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 --> 00:00:04.534 maybe I'll go ahead and introduce

NOTE Confidence: 0.852992580466667

00:00:04.534 --> 00:00:08.070 you and then you can get started.

NOTE Confidence: 0.852992580466667

00:00:08.070 --> 00:00:11.346 So it's my honor to introduce Eric Baraki as

NOTE Confidence: 0.852992580466667

00:00:11.346 --> 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 --> 00:00:17.524 University of Wisconsin, Madison,

NOTE Confidence: 0.852992580466667

00:00:17.524 --> 00:00:19.594 with Michael Strand on embryonic

NOTE Confidence: 0.852992580466667

00:00:19.594 --> 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 --> 00:00:26.374 In the HHMI lab of Carl Thummel on

NOTE Confidence: 0.852992580466667

00:00:26.374 --> 00:00:28.346 steroid triggered cell death and

NOTE Confidence: 0.852992580466667

00:00:28.346 --> 00:00:30.034 resala became an assistant professor

NOTE Confidence: 0.852992580466667

00:00:30.034 --> 00:00:32.028 at University of Maryland in 1995

NOTE Confidence: 0.852992580466667

00:00:32.028 --> 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 --> 00:00:39.018 he was promoted to full professor in 2015.

NOTE Confidence: 0.852992580466667

00:00:39.020 --> 00:00:41.220 He's a leader in the field of atop a G,

NOTE Confidence: 0.852992580466667

00:00:41.220 --> 00:00:42.865 having to help define when

NOTE Confidence: 0.852992580466667

00:00:42.865 --> 00:00:44.510 autophagy is associated with cell

NOTE Confidence: 0.852992580466667

00:00:44.572 --> 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 --> 00:00:51.417 in autophagy that utilize ubiquitin

NOTE Confidence: 0.852992580466667

00:00:51.417 --> 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 --> 00:00:56.823 studies of autophagy and recycle.

NOTE Confidence: 0.852992580466667

00:00:56.830 --> 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 --> 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 --> 00:01:06.446 He served on numerous advisory committees.

NOTE Confidence: 0.852992580466667

00:01:06.450 --> 00:01:07.464 Often his chair,

NOTE Confidence: 0.852992580466667

00:01:07.464 --> 00:01:09.492 ranging from the NIH panels to

NOTE Confidence: 0.852992580466667

00:01:09.492 --> 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 --> 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 --> 00:01:18.428 currently for cell death and differentiation,

NOTE Confidence: 0.852992580466667

00:01:18.430 --> 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 --> 00:01:24.990 Is a widely sought speaker

NOTE Confidence: 0.852992580466667

00:01:24.990 --> 00:01:26.570 with over 40 invited seminars.

NOTE Confidence: 0.852992580466667

00:01:26.570 --> 00:01:28.010 In the past five years,

NOTE Confidence: 0.852992580466667

00:01:28.010 --> 00:01:29.650 but most notably to me,

NOTE Confidence: 0.852992580466667

00:01:29.650 --> 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 --> 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 --> 00:01:41.714 so I have no doubt that he'll be

NOTE Confidence: 0.852992580466667

00:01:41.714 --> 00:01:44.335 able to help us understand the

NOTE Confidence: 0.852992580466667

00:01:44.335 --> 00:01:47.026 field much better with this audience

NOTE Confidence: 0.852992580466667

00:01:47.026 --> 00:01:50.930 as he talks to us on Ora Boris on

NOTE Confidence: 0.852992580466667

00:01:50.930 --> 00:01:53.635 top OG mitochondria and disease.

NOTE Confidence: 0.852992580466667

00:01:53.640 --> 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 --> 00:02:00.280 kind and thoughtful introduction.

NOTE Confidence: 0.832739852

00:02:00.280 --> 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 --> 00:02:07.850 Susanna and all the people

NOTE Confidence: 0.832739852

00:02:07.850 --> 00:02:09.490 I met with this morning.

NOTE Confidence: 0.832739852

00:02:09.490 --> 00:02:11.906 Very stimulating morning discussions.

NOTE Confidence: 0.832739852

00:02:11.906 --> 00:02:15.180 And for me, coming to Yale is a

NOTE Confidence: 0.832739852

00:02:15.180 --> 00:02:16.640 little or virtually coming to.

NOTE Confidence: 0.832739852

00:02:16.640 --> 00:02:18.744 Yale is a little bit like coming to

NOTE Confidence: 0.832739852

00:02:18.744 --> 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 --> 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 --> 00:02:34.440 that if you can start with a simple

NOTE Confidence: 0.7678083

00:02:34.440 --> 00:02:36.930 message that at least everyone can

NOTE Confidence: 0.7678083

00:02:36.930 --> 00:02:38.950 understand from the very beginning,

NOTE Confidence: 0.7678083

00:02:38.950 --> 00:02:40.605 then you've accomplished at least

NOTE Confidence: 0.7678083

00:02:40.605 --> 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 --> 00:02:46.495 you this creature.

NOTE Confidence: 0.7678083

00:02:46.500 --> 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 --> 00:02:56.100 that's on many Egyptian tombs.

NOTE Confidence: 0.7678083

00:02:56.100 --> 00:02:58.758 It's been used by union philosophers,

NOTE Confidence: 0.7678083

00:02:58.760 --> 00:03:01.288 and I think it's reflective of the process

NOTE Confidence: 0.7678083

00:03:01.288 --> 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 --> 00:03:08.519 of ourselves is really used in many

NOTE Confidence: 0.7678083

00:03:08.519 --> 00:03:10.607 ways to promote self health and

NOTE Confidence: 0.7678083

00:03:10.607 --> 00:03:12.398 promote longevity and 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 --> 00:03:17.770 definition of autophagy based on on

NOTE Confidence: 0.7678083

00:03:17.770 --> 00:03:20.358 this ancient symbol of horror works.

NOTE Confidence: 0.7678083

00:03:20.360 --> 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 --> 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 --> 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 --> 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 --> 00:03:47.018 of a grand rounds format.

NOTE Confidence: 0.55679458625

00:03:47.020 --> 00:03:49.120 So this story starts with a 50

NOTE Confidence: 0.55679458625

00:03:49.120 --> 00:03:51.844 or 4 year old male patient with

NOTE Confidence: 0.55679458625

00:03:51.844 --> 00:03:54.020 history of reading problems

NOTE Confidence: 0.55679458625

00:03:54.020 --> 00:03:55.825 that presented to his physician

NOTE Confidence: 0.55679458625

00:03:55.825 --> 00:03:56.908 with gait difficulties.

NOTE Confidence: 0.91867951375

00:04:00.200 --> 00:04:02.450 First vision problems presented at the

NOTE Confidence: 0.91867951375

00:04:02.450 --> 00:04:07.064 age of 36 and four siblings of 14 total,

NOTE Confidence: 0.91867951375

00:04:07.070 --> 00:04:09.618 so this is what I consider a

NOTE Confidence: 0.91867951375

00:04:09.618 --> 00:04:11.540 remarkable human genetic experiment.

NOTE Confidence: 0.91867951375

00:04:11.540 --> 00:04:14.180 Reported similar vision and walking

NOTE Confidence: 0.91867951375

00:04:14.180 --> 00:04:17.430 difficulties at the ages of 2326.

NOTE Confidence: 0.89488352

00:04:21.430 --> 00:04:24.640 And importantly.

NOTE Confidence: 0.89488352

00:04:24.640 --> 00:04:26.170 Some reason I'm having trouble events.

NOTE Confidence: 0.89488352

00:04:26.170 --> 00:04:27.901 Importantly, the parents

NOTE Confidence: 0.89488352

00:04:27.901 --> 00:04:30.209 exhibit exhibited no symptoms.

NOTE Confidence: 0.89488352

00:04:30.210 --> 00:04:32.026 So as a geneticist,

NOTE Confidence: 0.89488352

00:04:32.026 --> 00:04:34.750 I am a classically trained geneticist.

NOTE Confidence: 0.89488352

00:04:34.750 --> 00:04:39.310 This is reflective of a recessive.

NOTE Confidence: 0.89488352

00:04:39.310 --> 00:04:41.053 Genetic trait where?

NOTE Confidence: 0.89488352

00:04:41.053 --> 00:04:44.539 Almost close to the proper medallion

NOTE Confidence: 0.89488352

00:04:44.539 --> 00:04:47.890 ratio of individuals from the from.

NOTE Confidence: 0.89488352

00:04:47.890 --> 00:04:49.890 These two parents resulted

NOTE Confidence: 0.89488352

00:04:49.890 --> 00:04:52.499 in this movement disorder.

NOTE Confidence: 0.8773515225

00:04:54.540 --> 00:04:57.188 They're hearing the patients.

NOTE Confidence: 0.8773515225

00:04:57.188 --> 00:04:59.836 They're had no hearing.

NOTE Confidence: 0.8773515225

00:04:59.840 --> 00:05:02.892 Cognitive or leg muscle

NOTE Confidence: 0.8773515225

00:05:02.892 --> 00:05:05.310 strength alterations and all

NOTE Confidence: 0.8773515225

00:05:05.310 --> 00:05:07.535 lower but all lower legs.

NOTE Confidence: 0.8773515225

00:05:07.540 --> 00:05:08.908 Hensher modalities square.

NOTE Confidence: 0.823773646666667

00:05:11.050 --> 00:05:14.350 And this was eventually diagnosed as

NOTE Confidence: 0.823773646666667

00:05:14.350 --> 00:05:19.342 spinal cerebellar ataxia and did disease

NOTE Confidence: 0.823773646666667

00:05:19.342 --> 00:05:22.172 progression increased with age and

NOTE Confidence: 0.823773646666667

00:05:22.172 --> 00:05:24.662 all five patients required walking.

NOTE Confidence: 0.823773646666667

00:05:24.670 --> 00:05:27.442 So this was published in 2003.

NOTE Confidence: 0.823773646666667

00:05:27.442 --> 00:05:28.610 Data from this family.

NOTE Confidence: 0.823773646666667

00:05:28.610 --> 00:05:31.748 This was originally a study initiated

NOTE Confidence: 0.823773646666667

00:05:31.750 --> 00:05:34.550 at Case Western, but at that time,

NOTE Confidence: 0.823773646666667

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

NOTE Confidence: 0.823773646666667

00:05:36.830 --> 00:05:38.846 who's at the University of Michigan,

NOTE Confidence: 0.823773646666667

00:05:38.850 --> 00:05:41.160 became very interested in this population.

NOTE Confidence: 0.823773646666667

00:05:41.160 --> 00:05:43.492 This patient population and

NOTE Confidence: 0.823773646666667

00:05:43.492 --> 00:05:46.990 started trying to identify the gene

NOTE Confidence: 0.823773646666667

00:05:47.083 --> 00:05:49.859 responsible for this disorder.

NOTE Confidence: 0.823773646666667

00:05:49.860 --> 00:05:51.450 And Fast forward.

NOTE Confidence: 0.854598672

00:05:54.700 --> 00:05:59.050 After a lot of work in 2018 Markets

NOTE Confidence: 0.854598672

00:05:59.050 --> 00:06:02.589 Lab published that this this

NOTE Confidence: 0.854598672

00:06:02.589 --> 00:06:06.084 disorder is because of mutations

NOTE Confidence: 0.854598672

00:06:06.084 --> 00:06:10.089 recessive mutations in the VPS 13 DJ.

NOTE Confidence: 0.854598672

00:06:10.090 --> 00:06:12.737 That's in this song and.

NOTE Confidence: 0.854598672

00:06:12.737 --> 00:06:14.365 Of neurology paper in

NOTE Confidence: 0.854598672

00:06:14.365 --> 00:06:15.993 parallel with this paper,

NOTE Confidence: 0.854598672

00:06:16.000 --> 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 --> 00:06:24.452 in Canada had a a subset of the

NOTE Confidence: 0.854598672

00:06:24.452 --> 00:06:26.760 patients that they were citing.

NOTE Confidence: 0.854598672

00:06:26.760 --> 00:06:31.920 Also had recessive mutations in the guest 13.

NOTE Confidence: 0.854598672

00:06:31.920 --> 00:06:35.308 And so although VPS 13D is an

NOTE Confidence: 0.854598672

00:06:35.308 --> 00:06:36.760 extraordinarily rare disease,

NOTE Confidence: 0.854598672

00:06:36.760 --> 00:06:39.040 and it's interesting that also patients

NOTE Confidence: 0.854598672

00:06:39.040 --> 00:06:41.694 with Leigh syndrome and this is an

NOTE Confidence: 0.854598672

00:06:41.694 --> 00:06:43.118 increasing population of patients

NOTE Confidence: 0.854598672

00:06:43.118 --> 00:06:46.188 that also have mutations in 13.

NOTE Confidence: 0.943741698888889

00:06:48.660 --> 00:06:51.180 So while they were actively trying

NOTE Confidence: 0.943741698888889

00:06:51.180 --> 00:06:54.552 to find the identity. Of of this,

NOTE Confidence: 0.943741698888889

00:06:54.552 --> 00:06:57.720 the gene responsible for this disorder,

NOTE Confidence: 0.943741698888889

00:06:57.720 --> 00:06:59.680 my lap was studying the process of

NOTE Confidence: 0.943741698888889

00:06:59.680 --> 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 --> 00:07:10.762 often the ER, where isolation or fagge

NOTE Confidence: 0.943741698888889

00:07:10.762 --> 00:07:13.319 for membrane forms around cargos.

NOTE Confidence: 0.943741698888889

00:07:13.319 --> 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 --> 00:07:21.102 but I think it increasing evidence

NOTE Confidence: 0.943741698888889

00:07:21.102 --> 00:07:22.710 exists that these cargoes

NOTE Confidence: 0.943741698888889

00:07:22.782 --> 00:07:24.658 can be exquisitely specific.

NOTE Confidence: 0.943741698888889

00:07:24.660 --> 00:07:27.372 And the inclusion of these cargoes

NOTE Confidence: 0.943741698888889

00:07:27.372 --> 00:07:31.115 into the fagge form to form and double

NOTE Confidence: 0.943741698888889

00:07:31.115 --> 00:07:33.527 membrane out of phagosome therefore

NOTE Confidence: 0.943741698888889

00:07:33.527 --> 00:07:36.362 targets these cargoes for degradation

NOTE Confidence: 0.943741698888889

00:07:36.362 --> 00:07:39.540 by fusion of autophagosomes Lisa zones,

NOTE Confidence: 0.943741698888889

00:07:39.540 --> 00:07:43.900 or vacuoles as they're called in plants.

NOTE Confidence: 0.943741698888889

00:07:43.900 --> 00:07:46.434 So we were studying this process and

NOTE Confidence: 0.943741698888889

00:07:46.434 --> 00:07:50.195 we were studying this in in in a model

NOTE Confidence: 0.943741698888889

00:07:50.195 --> 00:07:52.520 Organism for Sofala Melanic Esther.

NOTE Confidence: 0.943741698888889

00:07:52.520 --> 00:07:54.935 And the question that many people ask,

NOTE Confidence: 0.943741698888889

00:07:54.940 --> 00:07:58.000 why do you study this this problem and flies,

NOTE Confidence: 0.943741698888889

00:07:58.000 --> 00:08:01.547 and I think the this cartoon that

NOTE Confidence: 0.943741698888889

00:08:01.547 --> 00:08:03.629 was devised by my collaborator and

NOTE Confidence: 0.943741698888889

00:08:03.629 --> 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 --> 00:08:12.312 Communicates this so we knew at

NOTE Confidence: 0.893958240909091

00:08:12.312 --> 00:08:15.378 the time that we were the early

NOTE Confidence: 0.893958240909091

00:08:15.378 --> 00:08:18.398 studies that we were investigating.

