WEBVTT

NOTE duration:"01:06:06"

NOTE recognizability:0.824

NOTE language:en-us

NOTE Confidence: 0.852992580466667

00:00:00.000 --> 00:00:02.310 Trying to normalize a bit now so

NOTE Confidence: 0.852992580466667

 $00:00:02.310 \rightarrow 00:00:04.534$ maybe I'll go ahead and introduce

NOTE Confidence: 0.852992580466667

 $00:00:04.534 \rightarrow 00:00:08.070$ you and then you can get started.

NOTE Confidence: 0.852992580466667

 $00{:}00{:}08{.}070 \dashrightarrow 00{:}00{:}11{.}346$ So it's my honor to introduce Eric Baraki as

NOTE Confidence: 0.852992580466667

 $00:00:11.346 \rightarrow 00:00:14.166$ today's grand round speaker for pathology.

NOTE Confidence: 0.852992580466667

00:00:14.170 --> 00:00:16.005 Eric completed his PhD at

NOTE Confidence: 0.852992580466667

 $00{:}00{:}16.005 \dashrightarrow 00{:}00{:}17.524$ University of Wisconsin, Madison,

NOTE Confidence: 0.852992580466667

 $00:00:17.524 \rightarrow 00:00:19.594$ with Michael Strand on embryonic

NOTE Confidence: 0.852992580466667

 $00:00:19.594 \rightarrow 00:00:21.650$ morphogenesis and Wasps and his

NOTE Confidence: 0.852992580466667

00:00:21.650 --> 00:00:23.350 postdoc at University of Utah.

NOTE Confidence: 0.852992580466667

 $00{:}00{:}23.350 \dashrightarrow 00{:}00{:}26.374$ In the HHMI lab of Carl Thummel on

NOTE Confidence: 0.852992580466667

 $00:00:26.374 \longrightarrow 00:00:28.346$ steroid triggered cell death and

NOTE Confidence: 0.852992580466667

 $00:00:28.346 \rightarrow 00:00:30.034$ resala became an assistant professor

 $00:00:30.034 \rightarrow 00:00:32.028$ at University of Maryland in 1995

NOTE Confidence: 0.852992580466667

 $00:00:32.028 \rightarrow 00:00:33.818$ and then an associate professor,

NOTE Confidence: 0.852992580466667

00:00:33.820 --> 00:00:36.312 before moving to UMass Medical School where

NOTE Confidence: 0.852992580466667

 $00:00:36.312 \rightarrow 00:00:39.018$ he was promoted to full professor in 2015.

NOTE Confidence: 0.852992580466667

 $00:00:39.020 \longrightarrow 00:00:41.220$ He's a leader in the field of atop a G,

NOTE Confidence: 0.852992580466667

 $00:00:41.220 \longrightarrow 00:00:42.865$ having to help define when

NOTE Confidence: 0.852992580466667

 $00:00:42.865 \rightarrow 00:00:44.510$ autophagy is associated with cell

NOTE Confidence: 0.852992580466667

 $00:00:44.572 \rightarrow 00:00:46.438$ survival as opposed to cell death,

NOTE Confidence: 0.852992580466667

00:00:46.440 --> 00:00:48.652 elucidating numerous regulatory mechanisms

NOTE Confidence: 0.852992580466667

 $00:00:48.652 \rightarrow 00:00:51.417$ in autophagy that utilize ubiquitin

NOTE Confidence: 0.852992580466667

 $00{:}00{:}51.417 \dashrightarrow 00{:}00{:}53.880$ micro RNA cell cell communication.

NOTE Confidence: 0.852992580466667

00:00:53.880 --> 00:00:55.188 Moreover, he's linked his

NOTE Confidence: 0.852992580466667

 $00:00:55.188 \rightarrow 00:00:56.823$ studies of autophagy and recycle.

NOTE Confidence: 0.852992580466667

 $00:00:56.830 \rightarrow 00:00:58.735$ It's a major human diseases

NOTE Confidence: 0.852992580466667

00:00:58.735 --> 00:00:59.878 including metabolic disorders,

NOTE Confidence: 0.852992580466667

 $00:00:59.880 \rightarrow 00:01:01.316$ neurodegenerative diseases,

- NOTE Confidence: 0.852992580466667
- 00:01:01.316 --> 00:01:04.188 cancer and movement disorders.
- NOTE Confidence: 0.852992580466667
- $00:01:04.190 \rightarrow 00:01:06.446$ He served on numerous advisory committees.
- NOTE Confidence: 0.852992580466667
- $00:01:06.450 \longrightarrow 00:01:07.464$ Often his chair,
- NOTE Confidence: 0.852992580466667
- $00:01:07.464 \rightarrow 00:01:09.492$ ranging from the NIH panels to
- NOTE Confidence: 0.852992580466667
- $00:01:09.492 \rightarrow 00:01:11.948$ Keystone Scientific advisory boards.
- NOTE Confidence: 0.852992580466667
- 00:01:11.950 --> 00:01:13.460 It's been on editorial board
- NOTE Confidence: 0.852992580466667
- $00:01:13.460 \longrightarrow 00:01:14.668$ of over 10 journals,
- NOTE Confidence: 0.852992580466667
- 00:01:14.670 --> 00:01:16.100 including Co Editor and chief,
- NOTE Confidence: 0.852992580466667
- $00:01:16.100 \longrightarrow 00:01:18.428$ currently for cell death and differentiation,
- NOTE Confidence: 0.852992580466667
- $00:01:18.430 \longrightarrow 00:01:21.265$ and mentored over 40 graduate students and
- NOTE Confidence: 0.852992580466667
- 00:01:21.265 --> 00:01:23.409 postdoctoral fellows within his laboratory.
- NOTE Confidence: 0.852992580466667
- $00:01:23.410 \longrightarrow 00:01:24.990$ Is a widely sought speaker
- NOTE Confidence: 0.852992580466667
- $00:01:24.990 \longrightarrow 00:01:26.570$ with over 40 invited seminars.
- NOTE Confidence: 0.852992580466667
- $00{:}01{:}26{.}570 \dashrightarrow 00{:}01{:}28{.}010$ In the past five years,
- NOTE Confidence: 0.852992580466667
- $00:01:28.010 \longrightarrow 00:01:29.650$ but most notably to me,
- NOTE Confidence: 0.852992580466667

 $00:01:29.650 \longrightarrow 00:01:31.666$ this includes the Boylston

NOTE Confidence: 0.852992580466667

00:01:31.666 --> 00:01:33.682 Elementary School lecture series

NOTE Confidence: 0.852992580466667

00:01:33.682 --> 00:01:35.769 to kindergarten to 4th graders,

NOTE Confidence: 0.852992580466667

 $00:01:35.770 \rightarrow 00:01:37.639$ where he serves serves on the STEM

NOTE Confidence: 0.852992580466667

00:01:37.639 --> 00:01:39.049 Advisory Board for the school,

NOTE Confidence: 0.852992580466667

 $00{:}01{:}39{.}050 \dashrightarrow 00{:}01{:}41{.}714$ so I have no doubt that he'll be

NOTE Confidence: 0.852992580466667

 $00:01:41.714 \longrightarrow 00:01:44.335$ able to help us understand the

NOTE Confidence: 0.852992580466667

 $00{:}01{:}44.335 \dashrightarrow 00{:}01{:}47.026$ field much better with this audience

NOTE Confidence: 0.852992580466667

 $00{:}01{:}47.026 \dashrightarrow 00{:}01{:}50.930$ as he talks to us on Ora Boris on

NOTE Confidence: 0.852992580466667

 $00:01:50.930 \rightarrow 00:01:53.635$ top OG mitochondria and disease.

NOTE Confidence: 0.852992580466667

 $00:01:53.640 \longrightarrow 00:01:54.748$ Floor is all yours.

NOTE Confidence: 0.832739852

00:01:56.340 --> 00:01:58.704 Thank you Sam. That's a very

NOTE Confidence: 0.832739852

 $00:01:58.704 \rightarrow 00:02:00.280$ kind and thoughtful introduction.

NOTE Confidence: 0.832739852

 $00:02:00.280 \longrightarrow 00:02:03.968$ I hope I can live up to that.

NOTE Confidence: 0.832739852

00:02:03.970 --> 00:02:06.210 So yeah, I want to thank Sam,

NOTE Confidence: 0.832739852

 $00:02:06.210 \longrightarrow 00:02:07.850$ Susanna and all the people

- NOTE Confidence: 0.832739852
- $00{:}02{:}07{.}850 \dashrightarrow 00{:}02{:}09{.}490$ I met with this morning.
- NOTE Confidence: 0.832739852
- $00:02:09.490 \rightarrow 00:02:11.906$ Very stimulating morning discussions.
- NOTE Confidence: 0.832739852
- $00:02:11.906 \longrightarrow 00:02:15.180$ And for me, coming to Yale is a
- NOTE Confidence: 0.832739852
- $00:02:15.180 \longrightarrow 00:02:16.640$ little or virtually coming to.
- NOTE Confidence: 0.832739852
- $00:02:16.640 \longrightarrow 00:02:18.744$ Yale is a little bit like coming to
- NOTE Confidence: 0.832739852
- $00{:}02{:}18.744 \dashrightarrow 00{:}02{:}20.811$ Mecca because of some of the overlapping
- NOTE Confidence: 0.832739852
- 00:02:20.811 --> 00:02:22.596 interests of your your faculty.
- NOTE Confidence: 0.832739852
- $00:02:22.596 \longrightarrow 00:02:23.940$ So thanks bro.
- NOTE Confidence: 0.832739852
- 00:02:23.940 --> 00:02:24.750 Great morning.
- NOTE Confidence: 0.7678083
- 00:02:27.110 --> 00:02:31.188 So just to begin, I was always taught
- NOTE Confidence: 0.7678083
- $00:02:31.188 \longrightarrow 00:02:34.440$ that if you can start with a simple
- NOTE Confidence: 0.7678083
- $00:02:34.440 \longrightarrow 00:02:36.930$ message that at least everyone can
- NOTE Confidence: 0.7678083
- $00:02:36.930 \rightarrow 00:02:38.950$ understand from the very beginning,
- NOTE Confidence: 0.7678083
- $00{:}02{:}38{.}950 \dashrightarrow 00{:}02{:}40{.}605$ then you've accomplished at least
- NOTE Confidence: 0.7678083
- $00:02:40.605 \rightarrow 00:02:42.669$ one goal in your lecture or so.
- NOTE Confidence: 0.7678083

00:02:42.670 --> 00:02:45.220 I'm going to begin by showing

NOTE Confidence: 0.7678083

 $00:02:45.220 \longrightarrow 00:02:46.495$ you this creature.

NOTE Confidence: 0.7678083

 $00{:}02{:}46{.}500 \dashrightarrow 00{:}02{:}49{.}680$ The Aura Boris the it's a.

NOTE Confidence: 0.7678083

00:02:49.680 --> 00:02:54.318 It's an ancient symbol of longevity

NOTE Confidence: 0.7678083

 $00:02:54.320 \rightarrow 00:02:56.100$ that's on many Egyptian tombs.

NOTE Confidence: 0.7678083

 $00:02:56.100 \rightarrow 00:02:58.758$ It's been used by union philosophers,

NOTE Confidence: 0.7678083

 $00{:}02{:}58.760 \dashrightarrow 00{:}03{:}01.288$ and I think it's reflective of the process

NOTE Confidence: 0.7678083

 $00:03:01.288 \rightarrow 00:03:03.249$ of autophagy that we studied at it.

NOTE Confidence: 0.7678083

00:03:03.250 --> 00:03:05.740 The the consumption or self consumption

NOTE Confidence: 0.7678083

 $00{:}03{:}05{.}740 \dashrightarrow 00{:}03{:}08{.}519$ of ourselves is really used in many

NOTE Confidence: 0.7678083

 $00{:}03{:}08{.}519 \dashrightarrow 00{:}03{:}10{.}607$ ways to promote self health and

NOTE Confidence: 0.7678083

 $00:03:10.607 \rightarrow 00:03:12.398$ promote longevity and that's

NOTE Confidence: 0.7678083

00:03:12.398 --> 00:03:15.280 how I just wanted to start with the

NOTE Confidence: 0.7678083

 $00{:}03{:}15{.}280 \dashrightarrow 00{:}03{:}17{.}770$ definition of autophagy based on on

NOTE Confidence: 0.7678083

 $00:03:17.770 \longrightarrow 00:03:20.358$ this ancient symbol of horror works.

NOTE Confidence: 0.7678083

 $00:03:20.360 \longrightarrow 00:03:22.538$ Now Full disclosure.

- NOTE Confidence: 0.840434572
- 00:03:25.050 --> 00:03:26.560 Why am I not advancing?
- NOTE Confidence: 0.57325464
- $00:03:29.260 \longrightarrow 00:03:29.590$ So.
- NOTE Confidence: 0.55679458625
- 00:03:32.290 --> 00:03:34.494 OK, so Full disclosure.
- NOTE Confidence: 0.55679458625
- 00:03:34.494 --> 00:03:36.698 I'm address off legend,
- NOTE Confidence: 0.55679458625
- $00{:}03{:}36{.}700 \dashrightarrow 00{:}03{:}38{.}565$ so giving a grand rounds
- NOTE Confidence: 0.55679458625
- 00:03:38.565 --> 00:03:40.730 lecture is not typical for me.
- NOTE Confidence: 0.55679458625
- $00:03:40.730 \longrightarrow 00:03:43.327$ So what I've tried to do is
- NOTE Confidence: 0.55679458625
- 00:03:43.327 -> 00:03:45.233 adapt my presentation to more
- NOTE Confidence: 0.55679458625
- $00:03:45.233 \longrightarrow 00:03:47.018$ of a grand rounds format.
- NOTE Confidence: 0.55679458625
- $00{:}03{:}47{.}020 \dashrightarrow 00{:}03{:}49{.}120$ So this story starts with a 50
- NOTE Confidence: 0.55679458625
- $00:03:49.120 \longrightarrow 00:03:51.844$ or 4 year old male patient with
- NOTE Confidence: 0.55679458625
- $00{:}03{:}51{.}844 \dashrightarrow 00{:}03{:}54{.}020$ history of reading problems
- NOTE Confidence: 0.55679458625
- $00{:}03{:}54{.}020 \dashrightarrow 00{:}03{:}55{.}825$ that presented to his physician
- NOTE Confidence: 0.55679458625
- $00{:}03{:}55{.}825 \dashrightarrow 00{:}03{:}56{.}908$ with gait difficulties.
- NOTE Confidence: 0.91867951375
- $00{:}04{:}00{.}200 \dashrightarrow 00{:}04{:}02{.}450$ First vision problems presented at the
- NOTE Confidence: 0.91867951375

 $00:04:02.450 \longrightarrow 00:04:07.064$ age of 36 and four siblings of 14 total,

NOTE Confidence: 0.91867951375

 $00{:}04{:}07{.}070 \dashrightarrow 00{:}04{:}09{.}618$ so this is what I consider a

NOTE Confidence: 0.91867951375

 $00:04:09.618 \rightarrow 00:04:11.540$ remarkable human genetic experiment.

NOTE Confidence: 0.91867951375

 $00:04:11.540 \rightarrow 00:04:14.180$ Reported similar vision and walking

NOTE Confidence: 0.91867951375

 $00:04:14.180 \longrightarrow 00:04:17.430$ difficulties at the ages of 2326.

NOTE Confidence: 0.89488352

 $00:04:21.430 \longrightarrow 00:04:24.640$ And importantly.

NOTE Confidence: 0.89488352

 $00:04:24.640 \rightarrow 00:04:26.170$ Some reason I'm having trouble events.

NOTE Confidence: 0.89488352

 $00:04:26.170 \longrightarrow 00:04:27.901$ Importantly, the parents

NOTE Confidence: 0.89488352

 $00{:}04{:}27{.}901 \dashrightarrow 00{:}04{:}30{.}209$ exhibit exhibited no symptoms.

NOTE Confidence: 0.89488352

 $00:04:30.210 \longrightarrow 00:04:32.026$ So as a geneticist,

NOTE Confidence: 0.89488352

 $00{:}04{:}32.026 \dashrightarrow 00{:}04{:}34.750$ I am a classically trained genetic ist.

NOTE Confidence: 0.89488352

 $00{:}04{:}34.750 \dashrightarrow 00{:}04{:}39.310$ This is reflective of a recessive.

NOTE Confidence: 0.89488352

 $00:04:39.310 \longrightarrow 00:04:41.053$ Genetic trait where?

NOTE Confidence: 0.89488352

 $00{:}04{:}41.053 \dashrightarrow 00{:}04{:}44.539$ Almost close to the proper medallion

NOTE Confidence: 0.89488352

 $00{:}04{:}44.539 \dashrightarrow 00{:}04{:}47.890$ ratio of individuals from the from.

NOTE Confidence: 0.89488352

 $00:04:47.890 \longrightarrow 00:04:49.890$ These two parents resulted

 $00:04:49.890 \longrightarrow 00:04:52.499$ in this movement disorder.

NOTE Confidence: 0.8773515225

 $00:04:54.540 \rightarrow 00:04:57.188$ They're hearing the patients.

NOTE Confidence: 0.8773515225

 $00:04:57.188 \longrightarrow 00:04:59.836$ They're had no hearing.

NOTE Confidence: 0.8773515225

 $00:04:59.840 \longrightarrow 00:05:02.892$ Cognitive or leg muscle

NOTE Confidence: 0.8773515225

 $00{:}05{:}02.892 \dashrightarrow 00{:}05{:}05.310$ strength alterations and all

NOTE Confidence: 0.8773515225

 $00:05:05.310 \longrightarrow 00:05:07.535$ lower but all lower legs.

NOTE Confidence: 0.8773515225

 $00:05:07.540 \longrightarrow 00:05:08.908$ Hensher modalities square.

NOTE Confidence: 0.8237736466666667

 $00:05:11.050 \dashrightarrow 00:05:14.350$ And this was eventually diagnosed as

NOTE Confidence: 0.8237736466666667

 $00:05:14.350 \rightarrow 00:05:19.342$ spinal cerebellar ataxia and did disease

NOTE Confidence: 0.8237736466666667

 $00:05:19.342 \longrightarrow 00:05:22.172$ progression increased with age and

NOTE Confidence: 0.8237736466666667

 $00:05:22.172 \rightarrow 00:05:24.662$ all five patients required walking.

NOTE Confidence: 0.8237736466666667

 $00{:}05{:}24.670 \dashrightarrow 00{:}05{:}27.442$ So this was published in 2003.

NOTE Confidence: 0.8237736466666667

 $00{:}05{:}27{.}442 \dashrightarrow 00{:}05{:}28{.}610$ Data from this family.

NOTE Confidence: 0.8237736466666667

 $00:05:28.610 \longrightarrow 00:05:31.748$ This was originally a study initiated

NOTE Confidence: 0.8237736466666667

 $00{:}05{:}31.750 \dashrightarrow 00{:}05{:}34.550$ at Case Western, but at that time,

00:05:34.550 --> 00:05:36.830 a human geneticist named Margit Burmeister,

NOTE Confidence: 0.8237736466666667

 $00{:}05{:}36{.}830 \dashrightarrow 00{:}05{:}38{.}846$ who's at the University of Michigan,

NOTE Confidence: 0.8237736466666667

 $00:05:38.850 \rightarrow 00:05:41.160$ became very interested in this population.

NOTE Confidence: 0.8237736466666667

 $00:05:41.160 \rightarrow 00:05:43.492$ This patient population and

NOTE Confidence: 0.8237736466666667

 $00:05:43.492 \rightarrow 00:05:46.990$ started trying to identify the gene

NOTE Confidence: 0.8237736466666667

 $00:05:47.083 \dashrightarrow 00:05:49.859$ responsible for this disorder.

NOTE Confidence: 0.8237736466666667

 $00{:}05{:}49{.}860 \dashrightarrow 00{:}05{:}51{.}450$ And Fast forward.

NOTE Confidence: 0.854598672

 $00{:}05{:}54{.}700 \dashrightarrow 00{:}05{:}59{.}050$ After a lot of work in 2018 Markets

NOTE Confidence: 0.854598672

 $00{:}05{:}59{.}050 \dashrightarrow 00{:}06{:}02{.}589$ Lab published that this this

NOTE Confidence: 0.854598672

 $00{:}06{:}02.589 \dashrightarrow 00{:}06{:}06{.}084$ disorder is because of mutations

NOTE Confidence: 0.854598672

 $00:06:06.084 \dashrightarrow 00:06:10.089$ recessive mutations in the VPS 13 DJ.

NOTE Confidence: 0.854598672

 $00:06:10.090 \rightarrow 00:06:12.737$ That's in this song and.

NOTE Confidence: 0.854598672

 $00:06:12.737 \longrightarrow 00:06:14.365$ Of neurology paper in

NOTE Confidence: 0.854598672

 $00:06:14.365 \longrightarrow 00:06:15.993$ parallel with this paper,

NOTE Confidence: 0.854598672

 $00:06:16.000 \rightarrow 00:06:18.180$ and through communication with Margit,

NOTE Confidence: 0.854598672

00:06:18.180 --> 00:06:21.380 the group studying Lee syndrome

- NOTE Confidence: 0.854598672
- $00{:}06{:}21.380 \dashrightarrow 00{:}06{:}24.452$ in Canada had a a subset of the
- NOTE Confidence: 0.854598672
- $00{:}06{:}24.452 \dashrightarrow 00{:}06{:}26.760$ patients that they were citing.
- NOTE Confidence: 0.854598672
- $00:06:26.760 \dashrightarrow 00:06:31.920$ Also had recessive mutations in the guest 13.
- NOTE Confidence: 0.854598672
- $00:06:31.920 \longrightarrow 00:06:35.308$ And so although VPS 13D is an
- NOTE Confidence: 0.854598672
- $00{:}06{:}35{.}308 \dashrightarrow 00{:}06{:}36{.}760$ extraordinarily rare disease,
- NOTE Confidence: 0.854598672
- $00{:}06{:}36{.}760 \dashrightarrow 00{:}06{:}39{.}040$ and it's interesting that also patients
- NOTE Confidence: 0.854598672
- $00{:}06{:}39{.}040 \dashrightarrow 00{:}06{:}41{.}694$ with Leigh syndrome and this is an
- NOTE Confidence: 0.854598672
- $00:06:41.694 \rightarrow 00:06:43.118$ increasing population of patients
- NOTE Confidence: 0.854598672
- $00:06:43.118 \longrightarrow 00:06:46.188$ that also have mutations in 13.
- NOTE Confidence: 0.943741698888889
- $00:06:48.660 \rightarrow 00:06:51.180$ So while they were actively trying
- NOTE Confidence: 0.943741698888889
- $00:06:51.180 \longrightarrow 00:06:54.552$ to find the identity. Of of this,
- NOTE Confidence: 0.943741698888889
- $00:06:54.552 \rightarrow 00:06:57.720$ the gene responsible for this disorder,
- NOTE Confidence: 0.943741698888889
- $00{:}06{:}57.720 \dashrightarrow 00{:}06{:}59.680$ my lap was studying the process of
- NOTE Confidence: 0.943741698888889
- $00{:}06{:}59{.}680 \dashrightarrow 00{:}07{:}01{.}260$ autophagy and more specifically,
- NOTE Confidence: 0.943741698888889
- 00:07:01.260 00:07:02.952 macroautophagy. In this process,
- NOTE Confidence: 0.943741698888889

00:07:02.952 --> 00:07:06.799 is initiated at A at a membrane source,

NOTE Confidence: 0.943741698888889

 $00:07:06.800 \rightarrow 00:07:10.762$ often the ER, where isolation or fagge

NOTE Confidence: 0.943741698888889

 $00:07:10.762 \dashrightarrow 00:07:13.319$ for membrane forms around cargos.

NOTE Confidence: 0.943741698888889

 $00:07:13.319 \rightarrow 00:07:16.157$ Miss cargos are generally generally been

NOTE Confidence: 0.943741698888889

00:07:16.157 --> 00:07:18.687 thought to be non specific in nature,

NOTE Confidence: 0.943741698888889

 $00:07:18.690 \rightarrow 00:07:21.102$ but I think it increasing evidence

NOTE Confidence: 0.943741698888889

 $00:07:21.102 \longrightarrow 00:07:22.710$ exists that these cargoes

NOTE Confidence: 0.943741698888889

 $00:07:22.782 \longrightarrow 00:07:24.658$ can be exquisitely specific.

NOTE Confidence: 0.943741698888889

 $00{:}07{:}24.660 \dashrightarrow 00{:}07{:}27.372$ And the inclusion of these cargoes

NOTE Confidence: 0.943741698888889

 $00{:}07{:}27.372 \dashrightarrow 00{:}07{:}31.115$ into the fagge form to form and double

NOTE Confidence: 0.943741698888889

 $00{:}07{:}31.115 \dashrightarrow 00{:}07{:}33.527$ membrane out of phagosome therefore

NOTE Confidence: 0.943741698888889

 $00:07:33.527 \rightarrow 00:07:36.362$ targets these cargoes for degradation

NOTE Confidence: 0.943741698888889

 $00:07:36.362 \dashrightarrow 00:07:39.540$ by fusion of autophagosomes Lisa zones,

NOTE Confidence: 0.943741698888889

 $00:07:39.540 \longrightarrow 00:07:43.900$ or vacuoles as they're called in plants.

NOTE Confidence: 0.943741698888889

 $00:07:43.900 \rightarrow 00:07:46.434$ So we were studying this process and

NOTE Confidence: 0.943741698888889

 $00:07:46.434 \rightarrow 00:07:50.195$ we were studying this in in a model

- NOTE Confidence: 0.943741698888889
- $00:07:50.195 \dashrightarrow 00:07:52.520$ Organism for Sofala Melanic Esther.
- NOTE Confidence: 0.943741698888889
- $00{:}07{:}52.520 \dashrightarrow 00{:}07{:}54.935$ And the question that many people ask,
- NOTE Confidence: 0.943741698888889
- $00:07:54.940 \rightarrow 00:07:58.000$ why do you study this this problem and flies,
- NOTE Confidence: 0.943741698888889
- $00:07:58.000 \dashrightarrow 00:08:01.547$ and I think the this cartoon that
- NOTE Confidence: 0.943741698888889
- $00{:}08{:}01{.}547 \dashrightarrow 00{:}08{:}03{.}629$ was devised by my collaborator and
- NOTE Confidence: 0.943741698888889
- $00:08:03.629 \rightarrow 00:08:06.055$ friend Hung Song while we were driving
- NOTE Confidence: 0.943741698888889
- 00:08:06.055 --> 00:08:08.029 to his remote village in China.
- NOTE Confidence: 0.893958240909091
- $00{:}08{:}10.110 \dashrightarrow 00{:}08{:}12.312$ Communicates this so we knew at
- NOTE Confidence: 0.893958240909091
- $00:08:12.312 \longrightarrow 00:08:15.378$ the time that we were the early
- NOTE Confidence: 0.893958240909091
- $00:08:15.378 \rightarrow 00:08:18.398$ studies that we were investigating.
- NOTE Confidence: 0.893958240909091
- $00{:}08{:}18{.}400 \dashrightarrow 00{:}08{:}20{.}485$ That Yoshinori Ohsumi's lab had
- NOTE Confidence: 0.893958240909091
- $00:08:20.485 \longrightarrow 00:08:23.026$ identified most of the genes that
- NOTE Confidence: 0.893958240909091
- $00:08:23.026 \dashrightarrow 00:08:25.700$ were required for what we call the
- NOTE Confidence: 0.893958240909091
- $00:08:25.700 \longrightarrow 00:08:27.911$ core autophagic machinery for studies
- NOTE Confidence: 0.893958240909091
- $00{:}08{:}27{.}911 \dashrightarrow 00{:}08{:}30{.}440$ of the sacrifice service and soon
- NOTE Confidence: 0.893958240909091

 $00:08:30.440 \longrightarrow 00:08:32.540$ after the publication of his work,

NOTE Confidence: 0.893958240909091

 $00:08:32.540 \longrightarrow 00:08:34.852$ a large number of labs and the

NOTE Confidence: 0.893958240909091

 $00:08:34.852 \rightarrow 00:08:36.908$ publication of the human genome.

