WEBVTT

NOTE duration: ”00:20:57.472”

NOTE Confidence: 0.99400795

00:00:00.320 --> 00:00:02.000 Now when we think about

NOTE Confidence: 0.99400795

00:00:02.000 --> 00:00:04.100 Parkinson's disease, we traditionally

NOTE Confidence: 0.9797373

00:00:04.799 --> 00:00:05.859 sort of oversimplify,

NOTE Confidence: 0.929308

00:00:06.879 --> 00:00:08.559 the disease into a a

NOTE Confidence: 0.929308

00:00:08.559 --> 00:00:09.059 pure

NOTE Confidence: 0.95451295

00:00:09.599 --> 00:00:10.099 synucleinopathy.

NOTE Confidence: 0.9978154

00:00:11.360 --> 00:00:12.559 But if you actually look

NOTE Confidence: 0.9978154

00:00:12.559 --> 00:00:13.940 at the brains of Parkinson's

NOTE Confidence: 0.9978154

00:00:14.160 --> 00:00:14.660 patients

NOTE Confidence: 0.979867

00:00:14.995 --> 00:00:15.735 at autopsy,

NOTE Confidence: 0.9602676

00:00:16.595 --> 00:00:18.855 sixty percent have amyloid plaques

NOTE Confidence: 0.9602676

00:00:19.075 --> 00:00:20.135 and forty percent,

NOTE Confidence: 0.9803803

00:00:20.755 --> 00:00:22.035 at least forty percent have

NOTE Confidence: 0.9803803

00:00:22.035 --> 00:00:22.535 tauopathies.

NOTE Confidence: 0.99757004

00:00:23.395 --> 00:00:25.015 And so it's my distinct

NOTE Confidence: 0.99757004

00:00:25.075 --> 00:00:25.974 pleasure to

NOTE Confidence: 0.99881184

00:00:26.275 --> 00:00:26.775 introduce

NOTE Confidence: 0.74829686

00:00:27.474 --> 00:00:28.375 Steven Strittmatter,

NOTE Confidence: 0.9895064

00:00:29.235 --> 00:00:30.455 the chair of the neuroscience

NOTE Confidence: 0.92729324

00:00:30.970 --> 00:00:32.890 department, and the Vincent Coates

NOTE Confidence: 0.92729324

00:00:32.890 --> 00:00:33.390 professor,

NOTE Confidence: 0.9050899

00:00:34.250 --> 00:00:35.870 recipient of the King Faisal

NOTE Confidence: 0.9050899

00:00:35.930 --> 00:00:36.430 award.

NOTE Confidence: 0.98072094

00:00:36.970 --> 00:00:37.450 And,

NOTE Confidence: 0.9967701

00:00:38.090 --> 00:00:40.010 it's just so great to

NOTE Confidence: 0.9967701

00:00:40.010 --> 00:00:41.530 be able to collaborate with

NOTE Confidence: 0.9967701

00:00:41.530 --> 00:00:42.190 your department.

NOTE Confidence: 0.9912989

00:00:46.555 --> 00:00:47.055 Well,

NOTE Confidence: 0.9561603

00:00:48.475 --> 00:00:49.675 thank you, Clemens. It's a

NOTE Confidence: 0.9561603

00:00:49.675 --> 00:00:50.635 great pleasure to be here

NOTE Confidence: 0.9561603

00:00:50.635 --> 00:00:51.934 to celebrate the,

NOTE Confidence: 0.917972

00:00:52.235 --> 00:00:53.595 really, the inauguration of the

NOTE Confidence: 0.917972

00:00:53.595 --> 00:00:54.335 ADaM Center.

NOTE Confidence: 0.9444921

00:00:54.795 --> 00:00:55.995 I'm gonna talk about two

NOTE Confidence: 0.9444921

00:00:55.995 --> 00:00:58.015 proteins, progranulin and TMEM

NOTE Confidence: 0.9775899

00:00:58.520 --> 00:00:59.800 one zero six b, and

NOTE Confidence: 0.9775899

00:00:59.800 --> 00:01:01.260 how they relate to neurodegeneration

NOTE Confidence: 0.93971175

00:01:01.719 --> 00:01:03.980 generally and Parkinson's in particular.

NOTE Confidence: 0.9901104

00:01:05.080 --> 00:01:06.119 So I wanna start with

NOTE Confidence: 0.9901104

00:01:06.119 --> 00:01:07.580 two points about neurodegeneration,

NOTE Confidence: 0.99917054

00:01:08.040 --> 00:01:09.479 which will be relevant further

NOTE Confidence: 0.99917054

00:01:09.479 --> 00:01:09.979 on.

NOTE Confidence: 0.99926376

00:01:10.360 --> 00:01:11.659 The first is the idea

NOTE Confidence: 0.99926376

00:01:11.720 --> 00:01:12.619 of templated

NOTE Confidence: 0.99161476

00:01:12.920 --> 00:01:14.565 misfolding and the spreading of

NOTE Confidence: 0.99161476

00:01:14.565 --> 00:01:16.345 protein aggregates in the brain.

NOTE Confidence: 0.99161476

00:01:16.565 --> 00:01:17.685 This is really something that's

NOTE Confidence: 0.99161476

00:01:17.685 --> 00:01:19.125 built upon a prion like

NOTE Confidence: 0.99161476

00:01:19.125 --> 00:01:19.625 mechanism,

NOTE Confidence: 0.98682314

00:01:20.165 --> 00:01:22.025 and Virginia Lee at UPenn

NOTE Confidence: 0.98682314

00:01:22.244 --> 00:01:24.165 popularized this. So here's an

NOTE Confidence: 0.98682314

00:01:24.165 --> 00:01:25.444 example from our lab where

NOTE Confidence: 0.98682314

00:01:25.444 --> 00:01:26.185 we injected

NOTE Confidence: 0.9479644

00:01:26.485 --> 00:01:28.805 fibrils, misfolded synuclein into the

NOTE Confidence: 0.9479644

00:01:28.805 --> 00:01:29.305 striatum.

NOTE Confidence: 0.97799665

00:01:30.750 --> 00:01:32.370 In this picture whoops.

NOTE Confidence: 0.9994892

00:01:33.470 --> 00:01:34.930 In this picture here,

NOTE Confidence: 0.99955136

00:01:35.470 --> 00:01:36.290 you can see

NOTE Confidence: 0.7885053

00:01:36.670 --> 00:01:37.170 dopamine,

NOTE Confidence: 0.9666292

00:01:37.950 --> 00:01:39.410 fibers in the striatum.

NOTE Confidence: 0.9300682

00:01:39.790 --> 00:01:41.069 In a control case, if

NOTE Confidence: 0.9300682

00:01:41.069 --> 00:01:43.330 you inject these synuclein fibrils,

NOTE Confidence: 0.97154355

00:01:43.745 --> 00:01:45.345 these start to degenerate, and

NOTE Confidence: 0.97154355

00:01:45.345 --> 00:01:47.665 these, red dots here are

NOTE Confidence: 0.97154355

00:01:47.665 --> 00:01:49.525 synuclein aggregates, phosphocinuclein

NOTE Confidence: 0.8002374

00:01:49.985 --> 00:01:50.645 that accumulate.

NOTE Confidence: 0.97497594

00:01:51.265 --> 00:01:52.865 The cell bodies of these

NOTE Confidence: 0.97497594

00:01:52.865 --> 00:01:54.965 dopamine fibers in the nigra

NOTE Confidence: 0.99117935

00:01:55.505 --> 00:01:57.265 are lost over several months,

NOTE Confidence: 0.99117935

00:01:57.265 --> 00:01:58.225 and you can see this

NOTE Confidence: 0.99117935

00:01:58.225 --> 00:01:59.740 decrease. This is true not

NOTE Confidence: 0.99117935

00:01:59.740 --> 00:02:00.720 just for synuclein.

NOTE Confidence: 0.9981472

00:02:01.340 --> 00:02:02.640 On the right hand side,

NOTE Confidence: 0.98690856

00:02:03.100 --> 00:02:04.320 is shown

NOTE Confidence: 0.98840374

00:02:05.420 --> 00:02:07.020 tau that's been extracted from

NOTE Confidence: 0.98840374

00:02:07.020 --> 00:02:08.700 an Alzheimer's brain and injected

NOTE Confidence: 0.98840374

00:02:08.700 --> 00:02:10.220 into the hippocampus, and the

NOTE Confidence: 0.98840374

00:02:10.220 --> 00:02:11.660 same kind of thing happens

NOTE Confidence: 0.98840374

00:02:11.660 --> 00:02:12.639 with this protein

NOTE Confidence: 0.9657945

00:02:13.180 --> 00:02:14.160 here in brown.

NOTE Confidence: 0.9911301

00:02:14.525 --> 00:02:16.285 The protein accumulates in cell

NOTE Confidence: 0.9911301

00:02:16.285 --> 00:02:18.125 bodies and neurites, and this

NOTE Confidence: 0.9911301

00:02:18.125 --> 00:02:20.205 spreads through the brain illustrated

NOTE Confidence: 0.9911301

00:02:20.205 --> 00:02:21.265 in that schematic.

NOTE Confidence: 0.9893667

00:02:21.885 --> 00:02:24.365 So templated misfolding, that's one

NOTE Confidence: 0.9893667

00:02:24.365 --> 00:02:24.865 point.

NOTE Confidence: 0.99767524

00:02:25.325 --> 00:02:27.105 A second point is that

NOTE Confidence: 0.9987859

00:02:27.650 --> 00:02:29.110 there's multiple pathologies

NOTE Confidence: 0.99955976

00:02:29.570 --> 00:02:30.870 in most of these neurodegenerative

NOTE Confidence: 0.99954975

00:02:31.250 --> 00:02:31.750 diseases.

