

WEBVTT

NOTE duration:"01:04:18"

NOTE recognizability:0.822

NOTE language:en-us

NOTE Confidence: 0.77382682125

00:00:00.000 --> 00:00:02.700 I'm gonna give Steve plenty of

NOTE Confidence: 0.77382682125

00:00:02.700 --> 00:00:05.650 time to share with us his talk,

NOTE Confidence: 0.77382682125

00:00:05.650 --> 00:00:08.242 but let me say at the outset that it's

NOTE Confidence: 0.77382682125

00:00:08.242 --> 00:00:10.698 a little daunting to introduce Doctor

NOTE Confidence: 0.77382682125

00:00:10.698 --> 00:00:13.730 Meredith to you and do him justice,

NOTE Confidence: 0.77382682125

00:00:13.730 --> 00:00:14.858 but I'll give it a shot.

NOTE Confidence: 0.77382682125

00:00:14.860 --> 00:00:17.877 So Steve was educated at Brandeis University

NOTE Confidence: 0.77382682125

00:00:17.877 --> 00:00:20.899 in both biology and English literature,

NOTE Confidence: 0.77382682125

00:00:20.900 --> 00:00:23.834 and then he next went to

NOTE Confidence: 0.77382682125

00:00:23.834 --> 00:00:26.542 Washington University in in medical

NOTE Confidence: 0.77382682125

00:00:26.542 --> 00:00:28.166 school after medical school,

NOTE Confidence: 0.77382682125

00:00:28.166 --> 00:00:30.098 he came up to University of

NOTE Confidence: 0.77382682125

00:00:30.098 --> 00:00:31.329 Chicago in the mid 70s.

NOTE Confidence: 0.77382682125

00:00:31.330 --> 00:00:34.288 In a joint residency in Pathology
NOTE Confidence: 0.77382682125

00:00:34.288 --> 00:00:37.590 and PhD program in Biochemistry,
NOTE Confidence: 0.77382682125

00:00:37.590 --> 00:00:40.782 where he studied emoji with the
NOTE Confidence: 0.77382682125

00:00:40.782 --> 00:00:42.910 noted biochemist Francois Kezdy,
NOTE Confidence: 0.77382682125

00:00:42.910 --> 00:00:47.180 who was sort of a central European
NOTE Confidence: 0.77382682125

00:00:47.180 --> 00:00:50.060 figure who came to Chicago and and did
NOTE Confidence: 0.77382682125

00:00:50.060 --> 00:00:52.590 some Seminole work in carboxypeptidase,
NOTE Confidence: 0.77382682125

00:00:52.590 --> 00:00:55.248 I think and was on faculty.
NOTE Confidence: 0.77382682125

00:00:55.250 --> 00:00:58.010 So Steve after following his education
NOTE Confidence: 0.77382682125

00:00:58.010 --> 00:01:00.930 in both pathology and biochemistry,
NOTE Confidence: 0.77382682125

00:01:00.930 --> 00:01:03.016 he was hired on to the Department
NOTE Confidence: 0.77382682125

00:01:03.016 --> 00:01:03.612 of Pathology.
NOTE Confidence: 0.77382682125

00:01:03.620 --> 00:01:06.252 As a junior faculty member in the
NOTE Confidence: 0.77382682125

00:01:06.252 --> 00:01:09.592 early 80s and he has developed an
NOTE Confidence: 0.77382682125

00:01:09.592 --> 00:01:11.740 international career in studying
NOTE Confidence: 0.77382682125