NOTE Confidence: 0.893958240909091

 $00:08:36.910 \rightarrow 00:08:39.654$ A large number of lab started racing

NOTE Confidence: 0.893958240909091

 $00:08:39.654 \rightarrow 00:08:42.649$ to identify the ortho locks and chains.

NOTE Confidence: 0.893958240909091

 $00:08:42.650 \longrightarrow 00:08:44.852$ But what we have learned from

NOTE Confidence: 0.893958240909091

00:08:44.852 --> 00:08:47.070 studying fruit flies and and worms,

NOTE Confidence: 0.893958240909091

 $00:08:47.070 \rightarrow 00:08:50.412$ and this these are both anatomically

NOTE Confidence: 0.893958240909091

 $00{:}08{:}50{.}412 \dashrightarrow 00{:}08{:}51{.}256$ incorrect animals.

NOTE Confidence: 0.893958240909091

 $00:08:51.256 \rightarrow 00:08:52.686$ I want to just mention,

NOTE Confidence: 0.893958240909091

 $00:08:52.690 \rightarrow 00:08:53.686$ because of course,

NOTE Confidence: 0.893958240909091

00:08:53.686 --> 00:08:55.678 the warm skeletons has no teeth.

NOTE Confidence: 0.827382486363636

 $00:08:57.780 \dashrightarrow 00:08:59.904$ By studying these organisms,

NOTE Confidence: 0.827382486363636

 $00:08:59.904 \rightarrow 00:09:03.090$ we've learned that autophagy is regulated

NOTE Confidence: 0.827382486363636

 $00:09:03.168 \dashrightarrow 00:09:06.410$ in cell and context dependent manner.

NOTE Confidence: 0.827382486363636

 $00:09:06.410 \longrightarrow 00:09:08.874$ And this underlies one of the fundamental

 $00:09:08.880 \rightarrow 00:09:11.408$ tenets of the way we do our science.

NOTE Confidence: 0.827382486363636

 $00:09:11.410 \rightarrow 00:09:14.588$ So we have decided to study autophagy

NOTE Confidence: 0.827382486363636

 $00{:}09{:}14.588 \dashrightarrow 00{:}09{:}15.950$ under developmental contexts.

NOTE Confidence: 0.827382486363636

 $00:09:15.950 \rightarrow 00:09:19.030$ So when autophagy is induced by development,

NOTE Confidence: 0.827382486363636

 $00:09:19.030 \rightarrow 00:09:21.550$ not through some sort of stress condition,

NOTE Confidence: 0.827382486363636

 $00{:}09{:}21.550 \dashrightarrow 00{:}09{:}23.470$ such as chronic starvation

NOTE Confidence: 0.827382486363636

 $00:09:23.470 \rightarrow 00:09:25.390$ or chronic cellular stress,

NOTE Confidence: 0.827382486363636

 $00:09:25.390 \longrightarrow 00:09:28.254$ but rather a development program at the top.

NOTE Confidence: 0.8098079575

00:09:30.510 - 00:09:33.030 Now what we know is in in animals,

NOTE Confidence: 0.8098079575

 $00{:}09{:}33.030 \dashrightarrow 00{:}09{:}35.195$ self context matters and this

NOTE Confidence: 0.8098079575

 $00:09:35.195 \rightarrow 00:09:37.922$ suggests that there could be self

NOTE Confidence: 0.8098079575

 $00:09:37.922 \rightarrow 00:09:40.347$ context specific regulators off G.

NOTE Confidence: 0.8098079575

 $00:09:40.350 \longrightarrow 00:09:41.520$ And just a few pieces of

NOTE Confidence: 0.8098079575

 $00{:}09{:}41.520 \dashrightarrow 00{:}09{:}42.550$ evidence in support of this.

NOTE Confidence: 0.8098079575

 $00:09:42.550 \longrightarrow 00:09:43.708$ There are many at this point,

 $00:09:43.710 \longrightarrow 00:09:45.836$ but I just want to highlight a few

NOTE Confidence: 0.8098079575

 $00{:}09{:}45.836 \dashrightarrow 00{:}09{:}48.251$ and this this is a paper from Kevin

NOTE Confidence: 0.8098079575

00:09:48.251 --> 00:09:50.507 Ryan's lab at the Beatson Institute,

NOTE Confidence: 0.8098079575

 $00{:}09{:}50{.}510 \dashrightarrow 00{:}09{:}52{.}540$ where he showed that the

NOTE Confidence: 0.8098079575

 $00{:}09{:}52.540 \dashrightarrow 00{:}09{:}54.570$ influence of autophagy on tumor

NOTE Confidence: 0.8098079575

 $00:09:54.644 \rightarrow 00:09:56.602$ growth depended on P53 status.

NOTE Confidence: 0.8098079575

 $00:09:56.602 \longrightarrow 00:09:57.906$ So, in other words,

NOTE Confidence: 0.8098079575

 $00:09:57.910 \longrightarrow 00:09:59.590$ if you may want to consider

NOTE Confidence: 0.8098079575

 $00{:}09{:}59{.}590 \dashrightarrow 00{:}10{:}01{.}755$ if you were going to modulate

NOTE Confidence: 0.8098079575

 $00{:}10{:}01.755 \dashrightarrow 00{:}10{:}03.707$ autophagy for the rapeutic purposes,

NOTE Confidence: 0.8098079575

 $00{:}10{:}03.710 \dashrightarrow 00{:}10{:}05.820$ whether or not that tumor

NOTE Confidence: 0.8098079575

 $00:10:05.820 \longrightarrow 00:10:08.400$ has a wild type P50, really.

NOTE Confidence: 0.7714114888888889

 $00{:}10{:}10{.}940 \dashrightarrow 00{:}10{:}14{.}188$ I'm in work that week's lab rated

NOTE Confidence: 0.7714114888888889

 $00:10:14.188 \longrightarrow 00:10:15.866$ with Andreas Bergmann's lab.

NOTE Confidence: 0.771411488888889

 $00{:}10{:}15{.}866 \dashrightarrow 00{:}10{:}18{.}477$ We were able to show that autophagy

NOTE Confidence: 0.771411488888889

 $00:10:18.477 \rightarrow 00:10:21.168$ could either enhance or suppress tissue

 $00:10:21.168 \rightarrow 00:10:24.396$ growth depending on the growth stimulus.

NOTE Confidence: 0.7714114888888889

 $00:10:24.400 \longrightarrow 00:10:25.898$ And so as well as cell type,

NOTE Confidence: 0.7714114888888889

 $00:10:25.900 \rightarrow 00:10:29.495$ what I mean by this it depended if you had

NOTE Confidence: 0.7714114888888889

 $00:10:29.495 \rightarrow 00:10:32.680$ a growth stimulus such as activated wrasse,

NOTE Confidence: 0.771411488888889

 $00{:}10{:}32.680 \dashrightarrow 00{:}10{:}34.800$ modulating autophagy had a

NOTE Confidence: 0.771411488888889

00:10:34.800 - 00:10:38.431 different phenotype than say an

NOTE Confidence: 0.771411488888889

00:10:38.431 --> 00:10:42.716 activated activity of PI3 kinds.

NOTE Confidence: 0.7714114888888889

 $00:10:42.720 \rightarrow 00:10:45.656$ So this also suggests that there's some self

NOTE Confidence: 0.7714114888888889

 $00:10:45.656 \rightarrow 00:10:48.860$ sort of cell or tissue convex specificity.

NOTE Confidence: 0.7714114888888889

00:10:48.860 --> 00:10:49.470 And finally,

NOTE Confidence: 0.7714114888888889

 $00:10:49.470 \rightarrow 00:10:51.300$ we had shown that during development,

NOTE Confidence: 0.771411488888889

 $00{:}10{:}51{.}300 \dashrightarrow 00{:}10{:}53{.}476$ that autophagy can also

NOTE Confidence: 0.771411488888889

 $00:10:53.476 \longrightarrow 00:10:56.196$ influence cell survival or cell,

NOTE Confidence: 0.7714114888888889

 $00{:}10{:}56{.}200 \dashrightarrow 00{:}11{:}00{.}010$ that depending on the developmental context.

NOTE Confidence: 0.771411488888889

 $00:11:00.010 \rightarrow 00:11:03.852$ So. In other words,

 $00:11:03.852 \rightarrow 00:11:06.636$ it is important to understand how

NOTE Confidence: 0.771411488888889

 $00:11:06.636 \rightarrow 00:11:09.950$ this process is regulated in mammals.

NOTE Confidence: 0.7714114888888889

 $00{:}11{:}09{.}950 \dashrightarrow 00{:}11{:}11{.}438$ So the model tissue tissue I'm

NOTE Confidence: 0.7714114888888889

 $00:11:11.438 \longrightarrow 00:11:13.285$ going to talk about today is the

NOTE Confidence: 0.771411488888889

 $00:11:13.285 \longrightarrow 00:11:14.620$ intestine of the flying larva.

NOTE Confidence: 0.762151301666667

 $00{:}11{:}16.790 \dashrightarrow 00{:}11{:}19.868$ In this tissue goes for dramatic

NOTE Confidence: 0.7621513016666667

 $00:11:19.870 \longrightarrow 00:11:21.940$ biological change that's

NOTE Confidence: 0.762151301666667

00:11:21.940 --> 00:11:24.700 triggered by steroid hormone.

NOTE Confidence: 0.762151301666667

00:11:24.700 --> 00:11:27.430 In this biological change shown

NOTE Confidence: 0.762151301666667

 $00:11:27.430 \longrightarrow 00:11:29.614$ in these composite images.

NOTE Confidence: 0.762151301666667

 $00:11:29.620 \longrightarrow 00:11:32.735$ Is that the midgut of the intestine,

NOTE Confidence: 0.762151301666667

 $00:11:32.740 \rightarrow 00:11:35.158$ which is the largely the absorptive

NOTE Confidence: 0.762151301666667

 $00{:}11{:}35{.}158 \dashrightarrow 00{:}11{:}37{.}100$ structure of the intestine that

NOTE Confidence: 0.7621513016666667

 $00:11:37.100 \longrightarrow 00:11:40.958$ at this stage is this long?

NOTE Confidence: 0.762151301666667

 $00:11:40.960 \longrightarrow 00:11:43.648$ In just 6 to 8 hours shrinks in

NOTE Confidence: 0.762151301666667

 $00{:}11{:}43.648 \dashrightarrow 00{:}11{:}46.050$ response to steroid to be missed.

 $00:11:46.050 \rightarrow 00:11:48.170$ So that's pretty remarkable biologically,

NOTE Confidence: 0.762151301666667

 $00:11:48.170 \longrightarrow 00:11:50.502$ but important for us.

NOTE Confidence: 0.762151301666667

 $00{:}11{:}50{.}502 \dashrightarrow 00{:}11{:}53{.}417$ This change in biology correlated

NOTE Confidence: 0.762151301666667

00:11:53.417 - 00:11:56.717 with the induction of autophagy.

NOTE Confidence: 0.762151301666667

00:11:56.720 --> 00:11:59.368 So I'm showing you data here that at

NOTE Confidence: 0.762151301666667

 $00:11:59.368 \rightarrow 00:12:02.072$ this early stage there's none of this

NOTE Confidence: 0.762151301666667

 $00:12:02.072 \rightarrow 00:12:04.821$ autophagia reporter GFP ATG 8 spots in

NOTE Confidence: 0.762151301666667

 $00:12:04.821 \rightarrow 00:12:07.637$ the cells of the intestine at this stage.

NOTE Confidence: 0.762151301666667

 $00{:}12{:}07.640 \dashrightarrow 00{:}12{:}09.386$ Or is it this later stage

NOTE Confidence: 0.762151301666667

 $00:12:09.386 \longrightarrow 00:12:11.040$ just a few hours later?

NOTE Confidence: 0.762151301666667

00:12:11.040 --> 00:12:14.490 You get this robust induction, but off.

NOTE Confidence: 0.762151301666667

 $00{:}12{:}14{.}490 \dashrightarrow 00{:}12{:}16{.}584$ Now I want to emphasize that

NOTE Confidence: 0.762151301666667

 $00{:}12{:}16{.}584 \dashrightarrow 00{:}12{:}18{.}529$ for the reporters that we use,

NOTE Confidence: 0.762151301666667

00:12:18.530 --> 00:12:20.665 these are not miss reporters

NOTE Confidence: 0.7621513016666667

 $00:12:20.665 \rightarrow 00:12:22.373$ that are miss expressed,

 $00:12:22.380 \longrightarrow 00:12:24.692$ but rather these are.

NOTE Confidence: 0.762151301666667

 $00:12:24.692 \rightarrow 00:12:26.426$ These are ATG.

NOTE Confidence: 0.762151301666667

00:12:26.430 --> 00:12:29.280 8 Reporters under control of the

NOTE Confidence: 0.762151301666667

 $00:12:29.280 \rightarrow 00:12:31.900$ endogenous promoter of this machine.

NOTE Confidence: 0.918976363333333

 $00:12:35.460 \longrightarrow 00:12:38.736$ So Fast forward a few years.

NOTE Confidence: 0.918976363333333

00:12:38.740 --> 00:12:42.549 Senkai Chang, who's now in

NOTE Confidence: 0.918976363333333

00:12:42.549 --> 00:12:44.481 biotech in Southern California

NOTE Confidence: 0.918976363333333

 $00:12:44.481 \rightarrow 00:12:46.620$ enjoying some lovely weather,

NOTE Confidence: 0.918976363333333

 $00{:}12{:}46.620 \dashrightarrow 00{:}12{:}49.206$ was able to show that this

NOTE Confidence: 0.918976363333333

 $00:12:49.206 \rightarrow 00:12:51.180$ change in intestines size is

NOTE Confidence: 0.918976363333333

 $00:12:51.180 \longrightarrow 00:12:53.434$ because of a change in cell size.

NOTE Confidence: 0.918976363333333

 $00:12:53.440 \longrightarrow 00:12:55.987$ That's dependent on autophagy.

NOTE Confidence: 0.918976363333333

 $00{:}12{:}55{.}987 \dashrightarrow 00{:}12{:}58{.}766$ So in the larval stage before the

NOTE Confidence: 0.918976363333333

00:12:58.766 --> 00:13:01.380 rise of hormone to cells, are this large,

NOTE Confidence: 0.918976363333333

 $00:13:01.380 \longrightarrow 00:13:03.550$ but following the induction but

NOTE Confidence: 0.918976363333333

 $00:13:03.550 \rightarrow 00:13:06.170$ prodigy is cells reduce in size.

 $00:13:06.170 \longrightarrow 00:13:08.690$ So if you have a single autophagy gene,

NOTE Confidence: 0.918976363333333

 $00{:}13{:}08.690 \dashrightarrow 00{:}13{:}12.526$ mutation cells fail to reduce in size.

NOTE Confidence: 0.918976363333333

 $00:13:12.530 \longrightarrow 00:13:14.133$ Kevin went on to show that this

NOTE Confidence: 0.918976363333333

 $00:13:14.133 \rightarrow 00:13:15.949$ is a cell autonomous process,

NOTE Confidence: 0.918976363333333

 $00:13:15.950 \longrightarrow 00:13:19.126$ so he used an apology reporter that is

NOTE Confidence: 0.918976363333333

 $00:13:19.126 \rightarrow 00:13:22.028$ encoded by every cell in the genome.

NOTE Confidence: 0.918976363333333

 $00:13:22.030 \longrightarrow 00:13:25.214$ When he could show by a single cell,

NOTE Confidence: 0.918976363333333

 $00:13:25.220 \longrightarrow 00:13:27.734$ either loss of function mutations or

NOTE Confidence: 0.918976363333333

 $00{:}13{:}27.734 \dashrightarrow 00{:}13{:}30.680$ RNA I expression in the green cells

NOTE Confidence: 0.918976363333333

 $00{:}13{:}30.680 \dashrightarrow 00{:}13{:}33.459$ that they fail to form these reporter

NOTE Confidence: 0.918976363333333

 $00:13:33.534 \rightarrow 00:13:36.078$ pocta and remained larger in size.

NOTE Confidence: 0.918976363333333

 $00:13:36.080 \longrightarrow 00:13:38.135$ And this was an incredibly

NOTE Confidence: 0.918976363333333

00:13:38.135 - 00:13:39.779 insightful observation for us,

NOTE Confidence: 0.918976363333333

 $00:13:39.780 \longrightarrow 00:13:41.520$ because for for my laboratory,

NOTE Confidence: 0.918976363333333

 $00:13:41.520 \longrightarrow 00:13:44.094$ because this enabled us to use

 $00:13:44.094 \rightarrow 00:13:46.962$ this as a screening platform to

NOTE Confidence: 0.918976363333333

00:13:46.962 --> 00:13:49.622 discover all potentially all of

NOTE Confidence: 0.918976363333333

 $00:13:49.622 \rightarrow 00:13:52.680$ the genes involved in this process.

NOTE Confidence: 0.918976363333333

00:13:52.680 --> 00:13:53.426 So again,

NOTE Confidence: 0.918976363333333

 $00:13:53.426 \longrightarrow 00:13:55.664$ Fast forward a few years and

NOTE Confidence: 0.918976363333333

 $00:13:55.664 \rightarrow 00:13:57.032$ enter Allison Dinding.

NOTE Confidence: 0.918976363333333

 $00:13:57.032 \dashrightarrow 00:14:00.504$ She's now a group leader at Sanofi.

NOTE Confidence: 0.918976363333333

 $00{:}14{:}00{.}510 \dashrightarrow 00{:}14{:}04{.}350$ Allison did us what we call a hypothesis

NOTE Confidence: 0.918976363333333

 $00:14:04.350 \rightarrow 00:14:08.098$ driven screen to identify genes that

NOTE Confidence: 0.918976363333333

 $00:14:08.098 \rightarrow 00:14:11.498$ encode putative ubiquitin binding domains.

NOTE Confidence: 0.918976363333333

00:14:11.498 --> 00:14:14.538 Because certain Chi had identified

NOTE Confidence: 0.918976363333333

00:14:14.538 --> 00:14:16.485 ubiquitous, ubiquitous as an

NOTE Confidence: 0.918976363333333

 $00:14:16.485 \rightarrow 00:14:18.710$ important regulator of this process,

NOTE Confidence: 0.918976363333333

 $00:14:18.710 \rightarrow 00:14:21.668$ she was interested in ubiquitin binding,

NOTE Confidence: 0.918976363333333

 $00{:}14{:}21.670 \dashrightarrow 00{:}14{:}25.919$ protein encoding genes, and she did screen.

NOTE Confidence: 0.918976363333333

 $00:14:25.920 \rightarrow 00:14:29.670$ I believe it was 136 jeans.

- NOTE Confidence: 0.918976363333333
- $00:14:29.670 \longrightarrow 00:14:31.730$ And identified 3 cheats with
- NOTE Confidence: 0.918976363333333
- $00:14:31.730 \longrightarrow 00:14:32.966$ very strong phenotypes.
- NOTE Confidence: 0.918976363333333
- $00{:}14{:}32{.}970 \dashrightarrow 00{:}14{:}35{.}106$ Two of them were in the escort pathway,
- NOTE Confidence: 0.918976363333333
- $00{:}14{:}35{.}110 \dashrightarrow 00{:}14{:}36{.}700$ the other G.
- NOTE Confidence: 0.918976363333333
- 00:14:36.700 --> 00:14:39.304 Plus of course, VPS 13D,
- NOTE Confidence: 0.918976363333333
- $00:14:39.304 \longrightarrow 00:14:42.346$ a somewhat star of this show,
- NOTE Confidence: 0.918976363333333
- $00:14:42.350 \longrightarrow 00:14:45.206$ so this is an example of the
- NOTE Confidence: 0.918976363333333
- $00:14:45.206 \longrightarrow 00:14:47.594$ type of data that we can obtain.
- NOTE Confidence: 0.918976363333333
- $00:14:47.594 \longrightarrow 00:14:48.467$ In this case.
- NOTE Confidence: 0.918976363333333
- 00:14:48.470 --> 00:14:51.025 Allison has expressed in RNA I in
- NOTE Confidence: 0.918976363333333
- $00:14:51.025 \rightarrow 00:14:53.789$ the green or GFP expressing cell.
- NOTE Confidence: 0.918976363333333
- 00:14:53.790 --> 00:14:55.925 You can't see from the data here,
- NOTE Confidence: 0.918976363333333
- $00{:}14{:}55{.}930 \dashrightarrow 00{:}14{:}57{.}687$ but these cells are larger in size.
- NOTE Confidence: 0.918976363333333
- $00{:}14{:}57{.}690 \dashrightarrow 00{:}14{:}59{.}121$ It's all quantified,
- NOTE Confidence: 0.918976363333333
- $00:14:59.121 \longrightarrow 00:15:02.453$ but also you can see that these
- NOTE Confidence: 0.918976363333333

00:15:02.453 --> 00:15:04.768 8G8 apunka fail to form,

NOTE Confidence: 0.918976363333333

 $00:15:04.770 \rightarrow 00:15:07.830$ and we've used other autophagy reporters.

NOTE Confidence: 0.918976363333333

00:15:07.830 --> 00:15:08.324 I I.

NOTE Confidence: 0.918976363333333

00:15:08.324 --> 00:15:10.300 I cannot I can get into more detail

NOTE Confidence: 0.918976363333333

 $00{:}15{:}10.364 \dashrightarrow 00{:}15{:}12.803$ later and I will get into a few more

NOTE Confidence: 0.918976363333333

 $00{:}15{:}12.803 \dashrightarrow 00{:}15{:}14.687$ details of these in a little bit.

NOTE Confidence: 0.918976363333333

 $00{:}15{:}14.690 \dashrightarrow 00{:}15{:}16.685$ But this is 1 important example of

NOTE Confidence: 0.918976363333333

 $00{:}15{:}16.685 \dashrightarrow 00{:}15{:}18.527$ how we can decrease the function

NOTE Confidence: 0.918976363333333

00:15:18.527 --> 00:15:21.106 of a gene in a single cell compared

NOTE Confidence: 0.918976363333333

 $00:15:21.106 \longrightarrow 00:15:22.249$ to its control.

NOTE Confidence: 0.918976363333333

 $00:15:22.250 \rightarrow 00:15:24.510$ Neighboring cells are very

NOTE Confidence: 0.918976363333333

 $00:15:24.510 \rightarrow 00:15:26.770$ powerful single cell approach.

NOTE Confidence: 0.918976363333333

 $00{:}15{:}26.770 \dashrightarrow 00{:}15{:}30.120$ It's not descriptive, it's functional.

NOTE Confidence: 0.918976363333333

 $00{:}15{:}30{.}120 \dashrightarrow 00{:}15{:}31{.}024$ In addition,

NOTE Confidence: 0.918976363333333

 $00:15:31.024 \rightarrow 00:15:33.736$ Allison made loss of function mutations,

NOTE Confidence: 0.918976363333333

 $00:15:33.740 \longrightarrow 00:15:36.008$ and these are true null alleles.

- NOTE Confidence: 0.918976363333333
- 00:15:36.010 00:15:38.450 This is actually a transposon
- NOTE Confidence: 0.918976363333333
- $00:15:38.450 \rightarrow 00:15:40.443$ insertion that completely removes
- NOTE Confidence: 0.918976363333333
- $00{:}15{:}40{.}443 \dashrightarrow 00{:}15{:}43{.}950$ the function of this gene based on
- NOTE Confidence: 0.918976363333333
- $00:15:44.046 \rightarrow 00:15:47.031$ traditional genetic analysis is about
- NOTE Confidence: 0.918976363333333
- $00{:}15{:}47.031 \dashrightarrow 00{:}15{:}49.713$ as well as now protein analysis.
- NOTE Confidence: 0.918976363333333
- $00{:}15{:}49{.}720 \dashrightarrow 00{:}15{:}53{.}104$ And the mutant cells lack GFP in this case,
- NOTE Confidence: 0.918976363333333
- $00{:}15{:}53{.}110 \dashrightarrow 00{:}15{:}55{.}126$ so the mutant cells are all in this
- NOTE Confidence: 0.918976363333333
- $00:15:55.126 \rightarrow 00:15:57.370$ end of this piece of the intestine.
- NOTE Confidence: 0.918976363333333
- $00{:}15{:}57{.}370 \dashrightarrow 00{:}16{:}02{.}170$ Here she's using a mitochondrial
- NOTE Confidence: 0.918976363333333
- $00{:}16{:}02{.}170 \dashrightarrow 00{:}16{:}05{.}376$ V80P SA TP5A antibody as a surrogate
- NOTE Confidence: 0.918976363333333
- $00:16:05.376 \longrightarrow 00:16:07.670$ marker of mitochondria that are
- NOTE Confidence: 0.918976363333333
- $00:16:07.670 \longrightarrow 00:16:09.765$ cargoes that get cleared by
- NOTE Confidence: 0.918976363333333
- 00:16:09.765 --> 00:16:11.650 autophagy in this tissue,
- NOTE Confidence: 0.918976363333333
- $00:16:11.650 \longrightarrow 00:16:13.954$ and you can see that only
- NOTE Confidence: 0.918976363333333
- $00{:}16{:}13.954 \dashrightarrow 00{:}16{:}15.490$ the mutant cells have
- NOTE Confidence: 0.746173798

00:16:15.490 --> 00:16:17.270 failure of clearance by Connor.

NOTE Confidence: 0.746173798

 $00:16:17.270 \longrightarrow 00:16:19.083$ In fact, this little bit of signal

NOTE Confidence: 0.746173798

00:16:19.083 --> 00:16:20.390 that's sticking out down here,

NOTE Confidence: 0.746173798

 $00:16:20.390 \rightarrow 00:16:23.582$ that's actually a mutant cell that's down

NOTE Confidence: 0.746173798

 $00:16:23.582 \rightarrow 00:16:26.428$ behind these control GFP positive cells.

NOTE Confidence: 0.77209772875

 $00:16:29.520 \longrightarrow 00:16:33.328$ So what is VPS? The VPS 13 family.