NOTE Confidence: 0.9838235

00:02:32.210 --> 00:02:33.570 We define them in a

NOTE Confidence: 0.9838235

00:02:33.570 --> 00:02:34.770 sort of pure way, but

NOTE Confidence: 0.9838235

00:02:34.770 --> 00:02:35.990 there's lots of overlap.

NOTE Confidence: 0.9931102

00:02:36.530 --> 00:02:37.010 Here's,

NOTE Confidence: 0.99947023

00:02:37.410 --> 00:02:38.950 two examples from

NOTE Confidence: 0.9852222

00:02:39.490 --> 00:02:41.010 Alzheimer's disease. We think of

NOTE Confidence: 0.9852222

00:02:41.010 --> 00:02:42.665 it as an a beta

NOTE Confidence: 0.9852222

00:02:42.665 --> 00:02:43.724 and tau disease,

NOTE Confidence: 0.9949909

00:02:44.025 --> 00:02:45.385 but that's only about thirty

NOTE Confidence: 0.9949909

00:02:45.385 --> 00:02:47.385 percent. Some seventy percent have

NOTE Confidence: 0.9949909

00:02:47.385 --> 00:02:48.764 synuclein or TDP

NOTE Confidence: 0.8966164

00:02:49.385 --> 00:02:51.385 pathology as well. And in

NOTE Confidence: 0.8966164

00:02:51.385 --> 00:02:52.444 progressive nuclear

NOTE Confidence: 0.98639184

00:02:53.385 --> 00:02:53.885 palsy,

NOTE Confidence: 0.95472175

00:02:54.870 --> 00:02:55.590 we think of this as

NOTE Confidence: 0.95472175

00:02:55.590 --> 00:02:56.230 a tau,

NOTE Confidence: 0.9817899

00:02:56.630 --> 00:02:58.230 disease, but lots of people

NOTE Confidence: 0.9817899

00:02:58.230 --> 00:02:59.850 have a beta synuclein

NOTE Confidence: 0.970757

00:03:00.310 --> 00:03:00.810 TDP.

NOTE Confidence: 0.99245954

00:03:01.270 --> 00:03:02.950 And this is important because,

NOTE Confidence: 0.99245954

00:03:03.190 --> 00:03:05.370 here's a diagram that illustrates

NOTE Confidence: 0.99245954

00:03:05.510 --> 00:03:07.190 the progression of Lewy body

NOTE Confidence: 0.99245954

00:03:07.190 --> 00:03:07.690 disease.

NOTE Confidence: 0.969793

00:03:08.135 --> 00:03:09.754 This, straight line,

NOTE Confidence: 0.9766149

00:03:10.215 --> 00:03:11.814 is what happens if you

NOTE Confidence: 0.9766149

00:03:11.814 --> 00:03:12.954 have pure pathology.

NOTE Confidence: 0.9995377

00:03:13.495 --> 00:03:14.694 But if you have mixed

NOTE Confidence: 0.9995377

00:03:14.694 --> 00:03:15.194 pathology,

NOTE Confidence: 0.97033715

00:03:15.974 --> 00:03:17.655 the progression of disease is

NOTE Confidence: 0.97033715

00:03:17.655 --> 00:03:19.194 faster. So comorbid,

NOTE Confidence: 0.99923134

00:03:19.655 --> 00:03:20.715 mixed pathology,

NOTE Confidence: 0.9867517

00:03:21.894 --> 00:03:23.674 and this templated spreading.

NOTE Confidence: 0.9614345

00:03:24.590 --> 00:03:25.790 K. Now I'm gonna come

NOTE Confidence: 0.9614345

00:03:25.790 --> 00:03:27.069 to pro granulan and say

NOTE Confidence: 0.9614345

00:03:27.069 --> 00:03:28.270 a few words about it.

NOTE Confidence: 0.9614345

00:03:28.270 --> 00:03:29.490 So this is a secreted,

NOTE Confidence: 0.96405005

00:03:30.190 --> 00:03:30.690 glycoprotein.

NOTE Confidence: 0.98433983

00:03:31.470 --> 00:03:32.610 It gets to the lysosome.

NOTE Confidence: 0.98433983

00:03:32.830 --> 00:03:34.690 It has seven granulan repeats.

NOTE Confidence: 0.9941035

00:03:35.069 --> 00:03:36.590 It's expressed in neurons and

NOTE Confidence: 0.9941035

00:03:36.590 --> 00:03:37.090 microglia.

NOTE Confidence: 0.97877353

00:03:37.545 --> 00:03:39.145 It was discovered, not in

NOTE Confidence: 0.97877353

00:03:39.145 --> 00:03:40.765 Parkinson's, but in frontotemporal

NOTE Confidence: 0.99312615

00:03:41.145 --> 00:03:41.885 lobe degeneration

NOTE Confidence: 0.99176383

00:03:42.265 --> 00:03:44.505 with TDP forty three. It

NOTE Confidence: 0.99176383

00:03:44.505 --> 00:03:45.224 accounts for about

NOTE Confidence: 0.99877036

00:03:46.025 --> 00:03:47.944 mutations in a dominant fashion

NOTE Confidence: 0.99877036

00:03:47.944 --> 00:03:49.485 account for about twenty percent

NOTE Confidence: 0.9930168

00:03:50.450 --> 00:03:51.730 due to loss of function,

NOTE Confidence: 0.9930168

00:03:51.730 --> 00:03:53.349 nonsense mediated decay.

NOTE Confidence: 0.9991276

00:03:53.890 --> 00:03:55.110 Rare people with

NOTE Confidence: 0.9796033

00:03:55.569 --> 00:03:56.069 no,

NOTE Confidence: 0.9223798

00:03:56.530 --> 00:03:57.670 expression of progranulin

NOTE Confidence: 0.99626637

00:03:57.970 --> 00:03:59.110 get early onset,

NOTE Confidence: 0.97629434

00:03:59.970 --> 00:04:01.510 neuronal steroid lipofuscinosis.

NOTE Confidence: 0.8528903

00:04:02.849 --> 00:04:03.349 But,

NOTE Confidence: 0.99606764

00:04:04.425 --> 00:04:05.785 the reason this is interesting,

NOTE Confidence: 0.99606764

00:04:05.785 --> 00:04:07.305 it's actually a risk factor

NOTE Confidence: 0.99606764

00:04:07.305 --> 00:04:08.605 for multiple neurodegenerative

NOTE Confidence: 0.9869066

00:04:08.985 --> 00:04:09.485 diseases.

NOTE Confidence: 0.9618101

00:04:10.025 --> 00:04:11.385 So it's a whoops. It's

NOTE Confidence: 0.9618101

00:04:11.385 --> 00:04:13.724 a GWAS hit in Parkinson's

NOTE Confidence: 0.9618101

00:04:13.864 --> 00:04:15.724 disease, in Alzheimer's disease.

NOTE Confidence: 0.9924097

00:04:16.264 --> 00:04:18.264 Variants are associated with multiple

NOTE Confidence: 0.9924097

00:04:18.264 --> 00:04:19.165 different cases.

NOTE Confidence: 0.9858924

00:04:19.779 --> 00:04:21.460 SNPs are actually associated with

NOTE Confidence: 0.9858924

00:04:21.460 --> 00:04:22.440 Gaucher disease.

NOTE Confidence: 0.88955605

00:04:23.060 --> 00:04:24.920 We showed that granulins SNPs

NOTE Confidence: 0.88955605

00:04:25.060 --> 00:04:27.080 regulate CSF tau levels.

NOTE Confidence: 0.9920071

00:04:27.460 --> 00:04:28.920 So it's really a broad,

NOTE Confidence: 0.9143839

00:04:29.380 --> 00:04:31.779 risk factor, genetic variation in

NOTE Confidence: 0.9143839

00:04:31.779 --> 00:04:32.279 progranulin

NOTE Confidence: 0.9387107

00:04:32.660 --> 00:04:33.800 for multiple neurodegenerative

NOTE Confidence: 0.99944574

00:04:34.260 --> 00:04:34.760 diseases.

NOTE Confidence: 0.96622264

00:04:36.714 --> 00:04:38.335 I'm gonna talk about progranulin

NOTE Confidence: 0.96622264

00:04:38.555 --> 00:04:39.915 biology a bit and, in

NOTE Confidence: 0.96622264

00:04:39.915 --> 00:04:41.935 particular, focus on this idea

NOTE Confidence: 0.9923644

00:04:42.315 --> 00:04:44.475 about tauopathy and linking with

NOTE Confidence: 0.9923644

00:04:44.475 --> 00:04:45.615 synuclein pathology.

NOTE Confidence: 0.95798486

00:04:47.275 --> 00:04:48.635 So we got into this,

NOTE Confidence: 0.95798486

00:04:48.875 --> 00:04:50.740 first knowing that pro granulan

NOTE Confidence: 0.95798486

00:04:50.800 --> 00:04:52.480 was a gene that caused

NOTE Confidence: 0.95798486

00:04:52.480 --> 00:04:54.560 FTLD, a secreted protein. We

NOTE Confidence: 0.95798486

00:04:54.560 --> 00:04:56.000 looked for binding sites on

NOTE Confidence: 0.95798486

00:04:56.000 --> 00:04:57.760 the cell, and what's shown

NOTE Confidence: 0.95798486

00:04:57.760 --> 00:04:58.640 here is that,

NOTE Confidence: 0.9494415

00:04:59.360 --> 00:05:01.220 pro granulan binds to sertilin

NOTE Confidence: 0.9494415

00:05:01.279 --> 00:05:03.140 on the cell surface identified

NOTE Confidence: 0.9494415

00:05:03.279 --> 00:05:04.580 by expression cloning.

