WEBVTT

NOTE duration: ”00:22:16.021”

NOTE Confidence: 0.8365429

00:00:00.080 --> 00:00:00.980 Pietro de Chamele,

NOTE Confidence: 0.98039114

00:00:02.480 --> 00:00:03.919 is a real titan of

NOTE Confidence: 0.98039114

00:00:03.919 --> 00:00:05.140 science, and

NOTE Confidence: 0.99527735

00:00:05.600 --> 00:00:06.720 it's such a pleasure to

NOTE Confidence: 0.99527735

00:00:06.720 --> 00:00:07.379 be able

NOTE Confidence: 0.9992821

00:00:07.919 --> 00:00:09.300 to interact and talk

NOTE Confidence: 0.99500203

00:00:09.679 --> 00:00:10.580 to you, Pietro.

NOTE Confidence: 0.9938021

00:00:11.200 --> 00:00:11.700 Pietro,

NOTE Confidence: 0.7758934

00:00:12.960 --> 00:00:14.340 actually was the

NOTE Confidence: 0.98231727

00:00:14.905 --> 00:00:16.364 the the chief of

NOTE Confidence: 0.96148777

00:00:16.825 --> 00:00:18.445 the department of cell biology

NOTE Confidence: 0.97945315

00:00:18.904 --> 00:00:20.345 and the chief of the

NOTE Confidence: 0.97945315

00:00:20.345 --> 00:00:22.345 department of neuroscience, the director

NOTE Confidence: 0.97945315

00:00:22.345 --> 00:00:23.564 of the Kavli Institute.

NOTE Confidence: 0.88989276

00:00:24.105 --> 00:00:26.445 He's also Howard Hughes investigator

NOTE Confidence: 0.98613596

00:00:27.224 --> 00:00:29.224 and a real legend in

NOTE Confidence: 0.98613596

00:00:29.224 --> 00:00:30.920 the field, and it's just

NOTE Confidence: 0.98613596

00:00:30.920 --> 00:00:32.440 a pleasure to to have

NOTE Confidence: 0.98613596

00:00:32.440 --> 00:00:33.820 you here. Thank you.

NOTE Confidence: 0.96596825

00:00:49.305 --> 00:00:50.045 Thank you,

NOTE Confidence: 0.98251706

00:00:51.145 --> 00:00:52.425 Clement, for your very nice

NOTE Confidence: 0.98251706

00:00:52.425 --> 00:00:52.925 introduction

NOTE Confidence: 0.9940732

00:00:53.225 --> 00:00:54.665 and for inviting me to

NOTE Confidence: 0.9940732

00:00:54.665 --> 00:00:55.405 this workshop.

NOTE Confidence: 0.9202959

00:00:57.320 --> 00:00:59.880 So, extensive genetic studies had

NOTE Confidence: 0.9202959

00:00:59.880 --> 00:01:02.140 identified more than twenty genes,

NOTE Confidence: 0.92470413

00:01:02.520 --> 00:01:04.520 which are responsible for familiar

NOTE Confidence: 0.92470413

00:01:04.520 --> 00:01:06.280 form of Parkinson's disease and

NOTE Confidence: 0.92470413

00:01:06.280 --> 00:01:07.340 many more genes

NOTE Confidence: 0.82922363

00:01:07.880 --> 00:01:08.860 would increase

NOTE Confidence: 0.9146273

00:01:09.160 --> 00:01:10.774 disease risk. And a key

NOTE Confidence: 0.9146273

00:01:10.774 --> 00:01:11.895 goal is to bridge the

NOTE Confidence: 0.9146273

00:01:11.895 --> 00:01:12.795 gap between

NOTE Confidence: 0.84054494

00:01:13.255 --> 00:01:15.494 genetics and disease mechanisms toward

NOTE Confidence: 0.84054494

00:01:15.494 --> 00:01:15.994 therapy.

NOTE Confidence: 0.9660403

00:01:16.774 --> 00:01:18.454 Really, an important goal is

NOTE Confidence: 0.9660403

00:01:18.454 --> 00:01:19.274 to identify

NOTE Confidence: 0.9434642

00:01:19.575 --> 00:01:20.774 the function of all these

NOTE Confidence: 0.9434642

00:01:20.774 --> 00:01:21.274 genes,

NOTE Confidence: 0.8935077

00:01:21.655 --> 00:01:23.435 and in particular, to understand

NOTE Confidence: 0.8935077

00:01:23.575 --> 00:01:25.260 whether the different genes lead

NOTE Confidence: 0.8935077

00:01:25.260 --> 00:01:26.959 to disease through different mechanisms

NOTE Confidence: 0.91298413

00:01:27.420 --> 00:01:28.459 or at least in part

NOTE Confidence: 0.91298413

00:01:28.459 --> 00:01:30.140 by converging on the same

NOTE Confidence: 0.91298413

00:01:30.140 --> 00:01:30.640 pathway.

NOTE Confidence: 0.9159726

00:01:31.020 --> 00:01:31.980 Because if this was the

NOTE Confidence: 0.9159726

00:01:31.980 --> 00:01:33.600 case as indicated here,

NOTE Confidence: 0.99196327

00:01:33.900 --> 00:01:36.000 therapeutic approaches to target

NOTE Confidence: 0.6761176

00:01:36.540 --> 00:01:37.760 a process downstream

NOTE Confidence: 0.9536512

00:01:38.459 --> 00:01:39.600 at the point of convergence

NOTE Confidence: 0.9536512

00:01:39.660 --> 00:01:40.400 of the gene

NOTE Confidence: 0.9942111

00:01:40.715 --> 00:01:42.795 would allow to use a

NOTE Confidence: 0.9942111

00:01:42.795 --> 00:01:43.694 single genetic

NOTE Confidence: 0.9995203

00:01:44.155 --> 00:01:44.655 strategy

NOTE Confidence: 0.9992484

00:01:45.194 --> 00:01:45.855 to cure

NOTE Confidence: 0.87497044

00:01:46.475 --> 00:01:46.975 Parkinson's

NOTE Confidence: 0.966792

00:01:47.275 --> 00:01:49.055 dependent on different genes.

NOTE Confidence: 0.9900397

00:01:49.835 --> 00:01:50.335 So,

NOTE Confidence: 0.9335142

00:01:52.155 --> 00:01:54.155 to address this question, we

NOTE Confidence: 0.9335142

00:01:54.155 --> 00:01:55.055 need cell biology.

NOTE Confidence: 0.95857453

00:01:56.159 --> 00:01:57.920 The understanding of disease mechanism

NOTE Confidence: 0.95857453

00:01:57.920 --> 00:01:59.119 is a key premise to

NOTE Confidence: 0.95857453

00:01:59.119 --> 00:02:01.860 precision medicine and precision neurology.

NOTE Confidence: 0.9536288

00:02:04.479 --> 00:02:06.020 This slide lists

NOTE Confidence: 0.9233032

00:02:07.439 --> 00:02:09.120 the more than twenty genes

NOTE Confidence: 0.9233032

00:02:09.120 --> 00:02:11.425 that cause Parkinson's disease. Actually,

NOTE Confidence: 0.9233032

00:02:11.425 --> 00:02:12.385 this list is now a

NOTE Confidence: 0.9233032

00:02:12.385 --> 00:02:13.365 little bit longer.

NOTE Confidence: 0.9848523

00:02:13.825 --> 00:02:14.885 And if you analyze

NOTE Confidence: 0.83829194

00:02:15.745 --> 00:02:17.585 the cutative or non function

NOTE Confidence: 0.83829194

00:02:17.585 --> 00:02:18.405 of the gene,

NOTE Confidence: 0.9934341

00:02:18.705 --> 00:02:19.205 three

NOTE Confidence: 0.9130621

00:02:19.665 --> 00:02:20.805 functions emerge:

NOTE Confidence: 0.8324046

00:02:21.345 --> 00:02:21.845 Mitochondrial

NOTE Confidence: 0.88665074

00:02:22.145 --> 00:02:23.365 function, endolysisomal

NOTE Confidence: 0.97236574

00:02:23.825 --> 00:02:24.325 system,

NOTE Confidence: 0.996547

00:02:25.040 --> 00:02:26.340 and synaptic transmission.

NOTE Confidence: 0.83254087

00:02:27.280 --> 00:02:28.240 As some of the gene

NOTE Confidence: 0.83254087

00:02:28.240 --> 00:02:29.220 are at the core

NOTE Confidence: 0.7627522

00:02:29.520 --> 00:02:29.840 of,

NOTE Confidence: 0.91881657

00:02:30.560 --> 00:02:32.020 projects from my own lab,

NOTE Confidence: 0.91881657

00:02:32.080 --> 00:02:33.200 from my career, I have

NOTE Confidence: 0.91881657

00:02:33.200 --> 00:02:34.960 been interested in membrane dynamics

NOTE Confidence: 0.91881657

00:02:34.960 --> 00:02:36.580 and membrane traffic in neurons.

NOTE Confidence: 0.95812726

00:02:36.935 --> 00:02:38.055 Some of these proteins are

NOTE Confidence: 0.95812726

00:02:38.055 --> 00:02:39.514 important in these processes,

NOTE Confidence: 0.89089656

00:02:39.894 --> 00:02:40.875 so I thought

NOTE Confidence: 0.9690536

00:02:41.254 --> 00:02:43.095 to exploit my expertise in

NOTE Confidence: 0.9690536

00:02:43.095 --> 00:02:45.034 cell biology to help learning

NOTE Confidence: 0.8165684

00:02:45.415 --> 00:02:47.275 about Parkinson's. And in particular,

NOTE Confidence: 0.8165684

00:02:47.495 --> 00:02:48.155 I focused

NOTE Confidence: 0.9428983

00:02:48.455 --> 00:02:49.514 on two genes,

NOTE Confidence: 0.8753533

00:02:50.135 --> 00:02:50.635 synaptogenin

NOTE Confidence: 0.6868228

00:02:51.095 --> 00:02:51.595 one

NOTE Confidence: 0.88695157

00:02:51.950 --> 00:02:53.090 and VP13C.

NOTE Confidence: 0.90728796

00:02:54.990 --> 00:02:55.490 Synaptogenin

NOTE Confidence: 0.94730985

00:02:55.870 --> 00:02:57.230 one is a gene that

NOTE Confidence: 0.94730985

00:02:57.230 --> 00:02:58.910 we identified many years ago.

NOTE Confidence: 0.94730985

00:02:58.910 --> 00:03:00.210 It is a gene implicated

NOTE Confidence: 0.94730985

00:03:00.430 --> 00:03:02.430 in synaptic transmission, particularly in

NOTE Confidence: 0.94730985

00:03:02.430 --> 00:03:03.889 synaptic vesicle recycling.