00:01:11.740 --> 00:01:14.440 disease from both a philosophical

NOTE Confidence: 0.77382682125
00:01:14.440 --> 00:01:16.060 and scientific perspective,
NOTE Confidence: 0.77382682125
00:01:16.060 --> 00:01:19.020 and so let me flesh that out for you a bit.
NOTE Confidence: 0.77382682125
00:01:19.020 --> 00:01:21.120 Doctor Meredith holds appointments
NOTE Confidence: 0.77382682125
00:01:21.120 --> 00:01:24.122 in the Divinity school, the College,
NOTE Confidence: 0.77382682125
00:01:24.122 --> 00:01:26.828 the Graduate School in Biochemistry and
NOTE Confidence: 0.77382682125
00:01:26.828 --> 00:01:28.436 Biophysics, and the medical school,
NOTE Confidence: 0.77382682125
00:01:28.436 --> 00:01:30.755 and he teaches in all of these
NOTE Confidence: 0.77382682125
00:01:30.755 --> 00:01:32.522 departments actively in the
NOTE Confidence: 0.77382682125
00:01:32.522 --> 00:01:33.966 Divinity School and college.
NOTE Confidence: 0.77382682125
00:01:33.970 --> 00:01:37.036 He has focused his career on
NOTE Confidence: 0.77382682125
00:01:37.036 --> 00:01:39.166 looking at disease philosophically.
NOTE Confidence: 0.77382682125
00:01:39.166 --> 00:01:43.338 Specifically the problem of pain and evil,
NOTE Confidence: 0.77382682125
00:01:43.340 --> 00:01:47.696 and he has taught for 20 years or more.
NOTE Confidence: 0.77382682125
00:01:47.700 --> 00:01:49.350 Courses in the Division school
NOTE Confidence: 0.77382682125
00:01:49.350 --> 00:01:51.000 and college on James Joyce,
NOTE Confidence: 0.77382682125

00:01:51.000 --> 00:01:56.178 Ulysses Thomas Mons, Magic Mountain, St.

NOTE Confidence: 0.77382682125

00:01:56.178 --> 00:01:57.374 Thomas Aquinas,

NOTE Confidence: 0.77382682125

00:01:57.374 --> 00:02:00.962 problem of evil and other brothers

NOTE Confidence: 0.77382682125

00:02:00.962 --> 00:02:04.158 K Dusty Zewski and he teaches these

NOTE Confidence: 0.77382682125

00:02:04.158 --> 00:02:06.653 courses regularly and they are a

NOTE Confidence: 0.77382682125

00:02:06.653 --> 00:02:09.175 well attended major courses in in in

NOTE Confidence: 0.77382682125

00:02:09.175 --> 00:02:12.524 these schools and he has a sort of

NOTE Confidence: 0.77382682125

00:02:12.524 --> 00:02:14.432 an international reputation looking

NOTE Confidence: 0.77382682125

00:02:14.432 --> 00:02:17.269 at disease from this perspective.

NOTE Confidence: 0.77382682125

00:02:17.270 --> 00:02:19.734 And now today we're going to hear

NOTE Confidence: 0.77382682125

00:02:19.734 --> 00:02:21.728 about his other half of him,

NOTE Confidence: 0.77382682125

00:02:21.730 --> 00:02:25.130 which is his scientific pursuits

NOTE Confidence: 0.77382682125

00:02:25.130 --> 00:02:27.167 in in the in the medical school

NOTE Confidence: 0.77382682125

00:02:27.167 --> 00:02:29.609 and and the biophysics department.

NOTE Confidence: 0.77382682125

00:02:29.610 --> 00:02:31.948 He has taught for 20 years the

NOTE Confidence: 0.77382682125

00:02:31.948 --> 00:02:33.889 foundational curriculum in medical school,

NOTE Confidence: 0.77382682125

00:02:33.890 --> 00:02:36.995 including the courses on biochemistry

NOTE Confidence: 0.77382682125

00:02:36.995 --> 00:02:40.100 and the courses on cellular

NOTE Confidence: 0.77382682125

00:02:40.200 --> 00:02:42.588 pathology and immunology.

NOTE Confidence: 0.77382682125

00:02:42.590 --> 00:02:45.702 He runs an active lab that has been

NOTE Confidence: 0.77382682125

00:02:45.702 --> 00:02:47.810 independently funded for 40 years

NOTE Confidence: 0.77382682125

00:02:47.810 --> 00:02:49.895 and he investigates the pathogenesis

NOTE Confidence: 0.77382682125

00:02:49.895 --> 00:02:52.059 of disease using biophysical

NOTE Confidence: 0.77382682125

00:02:52.059 --> 00:02:53.937 and biochemical techniques,

NOTE Confidence: 0.77382682125

00:02:53.940 --> 00:02:57.084 specifically focused on structure,

NOTE Confidence: 0.77382682125

00:02:57.084 --> 00:02:59.769 determination, and disease pathogenesis.

