrightarrow 00{:}37{:}34.885$ own cells and tissues.

NOTE Confidence: 0.936914994705882

 $00{:}37{:}34.890 \dashrightarrow 00{:}37{:}36.948$ And one of the laboratory hallmarks of

NOTE Confidence: 0.936914994705882

 $00:37:36.948 \rightarrow 00:37:39.194$ lupus is the presence of circulating

NOTE Confidence: 0.936914994705882

 $00{:}37{:}39{.}194 \dashrightarrow 00{:}37{:}40{.}934$ autoantibodies that are reactive

NOTE Confidence: 0.936914994705882

 $00:37:40.934 \rightarrow 00:37:44.108$ against the patient's own DNA.

NOTE Confidence: 0.936914994705882

 $00:37:44.110 \longrightarrow 00:37:46.280$ Now those antibodies are a big mystery.

- NOTE Confidence: 0.936914994705882
- $00:37:46.280 \longrightarrow 00:37:48.261$ We still don't know exactly how they
- NOTE Confidence: 0.936914994705882
- $00:37:48.261 \rightarrow 00:37:49.980$ contribute to lupus pathophysiology,
- NOTE Confidence: 0.936914994705882
- $00:37:49.980 \longrightarrow 00:37:53.004$ but remarkably it is now finally
- NOTE Confidence: 0.936914994705882
- $00:37:53.004 \rightarrow 00:37:55.018$ accepted that a small percentage
- NOTE Confidence: 0.936914994705882
- $00:37:55.018 \rightarrow 00:37:57.280$ of them actually have the ability
- NOTE Confidence: 0.936914994705882
- $00{:}37{:}57{.}354 \dashrightarrow 00{:}37{:}59{.}439$ to cross through membranes and
- NOTE Confidence: 0.936914994705882
- $00:37:59.439 \dashrightarrow 00:38:01.524$ penetrate into live cell nuclei.
- NOTE Confidence: 0.936914994705882
- $00:38:01.530 \rightarrow 00:38:02.906$ Well, hey, so there we have it right.
- NOTE Confidence: 0.936914994705882
- $00:38:02.910 \longrightarrow 00:38:04.896$ We have a source of naturally
- NOTE Confidence: 0.936914994705882
- 00:38:04.896 --> 00:38:06.220 occurring cell penetrating antibodies.
- NOTE Confidence: 0.936914994705882
- $00:38:06.220 \rightarrow 00:38:08.002$ We can use those for all kinds of therapies,
- NOTE Confidence: 0.936914994705882
- 00:38:08.010 --> 00:38:08.438 right?
- NOTE Confidence: 0.936914994705882
- $00{:}38{:}08{.}438 \dashrightarrow 00{:}38{:}10{.}578$ Well, hold on now every body
- NOTE Confidence: 0.936914994705882
- $00:38:10.578 \dashrightarrow 00:38:12.790$ we're talking about Lupus right?
- NOTE Confidence: 0.936914994705882
- 00:38:12.790 --> 00:38:15.163 At last I checked Lupus is still
- NOTE Confidence: 0.936914994705882

 $00{:}38{:}15{.}163 \dashrightarrow 00{:}38{:}17{.}158$ in the textbooks as a disease.

NOTE Confidence: 0.936914994705882

00:38:17.160 --> 00:38:17.822 And indeed,

NOTE Confidence: 0.936914994705882

 $00:38:17.822 \rightarrow 00:38:20.139$ a lot of these cell penetrating lupus

NOTE Confidence: 0.936914994705882

00:38:20.139 --> 00:38:21.919 autoantibodies are just broadly cytotoxic.

NOTE Confidence: 0.936914994705882

 $00:38:21.920 \longrightarrow 00:38:23.630$ And there there wouldn't be any

NOTE Confidence: 0.936914994705882

 $00:38:23.630 \rightarrow 00:38:25.508$ benefit to giving them to a patient.

NOTE Confidence: 0.936914994705882

00:38:25.510 --> 00:38:26.158 But thankfully,

NOTE Confidence: 0.936914994705882

 $00:38:26.158 \longrightarrow 00:38:28.426$ that's not true for all of them.

NOTE Confidence: 0.936914994705882

 $00:38:28.430 \longrightarrow 00:38:30.690$ There's an antibody called 310,

NOTE Confidence: 0.936914994705882

 $00:38:30.690 \rightarrow 00:38:32.846$ which is the hero of this story.

NOTE Confidence: 0.936914994705882

 $00:38:32.850 \longrightarrow 00:38:34.392$ It was discovered in the early

NOTE Confidence: 0.936914994705882

00:38:34.392 --> 00:38:36.157 1990s at UCLA by Richard Weisbart

NOTE Confidence: 0.936914994705882

 $00{:}38{:}36{.}157 \dashrightarrow 00{:}38{:}38{.}203$ who's pictured there at the left,

NOTE Confidence: 0.936914994705882

 $00{:}38{:}38{.}210 \dashrightarrow 00{:}38{:}40{.}156$ along with his technician Grace Chan and

NOTE Confidence: 0.936914994705882

 $00{:}38{:}40{.}156 \dashrightarrow 00{:}38{:}41{.}829$ his great colleague Robert Nishimura.

NOTE Confidence: 0.936914994705882

 $00:38:41.830 \longrightarrow 00:38:42.852$ Their great,

- NOTE Confidence: 0.936914994705882
- $00:38:42.852 \rightarrow 00:38:44.896$ great friends and colleagues.
- NOTE Confidence: 0.936914994705882
- $00{:}38{:}44{.}900 \dashrightarrow 00{:}38{:}47{.}609$ What makes 310 so remarkable is that
- NOTE Confidence: 0.936914994705882
- $00:38:47.609 \dashrightarrow 00:38:50.269$ it was isolated from a lupus mouse.
- NOTE Confidence: 0.936914994705882
- $00:38:50.270 \rightarrow 00:38:51.914$ It penetrates extremely effectively
- NOTE Confidence: 0.936914994705882
- $00:38:51.914 \rightarrow 00:38:54.780$ specifically into the nucleus of live cells,
- NOTE Confidence: 0.936914994705882
- $00:38:54.780 \dashrightarrow 00:38:56.860$ and so it does not go through endosomes,
- NOTE Confidence: 0.936914994705882
- $00:38:56.860 \longrightarrow 00:38:59.420$ and it does not kill or is not
- NOTE Confidence: 0.936914994705882
- $00:38:59.420 \longrightarrow 00:39:02.118$ toxic in any way to normal cells.
- NOTE Confidence: 0.936914994705882
- 00:39:02.120 -> 00:39:03.740 So now we've got our chance.
- NOTE Confidence: 0.936914994705882
- $00:39:03.740 \longrightarrow 00:39:06.588$ Now we have an opportunity to use a
- NOTE Confidence: 0.936914994705882
- $00:39:06.588 \rightarrow 00:39:08.850$ platform antibody that penetrates cells.
- NOTE Confidence: 0.936914994705882
- $00{:}39{:}08.850 \dashrightarrow 00{:}39{:}10.068$ And in fact,
- NOTE Confidence: 0.936914994705882
- $00{:}39{:}10.068 \dashrightarrow 00{:}39{:}12.950$ as we dive a little deeper into
- NOTE Confidence: 0.936914994705882
- $00:39{:}12.950 \dashrightarrow 00{:}39{:}15.150$ how this antibody really works,
- NOTE Confidence: 0.936914994705882
- $00{:}39{:}15{.}150 \dashrightarrow 00{:}39{:}17{.}418$ it turns out this antibody is really
- NOTE Confidence: 0.936914994705882

 $00:39:17.418 \rightarrow 00:39:19.189$ well situated for targeting things

NOTE Confidence: 0.936914994705882

00:39:19.189 --> 00:39:21.758 like tumors or sites of tissue damage.

NOTE Confidence: 0.936914994705882

 $00:39:21.760 \longrightarrow 00:39:24.518$ And that is because part of its

NOTE Confidence: 0.936914994705882

 $00:39:24.518 \rightarrow 00:39:26.658$ mechanism of penetration is dependent

NOTE Confidence: 0.936914994705882

 $00:39:26.658 \longrightarrow 00:39:28.430$ on presence of extracellular

NOTE Confidence: 0.936914994705882

 $00{:}39{:}28{.}430 \dashrightarrow 00{:}39{:}30{.}909$ DNA or nucleosides in the area.

NOTE Confidence: 0.936914994705882

 $00:39:30.910 \dashrightarrow 00:39:32.464$ So what we're showing on the left

NOTE Confidence: 0.936914994705882

 $00:39:32.464 \rightarrow 00:39:33.781$ here is something we call the

NOTE Confidence: 0.936914994705882

00:39:33.781 - > 00:39:35.181 three E 10 bullseye effect of the.

NOTE Confidence: 0.936914994705882

 $00{:}39{:}35{.}190 \dashrightarrow 00{:}39{:}36{.}765$ The dark stain represents where

NOTE Confidence: 0.936914994705882

00:39:36.765 - 00:39:38.702 the antibody is, and as you see,

NOTE Confidence: 0.936914994705882

 $00:39:38.702 \rightarrow 00:39:40.190$ that dark stain is getting lighter

NOTE Confidence: 0.936914994705882

 $00:39:40.240 \longrightarrow 00:39:41.758$ and lighter as you get further

NOTE Confidence: 0.936914994705882

 $00:39:41.758 \longrightarrow 00:39:42.770$ out from the center,

NOTE Confidence: 0.936914994705882

 $00{:}39{:}42.770 \dashrightarrow 00{:}39{:}44.040$ and that's because there's a

NOTE Confidence: 0.936914994705882

 $00:39:44.040 \longrightarrow 00:39:45.710$ dead cell there in the middle.

- NOTE Confidence: 0.936914994705882
- $00:39:45.710 \dashrightarrow 00:39:47.432$ And it's releasing DNA into its
- NOTE Confidence: 0.936914994705882
- $00:39:47.432 \rightarrow 00:39:48.909$ surroundings and helping the antibody
- NOTE Confidence: 0.936914994705882
- $00:39:48.909 \longrightarrow 00:39:50.547$ penetrate the live cells that are
- NOTE Confidence: 0.936914994705882
- $00:39:50.547 \rightarrow 00:39:52.450$ closest to it, but less effective.
- NOTE Confidence: 0.936914994705882
- $00:39:52.450 \longrightarrow 00:39:54.250$ As we get further out.
- NOTE Confidence: 0.936914994705882
- $00{:}39{:}54{.}250 \dashrightarrow 00{:}39{:}56{.}058$ And in the middle we showed we can
- NOTE Confidence: 0.936914994705882
- $00:39:56.058 \rightarrow 00:39:57.293$ reproduce this in the laboratory
- NOTE Confidence: 0.936914994705882
- $00:39:57.293 \rightarrow 00:39:59.001$ just by adding DNA to the antibody.
- NOTE Confidence: 0.936914994705882
- $00{:}39{:}59{.}010 \dashrightarrow 00{:}40{:}01{.}490$ At the bottom we allow the antibody to
- NOTE Confidence: 0.936914994705882
- $00:40:01.490 \longrightarrow 00:40:03.370$ penetrate 100% of the cells in the culture,
- NOTE Confidence: 0.936914994705882
- $00:40:03.370 \longrightarrow 00:40:05.925$ so the DNA has to be there.
- NOTE Confidence: 0.936914994705882
- $00:40:05.930 \longrightarrow 00:40:07.736$ And then if you take this antibody
- NOTE Confidence: 0.936914994705882
- $00{:}40{:}07{.}736 \dashrightarrow 00{:}40{:}10{.}117$ to mice and you give it to mice that
- NOTE Confidence: 0.936914994705882
- $00{:}40{:}10.117 \dashrightarrow 00{:}40{:}11.770$ don't have any tumors or damage,
- NOTE Confidence: 0.936914994705882
- $00:40:11.770 \longrightarrow 00:40:14.212$ you don't see the antibody really
- NOTE Confidence: 0.936914994705882