NOTE Confidence: 0.94531053

00:05:05.245 --> 00:05:07.005 Once this binding happens, here

NOTE Confidence: 0.94531053

00:05:07.005 --> 00:05:08.305 is a cell with sordolan,

NOTE Confidence: 0.94531053

00:05:08.525 --> 00:05:10.285 progranulins bound to it. Very

NOTE Confidence: 0.94531053

00:05:10.285 --> 00:05:11.725 quickly, it's taken up and

NOTE Confidence: 0.94531053

00:05:11.725 --> 00:05:13.025 delivered to the lysosome.

NOTE Confidence: 0.9974647

00:05:13.805 --> 00:05:15.085 And this is important for

NOTE Confidence: 0.9974647

00:05:15.085 --> 00:05:16.305 the levels of progranulins.

NOTE Confidence: 0.9960603

00:05:16.764 --> 00:05:17.264 So

NOTE Confidence: 0.96691144

00:05:17.565 --> 00:05:18.384 shown here,

NOTE Confidence: 0.9505701

00:05:18.779 --> 00:05:19.680 in a progranulins

NOTE Confidence: 0.9695802

00:05:20.060 --> 00:05:20.560 heterozygote,

NOTE Confidence: 0.9798622

00:05:20.860 --> 00:05:21.820 you lose a lot of

NOTE Confidence: 0.9798622

00:05:21.820 --> 00:05:23.040 this progranulins,

NOTE Confidence: 0.9855916

00:05:23.820 --> 00:05:26.400 but if the, this mouse

NOTE Confidence: 0.9535247

00:05:26.779 --> 00:05:28.380 has no sordolin, this is

NOTE Confidence: 0.9535247

00:05:28.380 --> 00:05:30.060 restored to normal because it's

NOTE Confidence: 0.9535247

00:05:30.060 --> 00:05:31.279 not being endocytosed.

NOTE Confidence: 0.9723067

00:05:32.764 --> 00:05:33.885 And now we know that,

NOTE Confidence: 0.9723067

00:05:34.205 --> 00:05:36.285 there's actually two receptors that

NOTE Confidence: 0.9723067

00:05:36.285 --> 00:05:37.985 are important here for

NOTE Confidence: 0.9984806

00:05:38.605 --> 00:05:39.105 delivering

NOTE Confidence: 0.997922

00:05:39.565 --> 00:05:40.065 extracellular

NOTE Confidence: 0.8374421

00:05:40.445 --> 00:05:42.145 pro granulant to the lysosome.

NOTE Confidence: 0.98385596

00:05:42.764 --> 00:05:44.285 It's actually typically in a

NOTE Confidence: 0.98385596

00:05:44.285 --> 00:05:45.585 complex with prosapacin.

NOTE Confidence: 0.9949386

00:05:46.044 --> 00:05:47.485 Both of these proteins get

NOTE Confidence: 0.9949386

00:05:47.485 --> 00:05:48.680 delivered to the lysosome.

NOTE Confidence: 0.9838074

00:05:49.220 --> 00:05:50.100 So that's a little bit

NOTE Confidence: 0.9838074

00:05:50.100 --> 00:05:52.020 of background. What happens, at

NOTE Confidence: 0.9838074

00:05:52.020 --> 00:05:53.140 least in mice, when you

NOTE Confidence: 0.9838074

00:05:53.140 --> 00:05:54.440 get rid of progranulin?

NOTE Confidence: 0.9833239

00:05:55.620 --> 00:05:56.820 So we did some omic

NOTE Confidence: 0.9833239

00:05:56.820 --> 00:05:58.660 studies, and what's shown here

NOTE Confidence: 0.9833239

00:05:58.660 --> 00:05:59.540 is that if you look

NOTE Confidence: 0.9833239

00:05:59.540 --> 00:06:00.660 at protein or you look

NOTE Confidence: 0.9833239

00:06:00.660 --> 00:06:01.400 at RNA,

NOTE Confidence: 0.8953678

00:06:02.375 --> 00:06:04.555 the major pathway that's altered,

NOTE Confidence: 0.9854633

00:06:05.654 --> 00:06:08.395 are are is lysosomal pathways.

NOTE Confidence: 0.9320435

00:06:10.135 --> 00:06:11.495 And in fact, if you

NOTE Confidence: 0.9320435

00:06:11.495 --> 00:06:13.675 stain for a lysosomal enzyme,

NOTE Confidence: 0.9320435

00:06:13.735 --> 00:06:14.714 this, peptidase,

NOTE Confidence: 0.99097323

00:06:15.895 --> 00:06:16.635 these are

NOTE Confidence: 0.9728489

00:06:17.170 --> 00:06:19.089 these are neurons here. The

NOTE Confidence: 0.9728489

00:06:19.089 --> 00:06:21.010 lysosomes become larger and more

NOTE Confidence: 0.9728489

00:06:21.010 --> 00:06:23.350 numerous when granulins not present.

NOTE Confidence: 0.9975532

00:06:23.650 --> 00:06:24.870 And this has consequences,

NOTE Confidence: 0.9955918

00:06:25.570 --> 00:06:27.170 for the function of neurons.

NOTE Confidence: 0.9955918

00:06:27.170 --> 00:06:28.770 So in the brain of

NOTE Confidence: 0.9955918

00:06:28.770 --> 00:06:29.510 these animals,

NOTE Confidence: 0.97485125

00:06:30.125 --> 00:06:31.985 they start piling up lipofusion,

NOTE Confidence: 0.9580365

00:06:33.005 --> 00:06:34.465 as the animals age.

NOTE Confidence: 0.9666005

00:06:35.005 --> 00:06:36.925 That's what's shown here. And,

NOTE Confidence: 0.9666005

00:06:37.085 --> 00:06:38.525 there's a reaction to this,

NOTE Confidence: 0.9666005

00:06:38.525 --> 00:06:40.545 so microglia become activated.

NOTE Confidence: 0.996106

00:06:41.005 --> 00:06:42.065 And if you profile,

NOTE Confidence: 0.9803324

00:06:42.605 --> 00:06:44.305 the single cell level, microglia

NOTE Confidence: 0.9803324

00:06:44.605 --> 00:06:45.570 turn on a bunch of

NOTE Confidence: 0.9803324

00:06:45.810 --> 00:06:46.950 inflammatory genes.

NOTE Confidence: 0.8177633

00:06:47.730 --> 00:06:48.550 Now this

NOTE Confidence: 0.94791424

00:06:49.089 --> 00:06:51.010 pro granulant in mice doesn't

NOTE Confidence: 0.94791424

00:06:51.010 --> 00:06:53.010 exactly replicate human in the

NOTE Confidence: 0.94791424

00:06:53.010 --> 00:06:54.290 sense that they don't get

NOTE Confidence: 0.94791424

00:06:54.290 --> 00:06:55.430 TDP pathology,

NOTE Confidence: 0.9930664

00:06:56.610 --> 00:06:58.850 and have an FTLD like

NOTE Confidence: 0.9930664

00:06:58.850 --> 00:06:59.350 picture.

NOTE Confidence: 0.98725903

00:06:59.955 --> 00:07:02.055 However, there is some, degeneration.

NOTE Confidence: 0.9760626

00:07:02.435 --> 00:07:03.714 Here's a collaboration we did

NOTE Confidence: 0.9760626

00:07:03.714 --> 00:07:05.475 with Brian Hafler. In the

NOTE Confidence: 0.9760626

00:07:05.475 --> 00:07:05.975 retina,

NOTE Confidence: 0.9746521

00:07:06.435 --> 00:07:08.595 these granulin knockout animals have

NOTE Confidence: 0.9746521

00:07:08.595 --> 00:07:09.794 a thinning of the retina

NOTE Confidence: 0.9746521

00:07:09.794 --> 00:07:11.655 and a loss of, ganglion

NOTE Confidence: 0.9746521

00:07:11.794 --> 00:07:12.294 cells.

NOTE Confidence: 0.9577092

00:07:12.755 --> 00:07:14.055 K. So that's the background

NOTE Confidence: 0.9577092

00:07:14.195 --> 00:07:15.014 on progranulin.

NOTE Confidence: 0.9986785

00:07:15.700 --> 00:07:17.060 How does it interact with

NOTE Confidence: 0.9986785

00:07:17.060 --> 00:07:17.560 neurodegeneration?

NOTE Confidence: 0.99353313

00:07:19.380 --> 00:07:20.660 We did some studies to

NOTE Confidence: 0.99353313

00:07:20.660 --> 00:07:21.060 look,

NOTE Confidence: 0.96704817

00:07:21.620 --> 00:07:23.300 in an Alzheimer's model. So

NOTE Confidence: 0.96704817

00:07:23.300 --> 00:07:24.420 these are mice that have

NOTE Confidence: 0.96704817

00:07:24.420 --> 00:07:26.280 APP and presenilin mutations.

NOTE Confidence: 0.9898359

00:07:26.900 --> 00:07:28.520 And, of course, they accumulate

NOTE Confidence: 0.93685853

00:07:28.900 --> 00:07:30.965 a beta plaques. Here, stained

NOTE Confidence: 0.93685853

00:07:30.965 --> 00:07:32.805 with an antibody or with

NOTE Confidence: 0.93685853

00:07:32.805 --> 00:07:33.305 thioflavin,

NOTE Confidence: 0.99701136

00:07:34.485 --> 00:07:35.845 to see the dense core

NOTE Confidence: 0.99701136

00:07:35.845 --> 00:07:36.345 plaques.