NOTE Confidence: 0.897246

00:03:04.750 --> 00:03:05.250 Interestingly,

NOTE Confidence: 0.84937304

00:03:05.710 --> 00:03:07.330 it is a functional part

NOTE Confidence: 0.86980057

00:03:08.055 --> 00:03:08.635 of DnaJ6,

NOTE Confidence: 0.91365594

00:03:09.014 --> 00:03:10.455 also called auxilin, that was

NOTE Confidence: 0.91365594

00:03:10.455 --> 00:03:12.135 mentioned before in the talk

NOTE Confidence: 0.91365594

00:03:12.135 --> 00:03:12.875 of circular,

NOTE Confidence: 0.57338166

00:03:14.694 --> 00:03:15.355 the MRNAs.

NOTE Confidence: 0.9544859

00:03:17.175 --> 00:03:19.194 We have generated a model

NOTE Confidence: 0.94037884

00:03:19.495 --> 00:03:21.175 of this Parkinson's disease. We

NOTE Confidence: 0.94037884

00:03:21.175 --> 00:03:22.875 put the mutation in mice.

NOTE Confidence: 0.94037884

00:03:23.090 --> 00:03:24.930 These mice have neurological defects

NOTE Confidence: 0.94037884

00:03:24.930 --> 00:03:27.090 that resemble the human patient.

NOTE Confidence: 0.94037884

00:03:27.090 --> 00:03:29.010 We have extensively characterized these

NOTE Confidence: 0.94037884

00:03:29.010 --> 00:03:30.549 mice. There is a generation

NOTE Confidence: 0.94037884

00:03:30.610 --> 00:03:31.750 of some a subset

NOTE Confidence: 0.8579107

00:03:32.290 --> 00:03:33.750 of the pulmonary nerve terminal,

NOTE Confidence: 0.8579107

00:03:33.889 --> 00:03:34.769 but we will not talk

NOTE Confidence: 0.8579107

00:03:34.769 --> 00:03:35.970 about this today. My talk

NOTE Confidence: 0.8579107

00:03:35.970 --> 00:03:37.829 today will be exclusively focused

NOTE Confidence: 0.8579107

00:03:37.925 --> 00:03:38.505 on VPAT13C.

NOTE Confidence: 0.8604673

00:03:40.805 --> 00:03:42.325 So first a work of

NOTE Confidence: 0.8604673

00:03:42.325 --> 00:03:43.545 introduction and background.

NOTE Confidence: 0.9748084

00:03:44.165 --> 00:03:46.185 This slide shows the convergence

NOTE Confidence: 0.9748084

00:03:46.325 --> 00:03:48.025 of the endolyzoma system

NOTE Confidence: 0.86762786

00:03:48.325 --> 00:03:49.545 and of the autophagematophagy

NOTE Confidence: 0.9869119

00:03:50.325 --> 00:03:50.825 pathway.

NOTE Confidence: 0.96319854

00:03:51.340 --> 00:03:53.099 The endolyzonal system is a

NOTE Confidence: 0.96319854

00:03:53.099 --> 00:03:54.239 complex of organelles

NOTE Confidence: 0.96770614

00:03:54.859 --> 00:03:55.599 through which

NOTE Confidence: 0.87162983

00:03:55.980 --> 00:03:58.079 material internalized for the extracellular

NOTE Confidence: 0.9879638

00:03:58.379 --> 00:03:58.879 medium

NOTE Confidence: 0.65086555

00:03:59.379 --> 00:03:59.879 is

NOTE Confidence: 0.6009065

00:04:00.379 --> 00:04:00.879 fluid

NOTE Confidence: 0.9171861

00:04:01.180 --> 00:04:02.939 is directed to lysosome for

NOTE Confidence: 0.9171861

00:04:02.939 --> 00:04:04.879 degradation and metabolic recycling.

NOTE Confidence: 0.8709623

00:04:06.275 --> 00:04:07.255 And the mitophagy,

NOTE Confidence: 0.9365123

00:04:07.635 --> 00:04:08.995 autophagy is the process through

NOTE Confidence: 0.9365123

00:04:08.995 --> 00:04:09.495 which,

NOTE Confidence: 0.9505884

00:04:12.755 --> 00:04:14.195 portion of the cell structure

NOTE Confidence: 0.9505884

00:04:14.195 --> 00:04:15.315 in the cell that undergo

NOTE Confidence: 0.9505884

00:04:15.315 --> 00:04:15.815 degeneration

NOTE Confidence: 0.9707797

00:04:16.275 --> 00:04:18.135 are encapsulated by a membrane

NOTE Confidence: 0.9707797

00:04:18.275 --> 00:04:19.795 and then directed to lysosome

NOTE Confidence: 0.9707797

00:04:19.795 --> 00:04:20.455 for degradation.

NOTE Confidence: 0.92614275

00:04:21.770 --> 00:04:22.270 And,

NOTE Confidence: 0.8907939

00:04:24.089 --> 00:04:25.449 lysosome are the point of

NOTE Confidence: 0.8907939

00:04:25.449 --> 00:04:26.830 conversion of this pathway.

NOTE Confidence: 0.91308624

00:04:27.370 --> 00:04:28.650 A key function of lysosome

NOTE Confidence: 0.91308624

00:04:28.650 --> 00:04:29.470 is to digest

NOTE Confidence: 0.73583645

00:04:30.250 --> 00:04:31.470 and recycle metabolites,

NOTE Confidence: 0.9712816

00:04:31.930 --> 00:04:33.930 but another important function is

NOTE Confidence: 0.9712816

00:04:33.930 --> 00:04:35.289 they have to protect the

NOTE Confidence: 0.9712816

00:04:35.289 --> 00:04:35.789 cytosol

NOTE Confidence: 0.9998193

00:04:36.305 --> 00:04:37.365 from substances

NOTE Confidence: 0.9452612

00:04:37.745 --> 00:04:39.025 which end up in lysosol

NOTE Confidence: 0.9452612

00:04:39.025 --> 00:04:39.845 that can be,

NOTE Confidence: 0.90387493

00:04:40.385 --> 00:04:41.825 damaging for the cells. So,

NOTE Confidence: 0.90387493

00:04:41.825 --> 00:04:43.425 leakage could result in toxic

NOTE Confidence: 0.90387493

00:04:43.425 --> 00:04:43.925 effect,

NOTE Confidence: 0.95394266

00:04:44.385 --> 00:04:46.385 activation of innate immunity because,

NOTE Confidence: 0.95394266

00:04:46.385 --> 00:04:47.985 for example, some pathogen can

NOTE Confidence: 0.95394266

00:04:47.985 --> 00:04:49.605 be internalized through the pathway,

NOTE Confidence: 0.7609799

00:04:49.960 --> 00:04:51.319 DNA can escape into the

NOTE Confidence: 0.7609799

00:04:51.319 --> 00:04:52.360 site, so they can activate

NOTE Confidence: 0.7609799

00:04:52.360 --> 00:04:52.860 immunity.

NOTE Confidence: 0.9636188

00:04:53.400 --> 00:04:54.520 And also, if you have

NOTE Confidence: 0.9636188

00:04:54.520 --> 00:04:56.919 leakage, the acidic environment in

NOTE Confidence: 0.9636188

00:04:56.919 --> 00:04:58.360 the lysosome, which is critical

NOTE Confidence: 0.9636188

00:04:58.360 --> 00:05:00.300 for the function, is dissipated,

NOTE Confidence: 0.9636188

00:05:00.440 --> 00:05:02.039 and so this creates even

NOTE Confidence: 0.9636188

00:05:02.039 --> 00:05:02.539 further

NOTE Confidence: 0.9398817

00:05:03.000 --> 00:05:04.620 defect in lysosomal function.

NOTE Confidence: 0.8399046

00:05:05.205 --> 00:05:06.985 Several parts of the gene

NOTE Confidence: 0.6884905

00:05:07.605 --> 00:05:08.105 involved,

NOTE Confidence: 0.9034548

00:05:08.645 --> 00:05:11.045 lysosomal protein or protein upstream

NOTE Confidence: 0.9034548

00:05:11.045 --> 00:05:11.705 or lysosome,

NOTE Confidence: 0.7063418

00:05:12.245 --> 00:05:13.625 including with BFT13C,

NOTE Confidence: 0.9632754

00:05:14.085 --> 00:05:15.125 which is a topic of

NOTE Confidence: 0.9632754

00:05:15.125 --> 00:05:16.105 my talk today.

NOTE Confidence: 0.9986394

00:05:17.330 --> 00:05:17.830 Other

NOTE Confidence: 0.8736514

00:05:18.370 --> 00:05:20.770 genes encode mitochondrial protein, in

NOTE Confidence: 0.8736514

00:05:20.770 --> 00:05:22.849 particular two important ones, pink

NOTE Confidence: 0.8736514

00:05:22.849 --> 00:05:24.370 one and parkin, which are

NOTE Confidence: 0.8736514

00:05:24.370 --> 00:05:26.150 involved in quality control.

NOTE Confidence: 0.8991432

00:05:26.529 --> 00:05:27.569 And the idea is that

NOTE Confidence: 0.8991432

00:05:27.569 --> 00:05:28.949 when a, when a mitochondria

NOTE Confidence: 0.8991432

00:05:29.169 --> 00:05:30.389 is old and damaged,

NOTE Confidence: 0.90708023

00:05:30.814 --> 00:05:31.794 they induce the ubiquitination

NOTE Confidence: 0.8770548

00:05:32.414 --> 00:05:33.615 of protein at the surface

NOTE Confidence: 0.8770548

00:05:33.615 --> 00:05:35.395 and, therefore, they target into,

NOTE Confidence: 0.93184483

00:05:36.175 --> 00:05:38.275 mitophagy and eventually to lysosome.

NOTE Confidence: 0.9641859

00:05:38.895 --> 00:05:39.615 If you do not have

NOTE Confidence: 0.9641859

00:05:39.615 --> 00:05:41.534 this protein, you can have,

NOTE Confidence: 0.92500573

00:05:41.935 --> 00:05:42.435 activation

NOTE Confidence: 0.8929088

00:05:43.009 --> 00:05:44.610 of innate immunity because the

NOTE Confidence: 0.8929088

00:05:44.610 --> 00:05:46.150 DNA leak into the cytosol.