NOTE Confidence: 0.77382682125

00:02:59.769 --> 00:03:01.668 He's used arcane,

NOTE Confidence: 0.77382682125

00:03:01.670 --> 00:03:02.454 you know,

NOTE Confidence: 0.77382682125

00:03:02.454 --> 00:03:04.414 difficult techniques such as solid

NOTE Confidence: 0.77382682125

00:03:04.414 --> 00:03:07.060 state NMR and has made Seminole

NOTE Confidence: 0.77382682125

00:03:07.060 --> 00:03:08.924 contributions in our understanding

NOTE Confidence: 0.77382682125

00:03:08.924 --> 00:03:11.478 of the structure of beta amyloid.

NOTE Confidence: 0.77382682125

00:03:11.480 --> 00:03:13.810 Which was really undetermined until

NOTE Confidence: 0.77382682125

00:03:13.810 --> 00:03:16.683 Steve and his group of collaborators

NOTE Confidence: 0.77382682125

00:03:16.683 --> 00:03:19.437 did it in the early 2000s.

NOTE Confidence: 0.77382682125

00:03:19.440 --> 00:03:22.880 He has also actively studied tumor

NOTE Confidence: 0.77382682125

00:03:22.880 --> 00:03:25.180 immunology with Hans Schreiber and,

NOTE Confidence: 0.77382682125

00:03:25.180 --> 00:03:27.556 specifically the development of

NOTE Confidence: 0.77382682125

00:03:27.556 --> 00:03:30.526 purification of tumor antigens for

NOTE Confidence: 0.77382682125

00:03:30.526 --> 00:03:33.686 cancer vaccines and his work in

NOTE Confidence: 0.77382682125

00:03:33.686 --> 00:03:36.166 peptide design and peptide structure

NOTE Confidence: 0.77382682125

00:03:36.255 --> 00:03:38.775 has been Seminole to my career.

NOTE Confidence: 0.77382682125

00:03:38.780 --> 00:03:41.706 In in in my journey as a.

NOTE Confidence: 0.77382682125

00:03:41.710 --> 00:03:42.478 Translational.

NOTE Confidence: 0.77382682125

00:03:42.478 --> 00:03:44.782 Biologists developing enzyme

NOTE Confidence: 0.77382682125

00:03:44.782 --> 00:03:47.086 therapies for diseases.

NOTE Confidence: 0.77382682125

00:03:47.090 --> 00:03:49.736 Steve has had a remarkable career

NOTE Confidence: 0.77382682125

00:03:49.736 --> 00:03:53.248 and it's he's a kind and gentle

NOTE Confidence: 0.77382682125

00:03:53.248 --> 00:03:56.003 mentor and an insightful scholar.

NOTE Confidence: 0.916554948181818

00:03:56.010 --> 00:03:58.600 And it's my pleasure to introduce you

NOTE Confidence: 0.916554948181818

00:03:58.600 --> 00:04:01.854 to him and to hear his talk today,

NOTE Confidence: 0.916554948181818

00:04:01.854 --> 00:04:04.710 which is on NMR and disease.

NOTE Confidence: 0.916554948181818

00:04:04.710 --> 00:04:06.200 So Steve take it away.

NOTE Confidence: 0.80618336

00:04:06.970 --> 00:04:09.525 Thank you Demetrius, that was a kind,

NOTE Confidence: 0.80618336

00:04:09.530 --> 00:04:11.765 even embarrassing introduction.

NOTE Confidence: 0.80618336

00:04:11.765 --> 00:04:16.235 Thank you also for the invitation

NOTE Confidence: 0.80618336

00:04:16.235 --> 00:04:19.468 and it's great to be here.

NOTE Confidence: 0.80618336

00:04:19.470 --> 00:04:24.644 Catch up with some old friends and share

NOTE Confidence: 0.80618336

00:04:24.644 --> 00:04:28.988 this this scientific data with you.

NOTE Confidence: 0.80618336

00:04:28.990 --> 00:04:30.747 Too bad it couldn't be in person,

NOTE Confidence: 0.80618336

00:04:30.750 --> 00:04:32.042 but as they say,

NOTE Confidence: 0.80618336

00:04:32.042 --> 00:04:34.440 half a loaf is better than none.

NOTE Confidence: 0.80618336

00:04:34.440 --> 00:04:37.960 And it's great to be able to talk to you.

NOTE Confidence: 0.80618336

00:04:37.960 --> 00:04:41.190 I'm gonna share my screen.

NOTE Confidence: 0.80618336

00:04:41.190 --> 00:04:42.828 And hopefully this will work again.

NOTE Confidence: 0.80618336

00:04:42.830 --> 00:04:46.130 Yes, there it is OK.