NOTE Confidence: 0.9067447

00:07:37.764 --> 00:07:39.444 When the animals don't have

NOTE Confidence: 0.9067447

00:07:39.444 --> 00:07:39.944 granulin,

NOTE Confidence: 0.9650442

00:07:40.324 --> 00:07:42.164 the thioflavin, the dense core

NOTE Confidence: 0.9650442

00:07:42.164 --> 00:07:43.910 plaques looks quite the same,

NOTE Confidence: 0.9650442

00:07:44.210 --> 00:07:46.370 but this diffuse halo of

NOTE Confidence: 0.9650442

00:07:46.370 --> 00:07:47.990 a beta around the plaques

NOTE Confidence: 0.9650442

00:07:48.130 --> 00:07:49.590 is reduced significantly.

NOTE Confidence: 0.9874795

00:07:50.610 --> 00:07:51.509 And that actually,

NOTE Confidence: 0.99252033

00:07:51.889 --> 00:07:53.669 lines up with this microglial

NOTE Confidence: 0.99938315

00:07:54.289 --> 00:07:55.889 change that happens in these

NOTE Confidence: 0.99938315

00:07:55.889 --> 00:07:56.389 animals.

NOTE Confidence: 0.97537357

00:07:56.914 --> 00:07:58.115 So in the if you

NOTE Confidence: 0.97537357

00:07:58.115 --> 00:07:59.395 look at a younger age,

NOTE Confidence: 0.97537357

00:07:59.395 --> 00:08:00.435 before there's a lot of

NOTE Confidence: 0.97537357

00:08:00.435 --> 00:08:01.955 plaques, the first plaques that

NOTE Confidence: 0.97537357

00:08:01.955 --> 00:08:02.455 form,

NOTE Confidence: 0.95185626

00:08:03.955 --> 00:08:05.255 shown here with a beta,

NOTE Confidence: 0.95185626

00:08:05.555 --> 00:08:06.514 there's more,

NOTE Confidence: 0.97255164

00:08:06.995 --> 00:08:09.235 activated microglia around them. And

NOTE Confidence: 0.97255164

00:08:09.235 --> 00:08:09.895 these microglia

NOTE Confidence: 0.99885046

00:08:10.275 --> 00:08:10.775 are

NOTE Confidence: 0.975944

00:08:12.500 --> 00:08:14.820 trapping or confining the plaques

NOTE Confidence: 0.975944

00:08:14.820 --> 00:08:15.780 so that they end up

NOTE Confidence: 0.975944

00:08:15.780 --> 00:08:17.780 being dense and smaller at

NOTE Confidence: 0.975944

00:08:17.780 --> 00:08:19.380 a later age. And this

NOTE Confidence: 0.975944

00:08:19.380 --> 00:08:21.780 has functional consequences in terms

NOTE Confidence: 0.975944

00:08:21.780 --> 00:08:22.600 of the neurites.

NOTE Confidence: 0.9838438

00:08:23.060 --> 00:08:24.180 So this is looking at

NOTE Confidence: 0.9838438

00:08:24.180 --> 00:08:26.500 dystrophic neurites around these plaques

NOTE Confidence: 0.9838438

00:08:26.500 --> 00:08:27.720 at the older age.

NOTE Confidence: 0.9461133

00:08:28.635 --> 00:08:30.335 And in the granular knockout,

NOTE Confidence: 0.9461133

00:08:30.395 --> 00:08:32.235 these dystrophic neurites are more

NOTE Confidence: 0.9461133

00:08:32.235 --> 00:08:33.615 confined and fewer.

NOTE Confidence: 0.98482245

00:08:34.715 --> 00:08:36.475 But this model doesn't have,

NOTE Confidence: 0.99693716

00:08:36.875 --> 00:08:38.155 is not a full blown

NOTE Confidence: 0.99693716

00:08:38.155 --> 00:08:39.755 Alzheimer's model. It has a

NOTE Confidence: 0.99693716

00:08:39.755 --> 00:08:40.255 beta

NOTE Confidence: 0.9481922

00:08:40.740 --> 00:08:42.420 pathology, but really not tau

NOTE Confidence: 0.9481922

00:08:42.420 --> 00:08:42.920 pathology.

NOTE Confidence: 0.9662581

00:08:43.540 --> 00:08:44.900 So we did another study

NOTE Confidence: 0.9662581

00:08:44.900 --> 00:08:45.940 here where we looked at

NOTE Confidence: 0.9662581

00:08:45.940 --> 00:08:48.360 tau transgenic mice. These have

NOTE Confidence: 0.9662581

00:08:48.420 --> 00:08:50.580 human mutant tau expressed in

NOTE Confidence: 0.9662581

00:08:50.580 --> 00:08:51.240 the mouse.

NOTE Confidence: 0.9709999

00:08:51.860 --> 00:08:53.780 And these mice develop a

NOTE Confidence: 0.9709999

00:08:53.780 --> 00:08:54.679 pretty clear,

NOTE Confidence: 0.99562854

00:08:55.615 --> 00:08:56.995 atrophy over time.

NOTE Confidence: 0.963816

00:08:57.455 --> 00:08:59.615 Their ventricles become larger, and

NOTE Confidence: 0.963816

00:08:59.615 --> 00:09:01.715 their hippocampus becomes smaller.

NOTE Confidence: 0.9352355

00:09:05.054 --> 00:09:06.495 And this both of these

NOTE Confidence: 0.9352355

00:09:06.495 --> 00:09:07.955 phenotypes are reduced

NOTE Confidence: 0.9646187

00:09:08.480 --> 00:09:09.300 when progranulin

NOTE Confidence: 0.98117113

00:09:09.759 --> 00:09:11.120 is eliminated from the mice.

NOTE Confidence: 0.98117113

00:09:11.120 --> 00:09:12.319 And, actually, even in the

NOTE Confidence: 0.98117113

00:09:12.319 --> 00:09:14.819 heterozygous mice, there's a significant

NOTE Confidence: 0.98117113

00:09:15.040 --> 00:09:16.420 reduction of this pathology.

NOTE Confidence: 0.9947342

00:09:17.360 --> 00:09:19.199 And the animals do somewhat

NOTE Confidence: 0.9947342

00:09:19.199 --> 00:09:20.959 better on memory tests. This

NOTE Confidence: 0.9947342

00:09:20.959 --> 00:09:23.139 is a spatial memory test.

NOTE Confidence: 0.98857135

00:09:23.804 --> 00:09:25.405 Wild type mice are trained

NOTE Confidence: 0.98857135

00:09:25.405 --> 00:09:26.845 to remember where a target

NOTE Confidence: 0.98857135

00:09:26.845 --> 00:09:27.345 is,

NOTE Confidence: 0.9512613

00:09:27.725 --> 00:09:28.545 shown here.

NOTE Confidence: 0.9380615

00:09:29.005 --> 00:09:29.325 But,

NOTE Confidence: 0.99600685

00:09:30.285 --> 00:09:30.945 in the

NOTE Confidence: 0.9338882

00:09:31.485 --> 00:09:33.325 tauopathy mice, they can't do

NOTE Confidence: 0.9338882

00:09:33.325 --> 00:09:35.005 this task at all. And

NOTE Confidence: 0.9338882

00:09:35.005 --> 00:09:37.085 this is partially recovered when

NOTE Confidence: 0.9338882

00:09:37.085 --> 00:09:37.285 there's less atrophy in the

NOTE Confidence: 0.9338882

00:09:37.285 --> 00:09:38.385 hippocampus and, smaller ventricles.

NOTE Confidence: 0.859945

00:09:46.400 --> 00:09:48.080 Molecular sense by a single

NOTE Confidence: 0.859945

00:09:48.080 --> 00:09:48.900 cell profiling.

NOTE Confidence: 0.98515445

00:09:49.760 --> 00:09:51.220 And across these genotypes,

NOTE Confidence: 0.9731518

00:09:51.525 --> 00:09:53.305 there's some pretty dramatic changes.

NOTE Confidence: 0.9731518

00:09:53.365 --> 00:09:55.305 This is shown for inhibitory

NOTE Confidence: 0.9731518

00:09:55.605 --> 00:09:57.705 neurons here and then against

NOTE Confidence: 0.9731518

00:09:57.765 --> 00:09:58.265 different,

NOTE Confidence: 0.99929893

00:09:58.725 --> 00:09:59.865 pathway clusters.

NOTE Confidence: 0.98210055

00:10:00.645 --> 00:10:02.405 The the tauopathy mice have

NOTE Confidence: 0.98210055

00:10:02.405 --> 00:10:03.684 a lot of changes, but

NOTE Confidence: 0.98210055

00:10:03.684 --> 00:10:06.265 these are essentially eliminated when,

NOTE Confidence: 0.9714235

00:10:06.760 --> 00:10:09.079 granulin is reduced. That's true

NOTE Confidence: 0.9714235

00:10:09.079 --> 00:10:10.519 in multiple cell types. So

NOTE Confidence: 0.9714235

00:10:10.519 --> 00:10:11.579 this is inhibitory

NOTE Confidence: 0.91002756

00:10:11.880 --> 00:10:12.779 neurons here,

NOTE Confidence: 0.9953091

00:10:13.720 --> 00:10:14.700 in oligodendrocytes.

NOTE Confidence: 0.9926047

00:10:15.800 --> 00:10:17.399 There's also a phenotype that's

NOTE Confidence: 0.9926047

00:10:17.399 --> 00:10:19.260 reduced by granulin knockouts.