NOTE Confidence: 0.893958240909091

00:08:18.400 --> 00:08:20.485 That Yoshinori Ohsumi's lab had

NOTE Confidence: 0.893958240909091

00:08:20.485 --> 00:08:23.026 identified most of the genes that

NOTE Confidence: 0.893958240909091

00:08:23.026 --> 00:08:25.700 were required for what we call the

NOTE Confidence: 0.893958240909091

00:08:25.700 --> 00:08:27.911 core autophagic machinery for studies

NOTE Confidence: 0.893958240909091

00:08:27.911 --> 00:08:30.440 of the sacrifice service and soon

NOTE Confidence: 0.893958240909091

00:08:30.440 --> 00:08:32.540 after the publication of his work,

NOTE Confidence: 0.893958240909091

00:08:32.540 --> 00:08:34.852 a large number of labs and and the

NOTE Confidence: 0.893958240909091

00:08:34.852 --> 00:08:36.908 publication of the of the human genome.

NOTE Confidence: 0.893958240909091

00:08:36.910 --> 00:08:39.654 A large number of lab started racing

NOTE Confidence: 0.893958240909091

00:08:39.654 --> 00:08:42.649 to identify the ortho locks and chains.

NOTE Confidence: 0.893958240909091

00:08:42.650 --> 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 --> 00:08:50.412 and this these are both anatomically

NOTE Confidence: 0.893958240909091

00:08:50.412 --> 00:08:51.256 incorrect animals.

NOTE Confidence: 0.893958240909091

00:08:51.256 --> 00:08:52.686 I want to just mention,

NOTE Confidence: 0.893958240909091

00:08:52.690 --> 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 --> 00:08:59.904 By studying these organisms,

NOTE Confidence: 0.827382486363636

00:08:59.904 --> 00:09:03.090 we've learned that autophagy is regulated

NOTE Confidence: 0.827382486363636

00:09:03.168 --> 00:09:06.410 in cell and context dependent manner.

NOTE Confidence: 0.827382486363636

00:09:06.410 --> 00:09:08.874 And this underlies one of the fundamental

NOTE Confidence: 0.827382486363636

00:09:08.880 --> 00:09:11.408 tenets of the way we do our science.

NOTE Confidence: 0.827382486363636

00:09:11.410 --> 00:09:14.588 So we have decided to study autophagy

NOTE Confidence: 0.827382486363636

00:09:14.588 --> 00:09:15.950 under developmental contexts.

NOTE Confidence: 0.827382486363636

00:09:15.950 --> 00:09:19.030 So when autophagy is induced by development,

NOTE Confidence: 0.827382486363636

00:09:19.030 --> 00:09:21.550 not through some sort of stress condition,

NOTE Confidence: 0.827382486363636

00:09:21.550 --> 00:09:23.470 such as chronic starvation

NOTE Confidence: 0.827382486363636

00:09:23.470 --> 00:09:25.390 or chronic cellular stress,

NOTE Confidence: 0.827382486363636

00:09:25.390 --> 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 --> 00:09:35.195 self context matters and this

NOTE Confidence: 0.8098079575

00:09:35.195 --> 00:09:37.922 suggests that there could be self

NOTE Confidence: 0.8098079575

00:09:37.922 --> 00:09:40.347 context specific regulators off G.

NOTE Confidence: 0.8098079575

00:09:40.350 --> 00:09:41.520 And just a few pieces of

NOTE Confidence: 0.8098079575

00:09:41.520 --> 00:09:42.550 evidence in support of this.

NOTE Confidence: 0.8098079575

00:09:42.550 --> 00:09:43.708 There are many at this point,

NOTE Confidence: 0.8098079575

00:09:43.710 --> 00:09:45.836 but I just want to highlight a few

NOTE Confidence: 0.8098079575

00:09:45.836 --> 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 --> 00:09:52.540 where he showed that the

NOTE Confidence: 0.8098079575

00:09:52.540 --> 00:09:54.570 influence of autophagy on tumor

NOTE Confidence: 0.8098079575

00:09:54.644 --> 00:09:56.602 growth depended on P53 status.

NOTE Confidence: 0.8098079575

00:09:56.602 --> 00:09:57.906 So, in other words,

NOTE Confidence: 0.8098079575

00:09:57.910 --> 00:09:59.590 if you may want to consider

NOTE Confidence: 0.8098079575

00:09:59.590 --> 00:10:01.755 if you were going to modulate

NOTE Confidence: 0.8098079575

00:10:01.755 --> 00:10:03.707 autophagy for therapeutic purposes,

NOTE Confidence: 0.8098079575

00:10:03.710 --> 00:10:05.820 whether or not that tumor

NOTE Confidence: 0.8098079575

00:10:05.820 --> 00:10:08.400 has a wild type P50, really.

NOTE Confidence: 0.771411488888889

00:10:10.940 --> 00:10:14.188 I'm in work that week's lab rated

NOTE Confidence: 0.771411488888889

00:10:14.188 --> 00:10:15.866 with Andreas Bergmann's lab.

NOTE Confidence: 0.771411488888889

00:10:15.866 --> 00:10:18.477 We were able to show that autophagy

NOTE Confidence: 0.771411488888889

00:10:18.477 --> 00:10:21.168 could either enhance or suppress tissue

NOTE Confidence: 0.771411488888889

00:10:21.168 --> 00:10:24.396 growth depending on the growth stimulus.

NOTE Confidence: 0.771411488888889

00:10:24.400 --> 00:10:25.898 And so as well as cell type,

NOTE Confidence: 0.771411488888889

00:10:25.900 --> 00:10:29.495 what I mean by this it depended if you had

NOTE Confidence: 0.771411488888889

00:10:29.495 --> 00:10:32.680 a growth stimulus such as activated wrasse,

NOTE Confidence: 0.771411488888889

00:10:32.680 --> 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: 0.771411488888889

00:10:42.720 --> 00:10:45.656 So this also suggests that there's some self

NOTE Confidence: 0.771411488888889

00:10:45.656 --> 00:10:48.860 sort of cell or tissue convex specificity.

NOTE Confidence: 0.771411488888889

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

NOTE Confidence: 0.771411488888889

00:10:49.470 --> 00:10:51.300 we had shown that during development,

NOTE Confidence: 0.771411488888889

00:10:51.300 --> 00:10:53.476 that autophagy can also

NOTE Confidence: 0.771411488888889

00:10:53.476 --> 00:10:56.196 influence cell survival or cell,

NOTE Confidence: 0.771411488888889

00:10:56.200 --> 00:11:00.010 that depending on the developmental context.

NOTE Confidence: 0.771411488888889

00:11:00.010 --> 00:11:03.852 So. In other words,

NOTE Confidence: 0.771411488888889

00:11:03.852 --> 00:11:06.636 it is important to understand how

NOTE Confidence: 0.771411488888889

00:11:06.636 --> 00:11:09.950 this process is regulated in mammals.

NOTE Confidence: 0.771411488888889

00:11:09.950 --> 00:11:11.438 So the model tissue tissue I'm

NOTE Confidence: 0.771411488888889

00:11:11.438 --> 00:11:13.285 going to talk about today is the

NOTE Confidence: 0.771411488888889

00:11:13.285 --> 00:11:14.620 intestine of the flying larva.

NOTE Confidence: 0.762151301666667

00:11:16.790 --> 00:11:19.868 In this tissue goes for dramatic

NOTE Confidence: 0.762151301666667

00:11:19.870 --> 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 --> 00:11:29.614 in these composite images.

NOTE Confidence: 0.762151301666667

00:11:29.620 --> 00:11:32.735 Is that the midgut of the intestine,

NOTE Confidence: 0.762151301666667

00:11:32.740 --> 00:11:35.158 which is the largely the absorptive

NOTE Confidence: 0.762151301666667

00:11:35.158 --> 00:11:37.100 structure of the intestine that

NOTE Confidence: 0.762151301666667

00:11:37.100 --> 00:11:40.958 at this stage is this long?

NOTE Confidence: 0.762151301666667

00:11:40.960 --> 00:11:43.648 In just 6 to 8 hours shrinks in

NOTE Confidence: 0.762151301666667

00:11:43.648 --> 00:11:46.050 response to steroid to be missed.

NOTE Confidence: 0.762151301666667

00:11:46.050 --> 00:11:48.170 So that's pretty remarkable biologically,

NOTE Confidence: 0.762151301666667

00:11:48.170 --> 00:11:50.502 but important for us.

NOTE Confidence: 0.762151301666667

00:11:50.502 --> 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 --> 00:12:02.072 this early stage there's none of this

NOTE Confidence: 0.762151301666667

00:12:02.072 --> 00:12:04.821 autophagia reporter GFP ATG 8 spots in

NOTE Confidence: 0.762151301666667

00:12:04.821 --> 00:12:07.637 the cells of the intestine at this stage.

NOTE Confidence: 0.762151301666667

00:12:07.640 --> 00:12:09.386 Or is it this later stage

NOTE Confidence: 0.762151301666667

00:12:09.386 --> 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 --> 00:12:16.584 Now I want to emphasize that

NOTE Confidence: 0.762151301666667

00:12:16.584 --> 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: 0.762151301666667

00:12:20.665 --> 00:12:22.373 that are miss expressed,

NOTE Confidence: 0.762151301666667

00:12:22.380 --> 00:12:24.692 but rather these are.

NOTE Confidence: 0.762151301666667

00:12:24.692 --> 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 --> 00:12:31.900 endogenous promoter of this machine.

NOTE Confidence: 0.918976363333333

00:12:35.460 --> 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 --> 00:12:46.620 enjoying some lovely weather,

NOTE Confidence: 0.918976363333333

00:12:46.620 --> 00:12:49.206 was able to show that this

NOTE Confidence: 0.918976363333333

00:12:49.206 --> 00:12:51.180 change in intestines size is

NOTE Confidence: 0.918976363333333

00:12:51.180 --> 00:12:53.434 because of a change in cell size.

NOTE Confidence: 0.918976363333333

00:12:53.440 --> 00:12:55.987 That's dependent on autophagy.

NOTE Confidence: 0.918976363333333

00:12:55.987 --> 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 --> 00:13:03.550 but following the induction but

NOTE Confidence: 0.918976363333333

00:13:03.550 --> 00:13:06.170 prodigy is cells reduce in size.

NOTE Confidence: 0.918976363333333

00:13:06.170 --> 00:13:08.690 So if you have a single autophagy gene,

NOTE Confidence: 0.918976363333333

00:13:08.690 --> 00:13:12.526 mutation cells fail to reduce in size.

NOTE Confidence: 0.918976363333333

00:13:12.530 --> 00:13:14.133 Kevin went on to show that this

NOTE Confidence: 0.918976363333333

00:13:14.133 --> 00:13:15.949 is a cell autonomous process,

NOTE Confidence: 0.918976363333333

00:13:15.950 --> 00:13:19.126 so he used an apology reporter that is

NOTE Confidence: 0.918976363333333

00:13:19.126 --> 00:13:22.028 encoded by every cell in the genome.

NOTE Confidence: 0.918976363333333

00:13:22.030 --> 00:13:25.214 When he could show by a single cell,

NOTE Confidence: 0.918976363333333

00:13:25.220 --> 00:13:27.734 either loss of function mutations or

NOTE Confidence: 0.918976363333333

00:13:27.734 --> 00:13:30.680 RNA I expression in the green cells

NOTE Confidence: 0.918976363333333

00:13:30.680 --> 00:13:33.459 that they fail to form these reporter

NOTE Confidence: 0.918976363333333

00:13:33.534 --> 00:13:36.078 pocta and remained larger in size.

NOTE Confidence: 0.918976363333333

00:13:36.080 --> 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 --> 00:13:41.520 because for for my laboratory,

NOTE Confidence: 0.918976363333333

00:13:41.520 --> 00:13:44.094 because this enabled us to use

NOTE Confidence: 0.918976363333333

00:13:44.094 --> 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 --> 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 --> 00:13:55.664 Fast forward a few years and

NOTE Confidence: 0.918976363333333

00:13:55.664 --> 00:13:57.032 enter Allison Dinding.

NOTE Confidence: 0.918976363333333

00:13:57.032 --> 00:14:00.504 She's now a group leader at Sanofi.

NOTE Confidence: 0.918976363333333

00:14:00.510 --> 00:14:04.350 Allison did us what we call a hypothesis

NOTE Confidence: 0.918976363333333

00:14:04.350 --> 00:14:08.098 driven screen to identify genes that

NOTE Confidence: 0.918976363333333

00:14:08.098 --> 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 --> 00:14:18.710 important regulator of this process,

NOTE Confidence: 0.918976363333333

00:14:18.710 --> 00:14:21.668 she was interested in ubiquitin binding,

NOTE Confidence: 0.918976363333333

00:14:21.670 --> 00:14:25.919 protein encoding genes, and she did screen.

NOTE Confidence: 0.918976363333333

00:14:25.920 --> 00:14:29.670 I believe it was 136 jeans.

NOTE Confidence: 0.918976363333333

00:14:29.670 --> 00:14:31.730 And identified 3 cheats with

NOTE Confidence: 0.918976363333333

00:14:31.730 --> 00:14:32.966 very strong phenotypes.

NOTE Confidence: 0.918976363333333

00:14:32.970 --> 00:14:35.106 Two of them were in the escort pathway,

NOTE Confidence: 0.918976363333333

00:14:35.110 --> 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 --> 00:14:42.346 a somewhat star of this show,

NOTE Confidence: 0.918976363333333

00:14:42.350 --> 00:14:45.206 so this is an example of the

NOTE Confidence: 0.918976363333333

00:14:45.206 --> 00:14:47.594 type of data that we can obtain.

NOTE Confidence: 0.918976363333333

00:14:47.594 --> 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 --> 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 --> 00:14:57.687 but these cells are larger in size.

NOTE Confidence: 0.918976363333333

00:14:57.690 --> 00:14:59.121 It's all quantified,

NOTE Confidence: 0.918976363333333

00:14:59.121 --> 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 --> 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 --> 00:15:12.803 later and I will get into a few more

NOTE Confidence: 0.918976363333333

00:15:12.803 --> 00:15:14.687 details of these in a little bit.

NOTE Confidence: 0.918976363333333

00:15:14.690 --> 00:15:16.685 But this is 1 important example of

NOTE Confidence: 0.918976363333333

00:15:16.685 --> 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 --> 00:15:22.249 to its control.

NOTE Confidence: 0.918976363333333

00:15:22.250 --> 00:15:24.510 Neighboring cells are very

NOTE Confidence: 0.918976363333333

00:15:24.510 --> 00:15:26.770 powerful single cell approach.

NOTE Confidence: 0.918976363333333

00:15:26.770 --> 00:15:30.120 It's not descriptive, it's functional.

NOTE Confidence: 0.918976363333333

00:15:30.120 --> 00:15:31.024 In addition,

NOTE Confidence: 0.918976363333333

00:15:31.024 --> 00:15:33.736 Allison made loss of function mutations,

NOTE Confidence: 0.918976363333333

00:15:33.740 --> 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 --> 00:15:40.443 insertion that completely removes

NOTE Confidence: 0.918976363333333

00:15:40.443 --> 00:15:43.950 the function of this gene based on

NOTE Confidence: 0.918976363333333

00:15:44.046 --> 00:15:47.031 traditional genetic analysis is about

NOTE Confidence: 0.918976363333333

00:15:47.031 --> 00:15:49.713 as well as now protein analysis.

NOTE Confidence: 0.918976363333333

00:15:49.720 --> 00:15:53.104 And the mutant cells lack GFP in this case,

NOTE Confidence: 0.918976363333333

00:15:53.110 --> 00:15:55.126 so the mutant cells are all in this

NOTE Confidence: 0.918976363333333

00:15:55.126 --> 00:15:57.370 end of this piece of the intestine.