NOTE Confidence: 0.77209772875

 $00{:}16{:}33{.}330 \dashrightarrow 00{:}16{:}35{.}442$ Well, as I said, I'm it's a little

NOTE Confidence: 0.77209772875

 $00:16:35.442 \longrightarrow 00:16:37.448$ bit like coming to Mecca because

NOTE Confidence: 0.77209772875

 $00{:}16{:}37{.}450 \dashrightarrow 00{:}16{:}42{.}346$ Pietro and Karen, who are here.

NOTE Confidence: 0.77209772875

 $00:16:42.350 \longrightarrow 00:16:44.594$ Have actively been actively

NOTE Confidence: 0.77209772875

 $00:16:44.594 \longrightarrow 00:16:47.399$ studying VPS 13 family proteins.

NOTE Confidence: 0.77209772875

 $00:16:47.400 \longrightarrow 00:16:51.852$ VPS 13, as name implies is a

NOTE Confidence: 0.77209772875

 $00:16:51.852 \rightarrow 00:16:54.094$ vacuole protein sorting encoding

NOTE Confidence: 0.77209772875

 $00{:}16{:}54.094 \dashrightarrow 00{:}16{:}56.098$ gene or that's how it's originally

NOTE Confidence: 0.77209772875

 $00:16:56.098 \rightarrow 00:16:58.139$ identified in the Sacrament service.

NOTE Confidence: 0.77209772875

 $00:16:58.140 \longrightarrow 00:17:01.455$ Yeah, there's one VPS 13

- NOTE Confidence: 0.77209772875
- $00{:}17{:}01.455 \dashrightarrow 00{:}17{:}04.107$ Gene and and sacrifices.
- NOTE Confidence: 0.77209772875
- $00:17:04.110 \rightarrow 00:17:07.568$ In organisms is versus worms to humans,
- NOTE Confidence: 0.77209772875
- $00:17:07.570 \longrightarrow 00:17:10.636$ there are three to four protein encoding
- NOTE Confidence: 0.77209772875
- $00:17:10.636 \rightarrow 00:17:13.849$ genes actually in the fly there are three,
- NOTE Confidence: 0.77209772875
- $00:17:13.850 \rightarrow 00:17:15.980$ and these have traditionally been named
- NOTE Confidence: 0.71485823
- $00:17:18.250 \longrightarrow 00:17:21.992$ VPS. 13 ABC&D. When the fly there
- NOTE Confidence: 0.71485823
- $00:17:21.992 \longrightarrow 00:17:23.900$ are three men code 4 potential
- NOTE Confidence: 0.71485823
- $00{:}17{:}23.965 \dashrightarrow 00{:}17{:}26.125$ proteins in the nomenclature gets
- NOTE Confidence: 0.71485823
- $00:17:26.125 \rightarrow 00:17:29.122$ confusing here because for VPS 13B.
- NOTE Confidence: 0.71485823
- 00:17:29.122 --> 00:17:32.111 They've named them subtype A&B.
- NOTE Confidence: 0.71485823
- $00:17:32.111 \rightarrow 00:17:34.877$ But what's important is that these
- NOTE Confidence: 0.71485823
- $00{:}17{:}34.877 \dashrightarrow 00{:}17{:}38.318$ proteins share a common domain structure,
- NOTE Confidence: 0.71485823
- $00{:}17{:}38{.}320 \dashrightarrow 00{:}17{:}40{.}705$ including a very important work
- NOTE Confidence: 0.71485823
- 00:17:40.705 --> 00:17:43.664 from Pietro and Karen have shown
- NOTE Confidence: 0.71485823
- $00{:}17{:}43.664 \dashrightarrow 00{:}17{:}46.556$ the importance of a lipid transport
- NOTE Confidence: 0.71485823

 $00:17:46.560 \rightarrow 00:17:51.300$ domain that's on the internal rate.

NOTE Confidence: 0.71485823

 $00{:}17{:}51{.}300 \dashrightarrow 00{:}17{:}53{.}362$ It's a very large domain. It's protein.

NOTE Confidence: 0.71485823

 $00{:}17{:}53.362 \dashrightarrow 00{:}17{:}55.768$ What distinguishes D from all other NOTE Confidence: 0.71485823

 $00:17:55.768 \longrightarrow 00:17:57.735$ members of this family, however,

NOTE Confidence: 0.71485823

 $00{:}17{:}57{.}735 \dashrightarrow 00{:}18{:}00{.}390$ is that it is the only member of the

NOTE Confidence: 0.71485823

 $00{:}18{:}00{.}462 \dashrightarrow 00{:}18{:}03{.}090$ family that includes a cute if ubiquitin.

NOTE Confidence: 0.71485823

 $00:18:03.090 \rightarrow 00:18:05.490$ Finding you be a donor.

NOTE Confidence: 0.71485823

 $00{:}18{:}05{.}490 \dashrightarrow 00{:}18{:}08{.}070$ This domain is highly conserved.

NOTE Confidence: 0.71485823

00:18:08.070 --> 00:18:09.966 And we have shown that both

NOTE Confidence: 0.71485823

 $00{:}18{:}09{.}966 \dashrightarrow 00{:}18{:}11{.}230$ humans and in flies.

NOTE Confidence: 0.71485823

00:18:11.230 --> 00:18:13.492 It binds ubiquitin,

NOTE Confidence: 0.71485823

 $00:18:13.492 \rightarrow 00:18:15.530$ preferentially binds K63

NOTE Confidence: 0.71485823

 $00:18:15.530 \longrightarrow 00:18:17.120$ linked ubiquitin chains.

NOTE Confidence: 0.747485610833333

 $00{:}18{:}19{.}310 \dashrightarrow 00{:}18{:}22{.}958$ And also these proteins have so-called

NOTE Confidence: 0.747485610833333

 $00{:}18{:}22{.}958 \dashrightarrow 00{:}18{:}27{.}569$ Lear or else free interaction motifs.

NOTE Confidence: 0.747485610833333

 $00:18:27.570 \rightarrow 00:18:29.558$ But this is a very degenerative sequence.

- NOTE Confidence: 0.747485610833333
- $00{:}18{:}29{.}560 \dashrightarrow 00{:}18{:}31{.}348$ But the reason we were interested
- NOTE Confidence: 0.747485610833333
- $00{:}18{:}31{.}348 \dashrightarrow 00{:}18{:}34{.}555$ in this idea is that then this VPS
- NOTE Confidence: 0.747485610833333
- $00{:}18{:}34{.}555 \dashrightarrow 00{:}18{:}36{.}860$ 13D would have the characteristics
- NOTE Confidence: 0.747485610833333
- $00:18:36.943 \rightarrow 00:18:39.533$ of a so-called autophagy receptor
- NOTE Confidence: 0.747485610833333
- $00:18:39.533 \rightarrow 00:18:42.123$ that might be involved cargo.
- NOTE Confidence: 0.747485610833333
- $00:18:42.130 \longrightarrow 00:18:44.290$ I think our data will later
- NOTE Confidence: 0.747485610833333
- 00:18:44.290 --> 00:18:45.730 debunk this potential function,
- NOTE Confidence: 0.747485610833333
- $00:18:45.730 \longrightarrow 00:18:47.501$ but I just wanted to mention that
- NOTE Confidence: 0.747485610833333
- $00{:}18{:}47{.}501 \dashrightarrow 00{:}18{:}49{.}730$ that was a possibility when we
- NOTE Confidence: 0.747485610833333
- $00:18:49.730 \longrightarrow 00:18:52.139$ started working on this on this gene.
- NOTE Confidence: 0.8532734675
- $00:18:54.490 \longrightarrow 00:18:57.810$ So why should you care about guest 13?
- NOTE Confidence: 0.8532734675
- 00:18:57.810 --> 00:18:59.986 Well, one of the reasons you should care
- NOTE Confidence: 0.8532734675
- $00{:}18{:}59{.}986 \dashrightarrow 00{:}19{:}01{.}686$ about because 13D is its essentiality.
- NOTE Confidence: 0.8532734675
- $00:19:01.686 \longrightarrow 00:19:03.420$ So as a geneticist we always
- NOTE Confidence: 0.8532734675
- $00:19:03.474 \rightarrow 00:19:05.106$ wonder if a gene is important,
- NOTE Confidence: 0.8532734675

 $00:19:05.110 \longrightarrow 00:19:07.987$ and that's typically measured by a valid.

NOTE Confidence: 0.8532734675

 $00:19:07.990 \longrightarrow 00:19:09.765$ So there's this great resource

NOTE Confidence: 0.8532734675

00:19:09.765 --> 00:19:11.995 available at the Broad Institute where

NOTE Confidence: 0.8532734675

 $00:19:11.995 \rightarrow 00:19:13.965$ they screened for gene essentiality.

NOTE Confidence: 0.8532734675

 $00:19:13.970 \rightarrow 00:19:17.085$ What they called in the Achilles score.

NOTE Confidence: 0.8532734675

 $00{:}19{:}17{.}090 \dashrightarrow 00{:}19{:}20{.}858$ And this score indicates if a gene is NOTE Confidence: 0.8532734675

00:19:20.858 --> 00:19:23.730 important, like m
tor or as essential.

NOTE Confidence: 0.8532734675

00:19:23.730 --> 00:19:26.306 A very strong score is minus one,

NOTE Confidence: 0.8532734675

00:19:26.310 --> 00:19:29.052 so she's like m
tor genes required

NOTE Confidence: 0.8532734675

 $00:19:29.052 \longrightarrow 00:19:30.423$ for nucleotide synthesis.

NOTE Confidence: 0.8532734675

 $00{:}19{:}30{.}430 \dashrightarrow 00{:}19{:}33{.}378$ They have scores of minus one genes that

NOTE Confidence: 0.8532734675

 $00{:}19{:}33{.}378 \dashrightarrow 00{:}19{:}35{.}506$ medium Lee are important would be at

NOTE Confidence: 0.8532734675

 $00{:}19{:}35{.}506 \dashrightarrow 00{:}19{:}37{.}964$ the similar to like brocco one and two,

NOTE Confidence: 0.8532734675

 $00:19:37.970 \rightarrow 00:19:41.330$ and genes that would be less important.

NOTE Confidence: 0.8532734675

 $00:19:41.330 \longrightarrow 00:19:42.630$ Maybe not to the Organism,

NOTE Confidence: 0.8532734675

 $00:19:42.630 \longrightarrow 00:19:45.923$ but certainly based on cell

- NOTE Confidence: 0.8532734675
- $00:19:45.923 \longrightarrow 00:19:47.036$ essentiality would be.
- NOTE Confidence: 0.8532734675
- $00{:}19{:}47.040 \dashrightarrow 00{:}19{:}49.469$ It's like Abelson wanted so when we
- NOTE Confidence: 0.8532734675
- $00:19:49.469 \rightarrow 00:19:52.659$ look at the VPS 13 family and this data,
- NOTE Confidence: 0.8532734675
- $00:19:52.660 \rightarrow 00:19:55.612$ this graph was derived when Rd
- NOTE Confidence: 0.8532734675
- $00{:}19{:}55{.}612 \dashrightarrow 00{:}19{:}57{.}384$ had screened 341's outlines.
- NOTE Confidence: 0.8532734675
- $00:19:57.384 \longrightarrow 00:19:59.724$ Some of these are not as such
- NOTE Confidence: 0.8532734675
- $00:19:59.724 \longrightarrow 00:20:00.597$ normal cell lines.
- NOTE Confidence: 0.8532734675
- $00:20:00.600 \longrightarrow 00:20:02.175$ They some of these are
- NOTE Confidence: 0.8532734675
- 00:20:02.175 --> 00:20:03.435 transformed cells of course,
- NOTE Confidence: 0.8532734675
- $00{:}20{:}03{.}440$ --> $00{:}20{:}06{.}660$ but when you compare VPS 13D to a B&C it
- NOTE Confidence: 0.8532734675
- $00{:}20{:}06.746 \dashrightarrow 00{:}20{:}09.889$ is much more essential than most genes.
- NOTE Confidence: 0.8532734675
- $00{:}20{:}09{.}890 \dashrightarrow 00{:}20{:}11{.}922$ In fact in the normal genes and this
- NOTE Confidence: 0.8532734675
- $00{:}20{:}11{.}922 \dashrightarrow 00{:}20{:}13{.}577$ is something Pietro rates with me.
- NOTE Confidence: 0.8532734675
- $00{:}20{:}13.580 \dashrightarrow 00{:}20{:}13.898$ Earlier.
- NOTE Confidence: 0.8532734675
- $00{:}20{:}13.898 \dashrightarrow 00{:}20{:}16.124$ It is one of the most essential

- NOTE Confidence: 0.8532734675
- $00:20:16.124 \rightarrow 00:20:17.528$ genes encoded by our gene.

00:20:17.530 --> 00:20:18.238 This time,

NOTE Confidence: 0.8532734675

 $00:20:18.238 \longrightarrow 00:20:21.667$ on the early day that I came on out

NOTE Confidence: 0.8532734675

 $00:20:21.667 \rightarrow 00:20:24.197$ on normal lawns transform cells.

NOTE Confidence: 0.8532734675

 $00{:}20{:}24{.}200 \dashrightarrow 00{:}20{:}26{.}260$ In addition.

NOTE Confidence: 0.8532734675

 $00{:}20{:}26{.}260 \dashrightarrow 00{:}20{:}29{.}690$ We know from flies that strong alleles

NOTE Confidence: 0.8532734675

00:20:29.690 --> 00:20:33.818 of VPS 13 VR laid embryonic people,

NOTE Confidence: 0.8532734675

 $00{:}20{:}33.820 \dashrightarrow 00{:}20{:}36.753$ and our recent studies of mice have

NOTE Confidence: 0.8532734675

 $00:20:36.753 \rightarrow 00:20:40.066$ also shown that it is an essential gene.

NOTE Confidence: 0.8532734675

00:20:40.070 --> 00:20:41.102 In fact,

NOTE Confidence: 0.8532734675

 $00:20:41.102 \longrightarrow 00:20:43.682$ using we've generated a floxed

NOTE Confidence: 0.8532734675

00:20:43.682 --> 00:20:46.864 mouse allele and when we combine

NOTE Confidence: 0.8532734675

00:20:46.864 --> 00:20:48.916 this with nest inquiry,

NOTE Confidence: 0.8532734675

 $00:20:48.920 \longrightarrow 00:20:51.410$ which is often used to study

NOTE Confidence: 0.8532734675

 $00:20:51.410 \longrightarrow 00:20:52.240$ neurological phenotypes,

 $00:20:52.240 \rightarrow 00:20:54.108$ these are embryonic lethal,

NOTE Confidence: 0.8532734675

 $00{:}20{:}54.108 \dashrightarrow 00{:}20{:}56.910$ so it is an incredibly important.

NOTE Confidence: 0.8532734675

 $00{:}20{:}56{.}910 \dashrightarrow 00{:}20{:}57{.}580$ Gene.

NOTE Confidence: 0.917001302

 $00{:}21{:}01.760 \dashrightarrow 00{:}21{:}04.118$ And therefore I should make this

NOTE Confidence: 0.917001302

 $00{:}21{:}04{.}118 \dashrightarrow 00{:}21{:}06{.}554$ important point there for UM in.

NOTE Confidence: 0.917001302

 $00{:}21{:}06{.}554 \dashrightarrow 00{:}21{:}09{.}578$ In humans, we assumed the patient alleles. NOTE Confidence: 0.81731535

INCITE Connuclice: 0.01101000

00:21:12.090 --> 00:21:17.160 Now every scientist that I know waits for

NOTE Confidence: 0.81731535

 $00{:}21{:}17.160 \dashrightarrow 00{:}21{:}20.530$ these what I call Eureka and one day.

NOTE Confidence: 0.81731535

 $00{:}21{:}20{.}530 \dashrightarrow 00{:}21{:}22{.}966$ Allison, who had discovered VPS 13D

NOTE Confidence: 0.81731535

 $00{:}21{:}22{.}966 \dashrightarrow 00{:}21{:}25{.}401$ in my lab and actually it was a nun

NOTE Confidence: 0.81731535

 $00{:}21{:}25{.}401 \dashrightarrow 00{:}21{:}27{.}487$ named Jean at that at that time.

NOTE Confidence: 0.81731535

 $00:21:27.490 \longrightarrow 00:21:31.396$ She had just obtained RNA I.

NOTE Confidence: 0.81731535

00:21:31.400 --> 00:21:36.458 TM data from knockdown, tested cells.

NOTE Confidence: 0.81731535

 $00:21:36.460 \longrightarrow 00:21:38.152$ And she came to my office

NOTE Confidence: 0.81731535

 $00{:}21{:}38{.}152 \dashrightarrow 00{:}21{:}39{.}280$ and she screamed out.

NOTE Confidence: 0.81731535

 $00:21:39.280 \longrightarrow 00:21:40.780$ We have mighty kandariya

- NOTE Confidence: 0.81731535
- $00{:}21{:}40.780 \dashrightarrow 00{:}21{:}42.655$ and I thought to myself,
- NOTE Confidence: 0.81731535
- $00{:}21{:}42.660 \dashrightarrow 00{:}21{:}45.030$ what are mighty kandariya and
- NOTE Confidence: 0.81731535
- $00:21:45.030 \rightarrow 00:21:48.140$ when she showed me the images,
- NOTE Confidence: 0.81731535
- $00{:}21{:}48.140 \dashrightarrow 00{:}21{:}51.860$ I really almost fell off my chair because
- NOTE Confidence: 0.81731535
- $00{:}21{:}51{.}860 \dashrightarrow 00{:}21{:}53{.}870$ the images of the control intestines
- NOTE Confidence: 0.81731535
- $00:21:53.870 \longrightarrow 00:21:56.487$ on the top are the same magnification
- NOTE Confidence: 0.81731535
- $00{:}21{:}56{.}487 \dashrightarrow 00{:}21{:}58{.}899$ as the intestines on the bottom.
- NOTE Confidence: 0.81731535
- $00:21:58.900 \longrightarrow 00:22:00.846$ And what you can see is that
- NOTE Confidence: 0.81731535
- $00{:}22{:}00{.}846 \dashrightarrow 00{:}22{:}02{.}230$ these mitochondria are enormous.
- NOTE Confidence: 0.81731535
- $00:22:02.230 \longrightarrow 00:22:04.456$ In fact, mitochondrial experts that see these
- NOTE Confidence: 0.81731535
- $00:22:04.456 \rightarrow 00:22:06.910$ say they're some of the largest mitochondria.
- NOTE Confidence: 0.81731535
- $00{:}22{:}06{.}910 \dashrightarrow 00{:}22{:}09{.}150$ There are some larger
- NOTE Confidence: 0.81731535
- $00{:}22{:}09{.}150 \dashrightarrow 00{:}22{:}11{.}390$ mitochondria in the literature.
- NOTE Confidence: 0.81731535
- $00{:}22{:}11{.}390 \dashrightarrow 00{:}22{:}12{.}940$ And and they they are.
- NOTE Confidence: 0.81731535
- $00:22:12.940 \rightarrow 00:22:14.110$ They are derived.
- NOTE Confidence: 0.81731535

 $00{:}22{:}14.110 \dashrightarrow 00{:}22{:}16.450$ Those mitochondria that occur are because

NOTE Confidence: 0.81731535

 $00{:}22{:}16.450 \dashrightarrow 00{:}22{:}19.366$ of different types of mutant combinations,

NOTE Confidence: 0.81731535

 $00{:}22{:}19{.}370 \dashrightarrow 00{:}22{:}21{.}200$ but it's pretty remarkable about

NOTE Confidence: 0.81731535

 $00:22:21.200 \rightarrow 00:22:23.030$ these giant mitochondria as they

NOTE Confidence: 0.81731535

 $00{:}22{:}23.090 \dashrightarrow 00{:}22{:}24.950$ seem to be relatively functional.

NOTE Confidence: 0.81731535

 $00:22:24.950 \longrightarrow 00:22:27.866$ Again, we can discuss that later.

NOTE Confidence: 0.81731535

00:22:27.870 --> 00:22:29.494 How functional they are,

NOTE Confidence: 0.81731535

 $00:22:29.494 \rightarrow 00:22:31.930$ but the from a morphological perspective,

NOTE Confidence: 0.81731535

 $00{:}22{:}31{.}930 \dashrightarrow 00{:}22{:}35{.}410$ they're Christy are juxtaposed and

NOTE Confidence: 0.81731535

 $00{:}22{:}35{.}410 \dashrightarrow 00{:}22{:}36{.}795$ and we've done some biochemical

NOTE Confidence: 0.81731535

 $00:22:36.795 \longrightarrow 00:22:38.609$ as says and they seem like they

NOTE Confidence: 0.81731535

 $00:22:38.609 \rightarrow 00:22:39.740$ are relatively functional.

NOTE Confidence: 0.813930169090909

 $00:22:41.800 \longrightarrow 00:22:43.310$ But this phenotype was so

NOTE Confidence: 0.813930169090909

 $00:22:43.310 \longrightarrow 00:22:45.060$ strong and so apparent to us,

NOTE Confidence: 0.813930169090909

 $00:22:45.060 \rightarrow 00:22:46.600$ this is something we pursued.

NOTE Confidence: 0.813930169090909

 $00:22:46.600 \rightarrow 00:22:49.072$ We continue to pursue it because

- NOTE Confidence: 0.813930169090909
- $00:22:49.072 \rightarrow 00:22:50.990$ it's extremely interesting to us.
- NOTE Confidence: 0.813930169090909
- $00{:}22{:}50{.}990 \dashrightarrow 00{:}22{:}53{.}078$ In addition, we collaborated with Richard
- NOTE Confidence: 0.813930169090909
- 00:22:53.078 --> 00:22:55.408 Uhl Slab and specifically Chung Wong,
- NOTE Confidence: 0.813930169090909
- $00:22:55.410 \longrightarrow 00:22:57.685$ who is his his before CRISPR was
- NOTE Confidence: 0.813930169090909
- 00:22:57.685 --> 00:22:59.449 an everyday thing for people.
- NOTE Confidence: 0.813930169090909
- $00{:}22{:}59{.}450 \dashrightarrow 00{:}23{:}02{.}836$ He he was knocking out genes and Richard
- NOTE Confidence: 0.813930169090909
- $00:23:02.836 \longrightarrow 00:23:06.700$ Lab and what he did is he generated
- NOTE Confidence: 0.813930169090909
- 00:23:06.812 --> 00:23:09.191 3 independent knockout cell line.
- NOTE Confidence: 0.813930169090909
- $00:23:09.191 \longrightarrow 00:23:12.552$ He la cell lines and what we saw you
- NOTE Confidence: 0.813930169090909
- $00:23:12.552 \rightarrow 00:23:15.114$ know typically was very similar between
- NOTE Confidence: 0.813930169090909
- 00:23:15.114 --> 00:23:19.538 control and VPS 13D Knockout cells.
- NOTE Confidence: 0.813930169090909
- $00:23:19.540 \longrightarrow 00:23:21.500$ Or was it should say,
- NOTE Confidence: 0.813930169090909
- $00:23:21.500 \longrightarrow 00:23:22.780$ common to all the VPS,
- NOTE Confidence: 0.813930169090909
- $00{:}23{:}22{.}780 \dashrightarrow 00{:}23{:}25{.}450$ 13 knock
out cells and that the
- NOTE Confidence: 0.813930169090909
- $00{:}23{:}25{.}450 \dashrightarrow 00{:}23{:}27{.}640$ mitochondria look larger and rounder in
- NOTE Confidence: 0.813930169090909
$00:23:27.640 \longrightarrow 00:23:30.620$ the heel of cells and not filamentous,

NOTE Confidence: 0.813930169090909

 $00{:}23{:}30{.}620 \dashrightarrow 00{:}23{:}33{.}356$ as we typically think of mitochondria

NOTE Confidence: 0.813930169090909

 $00:23:33.356 \longrightarrow 00:23:34.188$ and yellow?

NOTE Confidence: 0.840020908181818

 $00:23:36.240 \longrightarrow 00:23:38.400$ And it's important to note that

NOTE Confidence: 0.840020908181818

 $00:23:38.400 \longrightarrow 00:23:40.211$ this mitochondrial phenotype in all

NOTE Confidence: 0.840020908181818

 $00:23:40.211 \rightarrow 00:23:42.409$ of these cell lines was rescued by

NOTE Confidence: 0.840020908181818

 $00:23:42.409 \rightarrow 00:23:43.958$ the introduction of its 13D plasma,

NOTE Confidence: 0.840020908181818

 $00{:}23{:}43.958 \dashrightarrow 00{:}23{:}46.030$ so this was not some sort of off

NOTE Confidence: 0.840020908181818

00:23:46.093 -> 00:23:47.977 target effect of the crystal.

NOTE Confidence: 0.9086001566666667

 $00{:}23{:}50{.}220 \dashrightarrow 00{:}23{:}52{.}453$ So some of the important questions that

NOTE Confidence: 0.9086001566666667

 $00{:}23{:}52{.}453 \dashrightarrow 00{:}23{:}54{.}586$ we would like to address our water,

NOTE Confidence: 0.9086001566666667

 $00:23:54.586 \longrightarrow 00:23:55.598$ the genes that function

NOTE Confidence: 0.9086001566666667

00:23:55.598 --> 00:23:57.080 of the VPS 13D pathway.

NOTE Confidence: 0.9086001566666667

 $00:23:57.080 \longrightarrow 00:23:58.431$ This is one of the strengths of

NOTE Confidence: 0.9086001566666667

 $00:23:58.431 \longrightarrow 00:23:59.838$ the lab is a fly geneticist.

NOTE Confidence: 0.9086001566666667

 $00:23:59.840 \longrightarrow 00:24:02.120$ We're always trying to identify

- NOTE Confidence: 0.9086001566666667
- $00:24:02.120 \longrightarrow 00:24:04.400$ more genes that functions pathway.
- NOTE Confidence: 0.9086001566666667
- $00{:}24{:}04{.}400 \dashrightarrow 00{:}24{:}06{.}687$ Where is the primary defect in V
- NOTE Confidence: 0.9086001566666667
- $00{:}24{:}06.687 \dashrightarrow 00{:}24{:}09.129$ PS13D cells that leads to disease.
- NOTE Confidence: 0.9086001566666667
- 00:24:09.130 --> 00:24:12.742 How does V PS13D influence such
- NOTE Confidence: 0.9086001566666667
- $00{:}24{:}12.742 \dashrightarrow 00{:}24{:}15.074$ diverse cellular processes and
- NOTE Confidence: 0.908600156666667
- $00:24:15.074 \rightarrow 00:24:17.170$ can ultimately for patients?
- NOTE Confidence: 0.9086001566666667
- $00:24:17.170 \longrightarrow 00:24:19.530$ It would be very useful if we can
- NOTE Confidence: 0.908600156666667
- $00:24:19.530 \rightarrow 00:24:21.109$ identify genetic suppressors and best
- NOTE Confidence: 0.9086001566666667
- $00:24:21.109 \longrightarrow 00:24:23.708$ 13 feet because of course if we can
- NOTE Confidence: 0.9086001566666667
- $00{:}24{:}23.708 \dashrightarrow 00{:}24{:}26.012$ identify suppressors then we can think
- NOTE Confidence: 0.9086001566666667
- $00:24:26.012 \longrightarrow 00:24:28.430$ about modulating these factors as
- NOTE Confidence: 0.9086001566666667
- $00:24:28.430 \longrightarrow 00:24:30.950$ potential therapeutic strategies and.
- NOTE Confidence: 0.9086001566666667
- $00:24:30.950 \longrightarrow 00:24:32.478$ I just want to step back to the
- NOTE Confidence: 0.9086001566666667
- $00{:}24{:}32{.}478 \dashrightarrow 00{:}24{:}34{.}190$ disease a little bit because at the
- NOTE Confidence: 0.9086001566666667
- 00:24:34.190 --> 00:24:35.779 beginning I introduced you to one
- NOTE Confidence: 0.9086001566666667

 $00:24:35.779 \rightarrow 00:24:37.571$ patient family that has some of the

NOTE Confidence: 0.9086001566666667

 $00:24:37.571 \rightarrow 00:24:39.654$ weaker alliance probably of the VPS.