- $00:40:14.212 \longrightarrow 00:40:15.026$ going anywhere.
- NOTE Confidence: 0.936914994705882
- $00{:}40{:}15{.}030 \dashrightarrow 00{:}40{:}17{.}270$ But if you give it to a mouse with a
- NOTE Confidence: 0.912835737222222
- $00:40:17.332 \rightarrow 00:40:20.068$ tumor that is necrotic and is releasing DNA,
- NOTE Confidence: 0.912835737222222
- 00:40:20.070 --> 00:40:21.335 you do see the antibody
- NOTE Confidence: 0.912835737222222
- $00:40:21.335 \longrightarrow 00:40:22.347$ localising to that tumor.
- NOTE Confidence: 0.912835737222222
- $00:40:22.350 \rightarrow 00:40:23.617$ That's what's shown in the top right.
- NOTE Confidence: 0.912835737222222
- $00{:}40{:}23.620 \dashrightarrow 00{:}40{:}26.230$ The brown stain are the nuclei
- NOTE Confidence: 0.912835737222222
- $00:40:26.230 \longrightarrow 00:40:27.970$ penetrated by this antibody.
- NOTE Confidence: 0.912835737222222
- $00:40:27.970 \longrightarrow 00:40:29.730$ So what on Earth is going on here?
- NOTE Confidence: 0.912835737222222
- $00:40:29.730 \longrightarrow 00:40:31.585$ Why is this antibody using
- NOTE Confidence: 0.912835737222222
- $00:40:31.585 \longrightarrow 00:40:33.069$ DNA to penetrate cells?
- NOTE Confidence: 0.912835737222222
- $00:40:33.070 \longrightarrow 00:40:34.030$ How is it doing that?
- NOTE Confidence: 0.912835737222222
- $00{:}40{:}34.030 \dashrightarrow 00{:}40{:}35.862$ Well, that's a little bit of a longer
- NOTE Confidence: 0.912835737222222
- $00{:}40{:}35.862 \dashrightarrow 00{:}40{:}37.466$ story than we have time for today,
- NOTE Confidence: 0.912835737222222
- 00:40:37.470 --> 00:40:39.710 but just to jump to the punch line,
- NOTE Confidence: 0.912835737222222
- $00:40:39.710 \longrightarrow 00:40:42.134$ it is using a specific nucleoside

- NOTE Confidence: 0.912835737222222
- 00:40:42.134 --> 00:40:44.549 salvage pathway to get into live

 $00{:}40{:}44{.}549 \dashrightarrow 00{:}40{:}46{.}510$ cells that are salvaging DNA and

NOTE Confidence: 0.912835737222222

 $00:40:46.510 \rightarrow 00:40:47.790$ nucleosides from their surroundings,

NOTE Confidence: 0.912835737222222

 $00:40:47.790 \rightarrow 00:40:50.764$ and that transporter is called ENT two.

NOTE Confidence: 0.912835737222222

 $00{:}40{:}50.764 \dashrightarrow 00{:}40{:}53.026$ It is my best friend transporter

NOTE Confidence: 0.912835737222222

 $00:40:53.026 \longrightarrow 00:40:56.259$ in the whole world stands for

NOTE Confidence: 0.912835737222222

 $00:40:56.259 \rightarrow 00:40:58.655$ equilibrated Nucleoside transporter 2.

NOTE Confidence: 0.912835737222222

 $00:40:58.660 \longrightarrow 00:41:00.940$ So in order for 3:10 to cross membranes

NOTE Confidence: 0.912835737222222

 $00:41:00.940 \longrightarrow 00:41:02.779$ to penetrate into cells and nuclei,

NOTE Confidence: 0.912835737222222

 $00:41:02.780 \longrightarrow 00:41:04.736$ you have to have two things.

NOTE Confidence: 0.912835737222222

 $00{:}41{:}04{.}740 \dashrightarrow 00{:}41{:}07{.}829$ The cell has to express ENT two and

NOTE Confidence: 0.912835737222222

 $00{:}41{:}07{.}829 \dashrightarrow 00{:}41{:}10{.}272$ there has to be DNA or nucleosides

NOTE Confidence: 0.912835737222222

 $00:41:10.272 \longrightarrow 00:41:12.816$ around that cell so that the antibody

NOTE Confidence: 0.912835737222222

 $00{:}41{:}12.816 \dashrightarrow 00{:}41{:}15.492$ can bind to the nucleosides and then

NOTE Confidence: 0.912835737222222

 $00{:}41{:}15{.}492 \dashrightarrow 00{:}41{:}18{.}364$ follow them through ENT 2 into the cell.

 $00:41:18.370 \rightarrow 00:41:20.290$ And that's why the antibody likes

NOTE Confidence: 0.912835737222222

00:41:20.290 --> 00:41:21.250 to preferentially accumulate

NOTE Confidence: 0.912835737222222

00:41:21.250 --> 00:41:22.810 in vivo insights of damage,

NOTE Confidence: 0.912835737222222

 $00:41:22.810 \rightarrow 00:41:26.044$ like tumors where DNA is being released

NOTE Confidence: 0.912835737222222

 $00{:}41{:}26.050 \dashrightarrow 00{:}41{:}28.354$ and ENT two is salvaging salvaging

NOTE Confidence: 0.912835737222222

 $00:41:28.354 \rightarrow 00:41:31.228$ the DNA and along with it the 3:10.

NOTE Confidence: 0.912835737222222

00:41:31.230 --> 00:41:33.150 Networks for injury sites as well,

NOTE Confidence: 0.912835737222222

 $00{:}41{:}33{.}150 \dashrightarrow 00{:}41{:}35{.}300$ and that's what we've seen

NOTE Confidence: 0.912835737222222

 $00:41:35.300 \longrightarrow 00:41:36.590$ in multiple studies.

NOTE Confidence: 0.912835737222222

 $00:41:36.590 \rightarrow 00:41:37.314$ For example,

NOTE Confidence: 0.912835737222222

 $00:41:37.314 \longrightarrow 00:41:39.124$ moving from left to right,

NOTE Confidence: 0.912835737222222

 $00{:}41{:}39{.}130 \dashrightarrow 00{:}41{:}41{.}875$ if you take the three E 10 antibody and

NOTE Confidence: 0.912835737222222

 $00{:}41{:}41{.}875 \dashrightarrow 00{:}41{:}44{.}524$ you link it to a heat shock protein.

NOTE Confidence: 0.912835737222222

 $00:41:44.530 \rightarrow 00:41:46.930$ And then give it to mice or rats.

NOTE Confidence: 0.912835737222222

 $00:41:46.930 \longrightarrow 00:41:48.350$ Actually that have had strokes.

NOTE Confidence: 0.912835737222222

 $00:41:48.350 \rightarrow 00:41:50.366$ You find the antibody gets the heat

 $00{:}41{:}50{.}366 \dashrightarrow 00{:}41{:}52{.}778$ shock protein into the ischemic brain and

NOTE Confidence: 0.912835737222222

00:41:52.778 --> 00:41:55.418 improves neurologic function and recovery.

NOTE Confidence: 0.912835737222222

 $00:41:55.420 \rightarrow 00:41:57.676$ In the middle here we're showing

NOTE Confidence: 0.912835737222222

 $00{:}41{:}57.676 \dashrightarrow 00{:}41{:}59.180$ heart attacks in rabbits.

NOTE Confidence: 0.912835737222222

 $00:41:59.180 \longrightarrow 00:42:00.896$ The 3:10 antibody finds the site

NOTE Confidence: 0.912835737222222

 $00{:}42{:}00{.}896 \dashrightarrow 00{:}42{:}02{.}758$ of the heart attack and delivers

NOTE Confidence: 0.912835737222222

 $00:42:02.758 \longrightarrow 00:42:04.078$ the heat shock protein.

NOTE Confidence: 0.912835737222222

 $00:42:04.080 \longrightarrow 00:42:05.240$ It works remarkably well.

NOTE Confidence: 0.912835737222222

 $00{:}42{:}05{.}240 \dashrightarrow 00{:}42{:}07{.}550$ And on the right we're looking at tumors.

NOTE Confidence: 0.912835737222222

00:42:07.550 --> 00:42:09.797 You take the antibody and you fuse it to P53.

NOTE Confidence: 0.912835737222222

 $00:42:09.797 \longrightarrow 00:42:11.699$ That protein from long time ago

NOTE Confidence: 0.912835737222222

 $00{:}42{:}11.699 \dashrightarrow 00{:}42{:}13.399$ and it absolutely localizes the

NOTE Confidence: 0.912835737222222

 $00{:}42{:}13.399 \dashrightarrow 00{:}42{:}15.119$ tumors and shuts them down.

NOTE Confidence: 0.912835737222222

 $00{:}42{:}15{.}120 \dashrightarrow 00{:}42{:}18{.}336$ So 310 has great potential as a delivery

NOTE Confidence: 0.912835737222222

 $00{:}42{:}18.336 \dashrightarrow 00{:}42{:}21.236$ vehicle for tumors or sites of damage,

 $00:42:21.240 \longrightarrow 00:42:23.525$ and there's now more companies

NOTE Confidence: 0.912835737222222

 $00{:}42{:}23.525 \dashrightarrow 00{:}42{:}27.190$ looking at this than I can even count.

NOTE Confidence: 0.912835737222222

 $00:42:27.190 \rightarrow 00:42:29.227$ But that's not all the antibody does.

NOTE Confidence: 0.912835737222222

 $00:42:29.230 \longrightarrow 00:42:30.847$ It turns out that it does more.

NOTE Confidence: 0.912835737222222

 $00:42:30.850 \longrightarrow 00:42:33.796$ It's not just a delivery agent.

NOTE Confidence: 0.912835737222222

 $00{:}42{:}33{.}800 \dashrightarrow 00{:}42{:}35{.}618$ When the antibody penetrates into the

NOTE Confidence: 0.912835737222222

00:42:35.618 --> 00:42:38.110 nucleus of a cell, it will bind DNA.

NOTE Confidence: 0.912835737222222

00:42:38.110 --> 00:42:40.030 But if it has its choice,

NOTE Confidence: 0.912835737222222

 $00:42:40.030 \longrightarrow 00:42:41.730$ it will preferentially bind

NOTE Confidence: 0.912835737222222

 $00{:}42{:}41.730 \dashrightarrow 00{:}42{:}43.430$ a DNA that's broken.

NOTE Confidence: 0.912835737222222

 $00{:}42{:}43{.}430 \dashrightarrow 00{:}42{:}44{.}982$ And then it's going to mess around with

NOTE Confidence: 0.912835737222222

00:42:44.982 --> 00:42:46.468 DNA repair so it blocks base excision,

NOTE Confidence: 0.912835737222222

00:42:46.470 --> 00:42:46.955 repair,

NOTE Confidence: 0.912835737222222

 $00{:}42{:}46.955 \dashrightarrow 00{:}42{:}49.865$ and rad 51 mediated molega's recombination.

NOTE Confidence: 0.912835737222222

 $00{:}42{:}49.870 \dashrightarrow 00{:}42{:}52.124$ And that means it can make cancer

NOTE Confidence: 0.912835737222222

 $00:42:52.124 \rightarrow 00:42:54.026$ cells more sensitive to DNA

 $00:42:54.026 \longrightarrow 00:42:55.774$ damaging therapy like certain

NOTE Confidence: 0.912835737222222

 $00:42:55.774 \longrightarrow 00:42:57.085$ chemotherapies and radiation.

NOTE Confidence: 0.912835737222222

00:42:57.090 --> 00:42:58.746 But even more significantly,

NOTE Confidence: 0.912835737222222

 $00{:}42{:}58.746 \dashrightarrow 00{:}43{:}02.610$ if the cancer cell or the tumor has a

NOTE Confidence: 0.912835737222222

 $00:43:02.610 \longrightarrow 00:43:05.136$ pre-existing defect in DNA repair due

NOTE Confidence: 0.912835737222222

 $00{:}43{:}05{.}136 \dashrightarrow 00{:}43{:}08{.}430$ to a mutation such as Bracco or P-10 loss.