NOTE Confidence: 0.918976363333333

00:15:57.370 --> 00:16:02.170 Here she's using a mitochondrial

NOTE Confidence: 0.918976363333333

00:16:02.170 --> 00:16:05.376 V80P SA TP5A antibody as a surrogate

NOTE Confidence: 0.918976363333333

00:16:05.376 --> 00:16:07.670 marker of mitochondria that are

NOTE Confidence: 0.918976363333333

00:16:07.670 --> 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 --> 00:16:13.954 and you can see that only

NOTE Confidence: 0.918976363333333

00:16:13.954 --> 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 --> 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 --> 00:16:23.582 that's actually a mutant cell that's down

NOTE Confidence: 0.746173798

00:16:23.582 --> 00:16:26.428 behind these control GFP positive cells.

NOTE Confidence: 0.77209772875

00:16:29.520 --> 00:16:33.328 So what is VPS? The VPS 13 family.

NOTE Confidence: 0.77209772875

00:16:33.330 --> 00:16:35.442 Well, as I said, I'm it's a little

NOTE Confidence: 0.77209772875

00:16:35.442 --> 00:16:37.448 bit like coming to Mecca because

NOTE Confidence: 0.77209772875

00:16:37.450 --> 00:16:42.346 Pietro and Karen, who are here.

NOTE Confidence: 0.77209772875

00:16:42.350 --> 00:16:44.594 Have actively been actively

NOTE Confidence: 0.77209772875

00:16:44.594 --> 00:16:47.399 studying VPS 13 family proteins.

NOTE Confidence: 0.77209772875

00:16:47.400 --> 00:16:51.852 VPS 13, as name implies is a

NOTE Confidence: 0.77209772875

00:16:51.852 --> 00:16:54.094 vacuole protein sorting encoding

NOTE Confidence: 0.77209772875

00:16:54.094 --> 00:16:56.098 gene or that's how it's originally

NOTE Confidence: 0.77209772875

00:16:56.098 --> 00:16:58.139 identified in the Sacrament service.

NOTE Confidence: 0.77209772875

00:16:58.140 --> 00:17:01.455 Yeah, there's one VPS 13

NOTE Confidence: 0.77209772875

00:17:01.455 --> 00:17:04.107 Gene and and sacrifices.

NOTE Confidence: 0.77209772875

00:17:04.110 --> 00:17:07.568 In organisms is versus worms to humans,

NOTE Confidence: 0.77209772875

00:17:07.570 --> 00:17:10.636 there are three to four protein encoding

NOTE Confidence: 0.77209772875

00:17:10.636 --> 00:17:13.849 genes actually in the fly there are three,

NOTE Confidence: 0.77209772875

00:17:13.850 --> 00:17:15.980 and these have traditionally been named

NOTE Confidence: 0.71485823

00:17:18.250 --> 00:17:21.992 VPS. 13 ABC&D. When the fly there

NOTE Confidence: 0.71485823

00:17:21.992 --> 00:17:23.900 are three men code 4 potential

NOTE Confidence: 0.71485823

00:17:23.965 --> 00:17:26.125 proteins in the nomenclature gets

NOTE Confidence: 0.71485823

00:17:26.125 --> 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 --> 00:17:34.877 But what's important is that these

NOTE Confidence: 0.71485823

00:17:34.877 --> 00:17:38.318 proteins share a common domain structure,

NOTE Confidence: 0.71485823

00:17:38.320 --> 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 --> 00:17:46.556 the importance of a lipid transport

NOTE Confidence: 0.71485823

00:17:46.560 --> 00:17:51.300 domain that's on the internal rate.

NOTE Confidence: 0.71485823

00:17:51.300 --> 00:17:53.362 It's a very large domain. It's protein.

NOTE Confidence: 0.71485823

00:17:53.362 --> 00:17:55.768 What distinguishes D from all other

NOTE Confidence: 0.71485823

00:17:55.768 --> 00:17:57.735 members of this family, however,

NOTE Confidence: 0.71485823

00:17:57.735 --> 00:18:00.390 is that it is the only member of the

NOTE Confidence: 0.71485823

00:18:00.462 --> 00:18:03.090 family that includes acute if ubiquitin.

NOTE Confidence: 0.71485823

00:18:03.090 --> 00:18:05.490 Finding you be a donor.

NOTE Confidence: 0.71485823

00:18:05.490 --> 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 --> 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 --> 00:18:15.530 preferentially binds K63

NOTE Confidence: 0.71485823

00:18:15.530 --> 00:18:17.120 linked ubiquitin chains.

NOTE Confidence: 0.747485610833333

00:18:19.310 --> 00:18:22.958 And also these proteins have so-called

NOTE Confidence: 0.747485610833333

00:18:22.958 --> 00:18:27.569 Lear or else free interaction motifs.

NOTE Confidence: 0.747485610833333

00:18:27.570 --> 00:18:29.558 But this is a very degenerative sequence.

NOTE Confidence: 0.747485610833333

00:18:29.560 --> 00:18:31.348 But the reason we were interested

NOTE Confidence: 0.747485610833333

00:18:31.348 --> 00:18:34.555 in this idea is that then this VPS

NOTE Confidence: 0.747485610833333

00:18:34.555 --> 00:18:36.860 13D would have the characteristics

NOTE Confidence: 0.747485610833333

00:18:36.943 --> 00:18:39.533 of a so-called autophagy receptor

NOTE Confidence: 0.747485610833333

00:18:39.533 --> 00:18:42.123 that might be involved cargo.

NOTE Confidence: 0.747485610833333

00:18:42.130 --> 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 --> 00:18:47.501 but I just wanted to mention that

NOTE Confidence: 0.747485610833333

00:18:47.501 --> 00:18:49.730 that was a possibility when we

NOTE Confidence: 0.747485610833333

00:18:49.730 --> 00:18:52.139 started working on this on this gene.

NOTE Confidence: 0.8532734675

00:18:54.490 --> 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 --> 00:19:01.686 about because 13D is its essentiality.

NOTE Confidence: 0.8532734675

00:19:01.686 --> 00:19:03.420 So as a geneticist we always

NOTE Confidence: 0.8532734675

00:19:03.474 --> 00:19:05.106 wonder if a gene is important,

NOTE Confidence: 0.8532734675

00:19:05.110 --> 00:19:07.987 and that's typically measured by a valid.

NOTE Confidence: 0.8532734675

00:19:07.990 --> 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 --> 00:19:13.965 they screened for gene essentiality.

NOTE Confidence: 0.8532734675

00:19:13.970 --> 00:19:17.085 What they called in the Achilles score.

NOTE Confidence: 0.8532734675

00:19:17.090 --> 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 mtor 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 mtor genes required

NOTE Confidence: 0.8532734675

00:19:29.052 --> 00:19:30.423 for nucleotide synthesis.

NOTE Confidence: 0.8532734675

00:19:30.430 --> 00:19:33.378 They have scores of minus one genes that

NOTE Confidence: 0.8532734675

00:19:33.378 --> 00:19:35.506 medium Lee are important would be at

NOTE Confidence: 0.8532734675

00:19:35.506 --> 00:19:37.964 the similar to like brocco one and two,

NOTE Confidence: 0.8532734675

00:19:37.970 --> 00:19:41.330 and genes that would be less important.

NOTE Confidence: 0.8532734675

00:19:41.330 --> 00:19:42.630 Maybe not to the Organism,

NOTE Confidence: 0.8532734675

00:19:42.630 --> 00:19:45.923 but certainly based on cell

NOTE Confidence: 0.8532734675

00:19:45.923 --> 00:19:47.036 essentiality would be.

NOTE Confidence: 0.8532734675

00:19:47.040 --> 00:19:49.469 It's like Abelson wanted so when we

NOTE Confidence: 0.8532734675

00:19:49.469 --> 00:19:52.659 look at the VPS 13 family and this data,

NOTE Confidence: 0.8532734675

00:19:52.660 --> 00:19:55.612 this graph was derived when Rd

NOTE Confidence: 0.8532734675

00:19:55.612 --> 00:19:57.384 had screened 341's outlines.

NOTE Confidence: 0.8532734675

00:19:57.384 --> 00:19:59.724 Some of these are not as such

NOTE Confidence: 0.8532734675

00:19:59.724 --> 00:20:00.597 normal cell lines.

NOTE Confidence: 0.8532734675

00:20:00.600 --> 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 --> 00:20:09.889 is much more essential than most genes.

NOTE Confidence: 0.8532734675

00:20:09.890 --> 00:20:11.922 In fact in the normal genes and this

NOTE Confidence: 0.8532734675

00:20:11.922 --> 00:20:13.577 is something Pietro rates with me.

NOTE Confidence: 0.8532734675

00:20:13.580 --> 00:20:13.898 Earlier.

NOTE Confidence: 0.8532734675

00:20:13.898 --> 00:20:16.124 It is one of the most essential

NOTE Confidence: 0.8532734675

00:20:16.124 --> 00:20:17.528 genes encoded by our gene.

NOTE Confidence: 0.8532734675

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

NOTE Confidence: 0.8532734675

00:20:18.238 --> 00:20:21.667 on the early day that I came on out

NOTE Confidence: 0.8532734675

00:20:21.667 --> 00:20:24.197 on normal lawns transform cells.

NOTE Confidence: 0.8532734675

00:20:24.200 --> 00:20:26.260 In addition.

NOTE Confidence: 0.8532734675

00:20:26.260 --> 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 --> 00:20:36.753 and our recent studies of mice have

NOTE Confidence: 0.8532734675

00:20:36.753 --> 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 --> 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 --> 00:20:51.410 which is often used to study

NOTE Confidence: 0.8532734675

00:20:51.410 --> 00:20:52.240 neurological phenotypes,

NOTE Confidence: 0.8532734675

00:20:52.240 --> 00:20:54.108 these are embryonic lethal,

NOTE Confidence: 0.8532734675

00:20:54.108 --> 00:20:56.910 so it is an incredibly important.

NOTE Confidence: 0.8532734675

00:20:56.910 --> 00:20:57.580 Gene.

NOTE Confidence: 0.917001302

00:21:01.760 --> 00:21:04.118 And therefore I should make this

NOTE Confidence: 0.917001302

00:21:04.118 --> 00:21:06.554 important point there for UM in.

NOTE Confidence: 0.917001302

00:21:06.554 --> 00:21:09.578 In humans, we assumed the patient alleles.

NOTE Confidence: 0.81731535

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

NOTE Confidence: 0.81731535

00:21:17.160 --> 00:21:20.530 these what I call Eureka and one day.

NOTE Confidence: 0.81731535

00:21:20.530 --> 00:21:22.966 Allison, who had discovered VPS 13D

NOTE Confidence: 0.81731535

00:21:22.966 --> 00:21:25.401 in my lab and actually it was a nun

NOTE Confidence: 0.81731535

00:21:25.401 --> 00:21:27.487 named Jean at that at that time.

NOTE Confidence: 0.81731535

00:21:27.490 --> 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 --> 00:21:38.152 And she came to my office

NOTE Confidence: 0.81731535

00:21:38.152 --> 00:21:39.280 and she screamed out.

NOTE Confidence: 0.81731535

00:21:39.280 --> 00:21:40.780 We have mighty kandariya

NOTE Confidence: 0.81731535

00:21:40.780 --> 00:21:42.655 and I thought to myself,

NOTE Confidence: 0.81731535

00:21:42.660 --> 00:21:45.030 what are mighty kandariya and

NOTE Confidence: 0.81731535

00:21:45.030 --> 00:21:48.140 when she showed me the images,

NOTE Confidence: 0.81731535

00:21:48.140 --> 00:21:51.860 I really almost fell off my chair because

NOTE Confidence: 0.81731535

00:21:51.860 --> 00:21:53.870 the images of the control intestines

NOTE Confidence: 0.81731535

00:21:53.870 --> 00:21:56.487 on the top are the same magnification

NOTE Confidence: 0.81731535

00:21:56.487 --> 00:21:58.899 as the intestines on the bottom.

NOTE Confidence: 0.81731535

00:21:58.900 --> 00:22:00.846 And what you can see is that

NOTE Confidence: 0.81731535

00:22:00.846 --> 00:22:02.230 these mitochondria are enormous.

NOTE Confidence: 0.81731535

00:22:02.230 --> 00:22:04.456 In fact, mitochondrial experts that see these

NOTE Confidence: 0.81731535

00:22:04.456 --> 00:22:06.910 say they're some of the largest mitochondria.

NOTE Confidence: 0.81731535

00:22:06.910 --> 00:22:09.150 There are some larger

NOTE Confidence: 0.81731535

00:22:09.150 --> 00:22:11.390 mitochondria in the literature.

NOTE Confidence: 0.81731535

00:22:11.390 --> 00:22:12.940 And and they they are.

NOTE Confidence: 0.81731535

00:22:12.940 --> 00:22:14.110 They are derived.

NOTE Confidence: 0.81731535

00:22:14.110 --> 00:22:16.450 Those mitochondria that occur are because

NOTE Confidence: 0.81731535

00:22:16.450 --> 00:22:19.366 of different types of mutant combinations,

NOTE Confidence: 0.81731535

00:22:19.370 --> 00:22:21.200 but it's pretty remarkable about

NOTE Confidence: 0.81731535

00:22:21.200 --> 00:22:23.030 these giant mitochondria as they

NOTE Confidence: 0.81731535

00:22:23.090 --> 00:22:24.950 seem to be relatively functional.

NOTE Confidence: 0.81731535

00:22:24.950 --> 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 --> 00:22:31.930 but the from a morphological perspective,

NOTE Confidence: 0.81731535

00:22:31.930 --> 00:22:35.410 they're Christy are juxtaposed and

NOTE Confidence: 0.81731535

00:22:35.410 --> 00:22:36.795 and we've done some biochemical

NOTE Confidence: 0.81731535

00:22:36.795 --> 00:22:38.609 assays and they seem like they

NOTE Confidence: 0.81731535

00:22:38.609 --> 00:22:39.740 are relatively functional.

NOTE Confidence: 0.813930169090909

00:22:41.800 --> 00:22:43.310 But this phenotype was so

NOTE Confidence: 0.813930169090909

00:22:43.310 --> 00:22:45.060 strong and so apparent to us,

NOTE Confidence: 0.813930169090909

00:22:45.060 --> 00:22:46.600 this is something we pursued.

NOTE Confidence: 0.813930169090909

00:22:46.600 --> 00:22:49.072 We continue to pursue it because

NOTE Confidence: 0.813930169090909

00:22:49.072 --> 00:22:50.990 it's extremely interesting to us.

NOTE Confidence: 0.813930169090909

00:22:50.990 --> 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 Chung Wong,

NOTE Confidence: 0.813930169090909

00:22:55.410 --> 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 --> 00:23:02.836 He he was knocking out genes and Richard

NOTE Confidence: 0.813930169090909

00:23:02.836 --> 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 --> 00:23:12.552 He la cell lines and what we saw you

NOTE Confidence: 0.813930169090909

00:23:12.552 --> 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 --> 00:23:21.500 Or was it should say,

NOTE Confidence: 0.813930169090909

00:23:21.500 --> 00:23:22.780 common to all the VPS,

NOTE Confidence: 0.813930169090909

00:23:22.780 --> 00:23:25.450 13 knockout cells and that the

NOTE Confidence: 0.813930169090909

00:23:25.450 --> 00:23:27.640 mitochondria look larger and rounder in

NOTE Confidence: 0.813930169090909

00:23:27.640 --> 00:23:30.620 the heel of cells and not filamentous,

NOTE Confidence: 0.813930169090909

00:23:30.620 --> 00:23:33.356 as we typically think of mitochondria

NOTE Confidence: 0.813930169090909

00:23:33.356 --> 00:23:34.188 and yellow?