NOTE Confidence: 0.80618336

00:04:46.130 --> 00:04:49.780 So I started out my professional

NOTE Confidence: 0.80618336

00:04:49.780 --> 00:04:51.820 life as an anatomic pathologist.

NOTE Confidence: 0.80618336

00:04:51.820 --> 00:04:54.762 I still consider myself one even

NOTE Confidence: 0.80618336

00:04:54.762 --> 00:04:58.276 though the clinical work as you age,

NOTE Confidence: 0.80618336

00:04:58.280 --> 00:05:01.024 you have to give up some things

NOTE Confidence: 0.80618336

00:05:01.024 --> 00:05:04.079 and that has gone by the wayside.

NOTE Confidence: 0.80618336

00:05:04.080 --> 00:05:06.656 But when I was doing clinical work,

NOTE Confidence: 0.80618336

00:05:06.660 --> 00:05:07.998 a lot of it was autopsies,

NOTE Confidence: 0.80618336

00:05:08.000 --> 00:05:09.862 and I really enjoyed it and thought

NOTE Confidence: 0.80618336

00:05:09.862 --> 00:05:12.109 it added a lot to medical practice.

NOTE Confidence: 0.909179375

00:05:14.340 --> 00:05:19.428 In fact, I lament that for the most,

NOTE Confidence: 0.909179375

00:05:19.428 --> 00:05:22.320 mostly for some very bad reasons,

NOTE Confidence: 0.909179375

00:05:22.320 --> 00:05:25.200 medical autopsies are now rather uncommon.

NOTE Confidence: 0.909179375

00:05:25.200 --> 00:05:27.732 I still think that even with

NOTE Confidence: 0.909179375

00:05:27.732 --> 00:05:29.420 all the incredible radiological

NOTE Confidence: 0.909179375

00:05:29.497 --> 00:05:31.468 technology that's available,

NOTE Confidence: 0.909179375

00:05:31.470 --> 00:05:34.865 all the rest of the biological world,

NOTE Confidence: 0.909179375

00:05:34.870 --> 00:05:38.478 autopsies still have a lot to teach us.

NOTE Confidence: 0.909179375

00:05:38.480 --> 00:05:42.904 Now, this statement should not be surprising.

NOTE Confidence: 0.909179375

00:05:42.910 --> 00:05:47.068 Considering how complex the human body is,

NOTE Confidence: 0.909179375

00:05:47.070 --> 00:05:49.650 clinicians.

NOTE Confidence: 0.909179375

00:05:49.650 --> 00:05:54.445 Still, amazingly, do get some things wrong.

NOTE Confidence: 0.909179375

00:05:54.450 --> 00:05:56.826 What's remarkable is how often they

NOTE Confidence: 0.909179375

00:05:56.826 --> 00:06:01.014 now get it right, but even that said,

NOTE Confidence: 0.909179375

00:06:01.014 --> 00:06:02.967 autopsies are illuminating,

NOTE Confidence: 0.909179375

00:06:02.970 --> 00:06:07.578 and I will quote here the great and

NOTE Confidence: 0.909179375

00:06:07.578 --> 00:06:10.918 pioneering pathologist and anatomist Bashat,

NOTE Confidence: 0.909179375

00:06:10.920 --> 00:06:14.126 who wrote open up a few corpses.
NOTE Confidence: 0.909179375

00:06:14.130 --> 00:06:17.217 You will dissipate it once the darkness
NOTE Confidence: 0.909179375

00:06:17.217 --> 00:06:20.038 that observation alone could not dissipate.
NOTE Confidence: 0.909179375

00:06:20.040 --> 00:06:22.819 In other words, he was talking about
NOTE Confidence: 0.909179375

00:06:22.819 --> 00:06:24.660 observation at the bedside.
NOTE Confidence: 0.909179375

00:06:24.660 --> 00:06:26.940 After death, open up the bodies,
NOTE Confidence: 0.909179375

00:06:26.940 --> 00:06:29.300 see what is inside.
NOTE Confidence: 0.909179375

00:06:29.300 --> 00:06:32.779 Now a friend and colleague of mine,
NOTE Confidence: 0.909179375

00:06:32.780 --> 00:06:35.480 Tobin Sosnik.
NOTE Confidence: 0.909179375

00:06:35.480 --> 00:06:36.960 In the biochemistry department
NOTE Confidence: 0.909179375