NOTE Confidence: 0.908600156666667

 $00{:}24{:}39{.}654 \dashrightarrow 00{:}24{:}42{.}000$ 13D patients that are like that

NOTE Confidence: 0.908600156666667

 $00:24:42.077 \longrightarrow 00:24:44.618$ and identified some of the some

NOTE Confidence: 0.9086001566666667

 $00{:}24{:}44{.}618 \dashrightarrow 00{:}24{:}46{.}850$ one of the saddest stories is

NOTE Confidence: 0.9086001566666667

 $00{:}24{:}46{.}937 \dashrightarrow 00{:}24{:}49{.}607$ that there are some children that

NOTE Confidence: 0.9086001566666667

00:24:49.610 --> 00:24:52.445 have mutations in VTS 13D they get

NOTE Confidence: 0.908600156666667

 $00:24:52.445 \rightarrow 00:24:55.090$ disease early in life or normally,

NOTE Confidence: 0.9086001566666667

 $00:24:55.090 \rightarrow 00:24:58.218$ but by three to five years their wheelchair

NOTE Confidence: 0.9086001566666667

 $00{:}24{:}58{.}218 \dashrightarrow 00{:}25{:}01{.}119$ about so it really is a very tragic.

NOTE Confidence: 0.9086001566666667

 $00{:}25{:}01{.}120 \dashrightarrow 00{:}25{:}03{.}730$ A disease that affects these children.

NOTE Confidence: 0.8839502

 $00{:}25{:}06{.}830 \dashrightarrow 00{:}25{:}11{.}139$ So. Big question for us was what genes?

NOTE Confidence: 0.8839502

 $00{:}25{:}11.140 \dashrightarrow 00{:}25{:}13.018$ Because we knew nothing about this

NOTE Confidence: 0.8839502

 $00{:}25{:}13.018 \dashrightarrow 00{:}25{:}15.420$ as we started and So what other genes

NOTE Confidence: 0.8839502

 $00{:}25{:}15{.}420 \dashrightarrow 00{:}25{:}18{.}115$ are in the BTS 13 pathway and a big

NOTE Confidence: 0.8839502

 $00{:}25{:}18.115 \dashrightarrow 00{:}25{:}19.890$ break through for us came through

- NOTE Confidence: 0.8839502
- 00:25:19.890 --> 00:25:22.248 my friend and colleague Hangzhou,

 $00{:}25{:}22{.}250 \dashrightarrow 00{:}25{:}24.756$ who's at the Institute of Biophysics in

NOTE Confidence: 0.8839502

00:25:24.756 --> 00:25:27.629 in Beijing but also has a small joint

NOTE Confidence: 0.8839502

 $00:25:27.629 \rightarrow 00:25:29.890$ appointment at U mass medical school.

NOTE Confidence: 0.8839502

00:25:29.890 --> 00:25:32.138 His postdoc yen Chow,

NOTE Confidence: 0.8839502

 $00:25:32.138 \longrightarrow 00:25:35.510$ who is now at SUS Tech.

NOTE Confidence: 0.8839502

00:25:35.510 -> 00:25:37.718 In in running her own lab,

NOTE Confidence: 0.8839502

 $00:25:37.720 \longrightarrow 00:25:39.862$ but in this photograph is shown here

NOTE Confidence: 0.8839502

 $00:25:39.862 \rightarrow 00:25:43.045$ in my lab and in Hong's graduates to

NOTE Confidence: 0.8839502

 $00{:}25{:}43.045 \dashrightarrow 00{:}25{:}46.704$ Twitch and what they did is they were

NOTE Confidence: 0.8839502

 $00:25:46.704 \rightarrow 00:25:49.470$ screening for genetic modifiers of a

NOTE Confidence: 0.8839502

 $00{:}25{:}49{.}564 \dashrightarrow 00{:}25{:}53{.}312$ gene called EPG three and WORMS it's V MP1.

NOTE Confidence: 0.8839502

 $00{:}25{:}53{.}312 \dashrightarrow 00{:}25{:}55{.}454$ This is a gene they've been very

NOTE Confidence: 0.8839502

 $00{:}25{:}55{.}454 \dashrightarrow 00{:}25{:}57{.}186$ interested in and they found

NOTE Confidence: 0.8839502

 $00{:}25{:}57.186 \dashrightarrow 00{:}26{:}00.390$ a genetic interaction today.

- $00:26:00.390 \longrightarrow 00:26:01.914$ So this was a.
- NOTE Confidence: 0.8839502
- $00:26:01.914 \rightarrow 00:26:04.550$ This is a very interesting to us,
- NOTE Confidence: 0.8839502
- $00:26:04.550 \rightarrow 00:26:08.366$ but also I think to your colleagues
- NOTE Confidence: 0.8839502
- $00:26:08.366 \rightarrow 00:26:11.594$ Karen Tom and yeah troll because
- NOTE Confidence: 0.8839502
- $00{:}26{:}11.594 \dashrightarrow 00{:}26{:}14.670$ VMP 1 encodes a lipid scramblers.
- NOTE Confidence: 0.662068463636364
- $00{:}26{:}17.340$ --> $00{:}26{:}20.382$ Importantly, Hong slab or yen specifically NOTE Confidence: 0.662068463636364
- 1011 Connuclee: 0.002000405050504
- $00{:}26{:}20{.}382 \dashrightarrow 00{:}26{:}25{.}010$ had shown that VMP 1 depletion results in
- NOTE Confidence: 0.662068463636364
- $00:26:25.010 \rightarrow 00:26:28.944$ an altered by chondral shape and Assoc.
- NOTE Confidence: 0.662068463636364
- $00{:}26{:}28{.}950 \dashrightarrow 00{:}26{:}31{.}890$ If you are in the mitochondrial shape
- NOTE Confidence: 0.662068463636364
- $00:26:31.890 \rightarrow 00:26:34.132$ change that Janss observed similar
- NOTE Confidence: 0.662068463636364
- $00:26:34.132 \longrightarrow 00:26:36.826$ to what we had observed blood.
- NOTE Confidence: 0.662068463636364
- 00:26:36.830 --> 00:26:40.603 So. Enter at the time MD PhD
- NOTE Confidence: 0.662068463636364
- 00:26:40.603 --> 00:26:43.458 candidate James sat in my lab,
- NOTE Confidence: 0.662068463636364
- 00:26:43.460 --> 00:26:46.987 he's now a PhD still at UMass, rotating.
- NOTE Confidence: 0.662068463636364
- $00:26:46.987 \rightarrow 00:26:50.269$ James is quite a remarkable student.
- NOTE Confidence: 0.662068463636364
- $00:26:50.270 \rightarrow 00:26:52.472$ He went through a remarkable transformation

- NOTE Confidence: 0.662068463636364
- 00:26:52.472 --> 00:26:54.380 in medical and Graduate School,
- NOTE Confidence: 0.662068463636364
- $00{:}26{:}54{.}380 \dashrightarrow 00{:}26{:}56{.}744$ and he went from this individual
- NOTE Confidence: 0.662068463636364
- $00:26:56.744 \rightarrow 00:26:59.448$ shown in his pre pre Med
- NOTE Confidence: 0.662068463636364
- $00:26:59.448 \longrightarrow 00:27:01.540$ application to being essential.
- NOTE Confidence: 0.662068463636364
- 00:27:01.540 --> 00:27:03.745 But he's also he's a he's a
- NOTE Confidence: 0.662068463636364
- $00{:}27{:}03.745 \dashrightarrow 00{:}27{:}04.375$ fearless scientist.
- NOTE Confidence: 0.662068463636364
- $00{:}27{:}04{.}380 \dashrightarrow 00{:}27{:}06{.}460$ He's taken on every problem that I feed
- NOTE Confidence: 0.662068463636364
- $00:27:06.460 \rightarrow 00:27:08.979$ him and got much more than I ever expected.
- NOTE Confidence: 0.891430079
- $00{:}27{:}11{.}370 \dashrightarrow 00{:}27{:}13{.}946$ So what James did first was to
- NOTE Confidence: 0.891430079
- 00:27:13.946 --> 00:27:16.106 actually knock down V MP1 in the
- NOTE Confidence: 0.891430079
- $00:27:16.106 \rightarrow 00:27:17.426$ intestine cells we were studying,
- NOTE Confidence: 0.891430079
- 00:27:17.430 --> 00:27:20.364 and what he saw that there was a huge
- NOTE Confidence: 0.891430079
- $00:27:20.364 \rightarrow 00:27:22.910$ influence on cell size reduction and
- NOTE Confidence: 0.891430079
- $00{:}27{:}22{.}910 \dashrightarrow 00{:}27{:}27{.}250$ locked the formation of M Cherry ATG,
- NOTE Confidence: 0.891430079
- $00:27:27.250 \rightarrow 00:27:30.786$ a puncta as you can save it RNA.
- NOTE Confidence: 0.891430079

00:27:30.790 --> 00:27:34.718 I expressing cells and grain have no ATG 8M.

NOTE Confidence: 0.688754621428571

 $00{:}27{:}36{.}960 \dashrightarrow 00{:}27{:}38{.}595$ 8:00 AM Cherry Puncta and

NOTE Confidence: 0.688754621428571

00:27:38.595 --> 00:27:40.230 they are clearly much larger

NOTE Confidence: 0.688754621428571

 $00:27:40.299 \rightarrow 00:27:42.059$ than their neighboring cells,

NOTE Confidence: 0.688754621428571

 $00:27:42.060 \longrightarrow 00:27:44.400$ similar to the past 13 D.

NOTE Confidence: 0.688754621428571

 $00{:}27{:}44{.}400 \dashrightarrow 00{:}27{:}46{.}944$ In addition, they accumulate a protein

NOTE Confidence: 0.688754621428571

 $00{:}27{:}46{.}944 \dashrightarrow 00{:}27{:}49{.}417$ that's called ref 2P and flies

NOTE Confidence: 0.688754621428571

 $00{:}27{:}49{.}417 \dashrightarrow 00{:}27{:}51{.}874$ because it was named before our P.

NOTE Confidence: 0.688754621428571

 $00{:}27{:}51{.}880 \dashrightarrow 00{:}27{:}53{.}480$ 62 was identified in mammals.

NOTE Confidence: 0.688754621428571

 $00{:}27{:}53.480 \dashrightarrow 00{:}27{:}56.258$ This is an autophagic cargo receptor,

NOTE Confidence: 0.688754621428571

00:27:56.260 --> 00:27:58.760 so when AUTOPHAGIA is active,

NOTE Confidence: 0.688754621428571

 $00:27:58.760 \longrightarrow 00:28:01.088$ P60 true gets recruited into auto

NOTE Confidence: 0.688754621428571

 $00{:}28{:}01{.}088 \dashrightarrow 00{:}28{:}03{.}239$ phagosomes and the levels go down.

NOTE Confidence: 0.688754621428571

 $00:28:03.240 \longrightarrow 00:28:05.190$ So when you block autophagy.

NOTE Confidence: 0.777906105714286

 $00{:}28{:}07{.}470 \dashrightarrow 00{:}28{:}09{.}745$ P 62 should accumulate and then see

NOTE Confidence: 0.777906105714286

 $00:28:09.745 \rightarrow 00:28:12.390$ shows here in quantified on the right.

00:28:12.390 --> 00:28:16.506 The F2P signal accumulated in VFP,

NOTE Confidence: 0.777906105714286

 $00:28:16.510 \rightarrow 00:28:18.130$ and these are actually knowledge.

NOTE Confidence: 0.777906105714286

 $00:28:18.130 \rightarrow 00:28:20.002$ Deletion of the open reading frame

NOTE Confidence: 0.777906105714286

00:28:20.002 --> 00:28:22.270 unit cells, and these are crisper

NOTE Confidence: 0.777906105714286

 $00{:}28{:}22{.}270 \dashrightarrow 00{:}28{:}24{.}320$ alleles that that James produced.

NOTE Confidence: 0.926115

00:28:28.050 --> 00:28:31.738 Importantly, V MP1 is required

NOTE Confidence: 0.926115

 $00:28:31.738 \longrightarrow 00:28:33.246$ for clearance of mitochondria.

NOTE Confidence: 0.926115

 $00:28:33.250 \longrightarrow 00:28:35.182$ So here again we're using this

NOTE Confidence: 0.926115

 $00{:}28{:}35{.}182 \dashrightarrow 00{:}28{:}37{.}330$ surrogate marker of of mitochondria.

NOTE Confidence: 0.926115

 $00{:}28{:}37{.}330 \dashrightarrow 00{:}28{:}43{.}400$ The antibody against ATP 5A and you can

NOTE Confidence: 0.926115

 $00:28:43.400 \longrightarrow 00:28:45.692$ also see that they have just superficially

NOTE Confidence: 0.926115

 $00:28:45.692 \rightarrow 00:28:47.918$ they look like larger mitochondria than

NOTE Confidence: 0.926115

 $00{:}28{:}47{.}918 \dashrightarrow 00{:}28{:}49{.}809$ we typically see in control cells,

NOTE Confidence: 0.926115

 $00{:}28{:}49{.}810 \dashrightarrow 00{:}28{:}52{.}050$ but the control cells are marked in red.

NOTE Confidence: 0.926115

 $00{:}28{:}52.050 \dashrightarrow 00{:}28{:}54.882$ Mutants lack red and you can see the

 $00{:}28{:}54{.}882 \dashrightarrow 00{:}28{:}57{.}368$ control cells you see no mitochondria.

NOTE Confidence: 0.926115

 $00{:}28{:}57{.}370 \dashrightarrow 00{:}29{:}00{.}919$ And mute cells have much more mitochondria.

NOTE Confidence: 0.846470827619048

 $00:29:04.520 \rightarrow 00:29:06.544$ I think I figured out why I can't

NOTE Confidence: 0.846470827619048

 $00{:}29{:}06{.}544 \dashrightarrow 00{:}29{:}08{.}347$ forward because if I move the toolbar

NOTE Confidence: 0.846470827619048

 $00{:}29{:}08{.}347 \dashrightarrow 00{:}29{:}09{.}900$ down there then it doesn't work.

NOTE Confidence: 0.849870185

 $00:29:14.100 \rightarrow 00:29:17.732$ And then we analyze this by transmission

NOTE Confidence: 0.849870185

00:29:17.732 --> 00:29:19.700 electron microscopy as well.

NOTE Confidence: 0.849870185

 $00:29:19.700 \longrightarrow 00:29:21.716$ And for this we used RNA.

NOTE Confidence: 0.849870185

 $00:29:21.720 \longrightarrow 00:29:24.240$ I because homozygous BMP one

NOTE Confidence: 0.849870185

00:29:24.240 --> 00:29:26.760 null animals are early lethal,

NOTE Confidence: 0.849870185

 $00:29:26.760 \longrightarrow 00:29:29.280$ so we could just specifically knockdown

NOTE Confidence: 0.849870185

 $00{:}29{:}29{.}280 \dashrightarrow 00{:}29{:}32{.}350$ VNP one in the intestine and you

NOTE Confidence: 0.849870185

 $00{:}29{:}32{.}350 \dashrightarrow 00{:}29{:}35{.}082$ can see that the mitochondria are

NOTE Confidence: 0.849870185

 $00{:}29{:}35{.}082 \dashrightarrow 00{:}29{:}38{.}076$ both larger in shape and and this is

NOTE Confidence: 0.849870185

 $00:29:38.076 \rightarrow 00:29:39.520$ mitochondrial area quantified here,

NOTE Confidence: 0.849870185

 $00:29:39.520 \longrightarrow 00:29:40.912$ so it looks very similar to

- NOTE Confidence: 0.849870185
- $00:29:40.912 \longrightarrow 00:29:42.770$ what we see with VPS 13D.
- NOTE Confidence: 0.874056986
- 00:29:45.040 --> 00:29:47.056 And I'm gonna just summarize for the sake
- NOTE Confidence: 0.874056986
- $00{:}29{:}47.056 \dashrightarrow 00{:}29{:}49.690$ of time, a few other points about the
- NOTE Confidence: 0.874056986
- 00:29:49.690 --> 00:29:51.738 relationship between VPS 13D and B and P1.
- NOTE Confidence: 0.874056986
- $00:29:51.740 \longrightarrow 00:29:53.690$ So double mutant analysis indicate that
- NOTE Confidence: 0.874056986
- $00:29:53.690 \rightarrow 00:29:55.919$ these genes function in the same pathway.
- NOTE Confidence: 0.874056986
- $00:29:55.920 \longrightarrow 00:29:58.524$ In other words, they do not have
- NOTE Confidence: 0.874056986
- $00:29:58.524 \longrightarrow 00:30:00.389$ an additive phenotype based on
- NOTE Confidence: 0.874056986
- $00:30:00.389 \longrightarrow 00:30:02.405$ any of the markers we've used.
- NOTE Confidence: 0.874056986
- $00:30:02.410 \dashrightarrow 00:30:05.722$ If we look at VPS, 13D protein puncta.
- NOTE Confidence: 0.874056986
- 00:30:05.722 -> 00:30:08.206 So this is we have monoclonal
- NOTE Confidence: 0.874056986
- $00{:}30{:}08{.}206 \dashrightarrow 00{:}30{:}10{.}483$ antibody that works in the fruit
- NOTE Confidence: 0.874056986
- 00:30:10.483 --> 00:30:13.305 fly against VPS 13D and the mutant
- NOTE Confidence: 0.874056986
- 00:30:13.305 --> 00:30:16.671 cell shown by the white outline here
- NOTE Confidence: 0.874056986
- 00:30:16.671 --> 00:30:19.298 has greatly reduced puncta compared
- NOTE Confidence: 0.874056986

 $00:30:19.298 \longrightarrow 00:30:21.468$ to the control neighboring cells.

NOTE Confidence: 0.748455450833333

00:30:23.530 --> 00:30:27.464 And also VPS 13D does not influence

NOTE Confidence: 0.748455450833333

 $00{:}30{:}27{.}464 \dashrightarrow 00{:}30{:}31{.}133$ BMP one puncta which is and I should

NOTE Confidence: 0.748455450833333

 $00:30:31.133 \dashrightarrow 00:30:33.660$ have mentioned that BMP one is an ER,

NOTE Confidence: 0.748455450833333

 $00{:}30{:}33{.}660 \dashrightarrow 00{:}30{:}38{.}860$ resides on ER both in mammals and influx.

NOTE Confidence: 0.748455450833333

 $00:30:38.860 \dashrightarrow 00:30:42.268$ So these data, no thinking simplistically,

NOTE Confidence: 0.748455450833333

 $00{:}30{:}42.270 \dashrightarrow 00{:}30{:}44.634$ as a geneticist, suggests that BMP

NOTE Confidence: 0.748455450833333

 $00:30:44.634 \rightarrow 00:30:48.052$ that BMP one is upstream of EPS 13D.

NOTE Confidence: 0.748455450833333

 $00{:}30{:}48.052 \dashrightarrow 00{:}30{:}50.728$ Of course, as you start thinking

NOTE Confidence: 0.748455450833333

 $00:30:50.728 \rightarrow 00:30:53.090$ about something, this is not like

NOTE Confidence: 0.748455450833333

 $00{:}30{:}53{.}090 \dashrightarrow 00{:}30{:}54{.}618$ a classic transcription factor.

NOTE Confidence: 0.748455450833333

 $00:30:54.620 \longrightarrow 00:30:56.820$ Gene target type of pathway.

NOTE Confidence: 0.748455450833333

 $00:30:56.820 \longrightarrow 00:30:58.404$ So there are many other explanations

NOTE Confidence: 0.748455450833333

 $00:30:58.404 \longrightarrow 00:31:00.070$ that need to be considered.

NOTE Confidence: 0.748455450833333

 $00:31:00.070 \longrightarrow 00:31:01.270$ When I think about these data,

NOTE Confidence: 0.748455450833333

 $00:31:01.270 \longrightarrow 00:31:03.268$ but from a sort of genetic

- NOTE Confidence: 0.748455450833333
- 00:31:03.268 --> 00:31:03.934 diagram perspective,
- NOTE Confidence: 0.748455450833333
- $00:31:03.940 \longrightarrow 00:31:05.494$ you would think about this as BMP,
- NOTE Confidence: 0.748455450833333
- $00{:}31{:}05{.}500 \dashrightarrow 00{:}31{:}07{.}808$ one being upstream did.
- NOTE Confidence: 0.917781288571429
- $00{:}31{:}10.600 \dashrightarrow 00{:}31{:}13.270$ So the question that comes up then RV
- NOTE Confidence: 0.917781288571429
- 00:31:13.270 --> 00:31:15.440 MP1 and VPS 13D required for mitophagy
- NOTE Confidence: 0.917781288571429
- $00{:}31{:}15{.}440 \dashrightarrow 00{:}31{:}18{.}035$ and I just wanted to throw in this.
- NOTE Confidence: 0.917781288571429
- 00:31:18.040 --> 00:31:22.219 This M micrograph taken by my my
- NOTE Confidence: 0.917781288571429
- $00:31:22.219 \rightarrow 00:31:23.880$ laboratory yam expert Tina 48.
- NOTE Confidence: 0.917781288571429
- $00:31:23.880 \longrightarrow 00:31:25.470$ She does all of our electron
- NOTE Confidence: 0.917781288571429
- $00:31:25.533 \rightarrow 00:31:27.423$ microscopy and she doesn't get enough
- NOTE Confidence: 0.917781288571429
- $00{:}31{:}27{.}423 \dashrightarrow 00{:}31{:}29{.}519$ credit for the work that she does.
- NOTE Confidence: 0.917781288571429
- 00:31:29.520 --> 00:31:31.848 To be honest she's always on
- NOTE Confidence: 0.917781288571429
- 00:31:31.848 --> 00:31:33.780 all of our manuscripts but.
- NOTE Confidence: 0.917781288571429
- $00{:}31{:}33{.}780 \dashrightarrow 00{:}31{:}34{.}692$ And as an author.
- NOTE Confidence: 0.917781288571429
- 00:31:34.692 --> 00:31:36.115 But you know, she doesn't doesn't doesn't
- NOTE Confidence: 0.917781288571429

 $00:31:36.115 \rightarrow 00:31:37.830$ get the same kind of attention that

NOTE Confidence: 0.917781288571429

 $00:31:37.878 \rightarrow 00:31:39.438$ graduate students and postdocs get,

NOTE Confidence: 0.917781288571429

 $00:31:39.440 \longrightarrow 00:31:41.614$ so I want to make that point, but also.

NOTE Confidence: 0.917781288571429

 $00:31:41.614 \rightarrow 00:31:44.918$ Just when we draw cartoons of mitophagy,

NOTE Confidence: 0.917781288571429

00:31:44.920 --> 00:31:47.086 we tend to show these, you know,

NOTE Confidence: 0.917781288571429

 $00{:}31{:}47.086 \dashrightarrow 00{:}31{:}48.338$ sort of glorified cartoons,

NOTE Confidence: 0.917781288571429

 $00:31:48.340 \longrightarrow 00:31:51.064$ and this is probably what an auto

NOTE Confidence: 0.917781288571429

 $00:31:51.064 \rightarrow 00:31:52.632$ phagosome membrane forming around

NOTE Confidence: 0.917781288571429

 $00{:}31{:}52.632 \dashrightarrow 00{:}31{:}54.612$ it mitochondria looks like and

NOTE Confidence: 0.917781288571429

 $00:31:54.612 \rightarrow 00:31:55.665$ what's particularly attractive

NOTE Confidence: 0.917781288571429

 $00:31:55.665 \longrightarrow 00:31:57.771$ about this image to me is,

NOTE Confidence: 0.917781288571429

 $00{:}31{:}57{.}780 \dashrightarrow 00{:}32{:}00{.}228$ it looks like this might be a mitochondria

NOTE Confidence: 0.917781288571429

 $00{:}32{:}00{.}228 \dashrightarrow 00{:}32{:}02{.}306$ that's going through a fission event

NOTE Confidence: 0.917781288571429

 $00{:}32{:}02{.}306 \dashrightarrow 00{:}32{:}04{.}061$ that there's this dumbbell shape

NOTE Confidence: 0.917781288571429

 $00:32:04.061 \longrightarrow 00:32:05.916$ that's at the ends of where this.

NOTE Confidence: 0.917781288571429

 $00:32:05.920 \rightarrow 00:32:08.026$ You know this membrane is juxtaposed.

 $00:32:10.860 \dashrightarrow 00:32:13.705$ So we investigated whether Vikas 13D

NOTE Confidence: 0.808904528

00:32:13.705 --> 00:32:16.400 and V MP1 or required for MATAJI

NOTE Confidence: 0.808904528

00:32:16.400 --> 00:32:19.399 using an assay called my Dokyusei.

NOTE Confidence: 0.808904528

 $00:32:19.400 \longrightarrow 00:32:22.541$ Well my to QC is a fusion of a

NOTE Confidence: 0.808904528

00:32:22.541 --> 00:32:25.358 mitochondrial protein with GFP and M cherry.

NOTE Confidence: 0.808904528

 $00{:}32{:}25{.}360 \dashrightarrow 00{:}32{:}27{.}656$ So when mitophagy is active and might

NOTE Confidence: 0.808904528

 $00{:}32{:}27.656 \dashrightarrow 00{:}32{:}29.924$ almost all the mitochondria get cleared

NOTE Confidence: 0.808904528

 $00:32:29.924 \rightarrow 00:32:32.752$ in the intestine is very narrow window.

NOTE Confidence: 0.808904528

 $00{:}32{:}32{.}760 \dashrightarrow 00{:}32{:}35{.}126$ I described the beginning so when that

NOTE Confidence: 0.808904528

 $00{:}32{:}35{.}126 \dashrightarrow 00{:}32{:}38{.}015$ happens you have very low GFP signal and

NOTE Confidence: 0.808904528

 $00:32:38.015 \rightarrow 00:32:41.190$ persistent and cherry signal because.

NOTE Confidence: 0.808904528

 $00{:}32{:}41{.}190 \dashrightarrow 00{:}32{:}44{.}880$ Once on Phagosomes containing mitochondria

NOTE Confidence: 0.808904528

 $00:32:44.880 \dashrightarrow 00:32:48.216$ fuse with lysosomes GFP signal,

NOTE Confidence: 0.808904528

 $00{:}32{:}48.216 \dashrightarrow 00{:}32{:}50.472$ but is no longer admitted because

NOTE Confidence: 0.808904528

 $00:32:50.472 \longrightarrow 00:32:53.528$ of the pH of the acidic pH license.