NOTE Confidence: 0.840020908181818

00:23:36.240 --> 00:23:38.400 And it's important to note that

NOTE Confidence: 0.840020908181818

00:23:38.400 --> 00:23:40.211 this mitochondrial phenotype in all

NOTE Confidence: 0.840020908181818

00:23:40.211 --> 00:23:42.409 of these cell lines was rescued by

NOTE Confidence: 0.840020908181818

00:23:42.409 --> 00:23:43.958 the introduction of its 13D plasma,

NOTE Confidence: 0.840020908181818

00:23:43.958 --> 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 of the crystal.

NOTE Confidence: 0.908600156666667

00:23:50.220 --> 00:23:52.453 So some of the important questions that

NOTE Confidence: 0.908600156666667

00:23:52.453 --> 00:23:54.586 we would like to address our water,

NOTE Confidence: 0.908600156666667

00:23:54.586 --> 00:23:55.598 the genes that function

NOTE Confidence: 0.908600156666667

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

NOTE Confidence: 0.908600156666667

00:23:57.080 --> 00:23:58.431 This is one of the strengths of

NOTE Confidence: 0.908600156666667

00:23:58.431 --> 00:23:59.838 the lab is a fly geneticist.

NOTE Confidence: 0.908600156666667

00:23:59.840 --> 00:24:02.120 We're always trying to identify

NOTE Confidence: 0.908600156666667

00:24:02.120 --> 00:24:04.400 more genes that functions pathway.

NOTE Confidence: 0.908600156666667

00:24:04.400 --> 00:24:06.687 Where is the primary defect in V

NOTE Confidence: 0.908600156666667

00:24:06.687 --> 00:24:09.129 PS13D cells that leads to disease.

NOTE Confidence: 0.908600156666667

00:24:09.130 --> 00:24:12.742 How does V PS13D influence such

NOTE Confidence: 0.908600156666667

00:24:12.742 --> 00:24:15.074 diverse cellular processes and

NOTE Confidence: 0.908600156666667

00:24:15.074 --> 00:24:17.170 can ultimately for patients?

NOTE Confidence: 0.908600156666667

00:24:17.170 --> 00:24:19.530 It would be very useful if we can

NOTE Confidence: 0.908600156666667

00:24:19.530 --> 00:24:21.109 identify genetic suppressors and best

NOTE Confidence: 0.908600156666667

00:24:21.109 --> 00:24:23.708 13 feet because of course if we can

NOTE Confidence: 0.908600156666667

00:24:23.708 --> 00:24:26.012 identify suppressors then we can think

NOTE Confidence: 0.908600156666667

00:24:26.012 --> 00:24:28.430 about modulating these factors as

NOTE Confidence: 0.908600156666667

00:24:28.430 --> 00:24:30.950 potential therapeutic strategies and.

NOTE Confidence: 0.908600156666667

00:24:30.950 --> 00:24:32.478 I just want to step back to the

NOTE Confidence: 0.908600156666667

00:24:32.478 --> 00:24:34.190 disease a little bit because at the

NOTE Confidence: 0.908600156666667

00:24:34.190 --> 00:24:35.779 beginning I introduced you to one

NOTE Confidence: 0.908600156666667

00:24:35.779 --> 00:24:37.571 patient family that has some of the

NOTE Confidence: 0.908600156666667

00:24:37.571 --> 00:24:39.654 weaker alliance probably of the VPS.

NOTE Confidence: 0.908600156666667

00:24:39.654 --> 00:24:42.000 13D patients that are like that

NOTE Confidence: 0.908600156666667

00:24:42.077 --> 00:24:44.618 and identified some of the some

NOTE Confidence: 0.908600156666667

00:24:44.618 --> 00:24:46.850 one of the saddest stories is

NOTE Confidence: 0.908600156666667

00:24:46.937 --> 00:24:49.607 that there are some children that

NOTE Confidence: 0.908600156666667

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

NOTE Confidence: 0.908600156666667

00:24:52.445 --> 00:24:55.090 disease early in life or normally,

NOTE Confidence: 0.908600156666667

00:24:55.090 --> 00:24:58.218 but by three to five years their wheelchair

NOTE Confidence: 0.908600156666667

00:24:58.218 --> 00:25:01.119 about so it really is a very tragic.

NOTE Confidence: 0.908600156666667

00:25:01.120 --> 00:25:03.730 A disease that affects these children.

NOTE Confidence: 0.8839502

00:25:06.830 --> 00:25:11.139 So. Big question for us was what genes?

NOTE Confidence: 0.8839502

00:25:11.140 --> 00:25:13.018 Because we knew nothing about this

NOTE Confidence: 0.8839502

00:25:13.018 --> 00:25:15.420 as we started and So what other genes

NOTE Confidence: 0.8839502

00:25:15.420 --> 00:25:18.115 are in the BTS 13 pathway and a big

NOTE Confidence: 0.8839502

00:25:18.115 --> 00:25:19.890 breakthrough for us came through

NOTE Confidence: 0.8839502

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

NOTE Confidence: 0.8839502

00:25:22.250 --> 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 --> 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 --> 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 --> 00:25:39.862 but in this photograph is shown here

NOTE Confidence: 0.8839502

00:25:39.862 --> 00:25:43.045 in my lab and in Hong's graduates to

NOTE Confidence: 0.8839502

00:25:43.045 --> 00:25:46.704 Twitch and what they did is they were

NOTE Confidence: 0.8839502

00:25:46.704 --> 00:25:49.470 screening for genetic modifiers of a

NOTE Confidence: 0.8839502

00:25:49.564 --> 00:25:53.312 gene called EPG three and WORMS it's V MP1.

NOTE Confidence: 0.8839502

00:25:53.312 --> 00:25:55.454 This is a gene they've been very

NOTE Confidence: 0.8839502

00:25:55.454 --> 00:25:57.186 interested in and they found

NOTE Confidence: 0.8839502

00:25:57.186 --> 00:26:00.390 a genetic interaction today.

NOTE Confidence: 0.8839502

00:26:00.390 --> 00:26:01.914 So this was a.

NOTE Confidence: 0.8839502

00:26:01.914 --> 00:26:04.550 This is a very interesting to us,

NOTE Confidence: 0.8839502

00:26:04.550 --> 00:26:08.366 but also I think to your colleagues

NOTE Confidence: 0.8839502

00:26:08.366 --> 00:26:11.594 Karen Tom and yeah troll because

NOTE Confidence: 0.8839502

00:26:11.594 --> 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

00:26:20.382 --> 00:26:25.010 had shown that VMP 1 depletion results in

NOTE Confidence: 0.662068463636364

00:26:25.010 --> 00:26:28.944 an altered by chondral shape and Assoc.

NOTE Confidence: 0.662068463636364

00:26:28.950 --> 00:26:31.890 If you are in the mitochondrial shape

NOTE Confidence: 0.662068463636364

00:26:31.890 --> 00:26:34.132 change that Janss observed similar

NOTE Confidence: 0.662068463636364

00:26:34.132 --> 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 --> 00:26:50.269 James is quite a remarkable student.

NOTE Confidence: 0.662068463636364

00:26:50.270 --> 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 --> 00:26:56.744 and he went from this individual

NOTE Confidence: 0.662068463636364

00:26:56.744 --> 00:26:59.448 shown in his pre pre Med

NOTE Confidence: 0.662068463636364

00:26:59.448 --> 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 --> 00:27:04.375 fearless scientist.

NOTE Confidence: 0.662068463636364

00:27:04.380 --> 00:27:06.460 He's taken on every problem that I feed

NOTE Confidence: 0.662068463636364

00:27:06.460 --> 00:27:08.979 him and got much more than I ever expected.

NOTE Confidence: 0.891430079

00:27:11.370 --> 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 --> 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 --> 00:27:22.910 influence on cell size reduction and

NOTE Confidence: 0.891430079

00:27:22.910 --> 00:27:27.250 locked the formation of M Cherry ATG,

NOTE Confidence: 0.891430079

00:27:27.250 --> 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 --> 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 --> 00:27:42.059 than their neighboring cells,

NOTE Confidence: 0.688754621428571

00:27:42.060 --> 00:27:44.400 similar to the past 13 D.

NOTE Confidence: 0.688754621428571

00:27:44.400 --> 00:27:46.944 In addition, they accumulate a protein

NOTE Confidence: 0.688754621428571

00:27:46.944 --> 00:27:49.417 that's called ref 2P and flies

NOTE Confidence: 0.688754621428571

00:27:49.417 --> 00:27:51.874 because it was named before our P.

NOTE Confidence: 0.688754621428571

00:27:51.880 --> 00:27:53.480 62 was identified in mammals.

NOTE Confidence: 0.688754621428571

00:27:53.480 --> 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 --> 00:28:01.088 P60 true gets recruited into auto

NOTE Confidence: 0.688754621428571

00:28:01.088 --> 00:28:03.239 phagosomes and the levels go down.

NOTE Confidence: 0.688754621428571

00:28:03.240 --> 00:28:05.190 So when you block autophagy.

NOTE Confidence: 0.777906105714286

00:28:07.470 --> 00:28:09.745 P 62 should accumulate and then see

NOTE Confidence: 0.777906105714286

00:28:09.745 --> 00:28:12.390 shows here in quantified on the right.

NOTE Confidence: 0.777906105714286

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

NOTE Confidence: 0.777906105714286

00:28:16.510 --> 00:28:18.130 and these are actually knowledge.

NOTE Confidence: 0.777906105714286

00:28:18.130 --> 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 --> 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 --> 00:28:33.246 for clearance of mitochondria.

NOTE Confidence: 0.926115

00:28:33.250 --> 00:28:35.182 So here again we're using this

NOTE Confidence: 0.926115

00:28:35.182 --> 00:28:37.330 surrogate marker of of mitochondria.

NOTE Confidence: 0.926115

00:28:37.330 --> 00:28:43.400 The antibody against ATP 5A and you can

NOTE Confidence: 0.926115

00:28:43.400 --> 00:28:45.692 also see that they have just superficially

NOTE Confidence: 0.926115

00:28:45.692 --> 00:28:47.918 they look like larger mitochondria than

NOTE Confidence: 0.926115

00:28:47.918 --> 00:28:49.809 we typically see in control cells,

NOTE Confidence: 0.926115

00:28:49.810 --> 00:28:52.050 but the control cells are marked in red.

NOTE Confidence: 0.926115

00:28:52.050 --> 00:28:54.882 Mutants lack red and you can see the

NOTE Confidence: 0.926115

00:28:54.882 --> 00:28:57.368 control cells you see no mitochondria.

NOTE Confidence: 0.926115

00:28:57.370 --> 00:29:00.919 And mute cells have much more mitochondria.

NOTE Confidence: 0.846470827619048

00:29:04.520 --> 00:29:06.544 I think I figured out why I can't

NOTE Confidence: 0.846470827619048

00:29:06.544 --> 00:29:08.347 forward because if I move the toolbar

NOTE Confidence: 0.846470827619048

00:29:08.347 --> 00:29:09.900 down there then it doesn't work.

NOTE Confidence: 0.849870185

00:29:14.100 --> 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 --> 00:29:21.716 And for this we used RNA.

NOTE Confidence: 0.849870185

00:29:21.720 --> 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 --> 00:29:29.280 so we could just specifically knockdown

NOTE Confidence: 0.849870185

00:29:29.280 --> 00:29:32.350 VNP one in the intestine and you

NOTE Confidence: 0.849870185

00:29:32.350 --> 00:29:35.082 can see that the mitochondria are

NOTE Confidence: 0.849870185

00:29:35.082 --> 00:29:38.076 both larger in shape and and this is

NOTE Confidence: 0.849870185

00:29:38.076 --> 00:29:39.520 mitochondrial area quantified here,

NOTE Confidence: 0.849870185

00:29:39.520 --> 00:29:40.912 so it looks very similar to

NOTE Confidence: 0.849870185

00:29:40.912 --> 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 --> 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 --> 00:29:53.690 So double mutant analysis indicate that

NOTE Confidence: 0.874056986

00:29:53.690 --> 00:29:55.919 these genes function in the same pathway.

NOTE Confidence: 0.874056986

00:29:55.920 --> 00:29:58.524 In other words, they do not have

NOTE Confidence: 0.874056986

00:29:58.524 --> 00:30:00.389 an additive phenotype based on

NOTE Confidence: 0.874056986

00:30:00.389 --> 00:30:02.405 any of the markers we've used.

NOTE Confidence: 0.874056986

00:30:02.410 --> 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 --> 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 --> 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 --> 00:30:31.133 BMP one puncta which is and I should

NOTE Confidence: 0.748455450833333

00:30:31.133 --> 00:30:33.660 have mentioned that BMP one is an ER,

NOTE Confidence: 0.748455450833333

00:30:33.660 --> 00:30:38.860 resides on ER both in mammals and influx.

NOTE Confidence: 0.748455450833333

00:30:38.860 --> 00:30:42.268 So these data, no thinking simplistically,

NOTE Confidence: 0.748455450833333

00:30:42.270 --> 00:30:44.634 as a geneticist, suggests that BMP

NOTE Confidence: 0.748455450833333

00:30:44.634 --> 00:30:48.052 that BMP one is upstream of EPS 13D.

NOTE Confidence: 0.748455450833333

00:30:48.052 --> 00:30:50.728 Of course, as you start thinking

NOTE Confidence: 0.748455450833333

00:30:50.728 --> 00:30:53.090 about something, this is not like

NOTE Confidence: 0.748455450833333

00:30:53.090 --> 00:30:54.618 a classic transcription factor.

NOTE Confidence: 0.748455450833333

00:30:54.620 --> 00:30:56.820 Gene target type of pathway.

NOTE Confidence: 0.748455450833333

00:30:56.820 --> 00:30:58.404 So there are many other explanations

NOTE Confidence: 0.748455450833333

00:30:58.404 --> 00:31:00.070 that need to be considered.

NOTE Confidence: 0.748455450833333

00:31:00.070 --> 00:31:01.270 When I think about these data,

NOTE Confidence: 0.748455450833333

00:31:01.270 --> 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 --> 00:31:05.494 you would think about this as BMP,

NOTE Confidence: 0.748455450833333

00:31:05.500 --> 00:31:07.808 one being upstream did.

NOTE Confidence: 0.917781288571429

00:31:10.600 --> 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 --> 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 --> 00:31:23.880 laboratory yam expert Tina 48.

NOTE Confidence: 0.917781288571429

00:31:23.880 --> 00:31:25.470 She does all of our electron

NOTE Confidence: 0.917781288571429

00:31:25.533 --> 00:31:27.423 microscopy and she doesn't get enough

NOTE Confidence: 0.917781288571429

00:31:27.423 --> 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 --> 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

NOTE Confidence: 0.917781288571429

00:31:36.115 --> 00:31:37.830 get the same kind of attention that

NOTE Confidence: 0.917781288571429

00:31:37.878 --> 00:31:39.438 graduate students and postdocs get,

NOTE Confidence: 0.917781288571429

00:31:39.440 --> 00:31:41.614 so I want to make that point, but also.