NOTE Confidence: 0.8929088

00:05:46.449 --> 00:05:48.070 But this protein is functionally

NOTE Confidence: 0.8929088

00:05:48.130 --> 00:05:49.729 functional, but, and you have

NOTE Confidence: 0.8929088

00:05:49.729 --> 00:05:51.250 a normal mitophagy, but then

NOTE Confidence: 0.8929088

00:05:51.250 --> 00:05:53.250 the lysosome leaks, then this

NOTE Confidence: 0.8929088

00:05:53.250 --> 00:05:54.229 DNA can,

NOTE Confidence: 0.94102067

00:05:54.529 --> 00:05:55.889 can leak into the cytosol

NOTE Confidence: 0.94102067

00:05:55.889 --> 00:05:57.695 and, again, produce this toxic

NOTE Confidence: 0.94102067

00:05:57.695 --> 00:05:58.975 effect. So, the lysosome are

NOTE Confidence: 0.94102067

00:05:58.975 --> 00:06:00.435 really critically important.

NOTE Confidence: 0.9038842

00:06:01.295 --> 00:06:01.955 And so,

NOTE Confidence: 0.9308621

00:06:02.255 --> 00:06:03.235 where is VP13C?

NOTE Confidence: 0.99113995

00:06:03.775 --> 00:06:04.275 VP13C

NOTE Confidence: 0.97631496

00:06:04.735 --> 00:06:06.335 is a protein that we

NOTE Confidence: 0.97631496

00:06:06.335 --> 00:06:07.235 have identified

NOTE Confidence: 0.8675496

00:06:08.415 --> 00:06:10.229 at the surface lysosome and

NOTE Confidence: 0.8675496

00:06:10.229 --> 00:06:12.389 the interface between lysosome and

NOTE Confidence: 0.8675496

00:06:12.389 --> 00:06:13.050 the endoplasmic

NOTE Confidence: 0.99393976

00:06:13.430 --> 00:06:13.930 reticulum.

NOTE Confidence: 0.90280235

00:06:15.190 --> 00:06:15.990 And so what does it

NOTE Confidence: 0.90280235

00:06:15.990 --> 00:06:16.970 do? And,

NOTE Confidence: 0.9262071

00:06:19.909 --> 00:06:20.810 this is the schematic

NOTE Confidence: 0.8804444

00:06:21.270 --> 00:06:22.375 drawing of a cell that

NOTE Confidence: 0.8804444

00:06:22.375 --> 00:06:23.735 show the different organelles present

NOTE Confidence: 0.8804444

00:06:23.735 --> 00:06:24.695 in the cell. All these

NOTE Confidence: 0.8804444

00:06:24.695 --> 00:06:26.475 organisms are surrounded by membrane.

NOTE Confidence: 0.913001

00:06:26.935 --> 00:06:28.375 And also it's important that

NOTE Confidence: 0.913001

00:06:28.375 --> 00:06:29.895 they receive the lipid because

NOTE Confidence: 0.913001

00:06:29.895 --> 00:06:32.235 obviously all lipids undergo turnover.

NOTE Confidence: 0.913001

00:06:32.375 --> 00:06:33.975 Most lipids are synthesized in

NOTE Confidence: 0.913001

00:06:33.975 --> 00:06:35.115 the plasma reticulum,

NOTE Confidence: 0.88211995

00:06:35.629 --> 00:06:37.330 are delivered to other organelles

NOTE Confidence: 0.88211995

00:06:37.470 --> 00:06:38.610 in part by a membrane

NOTE Confidence: 0.88211995

00:06:38.669 --> 00:06:39.949 traffic as part of the

NOTE Confidence: 0.88211995

00:06:39.949 --> 00:06:41.729 membrane of the circular organelle.

NOTE Confidence: 0.96812654

00:06:42.349 --> 00:06:44.449 But an equally important pathway

NOTE Confidence: 0.96812654

00:06:44.669 --> 00:06:46.210 is a protein mediated,

NOTE Confidence: 0.9310813

00:06:47.550 --> 00:06:48.050 transport.

NOTE Confidence: 0.9113561

00:06:48.574 --> 00:06:49.775 So they are taken up

NOTE Confidence: 0.9113561

00:06:49.775 --> 00:06:51.375 into proteins that allow them

NOTE Confidence: 0.9113561

00:06:51.375 --> 00:06:52.895 to travel to, to cross

NOTE Confidence: 0.9113561

00:06:52.895 --> 00:06:54.815 the apous environment of the

NOTE Confidence: 0.9113561

00:06:54.815 --> 00:06:56.095 cell. And much of this

NOTE Confidence: 0.9113561

00:06:56.095 --> 00:06:56.595 protein

NOTE Confidence: 0.84633195

00:06:57.214 --> 00:06:59.214 dependent transport occur in membrane

NOTE Confidence: 0.84633195

00:06:59.214 --> 00:07:01.714 contact site because endoplasmic reticulum

NOTE Confidence: 0.84633195

00:07:01.935 --> 00:07:03.055 make contact with all the

NOTE Confidence: 0.84633195

00:07:03.055 --> 00:07:04.689 different organelle of the cell.

NOTE Confidence: 0.8537003

00:07:05.150 --> 00:07:06.029 And there are two types

NOTE Confidence: 0.8537003

00:07:06.029 --> 00:07:07.949 of lipid transfer proteins. One

NOTE Confidence: 0.8537003

00:07:07.949 --> 00:07:09.229 class has so called shuttle

NOTE Confidence: 0.8537003

00:07:09.229 --> 00:07:11.310 like lipid transfer proteins. The

NOTE Confidence: 0.8537003

00:07:11.310 --> 00:07:13.069 proteins that have lipid binding

NOTE Confidence: 0.8537003

00:07:13.069 --> 00:07:14.509 module, they shuttle back and

NOTE Confidence: 0.8537003

00:07:14.509 --> 00:07:15.969 forth between two membranes.

NOTE Confidence: 0.8916392

00:07:16.715 --> 00:07:17.835 And then there is another

NOTE Confidence: 0.8916392

00:07:17.835 --> 00:07:19.435 class of protein that had

NOTE Confidence: 0.8916392

00:07:19.435 --> 00:07:21.615 been identified here at Yale.

NOTE Confidence: 0.8322872

00:07:22.795 --> 00:07:23.755 This is work from our

NOTE Confidence: 0.8322872

00:07:23.755 --> 00:07:24.575 lab in collaboration

NOTE Confidence: 0.72388846

00:07:25.355 --> 00:07:26.495 with Karrie Reinisch,

NOTE Confidence: 0.987488

00:07:26.955 --> 00:07:28.014 a colleague in

NOTE Confidence: 0.82700026

00:07:28.680 --> 00:07:30.380 cell biology, structural biology,

NOTE Confidence: 0.3869984

00:07:30.920 --> 00:07:31.420 identified

NOTE Confidence: 0.9537567

00:07:31.800 --> 00:07:33.180 a new class of protein

NOTE Confidence: 0.8711454

00:07:33.480 --> 00:07:35.240 that function is bridging. They

NOTE Confidence: 0.8711454

00:07:35.240 --> 00:07:37.020 directly connect two membranes

NOTE Confidence: 0.79008466

00:07:37.720 --> 00:07:39.240 and they can transport lipids

NOTE Confidence: 0.79008466

00:07:39.240 --> 00:07:41.100 with an hydrophobic group that

NOTE Confidence: 0.8384654

00:07:42.884 --> 00:07:44.884 go directly from one membrane

NOTE Confidence: 0.8384654

00:07:44.884 --> 00:07:46.324 to another, and this protein

NOTE Confidence: 0.8384654

00:07:46.324 --> 00:07:48.565 functions as cariurhinase, so in

NOTE Confidence: 0.8384654

00:07:48.565 --> 00:07:49.865 cooperation with scramblazers.

NOTE Confidence: 0.80466163

00:07:50.485 --> 00:07:51.145 And VBR13c

NOTE Confidence: 0.9343529

00:07:51.845 --> 00:07:53.044 is a founding member of

NOTE Confidence: 0.9343529

00:07:53.044 --> 00:07:54.745 this lamellar bridge like protein.

NOTE Confidence: 0.8755086

00:07:55.770 --> 00:07:57.530 So this is DBR322 c,

NOTE Confidence: 0.8755086

00:07:57.530 --> 00:07:59.530 the domain structure here, the

NOTE Confidence: 0.8755086

00:07:59.530 --> 00:08:01.610 predicted structure by alpha fold,

NOTE Confidence: 0.8755086

00:08:01.610 --> 00:08:02.110 and,

NOTE Confidence: 0.89951235

00:08:03.290 --> 00:08:04.990 the structure is being anticipated

NOTE Confidence: 0.89951235

00:08:05.290 --> 00:08:07.470 and confirmed by analysis of

NOTE Confidence: 0.89951235

00:08:07.685 --> 00:08:09.525 some fragment by carolinetr, by

NOTE Confidence: 0.89951235

00:08:09.525 --> 00:08:11.945 by crystallography and cryo EM.

NOTE Confidence: 0.89951235

00:08:12.165 --> 00:08:13.705 This is a surface representation

NOTE Confidence: 0.89951235

00:08:14.005 --> 00:08:14.825 of the molecule.

NOTE Confidence: 0.98683655

00:08:15.605 --> 00:08:16.745 Red and blue are

NOTE Confidence: 0.62721485

00:08:17.845 --> 00:08:18.825 positive charges.

NOTE Confidence: 0.92620784

00:08:19.205 --> 00:08:20.425 Gray is hydrophobic.

NOTE Confidence: 0.9290433

00:08:20.880 --> 00:08:21.760 And you can see that

NOTE Confidence: 0.9290433

00:08:21.760 --> 00:08:23.360 there is this hydrophobic group

NOTE Confidence: 0.9290433

00:08:23.360 --> 00:08:24.560 that go from one membrane

NOTE Confidence: 0.9290433

00:08:24.560 --> 00:08:26.160 to another through which lipid

NOTE Confidence: 0.9290433

00:08:26.160 --> 00:08:27.760 can slide as indicated in

NOTE Confidence: 0.9290433

00:08:27.760 --> 00:08:28.500 this cartoon.

NOTE Confidence: 0.7720358

00:08:29.120 --> 00:08:31.280 BPA, there are several BPA,

NOTE Confidence: 0.7720358

00:08:31.280 --> 00:08:33.220 four BPA thirteen isoform

NOTE Confidence: 0.88136894

00:08:33.995 --> 00:08:35.274 c is the one that

NOTE Confidence: 0.88136894

00:08:35.274 --> 00:08:36.714 is localized in contact as

NOTE Confidence: 0.88136894

00:08:36.714 --> 00:08:38.735 we've seen shown between endoplasmic

NOTE Confidence: 0.88136894

00:08:38.875 --> 00:08:40.015 reticulum and lysosome.