NOTE Confidence: 0.9994566

00:10:19.800 --> 00:10:20.620 In microglia,

NOTE Confidence: 0.95020396

00:10:21.524 --> 00:10:22.024 there's

NOTE Confidence: 0.96570575

00:10:22.404 --> 00:10:24.425 another phenotype, and it overlaps

NOTE Confidence: 0.96570575

00:10:24.485 --> 00:10:26.084 with the so called DAM

NOTE Confidence: 0.96570575

00:10:26.084 --> 00:10:28.665 phenotype or disease associated microglial

NOTE Confidence: 0.96570575

00:10:28.884 --> 00:10:29.384 phenotype.

NOTE Confidence: 0.94790864

00:10:30.485 --> 00:10:31.444 And this is,

NOTE Confidence: 0.9993472

00:10:32.245 --> 00:10:33.384 reduced by

NOTE Confidence: 0.9225334

00:10:34.640 --> 00:10:36.320 loss of pro granulant, again,

NOTE Confidence: 0.9225334

00:10:36.320 --> 00:10:38.179 even in the heterozygous state.

NOTE Confidence: 0.8885615

00:10:38.559 --> 00:10:40.000 Same thing in astrocytes. So

NOTE Confidence: 0.8885615

00:10:40.000 --> 00:10:40.980 really a reduction,

NOTE Confidence: 0.9996145

00:10:41.840 --> 00:10:42.340 molecular

NOTE Confidence: 0.9780682

00:10:43.120 --> 00:10:44.340 atrophy, etcetera.

NOTE Confidence: 0.97300565

00:10:47.045 --> 00:10:48.804 So quite a a strong

NOTE Confidence: 0.97300565

00:10:48.804 --> 00:10:50.665 effect on, tau.

NOTE Confidence: 0.99273854

00:10:51.285 --> 00:10:52.804 So what is tau actually

NOTE Confidence: 0.99273854

00:10:52.964 --> 00:10:54.665 what's happening to the tau?

NOTE Confidence: 0.99273854

00:10:54.725 --> 00:10:56.404 So this is looking at

NOTE Confidence: 0.99273854

00:10:56.404 --> 00:10:58.804 phospho tau epitopes that mark

NOTE Confidence: 0.99273854

00:10:58.804 --> 00:11:00.584 aggregates of the tau protein.

NOTE Confidence: 0.9857955

00:11:01.020 --> 00:11:02.140 And, of course, in these

NOTE Confidence: 0.9857955

00:11:02.140 --> 00:11:03.360 transgenic mice,

NOTE Confidence: 0.9910153

00:11:04.380 --> 00:11:05.200 they develop

NOTE Confidence: 0.87727517

00:11:05.740 --> 00:11:06.240 aggregates,

NOTE Confidence: 0.99494785

00:11:06.860 --> 00:11:08.700 but these aggregates are actually

NOTE Confidence: 0.99494785

00:11:08.700 --> 00:11:10.220 increased. So even though there's

NOTE Confidence: 0.99494785

00:11:10.220 --> 00:11:10.720 less

NOTE Confidence: 0.99909383

00:11:11.500 --> 00:11:12.000 degeneration,

NOTE Confidence: 0.9995947

00:11:12.460 --> 00:11:15.120 less atrophy, there's more aggregates

NOTE Confidence: 0.960012

00:11:15.525 --> 00:11:16.885 in the absence of pro

NOTE Confidence: 0.960012

00:11:16.885 --> 00:11:18.405 granulant, which is a little

NOTE Confidence: 0.960012

00:11:18.405 --> 00:11:18.905 counterintuitive.

NOTE Confidence: 0.99582213

00:11:21.445 --> 00:11:23.145 But this is perhaps explained

NOTE Confidence: 0.99582213

00:11:23.285 --> 00:11:24.725 by this panel at the

NOTE Confidence: 0.99582213

00:11:24.725 --> 00:11:26.265 bottom. So it's been recognized

NOTE Confidence: 0.99582213

00:11:26.325 --> 00:11:27.545 that if you study

NOTE Confidence: 0.9945971

00:11:28.005 --> 00:11:29.945 tau aggregation in this strain,

NOTE Confidence: 0.9963835

00:11:30.790 --> 00:11:32.170 there's kind of a progression.

NOTE Confidence: 0.9701985

00:11:33.350 --> 00:11:35.429 Early aggregates tend to be

NOTE Confidence: 0.9701985

00:11:35.429 --> 00:11:37.190 cellular and large as you're

NOTE Confidence: 0.9701985

00:11:37.190 --> 00:11:38.730 seeing in the upper panel.

NOTE Confidence: 0.9701985

00:11:39.030 --> 00:11:40.470 But as the the most

NOTE Confidence: 0.9701985

00:11:40.470 --> 00:11:42.710 severely affected animals that really

NOTE Confidence: 0.9701985

00:11:42.710 --> 00:11:43.450 have atrophy

NOTE Confidence: 0.97856647

00:11:43.830 --> 00:11:45.050 have this diffuse

NOTE Confidence: 0.9850914

00:11:46.434 --> 00:11:47.415 type four pattern,

NOTE Confidence: 0.9809659

00:11:48.275 --> 00:11:49.895 which fills the whole hippocampus.

NOTE Confidence: 0.97375894

00:11:50.434 --> 00:11:52.755 And the granuline loss shifts

NOTE Confidence: 0.97375894

00:11:52.755 --> 00:11:54.515 to this earlier sort of

NOTE Confidence: 0.97375894

00:11:54.515 --> 00:11:56.195 cellular aggregation, so a change

NOTE Confidence: 0.97375894

00:11:56.195 --> 00:11:57.095 in the quality

NOTE Confidence: 0.87945604

00:11:59.795 --> 00:12:01.015 of the tau aggregation.

NOTE Confidence: 0.97033083

00:12:02.670 --> 00:12:04.929 Based on, this tau aggregation,

NOTE Confidence: 0.97033083

00:12:05.150 --> 00:12:07.309 we thought about there's an

NOTE Confidence: 0.97033083

00:12:07.309 --> 00:12:08.510 effect on I beta, there's

NOTE Confidence: 0.97033083

00:12:08.510 --> 00:12:10.270 an effect on tau, maybe

NOTE Confidence: 0.97033083

00:12:10.270 --> 00:12:11.809 there's an effect on synuclein

NOTE Confidence: 0.97033083

00:12:12.030 --> 00:12:12.770 as well

NOTE Confidence: 0.91958064

00:12:13.230 --> 00:12:13.970 through this

NOTE Confidence: 0.9938871

00:12:14.334 --> 00:12:15.795 as part of this comorbid

NOTE Confidence: 0.9938871

00:12:16.015 --> 00:12:16.515 pathology,

NOTE Confidence: 0.9974957

00:12:17.295 --> 00:12:18.195 type of pattern.

NOTE Confidence: 0.9858739

00:12:18.735 --> 00:12:20.095 So in these mice that

NOTE Confidence: 0.9858739

00:12:20.095 --> 00:12:21.214 I've been telling you about,

NOTE Confidence: 0.9858739

00:12:21.214 --> 00:12:23.455 the tauopathy mice, we looked

NOTE Confidence: 0.9858739

00:12:23.455 --> 00:12:23.855 at,

NOTE Confidence: 0.9384304

00:12:24.894 --> 00:12:25.394 phosphocinuclein

NOTE Confidence: 0.9917488

00:12:26.255 --> 00:12:27.475 that marks aggregates.

NOTE Confidence: 0.9818353

00:12:27.900 --> 00:12:29.660 When there's pure tauopathy, we

NOTE Confidence: 0.9818353

00:12:29.660 --> 00:12:31.040 really don't see any synuclein

NOTE Confidence: 0.9818353

00:12:31.180 --> 00:12:31.680 aggregates.

NOTE Confidence: 0.8716072

00:12:32.220 --> 00:12:34.320 But when granuline is reduced,

NOTE Confidence: 0.9984081

00:12:34.700 --> 00:12:35.520 the tauopathy

NOTE Confidence: 0.91304076

00:12:35.900 --> 00:12:37.580 goes up and now it

NOTE Confidence: 0.91304076

00:12:37.580 --> 00:12:38.640 becomes colocalized

NOTE Confidence: 0.97691315

00:12:39.100 --> 00:12:41.535 with synuclein aggregates as well.

NOTE Confidence: 0.97691315

00:12:41.615 --> 00:12:43.694 So copathology is now happening

NOTE Confidence: 0.97691315

00:12:43.694 --> 00:12:44.595 in these animals.

NOTE Confidence: 0.98672897

00:12:45.134 --> 00:12:46.334 And this is perhaps not

NOTE Confidence: 0.98672897

00:12:46.334 --> 00:12:49.154 surprising. There's some autopsy description

NOTE Confidence: 0.8978787

00:12:49.535 --> 00:12:51.554 from granuline mutation cases

NOTE Confidence: 0.99138343

00:12:52.095 --> 00:12:53.295 that showed of course, these

NOTE Confidence: 0.99138343

00:12:53.295 --> 00:12:55.529 have TDP forty three aggregates,

NOTE Confidence: 0.9255422

00:12:56.070 --> 00:12:57.769 but they also have tau,

NOTE Confidence: 0.9255422

00:12:57.910 --> 00:13:00.010 phospho tau aggregates and phosphosinuclein

NOTE Confidence: 0.9843965

00:13:00.709 --> 00:13:01.209 aggregates,

NOTE Confidence: 0.9993768

00:13:01.910 --> 00:13:02.730 in the brain.

NOTE Confidence: 0.99777824

00:13:03.990 --> 00:13:05.110 So how might this be

NOTE Confidence: 0.99777824

00:13:05.110 --> 00:13:05.610 happening?