NOTE Confidence: 0.912835737222222

 $00:43:08.430 \longrightarrow 00:43:10.030$ The antibody doesn't need radiation.

NOTE Confidence: 0.934912074166667

 $00{:}43{:}10.030 \dashrightarrow 00{:}43{:}11.294$ It doesn't need chemotherapy.

NOTE Confidence: 0.934912074166667

 $00:43:11.294 \longrightarrow 00:43:13.190$ It will kill that cancer cell

NOTE Confidence: 0.934912074166667

 $00:43:13.247 \rightarrow 00:43:14.981$ by itself by causing persistence

NOTE Confidence: 0.934912074166667

00:43:14.981 --> 00:43:17.066 of DNA double strand breaks,

NOTE Confidence: 0.934912074166667

 $00{:}43{:}17.070 \dashrightarrow 00{:}43{:}18.804$ but that doesn't happen in normal

NOTE Confidence: 0.934912074166667

 $00{:}43{:}18.804 \dashrightarrow 00{:}43{:}20.589$ cells that have intact DNA repair,

NOTE Confidence: 0.934912074166667

 $00{:}43{:}20.590 \dashrightarrow 00{:}43{:}23.500$ so we have a selective toxicity.

NOTE Confidence: 0.934912074166667

 $00{:}43{:}23.500 \dashrightarrow 00{:}43{:}27.777$ 4HR deficient tumor cells with this antibody.

 $00:43:27.780 \longrightarrow 00:43:31.540$ So we reported that quite a while ago,

NOTE Confidence: 0.934912074166667

 $00{:}43{:}31{.}540 \dashrightarrow 00{:}43{:}33{.}016$ and then we asked the question,

NOTE Confidence: 0.934912074166667

00:43:33.020 --> 00:43:34.088 is it just 310?

NOTE Confidence: 0.934912074166667

 $00:43:34.088 \rightarrow 00:43:35.690$ Is this just something magic about

NOTE Confidence: 0.934912074166667

 $00:43:35.753 \longrightarrow 00:43:37.356$ 3:10 or is this true for other

NOTE Confidence: 0.934912074166667

 $00:43:37.360 \longrightarrow 00:43:38.503$ cell penetrating antibodies?

NOTE Confidence: 0.934912074166667

 $00{:}43{:}38{.}503 \dashrightarrow 00{:}43{:}40{.}408$ And it turns out indeed

NOTE Confidence: 0.934912074166667

 $00:43:40.408 \longrightarrow 00:43:42.180$ it's not just three ten.

NOTE Confidence: 0.934912074166667

 $00:43:42.180 \longrightarrow 00:43:43.572$ There are antibodies that

NOTE Confidence: 0.934912074166667

 $00{:}43{:}43{.}572 \dashrightarrow 00{:}43{:}45{.}660$ penetrate cells and cut DNA and

NOTE Confidence: 0.934912074166667

 $00{:}43{:}45{.}721 \dashrightarrow 00{:}43{:}47{.}426$ kill the HR deficient cells.

NOTE Confidence: 0.934912074166667

00:43:47.430 --> 00:43:49.680 So there's a pattern emerging here

NOTE Confidence: 0.934912074166667

 $00:43:49.680 \rightarrow 00:43:51.564$ where lupus antibodies some lupus

NOTE Confidence: 0.934912074166667

 $00{:}43{:}51{.}564 \dashrightarrow 00{:}43{:}53{.}472$ anti DNA antibodies seem to be

NOTE Confidence: 0.934912074166667

 $00:43:53.472 \rightarrow 00:43:56.410$ toxic to HR deficient cancer cells,

NOTE Confidence: 0.934912074166667

 $00:43:56.410 \longrightarrow 00:43:58.466$ and so then that led us to start
- NOTE Confidence: 0.934912074166667
- $00:43:58.466 \rightarrow 00:43:59.980$ asking some questions about.
- NOTE Confidence: 0.934912074166667
- $00:43:59.980 \longrightarrow 00:44:01.582$ What does this mean for lupus
- NOTE Confidence: 0.934912074166667
- 00:44:01.582 --> 00:44:03.199 and and cancer risk in lupus?
- NOTE Confidence: 0.934912074166667
- 00:44:03.200 --> 00:44:05.500 And I'm not a rheumatologist.
- NOTE Confidence: 0.934912074166667
- 00:44:05.500 --> 00:44:06.668 I did not know,
- NOTE Confidence: 0.934912074166667
- 00:44:06.668 --> 00:44:08.420 but we started reading and looking.
- NOTE Confidence: 0.934912074166667
- $00:44:08.420 \longrightarrow 00:44:09.614$ And overall,
- NOTE Confidence: 0.934912074166667
- 00:44:09.614 --> 00:44:13.196 cancer risk is increased in lupus,
- NOTE Confidence: 0.934912074166667
- $00:44:13.200 \longrightarrow 00:44:15.340$ but it's driven mostly by
- NOTE Confidence: 0.934912074166667
- 00:44:15.340 --> 00:44:16.196 haematological legacy.
- NOTE Confidence: 0.934912074166667
- 00:44:16.200 --> 00:44:18.215 So if you back up and you say, well,
- NOTE Confidence: 0.934912074166667
- 00:44:18.215 --> 00:44:20.420 let's go tumor type by tumor type,
- NOTE Confidence: 0.934912074166667
- $00:44:20.420 \longrightarrow 00:44:22.598$ you get a surprising finding in
- NOTE Confidence: 0.934912074166667
- $00{:}44{:}22.598 \dashrightarrow 00{:}44{:}24.743$ that breast cancer occurs at a
- NOTE Confidence: 0.934912074166667
- $00{:}44{:}24.743 \dashrightarrow 00{:}44{:}26.609$ lower than expected rate in lupus.
- NOTE Confidence: 0.934912074166667

 $00:44:26.610 \longrightarrow 00:44:28.290$ And this has been widely recognized

NOTE Confidence: 0.934912074166667

 $00:44:28.290 \longrightarrow 00:44:28.850$ for years,

NOTE Confidence: 0.934912074166667

 $00{:}44{:}28.850 \dashrightarrow 00{:}44{:}30.370$ but no one can figure out exactly why.

NOTE Confidence: 0.934912074166667

 $00:44:30.370 \rightarrow 00:44:33.540$ There's no clear associating factor.

NOTE Confidence: 0.934912074166667

 $00:44:33.540 \longrightarrow 00:44:34.758$ But if you look a little deeper,

NOTE Confidence: 0.934912074166667

 $00:44:34.760 \longrightarrow 00:44:36.590$ it looks like it's the triple

NOTE Confidence: 0.934912074166667

 $00{:}44{:}36{.}590 \dashrightarrow 00{:}44{:}38{.}249$ negative breast cancer that is

NOTE Confidence: 0.934912074166667

 $00:44:38.249 \rightarrow 00:44:39.789$ specifically suppressed in lupus.

NOTE Confidence: 0.934912074166667

 $00:44:39.790 \longrightarrow 00:44:41.939$ And we do know that triple negative

NOTE Confidence: 0.934912074166667

 $00{:}44{:}41{.}939 \dashrightarrow 00{:}44{:}44{.}131$ breast cancer is associated with the

NOTE Confidence: 0.934912074166667

 $00:44:44.131 \rightarrow 00:44:46.537$ braknis phenotypes and the HR deficiency.

NOTE Confidence: 0.934912074166667

 $00:44:46.540 \longrightarrow 00:44:48.016$ So then we start to think,

NOTE Confidence: 0.934912074166667

00:44:48.020 --> 00:44:49.940 well, if that's true, like why?

NOTE Confidence: 0.934912074166667

 $00{:}44{:}49{.}940 \dashrightarrow 00{:}44{:}51{.}986$ Why aren't lupus patients making these

NOTE Confidence: 0.934912074166667

 $00:44:51.986 \rightarrow 00:44:53.800$ triple negative breast cancers as much?

NOTE Confidence: 0.934912074166667

 $00:44:53.800 \rightarrow 00:44:54.062$ Well,

- NOTE Confidence: 0.934912074166667
- $00:44:54.062 \rightarrow 00:44:55.634$ we know about these DNA damaging
- NOTE Confidence: 0.934912074166667
- $00:44:55.634 \rightarrow 00:44:56.743$ autoantibodies that are killing
- NOTE Confidence: 0.934912074166667
- $00:44:56.743 \longrightarrow 00:44:57.859$ these HR deficient cells.
- NOTE Confidence: 0.934912074166667
- $00:44:57.860 \longrightarrow 00:44:59.816$ Is it possible that lupus anti
- NOTE Confidence: 0.934912074166667
- $00:44:59.816 \longrightarrow 00:45:01.120$ DNA antibodies actually are
- NOTE Confidence: 0.934912074166667
- $00:45:01.182 \rightarrow 00:45:03.038$ protective against breast cancer?
- NOTE Confidence: 0.934912074166667
- 00:45:03.040 --> 00:45:03.808 And if so,
- NOTE Confidence: 0.934912074166667
- 00:45:03.808 00:45:05.344 maybe we can re engineer them
- NOTE Confidence: 0.934912074166667
- $00:45:05.344 \longrightarrow 00:45:07.259$ and use them to treat triple
- NOTE Confidence: 0.934912074166667
- $00:45:07.259 \rightarrow 00:45:08.859$ negative breast cancer and so?
- NOTE Confidence: 0.934912074166667
- $00:45:08.860 \longrightarrow 00:45:09.848$ We're excited about this.
- NOTE Confidence: 0.934912074166667
- $00{:}45{:}09{.}848 \dashrightarrow 00{:}45{:}12{.}210$ We sent it in as an opinion letter.
- NOTE Confidence: 0.934912074166667
- 00:45:12.210 --> 00:45:13.986 I thought I was extremely clever.
- NOTE Confidence: 0.934912074166667
- $00{:}45{:}13.990 \dashrightarrow 00{:}45{:}15.260$ I was very impressed with
- NOTE Confidence: 0.934912074166667
- $00:45:15.260 \longrightarrow 00:45:16.530$ myself when I called it.
- NOTE Confidence: 0.934912074166667

 $00:45:16.530 \rightarrow 00:45:18.306$ The lupus butterfly effect,

NOTE Confidence: 0.934912074166667

00:45:18.306 --> 00:45:21.430 because lupus is the symbol of that.

NOTE Confidence: 0.934912074166667

 $00:45:21.430 \rightarrow 00:45:23.886$ Sorry, the butterfly is a symbol of lupus.

NOTE Confidence: 0.934912074166667

 $00:45:23.890 \rightarrow 00:45:25.810$ The butterfly effect is a symbol of chaos.

NOTE Confidence: 0.934912074166667

 $00{:}45{:}25{.}810 \dashrightarrow 00{:}45{:}27{.}710$ There's chaos and immunology.

NOTE Confidence: 0.934912074166667

00:45:27.710 --> 00:45:29.610 Chaos of using lupus

NOTE Confidence: 0.934912074166667

 $00{:}45{:}29.610 \dashrightarrow 00{:}45{:}31.120$ antibodies against cancer.

NOTE Confidence: 0.934912074166667

 $00{:}45{:}31{.}120 \dashrightarrow 00{:}45{:}32{.}408$ I thought it was great title and then

NOTE Confidence: 0.934912074166667

00:45:32.408 --> 00:45:33.658 rear said now you haven't proven it.