NOTE Confidence: 0.94113576

00:08:41.195 --> 00:08:42.554 The protein is anchored to

NOTE Confidence: 0.94113576

00:08:42.554 --> 00:08:44.635 endoplasmic reticulum through a protein

NOTE Confidence: 0.94113576

00:08:44.635 --> 00:08:46.554 called VAP and bind the

NOTE Confidence: 0.94113576

00:08:46.554 --> 00:08:47.054 lysosome

NOTE Confidence: 0.98029256

00:08:47.675 --> 00:08:48.495 by interacting

NOTE Confidence: 0.8706053

00:08:49.179 --> 00:08:50.460 with an adapter at the

NOTE Confidence: 0.8706053

00:08:50.460 --> 00:08:52.780 surface or lysosome called RAP

NOTE Confidence: 0.8706053

00:08:52.780 --> 00:08:53.280 seven.

NOTE Confidence: 0.9947182

00:08:54.059 --> 00:08:55.760 And what you see here

NOTE Confidence: 0.9947182

00:08:55.820 --> 00:08:56.640 is now

NOTE Confidence: 0.8554738

00:08:57.260 --> 00:08:58.780 the VPA thirteen c in

NOTE Confidence: 0.8554738

00:08:58.780 --> 00:08:59.980 real cells. This is the

NOTE Confidence: 0.8554738

00:08:59.980 --> 00:09:01.520 lysosome, so very high magnification

NOTE Confidence: 0.8554738

00:09:01.740 --> 00:09:02.620 while you're looking at the

NOTE Confidence: 0.8554738

00:09:02.620 --> 00:09:03.120 lysosome.

NOTE Confidence: 0.91670746

00:09:03.420 --> 00:09:04.960 Magenta is VPA thirteen

NOTE Confidence: 0.8927374

00:09:05.395 --> 00:09:07.235 expressing this cell. Green is

NOTE Confidence: 0.8927374

00:09:07.235 --> 00:09:09.255 the lysosomal membrane. The endoplasmic

NOTE Confidence: 0.8927374

00:09:09.315 --> 00:09:10.995 reticulum is not shown here,

NOTE Confidence: 0.8927374

00:09:10.995 --> 00:09:12.615 but the cartoon here illustrates

NOTE Confidence: 0.9059701

00:09:13.154 --> 00:09:14.934 the organization of this molecule

NOTE Confidence: 0.9059701

00:09:14.995 --> 00:09:15.815 at the interface.

NOTE Confidence: 0.91562873

00:09:16.275 --> 00:09:17.554 And this is actually the

NOTE Confidence: 0.91562873

00:09:17.554 --> 00:09:18.915 real thing. This is cryo

NOTE Confidence: 0.91562873

00:09:18.915 --> 00:09:19.890 electron tomography

NOTE Confidence: 0.93289214

00:09:23.570 --> 00:09:25.090 endoplasmic reticulum. This is a

NOTE Confidence: 0.93289214

00:09:25.090 --> 00:09:26.870 very thin endoplasmic reticulum,

NOTE Confidence: 0.9117744

00:09:27.250 --> 00:09:28.450 engrained the membrane of the

NOTE Confidence: 0.9117744

00:09:28.450 --> 00:09:29.970 lysosome, and this is the

NOTE Confidence: 0.9117744

00:09:29.970 --> 00:09:30.470 reconstruction.

NOTE Confidence: 0.81472343

00:09:31.010 --> 00:09:32.370 And this peg here are

NOTE Confidence: 0.81472343

00:09:32.370 --> 00:09:33.110 the VPIAT3C

NOTE Confidence: 0.9292668

00:09:33.490 --> 00:09:35.385 molecule, the interface between these

NOTE Confidence: 0.9292668

00:09:35.385 --> 00:09:36.825 two organelles. Keep in mind

NOTE Confidence: 0.9292668

00:09:36.825 --> 00:09:38.425 that in this particular case,

NOTE Confidence: 0.9292668

00:09:38.425 --> 00:09:40.045 the protein has been overexpressed.

NOTE Confidence: 0.9292668

00:09:40.345 --> 00:09:41.705 There are fewer molecules like

NOTE Confidence: 0.9292668

00:09:41.705 --> 00:09:42.585 this in a real cell,

NOTE Confidence: 0.9292668

00:09:42.585 --> 00:09:43.945 in a normal cell, but

NOTE Confidence: 0.9292668

00:09:43.945 --> 00:09:45.465 that's where VPF that is

NOTE Confidence: 0.9292668

00:09:45.465 --> 00:09:46.205 c is.

NOTE Confidence: 0.9997273

00:09:47.880 --> 00:09:48.380 So

NOTE Confidence: 0.8118124

00:09:48.760 --> 00:09:50.120 as I mentioned, it's the

NOTE Confidence: 0.8118124

00:09:50.120 --> 00:09:51.579 Parkinson's disease gene.

NOTE Confidence: 0.75006676

00:09:53.480 --> 00:09:54.139 It generated

NOTE Confidence: 0.93093425

00:09:54.679 --> 00:09:56.760 mice, which, like VBF thirteen

NOTE Confidence: 0.93093425

00:09:56.760 --> 00:09:58.679 c, this might actually do

NOTE Confidence: 0.93093425

00:09:58.679 --> 00:09:59.500 not reproduce,

NOTE Confidence: 0.9977499

00:10:00.204 --> 00:10:00.704 well,

NOTE Confidence: 0.9045143

00:10:01.245 --> 00:10:03.325 the the human pathology. This

NOTE Confidence: 0.9045143

00:10:03.325 --> 00:10:04.625 is a case for many

NOTE Confidence: 0.6592145

00:10:05.084 --> 00:10:05.985 model system

NOTE Confidence: 0.8993766

00:10:06.365 --> 00:10:08.365 of neurodegenerative diseases in mice.

NOTE Confidence: 0.8993766

00:10:08.365 --> 00:10:09.725 They have some behavioral defect

NOTE Confidence: 0.8993766

00:10:09.725 --> 00:10:11.725 by relatively mild defect. However,

NOTE Confidence: 0.8993766

00:10:11.725 --> 00:10:12.764 if you look at cells,

NOTE Confidence: 0.8993766

00:10:12.764 --> 00:10:13.964 a variety of cell type,

NOTE Confidence: 0.8993766

00:10:13.964 --> 00:10:15.839 in particular human cell, we

NOTE Confidence: 0.8993766

00:10:15.839 --> 00:10:17.120 see that in fact something

NOTE Confidence: 0.8993766

00:10:17.120 --> 00:10:18.559 is wrong with lysosome. There

NOTE Confidence: 0.8993766

00:10:18.559 --> 00:10:19.600 is an increased number of

NOTE Confidence: 0.8993766

00:10:19.600 --> 00:10:21.519 lysosome inactivation of Tfeb, which

NOTE Confidence: 0.8993766

00:10:21.519 --> 00:10:23.279 is a multi transcriptional regulator

NOTE Confidence: 0.8993766

00:10:23.279 --> 00:10:25.279 of lysomal gene, alteration of

NOTE Confidence: 0.8993766

00:10:25.279 --> 00:10:27.220 lysosomal lipids, and in particular,

NOTE Confidence: 0.8993766

00:10:27.279 --> 00:10:29.120 an activation of signaling pathway

NOTE Confidence: 0.8993766

00:10:29.120 --> 00:10:30.100 of innate immunity,

NOTE Confidence: 0.8905002

00:10:30.695 --> 00:10:31.895 which is the pathway they

NOTE Confidence: 0.8905002

00:10:31.895 --> 00:10:33.095 sense, at least in in

NOTE Confidence: 0.8905002

00:10:33.255 --> 00:10:34.535 this was an inner cell,

NOTE Confidence: 0.8905002

00:10:34.535 --> 00:10:35.675 human inner cells,

NOTE Confidence: 0.5625689

00:10:36.934 --> 00:10:38.235 the pathway of autoimmune

NOTE Confidence: 0.79431534

00:10:38.774 --> 00:10:39.095 of,

NOTE Confidence: 0.8584516

00:10:39.735 --> 00:10:40.955 a pathway that senses

NOTE Confidence: 0.9996657

00:10:41.334 --> 00:10:41.834 cytosolic

NOTE Confidence: 0.99487555

00:10:42.135 --> 00:10:43.675 DNA in the cytosol.

NOTE Confidence: 0.90089947

00:10:44.360 --> 00:10:46.060 This pathway is developed evolutionarily

NOTE Confidence: 0.90089947

00:10:46.280 --> 00:10:47.900 to protect cells from microbial

NOTE Confidence: 0.90089947

00:10:47.960 --> 00:10:48.460 invasion,

NOTE Confidence: 0.87925595

00:10:48.920 --> 00:10:51.160 but since mitochondria are evolution

NOTE Confidence: 0.87925595

00:10:51.160 --> 00:10:52.840 related to pathogen, they contain

NOTE Confidence: 0.87925595

00:10:52.840 --> 00:10:54.600 their own DNA, leakage of

NOTE Confidence: 0.87925595

00:10:54.600 --> 00:10:56.780 DNA from mitochondria can activate

NOTE Confidence: 0.87925595

00:10:56.920 --> 00:10:58.200 this pathway. And we found

NOTE Confidence: 0.87925595

00:10:58.200 --> 00:11:00.025 in VPA thirteen c, hila

NOTE Confidence: 0.87925595

00:11:00.025 --> 00:11:00.525 cell

NOTE Confidence: 0.8698175

00:11:01.145 --> 00:11:02.605 that is present of mitochondrial

NOTE Confidence: 0.8698175

00:11:02.825 --> 00:11:03.885 DNA in the cytosol,

NOTE Confidence: 0.9831255

00:11:04.425 --> 00:11:05.725 so there is a constitutive

NOTE Confidence: 0.9831255

00:11:05.945 --> 00:11:07.485 activation of the STING pathway.

NOTE Confidence: 0.96635497

00:11:07.865 --> 00:11:08.365 Also,

NOTE Confidence: 0.8776579

00:11:09.065 --> 00:11:09.565 Vp13C

NOTE Confidence: 0.83423316

00:11:09.945 --> 00:11:11.304 hila cell appears to have

NOTE Confidence: 0.83423316

00:11:11.304 --> 00:11:12.605 lysosomal defect

NOTE Confidence: 0.95898867

00:11:13.240 --> 00:11:15.660 that are responsible for defective

NOTE Confidence: 0.8925468

00:11:16.040 --> 00:11:17.800 degradation of activated stings. So,

NOTE Confidence: 0.8925468

00:11:17.800 --> 00:11:19.320 there is two mechanisms through

NOTE Confidence: 0.8925468

00:11:19.320 --> 00:11:21.260 which this pathway gets activated.