 $00:32:53.530 \rightarrow 00:32:56.026$ So we do the same assay with either

NOTE Confidence: 0.808904528

00:32:56.030 --> 00:32:57.478 VPS 13D Knock down.

NOTE Confidence: 0.808904528

 $00{:}32{:}57{.}478 \dashrightarrow 00{:}33{:}00{.}298$ You can see that the majority that

NOTE Confidence: 0.808904528

 $00:33:00.298 \rightarrow 00:33:04.186$ many of the GFP signals persist,

NOTE Confidence: 0.808904528

 $00{:}33{:}04{.}190 \dashrightarrow 00{:}33{:}06{.}896$ and using two independent RNA eyes

NOTE Confidence: 0.808904528

00:33:06.896 --> 00:33:09.853 against one obtain very similar results NOTE Confidence: 0.808904528

 $00{:}33{:}09{.}853 \dashrightarrow 00{:}33{:}13{.}069$ or influence on the medical clearance

NOTE Confidence: 0.808904528

 $00:33:13.069 \rightarrow 00:33:15.418$ of mitochondria based on this asset.

NOTE Confidence: 0.95018749

 $00{:}33{:}18.660 \dashrightarrow 00{:}33{:}22.116$ So we wanted to examine whether or not NOTE Confidence: 0.95018749

 $00:33:22.120 \dashrightarrow 00:33:25.179$ VPS 13D fit into the existing mitophagy

NOTE Confidence: 0.95018749

 $00:33:25.179 \rightarrow 00:33:28.562$ paradigm and at the time we're investigating NOTE Confidence: 0.95018749

 $00:33:28.562 \dashrightarrow 00:33:32.098$ this was when Richard Richard Ewell's lab NOTE Confidence: 0.95018749

 $00:33:32.098 \rightarrow 00:33:35.194$ was pioneering our understanding of the

NOTE Confidence: 0.95018749

00:33:35.194 --> 00:33:37.180 Parkinson's disease risk predisposition.

NOTE Confidence: 0.95018749

 $00{:}33{:}37{.}180 \dashrightarrow 00{:}33{:}40{.}084$ Genes, pink one and Parkin on

NOTE Confidence: 0.95018749

 $00:33:40.084 \rightarrow 00:33:41.300$ the clearance of mitochondria.

- NOTE Confidence: 0.95018749
- 00:33:41.300 > 00:33:44.198 So just a brief primer on what

 $00:33:44.198 \longrightarrow 00:33:45.440$ these genes do.

NOTE Confidence: 0.95018749

 $00:33:45.440 \rightarrow 00:33:48.688$ So typically pink one is mine.

NOTE Confidence: 0.95018749

00:33:48.688 --> 00:33:49.924 Mitochondrial localized,

NOTE Confidence: 0.95018749

 $00:33:49.924 \rightarrow 00:33:53.632$ but upon mitochondrial damage shown by

NOTE Confidence: 0.95018749

 $00{:}33{:}53.632 \dashrightarrow 00{:}33{:}56.650$ these stars Pink 1 translocates for a

NOTE Confidence: 0.95018749

 $00{:}33{:}56.650 \dashrightarrow 00{:}33{:}58.170$ complicated biochemical mechanism to

NOTE Confidence: 0.95018749

 $00:33:58.170 \longrightarrow 00:34:00.566$ the outer leaflet of the mitochondria,

NOTE Confidence: 0.95018749

 $00{:}34{:}00{.}570 \dashrightarrow 00{:}34{:}03{.}410$ where it phosphorylates both ubiquitin

NOTE Confidence: 0.95018749

 $00{:}34{:}03{.}410 \dashrightarrow 00{:}34{:}06{.}246$ and parking and enables chain elongation

NOTE Confidence: 0.95018749

 $00{:}34{:}06{.}246 \dashrightarrow 00{:}34{:}08{.}790$ on mitochondrial proteins as well as

NOTE Confidence: 0.95018749

00:34:08.862 --> 00:34:11.278 neighboring proteins to mitochondria,

NOTE Confidence: 0.95018749

 $00:34:11.280 \longrightarrow 00:34:13.570$ and it's thought that this

NOTE Confidence: 0.95018749

 $00:34:13.570 \longrightarrow 00:34:15.402$ ubiquitination is actually relatively.

NOTE Confidence: 0.95018749

 $00:34:15.410 \rightarrow 00:34:16.661$ I should say,

 $00:34:16.661 \rightarrow 00:34:19.163$ very strong data indicate that this.

NOTE Confidence: 0.95018749

 $00:34:19.170 \longrightarrow 00:34:21.314$ Ubiquitination of these mitochondrial

NOTE Confidence: 0.95018749

 $00{:}34{:}21{.}314 \dashrightarrow 00{:}34{:}23{.}994$ proteins is how mitochondria get

NOTE Confidence: 0.95018749

 $00{:}34{:}24.000 \dashrightarrow 00{:}34{:}27.170$ recognized by autophagy cargo receptors

NOTE Confidence: 0.95018749

 $00{:}34{:}27{.}170 \dashrightarrow 00{:}34{:}30{.}340$ that interact with both ubiquitin

NOTE Confidence: 0.95018749

 $00{:}34{:}30{.}340 \dashrightarrow 00{:}34{:}32{.}839$ and ATG 8 or its mammalian ortholog

NOTE Confidence: 0.95018749

 $00{:}34{:}32{.}839 \dashrightarrow 00{:}34{:}35{.}754$ bail C3 got Rep family so that

NOTE Confidence: 0.95018749

 $00:34:35.754 \rightarrow 00:34:38.400$ mitochondria can get cleared by office.

NOTE Confidence: 0.94452256

 $00{:}34{:}40{.}810 \dashrightarrow 00{:}34{:}43{.}720$ So we wanted to ask.

NOTE Confidence: 0.94452256

 $00{:}34{:}43.720 \dashrightarrow 00{:}34{:}45.505$ Whether or not pink one

NOTE Confidence: 0.94452256

 $00:34:45.505 \longrightarrow 00:34:46.576$ has similar phenotypes,

NOTE Confidence: 0.94452256

00:34:46.580 - 00:34:49.060 just 13D and the short answer is yes,

NOTE Confidence: 0.94452256

00:34:49.060 --> 00:34:51.408 it's almost identical right?

NOTE Confidence: 0.94452256

 $00:34:51.408 \rightarrow 00:34:54.343$ In the way they're phenotypes.

NOTE Confidence: 0.94452256

00:34:54.350 --> 00:34:58.148 Here you can see in magenta,

NOTE Confidence: 0.94452256

00:34:58.150 --> 00:34:59.170 80P5A in a pink one,

- NOTE Confidence: 0.94452256
- $00{:}34{:}59{.}170 \dashrightarrow 00{:}35{:}03{.}010$ null loss of function salad you
- NOTE Confidence: 0.94452256
- $00:35:03.010 \dashrightarrow 00:35:05.570$ see persistence in mitochondria.
- NOTE Confidence: 0.94452256
- 00:35:05.570 --> 00:35:05.976 Interestingly,
- NOTE Confidence: 0.94452256
- $00{:}35{:}05{.}976$ --> $00{:}35{:}09{.}224$ Pink one using the sort of classic genetic
- NOTE Confidence: 0.94452256
- 00:35:09.224 --> 00:35:11.549 paradigm I told you about a moment ago,
- NOTE Confidence: 0.94452256
- $00:35:11.550 \dashrightarrow 00:35:17.520$ loss of Pig 1 results in a loss of VPS 13D.
- NOTE Confidence: 0.94452256
- 00:35:17.520 --> 00:35:21.190 Protein puncta suggesting that
- NOTE Confidence: 0.94452256
- 00:35:21.190 --> 00:35:23.710 pink one is upstream somehow of
- NOTE Confidence: 0.94452256
- $00:35:23.710 \longrightarrow 00:35:26.896$ EPS 13D in these mutant cells.
- NOTE Confidence: 0.94452256
- 00:35:26.900 --> 00:35:29.320 And interestingly.
- NOTE Confidence: 0.94452256
- $00:35:29.320 \longrightarrow 00:35:31.580$ Because we have this classic
- NOTE Confidence: 0.94452256
- $00{:}35{:}31{.}580 \dashrightarrow 00{:}35{:}33{.}840$ pink one Parkin like pathway,
- NOTE Confidence: 0.94452256
- $00:35:33.840 \longrightarrow 00:35:35.616$ we were shocked when we could
- NOTE Confidence: 0.94452256
- $00:35:35.616 \rightarrow 00:35:37.359$ started analyzing park it and again
- NOTE Confidence: 0.94452256
- $00{:}35{:}37{.}359 \dashrightarrow 00{:}35{:}39{.}116$ there's a there's a lot of data.
- NOTE Confidence: 0.94452256

 $00:35:39.120 \longrightarrow 00:35:41.864$ Actually most of this data is published

NOTE Confidence: 0.94452256

 $00{:}35{:}41{.}864 \dashrightarrow 00{:}35{:}44{.}960$ in a in a JCB paper last year.

NOTE Confidence: 0.94452256

 $00{:}35{:}44{.}960 \dashrightarrow 00{:}35{:}47{.}172$ But what we saw in on the

NOTE Confidence: 0.94452256

 $00:35:47.172 \longrightarrow 00:35:49.340$ left here are control cells.

NOTE Confidence: 0.94452256

00:35:49.340 --> 00:35:51.128 Electron micrograph of

NOTE Confidence: 0.94452256

 $00:35:51.128 \longrightarrow 00:35:52.916$ control intestine cells.

NOTE Confidence: 0.94452256

 $00:35:52.920 \dashrightarrow 00:35:55.085$ This is a parking homozygous

NOTE Confidence: 0.94452256

 $00:35:55.085 \rightarrow 00:35:57.480$ mutant with lacking 1 allele of

NOTE Confidence: 0.94452256

 $00{:}35{:}57{.}480 \dashrightarrow 00{:}36{:}00{.}810$ EPS 13D and this a heterozygous

NOTE Confidence: 0.94452256

00:36:00.810 --> 00:36:03.432 Parkin mutant with homozygous VPS

NOTE Confidence: 0.94452256

00:36:03.432 $\operatorname{-->}$ 00:36:06.005 13 day and what we observed was

NOTE Confidence: 0.94452256

00:36:06.005 --> 00:36:07.970 that parking mutants although they NOTE Confidence: 0.94452256

00:36:08.037 --> 00:36:10.367 had more mitochondria they weren't NOTE Confidence: 0.94452256

00:36:10.367 --> 00:36:12.231 these enormous mitochondria that

NOTE Confidence: 0.94452256

 $00:36:12.231 \longrightarrow 00:36:14.722$ we saw both because 13D mutants

NOTE Confidence: 0.94452256

 $00:36:14.722 \longrightarrow 00:36:17.566$ as well as in pink ones.

- NOTE Confidence: 0.9446667375
- $00:36:20.330 \longrightarrow 00:36:24.050$ So one last piece of this puzzle is
- NOTE Confidence: 0.9446667375
- 00:36:24.050 --> 00:36:27.970 that when we analyze. Park in punked
- NOTE Confidence: 0.9446667375
- $00:36:27.970 \longrightarrow 00:36:31.150$ up formation in in mutant cells.
- NOTE Confidence: 0.9446667375
- $00:36:31.150 \rightarrow 00:36:34.981$ We saw that as the the usual and many other
- NOTE Confidence: 0.9446667375
- $00:36:34.981 \longrightarrow 00:36:38.252$ lab model would predict when pink is one
- NOTE Confidence: 0.9446667375
- $00{:}36{:}38.252 \dashrightarrow 00{:}36{:}42.034$ is lost in these mutant cells. You see,
- NOTE Confidence: 0.9446667375
- $00:36:42.034 \rightarrow 00:36:45.586$ reduction of parking protein pump to.
- NOTE Confidence: 0.9446667375
- 00:36:45.590 --> 00:36:49.294 However, in a VPS 13 deed null cell
- NOTE Confidence: 0.9446667375
- $00{:}36{:}49{.}294 \dashrightarrow 00{:}36{:}53{.}468$ outlined in white here you see no reduction.
- NOTE Confidence: 0.9446667375
- 00:36:53.470 --> 00:36:57.886 In a parking park to formation.
- NOTE Confidence: 0.9446667375
- $00{:}36{:}57{.}890 \dashrightarrow 00{:}37{:}01{.}098$ This and a large amount of single and
- NOTE Confidence: 0.9446667375
- 00:37:01.098 --> 00:37:03.868 double mutant analysis have led us to
- NOTE Confidence: 0.9446667375
- 00:37:03.868 --> 00:37:07.356 believe that pink one is upstream in in
- NOTE Confidence: 0.9446667375
- $00:37:07.356 \longrightarrow 00:37:10.014$ the intestine that pink one functions
- NOTE Confidence: 0.9446667375
- 00:37:10.014 --> 00:37:13.232 upstream on both parking and VPS 13B.
- NOTE Confidence: 0.9446667375

 $00:37:13.232 \rightarrow 00:37:15.637$ And we're working to better

NOTE Confidence: 0.9446667375

 $00{:}37{:}15.637 \dashrightarrow 00{:}37{:}17.470$ understand its mechanisms now.

NOTE Confidence: 0.79214492

 $00:37:20.460 \longrightarrow 00:37:25.975$ So the. One of the last parts

NOTE Confidence: 0.79214492

 $00{:}37{:}25{.}975 \dashrightarrow 00{:}37{:}28{.}486$ I want to start addressing is

NOTE Confidence: 0.79214492

00:37:28.486 --> 00:37:30.896 does does VPS start today?

NOTE Confidence: 0.79214492

00:37:30.900 --> 00:37:32.976 Like BMP? One influence,

NOTE Confidence: 0.79214492

 $00{:}37{:}32.976 \dashrightarrow 00{:}37{:}36.090$ the proximity of ER and mitochondria.

NOTE Confidence: 0.79214492

00:37:36.090 --> 00:37:40.202 And so. Again, James Shannon Tina

NOTE Confidence: 0.79214492

 $00{:}37{:}40.202 \dashrightarrow 00{:}37{:}42.980$ 48 started analyzing this in all

NOTE Confidence: 0.79214492

 $00{:}37{:}43.066 \dashrightarrow 00{:}37{:}45.691$ of our models and flies Hila as

NOTE Confidence: 0.79214492

00:37:45.691 --> 00:37:47.861 well as patient arrives cells

NOTE Confidence: 0.79214492

 $00:37:47.861 \longrightarrow 00:37:50.452$ and what they observed was that

NOTE Confidence: 0.79214492

 $00:37:50.452 \rightarrow 00:37:52.804$ in in the fruit fly in testing,

NOTE Confidence: 0.79214492

 $00:37:52.810 \longrightarrow 00:37:55.561$ which is the first model that we

NOTE Confidence: 0.79214492

 $00:37:55.561 \rightarrow 00:37:57.996$ studied that animals lacking VPS 13D

NOTE Confidence: 0.79214492

 $00{:}37{:}57{.}996 \dashrightarrow 00{:}37{:}59{.}964$ and these are two different allele

 $00:37:59.964 \rightarrow 00:38:01.835$ combinations and all these electron

NOTE Confidence: 0.79214492

00:38:01.835 --> 00:38:04.139 micrographs going to show you lower

NOTE Confidence: 0.79214492

 $00:38:04.139 \longrightarrow 00:38:05.420$ magnifications are in the top.

NOTE Confidence: 0.79214492

 $00:38:05.420 \rightarrow 00:38:08.280$ Enlargements are on the bottom.

NOTE Confidence: 0.79214492

 $00{:}38{:}08{.}280 \dashrightarrow 00{:}38{:}10{.}525$ And quantification is shown here

NOTE Confidence: 0.79214492

00:38:10.525 --> 00:38:13.250 and the definition of what will

NOTE Confidence: 0.79214492

 $00{:}38{:}13.250 \dashrightarrow 00{:}38{:}15.668$ be a mitochondria ER contact is

NOTE Confidence: 0.79214492

 $00{:}38{:}15.668 \dashrightarrow 00{:}38{:}18.100$ defined based on the literature.

NOTE Confidence: 0.79214492

 $00{:}38{:}18.100 \dashrightarrow 00{:}38{:}20.626$ So what they observed is like V.

NOTE Confidence: 0.79214492

00:38:20.626 --> 00:38:25.928 MP1 loss of EPS 13D resulted in hanst of

NOTE Confidence: 0.79214492

 $00{:}38{:}25{.}928 \dashrightarrow 00{:}38{:}29{.}638$ proximity between mitochondria and ER.

NOTE Confidence: 0.79214492

00:38:29.640 --> 00:38:32.566 We observed similar results in he LA

NOTE Confidence: 0.79214492

00:38:32.566 --> 00:38:35.704 cells and importantly when we move to NOTE Confidence: 0.79214492

 $00{:}38{:}35{.}704 \dashrightarrow 00{:}38{:}38{.}059$ analyzing patient provide cells and

NOTE Confidence: 0.79214492

 $00{:}38{:}38{.}059 \dashrightarrow 00{:}38{:}41.745$ in these cases we have very nice both

 $00:38:41.745 \rightarrow 00:38:45.535$ patient and either heterozygous sibling

NOTE Confidence: 0.79214492

 $00{:}38{:}45{.}535 \dashrightarrow 00{:}38{:}49{.}088$ or heterozygous parent mutations.

NOTE Confidence: 0.79214492

 $00:38:49.088 \longrightarrow 00:38:52.378$ So this is the original.

NOTE Confidence: 0.79214492

 $00{:}38{:}52{.}380 \dashrightarrow 00{:}38{:}55{.}260$ University of Michigan derived cells.

NOTE Confidence: 0.79214492

 $00:38:55.260 \rightarrow 00:38:57.606$ The first allele that was actually

NOTE Confidence: 0.79214492

 $00{:}38{:}57{.}606 \dashrightarrow 00{:}39{:}02{.}098$ identified as Avycaz 13D patient ride cell.

NOTE Confidence: 0.79214492

00:39:02.100 --> 00:39:04.340 And I particularly like this

NOTE Confidence: 0.79214492

 $00:39:04.340 \longrightarrow 00:39:06.132$ this image here so.

NOTE Confidence: 0.79214492

 $00{:}39{:}06{.}140 \dashrightarrow 00{:}39{:}10{.}040$ Unrelated fibroblast and these are.

NOTE Confidence: 0.79214492

 $00:39:10.040 \rightarrow 00:39:12.824$ This is apparent dry fibroblast and

NOTE Confidence: 0.79214492

 $00:39:12.824 \rightarrow 00:39:15.630$ this is a patient, right fiberglass?

NOTE Confidence: 0.79214492

 $00:39:15.630 \longrightarrow 00:39:17.040$ If you look.

NOTE Confidence: 0.79214492

00:39:17.040 $\operatorname{-->}$ 00:39:18.750 Actually James selected this region

NOTE Confidence: 0.79214492

 $00:39{:}18.750 \dashrightarrow 00{:}39{:}20.876$ for the enlargement where you can

NOTE Confidence: 0.79214492

 $00{:}39{:}20.876$ --> $00{:}39{:}22.320$ see these enhanced mitochondrial

NOTE Confidence: 0.79214492

00:39:22.320 --> 00:39:23.403 New York contacts,

 $00:39:23.410 \rightarrow 00:39:25.489$ but actually my favorite part of the

NOTE Confidence: 0.79214492

 $00:39:25.489 \rightarrow 00:39:27.736$ image is down here where it really

NOTE Confidence: 0.79214492

00:39:27.736 $\operatorname{-->}$ 00:39:30.200 looks like the ER extends and wraps

NOTE Confidence: 0.79214492

 $00{:}39{:}30{.}276 \dashrightarrow 00{:}39{:}32{.}332$ around this particular mitochondria

NOTE Confidence: 0.79214492

 $00:39:32.332 \dashrightarrow 00:39:34.902$ and that's all quantified over.

NOTE Confidence: 0.79214492

 $00{:}39{:}34{.}910 \dashrightarrow 00{:}39{:}38{.}114$ We also looked at that as a distinct family.

NOTE Confidence: 0.79214492

 $00:39:38.120 \longrightarrow 00:39:42.327$ These are cells that were collected by.

NOTE Confidence: 0.79214492

 $00{:}39{:}42{.}330 \dashrightarrow 00{:}39{:}46{.}478$ Katya lowman and sadly I was

NOTE Confidence: 0.79214492

 $00:39{:}46.478 \dashrightarrow 00{:}39{:}48.500$ just reminded me giving a tragedy

NOTE Confidence: 0.79214492

 $00:39:48.572 \longrightarrow 00:39:50.498$ in the world and in Ukraine.

NOTE Confidence: 0.79214492

00:39:50.500 --> 00:39:53.060 This is from a Ukrainian family

NOTE Confidence: 0.79214492

00:39:53.060 --> 00:39:55.940 that Katja who's based in Lubeck

NOTE Confidence: 0.79214492

 $00{:}39{:}55{.}940 \dashrightarrow 00{:}39{:}58{.}380$ obtained these cells but again.

NOTE Confidence: 0.79214492

00:39:58.380 --> 00:39:59.694 Unrelated fibroblast.

NOTE Confidence: 0.79214492

 $00:39:59.694 \longrightarrow 00:40:04.044$ In this case it's a sibling loss

 $00:40:04.044 \longrightarrow 00:40:06.468$ of 1 allele and the homozygous.

NOTE Confidence: 0.64835307625

 $00:40:08.520 \longrightarrow 00:40:10.130$ The patient O'Neal. And where

NOTE Confidence: 0.64835307625

00:40:10.130 --> 00:40:12.261 you can see it again enhanced

NOTE Confidence: 0.64835307625

 $00:40:12.261 \rightarrow 00:40:14.516$ mitochondria in New York contact.

NOTE Confidence: 0.872193747586207

 $00{:}40{:}18.170 \dashrightarrow 00{:}40{:}19.766$ So the big question then for

NOTE Confidence: 0.872193747586207

 $00:40:19.766 \longrightarrow 00:40:21.510$ these patients is can we identify

NOTE Confidence: 0.872193747586207

 $00:40:21.510 \rightarrow 00:40:23.364$ suppressors and you know we're very

NOTE Confidence: 0.872193747586207

 $00:40:23.364 \rightarrow 00:40:24.983$ lucky that actually patients you

NOTE Confidence: 0.872193747586207

 $00:40:24.983 \longrightarrow 00:40:26.867$ know from all around the world,

NOTE Confidence: 0.872193747586207

 $00{:}40{:}26.870 \dashrightarrow 00{:}40{:}29.530$ so rare disease but have been trying

NOTE Confidence: 0.872193747586207

 $00{:}40{:}29{.}530 \dashrightarrow 00{:}40{:}32{.}274$ to get us selves and so that we

NOTE Confidence: 0.872193747586207

 $00:40:32.274 \rightarrow 00:40:33.642$ can study this in more patients.

NOTE Confidence: 0.872193747586207

 $00:40:33.650 \rightarrow 00:40:36.338$ And what's important is can we

NOTE Confidence: 0.872193747586207

 $00:40:36.338 \longrightarrow 00:40:38.966$ identify suppressors of this as

NOTE Confidence: 0.872193747586207

00:40:38.966 --> 00:40:41.686 potential drug therapies down Rd?

NOTE Confidence: 0.872193747586207

 $00{:}40{:}41{.}690 \dashrightarrow 00{:}40{:}43{.}922$ And so I want to introduce you to the

- NOTE Confidence: 0.872193747586207
- $00:40:43.922 \rightarrow 00:40:45.249$ mitochondrial fission fusion cycle.
- NOTE Confidence: 0.872193747586207
- $00:40:45.250 \longrightarrow 00:40:46.390$ In case you don't know it.
- NOTE Confidence: 0.9255514166666667
- $00:40:48.810 \longrightarrow 00:40:51.494$ What we know is that fusion is regulated
- NOTE Confidence: 0.9255514166666667
- $00:40:51.494 \rightarrow 00:40:53.830$ some some of this fly protein names and
- NOTE Confidence: 0.9255514166666667
- $00{:}40{:}53.890 \dashrightarrow 00{:}40{:}55.970$ some of them are the same in mammals,
- NOTE Confidence: 0.9255514166666667
- $00{:}40{:}55{.}970 \dashrightarrow 00{:}40{:}57{.}044$ but I'll try to remember to
- NOTE Confidence: 0.9255514166666667
- $00:40:57.044 \rightarrow 00:40:58.030$ give you the mammal names.
- NOTE Confidence: 0.9255514166666667
- $00:40:58.030 \rightarrow 00:41:01.285$ So what happens when mitochondrial
- NOTE Confidence: 0.9255514166666667
- 00:41:01.285 --> 00:41:02.587 damage accumulates?
- NOTE Confidence: 0.9255514166666667
- $00:41:02.590 \longrightarrow 00:41:04.042$ It's thought to be dealt with
- NOTE Confidence: 0.9255514166666667
- $00:41:04.042 \longrightarrow 00:41:05.010$ in two different ways.
- NOTE Confidence: 0.9255514166666667
- 00:41:05.010 --> 00:41:06.830 One possible mechanism is
- NOTE Confidence: 0.9255514166666667
- $00{:}41{:}06{.}830 \dashrightarrow 00{:}41{:}08{.}650$ to dilute that damage.
- NOTE Confidence: 0.9255514166666667
- 00:41:08.650 --> 00:41:11.586 It's sort of like bold Dow Chemical slogan.
- NOTE Confidence: 0.9255514166666667
- $00{:}41{:}11{.}590 \dashrightarrow 00{:}41{:}14{.}418$ I believe it was solution to pollution
- NOTE Confidence: 0.9255514166666667

 $00:41:14.418 \rightarrow 00:41:18.210$ is dilution so and this fusion event.

NOTE Confidence: 0.9255514166666667

00:41:18.210 --> 00:41:21.690 Is regulated by Opal one or more facets,

NOTE Confidence: 0.9255514166666667

 $00:41:21.690 \rightarrow 00:41:24.180$ called in flies marfisi ortholog of

NOTE Confidence: 0.9255514166666667

 $00{:}41{:}24{.}180 \dashrightarrow 00{:}41{:}27{.}839$ M FM one and MF and two and humans.

NOTE Confidence: 0.9255514166666667

00:41:27.840 --> 00:41:30.153 So that's one mechanism to get rid of damage,

NOTE Confidence: 0.9255514166666667

 $00:41:30.160 \longrightarrow 00:41:31.532$ but the other approach,

NOTE Confidence: 0.9255514166666667

 $00:41:31.532 \rightarrow 00:41:34.171$ and which is you know more sophisticated

NOTE Confidence: 0.9255514166666667

00:41:34.171 -> 00:41:36.626 and more approaches to jettison

NOTE Confidence: 0.9255514166666667

 $00:41:36.626 \longrightarrow 00:41:39.036$ the bad piece of mitochondria.