NOTE Confidence: 0.934912074166667

 $00{:}45{:}33.660 \dashrightarrow 00{:}45{:}35.596$ You gotta call the theory so it was

NOTE Confidence: 0.934912074166667

 $00{:}45{:}35{.}596 \dashrightarrow 00{:}45{:}37{.}500$ published as the lupus butterfly theory,

NOTE Confidence: 0.934912074166667

 $00{:}45{:}37{.}500 \dashrightarrow 00{:}45{:}38{.}724$ but I will for ever want to

NOTE Confidence: 0.934912074166667

 $00:45:38.724 \rightarrow 00:45:40.340$ remember it as the lupus butterfly

NOTE Confidence: 0.934912074166667

 $00:45:40.340 \longrightarrow 00:45:41.459$ effect theory hypothesis.

NOTE Confidence: 0.934912074166667

 $00:45:41.460 \longrightarrow 00:45:44.876$ Postulate whatever you want to call it.

NOTE Confidence: 0.934912074166667

 $00:45:44.880 \longrightarrow 00:45:45.776$ But we do need to prove it,

- NOTE Confidence: 0.934912074166667
- $00{:}45{:}45{.}780 \dashrightarrow 00{:}45{:}47{.}616$ so we published that in 2016
- NOTE Confidence: 0.934912074166667
- $00:45:47.616 \longrightarrow 00:45:50.096$ and we started asking around.
- NOTE Confidence: 0.934912074166667
- $00:45:50.100 \longrightarrow 00:45:51.565$ Anybody can help us with
- NOTE Confidence: 0.934912074166667
- $00{:}45{:}51{.}565 \dashrightarrow 00{:}45{:}53{.}368$ epidemiology 'cause we have no idea
- NOTE Confidence: 0.934912074166667
- $00{:}45{:}53{.}368 \dashrightarrow 00{:}45{:}55{.}054$ what we're doing in that regard.
- NOTE Confidence: 0.910918758181818
- $00{:}45{:}55{.}060 \dashrightarrow 00{:}45{:}56{.}590$ And it turns out Lupus is
- NOTE Confidence: 0.910918758181818
- $00:45:56.590 \longrightarrow 00:45:57.780$ rare enough that it's a.
- NOTE Confidence: 0.910918758181818
- $00{:}45{:}57.780 \dashrightarrow 00{:}46{:}00{.}354$ It's a challenge to actually prove
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}00{.}354 \dashrightarrow 00{:}46{:}02{.}070$ the association between lupus
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}02.146 \dashrightarrow 00{:}46{:}04.426$ antibodies and breast cancer risk.
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}04{.}430 \dashrightarrow 00{:}46{:}05{.}954$ But not an insurmountable one because
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}05{.}954 \dashrightarrow 00{:}46{:}07{.}814$ John Hopkins was able to do it and
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}07{.}814 \dashrightarrow 00{:}46{:}09{.}002$ they published it just last year.
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}09{.}010 \dashrightarrow 00{:}46{:}10{.}781$ So this. Kind of blew my mind
- NOTE Confidence: 0.910918758181818
- $00{:}46{:}10.781 \dashrightarrow 00{:}46{:}12.913$ and I was very exciting to see
- NOTE Confidence: 0.910918758181818

 $00:46:12.913 \longrightarrow 00:46:15.008$ this the Hopkins Lupus cohort.

NOTE Confidence: 0.910918758181818

 $00{:}46{:}15{.}008 \dashrightarrow 00{:}46{:}17{.}218$ They were able to treat.

NOTE Confidence: 0.910918758181818

 $00:46:17.220 \longrightarrow 00:46:19.199$ Sorry they were able to analyze

NOTE Confidence: 0.910918758181818

 $00:46:19.199 \longrightarrow 00:46:20.994$ 2000 plus lupus patients that

NOTE Confidence: 0.910918758181818

 $00{:}46{:}20.994 \dashrightarrow 00{:}46{:}22.799$ entered their cohort without a

NOTE Confidence: 0.910918758181818

 $00{:}46{:}22.799 \dashrightarrow 00{:}46{:}24.349$ cancer diagnosis and then evaluate

NOTE Confidence: 0.910918758181818

 $00{:}46{:}24{.}349 \dashrightarrow 00{:}46{:}26{.}030$ their risk of breast cancer.

NOTE Confidence: 0.898002588461539

00:46:28.070 --> 00:46:29.855 Over the years and they were able

NOTE Confidence: 0.898002588461539

 $00:46:29.855 \rightarrow 00:46:31.570$ to associate that with the patients,

NOTE Confidence: 0.898002588461539

 $00:46:31.570 \longrightarrow 00:46:33.678$ laboratory studies and anti

NOTE Confidence: 0.898002588461539

 $00{:}46{:}33.678 \dashrightarrow 00{:}46{:}35.259$ DNA antibody profiles.

NOTE Confidence: 0.898002588461539

 $00:46:35.260 \longrightarrow 00:46:37.878$ And we do see finally proof that

NOTE Confidence: 0.898002588461539

 $00{:}46{:}37.878 \dashrightarrow 00{:}46{:}40.699$ there is an association between

NOTE Confidence: 0.898002588461539

00:46:40.700 --> 00:46:42.645 anti double stranded DNA antibody

NOTE Confidence: 0.898002588461539

 $00{:}46{:}42.645 \dashrightarrow 00{:}46{:}44.590$ positivity and that reduction in

NOTE Confidence: 0.898002588461539

 $00{:}46{:}44{.}649 \dashrightarrow 00{:}46{:}46{.}803$ breast cancer risk patients that make

- NOTE Confidence: 0.898002588461539
- 00:46:46.803 --> 00:46:49.057 those anti D antibodies have 45%
- NOTE Confidence: 0.898002588461539
- $00{:}46{:}49.057 \dashrightarrow 00{:}46{:}52.159$ reduction in the breast cancer risk.
- NOTE Confidence: 0.898002588461539
- $00{:}46{:}52{.}160 \dashrightarrow 00{:}46{:}54{.}184$ And if you dig even deeper and you
- NOTE Confidence: 0.898002588461539
- $00{:}46{:}54{.}184 \dashrightarrow 00{:}46{:}56{.}286$ stratify the patients based on the amount
- NOTE Confidence: 0.898002588461539
- $00:46:56.286 \rightarrow 00:46:58.260$ of those antibodies they are making,
- NOTE Confidence: 0.898002588461539
- $00:46:58.260 \longrightarrow 00:47:00.500$ the low producers did not have any
- NOTE Confidence: 0.898002588461539
- $00{:}47{:}00{.}500 \dashrightarrow 00{:}47{:}02{.}239$ reduction in breast cancer risk.
- NOTE Confidence: 0.898002588461539
- 00:47:02.240 --> 00:47:04.190 But the high producers had
- NOTE Confidence: 0.898002588461539
- 00:47:04.190 --> 00:47:05.788 a 59% reduction in risk,
- NOTE Confidence: 0.898002588461539
- $00:47:05.788 \longrightarrow 00:47:07.600$ so I've I'm taking this as
- NOTE Confidence: 0.898002588461539
- $00:47:07.665 \longrightarrow 00:47:08.957$ backing up my theory.
- NOTE Confidence: 0.898002588461539
- $00:47:08.960 \longrightarrow 00:47:10.640$ I think the lupus butterfly theory can be
- NOTE Confidence: 0.898002588461539
- $00:47:10.640 \longrightarrow 00:47:12.199$ called the lupus butterfly effect now,
- NOTE Confidence: 0.898002588461539
- $00{:}47{:}12.200 \dashrightarrow 00{:}47{:}13.838$ so I might ask for a revision
- NOTE Confidence: 0.898002588461539
- $00{:}47{:}13.838 \dashrightarrow 00{:}47{:}14.540$ to that article.
- NOTE Confidence: 0.898002588461539

 $00:47:14.540 \rightarrow 00:47:16.916$ Although it's been five years here.

NOTE Confidence: 0.898002588461539

 $00{:}47{:}16{.}920 \dashrightarrow 00{:}47{:}17{.}624$ But regardless,

NOTE Confidence: 0.898002588461539

00:47:17.624 --> 00:47:19.736 it's it seems like we're learning

NOTE Confidence: 0.898002588461539

 $00:47:19.736 \longrightarrow 00:47:21.176$ something about lupus antibodies

NOTE Confidence: 0.898002588461539

 $00{:}47{:}21.176 \dashrightarrow 00{:}47{:}22.876$ and at least breast cancer,

NOTE Confidence: 0.898002588461539

 $00{:}47{:}22.880 \dashrightarrow 00{:}47{:}24.524$ and it gives me more confidence

NOTE Confidence: 0.898002588461539

 $00:47:24.524 \rightarrow 00:47:26.286$ in what we're doing and trying

NOTE Confidence: 0.898002588461539

 $00:47:26.286 \rightarrow 00:47:28.070$ to reengineer lupus antibodies

NOTE Confidence: 0.898002588461539

 $00:47:28.070 \longrightarrow 00:47:30.300$ to treat triple negative breast

NOTE Confidence: 0.898002588461539

 $00{:}47{:}30{.}368 \dashrightarrow 00{:}47{:}31{.}920$ cancer and other tumors.

NOTE Confidence: 0.898002588461539

 $00:47:31.920 \longrightarrow 00:47:33.440$ So what are we doing in that regard?

NOTE Confidence: 0.898002588461539

 $00:47:33.440 \longrightarrow 00:47:34.802$ Well? Again.

NOTE Confidence: 0.898002588461539

00:47:34.802 --> 00:47:38.888 I remember and I recognize 310,

NOTE Confidence: 0.898002588461539

00:47:38.890 --> 00:47:39.865 although it's technically

NOTE Confidence: 0.898002588461539

 $00{:}47{:}39{.}865 \dashrightarrow 00{:}47{:}41{.}165$ safe in normal cells.

NOTE Confidence: 0.898002588461539

00:47:41.170 --> 00:47:44.397 It's still a lupus anti DNA antibody.

00:47:44.400 --> 00:47:45.816 And you don't want to give

NOTE Confidence: 0.898002588461539

00:47:45.816 --> 00:47:46.760 anybody lupus like symptoms.

NOTE Confidence: 0.898002588461539

 $00:47:46.760 \longrightarrow 00:47:48.832$ So we gotta rethink this a little

NOTE Confidence: 0.898002588461539

 $00:47:48.832 \longrightarrow 00:47:50.563$ bit before we start taking

NOTE Confidence: 0.898002588461539

 $00:47:50.563 \longrightarrow 00:47:52.115$ this to clinical trials.

NOTE Confidence: 0.898002588461539

 $00{:}47{:}52.120 \dashrightarrow 00{:}47{:}54.325$ The last thing you want is a lupus FC

NOTE Confidence: 0.898002588461539

 $00:47:54.325 \rightarrow 00:47:56.359$ region being administered to patients,

NOTE Confidence: 0.898002588461539

 $00{:}47{:}56{.}360 \dashrightarrow 00{:}47{:}58{.}712$ because the FC is going to activate

NOTE Confidence: 0.898002588461539

 $00{:}47{:}58.712 \dashrightarrow 00{:}48{:}01{.}346$ compliment and ABC and all kinds of madness.

NOTE Confidence: 0.898002588461539

 $00:48:01.350 \rightarrow 00:48:03.499$ But the good news is, 310 does not

NOTE Confidence: 0.898002588461539

 $00{:}48{:}03{.}499 \dashrightarrow 00{:}48{:}05{.}710$ care whether or not it has the FC tail.

NOTE Confidence: 0.898002588461539

 $00{:}48{:}05{.}710 \dashrightarrow 00{:}48{:}08{.}190$ It'll penetrate cells with or without the FC.

NOTE Confidence: 0.898002588461539

 $00{:}48{:}08{.}190 \dashrightarrow 00{:}48{:}10{.}032$ It'll bind DNA and inhibit DNA

NOTE Confidence: 0.898002588461539

 $00{:}48{:}10.032 \dashrightarrow 00{:}48{:}11.730$ repair with or without the FC.

NOTE Confidence: 0.898002588461539

 $00{:}48{:}11.730 \dashrightarrow 00{:}48{:}13.790$ So first thing we've done, cut it off.