NOTE Confidence: 0.917781288571429

00:31:41.614 --> 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 --> 00:31:48.338 sort of glorified cartoons,

NOTE Confidence: 0.917781288571429

00:31:48.340 --> 00:31:51.064 and this is probably what an auto

NOTE Confidence: 0.917781288571429

00:31:51.064 --> 00:31:52.632 phagosome membrane forming around

NOTE Confidence: 0.917781288571429

00:31:52.632 --> 00:31:54.612 it mitochondria looks like and

NOTE Confidence: 0.917781288571429

00:31:54.612 --> 00:31:55.665 what's particularly attractive

NOTE Confidence: 0.917781288571429

00:31:55.665 --> 00:31:57.771 about this image to me is,

NOTE Confidence: 0.917781288571429

00:31:57.780 --> 00:32:00.228 it looks like this might be a mitochondria

NOTE Confidence: 0.917781288571429

00:32:00.228 --> 00:32:02.306 that's going through a fission event

NOTE Confidence: 0.917781288571429

00:32:02.306 --> 00:32:04.061 that there's this dumbbell shape

NOTE Confidence: 0.917781288571429

00:32:04.061 --> 00:32:05.916 that's at the ends of where this.

NOTE Confidence: 0.917781288571429

00:32:05.920 --> 00:32:08.026 You know this membrane is juxtaposed.

NOTE Confidence: 0.808904528

00:32:10.860 --> 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 --> 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 --> 00:32:27.656 So when mitophagy is active and might

NOTE Confidence: 0.808904528

00:32:27.656 --> 00:32:29.924 almost all the mitochondria get cleared

NOTE Confidence: 0.808904528

00:32:29.924 --> 00:32:32.752 in the intestine is very narrow window.

NOTE Confidence: 0.808904528

00:32:32.760 --> 00:32:35.126 I described the beginning so when that

NOTE Confidence: 0.808904528

00:32:35.126 --> 00:32:38.015 happens you have very low GFP signal and

NOTE Confidence: 0.808904528

00:32:38.015 --> 00:32:41.190 persistent and cherry signal because.

NOTE Confidence: 0.808904528

00:32:41.190 --> 00:32:44.880 Once on Phagosomes containing mitochondria

NOTE Confidence: 0.808904528

00:32:44.880 --> 00:32:48.216 fuse with lysosomes GFP signal,

NOTE Confidence: 0.808904528

00:32:48.216 --> 00:32:50.472 but is no longer admitted because

NOTE Confidence: 0.808904528

00:32:50.472 --> 00:32:53.528 of the pH of the acidic pH license.

NOTE Confidence: 0.808904528

00:32:53.530 --> 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 --> 00:33:00.298 You can see that the majority that

NOTE Confidence: 0.808904528

00:33:00.298 --> 00:33:04.186 many of the GFP signals persist,

NOTE Confidence: 0.808904528

00:33:04.190 --> 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 --> 00:33:13.069 or influence on the medical clearance

NOTE Confidence: 0.808904528

00:33:13.069 --> 00:33:15.418 of mitochondria based on this asset.

NOTE Confidence: 0.95018749

00:33:18.660 --> 00:33:22.116 So we wanted to examine whether or not

NOTE Confidence: 0.95018749

00:33:22.120 --> 00:33:25.179 VPS 13D fit into the existing mitophagy

NOTE Confidence: 0.95018749

00:33:25.179 --> 00:33:28.562 paradigm and at the time we're investigating

NOTE Confidence: 0.95018749

00:33:28.562 --> 00:33:32.098 this was when Richard Richard Ewell's lab

NOTE Confidence: 0.95018749

00:33:32.098 --> 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 --> 00:33:40.084 Genes, pink one and Parkin on

NOTE Confidence: 0.95018749

00:33:40.084 --> 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

NOTE Confidence: 0.95018749

00:33:44.198 --> 00:33:45.440 these genes do.

NOTE Confidence: 0.95018749

00:33:45.440 --> 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 --> 00:33:53.632 but upon mitochondrial damage shown by

NOTE Confidence: 0.95018749

00:33:53.632 --> 00:33:56.650 these stars Pink 1 translocates for a

NOTE Confidence: 0.95018749

00:33:56.650 --> 00:33:58.170 complicated biochemical mechanism to

NOTE Confidence: 0.95018749

00:33:58.170 --> 00:34:00.566 the outer leaflet of the mitochondria,

NOTE Confidence: 0.95018749

00:34:00.570 --> 00:34:03.410 where it phosphorylates both ubiquitin

NOTE Confidence: 0.95018749

00:34:03.410 --> 00:34:06.246 and parking and enables chain elongation

NOTE Confidence: 0.95018749

00:34:06.246 --> 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 --> 00:34:13.570 and it's thought that this

NOTE Confidence: 0.95018749

00:34:13.570 --> 00:34:15.402 ubiquitination is actually relatively.

NOTE Confidence: 0.95018749

00:34:15.410 --> 00:34:16.661 I should say,

NOTE Confidence: 0.95018749

00:34:16.661 --> 00:34:19.163 very strong data indicate that this.

NOTE Confidence: 0.95018749

00:34:19.170 --> 00:34:21.314 Ubiquitination of these mitochondrial

NOTE Confidence: 0.95018749

00:34:21.314 --> 00:34:23.994 proteins is how mitochondria get

NOTE Confidence: 0.95018749

00:34:24.000 --> 00:34:27.170 recognized by autophagy cargo receptors

NOTE Confidence: 0.95018749

00:34:27.170 --> 00:34:30.340 that interact with both ubiquitin

NOTE Confidence: 0.95018749

00:34:30.340 --> 00:34:32.839 and ATG 8 or its mammalian ortholog

NOTE Confidence: 0.95018749

00:34:32.839 --> 00:34:35.754 bail C3 got Rep family so that

NOTE Confidence: 0.95018749

00:34:35.754 --> 00:34:38.400 mitochondria can get cleared by office.

NOTE Confidence: 0.94452256

00:34:40.810 --> 00:34:43.720 So we wanted to ask.

NOTE Confidence: 0.94452256

00:34:43.720 --> 00:34:45.505 Whether or not pink one

NOTE Confidence: 0.94452256

00:34:45.505 --> 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 --> 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 --> 00:35:03.010 null loss of function salad you

NOTE Confidence: 0.94452256

00:35:03.010 --> 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 --> 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 --> 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 --> 00:35:31.580 Because we have this classic

NOTE Confidence: 0.94452256

00:35:31.580 --> 00:35:33.840 pink one Parkin like pathway,

NOTE Confidence: 0.94452256

00:35:33.840 --> 00:35:35.616 we were shocked when we could

NOTE Confidence: 0.94452256

00:35:35.616 --> 00:35:37.359 started analyzing park it and again

NOTE Confidence: 0.94452256

00:35:37.359 --> 00:35:39.116 there's a there's a lot of data.

NOTE Confidence: 0.94452256

00:35:39.120 --> 00:35:41.864 Actually most of this data is published

NOTE Confidence: 0.94452256

00:35:41.864 --> 00:35:44.960 in a in a JCB paper last year.

NOTE Confidence: 0.94452256

00:35:44.960 --> 00:35:47.172 But what we saw in on the

NOTE Confidence: 0.94452256

00:35:47.172 --> 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 --> 00:35:52.916 control intestine cells.

NOTE Confidence: 0.94452256

00:35:52.920 --> 00:35:55.085 This is a parking homozygous

NOTE Confidence: 0.94452256

00:35:55.085 --> 00:35:57.480 mutant with lacking 1 allele of

NOTE Confidence: 0.94452256

00:35:57.480 --> 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 --> 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 --> 00:36:14.722 we saw both because 13D mutants

NOTE Confidence: 0.94452256

00:36:14.722 --> 00:36:17.566 as well as in pink ones.

NOTE Confidence: 0.9446667375

00:36:20.330 --> 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 --> 00:36:31.150 up formation in in in mutant cells.

NOTE Confidence: 0.9446667375

00:36:31.150 --> 00:36:34.981 We saw that as the the usual and many other

NOTE Confidence: 0.9446667375

00:36:34.981 --> 00:36:38.252 lab model would predict when pink is one

NOTE Confidence: 0.9446667375

00:36:38.252 --> 00:36:42.034 is lost in these mutant cells. You see,

NOTE Confidence: 0.9446667375

00:36:42.034 --> 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 --> 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 --> 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 --> 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 --> 00:37:15.637 And we're working to better

NOTE Confidence: 0.9446667375

00:37:15.637 --> 00:37:17.470 understand its mechanisms now.

NOTE Confidence: 0.79214492

00:37:20.460 --> 00:37:25.975 So the. One of the last parts

NOTE Confidence: 0.79214492

00:37:25.975 --> 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 --> 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 --> 00:37:42.980 48 started analyzing this in all

NOTE Confidence: 0.79214492

00:37:43.066 --> 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 --> 00:37:50.452 and what they observed was that

NOTE Confidence: 0.79214492

00:37:50.452 --> 00:37:52.804 in in the fruit fly in testing,

NOTE Confidence: 0.79214492

00:37:52.810 --> 00:37:55.561 which is the first model that we

NOTE Confidence: 0.79214492

00:37:55.561 --> 00:37:57.996 studied that animals lacking VPS 13D

NOTE Confidence: 0.79214492

00:37:57.996 --> 00:37:59.964 and these are two different allele

NOTE Confidence: 0.79214492

00:37:59.964 --> 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 --> 00:38:05.420 magnifications are in the top.

NOTE Confidence: 0.79214492

00:38:05.420 --> 00:38:08.280 Enlargements are on the bottom.

NOTE Confidence: 0.79214492

00:38:08.280 --> 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 --> 00:38:15.668 be a mitochondria ER contact is

NOTE Confidence: 0.79214492

00:38:15.668 --> 00:38:18.100 defined based on the literature.

NOTE Confidence: 0.79214492

00:38:18.100 --> 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 --> 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 --> 00:38:38.059 analyzing patient provide cells and

NOTE Confidence: 0.79214492

00:38:38.059 --> 00:38:41.745 in these cases we have very nice both

NOTE Confidence: 0.79214492

00:38:41.745 --> 00:38:45.535 patient and either heterozygous sibling

NOTE Confidence: 0.79214492

00:38:45.535 --> 00:38:49.088 or heterozygous parent mutations.

NOTE Confidence: 0.79214492

00:38:49.088 --> 00:38:52.378 So this is the original.

NOTE Confidence: 0.79214492

00:38:52.380 --> 00:38:55.260 University of Michigan derived cells.

NOTE Confidence: 0.79214492

00:38:55.260 --> 00:38:57.606 The first allele that was actually

NOTE Confidence: 0.79214492

00:38:57.606 --> 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 --> 00:39:06.132 this image here so.

NOTE Confidence: 0.79214492

00:39:06.140 --> 00:39:10.040 Unrelated fibroblast and these are.

NOTE Confidence: 0.79214492

00:39:10.040 --> 00:39:12.824 This is apparent dry fibroblast and

NOTE Confidence: 0.79214492

00:39:12.824 --> 00:39:15.630 this is a patient, right fiberglass?

NOTE Confidence: 0.79214492

00:39:15.630 --> 00:39:17.040 If you look.

NOTE Confidence: 0.79214492

00:39:17.040 --> 00:39:18.750 Actually James selected this region

NOTE Confidence: 0.79214492

00:39:18.750 --> 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,

NOTE Confidence: 0.79214492

00:39:23.410 --> 00:39:25.489 but actually my favorite part of the

NOTE Confidence: 0.79214492

00:39:25.489 --> 00:39:27.736 image is down here where it really

NOTE Confidence: 0.79214492

00:39:27.736 --> 00:39:30.200 looks like the ER extends and wraps

NOTE Confidence: 0.79214492

00:39:30.276 --> 00:39:32.332 around this particular mitochondria

NOTE Confidence: 0.79214492

00:39:32.332 --> 00:39:34.902 and that's all quantified over.

NOTE Confidence: 0.79214492

00:39:34.910 --> 00:39:38.114 We also looked at that as a distinct family.

NOTE Confidence: 0.79214492

00:39:38.120 --> 00:39:42.327 These are cells that were collected by.

NOTE Confidence: 0.79214492

00:39:42.330 --> 00:39:46.478 Katya lowman and sadly I was

NOTE Confidence: 0.79214492

00:39:46.478 --> 00:39:48.500 just reminded me giving a tragedy

NOTE Confidence: 0.79214492

00:39:48.572 --> 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 --> 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 --> 00:40:04.044 In this case it's a sibling loss

NOTE Confidence: 0.79214492

00:40:04.044 --> 00:40:06.468 of 1 allele and the homozygous.

NOTE Confidence: 0.64835307625

00:40:08.520 --> 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 --> 00:40:14.516 mitochondria in New York contact.

NOTE Confidence: 0.872193747586207

00:40:18.170 --> 00:40:19.766 So the big question then for

NOTE Confidence: 0.872193747586207

00:40:19.766 --> 00:40:21.510 these patients is can we identify

NOTE Confidence: 0.872193747586207

00:40:21.510 --> 00:40:23.364 suppressors and you know we're very

NOTE Confidence: 0.872193747586207

00:40:23.364 --> 00:40:24.983 lucky that actually patients you

NOTE Confidence: 0.872193747586207

00:40:24.983 --> 00:40:26.867 know from all around the world,

NOTE Confidence: 0.872193747586207

00:40:26.870 --> 00:40:29.530 so rare disease but have been trying

NOTE Confidence: 0.872193747586207

00:40:29.530 --> 00:40:32.274 to get us selves and so that we

NOTE Confidence: 0.872193747586207

00:40:32.274 --> 00:40:33.642 can study this in more patients.

NOTE Confidence: 0.872193747586207

00:40:33.650 --> 00:40:36.338 And what's important is can we

NOTE Confidence: 0.872193747586207

00:40:36.338 --> 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 --> 00:40:43.922 And so I want to introduce you to the

NOTE Confidence: 0.872193747586207

00:40:43.922 --> 00:40:45.249 mitochondrial fission fusion cycle.

NOTE Confidence: 0.872193747586207

00:40:45.250 --> 00:40:46.390 In case you don't know it.

NOTE Confidence: 0.925551416666667

00:40:48.810 --> 00:40:51.494 What we know is that fusion is regulated

NOTE Confidence: 0.925551416666667

00:40:51.494 --> 00:40:53.830 some some of this fly protein names and

NOTE Confidence: 0.925551416666667

00:40:53.890 --> 00:40:55.970 some of them are the same in mammals,

NOTE Confidence: 0.925551416666667

00:40:55.970 --> 00:40:57.044 but I'll try to remember to

NOTE Confidence: 0.925551416666667

00:40:57.044 --> 00:40:58.030 give you the mammal names.

NOTE Confidence: 0.925551416666667

00:40:58.030 --> 00:41:01.285 So what happens when mitochondrial

NOTE Confidence: 0.925551416666667

00:41:01.285 --> 00:41:02.587 damage accumulates?

NOTE Confidence: 0.925551416666667

00:41:02.590 --> 00:41:04.042 It's thought to be dealt with

NOTE Confidence: 0.925551416666667

00:41:04.042 --> 00:41:05.010 in two different ways.

NOTE Confidence: 0.925551416666667

00:41:05.010 --> 00:41:06.830 One possible mechanism is

NOTE Confidence: 0.925551416666667

00:41:06.830 --> 00:41:08.650 to dilute that damage.

NOTE Confidence: 0.925551416666667

00:41:08.650 --> 00:41:11.586 It's sort of like bold Dow Chemical slogan.

NOTE Confidence: 0.925551416666667

00:41:11.590 --> 00:41:14.418 I believe it was solution to pollution

NOTE Confidence: 0.925551416666667

00:41:14.418 --> 00:41:18.210 is dilution so and this fusion event.

NOTE Confidence: 0.925551416666667

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

NOTE Confidence: 0.925551416666667

00:41:21.690 --> 00:41:24.180 called in flies marfisi ortholog of

NOTE Confidence: 0.925551416666667

00:41:24.180 --> 00:41:27.839 M FM one and MF and two and humans.

