WEBVTT

00:00:05.922 --> 00:00:09.175 The brain is a connection of neurons.

00:00:09.175 --> 00:00:11.344 Each neuron has to talk to one another.

00:00:11.344 --> 00:00:15.432 They extend over long distances, but at their very tip,

00:00:15.515 --> 00:00:20.895 they release a chemical onto a second neuron, which then creates a network.

00:00:21.062 --> 00:00:23.565 If you don't have synapses, the neurons might be there,

00:00:23.565 --> 00:00:25.150 but they can't talk to one another.

00:00:25.150 --> 00:00:29.738 You don't have a neural network and you can't carry out any cognitive functions.

00:00:29.904 --> 00:00:33.742 Unfortunately, what happens in a lot of these different neurodegenerative diseases

00:00:33.742 --> 00:00:35.785 they start losing synapses

00:00:35.785 --> 00:00:39.497 and whatever part of the brain is affected,

00:00:39.497 --> 00:00:42.292 it's normal job is lost.

00:00:42.292 --> 00:00:44.586 In Alzheimer's, It's quite widespread

00:00:44.586 --> 00:00:48.131 but of course most affects the memory areas of the brain.

00:00:48.131 --> 00:00:53.261 Whereas in Parkinson's disease, this may be more in the motor circuits

00:00:53.261 --> 00:00:56.097 and that's why people have more trouble moving

00:00:56.097 --> 00:00:58.892 rather than trouble with cognition in most cases.

00:01:04.898 --> 00:01:11.654 In these different diseases, certain proteins start piling up in excess in big aggregates,

00:01:11.654 --> 00:01:13.073 clumps in the brain.

00:01:13.073 --> 00:01:17.410 Each neurodegenerative disease, there's a different protein piling up.

00:01:17.827 --> 00:01:22.332 Somehow these protein aggregates cause the synapse loss.

00:01:22.332 --> 00:01:29.547 So what we're interested in is what is the biochemical, cellular, molecular basis

00:01:29.547 --> 00:01:33.301 for these protein aggregates damaging the synapses.

00:01:33.343 --> 00:01:39.182 We've worked hard to figure out a way to target those proteins with drugs.

00:01:39.182 --> 00:01:42.477 The striking thing is, if we can stop this damage,

00:01:42.477 --> 00:01:45.355 how can we get recovery of function?

00:01:45.355 --> 00:01:49.234 So we've also had a long standing interest in how to repair

00:01:49.234 --> 00:01:51.611 connections in the brain.

00:01:59.160 --> 00:02:04.457 We want to model things that are based on human cells and human disease.

00:02:04.457 --> 00:02:09.754 So a key thing that we do is culture human neurons

00:02:09.754 --> 00:02:12.423 from induced pluripotent stem cells.

00:02:12.423 --> 00:02:15.510 So we have human neurons in a dish

00:02:15.510 --> 00:02:19.597 and then we can extract the misfolded

00:02:19.597 --> 00:02:23.685 amyloid beta protein from a human autopsy

00:02:23.685 --> 00:02:28.773 and add it to those neurons and demonstrate that it causes synapse loss there.

00:02:28.773 --> 00:02:32.986 And again, these drugs we test in a human cell model.

00:02:32.986 --> 00:02:34.737 That's entering clinical trials.

00:02:34.737 --> 00:02:37.740 Our hope is that it stops the disease process,

00:02:37.740 --> 00:02:41.703 that is the loss of synapses actually restores memory function.

00:02:42.829 --> 00:02:48.293 In terms of understanding how these drugs work at a detailed level,

00:02:48.293 --> 00:02:50.753 even at atomic resolution,

00:02:50.753 --> 00:02:55.633 we use a number of techniques like cryo-electron microscopy

00:02:55.633 --> 00:02:57.927 which allows us to actually look

00:02:57.927 --> 00:03:02.765 beyond the limits of light microscopy, to see the actual atomic structure

00:03:02.765 --> 00:03:07.103 of these receptor proteins and how the drug binds to them.

00:03:08.396 --> 00:03:11.107 Another key tool that we use

00:03:11.107 --> 00:03:15.612 is based on what's called transcriptomics,

00:03:15.612 --> 00:03:19.324 which allows us to look at all the genes that are expressed

00:03:19.324 --> 00:03:21.868 in all the different cells in the brain.

00:03:21.868 --> 00:03:27.290 When we expose them to amyloid beta or other aggregated proteins,

00:03:27.290 --> 00:03:31.336 we could ask, how do all the genes go up or down

00:03:31.377 --> 00:03:36.216 in different cell types in the brain and understand what the entire

00:03:36.257 --> 00:03:39.469 sort of genomic response to this pathology is,

00:03:39.469 --> 00:03:43.306 and the extent to which the drug will reverse

00:03:43.306 --> 00:03:46.517 some or all of those gene expression changes.

00:03:52.398 --> 00:03:55.944 We'd like to sort out the different mechanisms

00:03:55.944 --> 00:03:59.614 for different neurodegenerative diseases and how we can intervene.

00:04:01.658 --> 00:04:06.246 We touch on a lot of different things from very basic molecular stuff

00:04:06.246 --> 00:04:10.250 to cellular stuff and then importantly to clinical applications,

00:04:10.250 --> 00:04:14.212 and I think a real benefit at Yale

00:04:14.212 --> 00:04:17.465 is the way it's so easy to collaborate here

00:04:17.465 --> 00:04:20.593 across disciplines, across laboratories,

00:04:20.635 --> 00:04:24.639 especially from laboratory basic science

00:04:24.639 --> 00:04:28.142 to clinical scientists and clinical trials.

00:04:28.393 --> 00:04:31.980 Sort of the collaboration and cross-disciplinary

00:04:32.605 --> 00:04:35.566 research at Yale is absolutely essential

00:04:35.566 --> 00:04:39.112 for this type of research, and it's very easy to achieve at Yale.