- 00:48:13.790 --> 00:48:15.530 There is no more FC tail,
- NOTE Confidence: 0.898002588461539
- $00:48:15.530 \longrightarrow 00:48:16.626$ the danger is gone.
- NOTE Confidence: 0.898002588461539
- $00:48:16.626 \longrightarrow 00:48:19.011$ And that's how we make what we call
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}19.011 \dashrightarrow 00{:}48{:}20.716$ a single chain variable fragment,
- NOTE Confidence: 0.898002588461539
- 00:48:20.720 --> 00:48:21.103 SCFE.
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}21.103 \dashrightarrow 00{:}48{:}23.018$ It's only the variable sequences
- NOTE Confidence: 0.898002588461539
- $00:48:23.018 \rightarrow 00:48:25.530$ of the light and heavy chains.
- NOTE Confidence: 0.898002588461539
- $00:48:25.530 \longrightarrow 00:48:27.205$ And that's been optimized to
- NOTE Confidence: 0.898002588461539
- 00:48:27.205 --> 00:48:28.880 increase the affinity for DNA.
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}28{.}880 \dashrightarrow 00{:}48{:}30{.}779$ And then we stuck a couple of those
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}30.779 \dashrightarrow 00{:}48{:}32.633$ together to make a dye single chain
- NOTE Confidence: 0.898002588461539
- $00:48:32.633 \rightarrow 00:48:34.679$ fragments to bump up the avidity for DNA.
- NOTE Confidence: 0.898002588461539
- $00:48:34.680 \longrightarrow 00:48:36.878$ And that works really well against HR
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}36{.}878 \dashrightarrow 00{:}48{:}38{.}450$ deficient cancer cells and tumors.
- NOTE Confidence: 0.898002588461539
- $00:48:38.450 \longrightarrow 00:48:40.280$ And that's the product that was
- NOTE Confidence: 0.898002588461539
- $00:48:40.280 \rightarrow 00:48:41.852$ finally licensed by biotech company

- NOTE Confidence: 0.898002588461539
- $00:48:41.852 \longrightarrow 00:48:43.579$ Patriss as we talked about who
- NOTE Confidence: 0.898002588461539
- $00:48:43.579 \longrightarrow 00:48:45.133$ then has helped with funds to
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}45{.}133 \dashrightarrow 00{:}48{:}47{.}112$ allow us to humanize and demonize
- NOTE Confidence: 0.898002588461539
- $00:48:47.112 \longrightarrow 00:48:49.056$ and further optimize the CDR's.
- NOTE Confidence: 0.898002588461539
- $00:48:49.056 \rightarrow 00:48:50.760$ To develop the antibody,
- NOTE Confidence: 0.898002588461539
- $00{:}48{:}50.760 \dashrightarrow 00{:}48{:}52.872$ I would like to now introduce
- NOTE Confidence: 0.898002588461539
- 00:48:52.872 --> 00:48:55.304 named Deoxy Mab one or DX1 deoxy
- NOTE Confidence: 0.898002588461539
- 00:48:55.304 --> 00:48:57.716 mab 'cause DNA mab for antibody.
- NOTE Confidence: 0.898002588461539
- 00:48:57.720 --> 00:48:58.312 Yeah,
- NOTE Confidence: 0.898002588461539
- $00:48:58.312 \rightarrow 00:49:00.088$ you get it.
- NOTE Confidence: 0.898002588461539
- $00:49:00.090 \rightarrow 00:49:03.354$ DX1 is well if ENT two is my
- NOTE Confidence: 0.898002588461539
- $00{:}49{:}03{.}354 \dashrightarrow 00{:}49{:}05{.}009$ favorite transporter DX one is
- NOTE Confidence: 0.898002588461539
- $00{:}49{:}05{.}010 \dashrightarrow 00{:}49{:}06{.}310$ probably my favorite antibody,
- NOTE Confidence: 0.898002588461539
- $00{:}49{:}06{.}310 \dashrightarrow 00{:}49{:}08{.}593$ although there is some other ones that
- NOTE Confidence: 0.898002588461539
- $00{:}49{:}08{.}593 \dashrightarrow 00{:}49{:}10{.}504$ are kind of catching my attention too.
- NOTE Confidence: 0.898002588461539

- $00:49:10.510 \longrightarrow 00:49:11.353$ It works great,
- NOTE Confidence: 0.898002588461539
- 00:49:11.353 00:49:12.758 penetrates so clearly into the
- NOTE Confidence: 0.898002588461539
- $00:49:12.758 \longrightarrow 00:49:14.190$ nucleus we see triple negative
- NOTE Confidence: 0.898002588461539
- $00:49:14.190 \longrightarrow 00:49:16.087$ breast cancer cells on the left and
- NOTE Confidence: 0.900309922857143
- $00{:}49{:}16.145 \dashrightarrow 00{:}49{:}18.265$ breast cancer brain Mets else on the right.
- NOTE Confidence: 0.900309922857143
- $00:49:18.270 \longrightarrow 00:49:19.938$ It's killing the cells,
- NOTE Confidence: 0.900309922857143
- 00:49:19.938 --> 00:49:21.606 it's sensitizing to radiation,
- NOTE Confidence: 0.900309922857143
- $00:49:21.610 \rightarrow 00:49:23.724$ but it's still leaving normal cells alone.
- NOTE Confidence: 0.900309922857143
- $00{:}49{:}23.730 \dashrightarrow 00{:}49{:}25.846$ Just what we want and we are
- NOTE Confidence: 0.900309922857143
- $00:49:25.846 \longrightarrow 00:49:27.486$ excited to move this towards
- NOTE Confidence: 0.900309922857143
- $00:49:27.486 \longrightarrow 00:49:28.470$ clinical trial testing.
- NOTE Confidence: 0.900309922857143
- $00:49:28.470 \longrightarrow 00:49:29.958$ But wait a second did I?
- NOTE Confidence: 0.900309922857143
- 00:49:29.960 --> 00:49:31.725 Am I saying something about
- NOTE Confidence: 0.900309922857143
- $00:49:31.725 \longrightarrow 00:49:33.230$ brain Mets cells but?
- NOTE Confidence: 0.834734662142857
- $00:49:35.650 \rightarrow 00:49:36.861$ Am I arguing that we could maybe
- NOTE Confidence: 0.834734662142857
- $00:49:36.861 \longrightarrow 00:49:38.170$ be using this to treat brain Mets?

- NOTE Confidence: 0.834734662142857
- $00:49:38.170 \longrightarrow 00:49:39.430$ This is an antibody, right?
- NOTE Confidence: 0.834734662142857
- $00:49:39.430 \longrightarrow 00:49:40.396$ I mean this, the story is
- NOTE Confidence: 0.834734662142857
- $00:49:40.396 \longrightarrow 00:49:41.663$ already kind of far fetched, but.
- NOTE Confidence: 0.834734662142857
- 00:49:41.663 --> 00:49:44.007 Brain Mets well, The thing is one of
- NOTE Confidence: 0.834734662142857
- $00:49:44.007 \rightarrow 00:49:46.446$ the key biologic markers that predict
- NOTE Confidence: 0.834734662142857
- $00:49:46.446 \rightarrow 00:49:48.910$ sensitivity to our antibody is loss
- NOTE Confidence: 0.834734662142857
- $00{:}49{:}48{.}910 \dashrightarrow 00{:}49{:}51{.}398$ of P-10 even more so than bracket for.
- NOTE Confidence: 0.834734662142857
- $00{:}49{:}51{.}400 \dashrightarrow 00{:}49{:}52{.}904$ And I know that all the DNA repair
- NOTE Confidence: 0.834734662142857
- 00:49:52.904 --> 00:49:53.790 experts are probably jumping
- NOTE Confidence: 0.834734662142857
- 00:49:53.790 --> 00:49:55.200 up and down right now saying,
- NOTE Confidence: 0.834734662142857
- $00:49:55.200 \longrightarrow 00:49:58.546$ well the P-10 HR link is not
- NOTE Confidence: 0.834734662142857
- $00:49:58.546 \rightarrow 00:50:01.048$ completely proven and fine, but.
- NOTE Confidence: 0.834734662142857
- 00:50:01.048 --> 00:50:04.088 Cells at a P-10 deficient are
- NOTE Confidence: 0.834734662142857
- $00{:}50{:}04.088 \dashrightarrow 00{:}50{:}06.306$ killed by this antibody and brain.
- NOTE Confidence: 0.834734662142857
- $00{:}50{:}06{.}306 \dashrightarrow 00{:}50{:}08{.}917$ Mints often exhibit P-10 loss even when
- NOTE Confidence: 0.834734662142857

00:50:08.917 --> 00:50:11.435 the primary tumor is P 10 positive

NOTE Confidence: 0.834734662142857

 $00:50:11.440 \longrightarrow 00:50:14.020$ and that's either evolution towards

NOTE Confidence: 0.834734662142857

00:50:14.020 --> 00:50:16.600 metastasis or secretion of P-10

NOTE Confidence: 0.834734662142857

 $00:50:16.686 \rightarrow 00:50:19.536$ suppressive micro RNAs by astrocytes.

NOTE Confidence: 0.834734662142857

 $00{:}50{:}19{.}540 \dashrightarrow 00{:}50{:}21{.}311$ It's also worth noting P-10 is lost

NOTE Confidence: 0.834734662142857

00:50:21.311 -> 00:50:23.448 an awful lot in primary GBM, so.

NOTE Confidence: 0.834734662142857

 $00{:}50{:}23.448 \dashrightarrow 00{:}50{:}27.672$ Maybe we've got treatment for GBM as well.

NOTE Confidence: 0.834734662142857

 $00:50:27.680 \rightarrow 00:50:30.200$ But I hear what you're saying.

NOTE Confidence: 0.834734662142857

 $00:50:30.200 \rightarrow 00:50:33.525$ Brain Mets brain tumors with an antibody.

NOTE Confidence: 0.834734662142857

 $00{:}50{:}33{.}530 \dashrightarrow 00{:}50{:}35{.}234$ I I don't understand what the

NOTE Confidence: 0.834734662142857

 $00:50:35.234 \rightarrow 00:50:36.086$ why the skepticism.

NOTE Confidence: 0.834734662142857

00:50:36.090 --> 00:50:36.662 I mean,

NOTE Confidence: 0.834734662142857

 $00{:}50{:}36{.}662 \dashrightarrow 00{:}50{:}38{.}806$ all we need is DNA and nucleosides

NOTE Confidence: 0.834734662142857

 $00:50:38.806 \rightarrow 00:50:41.130$ and the E NT 2 transporter right?

NOTE Confidence: 0.834734662142857

 $00:50:41.130 \longrightarrow 00:50:43.090$ It seems like the antibody should be able

NOTE Confidence: 0.834734662142857

 $00:50:43.090 \rightarrow 00:50:45.430$ to get into the brain tumors just fine it.