NOTE Confidence: 0.96229136

00:13:06.550 --> 00:13:07.929 We were struck that,

NOTE Confidence: 0.839288

00:13:08.585 --> 00:13:10.125 progranulin is a lysosomal

NOTE Confidence: 0.9639186

00:13:10.665 --> 00:13:11.165 delivered

NOTE Confidence: 0.90323144

00:13:11.465 --> 00:13:11.965 glycoprotein,

NOTE Confidence: 0.9953089

00:13:12.825 --> 00:13:14.285 and one of the strongest

NOTE Confidence: 0.9953089

00:13:14.425 --> 00:13:16.125 risks in Parkinson's disease

NOTE Confidence: 0.9476912

00:13:16.665 --> 00:13:17.645 relates to,

NOTE Confidence: 0.84562695

00:13:18.585 --> 00:13:19.085 glucoscerebrocidase,

NOTE Confidence: 0.8661116

00:13:20.184 --> 00:13:20.684 GBA.

NOTE Confidence: 0.9785674

00:13:21.350 --> 00:13:22.470 And so we looked into

NOTE Confidence: 0.9785674

00:13:22.470 --> 00:13:23.910 whether there might be an

NOTE Confidence: 0.9785674

00:13:23.910 --> 00:13:25.690 interaction there. And in fact,

NOTE Confidence: 0.65922123

00:13:26.470 --> 00:13:27.450 glucose cerebralidase,

NOTE Confidence: 0.5920997

00:13:27.830 --> 00:13:29.210 g c ase,

NOTE Confidence: 0.9634639

00:13:30.790 --> 00:13:31.290 coimmunoprecipitates

NOTE Confidence: 0.93696225

00:13:32.390 --> 00:13:33.210 with progranulin.

NOTE Confidence: 0.9991704

00:13:33.990 --> 00:13:35.210 And if one measures

NOTE Confidence: 0.9811944

00:13:36.575 --> 00:13:38.275 the levels of this enzyme

NOTE Confidence: 0.9811944

00:13:38.335 --> 00:13:39.615 activity in the brain of

NOTE Confidence: 0.9811944

00:13:39.615 --> 00:13:41.475 granuline knockouts, it's reduced.

NOTE Confidence: 0.9815592

00:13:42.015 --> 00:13:42.815 And that led us to

NOTE Confidence: 0.9815592

00:13:42.815 --> 00:13:44.495 this kind of idea that

NOTE Confidence: 0.9815592

00:13:44.495 --> 00:13:44.995 progranuline

NOTE Confidence: 0.9731922

00:13:45.375 --> 00:13:47.154 reduction may reduce the enzyme

NOTE Confidence: 0.9731922

00:13:47.214 --> 00:13:47.714 activity,

NOTE Confidence: 0.9458181

00:13:48.335 --> 00:13:50.015 then increase the substrate, and

NOTE Confidence: 0.9458181

00:13:50.015 --> 00:13:51.809 that this participates in the

NOTE Confidence: 0.9458181

00:13:51.809 --> 00:13:52.309 inclusions.

NOTE Confidence: 0.9019054

00:13:53.170 --> 00:13:54.450 And in fact, we when

NOTE Confidence: 0.9019054

00:13:54.450 --> 00:13:55.910 we looked at the substrate

NOTE Confidence: 0.9019054

00:13:56.130 --> 00:13:57.990 of GCase, this glucoseremide,

NOTE Confidence: 0.99633723

00:13:59.970 --> 00:14:01.110 there was a strong,

NOTE Confidence: 0.969637

00:14:01.730 --> 00:14:02.230 colocalization

NOTE Confidence: 0.97427195

00:14:03.010 --> 00:14:04.950 with the phospho tau deposits.

NOTE Confidence: 0.986154

00:14:05.585 --> 00:14:07.425 And this showed, again, very

NOTE Confidence: 0.986154

00:14:07.425 --> 00:14:08.485 striking colocalization

NOTE Confidence: 0.85672283

00:14:09.105 --> 00:14:09.925 and increase,

NOTE Confidence: 0.9306971

00:14:11.345 --> 00:14:13.445 as granuline was reduced.

NOTE Confidence: 0.9786135

00:14:15.665 --> 00:14:17.345 This is also detectable in

NOTE Confidence: 0.9786135

00:14:17.345 --> 00:14:18.865 sort of the biochemical level.

NOTE Confidence: 0.9786135

00:14:18.865 --> 00:14:19.845 If you do lipidomics,

NOTE Confidence: 0.9318322

00:14:20.660 --> 00:14:23.160 The total amount of, glucosylceramide

NOTE Confidence: 0.9772358

00:14:23.860 --> 00:14:25.060 in the brain goes up

NOTE Confidence: 0.9772358

00:14:25.060 --> 00:14:25.880 when progranulin

NOTE Confidence: 0.9993027

00:14:26.980 --> 00:14:27.720 is reduced.

NOTE Confidence: 0.99840045

00:14:29.620 --> 00:14:31.480 Is this actually causative

NOTE Confidence: 0.99729353

00:14:31.860 --> 00:14:33.380 in the way tau is

NOTE Confidence: 0.99729353

00:14:33.380 --> 00:14:33.880 aggregating?

NOTE Confidence: 0.92123

00:14:34.340 --> 00:14:35.595 So here we've looked at

NOTE Confidence: 0.92123

00:14:35.834 --> 00:14:37.454 cortical neurons in culture,

NOTE Confidence: 0.9172356

00:14:37.995 --> 00:14:39.274 and we exposed them to

NOTE Confidence: 0.9172356

00:14:39.274 --> 00:14:41.514 a GCase inhibitor, this drug

NOTE Confidence: 0.9172356

00:14:41.514 --> 00:14:42.014 CBE,

NOTE Confidence: 0.95975655

00:14:42.714 --> 00:14:44.394 and then we triggered tau

NOTE Confidence: 0.95975655

00:14:44.394 --> 00:14:47.134 pathology by adding human autopsy

NOTE Confidence: 0.95975655

00:14:47.274 --> 00:14:49.295 brain purified tau,

NOTE Confidence: 0.96880674

00:14:50.154 --> 00:14:50.654 that

NOTE Confidence: 0.98984075

00:14:51.540 --> 00:14:52.899 the neurons are in red.

NOTE Confidence: 0.98984075

00:14:52.899 --> 00:14:54.580 The tau aggregates that are

NOTE Confidence: 0.98984075

00:14:54.580 --> 00:14:56.420 formed over several weeks in

NOTE Confidence: 0.98984075

00:14:56.420 --> 00:14:56.920 culture

NOTE Confidence: 0.9735673

00:14:57.380 --> 00:14:59.000 are shown in green here.

NOTE Confidence: 0.9735673

00:14:59.300 --> 00:15:01.399 When GAC ACE is inhibited,

NOTE Confidence: 0.9967544

00:15:01.779 --> 00:15:03.140 this goes up. So there

NOTE Confidence: 0.9967544

00:15:03.140 --> 00:15:04.279 seems to be some

NOTE Confidence: 0.99983716

00:15:04.944 --> 00:15:05.444 interaction

NOTE Confidence: 0.98993456

00:15:05.745 --> 00:15:06.464 here where,

NOTE Confidence: 0.94479936

00:15:06.865 --> 00:15:09.425 GCase inhibition drives more tau

NOTE Confidence: 0.94479936

00:15:09.425 --> 00:15:09.925 pathology.

NOTE Confidence: 0.989373

00:15:11.425 --> 00:15:12.944 So then we've asked whether

NOTE Confidence: 0.989373

00:15:12.944 --> 00:15:14.404 this is a direct effect.

NOTE Confidence: 0.989373

00:15:14.545 --> 00:15:15.685 So, we

NOTE Confidence: 0.92835796

00:15:16.464 --> 00:15:18.324 polymerize or or fibrilize

NOTE Confidence: 0.97148055

00:15:18.630 --> 00:15:20.150 tau in the test tube,

NOTE Confidence: 0.97148055

00:15:20.150 --> 00:15:21.530 so purified tau

NOTE Confidence: 0.8635723

00:15:21.990 --> 00:15:23.610 together with this glucosiramide

NOTE Confidence: 0.7792487

00:15:24.870 --> 00:15:25.370 lipid.

NOTE Confidence: 0.993295

00:15:25.830 --> 00:15:27.050 And we oops.

NOTE Confidence: 0.97611874

00:15:27.990 --> 00:15:29.350 Can we go back? And

NOTE Confidence: 0.97611874

00:15:29.350 --> 00:15:31.130 we monitored that with thioflavin

NOTE Confidence: 0.97611874

00:15:31.430 --> 00:15:32.870 fluorescence, and you can see

NOTE Confidence: 0.97611874

00:15:32.870 --> 00:15:33.610 that there's

NOTE Confidence: 0.9281049

00:15:34.764 --> 00:15:35.505 how itself,

NOTE Confidence: 0.9298557

00:15:36.285 --> 00:15:36.785 fibrilizes

NOTE Confidence: 0.9899897

00:15:37.165 --> 00:15:38.925 only quite slowly down here

NOTE Confidence: 0.9899897

00:15:38.925 --> 00:15:39.885 at the bottom. This is

NOTE Confidence: 0.9899897

00:15:39.885 --> 00:15:41.885 greatly accelerated by the presence

NOTE Confidence: 0.9899897

00:15:41.885 --> 00:15:43.005 of this lipid, so a

NOTE Confidence: 0.9899897

00:15:43.005 --> 00:15:43.824 direct effect.