NOTE Confidence: 0.925551416666667

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

NOTE Confidence: 0.925551416666667

00:41:30.160 --> 00:41:31.532 but the other approach,

NOTE Confidence: 0.925551416666667

00:41:31.532 --> 00:41:34.171 and which is you know more sophisticated

NOTE Confidence: 0.925551416666667

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

NOTE Confidence: 0.925551416666667

00:41:36.626 --> 00:41:39.036 the bad piece of mitochondria.

NOTE Confidence: 0.925551416666667

00:41:39.040 --> 00:41:41.852 So through a vision of it be cut off

NOTE Confidence: 0.925551416666667

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

NOTE Confidence: 0.925551416666667

00:41:43.900 --> 00:41:46.217 eaten by an auto phagosome or clearance,

NOTE Confidence: 0.925551416666667

00:41:46.220 --> 00:41:48.266 and the vision events are regulated

NOTE Confidence: 0.925551416666667

00:41:48.266 --> 00:41:50.334 by proteins, including PR,

NOTE Confidence: 0.925551416666667

00:41:50.334 --> 00:41:53.794 P1 phase one and MF.

NOTE Confidence: 0.925551416666667

00:41:53.800 --> 00:41:56.040 And so.

NOTE Confidence: 0.925551416666667

00:41:56.040 --> 00:41:58.854 We had identified Marfan flies or

NOTE Confidence: 0.925551416666667

00:41:58.854 --> 00:42:02.384 orthologue of MFN one and two as a

NOTE Confidence: 0.925551416666667

00:42:02.384 --> 00:42:04.736 gene that had a similar phenotype

NOTE Confidence: 0.925551416666667

00:42:04.740 --> 00:42:10.232 to VPS 13 that had that could

NOTE Confidence: 0.925551416666667

00:42:10.232 --> 00:42:13.056 suppress VPS 13D mitochondria.

NOTE Confidence: 0.925551416666667

00:42:13.060 --> 00:42:16.196 So the question we wanted to ask that.

NOTE Confidence: 0.925551416666667

00:42:16.200 --> 00:42:19.800 Is is this a potential genetic

NOTE Confidence: 0.925551416666667

00:42:19.800 --> 00:42:22.389 suppressor of this phenotype?

NOTE Confidence: 0.925551416666667

00:42:22.389 --> 00:42:24.378 Ultimately patient sounds.

NOTE Confidence: 0.925551416666667

00:42:24.380 --> 00:42:27.796 So a few details. Mark and MFN.

NOTE Confidence: 0.925551416666667

00:42:27.800 --> 00:42:29.210 2 but not.

NOTE Confidence: 0.925551416666667

00:42:29.210 --> 00:42:32.302 MFN, one physically interacts with VPS 13D.

NOTE Confidence: 0.925551416666667

00:42:32.302 --> 00:42:34.528 We've done this in our lab,

NOTE Confidence: 0.925551416666667

00:42:34.530 --> 00:42:36.118 but also in plot.

NOTE Confidence: 0.925551416666667

00:42:36.118 --> 00:42:39.216 Gingras identified MFN 2 as a strong

NOTE Confidence: 0.925551416666667

00:42:39.216 --> 00:42:42.370 physical interact with because 13D in

NOTE Confidence: 0.925551416666667

00:42:42.370 --> 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 --> 00:42:52.284 13D Mutant cells, and the reason I

NOTE Confidence: 0.655386948

00:42:52.284 --> 00:42:54.328 think this could be important is this

NOTE Confidence: 0.655386948

00:42:54.328 --> 00:42:56.124 could be a potential biomarker for

NOTE Confidence: 0.655386948

00:42:56.124 --> 00:42:57.979 first task at some of these patients,

NOTE Confidence: 0.655386948

00:42:57.980 --> 00:43:00.636 and this is no shown to be true

NOTE Confidence: 0.655386948

00:43:00.636 --> 00:43:02.890 across a larger population.

NOTE Confidence: 0.655386948

00:43:02.890 --> 00:43:06.146 And interestingly, in our hands in the fly,

NOTE Confidence: 0.655386948

00:43:06.150 --> 00:43:09.867 if we miss Express Mark in this green cell,

NOTE Confidence: 0.655386948

00:43:09.870 --> 00:43:12.995 this is sufficient to impair

NOTE Confidence: 0.655386948

00:43:12.995 --> 00:43:15.495 the clearance of mitochondria.

NOTE Confidence: 0.655386948

00:43:15.500 --> 00:43:16.980 So. In other words,

NOTE Confidence: 0.655386948

00:43:16.980 --> 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 --> 00:43:25.068 all the data .2 MF N2RR marfin

NOTE Confidence: 0.655386948

00:43:25.068 --> 00:43:28.600 the fly as regulators of 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 --> 00:43:33.880 So we wanted to ask whether or not

NOTE Confidence: 0.655386948

00:43:33.880 --> 00:43:37.009 knock down of Marfan the fly could

NOTE Confidence: 0.655386948

00:43:37.009 --> 00:43:39.358 suppress the phenotypes that we see,

NOTE Confidence: 0.655386948

00:43:39.360 --> 00:43:42.552 so we'll want to find mitochondrial

NOTE Confidence: 0.655386948

00:43:42.552 --> 00:43:45.070 area in contact with ER.

NOTE Confidence: 0.655386948

00:43:45.070 --> 00:43:50.012 So all of these are VPS 13D mutant cells.

NOTE Confidence: 0.655386948

00:43:50.012 --> 00:43:52.404 In these image transmission

NOTE Confidence: 0.655386948

00:43:52.404 --> 00:43:54.300 electron microscopy images.

NOTE Confidence: 0.655386948

00:43:54.300 --> 00:43:57.477 Lomax on the top higher Max on the bottom.

NOTE Confidence: 0.655386948

00:43:57.480 --> 00:44:02.014 And what you can see is that and

NOTE Confidence: 0.655386948

00:44:02.014 --> 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 --> 00:44:08.857 I knockdown in the fly and what

NOTE Confidence: 0.655386948

00:44:08.857 --> 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 --> 00:44:16.185 area with Mark knock down as well

NOTE Confidence: 0.655386948

00:44:16.185 --> 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 --> 00:44:26.300 this was true in the patient cells.

NOTE Confidence: 0.897546818125

00:44:26.300 --> 00:44:30.916 So again, all of these are the homozygous.

NOTE Confidence: 0.897546818125

00:44:30.920 --> 00:44:32.920 These are the page all the patients else,

NOTE Confidence: 0.897546818125

00:44:32.920 --> 00:44:36.392 but on the left is a mock siRNA in

NOTE Confidence: 0.897546818125

00:44:36.392 --> 00:44:39.480 the left and the right is a MFN,

NOTE Confidence: 0.897546818125

00:44:39.480 --> 00:44:42.702 two RNA I and what you can see in

NOTE Confidence: 0.897546818125

00:44:42.702 --> 00:44:46.058 all quantified appropriately here.

NOTE Confidence: 0.897546818125

00:44:46.060 --> 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 --> 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 --> 00:45:03.790 and some of the conclusions.

NOTE Confidence: 0.937386631428571

00:45:03.790 --> 00:45:05.314 So these were the questions I

NOTE Confidence: 0.937386631428571

00:45:05.314 --> 00:45:07.208 wanted to try to address and I

NOTE Confidence: 0.937386631428571

00:45:07.208 --> 00:45:09.105 think I've at least done this part.

NOTE Confidence: 0.937386631428571

00:45:09.110 --> 00:45:10.838 What genes are in the function

NOTE Confidence: 0.937386631428571

00:45:10.838 --> 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 --> 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 --> 00:45:22.735 we're excited that we have multiple

NOTE Confidence: 0.937386631428571

00:45:22.735 --> 00:45:25.000 other factors in this pathway that

NOTE Confidence: 0.937386631428571

00:45:25.000 --> 00:45:28.300 we're processing characterizing. No.

NOTE Confidence: 0.937386631428571

00:45:28.300 --> 00:45:30.956 Where is the primary defect in these cells?

NOTE Confidence: 0.937386631428571

00:45:30.960 --> 00:45:34.470 Well, but the thing that we come back to

NOTE Confidence: 0.937386631428571

00:45:34.470 --> 00:45:38.497 is this mitochondria and ER proximity and.

NOTE Confidence: 0.937386631428571

00:45:38.500 --> 00:45:40.334 Perhaps this is caused by something else,

NOTE Confidence: 0.937386631428571

00:45:40.340 --> 00:45:42.908 but this is the earlier what we could

NOTE Confidence: 0.937386631428571

00:45:42.908 --> 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 --> 00:45:50.105 diverse cellular processes?

NOTE Confidence: 0.937386631428571

00:45:50.110 --> 00:45:51.850 They answer is the same.

NOTE Confidence: 0.937386631428571

00:45:51.850 --> 00:45:54.748 It appears that this inter organelle

NOTE Confidence: 0.937386631428571

00:45:54.748 --> 00:45:58.770 communication is a big part of what's why

NOTE Confidence: 0.937386631428571

00:45:58.770 --> 00:46:02.345 we're impacting multiple cell processes?

NOTE Confidence: 0.937386631428571

00:46:02.350 --> 00:46:04.110 And can we identify suppressors,

NOTE Confidence: 0.937386631428571

00:46:04.110 --> 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 --> 00:46:12.220 other possible suppressors and but

NOTE Confidence: 0.937386631428571

00:46:12.220 --> 00:46:14.565 right now this is the full lead.

NOTE Confidence: 0.937386631428571

00:46:14.570 --> 00:46:19.130 The one that's best characterized in the lab.

NOTE Confidence: 0.937386631428571

00:46:19.130 --> 00:46:22.378 So just a more global overall model

NOTE Confidence: 0.937386631428571

00:46:22.378 --> 00:46:25.306 shown here is am I to phagosome

NOTE Confidence: 0.937386631428571

00:46:25.306 --> 00:46:27.610 information that I showed you earlier.

NOTE Confidence: 0.937386631428571

00:46:27.610 --> 00:46:29.745 We had originally identified VPS

NOTE Confidence: 0.937386631428571

00:46:29.745 --> 00:46:32.650 13D and we're thinking about it as

NOTE Confidence: 0.937386631428571

00:46:32.650 --> 00:46:34.750 a tough guy cargo receptor that

NOTE Confidence: 0.937386631428571

00:46:34.750 --> 00:46:36.552 might bridge between ubiquitinated

NOTE Confidence: 0.937386631428571

00:46:36.552 --> 00:46:39.648 proteins on mitochondria and and and.

NOTE Confidence: 0.937386631428571

00:46:39.650 --> 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 --> 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 --> 00:46:54.052 Miss 13 today seems to be acting

NOTE Confidence: 0.937386631428571

00:46:54.052 --> 00:46:55.658 more earlier than than at this.

NOTE Confidence: 0.937386631428571

00:46:55.660 --> 00:46:58.528 This phase that have been defined

NOTE Confidence: 0.937386631428571

00:46:58.528 --> 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 --> 00:47:05.629 affecting the the fission pathway.

NOTE Confidence: 0.937386631428571

00:47:05.630 --> 00:47:08.912 And if it is affecting vision

NOTE Confidence: 0.937386631428571

00:47:08.912 --> 00:47:10.006 of mitochondria.

NOTE Confidence: 0.937386631428571

00:47:10.010 --> 00:47:12.740 Our data suggests that this is

NOTE Confidence: 0.937386631428571

00:47:12.740 --> 00:47:15.109 downstream of of activities of Dr.

NOTE Confidence: 0.937386631428571

00:47:15.110 --> 00:47:16.238 P1 and MFF.

NOTE Confidence: 0.730454781875

00:47:18.500 --> 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 --> 00:47:25.108 or at least is influencing VPF

NOTE Confidence: 0.730454781875

00:47:25.108 --> 00:47:27.310 13 deactivity in some way.

NOTE Confidence: 0.730454781875

00:47:27.310 --> 00:47:31.038 And we have also and it's a very

NOTE Confidence: 0.730454781875

00:47:31.038 --> 00:47:32.831 interesting relationship between the

NOTE Confidence: 0.730454781875

00:47:32.831 --> 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 --> 00:47:42.767 by thanking the people that really

NOTE Confidence: 0.730454781875

00:47:42.767 --> 00:47:44.787 contributed to this study I

NOTE Confidence: 0.730454781875

00:47:44.787 --> 00:47:47.120 mentioned at the beginning of the

NOTE Confidence: 0.730454781875

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

NOTE Confidence: 0.730454781875

00:47:49.300 --> 00:47:50.280 the work that I showed you was,

NOTE Confidence: 0.730454781875

00:47:50.280 --> 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 --> 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 --> 00:48:07.970 This is actually an incomplete list.

NOTE Confidence: 0.730454781875

00:48:07.970 --> 00:48:10.350 These are the people that were involved

NOTE Confidence: 0.730454781875

00:48:10.350 --> 00:48:12.947 in the studies that I showed you today.

NOTE Confidence: 0.730454781875

00:48:12.950 --> 00:48:15.116 And with that I'm happy to

NOTE Confidence: 0.730454781875

00:48:15.116 --> 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 --> 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 --> 00:48:30.255 so why don't we start with why?

NOTE Confidence: 0.589322213333333

00:48:32.910 --> 00:48:35.730 Eric, this is ahoy from Physiology.

NOTE Confidence: 0.589322213333333

00:48:35.730 --> 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 --> 00:48:41.219 that when you mentioned.

NOTE Confidence: 0.589322213333333

00:48:41.220 --> 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 --> 00:48:49.340 mythological change actually functional.

NOTE Confidence: 0.589322213333333

00:48:49.340 --> 00:48:51.458 Can you expand a little bit

NOTE Confidence: 0.589322213333333

00:48:51.458 --> 00:48:52.870 on that part please?

NOTE Confidence: 0.589322213333333

00:48:52.870 --> 00:48:54.742 On the functionality, well,

NOTE Confidence: 0.589322213333333

00:48:54.742 --> 00:48:57.516 so I'll tell you mostly negative data I

NOTE Confidence: 0.589322213333333

00:48:57.516 --> 00:48:59.510 guess is the way you would interpret it.

NOTE Confidence: 0.589322213333333

00:48:59.510 --> 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 --> 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 --> 00:49:09.815 an expert on mitochondrial function,

NOTE Confidence: 0.589322213333333

00:49:09.820 --> 00:49:12.244 so we you know had a drink

NOTE Confidence: 0.589322213333333

00:49:12.244 --> 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 --> 00:49:20.632 we've run these cells through seahorse

NOTE Confidence: 0.589322213333333

00:49:20.632 --> 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 --> 00:49:26.549 you know they they don't they.

NOTE Confidence: 0.589322213333333

00:49:26.550 --> 00:49:28.071 We don't really.

NOTE Confidence: 0.589322213333333

00:49:28.071 --> 00:49:30.099 Although their function is

NOTE Confidence: 0.589322213333333

00:49:30.099 --> 00:49:32.670 slightly altered by the typical.

NOTE Confidence: 0.589322213333333

00:49:32.670 --> 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 --> 00:49:39.895 We don't see any dramatic shifts in

NOTE Confidence: 0.589322213333333

00:49:39.895 --> 00:49:42.146 their ability to undergo respiration,

NOTE Confidence: 0.589322213333333

00:49:42.146 --> 00:49:43.090 for example,

NOTE Confidence: 0.589322213333333

00:49:43.090 --> 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 --> 00:49:53.379 these cells and but they appear that

NOTE Confidence: 0.589322213333333

00:49:53.379 --> 00:49:55.394 mitochondria seem to be functional.