- NOTE Confidence: 0.834734662142857
- $00{:}50{:}45{.}430 \dashrightarrow 00{:}50{:}49{.}288$ Oh oh right.
- NOTE Confidence: 0.834734662142857
- $00:50:49.290 \longrightarrow 00:50:50.738$ The blood brain barrier.
- NOTE Confidence: 0.94686102
- $00{:}50{:}52{.}760 \dashrightarrow 00{:}50{:}56{.}810$ I guess that does pose something of an issue.
- NOTE Confidence: 0.94686102
- $00{:}50{:}56{.}810 \dashrightarrow 00{:}50{:}58{.}595$ Maybe I should have thought this through
- NOTE Confidence: 0.94686102
- $00{:}50{:}58{.}595 \dashrightarrow 00{:}51{:}00{.}178$ before I signed up for this talk.
- NOTE Confidence: 0.94686102
- $00{:}51{:}00{.}180 \dashrightarrow 00{:}51{:}03{.}230$ I guess it's too late to back out now though.
- NOTE Confidence: 0.94686102
- $00:51:03.230 \longrightarrow 00:51:05.981$ If we look really closely at the
- NOTE Confidence: 0.94686102
- $00{:}51{:}05{.}981 \dashrightarrow 00{:}51{:}08{.}463$ blood brain barrier and we look in
- NOTE Confidence: 0.94686102
- $00{:}51{:}08{.}463 \dashrightarrow 00{:}51{:}10{.}428$ at the brain endothelial cells.
- NOTE Confidence: 0.94686102
- $00:51:10.430 \longrightarrow 00:51:12.594$ Whoa, there's my buddy.
- NOTE Confidence: 0.94686102
- $00:51:12.594 \rightarrow 00:51:15.153 \text{ E}$ and T2. The luminal surface
- NOTE Confidence: 0.94686102
- $00{:}51{:}15{.}153 \dashrightarrow 00{:}51{:}16.708$ of the brain endothelial cell.
- NOTE Confidence: 0.94686102
- 00:51:16.710 --> 00:51:19.218 And it actually regulates nucleoside flux
- NOTE Confidence: 0.94686102
- $00{:}51{:}19{.}220 \dashrightarrow 00{:}51{:}22{.}036$ into and out of the central nervous system.
- NOTE Confidence: 0.94686102
- $00:51:22.040 \longrightarrow 00:51:23.120$ So wait a second.
- NOTE Confidence: 0.94686102

 $00:51:23.120 \rightarrow 00:51:25.739$ This is all starting to come full circle now.

NOTE Confidence: 0.94686102

00:51:25.740 --> 00:51:27.786 I think I'm arguing that our

NOTE Confidence: 0.94686102

00:51:27.786 --> 00:51:30.269 antibody DX1 can get over the river,

NOTE Confidence: 0.94686102

 $00:51:30.270 \rightarrow 00:51:32.700$ the bloodstream, and through the woods.

NOTE Confidence: 0.94686102

 $00{:}51{:}32{.}700 \dashrightarrow 00{:}51{:}34{.}240$ The blood brain barrier and

NOTE Confidence: 0.94686102

 $00{:}51{:}34{.}240 \dashrightarrow 00{:}51{:}35{.}472$ into the brain tumor.

NOTE Confidence: 0.94686102

 $00:51:35.480 \longrightarrow 00:51:38.112$ We will go where the antibody will

NOTE Confidence: 0.94686102

 $00:51:38.112 \longrightarrow 00:51:40.950$ then bind DNA and inhibit DNA repair

NOTE Confidence: 0.94686102

 $00{:}51{:}40{.}950 \dashrightarrow 00{:}51{:}43{.}870$ and kill those brain Mets and also.

NOTE Confidence: 0.94686102

 $00:51:43.870 \longrightarrow 00:51:46.018$ The possibly last owner.

NOTE Confidence: 0.966709268333333

 $00{:}51{:}48{.}370 \dashrightarrow 00{:}51{:}50{.}706$ And we are seeing that this indeed is

NOTE Confidence: 0.966709268333333

00:51:50.706 --> 00:51:55.460 working out very well season. Sorry.

NOTE Confidence: 0.966709268333333

 $00{:}51{:}55{.}460 \dashrightarrow 00{:}51{:}57{.}788$ We are finding that DX1 does cross transwell

NOTE Confidence: 0.966709268333333

 $00{:}51{:}57{.}788 \dashrightarrow 00{:}51{:}59{.}851$ models of the blood brain barrier and it

NOTE Confidence: 0.966709268333333

 $00{:}51{:}59{.}851 \dashrightarrow 00{:}52{:}02{.}098$ does so in an EMT 2 dependent manner.

NOTE Confidence: 0.966709268333333

 $00:52:02.100 \rightarrow 00:52:04.020$ If you shut down EMT 2 the antibody

 $00:52:04.020 \rightarrow 00:52:05.998$ can't get across in the middle panel.

NOTE Confidence: 0.966709268333333

 $00:52:06.000 \longrightarrow 00:52:07.775$ Here we're showing mice with

NOTE Confidence: 0.966709268333333

 $00{:}52{:}07{.}775 \dashrightarrow 00{:}52{:}08{.}840$ orthotopic brain tumors.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}08{.}840 \dashrightarrow 00{:}52{:}10{.}520$ GBM in this case.

NOTE Confidence: 0.966709268333333

 $00:52:10.520 \longrightarrow 00:52:12.620$ And we gave the antibodies.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}12.620 \dashrightarrow 00{:}52{:}14.398$ We gave the mice antibodies labeled so

NOTE Confidence: 0.966709268333333

 $00:52:14.398 \longrightarrow 00:52:16.682$ that we can see it on imaging and the

NOTE Confidence: 0.966709268333333

 $00:52:16.682 \rightarrow 00:52:18.628$ antibody gets into the brain tumor great.

NOTE Confidence: 0.966709268333333

 $00:52:18.630 \longrightarrow 00:52:20.303$ But not if we treat the mice

NOTE Confidence: 0.966709268333333

00:52:20.303 - 00:52:21.650 with an inhibitor of ENT two,

NOTE Confidence: 0.966709268333333

00:52:21.650 --> 00:52:23.126 so you shut down ENT 2,

NOTE Confidence: 0.966709268333333

 $00:52:23.130 \longrightarrow 00:52:25.050$ the antibody can't get into the brain tumor,

NOTE Confidence: 0.966709268333333

 $00:52:25.050 \longrightarrow 00:52:27.378$ so it's working like we think.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}27{.}380 \dashrightarrow 00{:}52{:}28{.}718$ And it seems to actually matter.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}28.720 \dashrightarrow 00{:}52{:}29.688$ It makes a difference.

 $00:52:29.688 \longrightarrow 00:52:30.898$ The panel on the right.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}30{.}900 \dashrightarrow 00{:}52{:}34{.}183$ These are mice treated with the antibody

NOTE Confidence: 0.966709268333333

 $00{:}52{:}34{.}183 \dashrightarrow 00{:}52{:}37{.}238$ with P-10 deficient patient derived GBM.

NOTE Confidence: 0.966709268333333

 $00:52:37.240 \longrightarrow 00:52:38.404$ DX1 by itself.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}38{.}404 \dashrightarrow 00{:}52{:}39{.}180$ No radiation.

NOTE Confidence: 0.966709268333333

 $00{:}52{:}39{.}180 \dashrightarrow 00{:}52{:}40{.}792$ No chemotherapy significantly suppresses

NOTE Confidence: 0.966709268333333

 $00{:}52{:}40.792 \dashrightarrow 00{:}52{:}43.210$ the tumor growth and extends survival.

NOTE Confidence: 0.95907728

00:52:48.680 - 00:52:51.720 There we go. Brain Mets are a little

NOTE Confidence: 0.95907728

 $00{:}52{:}51{.}720$ --> $00{:}52{:}54{.}234$ harder to study, and GBM in mice.

NOTE Confidence: 0.95907728

 $00{:}52{:}54{.}234 \dashrightarrow 00{:}52{:}56{.}539$ Just implant the tumor intracranially

NOTE Confidence: 0.95907728

 $00{:}52{:}56{.}539 \dashrightarrow 00{:}52{:}59{.}183$ and watch and it goes, but that's not

NOTE Confidence: 0.95907728

 $00{:}52{:}59{.}183 \dashrightarrow 00{:}53{:}00{.}730$ really fair for a brain met model.

NOTE Confidence: 0.95907728

00:53:00.730 --> 00:53:03.232 So the way we study brain Mets has been

NOTE Confidence: 0.95907728

 $00{:}53{:}03{.}232 \dashrightarrow 00{:}53{:}05{.}783$ taught to us by our good friend and

NOTE Confidence: 0.95907728

 $00{:}53{:}05{.}783$ --> $00{:}53{:}07{.}915$ colleague Jangling Zhao and mastered by NOTE Confidence: 0.95907728

 $00:53:07.915 \rightarrow 00:53:10.285$ research associate my lab benedet caffari.

- NOTE Confidence: 0.95907728
- $00:53:10.290 \rightarrow 00:53:14.000$ These are not easy experiments.

00:53:14.000 --> 00:53:15.370 Breast cancer cells are injected

NOTE Confidence: 0.95907728

 $00:53:15.370 \longrightarrow 00:53:17.674$ into the hearts of the mice to allow

NOTE Confidence: 0.95907728

 $00{:}53{:}17.674 \dashrightarrow 00{:}53{:}19.139$ them exposure to the circulation,

NOTE Confidence: 0.95907728

00:53:19.140 --> 00:53:21.417 and we use a brain seeking some type of

NOTE Confidence: 0.95907728

 $00{:}53{:}21{.}417 \dashrightarrow 00{:}53{:}23{.}668$ the cancer cells to go to the brains.

NOTE Confidence: 0.95907728

 $00{:}53{:}23{.}670 \dashrightarrow 00{:}53{:}25{.}917$ And you can then track those based

NOTE Confidence: 0.95907728

 $00:53:25.917 \rightarrow 00:53:28.110$ on their signal on serial imaging.

NOTE Confidence: 0.95907728

00:53:28.110 --> 00:53:29.964 So if we give the mice brain mats and

NOTE Confidence: 0.95907728

 $00{:}53{:}29{.}964 \dashrightarrow 00{:}53{:}32{.}089$ we treat them with tail vein injections

NOTE Confidence: 0.95907728

 $00:53:32.090 \longrightarrow 00:53:34.030$ with control, or the antibody,

NOTE Confidence: 0.95907728

 $00{:}53{:}34{.}030 \dashrightarrow 00{:}53{:}35{.}880$ just the antibody, no radiation,

NOTE Confidence: 0.95907728

00:53:35.880 --> 00:53:36.578 no chemotherapy.

NOTE Confidence: 0.95907728

 $00{:}53{:}36{.}578 \dashrightarrow 00{:}53{:}39{.}021$ I think that picture up in the

NOTE Confidence: 0.95907728

 $00:53:39.021 \longrightarrow 00:53:40.670$ top right says it all.

- 00:53:40.670 00:53:42.094 It suppresses the brain
- NOTE Confidence: 0.95907728
- $00:53:42.094 \longrightarrow 00:53:43.634$ Mets quite phenomenally,
- NOTE Confidence: 0.95907728
- $00:53:43.634 \rightarrow 00:53:47.186$ and it does also extend survival,
- NOTE Confidence: 0.95907728
- $00:53:47.190 \rightarrow 00:53:48.550$ so this is looking really, really good.
- NOTE Confidence: 0.95907728
- $00{:}53{:}48{.}550 \dashrightarrow 00{:}53{:}50{.}470$ But now I start to hear the words
- NOTE Confidence: 0.95907728
- $00:53:50.531 \longrightarrow 00:53:52.050$ again in the back of my head.
- NOTE Confidence: 0.95907728
- $00:53:52.050 \rightarrow 00:53:54.462$ I don't know if anybody else can hear them.
- NOTE Confidence: 0.95907728
- $00:53:54.470 \longrightarrow 00:53:55.640$ Do we really need a new
- NOTE Confidence: 0.95907728
- $00:53:55.640 \longrightarrow 00:53:56.790$ way to treat breast cancer?
- NOTE Confidence: 0.95907728
- $00{:}53{:}56{.}790 \dashrightarrow 00{:}53{:}58{.}014$ Brain Mets, I think isn't that
- NOTE Confidence: 0.95907728
- $00:53:58.014 \rightarrow 00:53:59.150$ what the gamma knife is for?
- NOTE Confidence: 0.95907728
- 00:53:59.150 --> 00:53:59.910 It's it's easy, right?
- NOTE Confidence: 0.95907728
- $00:53:59.910 \longrightarrow 00:54:00.670$ You see a brain,
- NOTE Confidence: 0.95907728
- $00{:}54{:}00{.}670 \dashrightarrow 00{:}54{:}02{.}480$ but you just send the patient to the
- NOTE Confidence: 0.95907728
- 00:54:02.480 --> 00:54:04.642 gamma knife and I would say, Oh no.
- NOTE Confidence: 0.95907728
- $00:54:04.642 \longrightarrow 00:54:06.266$ It's not so easy.