NOTE Confidence: 0.8034727

00:11:21.800 --> 00:11:22.680 So, the fact that this

NOTE Confidence: 0.8034727

00:11:22.680 --> 00:11:24.200 pathway is activated may distinct

NOTE Confidence: 0.8034727

00:11:24.200 --> 00:11:24.855 the parac

NOTE Confidence: 0.9913001

00:11:25.175 --> 00:11:25.675 lysosome

NOTE Confidence: 0.8736554

00:11:26.214 --> 00:11:28.454 have a defect, are more

NOTE Confidence: 0.8736554

00:11:28.454 --> 00:11:28.954 fragile.

NOTE Confidence: 0.636794

00:11:29.654 --> 00:11:30.154 And,

NOTE Confidence: 0.837959

00:11:31.654 --> 00:11:33.355 so we wanted to test

NOTE Confidence: 0.837959

00:11:33.415 --> 00:11:36.135 directly whether lysosome of VPAT13

NOTE Confidence: 0.837959

00:11:36.135 --> 00:11:37.495 C knockout cells are more

NOTE Confidence: 0.837959

00:11:37.495 --> 00:11:37.995 fragile.

NOTE Confidence: 0.8924062

00:11:38.559 --> 00:11:39.520 And we use,

NOTE Confidence: 0.7557094

00:11:39.920 --> 00:11:40.420 the,

NOTE Confidence: 0.8163756

00:11:40.880 --> 00:11:42.400 when we studied the response

NOTE Confidence: 0.8163756

00:11:42.400 --> 00:11:43.140 to Lomi.

NOTE Confidence: 0.91683817

00:11:43.520 --> 00:11:46.020 Lomi is a small peptide,

NOTE Confidence: 0.91683817

00:11:46.080 --> 00:11:47.280 which is frequently used in

NOTE Confidence: 0.91683817

00:11:47.280 --> 00:11:48.900 study of lysosomal fragility.

NOTE Confidence: 0.95588285

00:11:49.680 --> 00:11:51.360 There is a compound that

NOTE Confidence: 0.95588285

00:11:51.360 --> 00:11:52.900 is taken up into cells,

NOTE Confidence: 0.8007627

00:11:53.565 --> 00:11:54.785 enter in lysosome,

NOTE Confidence: 0.99315864

00:11:55.165 --> 00:11:56.785 and there it is metabolized

NOTE Confidence: 0.8832828

00:11:57.245 --> 00:11:57.985 to membranolytic,

NOTE Confidence: 0.62628436

00:11:59.565 --> 00:12:00.385 small molecule,

NOTE Confidence: 0.8194986

00:12:00.765 --> 00:12:01.505 which produce

NOTE Confidence: 0.97775596

00:12:01.885 --> 00:12:03.905 holes or damage the lysomal

NOTE Confidence: 0.97775596

00:12:03.965 --> 00:12:04.465 membrane.

NOTE Confidence: 0.97095346

00:12:04.925 --> 00:12:05.905 And to test,

NOTE Confidence: 0.93695736

00:12:06.525 --> 00:12:08.065 to analyze this,

NOTE Confidence: 0.6585138

00:12:09.300 --> 00:12:11.080 GBSHD in single cell amorphragile,

NOTE Confidence: 0.6585138

00:12:11.220 --> 00:12:12.120 we use the galactin

NOTE Confidence: 0.76468176

00:12:12.500 --> 00:12:14.519 III assay. This galactin

NOTE Confidence: 0.85947496

00:12:14.899 --> 00:12:16.899 is a, is a, is

NOTE Confidence: 0.85947496

00:12:16.899 --> 00:12:17.559 a lectin

NOTE Confidence: 0.9190159

00:12:17.940 --> 00:12:19.779 that can express in the

NOTE Confidence: 0.9190159

00:12:19.779 --> 00:12:21.459 cytosol. We can actually express

NOTE Confidence: 0.9190159

00:12:21.459 --> 00:12:22.440 fluorescent galactin,

NOTE Confidence: 0.97909546

00:12:22.804 --> 00:12:24.644 and the protein normally is

NOTE Confidence: 0.97909546

00:12:24.644 --> 00:12:25.944 diffused through the cytosol,

NOTE Confidence: 0.81831765

00:12:27.285 --> 00:12:28.505 under normal condition.

NOTE Confidence: 0.9390902

00:12:29.365 --> 00:12:30.964 But if there are lesion

NOTE Confidence: 0.9390902

00:12:30.964 --> 00:12:31.944 in the lysosome,

NOTE Confidence: 0.9102052

00:12:32.245 --> 00:12:34.084 the galactin can enter the

NOTE Confidence: 0.9102052

00:12:34.084 --> 00:12:36.139 lysomal membrane and since selected,

NOTE Confidence: 0.92265815

00:12:36.440 --> 00:12:38.279 it recognizes the glycoprotein on

NOTE Confidence: 0.92265815

00:12:38.279 --> 00:12:39.579 the internal surface

NOTE Confidence: 0.94840133

00:12:40.040 --> 00:12:41.639 of the lysomal membrane. And

NOTE Confidence: 0.94840133

00:12:41.639 --> 00:12:43.019 so it can be visualized

NOTE Confidence: 0.94840133

00:12:43.079 --> 00:12:44.519 by the appearance of green

NOTE Confidence: 0.94840133

00:12:44.519 --> 00:12:45.019 lysosome.

NOTE Confidence: 0.9033159

00:12:45.559 --> 00:12:46.920 This cell has also been

NOTE Confidence: 0.9033159

00:12:46.920 --> 00:12:48.360 pre incubated. This is a

NOTE Confidence: 0.9033159

00:12:48.360 --> 00:12:49.965 high magnification of a cell.

NOTE Confidence: 0.9033159

00:12:50.045 --> 00:12:51.825 It's been pre incubated with,

NOTE Confidence: 0.9166648

00:12:53.885 --> 00:12:55.325 with a fluorescent dye, which

NOTE Confidence: 0.9166648

00:12:55.325 --> 00:12:56.625 is taken up in lysosome.

NOTE Confidence: 0.9166648

00:12:56.845 --> 00:12:58.525 So, when the lysosome breaks,

NOTE Confidence: 0.9166648

00:12:58.525 --> 00:12:59.905 you will see that this

NOTE Confidence: 0.9166648

00:13:00.205 --> 00:13:02.285 magenta dye is lost and

NOTE Confidence: 0.9166648

00:13:02.285 --> 00:13:04.705 instead the green accumulate into

NOTE Confidence: 0.8538944

00:13:05.110 --> 00:13:06.470 the lysosome because now the

NOTE Confidence: 0.8538944

00:13:06.470 --> 00:13:08.490 galactin entered this damaged lysosome.

NOTE Confidence: 0.99184287

00:13:08.950 --> 00:13:10.890 And when we measure the

NOTE Confidence: 0.9020564

00:13:11.350 --> 00:13:12.330 time it takes

NOTE Confidence: 0.95915663

00:13:12.790 --> 00:13:14.390 for this to happen in

NOTE Confidence: 0.95915663

00:13:14.390 --> 00:13:15.270 a wild type or in

NOTE Confidence: 0.95915663

00:13:15.270 --> 00:13:16.330 a mutant lysosome,

NOTE Confidence: 0.68531704

00:13:16.950 --> 00:13:17.610 in VPATC,

NOTE Confidence: 0.8934124

00:13:19.285 --> 00:13:20.405 knockout cell. And you can

NOTE Confidence: 0.8934124

00:13:20.405 --> 00:13:21.945 see there is a faster

NOTE Confidence: 0.9930409

00:13:22.645 --> 00:13:25.225 break of the lysosome of

NOTE Confidence: 0.7692759

00:13:25.684 --> 00:13:26.745 knockout cells.

NOTE Confidence: 0.95748585

00:13:27.365 --> 00:13:29.225 So if there is this

NOTE Confidence: 0.95748585

00:13:29.445 --> 00:13:30.425 faster break,

NOTE Confidence: 0.99510497

00:13:31.285 --> 00:13:32.184 does it mean

NOTE Confidence: 0.86737645

00:13:32.790 --> 00:13:34.250 that the under normal condition,

NOTE Confidence: 0.86737645

00:13:34.309 --> 00:13:36.230 VPAT thirteen c is actually

NOTE Confidence: 0.86737645

00:13:36.230 --> 00:13:38.330 recruited there to help repair.

NOTE Confidence: 0.77438104

00:13:39.590 --> 00:13:40.330 And so,

NOTE Confidence: 0.9144614

00:13:41.029 --> 00:13:42.309 there are what I just

NOTE Confidence: 0.9144614

00:13:42.309 --> 00:13:43.850 told you that this lysosome

NOTE Confidence: 0.9144614

00:13:43.990 --> 00:13:44.730 are more fragile

NOTE Confidence: 0.879394

00:13:45.355 --> 00:13:46.795 and a fragile, a broken

NOTE Confidence: 0.879394

00:13:46.795 --> 00:13:48.655 lysosome can undergo two phase,

NOTE Confidence: 0.879394

00:13:48.795 --> 00:13:50.395 can either be degraded by

NOTE Confidence: 0.879394

00:13:50.395 --> 00:13:50.895 lysophagy,

NOTE Confidence: 0.99940264

00:13:51.355 --> 00:13:51.855 or

NOTE Confidence: 0.9675055

00:13:52.235 --> 00:13:53.755 the damage can be repaired.

NOTE Confidence: 0.9675055

00:13:53.755 --> 00:13:55.035 So, now the question was,

NOTE Confidence: 0.9675055

00:13:55.035 --> 00:13:56.175 do we have any evidence

NOTE Confidence: 0.811874

00:13:56.475 --> 00:13:57.215 that BPH10C

NOTE Confidence: 0.9732422

00:13:57.915 --> 00:13:59.054 can come and repair?

NOTE Confidence: 0.9993934

00:13:59.630 --> 00:14:00.690 And this is something

NOTE Confidence: 0.99889344

00:14:01.550 --> 00:14:02.769 that was tested

NOTE Confidence: 0.89988923

00:14:03.630 --> 00:14:05.149 by, Xinbo Wang in the

NOTE Confidence: 0.89988923

00:14:05.149 --> 00:14:05.649 lab.

NOTE Confidence: 0.9103305

00:14:06.510 --> 00:14:07.870 So, these are cells in

NOTE Confidence: 0.9103305

00:14:07.870 --> 00:14:09.010 which we have expressed

NOTE Confidence: 0.67550087

00:14:09.390 --> 00:14:10.529 fluorescent VP13C,

NOTE Confidence: 0.997154

00:14:12.190 --> 00:14:13.070 and you can see some

NOTE Confidence: 0.997154

00:14:13.070 --> 00:14:13.570 VP13C

NOTE Confidence: 0.9979215

00:14:14.429 --> 00:14:14.929 accumulated

NOTE Confidence: 0.958052

00:14:15.625 --> 00:14:17.945 a lysosome. However, relatively few

NOTE Confidence: 0.958052

00:14:17.945 --> 00:14:19.165 lysosome are

NOTE Confidence: 0.8608819

00:14:19.785 --> 00:14:21.885 are labeled under control condition.