00:06:36.960 --> 00:06:38.440 likes to say this,
NOTE Confidence: 0.909179375

00:06:38.440 --> 00:06:43.000 biology works on all length scales.
NOTE Confidence: 0.909179375

00:06:43.000 --> 00:06:45.100 When I started my residency
NOTE Confidence: 0.909179375

00:06:45.100 --> 00:06:46.360 in anatomic pathology,
NOTE Confidence: 0.909179375

00:06:46.360 --> 00:06:50.924 this was sometime before the Polynesian War.
NOTE Confidence: 0.909179375

00:06:50.930 --> 00:06:53.996 I had this opportunity as Demetrius was

NOTE Confidence: 0.909179375

00:06:53.996 --> 00:06:56.901 saying to study biochemistry and I did

NOTE Confidence: 0.909179375

00:06:56.901 --> 00:06:59.323 my work on collagen's collagen structure.

NOTE Confidence: 0.909179375

00:06:59.323 --> 00:07:02.814 And at the same time I was doing

NOTE Confidence: 0.909179375

00:07:02.814 --> 00:07:05.565 bone biopsies and I mean the whole

NOTE Confidence: 0.909179375

00:07:05.565 --> 00:07:08.249 thing going into the operating room,

NOTE Confidence: 0.909179375

00:07:08.250 --> 00:07:11.020 getting the core, embedding it,

NOTE Confidence: 0.909179375

00:07:11.020 --> 00:07:12.394 cutting the slices,

NOTE Confidence: 0.909179375

00:07:12.394 --> 00:07:15.142 staining and then reading it and

NOTE Confidence: 0.909179375

00:07:15.142 --> 00:07:18.059 doing quantitative histomorphometry.

NOTE Confidence: 0.909179375

00:07:18.060 --> 00:07:21.030 Now I mentioned that because.

NOTE Confidence: 0.909179375

00:07:21.030 --> 00:07:25.044 I had on the one hand pathology and on

NOTE Confidence: 0.909179375

00:07:25.044 --> 00:07:28.898 the other hand protein science and.

NOTE Confidence: 0.909179375

00:07:28.900 --> 00:07:31.060 When I was working on college and this

NOTE Confidence: 0.909179375

00:07:31.060 --> 00:07:33.020 was again before the dawn of time,

NOTE Confidence: 0.909179375

00:07:33.020 --> 00:07:36.834 it was at that time big news that there

NOTE Confidence: 0.909179375

00:07:36.834 --> 00:07:38.598 was more than one type of collagen.
NOTE Confidence: 0.909179375

00:07:38.600 --> 00:07:41.180 At last count there were 29.
NOTE Confidence: 0.909179375

00:07:41.180 --> 00:07:45.824 Now I mentioned this because I think it is.
NOTE Confidence: 0.909179375

00:07:45.830 --> 00:07:48.840 I will lament about one more thing
NOTE Confidence: 0.909179375

00:07:48.840 --> 00:07:51.892 and that is that the tension that
NOTE Confidence: 0.909179375

00:07:51.892 --> 00:07:53.711 sometimes exists within pathology
NOTE Confidence: 0.909179375

00:07:53.711 --> 00:07:56.707 departments and I'm happy to say this
NOTE Confidence: 0.909179375

00:07:56.707 --> 00:07:59.869 has been minimal in my own department.
NOTE Confidence: 0.909179375

00:07:59.870 --> 00:08:04.730 But that tension is describable.
NOTE Confidence: 0.909179375

00:08:04.730 --> 00:08:07.559 On this slide.
NOTE Confidence: 0.909179375

00:08:07.560 --> 00:08:09.980 Channeling the song from the
NOTE Confidence: 0.909179375

00:08:09.980 --> 00:08:10.948 musical Oklahoma,
NOTE Confidence: 0.909179375

00:08:10.950 --> 00:08:13.876 the the farmer and the cowman shouldn't
NOTE Confidence: 0.909179375

00:08:13.876 --> 00:08:17.392 be friends and I would say that of
NOTE Confidence: 0.909179375

00:08:17.392 --> 00:08:20.068 the anatomic pathologists and the
NOTE Confidence: 0.909179375

00:08:20.068 --> 00:08:23.488 biochemist as someone who throughout

NOTE Confidence: 0.909179375

00:08:23.488 --> 00:08:28.349 my career has on occasion in both the

NOTE Confidence: 0.909179375

00:08:28.349 --> 00:08:30.201 pathology and biochemistry departments

NOTE Confidence: 0.909179375

00:08:30.201 --> 00:08:32.554 sometimes been a pathologist to

NOTE Confidence: 0.909179375

00:08:32.554 --> 00:08:34.769 the biochemist and sometimes been

NOTE Confidence: 0.909179375

00:08:34.769 --> 00:08:37.196 a biochemist to the pathologist.