- NOTE Confidence: 0.95907728
- $00:54:06.270 \longrightarrow 00:54:06.891$ First of all,
- NOTE Confidence: 0.95907728
- $00:54:06.891 \rightarrow 00:54:08.133$ not everybody is a candidate for
- NOTE Confidence: 0.95907728
- $00{:}54{:}08{.}133 \dashrightarrow 00{:}54{:}09{.}546$ the gamma knife and gamma knife
- NOTE Confidence: 0.95907728
- 00:54:09.546 --> 00:54:10.706 does work really quite well,
- NOTE Confidence: 0.95907728
- $00{:}54{:}10.710 \dashrightarrow 00{:}54{:}12.286$ but there are risks.
- NOTE Confidence: 0.95907728
- 00:54:12.286 --> 00:54:13.014 Radiation, necrosis,
- NOTE Confidence: 0.95907728
- $00:54:13.014 \longrightarrow 00:54:14.684$ as Doctor Chang will attest
- NOTE Confidence: 0.95907728
- $00:54:14.684 \rightarrow 00:54:16.650$ to is a problem,
- NOTE Confidence: 0.95907728
- $00{:}54{:}16.650 \dashrightarrow 00{:}54{:}19.360$ and there's a lot of a lot of it that occurs.
- NOTE Confidence: 0.95907728
- $00{:}54{:}19{.}360 \dashrightarrow 00{:}54{:}20{.}896$ And when disease comes back after the game,
- NOTE Confidence: 0.95907728
- $00:54:20.900 \rightarrow 00:54:23.012$ and if it's even harder to take care
- NOTE Confidence: 0.95907728
- $00{:}54{:}23.012 \dashrightarrow 00{:}54{:}25.030$ of and then there are the patients for
- NOTE Confidence: 0.95907728
- $00{:}54{:}25{.}030 \dashrightarrow 00{:}54{:}27{.}084$ which gamma knife is unfortunately not an
- NOTE Confidence: 0.95907728
- $00{:}54{:}27.084 \dashrightarrow 00{:}54{:}28.956$ option that require whole brain radiation.
- NOTE Confidence: 0.95907728
- $00:54:28.960 \rightarrow 00:54:30.290$ And even with our fancy
- NOTE Confidence: 0.95907728

 $00:54:30.290 \longrightarrow 00:54:31.354$ spinning of the beams,

NOTE Confidence: 0.95907728

 $00:54:31.360 \rightarrow 00:54:33.420$ hippocampal sparing in the manting,

NOTE Confidence: 0.95907728

 $00:54:33.420 \rightarrow 00:54:36.846$ it carries risks of neurotoxicity so.

NOTE Confidence: 0.95907728

 $00:54:36.850 \rightarrow 00:54:38.544$ I, I don't think there's any question.

NOTE Confidence: 0.95907728

 $00{:}54{:}38{.}550 \dashrightarrow 00{:}54{:}40{.}134$ If there was a way to reduce the

NOTE Confidence: 0.95907728

 $00{:}54{:}40{.}134 \dashrightarrow 00{:}54{:}42{.}004$ need for radiation or at least lower NOTE Confidence: 0.95907728

 $00:54:42.004 \rightarrow 00:54:43.429$ the dose of radiation required,

NOTE Confidence: 0.95907728

 $00:54:43.430 \longrightarrow 00:54:45.496$ that would make a big benefit for

NOTE Confidence: 0.95907728

 $00:54:45.496 \rightarrow 00:54:47.572$ patients with breast cancer and brain NOTE Confidence: 0.95907728

 $00{:}54{:}47{.}572$ --> $00{:}54{:}49{.}509$ metastases and other tumors as well.

NOTE Confidence: 0.95907728

 $00{:}54{:}49{.}510 \dashrightarrow 00{:}54{:}53{.}902$ So we have already started looking.

NOTE Confidence: 0.95907728

00:54:53.902 -> 00:54:56.878 Into this and we have a DoD grant

NOTE Confidence: 0.95907728

 $00{:}54{:}56.878 \dashrightarrow 00{:}54{:}59.488$ to help us conduct this work.

NOTE Confidence: 0.95907728

00:54:59.490 --> 00:55:01.730 I think DX one is perfectly poised to

NOTE Confidence: 0.95907728

 $00:55:01.730 \dashrightarrow 00:55:03.849$ lower the needed dose of radiation,

NOTE Confidence: 0.95907728

 $00:55:03.850 \dashrightarrow 00:55:05.698$ and I think radiation is perfectly

- NOTE Confidence: 0.95907728
- $00:55:05.698 \rightarrow 00:55:08.210$ poised to help the X one get into

 $00:55:08.210 \dashrightarrow 00:55:09.730$ the brain nuts because remember.

NOTE Confidence: 0.95907728

 $00:55:09.730 \longrightarrow 00:55:12.862$ DX1 is looking for and using DNA to get

NOTE Confidence: 0.95907728

 $00{:}55{:}12.862 \dashrightarrow 00{:}55{:}15.332$ into the tumors so dose of radiation

NOTE Confidence: 0.95907728

 $00{:}55{:}15{.}332 \dashrightarrow 00{:}55{:}17{.}210$ to increase tumor death and release

NOTE Confidence: 0.95907728

 $00{:}55{:}17.273 \dashrightarrow 00{:}55{:}19.569$ DNA should recruit more DX1 to the brain.

NOTE Confidence: 0.95907728

00:55:19.570 - 00:55:21.082 Mets and the bar graphs are

NOTE Confidence: 0.95907728

 $00:55:21.082 \longrightarrow 00:55:22.470$ shown on the bottom there.

NOTE Confidence: 0.95907728

 $00{:}55{:}22.470 \dashrightarrow 00{:}55{:}24.724$ That's so that's exactly what we see.

NOTE Confidence: 0.837978879

 $00:55:24.730 \longrightarrow 00:55:25.434$ We see the most.

NOTE Confidence: 0.837978879

 $00{:}55{:}25{.}434 \dashrightarrow 00{:}55{:}26{.}490$ DX one get in the brain.

NOTE Confidence: 0.837978879

 $00{:}55{:}26{.}490 \dashrightarrow 00{:}55{:}28{.}758$ Mets in the mice that get treated

NOTE Confidence: 0.837978879

 $00:55:28.758 \rightarrow 00:55:30.380$ concurrently with the radiation.

NOTE Confidence: 0.837978879

 $00{:}55{:}30{.}380 \dashrightarrow 00{:}55{:}32{.}599$ And take it to the obvious extreme.

NOTE Confidence: 0.837978879

 $00{:}55{:}32.600 \dashrightarrow 00{:}55{:}34.833$ Those mice that get DX1 with the

 $00{:}55{:}34{.}833 \dashrightarrow 00{:}55{:}36{.}873$ radiation also have the best response

NOTE Confidence: 0.837978879

 $00{:}55{:}36{.}873 \dashrightarrow 00{:}55{:}39{.}239$ we see the less number of metastases,

NOTE Confidence: 0.837978879

 $00{:}55{:}39{.}240 \dashrightarrow 00{:}55{:}40{.}856$ so it's all working the way we expect.

NOTE Confidence: 0.837978879

00:55:40.860 --> 00:55:43.120 I understand it's all preclinical,

NOTE Confidence: 0.837978879

 $00{:}55{:}43.120 \dashrightarrow 00{:}55{:}45.208$ it's in mice, but sometimes things

NOTE Confidence: 0.837978879

 $00{:}55{:}45{.}208 \dashrightarrow 00{:}55{:}47{.}325$ start to come together and it's

NOTE Confidence: 0.837978879

 $00:55:47.325 \rightarrow 00:55:49.293$ it's looking very promising to me.

NOTE Confidence: 0.837978879

 $00:55:49.300 \rightarrow 00:55:50.804$ Obviously very biased and.

NOTE Confidence: 0.837978879

 $00{:}55{:}50{.}804 \dashrightarrow 00{:}55{:}53{.}060$ Very grateful to Benedet and Marta

NOTE Confidence: 0.837978879

 $00{:}55{:}53{.}123 \dashrightarrow 00{:}55{:}55{.}237$ and Caroline and who for all their

NOTE Confidence: 0.837978879

 $00{:}55{:}55{.}237 \dashrightarrow 00{:}55{:}57{.}439$ work with this it's it's been tough

NOTE Confidence: 0.837978879

 $00{:}55{:}57{.}440 \dashrightarrow 00{:}55{:}58{.}980$ but we've hung through here and it's

NOTE Confidence: 0.837978879

 $00{:}55{:}58{.}980 \dashrightarrow 00{:}56{:}00{.}299$ it's going really quite well now.

NOTE Confidence: 0.928401989166667

 $00{:}56{:}02{.}380 \dashrightarrow 00{:}56{:}04{.}165$ And again, can't do any of this

NOTE Confidence: 0.928401989166667

 $00:56:04.165 \dashrightarrow 00:56:05.659$ without help from your friends.

NOTE Confidence: 0.928401989166667

 $00:56:05.660 \rightarrow 00:56:08.090$ I had to cross out the word little and say

 $00:56:08.155 \rightarrow 00:56:10.647$ a lot because jangle from neurosurgery has.

NOTE Confidence: 0.928401989166667

00:56:10.650 --> 00:56:11.634 Been great friend and

NOTE Confidence: 0.928401989166667

 $00:56:11.634 \rightarrow 00:56:12.864$ colleague to me for years.

NOTE Confidence: 0.928401989166667

 $00{:}56{:}12.870 \dashrightarrow 00{:}56{:}15.327$ Now he is an expert in all things related

NOTE Confidence: 0.928401989166667

 $00:56:15.327 \longrightarrow 00:56:17.722$ to the brain and brain tumors and ways

NOTE Confidence: 0.928401989166667

 $00{:}56{:}17.722 \dashrightarrow 00{:}56{:}19.450$ to treat tumors in the brain and he's

NOTE Confidence: 0.928401989166667

 $00:56:19.507 \rightarrow 00:56:21.109$ helped us figure out these models.

NOTE Confidence: 0.928401989166667

 $00:56:21.110 \rightarrow 00:56:22.867$ He's very interested in the dxy antibody.

NOTE Confidence: 0.928401989166667

 $00:56:22.870 \rightarrow 00:56:24.586$ We work together all the time,

NOTE Confidence: 0.928401989166667

 $00:56:24.590 \rightarrow 00:56:26.144$ but he also does some other things.

NOTE Confidence: 0.928401989166667

 $00:56:26.150 \longrightarrow 00:56:27.406$ Believe it or not,

NOTE Confidence: 0.928401989166667

 $00{:}56{:}27{.}406 \dashrightarrow 00{:}56{:}28{.}976$ a lot of other things.

NOTE Confidence: 0.928401989166667

 $00{:}56{:}28{.}980 \dashrightarrow 00{:}56{:}31{.}056$ And just recently had a great

NOTE Confidence: 0.928401989166667

 $00{:}56{:}31.056 \dashrightarrow 00{:}56{:}33.171$ paper in nature cell biology where

NOTE Confidence: 0.928401989166667

 $00{:}56{:}33.171 \dashrightarrow 00{:}56{:}35.779$ he reported on a new effect of an

00:56:35.780 --> 00:56:38.305 LRRC 31 protein that significantly

NOTE Confidence: 0.928401989166667

00:56:38.305 --> 00:56:40.325 sensitizes breast cancer brain

NOTE Confidence: 0.928401989166667

 $00:56:40.325 \rightarrow 00:56:42.298$ metastases to radiation therapy.

NOTE Confidence: 0.928401989166667

 $00:56:42.300 \longrightarrow 00:56:44.414$ So it's almost like the universe is.