NOTE Confidence: 0.8524732

00:14:22.265 --> 00:14:24.105 However, if we damage the

NOTE Confidence: 0.8524732

00:14:24.105 --> 00:14:26.745 cell with lomi, induced leak

NOTE Confidence: 0.8524732

00:14:26.905 --> 00:14:28.160 leakage, you will see that

NOTE Confidence: 0.8524732

00:14:28.160 --> 00:14:29.519 there is a dramatic and

NOTE Confidence: 0.8524732

00:14:29.519 --> 00:14:30.959 fast recruitment of the p

NOTE Confidence: 0.8524732

00:14:30.959 --> 00:14:32.639 f thirteen c. And this

NOTE Confidence: 0.8524732

00:14:32.639 --> 00:14:34.319 is shown here. And this

NOTE Confidence: 0.8524732

00:14:34.319 --> 00:14:36.319 happened literally in less than

NOTE Confidence: 0.8524732

00:14:36.319 --> 00:14:36.899 a minute.

NOTE Confidence: 0.83914346

00:14:37.360 --> 00:14:39.040 After thirty seconds, you already

NOTE Confidence: 0.83914346

00:14:39.040 --> 00:14:40.560 did strong accumulation, and then

NOTE Confidence: 0.83914346

00:14:40.560 --> 00:14:41.685 it keeps going up. And

NOTE Confidence: 0.83914346

00:14:41.685 --> 00:14:43.605 then there is a, eventually,

NOTE Confidence: 0.83914346

00:14:43.605 --> 00:14:44.505 the thing is reversed.

NOTE Confidence: 0.9203725

00:14:45.365 --> 00:14:46.965 If this is, if this

NOTE Confidence: 0.9203725

00:14:46.965 --> 00:14:49.204 recruitment correlates with the ability

NOTE Confidence: 0.9203725

00:14:49.204 --> 00:14:51.285 of, of VPM10C to bring

NOTE Confidence: 0.9203725

00:14:51.285 --> 00:14:52.725 lipid to the lysosome, we

NOTE Confidence: 0.9203725

00:14:52.725 --> 00:14:54.345 should see also the recruitment

NOTE Confidence: 0.9203725

00:14:54.405 --> 00:14:56.279 of the endoplasmic reticulum and

NOTE Confidence: 0.9203725

00:14:56.279 --> 00:14:57.980 lysosome to create this bridge.

NOTE Confidence: 0.9203725

00:14:58.040 --> 00:14:59.079 And this, in fact, is

NOTE Confidence: 0.9203725

00:14:59.079 --> 00:14:59.740 the case.

NOTE Confidence: 0.937884

00:15:00.199 --> 00:15:02.040 These are cells before the

NOTE Confidence: 0.937884

00:15:02.040 --> 00:15:02.699 high magnification

NOTE Confidence: 0.87018347

00:15:03.000 --> 00:15:05.079 of the cell before and

NOTE Confidence: 0.87018347

00:15:05.079 --> 00:15:07.560 after lomi. Here, we what

NOTE Confidence: 0.87018347

00:15:07.560 --> 00:15:09.079 you see at left right

NOTE Confidence: 0.87018347

00:15:09.079 --> 00:15:10.699 is this protein VAP,

NOTE Confidence: 0.88153934

00:15:11.365 --> 00:15:12.485 the anchoring site on the

NOTE Confidence: 0.88153934

00:15:12.485 --> 00:15:13.685 arm, and the left would

NOTE Confidence: 0.88153934

00:15:13.685 --> 00:15:15.205 be epitaxy. You can see

NOTE Confidence: 0.88153934

00:15:15.205 --> 00:15:16.645 here there are only few

NOTE Confidence: 0.88153934

00:15:16.645 --> 00:15:18.585 lysosome positive, but after Lomi,

NOTE Confidence: 0.88153934

00:15:18.725 --> 00:15:20.405 many lysosome are positive, and

NOTE Confidence: 0.88153934

00:15:20.405 --> 00:15:21.685 you have an accumulation of

NOTE Confidence: 0.88153934

00:15:21.685 --> 00:15:23.305 VAP at the same site.

NOTE Confidence: 0.95076185

00:15:24.389 --> 00:15:25.829 This is a fibroblastic cell.

NOTE Confidence: 0.95076185

00:15:25.829 --> 00:15:26.950 What about cells of the

NOTE Confidence: 0.95076185

00:15:26.950 --> 00:15:28.149 brain? So, we wanted to

NOTE Confidence: 0.95076185

00:15:28.149 --> 00:15:29.269 see whether this can happen

NOTE Confidence: 0.95076185

00:15:29.269 --> 00:15:30.230 in cells of the brain,

NOTE Confidence: 0.95076185

00:15:30.230 --> 00:15:32.490 in neuron, and microglial cells.

NOTE Confidence: 0.85781246

00:15:33.029 --> 00:15:33.910 And we know that there

NOTE Confidence: 0.85781246

00:15:33.910 --> 00:15:34.790 is a lot of IP

NOTE Confidence: 0.85781246

00:15:34.790 --> 00:15:36.230 activity in the brain and

NOTE Confidence: 0.85781246

00:15:36.230 --> 00:15:38.329 in particular microglial cells.

NOTE Confidence: 0.94317174

00:15:39.345 --> 00:15:40.245 So, we,

NOTE Confidence: 0.88712066

00:15:41.105 --> 00:15:42.145 this is, oh, by the

NOTE Confidence: 0.88712066

00:15:42.145 --> 00:15:43.585 way, before I go on,

NOTE Confidence: 0.88712066

00:15:43.585 --> 00:15:44.625 I wanted to share that

NOTE Confidence: 0.88712066

00:15:44.625 --> 00:15:46.145 this recruitment was confirmed by

NOTE Confidence: 0.88712066

00:15:46.145 --> 00:15:47.685 biochemistry. It was a collaboration

NOTE Confidence: 0.88712066

00:15:47.745 --> 00:15:48.645 by Shawn Ferguson

NOTE Confidence: 0.73801684

00:15:49.265 --> 00:15:50.085 that Amanda

NOTE Confidence: 0.46935782

00:15:50.465 --> 00:15:52.245 Bentley, the Susanist's lab,

NOTE Confidence: 0.5130267

00:15:52.880 --> 00:15:53.380 uses

NOTE Confidence: 0.81603944

00:15:53.760 --> 00:15:54.260 a,

NOTE Confidence: 0.930989

00:15:54.640 --> 00:15:56.020 a magnetic procedure

NOTE Confidence: 0.99605954

00:15:56.560 --> 00:15:57.220 to purify

NOTE Confidence: 0.88101834

00:15:57.680 --> 00:15:58.960 a lysosome with a degree

NOTE Confidence: 0.88101834

00:15:58.960 --> 00:16:01.060 of purity. Cells are fed

NOTE Confidence: 0.88101834

00:16:01.120 --> 00:16:02.960 small iron particles. Then the

NOTE Confidence: 0.88101834

00:16:02.960 --> 00:16:03.460 lysosome,

NOTE Confidence: 0.89830744

00:16:05.125 --> 00:16:06.005 you are one way long

NOTE Confidence: 0.89830744

00:16:06.005 --> 00:16:07.365 enough for this particle to

NOTE Confidence: 0.89830744

00:16:07.365 --> 00:16:08.185 go in lysosome.

NOTE Confidence: 0.9607504

00:16:08.565 --> 00:16:09.305 The lysosome

NOTE Confidence: 0.8968731

00:16:09.685 --> 00:16:10.265 are affinity,

NOTE Confidence: 0.9454539

00:16:11.045 --> 00:16:12.405 are purified by a magnetic

NOTE Confidence: 0.9454539

00:16:12.405 --> 00:16:13.605 beads, and you can see

NOTE Confidence: 0.9454539

00:16:13.605 --> 00:16:14.665 that after purification,

NOTE Confidence: 0.94218177

00:16:15.125 --> 00:16:16.485 LAP1 is there before and

NOTE Confidence: 0.94218177

00:16:16.485 --> 00:16:18.485 after and only after there

NOTE Confidence: 0.94218177

00:16:18.485 --> 00:16:20.185 is an accumulation of EP13C.

NOTE Confidence: 0.9068014

00:16:23.020 --> 00:16:24.940 These are microglial cells. These

NOTE Confidence: 0.9068014

00:16:24.940 --> 00:16:26.300 are a cell of micro

NOTE Confidence: 0.9068014

00:16:26.700 --> 00:16:27.920 of microglial

NOTE Confidence: 0.9963563

00:16:28.220 --> 00:16:30.160 lineage. This is actually before

NOTE Confidence: 0.895376

00:16:30.620 --> 00:16:32.380 microglia. This is derived from

NOTE Confidence: 0.895376

00:16:32.380 --> 00:16:34.400 iPS cells. These iPS cells

NOTE Confidence: 0.895376

00:16:34.620 --> 00:16:35.280 have been

NOTE Confidence: 0.9935324

00:16:37.605 --> 00:16:38.425 gene edited

NOTE Confidence: 0.85860884

00:16:39.524 --> 00:16:41.285 to FUSE HALO, which is

NOTE Confidence: 0.85860884

00:16:41.285 --> 00:16:42.404 a protein which can be

NOTE Confidence: 0.85860884

00:16:42.404 --> 00:16:44.024 tagged by fluorescent compound

NOTE Confidence: 0.8356225

00:16:44.565 --> 00:16:46.505 in the, in the genome.

NOTE Confidence: 0.8356225

00:16:46.725 --> 00:16:48.084 So, this cell expressed at

NOTE Confidence: 0.8356225

00:16:48.084 --> 00:16:49.464 the endogenous level,

NOTE Confidence: 0.6295148

00:16:49.845 --> 00:16:50.345 VTR13C.

NOTE Confidence: 0.91973454

00:16:51.600 --> 00:16:52.959 In green are the lysosome,

NOTE Confidence: 0.91973454

00:16:52.959 --> 00:16:54.560 which has been loaded with

NOTE Confidence: 0.91973454

00:16:54.560 --> 00:16:55.839 lyso tracker, a marker of

NOTE Confidence: 0.91973454

00:16:55.839 --> 00:16:57.360 the lysolome lumen. In red

NOTE Confidence: 0.91973454

00:16:57.360 --> 00:16:58.019 is VPAT13C.