NOTE Confidence: 0.99095756

00:15:45.485 --> 00:15:46.685 And this is also true

NOTE Confidence: 0.99095756

00:15:46.685 --> 00:15:48.365 in human brain samples. So

NOTE Confidence: 0.99095756

00:15:48.365 --> 00:15:49.985 these are from some autopsy

NOTE Confidence: 0.99095756

00:15:50.270 --> 00:15:51.730 samples that have neurofibrillary

NOTE Confidence: 0.9911499

00:15:52.030 --> 00:15:52.530 tangles,

NOTE Confidence: 0.98353565

00:15:53.470 --> 00:15:55.170 stained with phospho tau.

NOTE Confidence: 0.97043157

00:15:55.710 --> 00:15:56.910 These the same thing that

NOTE Confidence: 0.97043157

00:15:56.910 --> 00:15:58.050 we saw in the animals

NOTE Confidence: 0.97043157

00:15:58.110 --> 00:15:59.090 is shown here.

NOTE Confidence: 0.9843965

00:16:00.270 --> 00:16:01.470 So this is present in

NOTE Confidence: 0.9843965

00:16:01.470 --> 00:16:02.670 human brain as well as

NOTE Confidence: 0.9843965

00:16:02.670 --> 00:16:03.730 these mouse samples.

NOTE Confidence: 0.9572019

00:16:04.395 --> 00:16:05.435 So that's the story on

NOTE Confidence: 0.9572019

00:16:05.435 --> 00:16:05.935 progranulin.

NOTE Confidence: 0.9565872

00:16:06.555 --> 00:16:08.235 TMEM is really tightly linked,

NOTE Confidence: 0.9565872

00:16:08.235 --> 00:16:09.115 and I'm gonna say a

NOTE Confidence: 0.9565872

00:16:09.115 --> 00:16:10.395 few words, a little bit

NOTE Confidence: 0.9565872

00:16:10.395 --> 00:16:11.915 about TMEM one zero six

NOTE Confidence: 0.9565872

00:16:11.915 --> 00:16:12.975 b as well.

NOTE Confidence: 0.9895838

00:16:13.355 --> 00:16:14.815 It's localized to the endolysosome.

NOTE Confidence: 0.99639875

00:16:15.435 --> 00:16:17.355 It was also identified as

NOTE Confidence: 0.99639875

00:16:17.355 --> 00:16:17.855 a,

NOTE Confidence: 0.8846297

00:16:18.235 --> 00:16:19.860 risk gene in,

NOTE Confidence: 0.9267828

00:16:20.420 --> 00:16:20.920 FTLD,

NOTE Confidence: 0.99883276

00:16:22.020 --> 00:16:23.620 and it's been linked to

NOTE Confidence: 0.99883276

00:16:23.620 --> 00:16:25.480 AD, PD, CTE,

NOTE Confidence: 0.9975179

00:16:25.780 --> 00:16:26.280 etcetera.

NOTE Confidence: 0.99839544

00:16:26.820 --> 00:16:28.180 So how does what is

NOTE Confidence: 0.99839544

00:16:28.180 --> 00:16:28.840 its role?

NOTE Confidence: 0.9795655

00:16:30.020 --> 00:16:30.900 This is just to show

NOTE Confidence: 0.9795655

00:16:30.900 --> 00:16:31.700 you that it is a

NOTE Confidence: 0.9795655

00:16:31.700 --> 00:16:34.180 lysosomal gene. It's localized with

NOTE Confidence: 0.9795655

00:16:34.180 --> 00:16:36.745 LAMP. You regulate tMEM levels.

NOTE Confidence: 0.997596

00:16:37.365 --> 00:16:39.524 Lysosomes go up with more

NOTE Confidence: 0.997596

00:16:39.524 --> 00:16:40.824 tMEM and down

NOTE Confidence: 0.9998524

00:16:41.125 --> 00:16:41.944 with less.

NOTE Confidence: 0.9975332

00:16:42.725 --> 00:16:44.404 This is something about the

NOTE Confidence: 0.9975332

00:16:44.404 --> 00:16:46.505 the molecular studies of tMEM.

NOTE Confidence: 0.97051215

00:16:47.605 --> 00:16:48.644 The site of it's

NOTE Confidence: 0.88162273

00:16:52.180 --> 00:16:52.680 carboxyl

NOTE Confidence: 0.96068305

00:16:53.140 --> 00:16:54.840 domain is inside the lysosome,

NOTE Confidence: 0.96068305

00:16:54.900 --> 00:16:56.520 and it can undergo proteolysis

NOTE Confidence: 0.98997617

00:16:56.980 --> 00:16:58.520 to release this fragment.

NOTE Confidence: 0.97041184

00:16:59.380 --> 00:17:00.580 And recently, it's been shown

NOTE Confidence: 0.97041184

00:17:00.580 --> 00:17:01.560 that this fragment

NOTE Confidence: 0.96395177

00:17:02.225 --> 00:17:04.405 with aging in humans or

NOTE Confidence: 0.96395177

00:17:04.465 --> 00:17:06.065 even more so with disease

NOTE Confidence: 0.96395177

00:17:06.065 --> 00:17:06.805 can fibrilize,

NOTE Confidence: 0.98499316

00:17:07.905 --> 00:17:09.825 and make amyloid deposits. Whether

NOTE Confidence: 0.98499316

00:17:09.825 --> 00:17:11.665 those are actually causative in

NOTE Confidence: 0.98499316

00:17:11.665 --> 00:17:13.185 disease is still a question

NOTE Confidence: 0.98499316

00:17:13.185 --> 00:17:15.185 mark, but it itself can,

NOTE Confidence: 0.9995456

00:17:15.585 --> 00:17:16.085 aggregate.

NOTE Confidence: 0.9775371

00:17:17.750 --> 00:17:19.590 We studied its interaction with

NOTE Confidence: 0.9775371

00:17:19.590 --> 00:17:20.090 progranulin.

NOTE Confidence: 0.99625987

00:17:20.710 --> 00:17:21.990 I showed you before that

NOTE Confidence: 0.99625987

00:17:21.990 --> 00:17:24.730 granulin causes these increased lysosomal

NOTE Confidence: 0.99245036

00:17:25.109 --> 00:17:27.529 profiles. This is decreased when

NOTE Confidence: 0.93805605

00:17:28.309 --> 00:17:30.149 in the double knockout where,

NOTE Confidence: 0.93805605

00:17:30.549 --> 00:17:32.070 TMEM is reduced. I should

NOTE Confidence: 0.93805605

00:17:32.070 --> 00:17:33.375 say this is a a

NOTE Confidence: 0.93805605

00:17:33.375 --> 00:17:35.695 hypomorphic allele of TMEM, partial

NOTE Confidence: 0.93805605

00:17:35.695 --> 00:17:37.555 reduction that causes this.

NOTE Confidence: 0.98909605

00:17:38.015 --> 00:17:39.855 And this partial reduction in

NOTE Confidence: 0.98909605

00:17:39.855 --> 00:17:40.835 the double knockout

NOTE Confidence: 0.99842626

00:17:41.215 --> 00:17:43.935 rescues this retinal degeneration that

NOTE Confidence: 0.99842626

00:17:43.935 --> 00:17:45.395 I told you about before.

NOTE Confidence: 0.9994866

00:17:46.175 --> 00:17:47.075 There's a small

NOTE Confidence: 0.9852436

00:17:47.550 --> 00:17:49.390 degree of retinal degeneration, but

NOTE Confidence: 0.9852436

00:17:49.390 --> 00:17:50.750 in the double knockout, this

NOTE Confidence: 0.9852436

00:17:50.750 --> 00:17:51.410 is rescued.

NOTE Confidence: 0.9955175

00:17:51.790 --> 00:17:53.090 It's a little more complicated

NOTE Confidence: 0.9955175

00:17:53.230 --> 00:17:54.190 in the sense that if

NOTE Confidence: 0.9955175

00:17:54.190 --> 00:17:55.550 you make a complete null

NOTE Confidence: 0.9955175

00:17:55.550 --> 00:17:56.290 of TMEM,

NOTE Confidence: 0.9718704

00:17:56.830 --> 00:17:58.590 the mice actually die. So

NOTE Confidence: 0.9718704

00:17:58.590 --> 00:17:59.250 a biphasic

NOTE Confidence: 0.9992827

00:17:59.550 --> 00:18:00.770 interaction between

NOTE Confidence: 0.98445016

00:18:01.390 --> 00:18:02.770 TMEM and granulant.

NOTE Confidence: 0.9894838

00:18:04.455 --> 00:18:06.315 We've also studied its interaction

NOTE Confidence: 0.9894838

00:18:06.455 --> 00:18:07.755 with other degeneration

NOTE Confidence: 0.977105

00:18:08.135 --> 00:18:09.835 models focusing on lysosomal

NOTE Confidence: 0.99919045

00:18:10.135 --> 00:18:10.635 disease.

NOTE Confidence: 0.9497315

00:18:11.335 --> 00:18:13.195 We used a a GBA

NOTE Confidence: 0.9497315

00:18:13.335 --> 00:18:14.215 model here,

NOTE Confidence: 0.8990607

00:18:14.615 --> 00:18:15.675 with this inhibitor,

NOTE Confidence: 0.45137838

00:18:16.770 --> 00:18:17.270 CMB,

NOTE Confidence: 0.99852073

00:18:18.210 --> 00:18:20.390 that causes some neuronal loss,

NOTE Confidence: 0.9839909

00:18:21.250 --> 00:18:22.609 which is corrected in the

NOTE Confidence: 0.9839909

00:18:22.609 --> 00:18:24.770 TMEM knockout. It also causes

NOTE Confidence: 0.9839909

00:18:24.770 --> 00:18:25.270 microgliosis,

NOTE Confidence: 0.98762107

00:18:25.810 --> 00:18:26.710 which is reduced.