NOTE Confidence: 0.9255514166666667

 $00:41:39.040 \rightarrow 00:41:41.852$ So through a vision of it be cut off

NOTE Confidence: 0.9255514166666667

00:41:41.852 --> 00:41:43.840 this piece of mitochondria that can be

NOTE Confidence: 0.9255514166666667

 $00:41:43.900 \rightarrow 00:41:46.217$ eaten by an auto phagosome or clearance,

NOTE Confidence: 0.9255514166666667

 $00:41:46.220 \rightarrow 00:41:48.266$ and the vision events are regulated

NOTE Confidence: 0.9255514166666667

 $00:41:48.266 \rightarrow 00:41:50.334$ by proteins, including PR,

NOTE Confidence: 0.9255514166666667

 $00:41:50.334 \rightarrow 00:41:53.794$ P1 phase one and MF.

NOTE Confidence: 0.9255514166666667

 $00:41:53.800 \longrightarrow 00:41:56.040$ And so.

- NOTE Confidence: 0.9255514166666667
- $00{:}41{:}56{.}040 \dashrightarrow 00{:}41{:}58{.}854$ We had identified Marfan flies or
- NOTE Confidence: 0.9255514166666667
- $00{:}41{:}58.854 \dashrightarrow 00{:}42{:}02{.}384$ orthologue of MFN one and two as a
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}02{.}384 \dashrightarrow 00{:}42{:}04{.}736$ gene that had a similar phenotype
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}04{.}740 \dashrightarrow 00{:}42{:}10{.}232$ to VPS 13 that had that could
- NOTE Confidence: 0.9255514166666667
- 00:42:10.232 --> 00:42:13.056 suppress VPS 13D mitochondria.
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}13.060 \dashrightarrow 00{:}42{:}16.196$ So the question we wanted to ask that.
- NOTE Confidence: 0.9255514166666667
- $00:42:16.200 \longrightarrow 00:42:19.800$ Is is this a potential genetic
- NOTE Confidence: 0.9255514166666667
- $00:42:19.800 \longrightarrow 00:42:22.389$ suppressor of this phenotype?
- NOTE Confidence: 0.9255514166666667
- $00:42:22.389 \longrightarrow 00:42:24.378$ Ultimately patient sounds.
- NOTE Confidence: 0.9255514166666667
- 00:42:24.380 --> 00:42:27.796 So a few details. Mark and MFN.
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}27.800 \dashrightarrow 00{:}42{:}29.210$ 2 but not.
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}29{.}210 \dashrightarrow 00{:}42{:}32{.}302$ MFN, one physically interacts with VPS 13D.
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}32{.}302 \dashrightarrow 00{:}42{:}34{.}528$ We've done this in our lab,
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}34{.}530 \dashrightarrow 00{:}42{:}36{.}118$ but also in plot.
- NOTE Confidence: 0.9255514166666667
- $00{:}42{:}36.118 \dashrightarrow 00{:}42{:}39.216$ Gingras identified MFN 2 as a strong
- NOTE Confidence: 0.9255514166666667

 $00:42:39.216 \rightarrow 00:42:42.370$ physical interact with because 13D in

NOTE Confidence: 0.9255514166666667

 $00:42:42.370 \rightarrow 00:42:44.320$ human cells independently of our interests.

NOTE Confidence: 0.655386948

00:42:46.620 --> 00:42:50.478 Importantly, Marfan MFN 2 accumulating VPS,

NOTE Confidence: 0.655386948

 $00:42:50.478 \rightarrow 00:42:52.284$ 13D Mutant cells, and the reason I

NOTE Confidence: 0.655386948

 $00{:}42{:}52{.}284 \dashrightarrow 00{:}42{:}54{.}328$ think this could be important is this

NOTE Confidence: 0.655386948

 $00{:}42{:}54{.}328 \dashrightarrow 00{:}42{:}56{.}124$ could be a potential biomarker for

NOTE Confidence: 0.655386948

 $00:42:56.124 \rightarrow 00:42:57.979$ first task at some of these patients,

NOTE Confidence: 0.655386948

 $00:42:57.980 \longrightarrow 00:43:00.636$ and this is no shown to be true

NOTE Confidence: 0.655386948

 $00:43:00.636 \longrightarrow 00:43:02.890$ across a larger population.

NOTE Confidence: 0.655386948

 $00{:}43{:}02{.}890 \dashrightarrow 00{:}43{:}06{.}146$ And interestingly, in our hands in the fly,

NOTE Confidence: 0.655386948

 $00{:}43{:}06{.}150 \dashrightarrow 00{:}43{:}09{.}867$ if we miss Express Mark in this green cell,

NOTE Confidence: 0.655386948

 $00:43:09.870 \longrightarrow 00:43:12.995$ this is sufficient to impair

NOTE Confidence: 0.655386948

 $00{:}43{:}12.995 \dashrightarrow 00{:}43{:}15.495$ the clearance of mitochondria.

NOTE Confidence: 0.655386948

 $00{:}43{:}15{.}500 \dashrightarrow 00{:}43{:}16{.}980$ So. In other words,

NOTE Confidence: 0.655386948

 $00{:}43{:}16{.}980 \dashrightarrow 00{:}43{:}19{.}200$ using a combination of loss and

NOTE Confidence: 0.655386948

00:43:19.280 --> 00:43:21.168 gain of function genetics,

- NOTE Confidence: 0.655386948
- $00{:}43{:}21.170 \dashrightarrow 00{:}43{:}25.068$ all the data .2 MF N2RR marfin
- NOTE Confidence: 0.655386948
- $00:43:25.068 \longrightarrow 00:43:28.600$ the fly as regulators of this
- NOTE Confidence: 0.655386948
- 00:43:28.600 --> 00:43:30.880 process and its pathway.
- NOTE Confidence: 0.655386948
- $00{:}43{:}30{.}880 \dashrightarrow 00{:}43{:}33{.}880$ So we wanted to ask whether or not
- NOTE Confidence: 0.655386948
- $00:43:33.880 \rightarrow 00:43:37.009$ knock down of Marfan the fly could
- NOTE Confidence: 0.655386948
- $00{:}43{:}37.009 \dashrightarrow 00{:}43{:}39.358$ suppress the phenotypes that we see,
- NOTE Confidence: 0.655386948
- $00{:}43{:}39{.}360 \dashrightarrow 00{:}43{:}42{.}552$ so we'll want to find mitochondrial
- NOTE Confidence: 0.655386948
- $00{:}43{:}42.552 \dashrightarrow 00{:}43{:}45.070$ area in contact with ER.
- NOTE Confidence: 0.655386948
- $00{:}43{:}45{.}070 \dashrightarrow 00{:}43{:}50{.}012$ So all of these are VPS 13D mutant cells.
- NOTE Confidence: 0.655386948
- $00:43:50.012 \longrightarrow 00:43:52.404$ In these image transmission
- NOTE Confidence: 0.655386948
- $00:43:52.404 \longrightarrow 00:43:54.300$ electron microscopy images.
- NOTE Confidence: 0.655386948
- $00{:}43{:}54{.}300 \dashrightarrow 00{:}43{:}57{.}477$ Lomax on the top higher Max on the bottom.
- NOTE Confidence: 0.655386948
- $00:43:57.480 \longrightarrow 00:44:02.014$ And what you can see is that and
- NOTE Confidence: 0.655386948
- $00{:}44{:}02.014 \dashrightarrow 00{:}44{:}04.498$ these are controls with an RFP
- NOTE Confidence: 0.655386948
- 00:44:04.498 --> 00:44:06.819 RNA I knockdown or marf RNA.
- NOTE Confidence: 0.655386948

 $00:44:06.820 \longrightarrow 00:44:08.857$ I knockdown in the fly and what

NOTE Confidence: 0.655386948

 $00:44:08.857 \longrightarrow 00:44:11.745$ we can see is that we were able

NOTE Confidence: 0.655386948

00:44:11.745 --> 00:44:13.297 to both suppress mitochondrial

NOTE Confidence: 0.655386948

 $00{:}44{:}13.297 \dashrightarrow 00{:}44{:}16.185$ area with Mark knock down as well

NOTE Confidence: 0.655386948

 $00{:}44{:}16.185 \dashrightarrow 00{:}44{:}18.330$ as mitochondria and ER contact.

NOTE Confidence: 0.897546818125

 $00{:}44{:}20.870$ --> $00{:}44{:}23.813$ So then of course we wanted to ask whether NOTE Confidence: 0.897546818125

 $00:44:23.813 \rightarrow 00:44:26.300$ this was true in the patient cells.

NOTE Confidence: 0.897546818125

 $00:44:26.300 \rightarrow 00:44:30.916$ So again, all of these are the homozygous.

NOTE Confidence: 0.897546818125

 $00{:}44{:}30{.}920 \dashrightarrow 00{:}44{:}32{.}920$ These are the page all the patients else,

NOTE Confidence: 0.897546818125

 $00{:}44{:}32{.}920 \dashrightarrow 00{:}44{:}36{.}392$ but on the left is a mock siRNA in

NOTE Confidence: 0.897546818125

 $00:44:36.392 \longrightarrow 00:44:39.480$ the left and the right is a MFN,

NOTE Confidence: 0.897546818125

 $00{:}44{:}39{.}480 \dashrightarrow 00{:}44{:}42{.}702$ two RNA I and what you can see in

NOTE Confidence: 0.897546818125

 $00:44:42.702 \rightarrow 00:44:46.058$ all quantified appropriately here.

NOTE Confidence: 0.897546818125

 $00{:}44{:}46.060 \dashrightarrow 00{:}44{:}50.676$ Knockdown of MF and two suppressed the

NOTE Confidence: 0.897546818125

00:44:50.676 --> 00:44:54.290 mitochondria and ER proximity Phoenix.

NOTE Confidence: 0.937386631428571

00:44:56.850 --> 00:44:58.684 So I'm just gonna wrap up now.

- NOTE Confidence: 0.937386631428571
- $00:44:58.690 \rightarrow 00:44:59.470$ Hopefully time.
- NOTE Confidence: 0.937386631428571
- 00:44:59.470 --> 00:45:02.590 Yeah, I look like I'm a good time
- NOTE Confidence: 0.937386631428571
- $00:45:02.590 \longrightarrow 00:45:03.790$ and some of the conclusions.
- NOTE Confidence: 0.937386631428571
- $00:45:03.790 \longrightarrow 00:45:05.314$ So these were the questions I
- NOTE Confidence: 0.937386631428571
- $00:45:05.314 \rightarrow 00:45:07.208$ wanted to try to address and I
- NOTE Confidence: 0.937386631428571
- $00{:}45{:}07{.}208 \dashrightarrow 00{:}45{:}09{.}105$ think I've at least done this part.
- NOTE Confidence: 0.937386631428571
- $00:45:09.110 \longrightarrow 00:45:10.838$ What genes are in the function
- NOTE Confidence: 0.937386631428571
- $00:45:10.838 \rightarrow 00:45:12.570$ in the VPS 13D pathway?
- NOTE Confidence: 0.937386631428571
- 00:45:12.570 --> 00:45:14.820 Today I presented you information
- NOTE Confidence: 0.937386631428571
- $00:45:14.820 \dashrightarrow 00:45:17.930$ about the MP1 Marvi also presented.
- NOTE Confidence: 0.937386631428571
- 00:45:17.930 -> 00:45:20.965 Think one is upstream of VPS 13 day and
- NOTE Confidence: 0.937386631428571
- $00{:}45{:}20{.}965 \dashrightarrow 00{:}45{:}22{.}735$ we're excited that we have multiple
- NOTE Confidence: 0.937386631428571
- $00{:}45{:}22.735 \dashrightarrow 00{:}45{:}25.000$ other factors in this pathway that
- NOTE Confidence: 0.937386631428571
- $00{:}45{:}25.000 \dashrightarrow 00{:}45{:}28.300$ we're processing characterizing. No.
- NOTE Confidence: 0.937386631428571
- $00:45:28.300 \rightarrow 00:45:30.956$ Where is the primary defect in these cells?
- NOTE Confidence: 0.937386631428571

 $00{:}45{:}30{.}960 \dashrightarrow 00{:}45{:}34{.}470$ Well, but the thing that we come back to

NOTE Confidence: 0.937386631428571

 $00:45:34.470 \rightarrow 00:45:38.497$ is this mitochondria and ER proximity and.

NOTE Confidence: 0.937386631428571

 $00:45:38.500 \rightarrow 00:45:40.334$ Perhaps this is caused by something else,

NOTE Confidence: 0.937386631428571

 $00:45:40.340 \rightarrow 00:45:42.908$ but this is the earlier what we could

NOTE Confidence: 0.937386631428571

 $00:45:42.908 \longrightarrow 00:45:45.648$ think is probably the earliest defect.

NOTE Confidence: 0.937386631428571

00:45:45.650 --> 00:45:48.620 How does V PS13D influence such

NOTE Confidence: 0.937386631428571

 $00:45:48.620 \longrightarrow 00:45:50.105$ diverse cellular processes?

NOTE Confidence: 0.937386631428571

 $00:45:50.110 \longrightarrow 00:45:51.850$ They answer is the same.

NOTE Confidence: 0.937386631428571

 $00{:}45{:}51{.}850 \dashrightarrow 00{:}45{:}54{.}748$ It appears that this inter organelle

NOTE Confidence: 0.937386631428571

 $00{:}45{:}54{.}748 \dashrightarrow 00{:}45{:}58{.}770$ communication is a big part of what's why

NOTE Confidence: 0.937386631428571

 $00:45:58.770 \rightarrow 00:46:02.345$ we're impacting multiple cell processes?

NOTE Confidence: 0.937386631428571

 $00{:}46{:}02.350 \dashrightarrow 00{:}46{:}04.110$ And can we identify suppressors,

NOTE Confidence: 0.937386631428571

 $00:46:04.110 \longrightarrow 00:46:07.269$ so I presented you data on Marfan MFN two.

NOTE Confidence: 0.937386631428571

00:46:07.270 --> 00:46:09.945 Of course we're interested in

NOTE Confidence: 0.937386631428571

 $00:46:09.945 \rightarrow 00:46:12.220$ other possible suppressors and but

NOTE Confidence: 0.937386631428571

 $00:46:12.220 \rightarrow 00:46:14.565$ right now this is the full lead.

 $00:46:14.570 \longrightarrow 00:46:19.130$ The one that's best characterized in the lab.

NOTE Confidence: 0.937386631428571

 $00{:}46{:}19.130 \dashrightarrow 00{:}46{:}22.378$ So just a more global overall model

NOTE Confidence: 0.937386631428571

 $00{:}46{:}22.378 \dashrightarrow 00{:}46{:}25.306$ shown here is am I to phagosome

NOTE Confidence: 0.937386631428571

 $00:46:25.306 \rightarrow 00:46:27.610$ information that I showed you earlier.

NOTE Confidence: 0.937386631428571

 $00{:}46{:}27.610 \dashrightarrow 00{:}46{:}29.745$ We had originally identified VPS

NOTE Confidence: 0.937386631428571

 $00{:}46{:}29{.}745 \dashrightarrow 00{:}46{:}32{.}650$ 13D and we're thinking about it as

NOTE Confidence: 0.937386631428571

 $00:46:32.650 \longrightarrow 00:46:34.750$ a tough guy cargo receptor that

NOTE Confidence: 0.937386631428571

 $00:46:34.750 \rightarrow 00:46:36.552$ might bridge between ubiquitinated

NOTE Confidence: 0.937386631428571

 $00:46:36.552 \rightarrow 00:46:39.648$ proteins on mitochondria and and and.

NOTE Confidence: 0.937386631428571

 $00:46:39.650 \longrightarrow 00:46:42.190$ Forming faga force that form

NOTE Confidence: 0.937386631428571

00:46:42.190 --> 00:46:43.714 out of phagosomes,

NOTE Confidence: 0.937386631428571

 $00:46:43.720 \rightarrow 00:46:46.008$ we think actually this could be the case,

NOTE Confidence: 0.937386631428571

00:46:46.010 --> 00:46:49.676 but we you know we're leaning

NOTE Confidence: 0.937386631428571

 $00{:}46{:}49.676$ --> $00{:}46{:}52.120$ toward other possible models.

NOTE Confidence: 0.937386631428571

 $00:46:52.120 \longrightarrow 00:46:54.052$ Miss 13 today seems to be acting

 $00:46:54.052 \longrightarrow 00:46:55.658$ more earlier than than at this.

NOTE Confidence: 0.937386631428571

 $00{:}46{:}55{.}660 \dashrightarrow 00{:}46{:}58{.}528$ This phase that have been defined

NOTE Confidence: 0.937386631428571

 $00:46:58.528 \longrightarrow 00:47:00.406$ by classical. This actors.

NOTE Confidence: 0.937386631428571

00:47:00.406 - 00:47:03.154 It seems like it's also potentially

NOTE Confidence: 0.937386631428571

 $00:47:03.154 \rightarrow 00:47:05.629$ affecting the fission pathway.

NOTE Confidence: 0.937386631428571

 $00{:}47{:}05{.}630 \dashrightarrow 00{:}47{:}08{.}912$ And if it is affecting vision

NOTE Confidence: 0.937386631428571

 $00{:}47{:}08{.}912 \dashrightarrow 00{:}47{:}10{.}006$ of mitochondria.

NOTE Confidence: 0.937386631428571

 $00:47:10.010 \longrightarrow 00:47:12.740$ Our data suggests that this is

NOTE Confidence: 0.937386631428571

 $00{:}47{:}12.740 \dashrightarrow 00{:}47{:}15.109$ downstream of of activities of Dr.

NOTE Confidence: 0.937386631428571

 $00{:}47{:}15{.}110 \dashrightarrow 00{:}47{:}16{.}238$ P1 and MFF.

NOTE Confidence: 0.730454781875

 $00{:}47{:}18.500 \dashrightarrow 00{:}47{:}20.257$ An important thing is that it appears

NOTE Confidence: 0.730454781875

00:47:20.257 --> 00:47:22.445 that the MP one is upstream of EPS 13D,

NOTE Confidence: 0.730454781875

 $00:47:22.450 \longrightarrow 00:47:25.108$ or at least is influencing VPF

NOTE Confidence: 0.730454781875

 $00:47:25.108 \longrightarrow 00:47:27.310$ 13 deactivity in some way.

NOTE Confidence: 0.730454781875

 $00:47:27.310 \longrightarrow 00:47:31.038$ And we have also and it's a very

NOTE Confidence: 0.730454781875

 $00:47:31.038 \rightarrow 00:47:32.831$ interesting relationship between the

 $00:47:32.831 \rightarrow 00:47:38.058$ test 13 endoplasmic or actively tested.

NOTE Confidence: 0.730454781875

00:47:38.060 - 00:47:40.454 So with that, let me just conclude

NOTE Confidence: 0.730454781875

 $00:47:40.454 \rightarrow 00:47:42.767$ by thanking the people that really

NOTE Confidence: 0.730454781875

 $00:47:42.767 \longrightarrow 00:47:44.787$ contributed to this study I

NOTE Confidence: 0.730454781875

 $00{:}47{:}44.787 \dashrightarrow 00{:}47{:}47.120$ mentioned at the beginning of the

NOTE Confidence: 0.730454781875

00:47:47.120 --> 00:47:49.298 impact of Senkai and Allison,

NOTE Confidence: 0.730454781875

 $00:47:49.300 \rightarrow 00:47:50.280$ the work that I showed you was,

NOTE Confidence: 0.730454781875

 $00:47:50.280 \longrightarrow 00:47:51.822$ almost, you know,

NOTE Confidence: 0.730454781875

00:47:51.822 --> 00:47:54.906 largely work of James Shen and

NOTE Confidence: 0.730454781875

00:47:54.906 --> 00:47:58.333 finally get to see all of our

NOTE Confidence: 0.730454781875

 $00{:}47{:}58{.}333 \dashrightarrow 00{:}48{:}00{.}226$ electron microscopy analysis.

NOTE Confidence: 0.730454781875

00:48:00.230 --> 00:48:01.862 Happy, thankful enough.

NOTE Confidence: 0.730454781875

00:48:01.862 -> 00:48:04.468 Have Tina. In my group,

NOTE Confidence: 0.730454781875

00:48:04.468 --> 00:48:05.986 I fantastic collaborators.

NOTE Confidence: 0.730454781875

 $00{:}48{:}05{.}990 \dashrightarrow 00{:}48{:}07{.}970$ This is actually an incomplete list.
$00:48:07.970 \longrightarrow 00:48:10.350$ These are the people that were involved

NOTE Confidence: 0.730454781875

 $00:48:10.350 \longrightarrow 00:48:12.947$ in the studies that I showed you today.

NOTE Confidence: 0.730454781875

 $00:48:12.950 \longrightarrow 00:48:15.116$ And with that I'm happy to

NOTE Confidence: 0.730454781875

 $00:48:15.116 \rightarrow 00:48:16.199$ take your questions.

NOTE Confidence: 0.719134098571429

00:48:23.460 --> 00:48:24.660 It was wonderful. Really,

NOTE Confidence: 0.719134098571429

 $00:48:24.660 \longrightarrow 00:48:27.610$ really great talk. Thank you.

NOTE Confidence: 0.719134098571429

00:48:27.610 --> 00:48:29.026 Yeah, we'll do questions by hand,

NOTE Confidence: 0.719134098571429

 $00:48:29.030 \rightarrow 00:48:30.255$ so why don't we start with why?

NOTE Confidence: 0.589322213333333

 $00:48:32.910 \longrightarrow 00:48:35.730$ Eric, this is aboy from Physiology.

NOTE Confidence: 0.589322213333333

 $00:48:35.730 \longrightarrow 00:48:36.966$ My lab study a little bit,

NOTE Confidence: 0.589322213333333

00:48:36.970 --> 00:48:38.325 but I kandariya so I felt

NOTE Confidence: 0.589322213333333

 $00{:}48{:}38{.}325 \dashrightarrow 00{:}48{:}41{.}219$ that when you mentioned.

NOTE Confidence: 0.589322213333333

 $00{:}48{:}41{.}220 \dashrightarrow 00{:}48{:}43{.}590$ There are those medical.

NOTE Confidence: 0.589322213333333

00:48:43.590 --> 00:48:46.864 Andrea was very amazing and

NOTE Confidence: 0.589322213333333

 $00:48:46.864 \rightarrow 00:48:49.340$ mythological change actually functional.

NOTE Confidence: 0.589322213333333

 $00:48:49.340 \longrightarrow 00:48:51.458$ Can you expand a little bit

- NOTE Confidence: 0.589322213333333
- $00:48:51.458 \longrightarrow 00:48:52.870$ on that part please?
- NOTE Confidence: 0.589322213333333
- $00:48:52.870 \longrightarrow 00:48:54.742$ On the functionality, well,
- NOTE Confidence: 0.589322213333333
- $00:48:54.742 \rightarrow 00:48:57.516$ so I'll tell you mostly negative data I
- NOTE Confidence: 0.589322213333333
- $00{:}48{:}57{.}516 \dashrightarrow 00{:}48{:}59{.}510$ guess is the way you would interpret it.
- NOTE Confidence: 0.589322213333333
- $00{:}48{:}59{.}510 \dashrightarrow 00{:}49{:}01{.}880$ We've you know.
- NOTE Confidence: 0.589322213333333
- 00:49:01.880 --> 00:49:03.716 Alright, I'll I'll preface this by
- NOTE Confidence: 0.589322213333333
- $00{:}49{:}03.716 \dashrightarrow 00{:}49{:}06.129$ saying my next door neighbor is a man
- NOTE Confidence: 0.589322213333333
- 00:49:06.129 --> 00:49:08.240 named Cole Haynes and Cole Haynes is
- NOTE Confidence: 0.589322213333333
- $00{:}49{:}08{.}240 \dashrightarrow 00{:}49{:}09{.}815$ an expert on mitochondrial function,
- NOTE Confidence: 0.589322213333333
- $00:49:09.820 \longrightarrow 00:49:12.244$ so we you know had a drink
- NOTE Confidence: 0.589322213333333
- $00:49:12.244 \rightarrow 00:49:14.004$ coffee with Cole you know,
- NOTE Confidence: 0.589322213333333
- 00:49:14.010 00:49:16.326 probably at least every other day.
- NOTE Confidence: 0.589322213333333
- 00:49:16.330 --> 00:49:17.764 And you know,
- NOTE Confidence: 0.589322213333333
- $00{:}49{:}17.764 \dashrightarrow 00{:}49{:}20.632$ we've run these cells through seahorse
- NOTE Confidence: 0.589322213333333
- $00:49:20.632 \dashrightarrow 00:49:23.927$ and different types of measures and.
- NOTE Confidence: 0.589322213333333

00:49:23.930 --> 00:49:24.803 They look functional,

NOTE Confidence: 0.589322213333333

 $00:49:24.803 \longrightarrow 00:49:26.549$ you know they they don't they.

NOTE Confidence: 0.589322213333333

 $00:49:26.550 \longrightarrow 00:49:28.071$ We don't really.

NOTE Confidence: 0.589322213333333

 $00:49:28.071 \longrightarrow 00:49:30.099$ Although their function is

NOTE Confidence: 0.589322213333333

 $00:49:30.099 \rightarrow 00:49:32.670$ slightly altered by the typical.

NOTE Confidence: 0.589322213333333

 $00{:}49{:}32.670 \dashrightarrow 00{:}49{:}34.555$ Challenges that are used either

NOTE Confidence: 0.589322213333333

00:49:34.555 --> 00:49:36.990 in seahorse or in other assays.

NOTE Confidence: 0.589322213333333

 $00{:}49{:}36{.}990 \dashrightarrow 00{:}49{:}39{.}895$ We don't see any dramatic shifts in

NOTE Confidence: 0.589322213333333

 $00:49:39.895 \rightarrow 00:49:42.146$ their ability to undergo respiration,

NOTE Confidence: 0.589322213333333

 $00:49:42.146 \longrightarrow 00:49:43.090$ for example,

NOTE Confidence: 0.589322213333333

 $00{:}49{:}43.090 \dashrightarrow 00{:}49{:}45.806$ and you know we haven't done thorough,

NOTE Confidence: 0.589322213333333

00:49:45.810 --> 00:49:49.626 you know metabolite profiling etc on

NOTE Confidence: 0.589322213333333

 $00{:}49{:}49{.}626 \dashrightarrow 00{:}49{:}53{.}379$ these cells and but they appear that

NOTE Confidence: 0.589322213333333

 $00:49:53.379 \rightarrow 00:49:55.394$ mitochondria seem to be functional.

NOTE Confidence: 0.87266716777778

 $00{:}49{:}57{.}850 \dashrightarrow 00{:}49{:}59{.}443$ You know when you get a phenotype like this,

NOTE Confidence: 0.87266716777778

 $00:49:59.450 \longrightarrow 00:50:00.935$ there are many factors that

00:50:00.935 --> 00:50:02.400 contribute to it, including you

NOTE Confidence: 0.87266716777778

00:50:02.400 --> 00:50:04.110 know I alluded to fission fusion,

NOTE Confidence: 0.87266716777778

 $00:50:04.110 \longrightarrow 00:50:06.242$ but you could also have mitochondrial

NOTE Confidence: 0.87266716777778

 $00:50:06.242 \rightarrow 00:50:09.434$ Biogenesis could contribute to it and.

NOTE Confidence: 0.928996654166667

 $00:50:11.470 \longrightarrow 00:50:14.150$ And all I can say is we haven't

NOTE Confidence: 0.928996654166667

 $00:50:14.150 \longrightarrow 00:50:15.750$ completed those analysis of,

NOTE Confidence: 0.928996654166667

 $00:50:15.750 \rightarrow 00:50:18.276$ say by Genesis using mutations and

NOTE Confidence: 0.928996654166667

 $00:50:18.276 \rightarrow 00:50:21.508$ say like GC alpha type of mutations.