NOTE Confidence: 0.872667167777778

00:49:57.850 --> 00:49:59.443 You know when you get a phenotype like this,

NOTE Confidence: 0.872667167777778

00:49:59.450 --> 00:50:00.935 there are many factors that

NOTE Confidence: 0.872667167777778

00:50:00.935 --> 00:50:02.400 contribute to it, including you

NOTE Confidence: 0.872667167777778

00:50:02.400 --> 00:50:04.110 know I alluded to fission fusion,

NOTE Confidence: 0.872667167777778

00:50:04.110 --> 00:50:06.242 but you could also have mitochondrial

NOTE Confidence: 0.872667167777778

00:50:06.242 --> 00:50:09.434 Biogenesis could contribute to it and.

NOTE Confidence: 0.928996654166667

00:50:11.470 --> 00:50:14.150 And all I can say is we haven't

NOTE Confidence: 0.928996654166667

00:50:14.150 --> 00:50:15.750 completed those analysis of,

NOTE Confidence: 0.928996654166667

00:50:15.750 --> 00:50:18.276 say by Genesis using mutations and

NOTE Confidence: 0.928996654166667

00:50:18.276 --> 00:50:21.508 say like GC alpha type of mutations.

NOTE Confidence: 0.928996654166667

00:50:21.510 --> 00:50:24.560 But our preliminary data suggested.

NOTE Confidence: 0.928996654166667

00:50:24.560 --> 00:50:27.500 That's not contributing.

NOTE Confidence: 0.928996654166667

00:50:27.500 --> 00:50:29.806 What I call my T cell.

NOTE Confidence: 0.928996654166667

00:50:29.806 --> 00:50:32.542 Yeah, interesting I I found this

NOTE Confidence: 0.928996654166667

00:50:32.542 --> 00:50:34.358 quite interesting that there

NOTE Confidence: 0.928996654166667

00:50:34.358 --> 00:50:36.869 appeared to be divergance that the

NOTE Confidence: 0.928996654166667

00:50:36.869 --> 00:50:39.486 mitochondria is not entirely for

NOTE Confidence: 0.928996654166667

00:50:39.486 --> 00:50:42.670 biogenics is do somehow trigger the

NOTE Confidence: 0.928996654166667

00:50:42.670 --> 00:50:44.450 self killing signal that require

NOTE Confidence: 0.791229168

00:50:44.460 --> 00:50:46.630 autophagy to eat it up. So

NOTE Confidence: 0.778893304

00:50:46.640 --> 00:50:48.016 there's some interesting aspects.

NOTE Confidence: 0.778893304

00:50:48.016 --> 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 --> 00:50:53.420 But we're going on to the next question.

NOTE Confidence: 0.778893304

00:50:53.420 --> 00:50:55.394 Say you know one one thing

NOTE Confidence: 0.778893304

00:50:55.394 --> 00:50:57.430 to consider is that you know.

NOTE Confidence: 0.778893304

00:50:57.430 --> 00:50:59.510 Metacrawler can also be signaling

NOTE Confidence: 0.778893304

00:50:59.510 --> 00:51:01.590 scaffolds or could influence other

NOTE Confidence: 0.778893304

00:51:01.652 --> 00:51:03.607 signaling scaffolds so you know,

NOTE Confidence: 0.778893304

00:51:03.610 --> 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 --> 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 --> 00:51:22.210 about the suppression by Matthews

NOTE Confidence: 0.599589576

00:51:22.210 --> 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 --> 00:51:33.120 suggest as suppresses everything. Uhm?

NOTE Confidence: 0.599589576

00:51:33.120 --> 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 --> 00:51:43.286 head what day do we have it it?

NOTE Confidence: 0.902848806923077

00:51:43.286 --> 00:51:45.618 It certainly suppresses the

NOTE Confidence: 0.902848806923077

00:51:45.618 --> 00:51:49.590 mitochondrial sides. Uhm? I.

NOTE Confidence: 0.828696285

00:51:51.730 --> 00:51:54.808 Yes, I I think it does.

NOTE Confidence: 0.828696285

00:51:54.810 --> 00:51:57.648 I don't think it actually is

NOTE Confidence: 0.828696285

00:51:57.648 --> 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 --> 00:52:09.518 I think the the cell size measurement.

NOTE Confidence: 0.828696285

00:52:09.518 --> 00:52:12.652 I think it's probably there are

NOTE Confidence: 0.828696285

00:52:12.652 --> 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 --> 00:52:19.624 and so it may be through, you know,

NOTE Confidence: 0.828696285

00:52:19.624 --> 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 --> 00:52:27.830 So there's something else.

NOTE Confidence: 0.828696285

00:52:27.830 --> 00:52:29.590 It's something beyond the

NOTE Confidence: 0.828696285

00:52:29.590 --> 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 --> 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 --> 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 --> 00:52:46.672 what do you think is behind

NOTE Confidence: 0.828696285

00:52:46.672 --> 00:52:48.740 the increase in cell size?

NOTE Confidence: 0.828696285

00:52:48.740 --> 00:52:50.420 Yeah, that's it.

NOTE Confidence: 0.828696285

00:52:50.420 --> 00:52:52.206 You know people are,

NOTE Confidence: 0.828696285

00:52:52.206 --> 00:52:54.204 especially when I first started talking

NOTE Confidence: 0.828696285

00:52:54.204 --> 00:52:56.025 about these phenotypes and that you

NOTE Confidence: 0.828696285

00:52:56.025 --> 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 --> 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 --> 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 --> 00:53:11.050 Maybe maybe it's about lipid redistribution.

NOTE Confidence: 0.828696285

00:53:11.050 --> 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 --> 00:53:20.149 the only way that what they said

NOTE Confidence: 0.828696285

00:53:20.149 --> 00:53:22.172 is the only way that you could

NOTE Confidence: 0.828696285

00:53:22.246 --> 00:53:24.318 make that big a change in cell

NOTE Confidence: 0.828696285

00:53:24.318 --> 00:53:27.090 size is through water plant.

NOTE Confidence: 0.828696285

00:53:27.090 --> 00:53:28.336 So they told me I should be

NOTE Confidence: 0.828696285

00:53:28.336 --> 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 --> 00:53:36.082 I think it's a fascinating biology and it's

NOTE Confidence: 0.863766652

00:53:36.082 --> 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 --> 00:53:46.770 Say that all of these

NOTE Confidence: 0.863766652

00:53:46.770 --> 00:53:47.790 things are interconnected.

NOTE Confidence: 0.863766652

00:53:47.790 --> 00:53:49.770 Some of the quick question,

NOTE Confidence: 0.863766652

00:53:49.770 --> 00:53:52.550 since you mentioned water possibility,

NOTE Confidence: 0.863766652

00:53:52.550 --> 00:53:53.756 just as welling.

NOTE Confidence: 0.863766652

00:53:53.756 --> 00:53:56.346 If you look at the marker,

NOTE Confidence: 0.863766652

00:53:56.346 --> 00:53:58.650 for example ER marker,

NOTE Confidence: 0.863766652

00:53:58.650 --> 00:54:01.169 do you see a more dispersed ER or

NOTE Confidence: 0.863766652

00:54:01.169 --> 00:54:04.790 do you see the same density there?

NOTE Confidence: 0.863766652

00:54:04.790 --> 00:54:07.540 Micro ceratitis beside the blast.

NOTE Confidence: 0.863766652

00:54:07.540 --> 00:54:10.460 Yeah so we we see so I should and I

NOTE Confidence: 0.863766652

00:54:10.549 --> 00:54:14.056 should have said this throughout the talk.

NOTE Confidence: 0.863766652

00:54:14.060 --> 00:54:17.090 Before the signal that activates

NOTE Confidence: 0.863766652

00:54:17.090 --> 00:54:18.908 the autophagy signal.

NOTE Confidence: 0.863766652

00:54:18.910 --> 00:54:20.870 In the different mutants that I've shown you,

NOTE Confidence: 0.863766652

00:54:20.870 --> 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 --> 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 --> 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 --> 00:54:35.110 starts to change dramatically.

NOTE Confidence: 0.863766652

00:54:35.110 --> 00:54:36.001 The mutant cells,

NOTE Confidence: 0.863766652

00:54:36.001 --> 00:54:38.080 most of them you know it depends

NOTE Confidence: 0.863766652

00:54:38.146 --> 00:54:40.169 on the mutant that I've shown you,

NOTE Confidence: 0.863766652

00:54:40.170 --> 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 --> 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 --> 00:54:52.058 but there are morphological.

NOTE Confidence: 0.863766652

00:54:52.060 --> 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 --> 00:55:00.190 Very dramatic yard changes taking place.

NOTE Confidence: 0.863766652

00:55:00.190 --> 00:55:03.930 And so I think a big part of the puzzle

NOTE Confidence: 0.863766652

00:55:04.034 --> 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 --> 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 --> 00:55:14.761 that the solution to our problem

NOTE Confidence: 0.863766652

00:55:14.761 --> 00:55:16.146 is coming from the ER,

NOTE Confidence: 0.863766652

00:55:16.150 --> 00:55:17.154 but it's my instinct.

NOTE Confidence: 0.863766652

00:55:17.154 --> 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 --> 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 --> 00:55:31.880 of a side project with EPS 13D.

NOTE Confidence: 0.48135173

00:55:31.880 --> 00:55:35.876 We have been very actively studying

NOTE Confidence: 0.48135173

00:55:35.880 --> 00:55:40.206 ER and in ER changes in themselves.

NOTE Confidence: 0.48135173

00:55:40.210 --> 00:55:44.830 And, and we're particularly interested in

NOTE Confidence: 0.48135173

00:55:44.830 --> 00:55:47.694 and this is something it's like my new

NOTE Confidence: 0.48135173

00:55:47.694 --> 00:55:50.240 seminar that I haven't quite prepared.

NOTE Confidence: 0.48135173

00:55:50.240 --> 00:55:52.592 We think this is also an excellent

NOTE Confidence: 0.48135173

00:55:52.592 --> 00:55:55.039 model for PR specific clearance.

NOTE Confidence: 0.48135173

00:55:55.040 --> 00:55:58.081 And so, and that's forthcoming,

NOTE Confidence: 0.48135173

00:55:58.081 --> 00:55:59.916 you know that's the that's.

NOTE Confidence: 0.48135173

00:55:59.920 --> 00:56:01.726 So there's one postdoc in my lab.

NOTE Confidence: 0.48135173

00:56:01.730 --> 00:56:05.188 It's very active working in that space.

NOTE Confidence: 0.48135173

00:56:05.190 --> 00:56:06.690 Thank you.

NOTE Confidence: 0.48135173

00:56:06.690 --> 00:56:10.338 So I'm interested in the tissue

NOTE Confidence: 0.48135173

00:56:10.338 --> 00:56:12.770 specificity in the disease.

NOTE Confidence: 0.48135173

00:56:12.770 --> 00:56:15.962 And I'm a little bit confused about the

NOTE Confidence: 0.48135173

00:56:15.962 --> 00:56:18.951 essay that you use or the the screen

NOTE Confidence: 0.48135173

00:56:18.951 --> 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 --> 00:56:28.226 he was showed lethality in those cell lines.

NOTE Confidence: 0.48135173

00:56:28.230 --> 00:56:29.502 Is that correct?

NOTE Confidence: 0.48135173

00:56:29.502 --> 00:56:29.926 Yes.

NOTE Confidence: 0.48135173

00:56:29.926 --> 00:56:31.334 Well, so so,

NOTE Confidence: 0.48135173

00:56:31.334 --> 00:56:33.794 the initial papers that were

NOTE Confidence: 0.48135173

00:56:33.794 --> 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 --> 00:56:40.746 They're both published in science.

NOTE Confidence: 0.48135173

00:56:40.750 --> 00:56:43.536 One from the Nki in the Netherlands

NOTE Confidence: 0.48135173

00:56:43.536 --> 00:56:46.440 and one from the Broad Broad

NOTE Confidence: 0.48135173

00:56:46.440 --> 00:56:48.720 Whitehead into collaboration from

NOTE Confidence: 0.48135173

00:56:48.720 --> 00:56:51.789 the Zhang and Sabatini Labs.

NOTE Confidence: 0.48135173

00:56:51.790 --> 00:56:53.674 When they published their list of

NOTE Confidence: 0.48135173

00:56:53.674 --> 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 --> 00:56:58.826 you know.

NOTE Confidence: 0.48135173

00:56:58.826 --> 00:57:01.190 So he lo is excluded but but you

NOTE Confidence: 0.48135173

00:57:01.190 --> 00:57:02.390 can get those cell lines.

NOTE Confidence: 0.48135173

00:57:02.390 --> 00:57:04.525 Their VPS 13D was among the most

NOTE Confidence: 0.48135173

00:57:04.525 --> 00:57:07.167 is I think it was one of the top

NOTE Confidence: 0.48135173

00:57:07.167 --> 00:57:09.129 ten jeans for for viability of

NOTE Confidence: 0.48135173

00:57:09.129 --> 00:57:11.469 those cells as they increase the

NOTE Confidence: 0.48135173

00:57:11.469 --> 00:57:13.744 number of cells so that I think I

NOTE Confidence: 0.48135173

00:57:13.744 --> 00:57:15.292 remember the statistic I showed you

NOTE Confidence: 0.48135173

00:57:15.292 --> 00:57:17.028 at that point we made the graph.

NOTE Confidence: 0.48135173

00:57:17.030 --> 00:57:19.820 I think it was over 300 cell lines that

NOTE Confidence: 0.48135173

00:57:19.820 --> 00:57:22.809 had been analyzed for gene essentiality.

NOTE Confidence: 0.48135173

00:57:22.810 --> 00:57:24.410 The significance of the PS13

NOTE Confidence: 0.48135173

00:57:24.410 --> 00:57:26.010 on down some but again,

NOTE Confidence: 0.48135173

00:57:26.010 --> 00:57:27.380 we're looking at transform cells.

NOTE Confidence: 0.48135173

00:57:27.380 --> 00:57:29.144 And I showed you data from yela.

NOTE Confidence: 0.48135173

00:57:29.150 --> 00:57:30.590 We were lucky we started in.

NOTE Confidence: 0.48135173

00:57:30.590 --> 00:57:32.378 He LA for mammalian cells because

NOTE Confidence: 0.48135173

00:57:32.378 --> 00:57:34.637 one of the few cell lines where

NOTE Confidence: 0.48135173

00:57:34.637 --> 00:57:36.629 they seem to be perfectly fine.

NOTE Confidence: 0.48135173

00:57:36.630 --> 00:57:38.758 Without VPS 13th day.

NOTE Confidence: 0.48135173

00:57:38.758 --> 00:57:42.450 It is remarkable that the phenotype is

NOTE Confidence: 0.48135173

00:57:42.450 --> 00:57:44.520 so limited to the OR maybe it's not,

NOTE Confidence: 0.48135173

00:57:44.520 --> 00:57:46.356 but it's from what you describe

NOTE Confidence: 0.48135173

00:57:46.356 --> 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 --> 00:57:54.314 but that I think that's also a little

NOTE Confidence: 0.48135173

00:57:54.314 --> 00:57:56.723 bit complicated by the fact that you

NOTE Confidence: 0.48135173

00:57:56.723 --> 00:57:58.745 know the patient alleles must be

NOTE Confidence: 0.48135173

00:57:58.745 --> 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 --> 00:58:05.673 which to me is a bit of a misnomer.

NOTE Confidence: 0.48135173

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 --> 00:58:09.390 experiments breeding humans.

NOTE Confidence: 0.48135173

00:58:09.390 --> 00:58:11.856 But but it's a little bit of an insight.

NOTE Confidence: 0.48135173

00:58:11.860 --> 00:58:15.070 Genesis Joe B.