NOTE Confidence: 0.909179375

00:08:37.196 --> 00:08:40.484 But in the spirit of interdisciplinarity.

NOTE Confidence: 0.909179375

00:08:40.490 --> 00:08:42.597 What I'm going to talk about for

NOTE Confidence: 0.909179375

00:08:42.597 --> 00:08:45.391 the range of the talk is 2 areas

NOTE Confidence: 0.909179375

00:08:45.391 --> 00:08:47.526 of structural biology research in

NOTE Confidence: 0.909179375

00:08:47.526 --> 00:08:50.279 which I am currently involved,

NOTE Confidence: 0.909179375

00:08:50.280 --> 00:08:52.145 and I believe that structural

NOTE Confidence: 0.909179375

00:08:52.145 --> 00:08:54.480 biology does at the atomic level,

NOTE Confidence: 0.909179375

00:08:54.480 --> 00:08:57.340 what anatomic pathology typically does

NOTE Confidence: 0.909179375

00:08:57.340 --> 00:09:00.780 at the cellular and macroscopic level,

NOTE Confidence: 0.909179375

00:09:00.780 --> 00:09:03.522 but it's all looking at structure

NOTE Confidence: 0.909179375

00:09:03.522 --> 00:09:07.219 to help help us understand disease.

NOTE Confidence: 0.909179375

00:09:07.220 --> 00:09:10.278 So the topics of the of the of

NOTE Confidence: 0.909179375

00:09:10.278 --> 00:09:12.280 this talk will be first a little.

NOTE Confidence: 0.909179375

00:09:12.280 --> 00:09:14.830 A few introductory remarks about

NOTE Confidence: 0.909179375

00:09:14.830 --> 00:09:17.380 structural biology and the use

NOTE Confidence: 0.909179375

00:09:17.464 --> 00:09:18.760 of NMR for that.

NOTE Confidence: 0.909179375

00:09:18.760 --> 00:09:21.910 Then I'll talk mostly about bein

NOTE Confidence: 0.909179375

00:09:21.910 --> 00:09:24.010 amyloid and Alzheimer's disease.

NOTE Confidence: 0.7785771325

00:09:24.010 --> 00:09:26.890 I will finish with a if there's time.

NOTE Confidence: 0.7785771325

00:09:26.890 --> 00:09:30.068 With a few remarks about a project

NOTE Confidence: 0.7785771325

00:09:30.068 --> 00:09:33.450 I'm involved in with Jerry Turner at

NOTE Confidence: 0.7785771325

00:09:33.450 --> 00:09:37.490 the Brigham on the pollutant and the

NOTE Confidence: 0.7785771325

00:09:37.490 --> 00:09:40.520 infant and inflammatory bowel disease.

NOTE Confidence: 0.7785771325

00:09:40.520 --> 00:09:44.264 OK, so. As I think you all know,

NOTE Confidence: 0.7785771325

00:09:44.270 --> 00:09:46.522 crystallography is still the

NOTE Confidence: 0.7785771325

00:09:46.522 --> 00:09:48.774 mainstay of structural biology.

NOTE Confidence: 0.7785771325

00:09:48.780 --> 00:09:51.636 It was determined it was developed 1st and

NOTE Confidence: 0.7785771325

00:09:51.636 --> 00:09:55.544 it is still an incredibly useful tool for

NOTE Confidence: 0.7785771325

00:09:55.544 --> 00:09:58.362 studying structural biology of proteins,

NOTE Confidence: 0.7785771325

00:09:58.362 --> 00:10:02.194 but somewhere around the 1980s and

NOTE Confidence: 0.7785771325

00:10:02.194 --> 00:10:06.166 1990s techniques were developed by NMR.