NOTE Confidence: 0.928401989166667

 $00{:}56{:}44{.}420 \dashrightarrow 00{:}56{:}47{.}580$ Telling us something because that

NOTE Confidence: 0.928401989166667

 $00:56:47.580 \longrightarrow 00:56:50.880$ LRRC 31 protein is great.

NOTE Confidence: 0.928401989166667

 $00:56:50.880 \rightarrow 00:56:54.184$ They can't cross the blood brain barrier.

NOTE Confidence: 0.928401989166667

 $00:56:54.190 \rightarrow 00:56:56.044$ I think I just spent the last 20 minutes

NOTE Confidence: 0.928401989166667

 $00:56:56.044 \rightarrow 00:56:57.565$ talking about an antibody that can

NOTE Confidence: 0.928401989166667

 $00:56:57.565 \dashrightarrow 00:56:59.770$ carry things across the blood brain barrier.

NOTE Confidence: 0.928401989166667

 $00{:}56{:}59{.}770 \dashrightarrow 00{:}57{:}01{.}914$ So we got the Hanson lab and the

NOTE Confidence: 0.928401989166667

 $00:57:01.914 \rightarrow 00:57:03.860$ shower lab working together and we

NOTE Confidence: 0.928401989166667

 $00{:}57{:}03.860 \dashrightarrow 00{:}57{:}06.010$ can put them together and make a

NOTE Confidence: 0.928401989166667

00:57:06.010 --> 00:57:09.098 DX1 LRRC 31 fusion protein that I'm

NOTE Confidence: 0.928401989166667

 $00:57:09.098 \rightarrow 00:57:11.290$ hopeful is going to be next in line

NOTE Confidence: 0.928401989166667

 $00:57:11.354 \rightarrow 00:57:13.531$ to cross over the river through the

- NOTE Confidence: 0.928401989166667
- $00:57:13.531 \longrightarrow 00:57:16.275$ woods and into the brain and increase
- NOTE Confidence: 0.928401989166667
- $00{:}57{:}16.275 \dashrightarrow 00{:}57{:}18.019$ sensitivity to radiation the rapy.
- NOTE Confidence: 0.928401989166667
- $00:57:18.020 \longrightarrow 00:57:21.180$ So hopefully that was of some
- NOTE Confidence: 0.928401989166667
- $00:57:21.180 \dashrightarrow 00:57:22.860$ interest to people listening here.
- NOTE Confidence: 0.928401989166667
- $00{:}57{:}22.860 \dashrightarrow 00{:}57{:}25.236$ I have a lot of people to thank.
- NOTE Confidence: 0.928401989166667
- $00:57:25.240 \longrightarrow 00:57:27.262$ Obviously jeongbang Zhao.
- NOTE Confidence: 0.928401989166667
- $00:57:27.262 \rightarrow 00:57:28.610$ Great colleague.
- NOTE Confidence: 0.928401989166667
- 00:57:28.610 --> 00:57:28.933 Of.
- NOTE Confidence: 0.928401989166667
- $00{:}57{:}28{.}933 \dashrightarrow 00{:}57{:}31{.}517$ Joe Contessa and Marta Bero in his lab
- NOTE Confidence: 0.928401989166667
- $00:57:31.517 \rightarrow 00:57:33.968$ have been incredibly helpful to us.
- NOTE Confidence: 0.928401989166667
- $00:57:33.970 \longrightarrow 00:57:34.882$ My own lab.
- NOTE Confidence: 0.928401989166667
- $00:57:34.882 \rightarrow 00:57:36.706$ I'm extremely grateful to your efforts.
- NOTE Confidence: 0.928401989166667
- 00:57:36.710 --> 00:57:38.486 I'm I'm usually at the gamma knife nowadays,
- NOTE Confidence: 0.928401989166667
- $00{:}57{:}38{.}490 \dashrightarrow 00{:}57{:}39{.}900$ so you probably are wondering
- NOTE Confidence: 0.928401989166667
- $00{:}57{:}39{.}900 \dashrightarrow 00{:}57{:}41{.}530$ where I've been here I am.
- NOTE Confidence: 0.928401989166667

 $00:57:41.530 \rightarrow 00:57:42.400$ If you're looking for me,

NOTE Confidence: 0.928401989166667

00:57:42.400 --> 00:57:43.430 it still looks like me,

NOTE Confidence: 0.928401989166667

00:57:43.430 --> 00:57:43.797 right?

NOTE Confidence: 0.928401989166667

00:57:43.797 $\operatorname{-->}$ 00:57:45.999 And the Yale Gamma knife team

NOTE Confidence: 0.928401989166667

00:57:45.999 - 00:57:47.949 everybody is is great help.

NOTE Confidence: 0.928401989166667

 $00{:}57{:}47{.}950 \dashrightarrow 00{:}57{:}49{.}595$ I'm appreciative to every body but

NOTE Confidence: 0.928401989166667

 $00{:}57{:}49{.}595 \dashrightarrow 00{:}57{:}51{.}548$ last anyone that knows me knows

NOTE Confidence: 0.928401989166667

 $00{:}57{:}51{.}548 \dashrightarrow 00{:}57{:}53{.}556$ that I'm a fan of the Marvel movies

NOTE Confidence: 0.928401989166667

 $00{:}57{:}53{.}556 \dashrightarrow 00{:}57{:}55{.}698$ and the best part about the Marvel

NOTE Confidence: 0.928401989166667

 $00{:}57{:}55{.}698 \dashrightarrow 00{:}57{:}57{.}384$ movies is always there's one more

NOTE Confidence: 0.928401989166667

 $00:57:57.384 \rightarrow 00:57:59.038$ cut scene at the very end, right?

NOTE Confidence: 0.928401989166667

00:57:59.038 --> 00:58:00.478 And I think if you.

NOTE Confidence: 0.928401989166667

 $00:58:00.480 \longrightarrow 00:58:02.020$ Listen very carefully and you

NOTE Confidence: 0.928401989166667

 $00{:}58{:}02{.}020 \dashrightarrow 00{:}58{:}03{.}560$ look off into the horizon.

NOTE Confidence: 0.928401989166667

 $00{:}58{:}03{.}560 \dashrightarrow 00{:}58{:}06{.}992$ You will see that there is a team

NOTE Confidence: 0.928401989166667

 $00:58:06.992 \dashrightarrow 00:58:09.750$ coming assembled led by Pi Megan King.

- NOTE Confidence: 0.928401989166667
- 00:58:09.750 --> 00:58:11.170 Getting the best breast cancer,
- NOTE Confidence: 0.928401989166667
- $00{:}58{:}11{.}170 \dashrightarrow 00{:}58{:}12{.}710$ brains researchers together to
- NOTE Confidence: 0.928401989166667
- $00:58:12.710 \rightarrow 00:58:14.635$ expand and improve DNA targeted
- NOTE Confidence: 0.928401989166667
- $00{:}58{:}14.635 \dashrightarrow 00{:}58{:}16.197$ the rapies towards better breast
- NOTE Confidence: 0.928401989166667
- $00:58:16.197 \rightarrow 00:58:18.067$ cancer treatment with Pat Larusso,
- NOTE Confidence: 0.928401989166667
- 00:58:18.070 --> 00:58:19.870 Megan Kingaby Patel, Ryan Jensen,
- NOTE Confidence: 0.928401989166667
- 00:58:19.870 --> 00:58:20.809 myself and Zhangzhou,
- NOTE Confidence: 0.928401989166667
- $00:58:20.809 \rightarrow 00:58:22.687$ and we're very thrilled to have
- NOTE Confidence: 0.928401989166667
- $00:58:22.687 \longrightarrow 00:58:23.550$ been notified.
- NOTE Confidence: 0.928401989166667
- $00:58:23.550 \rightarrow 00:58:25.485$ Just recently that we've received
- NOTE Confidence: 0.928401989166667
- 00:58:25.485 --> 00:58:27.420 the YCC Team Challenge Award
- NOTE Confidence: 0.928401989166667
- $00{:}58{:}27{.}487 \dashrightarrow 00{:}58{:}28{.}799$ to conduct this work.
- NOTE Confidence: 0.928401989166667
- $00{:}58{:}28{.}800 \dashrightarrow 00{:}58{:}31{.}754$ With that I will take a breath
- NOTE Confidence: 0.928401989166667
- $00:58:31.754 \dashrightarrow 00:58:33.938$ and stop talking and answer any
- NOTE Confidence: 0.928401989166667
- $00:58:33.938 \longrightarrow 00:58:34.730$ questions if there are.
- NOTE Confidence: 0.857410055555556

00:58:36.320 --> 00:58:39.803 Well, I think we're a little short on time,

NOTE Confidence: 0.857410055555556

 $00{:}58{:}39{.}810 \dashrightarrow 00{:}58{:}42{.}960$ so it's it's exactly 1 now.

NOTE Confidence: 0.857410055555556

 $00{:}58{:}42{.}960 \dashrightarrow 00{:}58{:}45{.}660$ James that was great.

NOTE Confidence: 0.857410055555556

00:58:45.660 --> 00:58:47.268 I'm certainly extraordinarily supportive

NOTE Confidence: 0.857410055555556

 $00:58:47.268 \longrightarrow 00:58:50.559$ of anyone who wants to study breast cancer.

NOTE Confidence: 0.857410055555556

 $00{:}58{:}50{.}560 \dashrightarrow 00{:}58{:}53{.}471$ Brain tests is an area that I've

NOTE Confidence: 0.857410055555556

 $00:58:53.471 \rightarrow 00:58:55.158$ thought about a lot over the years,

NOTE Confidence: 0.857410055555556

 $00:58:55.160 \rightarrow 00:58:59.261$ and I would agree with you 100% that it's

NOTE Confidence: 0.857410055555556

 $00:58:59.261 \rightarrow 00:59:03.760$ an area that's perhaps the most in need,

NOTE Confidence: 0.857410055555556

 $00:59:03.760 \longrightarrow 00:59:04.888$ and potentially the most

NOTE Confidence: 0.857410055555556

 $00{:}59{:}04.888 \dashrightarrow 00{:}59{:}06.298$ in need in breast cancer.

NOTE Confidence: 0.857410055555556

00:59:06.300 - 00:59:08.484 Because we we we may well be able

NOTE Confidence: 0.85741005555556

 $00{:}59{:}08{.}484 \dashrightarrow 00{:}59{:}10{.}260$ to eradicate disease elsewhere in

NOTE Confidence: 0.857410055555556

 $00:59:10.260 \rightarrow 00:59:12.594$ virtually everyone in the next decade.

NOTE Confidence: 0.857410055555556

00:59:12.600 -> 00:59:14.196 But the brain is the hardest place,

NOTE Confidence: 0.857410055555556

 $00:59:14.200 \longrightarrow 00:59:15.679$ it seems so.

- NOTE Confidence: 0.857410055555556
- $00{:}59{:}15.679 \dashrightarrow 00{:}59{:}18.587$ With that I wanna thank both
- NOTE Confidence: 0.857410055555556
- $00{:}59{:}18{.}587 \dashrightarrow 00{:}59{:}21{.}209$ both of you for great talks.
- NOTE Confidence: 0.857410055555556
- $00:59:21.210 \dashrightarrow 00:59:23.146$ It's been a great grand rounds and James.
- NOTE Confidence: 0.857410055555556
- $00{:}59{:}23.150 \dashrightarrow 00{:}59{:}25.338$ Congratulations on the on
- NOTE Confidence: 0.85741005555556
- $00:59:25.338 \longrightarrow 00:59:26.979$ the challenge award.
- NOTE Confidence: 0.970526285
- $00{:}59{:}27{.}970 \dashrightarrow 00{:}59{:}30{.}630$ Thank you so much, alright?
- NOTE Confidence: 0.713830828
- 00:59:30.630 -> 00:59:32.460 I made thanks again by e by.
- NOTE Confidence: 0.91101235
- $00:59:35.260 \longrightarrow 00:59:38.000$ And thanks to our audience.