NOTE Confidence: 0.9753594

00:18:27.250 --> 00:18:28.710 But in a different model,

NOTE Confidence: 0.9753594

00:18:28.930 --> 00:18:31.109 an NCL model where PPT

NOTE Confidence: 0.9753594

00:18:31.170 --> 00:18:32.150 one is deleted,

NOTE Confidence: 0.9994991

00:18:32.505 --> 00:18:34.205 there's a strong exacerbation

NOTE Confidence: 0.9798339

00:18:34.585 --> 00:18:36.425 of the phenotype with TMEM

NOTE Confidence: 0.9798339

00:18:36.425 --> 00:18:36.925 loss.

NOTE Confidence: 0.9981954

00:18:38.105 --> 00:18:39.305 Finally, I wanted to touch

NOTE Confidence: 0.9981954

00:18:39.305 --> 00:18:40.744 on one thing about the

NOTE Confidence: 0.9981954

00:18:40.744 --> 00:18:41.885 interaction partners.

NOTE Confidence: 0.9336195

00:18:42.185 --> 00:18:43.405 So we did some IPs

NOTE Confidence: 0.9336195

00:18:43.545 --> 00:18:45.385 using knockout brain, looked for

NOTE Confidence: 0.9336195

00:18:45.385 --> 00:18:46.445 things that interacted

NOTE Confidence: 0.90950584

00:18:47.359 --> 00:18:48.580 selectively with TMEM,

NOTE Confidence: 0.9991274

00:18:48.960 --> 00:18:50.480 and that identified a number

NOTE Confidence: 0.9991274

00:18:50.480 --> 00:18:51.140 of lysosomal

NOTE Confidence: 0.99398154

00:18:51.520 --> 00:18:52.020 proteins,

NOTE Confidence: 0.9824024

00:18:53.200 --> 00:18:55.060 including endosomal adapters,

NOTE Confidence: 0.67899233

00:18:56.240 --> 00:18:57.619 the vesicular ATPase.

NOTE Confidence: 0.96962154

00:18:57.920 --> 00:18:59.200 We showed an effect on

NOTE Confidence: 0.96962154

00:18:59.200 --> 00:19:00.500 the pH of the lysosome.

NOTE Confidence: 0.8940055

00:19:01.144 --> 00:19:02.744 What I wanna highlight here

NOTE Confidence: 0.8940055

00:19:02.744 --> 00:19:04.365 is, gal c,

NOTE Confidence: 0.9578082

00:19:04.825 --> 00:19:06.904 an enzyme involved in, lipid

NOTE Confidence: 0.9578082

00:19:06.904 --> 00:19:07.404 metabolism,

NOTE Confidence: 0.78555465

00:19:08.264 --> 00:19:09.325 galactose cerebrocytase

NOTE Confidence: 0.94355136

00:19:11.625 --> 00:19:12.125 ceramidase.

NOTE Confidence: 0.90599185

00:19:13.400 --> 00:19:15.740 And this enzyme, galsy, interacts

NOTE Confidence: 0.90599185

00:19:15.880 --> 00:19:18.380 directly with tMEM by, immunoprecipitation.

NOTE Confidence: 0.99049157

00:19:19.960 --> 00:19:21.080 This is a little diagram

NOTE Confidence: 0.99049157

00:19:21.080 --> 00:19:22.760 of the substrates and products

NOTE Confidence: 0.99049157

00:19:22.760 --> 00:19:24.059 of the enzyme activity,

NOTE Confidence: 0.99488354

00:19:24.520 --> 00:19:25.720 and it looks like this,

NOTE Confidence: 0.99962187

00:19:26.279 --> 00:19:26.779 interaction

NOTE Confidence: 0.9903947

00:19:27.159 --> 00:19:28.059 is inhibitory.

NOTE Confidence: 0.77968633

00:19:28.555 --> 00:19:30.234 TMEM interaction with gal C

NOTE Confidence: 0.77968633

00:19:30.234 --> 00:19:30.975 is inhibitory

NOTE Confidence: 0.72484255

00:19:31.755 --> 00:19:32.635 because the,

NOTE Confidence: 0.97994155

00:19:33.675 --> 00:19:35.755 substrates of gal C in

NOTE Confidence: 0.97994155

00:19:35.755 --> 00:19:36.255 lipidomic

NOTE Confidence: 0.9847183

00:19:36.555 --> 00:19:38.655 analysis from these tMEM brains

NOTE Confidence: 0.9847183

00:19:38.715 --> 00:19:39.615 goes down.

NOTE Confidence: 0.9973447

00:19:40.490 --> 00:19:41.609 And that leads us to

NOTE Confidence: 0.9973447

00:19:41.609 --> 00:19:43.230 this kind of overall,

NOTE Confidence: 0.99969447

00:19:43.850 --> 00:19:45.630 summation of these interactions

NOTE Confidence: 0.82172984

00:19:46.250 --> 00:19:48.330 where progranulin is interacting with

NOTE Confidence: 0.82172984

00:19:48.330 --> 00:19:49.869 g c ACE and tmem

NOTE Confidence: 0.9271712

00:19:50.330 --> 00:19:51.850 with gal c. They're both

NOTE Confidence: 0.9271712

00:19:51.850 --> 00:19:53.070 regulating these,

NOTE Confidence: 0.9987327

00:19:53.595 --> 00:19:54.975 lipids in the lysosome

NOTE Confidence: 0.9863665

00:19:55.595 --> 00:19:56.415 and affecting,

NOTE Confidence: 0.99979687

00:19:57.035 --> 00:19:58.655 the aggregation of proteins.

NOTE Confidence: 0.99802095

00:19:59.195 --> 00:20:00.315 So I'm gonna sum up

NOTE Confidence: 0.99802095

00:20:00.315 --> 00:20:01.695 here with a few points.

NOTE Confidence: 0.98210317

00:20:02.395 --> 00:20:03.994 These proteins are really critical

NOTE Confidence: 0.98210317

00:20:03.994 --> 00:20:04.734 in the endolysisomal

NOTE Confidence: 0.97622347

00:20:05.195 --> 00:20:06.975 pathway. Although both were identified

NOTE Confidence: 0.987471

00:20:07.275 --> 00:20:08.095 in FTLD,

NOTE Confidence: 0.9972677

00:20:09.140 --> 00:20:10.740 they modulate the risk in

NOTE Confidence: 0.9972677

00:20:10.740 --> 00:20:11.720 multiple neurodegeneration

NOTE Confidence: 0.98453

00:20:12.420 --> 00:20:14.360 syndromes, and they interact genetically.

NOTE Confidence: 0.9994273

00:20:15.140 --> 00:20:16.500 They interact with these two

NOTE Confidence: 0.9994273

00:20:16.500 --> 00:20:17.640 particular lysosomal

NOTE Confidence: 0.9831123

00:20:18.020 --> 00:20:19.240 enzymes to regulate,

NOTE Confidence: 0.96191794

00:20:20.180 --> 00:20:21.080 lipid metabolism.

NOTE Confidence: 0.98690295

00:20:22.100 --> 00:20:22.500 And,

NOTE Confidence: 0.9423019

00:20:22.980 --> 00:20:24.440 that leads to a conclusion

NOTE Confidence: 0.9423019

00:20:24.580 --> 00:20:27.515 that targeting either progranulin and

NOTE Confidence: 0.9423019

00:20:27.515 --> 00:20:28.015 tmam

NOTE Confidence: 0.8142533

00:20:28.475 --> 00:20:30.155 or gal c and g

NOTE Confidence: 0.8142533

00:20:30.155 --> 00:20:30.655 case

NOTE Confidence: 0.9967163

00:20:30.955 --> 00:20:31.915 may be a way to

NOTE Confidence: 0.9967163

00:20:31.915 --> 00:20:33.135 modulate the neurodegenerative

NOTE Confidence: 0.956941

00:20:33.515 --> 00:20:35.295 process, including in Parkinson's,

NOTE Confidence: 0.98481715

00:20:35.994 --> 00:20:37.035 but one that would be

NOTE Confidence: 0.98481715

00:20:37.035 --> 00:20:38.734 based on the genetic variation

NOTE Confidence: 0.98481715

00:20:38.875 --> 00:20:40.015 in these two,

NOTE Confidence: 0.9733889

00:20:41.250 --> 00:20:41.990 risk genes.

NOTE Confidence: 0.9971693

00:20:43.170 --> 00:20:44.210 So I'm gonna stop there

NOTE Confidence: 0.9971693

00:20:44.210 --> 00:20:44.930 and and,

NOTE Confidence: 0.995526

00:20:45.250 --> 00:20:46.530 point out the people who

NOTE Confidence: 0.995526

00:20:46.530 --> 00:20:47.270 worked on

NOTE Confidence: 0.91140586

00:20:47.597 --> 00:20:48.957 this in my lab on

NOTE Confidence: 0.91140586

00:20:48.957 --> 00:20:50.497 the left hand side here.

NOTE Confidence: 0.91267973

00:20:50.877 --> 00:20:52.497 And in particular, Hideaki,

NOTE Confidence: 0.99976915

00:20:53.037 --> 00:20:53.537 Takahashi

NOTE Confidence: 0.9915242

00:20:53.917 --> 00:20:54.877 did a lot of this,

NOTE Confidence: 0.9915242

00:20:55.196 --> 00:20:56.977 work. So thanks very much.