NOTE Confidence: 0.7785771325

00:10:06.170 --> 00:10:09.650 Come to determine protein structures

NOTE Confidence: 0.7785771325

00:10:09.650 --> 00:10:12.505 and for a while in the early 1990s

NOTE Confidence: 0.7785771325

00:10:12.505 --> 00:10:15.270 it looked as if these would be

NOTE Confidence: 0.7785771325

00:10:15.270 --> 00:10:18.154 two more or less coequal methods

NOTE Confidence: 0.7785771325

00:10:18.154 --> 00:10:20.890 for determining protein structure,

NOTE Confidence: 0.7785771325

00:10:20.890 --> 00:10:22.801 but that is not in fact the

NOTE Confidence: 0.7785771325

00:10:22.801 --> 00:10:25.420 case because if you have your.

NOTE Confidence: 0.7785771325

00:10:25.420 --> 00:10:27.890 As I like to say, garden variety,

NOTE Confidence: 0.7785771325

00:10:27.890 --> 00:10:30.860 small globular protein that you want

NOTE Confidence: 0.7785771325

00:10:30.860 --> 00:10:33.240 some structural information about,

NOTE Confidence: 0.7785771325

00:10:33.240 --> 00:10:36.901 you will almost certainly get there faster
NOTE Confidence: 0.7785771325

00:10:36.901 --> 00:10:41.180 and easier by doing X ray crystallography.
NOTE Confidence: 0.7785771325

00:10:41.180 --> 00:10:45.268 And the reason for that is that there
NOTE Confidence: 0.7785771325

00:10:45.268 --> 00:10:48.319 are limitations in NMR spectroscopy.
NOTE Confidence: 0.7785771325

00:10:48.320 --> 00:10:49.295 Now, of course,
NOTE Confidence: 0.7785771325

00:10:49.295 --> 00:10:50.920 if there were only limitations,
NOTE Confidence: 0.7785771325

00:10:50.920 --> 00:10:52.720 one wouldn't do it at all,
NOTE Confidence: 0.7785771325

00:10:52.720 --> 00:10:54.484 but the limitations.
NOTE Confidence: 0.7785771325

00:10:54.484 --> 00:10:56.836 There are two problems.
NOTE Confidence: 0.7785771325

00:10:56.840 --> 00:10:58.680 The first problem is that
NOTE Confidence: 0.7785771325

00:10:58.680 --> 00:11:00.152 NMR is structural data.
NOTE Confidence: 0.7785771325

00:11:00.160 --> 00:11:02.050 These are some of the techniques
NOTE Confidence: 0.7785771325

00:11:02.050 --> 00:11:04.662 on the top of the slide for
NOTE Confidence: 0.7785771325

00:11:04.662 --> 00:11:07.030 determining protein structure by NMR,
NOTE Confidence: 0.7785771325

00:11:07.030 --> 00:11:11.205 but the two problems are first that NMR
NOTE Confidence: 0.7785771325

00:11:11.205 --> 00:11:14.715 structural data are usually under determined.

NOTE Confidence: 0.7785771325

00:11:14.720 --> 00:11:15.608 In other words,

NOTE Confidence: 0.7785771325

00:11:15.608 --> 00:11:17.384 what you get from NMR is

NOTE Confidence: 0.7785771325

00:11:17.384 --> 00:11:19.160 two kinds of information.

NOTE Confidence: 0.7785771325

00:11:19.160 --> 00:11:21.520 You get interatomic distances

NOTE Confidence: 0.7785771325

00:11:21.520 --> 00:11:25.060 and you get bond torsional angles

NOTE Confidence: 0.7785771325

00:11:25.060 --> 00:11:26.930 and you put them together.

NOTE Confidence: 0.7785771325

00:11:26.930 --> 00:11:29.230 Using molecular dynamics simulation

NOTE Confidence: 0.7785771325

00:11:29.230 --> 00:11:32.402 constrained by the NMR data and

NOTE Confidence: 0.7785771325

00:11:32.402 --> 00:11:34.731 you get a structure, but it's not.

NOTE Confidence: 0.7785771325

00:11:34.731 --> 00:11:36.279 It's not fully determined

NOTE Confidence: 0.7785771325

00:11:36.279 --> 00:11:37.990 or not determined enough.

NOTE Confidence: 0.7785771325

00:11:37.990 --> 00:11:40.498 In many cases there simply aren't

NOTE Confidence: 0.7785771325

00:11:40.498 --> 00:11:42.543 enough interatomic distances and

NOTE Confidence: 0.7785771325

00:11:42.543 --> 00:11:45.789 torsional angles as you would like.