NOTE Confidence: 0.928996654166667

 $00:50:21.510 \longrightarrow 00:50:24.560$ But our preliminary data suggested.

NOTE Confidence: 0.928996654166667

 $00:50:24.560 \longrightarrow 00:50:27.500$ That's not contributing.

NOTE Confidence: 0.928996654166667

 $00:50:27.500 \longrightarrow 00:50:29.806$ What I call my T cell.

NOTE Confidence: 0.928996654166667

 $00{:}50{:}29{.}806 \dashrightarrow 00{:}50{:}32{.}542$ Yeah, interesting I I found this

NOTE Confidence: 0.928996654166667

 $00{:}50{:}32{.}542 \dashrightarrow 00{:}50{:}34{.}358$ quite interesting that there

NOTE Confidence: 0.928996654166667

 $00{:}50{:}34{.}358 \dashrightarrow 00{:}50{:}36{.}869$ appeared to be divergance that the

NOTE Confidence: 0.928996654166667

 $00{:}50{:}36{.}869 \dashrightarrow 00{:}50{:}39{.}486$ mitochondria is not entirely for

 $00:50:39.486 \rightarrow 00:50:42.670$ biogenics is do somehow trigger the

NOTE Confidence: 0.928996654166667

 $00{:}50{:}42.670 \dashrightarrow 00{:}50{:}44.450$ self killing signal that require

NOTE Confidence: 0.791229168

 $00:50:44.460 \rightarrow 00:50:46.630$ autophagy to eat it up. So

NOTE Confidence: 0.778893304

 $00:50:46.640 \rightarrow 00:50:48.016$ there's some interesting aspects.

NOTE Confidence: 0.778893304

 $00{:}50{:}48.016 \dashrightarrow 00{:}50{:}49.224$ Yeah, thank you.

NOTE Confidence: 0.778893304

00:50:49.224 --> 00:50:51.816 Yeah, I'll just expand upon that.

NOTE Confidence: 0.778893304

 $00:50:51.820 \rightarrow 00:50:53.420$ But we're going on to the next question.

NOTE Confidence: 0.778893304

 $00:50:53.420 \longrightarrow 00:50:55.394$ Say you know one one thing

NOTE Confidence: 0.778893304

 $00{:}50{:}55{.}394 \dashrightarrow 00{:}50{:}57{.}430$ to consider is that you know.

NOTE Confidence: 0.778893304

 $00{:}50{:}57{.}430 \dashrightarrow 00{:}50{:}59{.}510$ Metacrawler can also be signaling

NOTE Confidence: 0.778893304

 $00{:}50{:}59{.}510 \dashrightarrow 00{:}51{:}01{.}590$ scaffolds or could influence other

NOTE Confidence: 0.778893304

 $00:51:01.652 \rightarrow 00:51:03.607$ signaling scaffolds so you know,

NOTE Confidence: 0.778893304

 $00:51:03.610 \longrightarrow 00:51:05.585$ I think, that the ramifications

NOTE Confidence: 0.778893304

00:51:05.585 - 00:51:08.356 could be quite broad or we need

NOTE Confidence: 0.778893304

00:51:08.356 --> 00:51:10.510 to think about this in its

NOTE Confidence: 0.778893304

 $00:51:10.510 \rightarrow 00:51:12.169$ broader context as possible.

- NOTE Confidence: 0.778893304
- 00:51:12.170 --> 00:51:12.950 Cool, thank you.
- NOTE Confidence: 0.599589576
- 00:51:16.930 --> 00:51:20.660 Yeah, you said that then you spoke
- NOTE Confidence: 0.599589576
- $00{:}51{:}20.660 \dashrightarrow 00{:}51{:}22.210$ about the suppression by Matthews
- NOTE Confidence: 0.599589576
- $00{:}51{:}22{.}210 \dashrightarrow 00{:}51{:}25{.}684$ in Matthews is suppressed just in
- NOTE Confidence: 0.599589576
- 00:51:25.684 --> 00:51:28.000 larger mitochondria or globally
- NOTE Confidence: 0.599589576
- $00:51:28.090 \rightarrow 00:51:33.120$ suggest as suppresses everything. Uhm?
- NOTE Confidence: 0.599589576
- $00:51:33.120 \rightarrow 00:51:35.750$ Yeah, that's a great question. Pietro so.
- NOTE Confidence: 0.902848806923077
- 00:51:38.620 --> 00:51:40.559 I just I just thinking in my
- NOTE Confidence: 0.902848806923077
- $00:51:40.559 \longrightarrow 00:51:43.286$ head what day do we have it it?
- NOTE Confidence: 0.902848806923077
- $00:51:43.286 \longrightarrow 00:51:45.618$ It certainly suppresses the
- NOTE Confidence: 0.902848806923077
- $00:51:45.618 \longrightarrow 00:51:49.590$ mitochondrial sides. Uhm? I.
- NOTE Confidence: 0.828696285
- $00{:}51{:}51{.}730 \dashrightarrow 00{:}51{:}54{.}808$ Yes, I I think it does.
- NOTE Confidence: 0.828696285
- $00{:}51{:}54{.}810 \dashrightarrow 00{:}51{:}57{.}648$ I don't think it actually is
- NOTE Confidence: 0.828696285
- $00{:}51{:}57.648 \dashrightarrow 00{:}51{:}59.540$ influencing the cell size.
- NOTE Confidence: 0.828696285
- 00:51:59.540 --> 00:52:03.875 Per say. But it does have some
- NOTE Confidence: 0.828696285

00:52:03.875 --> 00:52:06.389 effect on autophagy, so you know,

NOTE Confidence: 0.828696285

 $00{:}52{:}06{.}389 \dashrightarrow 00{:}52{:}09{.}518$ I think the the cell size measurement.

NOTE Confidence: 0.828696285

 $00:52:09.518 \longrightarrow 00:52:12.652$ I think it's probably there are

NOTE Confidence: 0.828696285

 $00{:}52{:}12.652 \dashrightarrow 00{:}52{:}13.736$ multiple factors that contribute

NOTE Confidence: 0.828696285

00:52:13.736 --> 00:52:15.140 to cell size, obviously,

NOTE Confidence: 0.828696285

 $00:52:15.140 \rightarrow 00:52:19.624$ and so it may be through, you know,

NOTE Confidence: 0.828696285

 $00{:}52{:}19.624 \dashrightarrow 00{:}52{:}22.928$ some partial effect on on cell size.

NOTE Confidence: 0.828696285

00:52:22.930 --> 00:52:26.070 And it's not surprisingly valid.

NOTE Confidence: 0.828696285

 $00{:}52{:}26.070 \dashrightarrow 00{:}52{:}27.830$ So there's something else.

NOTE Confidence: 0.828696285

 $00:52:27.830 \longrightarrow 00:52:29.590$ It's something beyond the

NOTE Confidence: 0.828696285

 $00:52:29.590 \longrightarrow 00:52:30.470$ mitochondrial aspect.

NOTE Confidence: 0.828696285

00:52:30.470 - 00:52:33.506 There's no question that. VPS 13D.

NOTE Confidence: 0.828696285

 $00:52:33.510 \rightarrow 00:52:36.198$ Effects more than just the large amount

NOTE Confidence: 0.828696285

00:52:36.198 --> 00:52:38.102 of kandariya based on our analysis,

NOTE Confidence: 0.828696285

00:52:38.102 --> 00:52:38.668 but again,

NOTE Confidence: 0.828696285

 $00:52:38.670 \rightarrow 00:52:41.334$ many probably need to do more in that.

- NOTE Confidence: 0.828696285
- 00:52:41.340 --> 00:52:44.320 But since you mentioned self size,
- NOTE Confidence: 0.828696285
- $00{:}52{:}44{.}320 \dashrightarrow 00{:}52{:}46{.}672$ what do you think is behind
- NOTE Confidence: 0.828696285
- $00:52:46.672 \rightarrow 00:52:48.740$ the increase in cell size?
- NOTE Confidence: 0.828696285
- $00{:}52{:}48.740 \dashrightarrow 00{:}52{:}50.420$ Yeah, that's it.
- NOTE Confidence: 0.828696285
- $00:52:50.420 \longrightarrow 00:52:52.206$ You know people are,
- NOTE Confidence: 0.828696285
- $00{:}52{:}52{.}206 \dashrightarrow 00{:}52{:}54{.}204$ especially when I first started talking
- NOTE Confidence: 0.828696285
- $00:52:54.204 \rightarrow 00:52:56.025$ about these phenotypes and that you
- NOTE Confidence: 0.828696285
- $00:52:56.025 \rightarrow 00:52:58.310$ know people said oh what you know maybe.
- NOTE Confidence: 0.828696285
- 00:52:58.310 --> 00:52:59.254 Maybe Plaza, you know,
- NOTE Confidence: 0.828696285
- $00:52:59.254 \longrightarrow 00:53:00.670$ people went as far as single.
- NOTE Confidence: 0.828696285
- 00:53:00.670 --> 00:53:02.700 Maybe plasma membranes is what
- NOTE Confidence: 0.828696285
- $00{:}53{:}02{.}700 \dashrightarrow 00{:}53{:}04{.}730$ she used to form autophagosomes.
- NOTE Confidence: 0.828696285
- 00:53:04.730 --> 00:53:06.350 Or maybe I you know,
- NOTE Confidence: 0.828696285
- 00:53:06.350 --> 00:53:08.230 I honestly don't know.
- NOTE Confidence: 0.828696285
- $00{:}53{:}08{.}230 \dashrightarrow 00{:}53{:}11{.}050$ Maybe maybe it's about lipid redistribution.
- NOTE Confidence: 0.828696285

 $00:53:11.050 \rightarrow 00:53:16.055$ I have no idea honestly and somebody. NOTE Confidence: 0.828696285 00:53:16.060 --> 00:53:17.950 Had made a suggestion once that NOTE Confidence: 0.828696285 $00:53:17.950 \longrightarrow 00:53:20.149$ the only way that what they said NOTE Confidence: 0.828696285 $00:53:20.149 \longrightarrow 00:53:22.172$ is the only way that you could NOTE Confidence: 0.828696285 $00:53:22.246 \longrightarrow 00:53:24.318$ make that big a change in cell NOTE Confidence: 0.828696285 $00:53:24.318 \rightarrow 00:53:27.090$ size is through water plant. NOTE Confidence: 0.828696285 $00:53:27.090 \longrightarrow 00:53:28.336$ So they told me I should be NOTE Confidence: 0.828696285 $00:53:28.336 \rightarrow 00:53:29.450$ looking at a performance. NOTE Confidence: 0.863766652 00:53:31.690 --> 00:53:33.210 I honestly don't know Pietro. NOTE Confidence: 0.863766652 $00:53:33.210 \rightarrow 00:53:36.082$ I think it's a fascinating biology and it's NOTE Confidence: 0.863766652 $00:53:36.082 \rightarrow 00:53:39.269$ a great surrogate screening marker for us. NOTE Confidence: 0.863766652 00:53:39.270 --> 00:53:41.289 'cause it's simple, NOTE Confidence: 0.863766652 00:53:41.290 --> 00:53:45.066 but I am reluctant to to sort of. NOTE Confidence: 0.863766652 $00:53:45.070 \longrightarrow 00:53:46.770$ Say that all of these NOTE Confidence: 0.863766652 $00:53:46.770 \rightarrow 00:53:47.790$ things are interconnected. NOTE Confidence: 0.863766652 $00:53:47.790 \longrightarrow 00:53:49.770$ Some of the quick question,

- NOTE Confidence: 0.863766652
- $00:53:49.770 \rightarrow 00:53:52.550$ since you mentioned water possibility,
- NOTE Confidence: 0.863766652
- $00:53:52.550 \longrightarrow 00:53:53.756$ just as welling.
- NOTE Confidence: 0.863766652
- $00:53:53.756 \longrightarrow 00:53:56.346$ If you look at the marker,
- NOTE Confidence: 0.863766652
- $00:53:56.346 \rightarrow 00:53:58.650$ for example ER marker,
- NOTE Confidence: 0.863766652
- $00{:}53{:}58{.}650 \dashrightarrow 00{:}54{:}01{.}169$ do you see a more dispersed ER or
- NOTE Confidence: 0.863766652
- $00{:}54{:}01{.}169 \dashrightarrow 00{:}54{:}04{.}790$ do you see the same density there?
- NOTE Confidence: 0.863766652
- $00{:}54{:}04.790 \dashrightarrow 00{:}54{:}07.540$ Micro ceratitis beside the blast.
- NOTE Confidence: 0.863766652
- $00{:}54{:}07{.}540 \dashrightarrow 00{:}54{:}10{.}460$ Yeah so we we see so I should and I
- NOTE Confidence: 0.863766652
- $00{:}54{:}10{.}549 \dashrightarrow 00{:}54{:}14{.}056$ should have said this throughout the talk.
- NOTE Confidence: 0.863766652
- $00{:}54{:}14.060 \dashrightarrow 00{:}54{:}17.090$ Before the signal that activates
- NOTE Confidence: 0.863766652
- $00:54:17.090 \longrightarrow 00:54:18.908$ the autophagy signal.
- NOTE Confidence: 0.863766652
- $00{:}54{:}18{.}910 \dashrightarrow 00{:}54{:}20{.}870$ In the different mutants that I've shown you,
- NOTE Confidence: 0.863766652
- $00:54:20.870 \longrightarrow 00:54:22.826$ they all look identical.
- NOTE Confidence: 0.863766652
- 00:54:22.826 --> 00:54:24.293 Side-by-side mutant didn't
- NOTE Confidence: 0.863766652
- $00:54:24.293 \longrightarrow 00:54:26.320$ control before that signal.
- NOTE Confidence: 0.863766652

00:54:26.320 --> 00:54:27.688 After autophagy is activated,

NOTE Confidence: 0.863766652

 $00{:}54{:}27.688 \dashrightarrow 00{:}54{:}30.330$ there's a big change in cell structure

NOTE Confidence: 0.863766652

00:54:30.330 --> 00:54:33.198 and including that the ER structure

NOTE Confidence: 0.863766652

 $00:54:33.198 \longrightarrow 00:54:35.110$ starts to change dramatically.

NOTE Confidence: 0.863766652

 $00{:}54{:}35{.}110 \dashrightarrow 00{:}54{:}36{.}001$ The mutant cells,

NOTE Confidence: 0.863766652

 $00:54:36.001 \rightarrow 00:54:38.080$ most of them you know it depends

NOTE Confidence: 0.863766652

 $00:54:38.146 \rightarrow 00:54:40.169$ on the mutant that I've shown you,

NOTE Confidence: 0.863766652

 $00:54:40.170 \longrightarrow 00:54:42.828$ but many of the mutant cells

NOTE Confidence: 0.863766652

00:54:42.828 --> 00:54:44.600 have similar ER structure.

NOTE Confidence: 0.863766652

 $00{:}54{:}44{.}600 \dashrightarrow 00{:}54{:}47{.}800$ Before and after the induction.

NOTE Confidence: 0.863766652

00:54:47.800 --> 00:54:50.326 About half a GI see,

NOTE Confidence: 0.863766652

 $00{:}54{:}50{.}326 \dashrightarrow 00{:}54{:}52{.}058$ but there are morphological.

NOTE Confidence: 0.863766652

 $00:54:52.060 \longrightarrow 00:54:53.509$ There's no question.

NOTE Confidence: 0.863766652

00:54:53.509 --> 00:54:56.890 There are dramatic yard changes taking place.

NOTE Confidence: 0.863766652

 $00{:}54{:}56{.}890 \dashrightarrow 00{:}55{:}00{.}190$ Very dramatic yard changes taking place.

NOTE Confidence: 0.863766652

 $00:55:00.190 \rightarrow 00:55:03.930$ And so I think a big part of the puzzle

- NOTE Confidence: 0.863766652
- $00:55:04.034 \rightarrow 00:55:07.405$ is going to be or the solution to our
- NOTE Confidence: 0.863766652
- 00:55:07.405 --> 00:55:09.258 puzzle I presented as mitochondria
- NOTE Confidence: 0.863766652
- $00{:}55{:}09{.}258 \dashrightarrow 00{:}55{:}11{.}430$ 'cause it's the most obvious phenotype.
- NOTE Confidence: 0.863766652
- 00:55:11.430 --> 00:55:12.925 But I actually think probably
- NOTE Confidence: 0.863766652
- $00{:}55{:}12.925 \dashrightarrow 00{:}55{:}14.761$ that the solution to our problem
- NOTE Confidence: 0.863766652
- $00:55:14.761 \longrightarrow 00:55:16.146$ is coming from the ER,
- NOTE Confidence: 0.863766652
- $00{:}55{:}16{.}150 \dashrightarrow 00{:}55{:}17{.}154$ but it's my instinct.
- NOTE Confidence: 0.863766652
- $00{:}55{:}17{.}154 \dashrightarrow 00{:}55{:}18{.}158$ It's not based on.
- NOTE Confidence: 0.48135173
- 00:55:20.890 --> 00:55:23.858 Yeah, a complete data set.
- NOTE Confidence: 0.48135173
- $00:55:23.858 \longrightarrow 00:55:25.814$ Let's say that. Thank you.
- NOTE Confidence: 0.48135173
- 00:55:25.814 --> 00:55:28.989 I I can say Pietro, that it's sort
- NOTE Confidence: 0.48135173
- $00:55:28.989 \longrightarrow 00:55:31.880$ of a side project with EPS 13D.
- NOTE Confidence: 0.48135173
- $00:55:31.880 \rightarrow 00:55:35.876$ We have been very actively studying
- NOTE Confidence: 0.48135173
- $00{:}55{:}35{.}880 \dashrightarrow 00{:}55{:}40{.}206$ ER and in ER changes in themselves.
- NOTE Confidence: 0.48135173
- $00{:}55{:}40{.}210 \dashrightarrow 00{:}55{:}44{.}830$ And, and we're particularly interested in
- NOTE Confidence: 0.48135173

 $00{:}55{:}44{.}830 \dashrightarrow 00{:}55{:}47{.}694$ and this is something it's like my new

NOTE Confidence: 0.48135173

 $00{:}55{:}47.694 \dashrightarrow 00{:}55{:}50.240$ seminar that I haven't quite prepared.

NOTE Confidence: 0.48135173

 $00{:}55{:}50{.}240 \dashrightarrow 00{:}55{:}52{.}592$ We think this is also an excellent

NOTE Confidence: 0.48135173

 $00:55:52.592 \dashrightarrow 00:55:55.039$ model for PR specific clearance.

NOTE Confidence: 0.48135173

 $00:55:55.040 \longrightarrow 00:55:58.081$ And so, and that's forthcoming,

NOTE Confidence: 0.48135173

 $00:55:58.081 \rightarrow 00:55:59.916$ you know that's the that's.

NOTE Confidence: 0.48135173

 $00:55:59.920 \longrightarrow 00:56:01.726$ So there's one postdoc in my lab.

NOTE Confidence: 0.48135173

 $00:56:01.730 \rightarrow 00:56:05.188$ It's very active working in that space.

NOTE Confidence: 0.48135173

 $00{:}56{:}05{.}190 \dashrightarrow 00{:}56{:}06{.}690$ Thank you.

NOTE Confidence: 0.48135173

 $00{:}56{:}06{.}690 \dashrightarrow 00{:}56{:}10{.}338$ So I'm interested in the tissue

NOTE Confidence: 0.48135173

 $00:56:10.338 \longrightarrow 00:56:12.770$ specificity in the disease.

NOTE Confidence: 0.48135173

 $00{:}56{:}12.770 \dashrightarrow 00{:}56{:}15.962$ And I'm a little bit confused about the

NOTE Confidence: 0.48135173

 $00:56:15.962 \rightarrow 00:56:18.951$ essay that you use or the the screen

NOTE Confidence: 0.48135173

 $00:56:18.951 \longrightarrow 00:56:21.560$ of the broad panel of cell lines.

NOTE Confidence: 0.48135173

00:56:21.560 -> 00:56:24.808 Because you said the original VSP 13,

NOTE Confidence: 0.48135173

 $00:56:24.810 \rightarrow 00:56:28.226$ he was showed lethality in those cell lines.

- NOTE Confidence: 0.48135173
- $00:56:28.230 \longrightarrow 00:56:29.502$ Is that correct?
- NOTE Confidence: 0.48135173
- $00:56:29.502 \rightarrow 00:56:29.926$ Yes.
- NOTE Confidence: 0.48135173
- $00{:}56{:}29{.}926 \dashrightarrow 00{:}56{:}31{.}334$ Well, so so,
- NOTE Confidence: 0.48135173
- $00:56:31.334 \longrightarrow 00:56:33.794$ the initial papers that were
- NOTE Confidence: 0.48135173
- $00{:}56{:}33.794 \dashrightarrow 00{:}56{:}36.570$ published on Gene essentiality.
- NOTE Confidence: 0.48135173
- 00:56:36.570 00:56:38.426 They're two parallel papers.
- NOTE Confidence: 0.48135173
- $00:56:38.426 \rightarrow 00:56:40.746$ They're both published in science.
- NOTE Confidence: 0.48135173
- $00{:}56{:}40.750 \dashrightarrow 00{:}56{:}43.536$ One from the Nki in the Netherlands
- NOTE Confidence: 0.48135173
- $00{:}56{:}43{.}536 \dashrightarrow 00{:}56{:}46{.}440$ and one from the Broad Broad
- NOTE Confidence: 0.48135173
- $00{:}56{:}46{.}440 \dashrightarrow 00{:}56{:}48{.}720$ Whitehead into collaboration from
- NOTE Confidence: 0.48135173
- $00:56:48.720 \longrightarrow 00:56:51.789$ the Zhang and Sabatini Labs.
- NOTE Confidence: 0.48135173
- $00{:}56{:}51{.}790 \dashrightarrow 00{:}56{:}53{.}674$ When they published their list of
- NOTE Confidence: 0.48135173
- $00:56:53.674 \rightarrow 00:56:55.950$ essential genes and these were in so called,
- NOTE Confidence: 0.48135173
- 00:56:55.950 --> 00:56:58.170 you know more normal cells,
- NOTE Confidence: 0.48135173
- $00:56:58.170 \longrightarrow 00:56:58.826$ you know.
- NOTE Confidence: 0.48135173

 $00{:}56{:}58{.}826 \dashrightarrow 00{:}57{:}01{.}190$ So he lo is excluded but but you

NOTE Confidence: 0.48135173

 $00{:}57{:}01{.}190 \dashrightarrow 00{:}57{:}02{.}390$ can get those cell lines.

NOTE Confidence: 0.48135173

 $00{:}57{:}02{.}390 \dashrightarrow 00{:}57{:}04{.}525$ Their VPS 13D was among the most

NOTE Confidence: 0.48135173

 $00:57:04.525 \longrightarrow 00:57:07.167$ is I think it was one of the top

NOTE Confidence: 0.48135173

 $00:57:07.167 \longrightarrow 00:57:09.129$ ten jeans for for viability of

NOTE Confidence: 0.48135173

 $00{:}57{:}09{.}129 \dashrightarrow 00{:}57{:}11{.}469$ those cells as they increase the

NOTE Confidence: 0.48135173

 $00{:}57{:}11{.}469 \dashrightarrow 00{:}57{:}13{.}744$ number of cells so that I think I

NOTE Confidence: 0.48135173

 $00{:}57{:}13.744 \dashrightarrow 00{:}57{:}15.292$ remember the statistic I showed you

NOTE Confidence: 0.48135173

 $00{:}57{:}15{.}292 \dashrightarrow 00{:}57{:}17{.}028$ at that point we made the graph.

NOTE Confidence: 0.48135173

 $00{:}57{:}17{.}030 \dashrightarrow 00{:}57{:}19{.}820$ I think it was over 300 cell lines that

NOTE Confidence: 0.48135173

 $00{:}57{:}19{.}820 \dashrightarrow 00{:}57{:}22{.}809$ had been analyzed for gene essentiality.

NOTE Confidence: 0.48135173

 $00:57:22.810 \longrightarrow 00:57:24.410$ The significance of the PS13

NOTE Confidence: 0.48135173

 $00:57:24.410 \longrightarrow 00:57:26.010$ on down some but again,

NOTE Confidence: 0.48135173

 $00:57:26.010 \rightarrow 00:57:27.380$ we're looking at transform cells.

NOTE Confidence: 0.48135173

 $00:57:27.380 \longrightarrow 00:57:29.144$ And I showed you data from yela.

NOTE Confidence: 0.48135173

 $00:57:29.150 \rightarrow 00:57:30.590$ We were lucky we started in.

 $00{:}57{:}30{.}590 \dashrightarrow 00{:}57{:}32{.}378$ He LA for mammalian cells because

NOTE Confidence: 0.48135173

 $00:57:32.378 \longrightarrow 00:57:34.637$ one of the few cell lines where

NOTE Confidence: 0.48135173

 $00:57:34.637 \rightarrow 00:57:36.629$ they seem to be perfectly fine.

NOTE Confidence: 0.48135173

 $00:57:36.630 \longrightarrow 00:57:38.758$ Without VPS 13th day.

NOTE Confidence: 0.48135173

 $00{:}57{:}38.758 \dashrightarrow 00{:}57{:}42.450$ It is remarkable that the phenotype is

NOTE Confidence: 0.48135173

 $00{:}57{:}42{.}450 \dashrightarrow 00{:}57{:}44{.}520$ so limited to the OR maybe it's not,

NOTE Confidence: 0.48135173

 $00{:}57{:}44{.}520 \dashrightarrow 00{:}57{:}46{.}356$ but it's from what you describe

NOTE Confidence: 0.48135173

 $00{:}57{:}46.356 \dashrightarrow 00{:}57{:}48.600$ the least to the nervous system.

NOTE Confidence: 0.48135173

00:57:48.600 --> 00:57:51.530 Yet these patients, Zoomer yeah,

NOTE Confidence: 0.48135173

 $00{:}57{:}51{.}530 \dashrightarrow 00{:}57{:}54{.}314$ but that I think that's also a little

NOTE Confidence: 0.48135173

 $00{:}57{:}54{.}314 \dashrightarrow 00{:}57{:}56{.}723$ bit complicated by the fact that you

NOTE Confidence: 0.48135173

 $00{:}57{:}56{.}723 \dashrightarrow 00{:}57{:}58{.}745$ know the patient alleles must be

NOTE Confidence: 0.48135173

 $00{:}57{:}58.745 \dashrightarrow 00{:}58{:}01.636$ weak alleles based on the you know I,

NOTE Confidence: 0.48135173

00:58:01.636 --> 00:58:03.896 I'm not a human geneticist,

NOTE Confidence: 0.48135173

 $00{:}58{:}03{.}900 \dashrightarrow 00{:}58{:}05{.}673$ which to me is a bit of a misnomer.