NOTE Confidence: 0.9380997

00:16:58.880 --> 00:17:00.240 As we add LOMA to

NOTE Confidence: 0.9380997

00:17:00.240 --> 00:17:01.839 the cell, there is immediate

NOTE Confidence: 0.9380997

00:17:01.839 --> 00:17:03.440 loss of lyso tracker because

NOTE Confidence: 0.9380997

00:17:03.440 --> 00:17:04.559 of rupture. This is a

NOTE Confidence: 0.9380997

00:17:04.559 --> 00:17:06.395 very rapid movie. So at

NOTE Confidence: 0.9380997

00:17:06.395 --> 00:17:07.475 the start of the movie,

NOTE Confidence: 0.9380997

00:17:07.475 --> 00:17:08.595 we see loss, but it's

NOTE Confidence: 0.9380997

00:17:08.595 --> 00:17:10.034 really one minute. But what

NOTE Confidence: 0.9380997

00:17:10.034 --> 00:17:10.934 you see dramatically

NOTE Confidence: 0.8778475

00:17:11.635 --> 00:17:13.315 is the accumulation of VPF

NOTE Confidence: 0.8778475

00:17:13.315 --> 00:17:14.615 thirty c at the lysosome.

NOTE Confidence: 0.8778475

00:17:14.914 --> 00:17:15.875 And this is shown at

NOTE Confidence: 0.8778475

00:17:15.875 --> 00:17:17.315 high magnification. Here, there is

NOTE Confidence: 0.8778475

00:17:17.315 --> 00:17:17.894 a lysosome.

NOTE Confidence: 0.8292607

00:17:18.195 --> 00:17:19.815 You had Lomi very rapidly.

NOTE Confidence: 0.8531578

00:17:20.434 --> 00:17:22.119 The grain is lost, and

NOTE Confidence: 0.8531578

00:17:22.119 --> 00:17:23.820 you have accumulation of EPFLT

NOTE Confidence: 0.8934897

00:17:24.119 --> 00:17:25.480 at the service, and by

NOTE Confidence: 0.8934897

00:17:25.480 --> 00:17:27.340 FIB SEM, we can reconstruct

NOTE Confidence: 0.8934897

00:17:27.480 --> 00:17:28.679 lysosome of cell, and this

NOTE Confidence: 0.8934897

00:17:28.679 --> 00:17:29.720 to give you an idea

NOTE Confidence: 0.8934897

00:17:29.720 --> 00:17:30.679 of how we look the

NOTE Confidence: 0.8934897

00:17:30.679 --> 00:17:31.580 ER accumulated

NOTE Confidence: 0.9387913

00:17:31.880 --> 00:17:32.380 at

NOTE Confidence: 0.84060335

00:17:32.760 --> 00:17:33.419 the lysome.

NOTE Confidence: 0.9188825

00:17:33.960 --> 00:17:34.460 So,

NOTE Confidence: 0.9540821

00:17:35.065 --> 00:17:36.905 I mentioned earlier that,

NOTE Confidence: 0.88625926

00:17:37.625 --> 00:17:39.225 CELE developed a variety of

NOTE Confidence: 0.88625926

00:17:39.225 --> 00:17:41.645 mechanisms to repair lysosome.

NOTE Confidence: 0.98386306

00:17:42.265 --> 00:17:43.405 So, how can we

NOTE Confidence: 0.89370847

00:17:43.785 --> 00:17:44.905 put this, what I just

NOTE Confidence: 0.89370847

00:17:44.905 --> 00:17:45.865 showed you, in the context

NOTE Confidence: 0.89370847

00:17:45.865 --> 00:17:46.744 of which is known in

NOTE Confidence: 0.89370847

00:17:46.744 --> 00:17:47.725 lysosome repair?

NOTE Confidence: 0.9033149

00:17:48.230 --> 00:17:50.090 One basic mechanism to repair

NOTE Confidence: 0.9033149

00:17:50.230 --> 00:17:51.750 lysosome in the recruitment of

NOTE Confidence: 0.9033149

00:17:51.750 --> 00:17:53.190 the eschar complex, which is

NOTE Confidence: 0.9033149

00:17:53.190 --> 00:17:54.970 something which is calcium dependent.

NOTE Confidence: 0.9033149

00:17:55.030 --> 00:17:56.410 When you release lysosome,

NOTE Confidence: 0.8707507

00:17:57.109 --> 00:17:58.250 calcium escape,

NOTE Confidence: 0.71492314

00:17:58.550 --> 00:17:59.050 recruit,

NOTE Confidence: 0.8439673

00:17:59.590 --> 00:18:00.570 deschar complex.

NOTE Confidence: 0.8567127

00:18:00.994 --> 00:18:02.755 These are molecules that form

NOTE Confidence: 0.8567127

00:18:02.755 --> 00:18:04.515 filament that organize in a

NOTE Confidence: 0.8567127

00:18:04.515 --> 00:18:06.135 spiral, and if the spiral

NOTE Confidence: 0.8567127

00:18:06.275 --> 00:18:06.775 caustic,

NOTE Confidence: 0.98266155

00:18:07.155 --> 00:18:08.675 the hole is closed with

NOTE Confidence: 0.98266155

00:18:08.675 --> 00:18:11.395 the generation of vesicle inside

NOTE Confidence: 0.98266155

00:18:11.395 --> 00:18:12.055 the lysosome.

NOTE Confidence: 0.9890123

00:18:13.170 --> 00:18:14.550 Another repair mechanism

NOTE Confidence: 0.9102701

00:18:15.010 --> 00:18:16.450 is via the recruitment of

NOTE Confidence: 0.9102701

00:18:16.450 --> 00:18:18.690 endoplasmic reticulum and lipid exchange

NOTE Confidence: 0.9102701

00:18:18.690 --> 00:18:19.190 protein

NOTE Confidence: 0.9056371

00:18:19.570 --> 00:18:21.190 that fine tune the composition

NOTE Confidence: 0.9056371

00:18:21.250 --> 00:18:22.130 of the lipids of the

NOTE Confidence: 0.9056371

00:18:22.130 --> 00:18:23.250 membrane. I don't have the

NOTE Confidence: 0.9056371

00:18:23.250 --> 00:18:24.850 time to go in detail,

NOTE Confidence: 0.9056371

00:18:24.850 --> 00:18:26.369 but what we discover now

NOTE Confidence: 0.9056371

00:18:26.369 --> 00:18:28.244 here is a mechanism to

NOTE Confidence: 0.9056371

00:18:28.244 --> 00:18:30.565 deliver embarked lipids. So, really,

NOTE Confidence: 0.9056371

00:18:30.565 --> 00:18:31.605 this is a very high

NOTE Confidence: 0.9056371

00:18:31.605 --> 00:18:33.845 capacity transport mechanism that allows

NOTE Confidence: 0.9056371

00:18:33.845 --> 00:18:34.885 the flow of lipid from

NOTE Confidence: 0.9056371

00:18:34.885 --> 00:18:36.425 the cytosine to the lysome.

NOTE Confidence: 0.9056371

00:18:36.645 --> 00:18:38.025 And what is very interesting

NOTE Confidence: 0.9056371

00:18:38.085 --> 00:18:39.605 in this machinery here, the

NOTE Confidence: 0.9056371

00:18:39.605 --> 00:18:40.105 ESCORP,

NOTE Confidence: 0.90160435

00:18:40.830 --> 00:18:42.669 who picks the hole, close

NOTE Confidence: 0.90160435

00:18:42.669 --> 00:18:43.470 the hole, but at the

NOTE Confidence: 0.90160435

00:18:43.470 --> 00:18:44.769 expense of consuming

NOTE Confidence: 0.8888114

00:18:45.390 --> 00:18:47.070 bilayer because as you generate

NOTE Confidence: 0.8888114

00:18:47.070 --> 00:18:48.529 an intracellular vesicle,

NOTE Confidence: 0.93870735

00:18:48.830 --> 00:18:50.049 you use that bilayer.

NOTE Confidence: 0.839897

00:18:50.350 --> 00:18:51.710 And we find that escort,

NOTE Confidence: 0.839897

00:18:51.710 --> 00:18:53.149 the VPS, the TNC are

NOTE Confidence: 0.839897

00:18:53.149 --> 00:18:54.190 recruited at the same time

NOTE Confidence: 0.839897

00:18:54.190 --> 00:18:55.549 as the we we we

NOTE Confidence: 0.839897

00:18:55.549 --> 00:18:57.045 function in close partnership.

NOTE Confidence: 0.9080784

00:18:58.545 --> 00:18:59.765 So, obviously,

NOTE Confidence: 0.50879943

00:19:00.385 --> 00:19:00.885 the,

NOTE Confidence: 0.8953982

00:19:01.905 --> 00:19:03.265 Shiba Wang was very interested

NOTE Confidence: 0.8953982

00:19:03.265 --> 00:19:04.945 in understanding how VP13 C

NOTE Confidence: 0.8953982

00:19:04.945 --> 00:19:06.065 is recruited. I do not

NOTE Confidence: 0.8953982

00:19:06.065 --> 00:19:06.865 have time to go in

NOTE Confidence: 0.8953982

00:19:06.865 --> 00:19:07.825 detail. I just show you

NOTE Confidence: 0.8953982

00:19:07.825 --> 00:19:09.425 this working model, and this

NOTE Confidence: 0.8953982

00:19:09.425 --> 00:19:11.045 working model shows that

NOTE Confidence: 0.87321883

00:19:11.669 --> 00:19:13.109 it is the occurrence of

NOTE Confidence: 0.87321883

00:19:13.109 --> 00:19:14.869 partial defect in the lysoral

NOTE Confidence: 0.87321883

00:19:14.869 --> 00:19:16.549 membrane that is able to

NOTE Confidence: 0.87321883

00:19:16.549 --> 00:19:17.929 recruit and activate VPA13C.

NOTE Confidence: 0.74771905

00:19:18.710 --> 00:19:20.070 We found AMFIID is in

NOTE Confidence: 0.74771905

00:19:20.070 --> 00:19:21.590 control condition. It is an

NOTE Confidence: 0.74771905

00:19:21.590 --> 00:19:22.889 out inhibitor configuration

NOTE Confidence: 0.7810688

00:19:23.509 --> 00:19:25.715 and the presence of packaging

NOTE Confidence: 0.7810688

00:19:25.775 --> 00:19:27.534 defect allows the binding of

NOTE Confidence: 0.7810688

00:19:27.534 --> 00:19:28.115 the lymphocytic

NOTE Confidence: 0.81756294

00:19:28.415 --> 00:19:29.775 heathies to the membrane and

NOTE Confidence: 0.81756294

00:19:29.775 --> 00:19:30.975 therefore to release the,

NOTE Confidence: 0.96170056

00:19:31.695 --> 00:19:32.734 the protein for an auto

NOTE Confidence: 0.96170056

00:19:32.734 --> 00:19:33.635 inhibitory configuration.