NOTE Confidence: 0.48135173

00:58:15.070 --> 00:58:17.500 You know the Margit Burmeister

NOTE Confidence: 0.48135173

00:58:17.500 --> 00:58:19.444 who identified these mutations,

NOTE Confidence: 0.48135173

00:58:19.450 --> 00:58:20.548 the original mutations,

NOTE Confidence: 0.48135173

00:58:20.548 --> 00:58:22.744 she said that the original family

NOTE Confidence: 0.48135173

00:58:22.744 --> 00:58:24.585 that they studied those are

NOTE Confidence: 0.48135173

00:58:24.585 --> 00:58:26.355 probably much weaker alleles based

NOTE Confidence: 0.48135173

00:58:26.355 --> 00:58:28.864 on where they are in the VPS 13D

NOTE Confidence: 0.48135173

00:58:28.864 --> 00:58:30.999 sequence compared to the pediatric

NOTE Confidence: 0.48135173

00:58:30.999 --> 00:58:33.489 alleles that have been identified.

NOTE Confidence: 0.48135173

00:58:33.490 --> 00:58:35.560 But none of them are probably

NOTE Confidence: 0.48135173

00:58:35.560 --> 00:58:37.985 true nuts and and so they have

NOTE Confidence: 0.48135173

00:58:37.985 --> 00:58:40.246 to be by necessity in our mouse

NOTE Confidence: 0.846710823478261

00:58:40.321 --> 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 --> 00:58:46.492 probably there's complexity in the

NOTE Confidence: 0.846710823478261

00:58:46.492 --> 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 --> 00:58:54.004 do they have more widespread

NOTE Confidence: 0.846710823478261

00:58:54.004 --> 00:58:56.170 phenotypes beyond the nervous system?

NOTE Confidence: 0.91425672

00:58:59.970 --> 00:59:01.438 That's a great question.

NOTE Confidence: 0.941979891111111

00:59:04.580 --> 00:59:07.667 I I, I'll have to say I don't know,

NOTE Confidence: 0.941979891111111

00:59:07.670 --> 00:59:12.540 but as far as I know no OK.

NOTE Confidence: 0.941979891111111

00:59:12.540 --> 00:59:15.452 As far as I know they don't, but actually

NOTE Confidence: 0.941979891111111

00:59:15.452 --> 00:59:19.204 that's a great question and I will.

NOTE Confidence: 0.941979891111111

00:59:19.210 --> 00:59:22.468 Aye. Yeah, So what I can address.

NOTE Confidence: 0.941979891111111

00:59:22.470 --> 00:59:24.654 Let me say this to try

NOTE Confidence: 0.941979891111111

00:59:24.654 --> 00:59:26.110 to address your question.

NOTE Confidence: 0.941979891111111

00:59:26.110 --> 00:59:29.140 There's a very interactive family in

NOTE Confidence: 0.941979891111111

00:59:29.140 --> 00:59:32.950 Australia and and their son was diagnosed.

NOTE Confidence: 0.941979891111111

00:59:32.950 --> 00:59:34.889 I think at the age of 15,

NOTE Confidence: 0.941979891111111

00:59:34.890 --> 00:59:36.924 so it's not one of these very strong cases,

NOTE Confidence: 0.941979891111111

00:59:36.930 --> 00:59:40.042 but he's stronger than the than the the

NOTE Confidence: 0.941979891111111

00:59:40.042 --> 00:59:42.240 Burmeister alleles that I talked about.

NOTE Confidence: 0.941979891111111

00:59:42.240 --> 00:59:47.960 And. He is normal other than

NOTE Confidence: 0.941979891111111

00:59:47.960 --> 00:59:49.934 some movement difficult.

NOTE Confidence: 0.941979891111111

00:59:49.940 --> 00:59:50.700 In fact, he's a.

NOTE Confidence: 0.941979891111111

00:59:50.700 --> 00:59:53.114 He's a, you know, a plus student and

NOTE Confidence: 0.941979891111111

00:59:53.114 --> 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: 0.941979891111111

00:59:57.878 --> 01:00:01.179 than the than the initial patient population,

NOTE Confidence: 0.941979891111111

01:00:01.180 --> 01:00:02.670 but still doesn't have any.

NOTE Confidence: 0.941979891111111

01:00:02.670 --> 01:00:05.256 I'm not part of any immune

NOTE Confidence: 0.941979891111111

01:00:05.256 --> 01:00:07.236 misregulation or any other thing,

NOTE Confidence: 0.941979891111111

01:00:07.236 --> 01:00:09.840 but I think probably these pediatric cases

NOTE Confidence: 0.941979891111111

01:00:09.903 --> 01:00:12.735 which there aren't a huge number of examples,

NOTE Confidence: 0.941979891111111

01:00:12.740 --> 01:00:14.855 but there are a couple and and and some

NOTE Confidence: 0.941979891111111

01:00:14.855 --> 01:00:16.830 of those families are quite interactive.

NOTE Confidence: 0.941979891111111

01:00:16.830 --> 01:00:19.140 They we might be able to find

NOTE Confidence: 0.941979891111111

01:00:19.140 --> 01:00:20.969 out some more information.

NOTE Confidence: 0.941979891111111

01:00:20.970 --> 01:00:25.116 Thank you. Thank you, motivated me.

NOTE Confidence: 0.941979891111111

01:00:25.120 --> 01:00:26.976 Edit just to clarify, what did you say?

NOTE Confidence: 0.941979891111111

01:00:26.980 --> 01:00:28.108 The family in Australia?

NOTE Confidence: 0.941979891111111

01:00:28.108 --> 01:00:30.580 What is the only symptom has only the

NOTE Confidence: 0.941979891111111

01:00:30.580 --> 01:00:33.460 clinical it's same, it's it's a, it's it's a.

NOTE Confidence: 0.941979891111111

01:00:33.460 --> 01:00:34.540 It's an attacks.

NOTE Confidence: 0.941979891111111

01:00:34.540 --> 01:00:37.915 Yeah it's a it's a loss of motor control

NOTE Confidence: 0.941979891111111

01:00:37.915 --> 01:00:40.886 it's started with gate difficulty but

NOTE Confidence: 0.941979891111111

01:00:40.886 --> 01:00:43.464 from talking to Margaret who talks

NOTE Confidence: 0.941979891111111

01:00:43.464 --> 01:00:45.970 more with these families than I do.

NOTE Confidence: 0.941979891111111

01:00:45.970 --> 01:00:49.040 Uhm? She said that you know,

NOTE Confidence: 0.941979891111111

01:00:49.040 --> 01:00:52.226 she thinks the initial problem that

NOTE Confidence: 0.941979891111111

01:00:52.226 --> 01:00:55.894 these individuals face is this, you know,

NOTE Confidence: 0.941979891111111

01:00:55.894 --> 01:00:58.429 reading. And tracking you know?

NOTE Confidence: 0.941979891111111

01:00:58.430 --> 01:01:00.728 So visual tracking she thinks might

NOTE Confidence: 0.941979891111111

01:01:00.728 --> 01:01:02.260 be the earliest phenotype.

NOTE Confidence: 0.941979891111111

01:01:02.260 --> 01:01:03.870 So things like you know,

NOTE Confidence: 0.941979891111111

01:01:03.870 --> 01:01:05.586 in America that might be catching

NOTE Confidence: 0.941979891111111

01:01:05.586 --> 01:01:07.520 a football and in Australia might

NOTE Confidence: 0.941979891111111

01:01:07.520 --> 01:01:09.710 be failing to catch an Australian

NOTE Confidence: 0.941979891111111

01:01:09.710 --> 01:01:10.440 rules football.

NOTE Confidence: 0.912938137692308

01:01:12.930 --> 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 --> 01:01:18.512 reading text on a line of a book

NOTE Confidence: 0.912938137692308

01:01:18.512 --> 01:01:20.448 is one of the most common first.

NOTE Confidence: 0.912938137692308

01:01:20.450 --> 01:01:22.130 Symptoms that these individuals

NOTE Confidence: 0.912938137692308

01:01:22.130 --> 01:01:24.650 all seem to have in common,

NOTE Confidence: 0.912938137692308

01:01:24.650 --> 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 --> 01:01:37.886 and I'm obviously not a neurologist

NOTE Confidence: 0.93070247

01:01:37.886 --> 01:01:40.560 pietros more of a neurologist than I am,

NOTE Confidence: 0.93070247

01:01:40.560 --> 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 --> 01:01:47.569 be really great to get and

NOTE Confidence: 0.93070247

01:01:47.569 --> 01:01:48.739 there is actually a you know,

NOTE Confidence: 0.93070247

01:01:48.740 --> 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 --> 01:01:54.250 there's a forum that meets

NOTE Confidence: 0.93070247

01:01:54.250 --> 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 --> 01:02:00.685 so that would be a great place

NOTE Confidence: 0.93070247

01:02:00.685 --> 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 --> 01:02:15.470 if I got this correctly.

NOTE Confidence: 0.971788674

01:02:15.470 --> 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 --> 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 --> 01:02:25.620 the mutation or when you have the

NOTE Confidence: 0.971788674

01:02:25.677 --> 01:02:27.838 loss of function you have increased

NOTE Confidence: 0.971788674

01:02:27.840 --> 01:02:30.584 my to ER context which we know

NOTE Confidence: 0.971788674

01:02:30.584 --> 01:02:34.885 has to do with vision and we have

NOTE Confidence: 0.971788674

01:02:34.885 --> 01:02:36.905 increased size of mitochondria.

NOTE Confidence: 0.971788674

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 --> 01:02:46.886 It's a. It's a great question

NOTE Confidence: 0.809338853333333

01:02:46.886 --> 01:02:49.190 that is a conundrum and I.

NOTE Confidence: 0.809338853333333

01:02:49.190 --> 01:02:49.823 I'm not really.

NOTE Confidence: 0.809338853333333

01:02:49.823 --> 01:02:51.490 I don't have a great answer to it.

NOTE Confidence: 0.809338853333333

01:02:51.490 --> 01:02:55.280 I'll start and so I'll have to ramble a bit.

NOTE Confidence: 0.809338853333333

01:02:55.280 --> 01:02:57.290 So the one the one connection

NOTE Confidence: 0.809338853333333

01:02:57.290 --> 01:02:58.295 the one connection,

NOTE Confidence: 0.809338853333333

01:02:58.300 --> 01:03:00.668 is it your everything you stated is correct

NOTE Confidence: 0.809338853333333

01:03:00.668 --> 01:03:03.237 way the field reads is that mitochondria,

NOTE Confidence: 0.809338853333333

01:03:03.240 --> 01:03:05.880 ER contacts lead to increased vision.

NOTE Confidence: 0.809338853333333

01:03:05.880 --> 01:03:08.034 Let's go bolts and many great

NOTE Confidence: 0.809338853333333

01:03:08.034 --> 01:03:10.389 scientists are doing this kind of work.

NOTE Confidence: 0.861749197142857

01:03:13.170 --> 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 --> 01:03:18.830 and it's fantastic scientist.

NOTE Confidence: 0.861749197142857

01:03:18.830 --> 01:03:21.526 And she said that she believes

NOTE Confidence: 0.861749197142857

01:03:21.526 --> 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 --> 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 --> 01:03:32.130 and so even though we see

NOTE Confidence: 0.861749197142857

01:03:32.207 --> 01:03:34.417 greater proximity and you know,

NOTE Confidence: 0.861749197142857

01:03:34.420 --> 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 --> 01:03:40.050 he's as he's more of an expert

NOTE Confidence: 0.861749197142857

01:03:40.050 --> 01:03:41.710 in this space than I am.

NOTE Confidence: 0.861749197142857

01:03:41.710 --> 01:03:43.630 But Jody implied that.

NOTE Confidence: 0.861749197142857

01:03:43.630 --> 01:03:46.030 The quality of these contacts

NOTE Confidence: 0.861749197142857

01:03:46.030 --> 01:03:49.635 is a big part of what drives

NOTE Confidence: 0.861749197142857

01:03:49.635 --> 01:03:51.150 the mitochondrial changes.

NOTE Confidence: 0.861749197142857

01:03:51.150 --> 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 --> 01:03:58.046 but she had presented this in

NOTE Confidence: 0.861749197142857

01:03:58.046 --> 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 --> 01:04:05.930 mitochondrial DNA replication.

NOTE Confidence: 0.861749197142857

01:04:05.930 --> 01:04:08.926 And so I'm fascinated by this concept

NOTE Confidence: 0.861749197142857

01:04:08.926 --> 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 --> 01:04:18.256 So maybe more is not better.

NOTE Confidence: 0.861749197142857

01:04:18.260 --> 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 --> 01:04:27.655 in the logic and it's it's something.

NOTE Confidence: 0.861749197142857

01:04:27.660 --> 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 --> 01:04:31.680 you're probably on to something.

NOTE Confidence: 0.90923877

01:04:31.680 --> 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 --> 01:04:37.363 in other places where the singling

NOTE Confidence: 0.90923877

01:04:37.363 --> 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 --> 01:04:43.970 so it probably does have a lot

NOTE Confidence: 0.90923877

01:04:43.970 --> 01:04:45.683 to do with the quality of the

NOTE Confidence: 0.90923877

01:04:45.683 --> 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 --> 01:04:50.650 positive or negative singles that

NOTE Confidence: 0.90923877

01:04:50.709 --> 01:04:52.299 are missing from that contact.

NOTE Confidence: 0.791899720909091

01:04:52.370 --> 01:04:53.198 Yeah, so I don't.

NOTE Confidence: 0.791899720909091

01:04:53.198 --> 01:04:54.870 I don't want to be protein centric,

NOTE Confidence: 0.791899720909091

01:04:54.870 --> 01:04:56.898 but maybe you know it takes

NOTE Confidence: 0.791899720909091

01:04:56.898 --> 01:04:58.679 something to assemble the right

NOTE Confidence: 0.791899720909091

01:04:58.679 --> 01:05:00.872 group of proteins to activate the

NOTE Confidence: 0.791899720909091

01:05:00.872 --> 01:05:03.420 right set of events and maybe the

NOTE Confidence: 0.791899720909091

01:05:03.502 --> 01:05:06.106 activation of in in some sub domain

NOTE Confidence: 0.791899720909091

01:05:06.106 --> 01:05:09.522 then leads to some change in other

NOTE Confidence: 0.791899720909091

01:05:09.522 --> 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 --> 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 --> 01:05:18.718 talk and thank you for coming

NOTE Confidence: 0.940390470909091

01:05:18.718 --> 01:05:20.400 to deliver a grand rounds today.

NOTE Confidence: 0.940390470909091

01:05:20.400 --> 01:05:22.122 We're bid after the hour and I

NOTE Confidence: 0.940390470909091

01:05:22.122 --> 01:05:23.774 think people are heading on to

NOTE Confidence: 0.940390470909091

01:05:23.774 --> 01:05:25.560 their next meeting, so again,

NOTE Confidence: 0.824668408

01:05:25.570 --> 01:05:27.760 understandably thank you very much,

NOTE Confidence: 0.824668408

01:05:27.760 --> 01:05:30.315 Sam, and thanks to all the people

NOTE Confidence: 0.824668408

01:05:30.315 --> 01:05:32.547 that came and also the people

NOTE Confidence: 0.824668408

01:05:32.547 --> 01:05:34.997 who I met with was my choice.

NOTE Confidence: 0.824668408

01:05:35.000 --> 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 --> 01:05:55.786 My pleasure, my pleasure.

NOTE Confidence: 0.891686697777778

01:05:55.786 --> 01:05:58.446 I hope it was clear as always,

NOTE Confidence: 0.891686697777778

01:05:58.446 --> 01:06:00.118 thank you very much.

NOTE Confidence: 0.891686697777778

01:06:00.120 --> 01:06:01.976 Thank you Sir and have a good day.

NOTE Confidence: 0.891686697777778

01:06:01.980 --> 01:06:03.230 I appreciate all you did.