- 00:58:05.680 --> 00:58:06.520 Anyway, you know,
- NOTE Confidence: 0.48135173
- 00:58:06.520 --> 00:58:08.200 I don't know how you do
- NOTE Confidence: 0.48135173
- $00:58:08.200 \rightarrow 00:58:09.390$ experiments breeding humans.
- NOTE Confidence: 0.48135173
- $00:58:09.390 \dashrightarrow 00:58:11.856$ But but it's a little bit of an insight.
- NOTE Confidence: 0.48135173
- $00{:}58{:}11.860 \dashrightarrow 00{:}58{:}15.070$ Genesis Joe B.
- NOTE Confidence: 0.48135173
- $00{:}58{:}15{.}070 \dashrightarrow 00{:}58{:}17{.}500$ You know the Margit Burmeister
- NOTE Confidence: 0.48135173
- $00:58:17.500 \rightarrow 00:58:19.444$ who identified these mutations,
- NOTE Confidence: 0.48135173
- $00:58:19.450 \longrightarrow 00:58:20.548$ the original mutations,
- NOTE Confidence: 0.48135173
- $00{:}58{:}20{.}548 \dashrightarrow 00{:}58{:}22{.}744$ she said that the original family
- NOTE Confidence: 0.48135173
- $00:58:22.744 \rightarrow 00:58:24.585$ that they studied those are
- NOTE Confidence: 0.48135173
- $00{:}58{:}24{.}585 \dashrightarrow 00{:}58{:}26{.}355$ probably much weaker alleles based NOTE Confidence: 0.48135173
- $00:58:26.355 \rightarrow 00:58:28.864$ on where they are in the VPS 13D
- NOTE Confidence: 0.48135173
- $00{:}58{:}28{.}864 \dashrightarrow 00{:}58{:}30{.}999$ sequence compared to the pediatric
- NOTE Confidence: 0.48135173
- $00{:}58{:}30{.}999 \dashrightarrow 00{:}58{:}33{.}489$ alleles that have been identified.
- NOTE Confidence: 0.48135173
- $00:58:33.490 \longrightarrow 00:58:35.560$ But none of them are probably
- NOTE Confidence: 0.48135173
- $00:58:35.560 \rightarrow 00:58:37.985$ true nuts and and so they have

 $00:58:37.985 \longrightarrow 00:58:40.246$ to be by necessity in our mouse

NOTE Confidence: 0.846710823478261

 $00:58:40.321 \longrightarrow 00:58:42.010$ weren't validates that.

NOTE Confidence: 0.846710823478261

00:58:42.010 - 00:58:44.410 That you know the patients are

NOTE Confidence: 0.846710823478261

 $00:58:44.410 \rightarrow 00:58:46.492$ probably there's complexity in the

NOTE Confidence: 0.846710823478261

 $00:58:46.492 \longrightarrow 00:58:48.567$ fact that they're probably weaker.

NOTE Confidence: 0.846710823478261

00:58:48.570 --> 00:58:51.934 Yes, I see. Cases,

NOTE Confidence: 0.846710823478261

 $00{:}58{:}51{.}934 \dashrightarrow 00{:}58{:}54{.}004$ do they have more wides pread

NOTE Confidence: 0.846710823478261

 $00:58:54.004 \rightarrow 00:58:56.170$ phenotypes beyond the nervous system?

NOTE Confidence: 0.91425672

 $00:58:59.970 \longrightarrow 00:59:01.438$ That's a great question.

NOTE Confidence: 0.94197989111111

00:59:04.580 --> 00:59:07.667 I I, I'll have to say I don't know,

NOTE Confidence: 0.94197989111111

00:59:07.670 - 00:59:12.540 but as far as I know no OK.

NOTE Confidence: 0.94197989111111

 $00:59:12.540 \rightarrow 00:59:15.452$ As far as I know they don't, but actually

NOTE Confidence: 0.94197989111111

 $00{:}59{:}15{.}452 \dashrightarrow 00{:}59{:}19{.}204$ that's a great question and I will.

NOTE Confidence: 0.94197989111111

 $00{:}59{:}19{.}210 \dashrightarrow 00{:}59{:}22{.}468$ Aye. Yeah, So what I can address.

NOTE Confidence: 0.941979891111111

 $00:59:22.470 \longrightarrow 00:59:24.654$ Let me say this to try

 $00:59:24.654 \rightarrow 00:59:26.110$ to address your question.

NOTE Confidence: 0.941979891111111

 $00{:}59{:}26.110 \dashrightarrow 00{:}59{:}29.140$ There's a very interactive family in

NOTE Confidence: 0.94197989111111

 $00:59:29.140 \dashrightarrow 00:59:32.950$ Australia and and their son was diagnosed.

NOTE Confidence: 0.94197989111111

 $00:59:32.950 \longrightarrow 00:59:34.889$ I think at the age of 15,

NOTE Confidence: 0.94197989111111

 $00{:}59{:}34{.}890 \dashrightarrow 00{:}59{:}36{.}924$ so it's not one of these very strong cases,

NOTE Confidence: 0.94197989111111

 $00{:}59{:}36{.}930 \dashrightarrow 00{:}59{:}40{.}042$ but he's stronger than the than the the

NOTE Confidence: 0.94197989111111

 $00{:}59{:}40.042 \dashrightarrow 00{:}59{:}42.240$ Burmeister alleles that I talked about.

NOTE Confidence: 0.94197989111111

 $00:59:42.240 \longrightarrow 00:59:47.960$ And. He is normal other than

NOTE Confidence: 0.94197989111111

 $00{:}59{:}47.960 \dashrightarrow 00{:}59{:}49.934$ some movement difficult.

NOTE Confidence: 0.94197989111111

00:59:49.940 --> 00:59:50.700 In fact, he's a.

NOTE Confidence: 0.94197989111111

00:59:50.700 --> 00:59:53.114 He's a, you know, a plus student and

NOTE Confidence: 0.94197989111111

 $00:59:53.114 \dashrightarrow 00:59:55.579$ he's you know all other factors.

NOTE Confidence: 0.941979891111111

00:59:55.580 --> 00:59:57.878 So somebody would probably stronger alleles

NOTE Confidence: 0.94197989111111

 $00:59:57.878 \rightarrow 01:00:01.179$ than the than the initial patient population,

NOTE Confidence: 0.94197989111111

 $01:00:01.180 \longrightarrow 01:00:02.670$ but still doesn't have any.

NOTE Confidence: 0.94197989111111

 $01:00:02.670 \rightarrow 01:00:05.256$ I'm not part of any immune

01:00:05.256 --> 01:00:07.236 misregulation or any other thing,

NOTE Confidence: 0.94197989111111

 $01:00:07.236 \longrightarrow 01:00:09.840$ but I think probably these pediatric cases

NOTE Confidence: 0.94197989111111

 $01:00:09.903 \rightarrow 01:00:12.735$ which there aren't a huge number of examples,

NOTE Confidence: 0.94197989111111

 $01:00:12.740 \longrightarrow 01:00:14.855$ but there are a couple and and some

NOTE Confidence: 0.94197989111111

 $01:00:14.855 \rightarrow 01:00:16.830$ of those families are quite interactive.

NOTE Confidence: 0.94197989111111

 $01:00:16.830 \longrightarrow 01:00:19.140$ They we might be able to find

NOTE Confidence: 0.94197989111111

 $01:00:19.140 \longrightarrow 01:00:20.969$ out some more information.

NOTE Confidence: 0.94197989111111

01:00:20.970 --> 01:00:25.116 Thank you. Thank you, motivated me.

NOTE Confidence: 0.94197989111111

01:00:25.120 --> 01:00:26.976 Edit just to clarify, what did you say?

NOTE Confidence: 0.94197989111111

01:00:26.980 --> 01:00:28.108 The family in Australia?

NOTE Confidence: 0.941979891111111

 $01:00:28.108 \rightarrow 01:00:30.580$ What is the only symptom has only the

NOTE Confidence: 0.94197989111111

01:00:30.580 --> 01:00:33.460 clinical it's same, it's it's a, it's it's a.

NOTE Confidence: 0.94197989111111

 $01{:}00{:}33.460 \dashrightarrow 01{:}00{:}34.540$ It's an attacks.

NOTE Confidence: 0.94197989111111

 $01{:}00{:}34{.}540 \dashrightarrow 01{:}00{:}37{.}915$ Yeah it's a it's a loss of motor control

NOTE Confidence: 0.94197989111111

 $01:00:37.915 \rightarrow 01:00:40.886$ it's started with gate difficulty but

 $01:00:40.886 \rightarrow 01:00:43.464$ from talking to Margaret who talks

NOTE Confidence: 0.94197989111111

 $01{:}00{:}43.464 \dashrightarrow 01{:}00{:}45.970$ more with these families than I do.

NOTE Confidence: 0.94197989111111

 $01:00:45.970 \longrightarrow 01:00:49.040$ Uhm? She said that you know,

NOTE Confidence: 0.94197989111111

 $01:00:49.040 \rightarrow 01:00:52.226$ she thinks the initial problem that

NOTE Confidence: 0.94197989111111

 $01{:}00{:}52.226 \dashrightarrow 01{:}00{:}55.894$ these individuals face is this, you know,

NOTE Confidence: 0.94197989111111

01:00:55.894 --> 01:00:58.429 reading. And tracking you know?

NOTE Confidence: 0.94197989111111

 $01:00:58.430 \rightarrow 01:01:00.728$ So visual tracking she thinks might

NOTE Confidence: 0.94197989111111

 $01:01:00.728 \rightarrow 01:01:02.260$ be the earliest phenotype.

NOTE Confidence: 0.94197989111111

01:01:02.260 --> 01:01:03.870 So things like you know,

NOTE Confidence: 0.94197989111111

 $01{:}01{:}03.870 \dashrightarrow 01{:}01{:}05.586$ in America that might be catching

NOTE Confidence: 0.94197989111111

01:01:05.586 --> 01:01:07.520 a football and in Australia might

NOTE Confidence: 0.94197989111111

 $01{:}01{:}07{.}520 \dashrightarrow 01{:}01{:}09{.}710$ be failing to catch an Australian

NOTE Confidence: 0.94197989111111

 $01{:}01{:}09.710 \dashrightarrow 01{:}01{:}10.440$ rules football.

NOTE Confidence: 0.912938137692308

 $01:01:12.930 \longrightarrow 01:01:14.964$ But you know the reading difficulties

NOTE Confidence: 0.912938137692308

01:01:14.964 --> 01:01:16.616 losing your place when you're

NOTE Confidence: 0.912938137692308

 $01:01:16.616 \rightarrow 01:01:18.512$ reading text on a line of a book

- NOTE Confidence: 0.912938137692308
- $01:01:18.512 \longrightarrow 01:01:20.448$ is one of the most common first.
- NOTE Confidence: 0.912938137692308
- $01{:}01{:}20{.}450 \dashrightarrow 01{:}01{:}22{.}130$ Symptoms that these individuals
- NOTE Confidence: 0.912938137692308
- $01:01:22.130 \longrightarrow 01:01:24.650$ all seem to have in common,
- NOTE Confidence: 0.912938137692308
- $01:01:24.650 \rightarrow 01:01:27.415$ but then it turns into gate difficulties.
- NOTE Confidence: 0.93070247
- 01:01:32.870 --> 01:01:33.890 So it does seem nervous,
- NOTE Confidence: 0.93070247
- 01:01:33.890 --> 01:01:35.222 system restricted but,
- NOTE Confidence: 0.93070247
- $01{:}01{:}35{.}222 \dashrightarrow 01{:}01{:}37{.}886$ and I'm obviously not a neurologist
- NOTE Confidence: 0.93070247
- $01:01:37.886 \rightarrow 01:01:40.560$ pietros more of a neurologist than I am,
- NOTE Confidence: 0.93070247
- $01{:}01{:}40.560 \dashrightarrow 01{:}01{:}44.918$ I know that. So to speak.
- NOTE Confidence: 0.93070247
- 01:01:44.920 --> 01:01:46.334 I mean it be it would actually
- NOTE Confidence: 0.93070247
- $01:01:46.334 \rightarrow 01:01:47.569$ be really great to get and
- NOTE Confidence: 0.93070247
- $01:01:47.569 \rightarrow 01:01:48.739$ there is actually a you know,
- NOTE Confidence: 0.93070247
- $01:01:48.740 \longrightarrow 01:01:50.999$ for those of us, those of us that were
- NOTE Confidence: 0.93070247
- 01:01:50.999 --> 01:01:52.478 interested in VPS 13 specifically,
- NOTE Confidence: 0.93070247
- $01{:}01{:}52{.}480 \dashrightarrow 01{:}01{:}54{.}250$ there's a forum that meets
- NOTE Confidence: 0.93070247

- $01:01:54.250 \rightarrow 01:01:56.020$ every three months I believe.
- NOTE Confidence: 0.93070247
- 01:01:56.020 --> 01:01:57.620 To discuss these things that
- NOTE Confidence: 0.93070247
- 01:01:57.620 --> 01:01:58.900 many Clement clinicians attend,
- NOTE Confidence: 0.93070247
- $01:01:58.900 \longrightarrow 01:02:00.685$ so that would be a great place
- NOTE Confidence: 0.93070247
- $01{:}02{:}00.685 \dashrightarrow 01{:}02{:}02.470$ to ask those those questions.
- NOTE Confidence: 0.8455219
- 01:02:09.260 --> 01:02:12.276 Great if I could ask just one other thing,
- NOTE Confidence: 0.971788674
- $01:02:12.280 \longrightarrow 01:02:15.470$ if I got this correctly.
- NOTE Confidence: 0.971788674
- $01{:}02{:}15{.}470 \dashrightarrow 01{:}02{:}16{.}918$ I was wondering the
- NOTE Confidence: 0.971788674
- 01:02:16.918 --> 01:02:18.366 connection between the Mytoi,
- NOTE Confidence: 0.971788674
- $01:02:18.370 \rightarrow 01:02:21.766$ our contacts and the mighty Kandariya.
- NOTE Confidence: 0.971788674
- 01:02:21.770 --> 01:02:23.751 If I if I follow it correctly,
- NOTE Confidence: 0.971788674
- $01:02:23.751 \longrightarrow 01:02:25.620$ the mutation or when you have the
- NOTE Confidence: 0.971788674
- $01:02:25.677 \rightarrow 01:02:27.838$ loss of function you have increased
- NOTE Confidence: 0.971788674
- $01:02:27.840 \longrightarrow 01:02:30.584$ my to ER context which we know
- NOTE Confidence: 0.971788674
- $01:02:30.584 \longrightarrow 01:02:34.885$ has to do with vision and we have
- NOTE Confidence: 0.971788674
- $01{:}02{:}34.885 \dashrightarrow 01{:}02{:}36.905$ increased size of mitochondria.

01:02:36.910 --> 01:02:38.440 How do you put that together?

NOTE Confidence: 0.809338853333333

01:02:39.910 --> 01:02:43.242 OK. Yeah. You had to bring it

NOTE Confidence: 0.809338853333333

01:02:43.242 --> 01:02:44.890 up now it's it's actually.

NOTE Confidence: 0.809338853333333

 $01:02:44.890 \longrightarrow 01:02:46.886$ It's a. It's a great question

NOTE Confidence: 0.809338853333333

 $01{:}02{:}46.886 \dashrightarrow 01{:}02{:}49.190$ that is a conundrum and I.

NOTE Confidence: 0.809338853333333

 $01:02:49.190 \longrightarrow 01:02:49.823$ I'm not really.

NOTE Confidence: 0.809338853333333

 $01:02:49.823 \rightarrow 01:02:51.490$ I don't have a great answer to it.

NOTE Confidence: 0.809338853333333

 $01:02:51.490 \dashrightarrow 01:02:55.280$ I'll start and so I'll have to ramble a bit.

NOTE Confidence: 0.809338853333333

 $01{:}02{:}55{.}280 \dashrightarrow 01{:}02{:}57{.}290$ So the one the one connection

NOTE Confidence: 0.809338853333333

 $01:02:57.290 \rightarrow 01:02:58.295$ the one connection,

NOTE Confidence: 0.809338853333333

 $01:02:58.300 \longrightarrow 01:03:00.668$ is it your everything you stated is correct

NOTE Confidence: 0.809338853333333

 $01{:}03{:}00.668 \dashrightarrow 01{:}03{:}03.237$ way the field reads is that mitochondria,

NOTE Confidence: 0.809338853333333

 $01{:}03{:}03{.}240 \dashrightarrow 01{:}03{:}05{.}880$ ER contacts lead to increased vision.

NOTE Confidence: 0.809338853333333

 $01{:}03{:}05{.}880 \dashrightarrow 01{:}03{:}08{.}034$ Let's go bolts and many great

NOTE Confidence: 0.809338853333333

 $01{:}03{:}08{.}034 \dashrightarrow 01{:}03{:}10{.}389$ scientists are doing this kind of work.

 $01:03:13.170 \longrightarrow 01:03:15.162$ And so I saw a talk by Jody

NOTE Confidence: 0.861749197142857

01:03:15.162 --> 01:03:17.047 Newman who works in this space,

NOTE Confidence: 0.861749197142857

 $01{:}03{:}17.050 \dashrightarrow 01{:}03{:}18.830$ and it's fantastic scientist.

NOTE Confidence: 0.861749197142857

 $01{:}03{:}18.830 \dashrightarrow 01{:}03{:}21.526$ And she said that she believes

NOTE Confidence: 0.861749197142857

 $01{:}03{:}21.526 \dashrightarrow 01{:}03{:}23.786$ there's something about quality of

NOTE Confidence: 0.861749197142857

01:03:23.786 --> 01:03:25.930 mitochondria in your contacts and

NOTE Confidence: 0.861749197142857

 $01{:}03{:}25{.}930 \dashrightarrow 01{:}03{:}28{.}276$ it's the quality of those contacts.

NOTE Confidence: 0.861749197142857

01:03:28.280 --> 01:03:29.820 That drives certain biology,

NOTE Confidence: 0.861749197142857

 $01{:}03{:}29{.}820 \dashrightarrow 01{:}03{:}32{.}130$ and so even though we see

NOTE Confidence: 0.861749197142857

 $01{:}03{:}32{.}207 \dashrightarrow 01{:}03{:}34{.}417$ greater proximity and you know,

NOTE Confidence: 0.861749197142857

 $01:03:34.420 \longrightarrow 01:03:36.000$ I welcome Pietro jumping in

NOTE Confidence: 0.861749197142857

01:03:36.000 --> 01:03:37.950 at anytime because I you know,

NOTE Confidence: 0.861749197142857

 $01:03:37.950 \longrightarrow 01:03:40.050$ he's as he's more of an expert

NOTE Confidence: 0.861749197142857

 $01:03:40.050 \longrightarrow 01:03:41.710$ in this space than I am.

NOTE Confidence: 0.861749197142857

 $01:03:41.710 \longrightarrow 01:03:43.630$ But Jody implied that.

NOTE Confidence: 0.861749197142857

 $01:03:43.630 \rightarrow 01:03:46.030$ The quality of these contacts

- NOTE Confidence: 0.861749197142857
- $01:03:46.030 \longrightarrow 01:03:49.635$ is a big part of what drives
- NOTE Confidence: 0.861749197142857
- $01:03:49.635 \rightarrow 01:03:51.150$ the mitochondrial changes.
- NOTE Confidence: 0.861749197142857
- $01:03:51.150 \longrightarrow 01:03:53.808$ And and you know, the I.
- NOTE Confidence: 0.861749197142857
- 01:03:53.810 --> 01:03:55.124 Yeah, I don't think I've seen
- NOTE Confidence: 0.861749197142857
- 01:03:55.124 --> 01:03:56.000 this data published yet,
- NOTE Confidence: 0.861749197142857
- $01:03:56.000 \dashrightarrow 01:03:58.046$ but she had presented this in
- NOTE Confidence: 0.861749197142857
- $01:03:58.046 \longrightarrow 01:04:00.206$ the context of these quality
- NOTE Confidence: 0.861749197142857
- 01:04:00.206 --> 01:04:03.614 contacts or related to sites of
- NOTE Confidence: 0.861749197142857
- $01:04:03.614 \rightarrow 01:04:05.930$ mitochondrial DNA replication.
- NOTE Confidence: 0.861749197142857
- $01:04:05.930 \longrightarrow 01:04:08.926$ And so I'm fascinated by this concept
- NOTE Confidence: 0.861749197142857
- $01:04:08.926 \longrightarrow 01:04:12.631$ of what makes a good and a bad
- NOTE Confidence: 0.861749197142857
- 01:04:12.631 --> 01:04:16.060 mitochondrial country, ER, contact?
- NOTE Confidence: 0.861749197142857
- $01{:}04{:}16.060 \dashrightarrow 01{:}04{:}18.256$ So may be more is not better.
- NOTE Confidence: 0.861749197142857
- 01:04:18.260 $\operatorname{-->}$ 01:04:20.076 I think that's the simple way to think
- NOTE Confidence: 0.861749197142857
- 01:04:20.076 --> 01:04:23.296 about it, but I frankly Sam, it's it's.
- NOTE Confidence: 0.861749197142857

- 01:04:23.300 --> 01:04:25.380 It's a dichotomy in in,
- NOTE Confidence: 0.861749197142857
- $01:04:25.380 \longrightarrow 01:04:27.655$ in the logic and it's it's something.
- NOTE Confidence: 0.861749197142857
- $01:04:27.660 \longrightarrow 01:04:28.968$ It must be telling us something
- NOTE Confidence: 0.861749197142857
- 01:04:28.968 --> 01:04:29.840 but I don't I.
- NOTE Confidence: 0.861749197142857
- 01:04:29.840 --> 01:04:30.302 I mean I,
- NOTE Confidence: 0.861749197142857
- 01:04:30.302 --> 01:04:30.610 I think
- NOTE Confidence: 0.90923877
- $01:04:30.620 \longrightarrow 01:04:31.680$ you're probably on to something.
- NOTE Confidence: 0.90923877
- $01{:}04{:}31{.}680 \dashrightarrow 01{:}04{:}33{.}190$ 'cause I I've come across.
- NOTE Confidence: 0.90923877
- 01:04:33.190 --> 01:04:35.281 I ask this 'cause I've come across this
- NOTE Confidence: 0.90923877
- $01:04:35.281 \rightarrow 01:04:37.363$ in other places where the singling
- NOTE Confidence: 0.90923877
- $01:04:37.363 \rightarrow 01:04:39.778$ is opposite what you might expect.
- NOTE Confidence: 0.90923877
- 01:04:39.780 --> 01:04:42.570 Yeah, yeah. Yeah,
- NOTE Confidence: 0.90923877
- $01:04:42.570 \longrightarrow 01:04:43.970$ so it probably does have a lot
- NOTE Confidence: 0.90923877
- $01:04:43.970 \longrightarrow 01:04:45.683$ to do with the quality of the
- NOTE Confidence: 0.90923877
- $01:04:45.683 \longrightarrow 01:04:47.210$ exact contact and how things
- NOTE Confidence: 0.90923877
- 01:04:47.210 --> 01:04:48.930 get rearranged and whether it's

- NOTE Confidence: 0.90923877
- $01:04:48.930 \longrightarrow 01:04:50.650$ positive or negative singles that
- NOTE Confidence: 0.90923877
- $01:04:50.709 \longrightarrow 01:04:52.299$ are missing from that contact.
- NOTE Confidence: 0.791899720909091
- $01:04:52.370 \longrightarrow 01:04:53.198$ Yeah, so I don't.
- NOTE Confidence: 0.791899720909091
- $01:04:53.198 \longrightarrow 01:04:54.870$ I don't want to be protein centric,
- NOTE Confidence: 0.791899720909091
- $01:04:54.870 \longrightarrow 01:04:56.898$ but maybe you know it takes
- NOTE Confidence: 0.791899720909091
- $01:04:56.898 \rightarrow 01:04:58.679$ something to assemble the right
- NOTE Confidence: 0.791899720909091
- $01:04:58.679 \rightarrow 01:05:00.872$ group of proteins to activate the
- NOTE Confidence: 0.791899720909091
- $01:05:00.872 \rightarrow 01:05:03.420$ right set of events and maybe the
- NOTE Confidence: 0.791899720909091
- $01{:}05{:}03{.}502 \dashrightarrow 01{:}05{:}06{.}106$ activation of in in some sub domain
- NOTE Confidence: 0.791899720909091
- $01{:}05{:}06{.}106 \dashrightarrow 01{:}05{:}09{.}522$ then leads to some change in other
- NOTE Confidence: 0.791899720909091
- $01:05:09.522 \rightarrow 01:05:12.020$ domains of of interaction but.
- NOTE Confidence: 0.791899720909091
- 01:05:12.020 --> 01:05:14.110 Well. In any
- NOTE Confidence: 0.940390470909091
- $01:05:14.120 \longrightarrow 01:05:15.660$ event, it was really fascinating
- NOTE Confidence: 0.940390470909091
- 01:05:15.660 --> 01:05:17.200 and I really appreciate your
- NOTE Confidence: 0.940390470909091
- $01:05:17.260 \longrightarrow 01:05:18.718$ talk and thank you for coming
- NOTE Confidence: 0.940390470909091

 $01:05:18.718 \rightarrow 01:05:20.400$ to deliver a grand rounds today.

NOTE Confidence: 0.940390470909091

 $01{:}05{:}20{.}400 \dashrightarrow 01{:}05{:}22{.}122$ We're bid after the hour and I

NOTE Confidence: 0.940390470909091

 $01:05:22.122 \longrightarrow 01:05:23.774$ think people are heading on to

NOTE Confidence: 0.940390470909091

 $01:05:23.774 \rightarrow 01:05:25.560$ their next meeting, so again,

NOTE Confidence: 0.824668408

 $01:05:25.570 \rightarrow 01:05:27.760$ understandably thank you very much,

NOTE Confidence: 0.824668408

 $01{:}05{:}27.760 \dashrightarrow 01{:}05{:}30.315$ Sam, and thanks to all the people

NOTE Confidence: 0.824668408

 $01{:}05{:}30{.}315 \dashrightarrow 01{:}05{:}32{.}547$ that came and also the people

NOTE Confidence: 0.824668408

 $01:05:32.547 \rightarrow 01:05:34.997$ who I met with was my choice.

NOTE Confidence: 0.824668408

 $01{:}05{:}35{.}000 \dashrightarrow 01{:}05{:}37{.}400$ Alright, we'll see you later on.

NOTE Confidence: 0.824668408

01:05:37.400 --> 01:05:41.970 Bye see you soon. By Pietro. Why?

NOTE Confidence: 0.906393735

01:05:46.710 --> 01:05:49.680 Thank you. Thanks, Susanna,

NOTE Confidence: 0.906393735

01:05:49.680 --> 01:05:51.810 thank you, thank you very much.

NOTE Confidence: 0.891686697777778

 $01:05:54.330 \longrightarrow 01:05:55.786$ My pleasure, my pleasure.

NOTE Confidence: 0.891686697777778

 $01:05:55.786 \longrightarrow 01:05:58.446$ I hope it was clear as always,

NOTE Confidence: 0.891686697777778

 $01:05:58.446 \longrightarrow 01:06:00.118$ thank you very much.

NOTE Confidence: 0.891686697777778

 $01:06:00.120 \longrightarrow 01:06:01.976$ Thank you Sir and have a good day.

01:06:01.980 --> 01:06:03.230 I appreciate all you did.