NOTE Confidence: 0.90248287

00:19:34.494 --> 00:19:35.775 Finally, let me go back

NOTE Confidence: 0.90248287

00:19:35.775 --> 00:19:37.215 to this cartoon here. This

NOTE Confidence: 0.90248287

00:19:37.215 --> 00:19:38.975 I spoke about three mechanisms

NOTE Confidence: 0.90248287

00:19:38.975 --> 00:19:40.169 of repair, but there is

NOTE Confidence: 0.90248287

00:19:40.169 --> 00:19:41.529 in the final one, which

NOTE Confidence: 0.90248287

00:19:41.529 --> 00:19:42.350 is CASM.

NOTE Confidence: 0.9150561

00:19:42.730 --> 00:19:43.929 CASM is the process through

NOTE Confidence: 0.9150561

00:19:43.929 --> 00:19:45.210 which when the lysosome is

NOTE Confidence: 0.9150561

00:19:45.210 --> 00:19:46.889 damaged, there is an activation

NOTE Confidence: 0.9150561

00:19:46.889 --> 00:19:48.570 of the proton pump because

NOTE Confidence: 0.9150561

00:19:48.570 --> 00:19:49.070 the,

NOTE Confidence: 0.8963481

00:19:49.369 --> 00:19:50.730 the, the acidic pH is

NOTE Confidence: 0.8963481

00:19:50.730 --> 00:19:52.509 lost and this is compensated

NOTE Confidence: 0.8296578

00:19:52.970 --> 00:19:54.570 by the activation of the

NOTE Confidence: 0.8296578

00:19:54.570 --> 00:19:56.355 proton pump. When the proton

NOTE Confidence: 0.8296578

00:19:56.355 --> 00:19:58.605 pump. When the proton pump

NOTE Confidence: 0.8296578

00:19:58.605 --> 00:20:00.085 is activated, it induces

NOTE Confidence: 0.99510473

00:20:00.625 --> 00:20:01.445 the activation

NOTE Confidence: 0.8406097

00:20:02.145 --> 00:20:04.625 of, the lipidation machinery for

NOTE Confidence: 0.8406097

00:20:04.625 --> 00:20:05.125 LC3.

NOTE Confidence: 0.8536261

00:20:05.505 --> 00:20:07.585 LC3, the small adapter present

NOTE Confidence: 0.8536261

00:20:07.585 --> 00:20:08.405 in the cytosol,

NOTE Confidence: 0.8668489

00:20:08.890 --> 00:20:10.410 which is the recruited lipid

NOTE Confidence: 0.8668489

00:20:10.410 --> 00:20:11.770 data recruited to the membrane

NOTE Confidence: 0.8668489

00:20:11.770 --> 00:20:13.609 by activation of spasm. And

NOTE Confidence: 0.8668489

00:20:13.609 --> 00:20:14.730 one of the effector of

NOTE Confidence: 0.8668489

00:20:14.730 --> 00:20:15.230 LC3

NOTE Confidence: 0.88872015

00:20:15.609 --> 00:20:16.990 is LER2. So LC3

NOTE Confidence: 0.862841

00:20:17.690 --> 00:20:18.990 is able is an adapter

NOTE Confidence: 0.862841

00:20:19.049 --> 00:20:20.169 that is able to bind

NOTE Confidence: 0.862841

00:20:20.169 --> 00:20:21.869 protein with a leer motif,

NOTE Confidence: 0.862841

00:20:22.085 --> 00:20:23.865 and Sean Ferguson has found

NOTE Confidence: 0.862841

00:20:23.925 --> 00:20:25.065 that a major,

NOTE Confidence: 0.9178855

00:20:25.685 --> 00:20:27.445 effector of LC3 at the

NOTE Confidence: 0.9178855

00:20:27.445 --> 00:20:28.505 surface of lysomal

NOTE Confidence: 0.86866796

00:20:29.125 --> 00:20:30.725 LARP2 that we well know

NOTE Confidence: 0.86866796

00:20:30.725 --> 00:20:32.565 is a major Parkinson's disease

NOTE Confidence: 0.86866796

00:20:32.565 --> 00:20:34.825 project. And it's very interesting

NOTE Confidence: 0.8513026

00:20:35.179 --> 00:20:37.020 that two Parkinson's disease proteins

NOTE Confidence: 0.8513026

00:20:37.020 --> 00:20:38.780 are implicated in this repair

NOTE Confidence: 0.8513026

00:20:38.780 --> 00:20:40.299 or lysosome. I should also

NOTE Confidence: 0.8513026

00:20:40.299 --> 00:20:41.840 mention that Sean has shown

NOTE Confidence: 0.9153895

00:20:42.140 --> 00:20:43.820 that the STING pathway, which

NOTE Confidence: 0.9153895

00:20:43.820 --> 00:20:44.619 I showed to you is

NOTE Confidence: 0.9153895

00:20:44.619 --> 00:20:45.919 activated by BPH13C,

NOTE Confidence: 0.89895475

00:20:46.780 --> 00:20:48.720 is upstream of CASM.

NOTE Confidence: 0.8762572

00:20:49.075 --> 00:20:50.835 So STIM can activate CASM

NOTE Confidence: 0.8762572

00:20:50.835 --> 00:20:52.595 and therefore can really induce

NOTE Confidence: 0.8762572

00:20:52.595 --> 00:20:54.915 a strong recruitment LR2. So,

NOTE Confidence: 0.8762572

00:20:54.915 --> 00:20:56.035 I believe it's very interesting.

NOTE Confidence: 0.8762572

00:20:56.035 --> 00:20:57.395 There is a relationship between

NOTE Confidence: 0.8762572

00:20:57.395 --> 00:20:58.994 the two pathways. We co

NOTE Confidence: 0.8762572

00:20:58.994 --> 00:20:59.895 expressed BPL13C

NOTE Confidence: 0.8529723

00:21:00.355 --> 00:21:01.795 LR2 in cells. This is

NOTE Confidence: 0.8529723

00:21:01.795 --> 00:21:02.775 my last slide.

NOTE Confidence: 0.9364893

00:21:03.150 --> 00:21:04.430 And, we have found that

NOTE Confidence: 0.9364893

00:21:04.430 --> 00:21:06.130 both are recruited by Lome,

NOTE Confidence: 0.7351759

00:21:06.510 --> 00:21:07.650 by, in response,

NOTE Confidence: 0.9571045

00:21:08.350 --> 00:21:09.630 both are recruited in response

NOTE Confidence: 0.9571045

00:21:09.630 --> 00:21:11.230 to damaging the lysosome by

NOTE Confidence: 0.9571045

00:21:11.230 --> 00:21:13.010 Lome, but with different kinetics.

NOTE Confidence: 0.73522854

00:21:13.310 --> 00:21:14.369 First comes VPAT13C,

NOTE Confidence: 0.7711366

00:21:14.910 --> 00:21:15.890 then as VPAT13C

NOTE Confidence: 0.8688861

00:21:16.590 --> 00:21:18.175 shed, there are two counts,

NOTE Confidence: 0.8688861

00:21:18.175 --> 00:21:19.135 and we are very interested

NOTE Confidence: 0.8688861

00:21:19.135 --> 00:21:20.415 together with sure to understand

NOTE Confidence: 0.8688861

00:21:20.415 --> 00:21:21.935 the functional relationship between these

NOTE Confidence: 0.8688861

00:21:21.935 --> 00:21:23.395 two proteins. Conclusion,

NOTE Confidence: 0.8965187

00:21:24.575 --> 00:21:26.435 the Parkinson's disease gene VPAT13C

NOTE Confidence: 0.8100242

00:21:27.135 --> 00:21:28.815 encode the lipid transfer protein

NOTE Confidence: 0.8100242

00:21:28.815 --> 00:21:30.494 expected to mediate net lipid

NOTE Confidence: 0.8100242

00:21:30.494 --> 00:21:32.015 transport in contact between the

NOTE Confidence: 0.8100242

00:21:32.015 --> 00:21:32.515 RN

NOTE Confidence: 0.8327313

00:21:33.310 --> 00:21:33.890 and lysosome.

NOTE Confidence: 0.79448885

00:21:35.150 --> 00:21:36.130 Loss of ATTC

NOTE Confidence: 0.87122256

00:21:36.510 --> 00:21:38.350 function due to Parkinson disease

NOTE Confidence: 0.87122256

00:21:38.350 --> 00:21:39.710 mutation has an impact on

NOTE Confidence: 0.87122256

00:21:39.710 --> 00:21:40.850 lysome member integrity

NOTE Confidence: 0.815184

00:21:41.230 --> 00:21:42.770 and on lysome member repair.

NOTE Confidence: 0.89989144

00:21:43.390 --> 00:21:45.550 Collectively, our results strengthen evidence

NOTE Confidence: 0.89989144

00:21:45.550 --> 00:21:47.650 that dysfunctional the endosomal system

NOTE Confidence: 0.89989144

00:21:47.855 --> 00:21:48.815 can play a role in

NOTE Confidence: 0.89989144

00:21:48.815 --> 00:21:49.795 Parkinson's disease.

NOTE Confidence: 0.9228218

00:21:50.415 --> 00:21:51.695 And finally, these are my

NOTE Confidence: 0.9228218

00:21:51.695 --> 00:21:52.195 collaborators

NOTE Confidence: 0.81308913

00:21:52.655 --> 00:21:53.775 and left a member of

NOTE Confidence: 0.81308913

00:21:53.775 --> 00:21:55.615 my lab, Elohira Sobeys, an

NOTE Confidence: 0.81308913

00:21:55.615 --> 00:21:56.895 alumna, and I want to

NOTE Confidence: 0.81308913

00:21:56.895 --> 00:21:58.115 acknowledge in particular

NOTE Confidence: 0.8379938

00:21:58.494 --> 00:22:00.335 our ACP team. They are

NOTE Confidence: 0.8379938

00:22:00.335 --> 00:22:01.799 the member of our team,

NOTE Confidence: 0.8379938

00:22:01.799 --> 00:22:02.919 which has been very,

NOTE Confidence: 0.9810856

00:22:03.320 --> 00:22:04.940 very powerful in,

NOTE Confidence: 0.9974741

00:22:05.720 --> 00:22:06.859 basically motivating

NOTE Confidence: 0.99823654

00:22:07.240 --> 00:22:07.740 us

NOTE Confidence: 0.9124433

00:22:08.359 --> 00:22:10.200 to study Parkinson's disease and

NOTE Confidence: 0.9124433

00:22:10.200 --> 00:22:11.740 to interact with each other

NOTE Confidence: 0.9124433

00:22:11.880 --> 00:22:13.399 to really advance the understanding

NOTE Confidence: 0.9124433

00:22:13.399 --> 00:22:14.619 of Parkinson's disease.