NOTE Confidence: 0.7785771325

00:11:45.790 --> 00:11:48.665 The second big problem is

NOTE Confidence: 0.7785771325

00:11:48.665 --> 00:11:50.965 the size limitation problem.
NOTE Confidence: 0.7785771325

00:11:50.970 --> 00:11:53.637 The sharpness of the peaks depends on
NOTE Confidence: 0.7785771325

00:11:53.637 --> 00:11:56.587 rapid tumbling of the molecule in solution.
NOTE Confidence: 0.7785771325

00:11:56.590 --> 00:11:56.895 Now,
NOTE Confidence: 0.7785771325

00:11:56.895 --> 00:11:59.335 as proteins get bigger and bigger and bigger,
NOTE Confidence: 0.7785771325

00:11:59.340 --> 00:12:02.155 they tumble more slowly and
NOTE Confidence: 0.7785771325

00:12:02.155 --> 00:12:03.844 through faster relaxation.
NOTE Confidence: 0.7785771325

00:12:03.850 --> 00:12:06.082 What that translates into in the
NOTE Confidence: 0.7785771325

00:12:06.082 --> 00:12:08.590 readout is broader and broader peaks,
NOTE Confidence: 0.7785771325

00:12:08.590 --> 00:12:10.234 and eventually you can't
NOTE Confidence: 0.7785771325

00:12:10.234 --> 00:12:12.289 distinguish one peak from another,
NOTE Confidence: 0.7785771325

00:12:12.290 --> 00:12:14.950 so there's a size limitation.
NOTE Confidence: 0.7785771325

00:12:14.950 --> 00:12:17.410 The world record for the molecular
NOTE Confidence: 0.7785771325

00:12:17.410 --> 00:12:19.624 weight of the biggest protein
NOTE Confidence: 0.7785771325

00:12:19.624 --> 00:12:21.118 determined structure determined
NOTE Confidence: 0.7785771325

00:12:21.118 --> 00:12:24.106 by NMR is 900 kilodaltons by

NOTE Confidence: 0.7785771325

00:12:24.181 --> 00:12:26.435 Kurt View Trick for Agro Yell,

NOTE Confidence: 0.7785771325

00:12:26.435 --> 00:12:29.570 but that's a kind of a special case

NOTE Confidence: 0.7785771325

00:12:29.570 --> 00:12:32.378 because that is a hep tumor with a

NOTE Confidence: 0.7785771325

00:12:32.378 --> 00:12:35.640 7 fold axis of rotational symmetry,

NOTE Confidence: 0.7785771325

00:12:35.640 --> 00:12:38.160 so you only have one seventh of the

NOTE Confidence: 0.7785771325

00:12:38.160 --> 00:12:40.405 peaks that you'd expect for a protein

NOTE Confidence: 0.7785771325

00:12:40.405 --> 00:12:45.350 of that size if it were a monomer, so.

NOTE Confidence: 0.7785771325

00:12:45.350 --> 00:12:47.830 So as I said.

NOTE Confidence: 0.7785771325

00:12:47.830 --> 00:12:49.610 If there were only limitations,

NOTE Confidence: 0.7785771325

00:12:49.610 --> 00:12:52.354 you'd consign NMR to the dust heap

NOTE Confidence: 0.7785771325

00:12:52.354 --> 00:12:54.888 of history and forget about it,

NOTE Confidence: 0.7785771325

00:12:54.890 --> 00:12:57.578 but obviously that is not the case.

NOTE Confidence: 0.7785771325

00:12:57.580 --> 00:12:59.048 So the question is,

NOTE Confidence: 0.7785771325

00:12:59.048 --> 00:13:00.883 what can NMR do that?

NOTE Confidence: 0.7785771325

00:13:00.890 --> 00:13:03.150 Other structural techniques cannot do,

NOTE Confidence: 0.7785771325

00:13:03.150 --> 00:13:06.797 and I say this even with the
NOTE Confidence: 0.7785771325

00:13:06.797 --> 00:13:09.300 amazing revolution in cryo EM.
NOTE Confidence: 0.7785771325

00:13:09.300 --> 00:13:10.945 The first thing is that
NOTE Confidence: 0.7785771325

00:13:10.945 --> 00:13:12.590 not every protein can be
NOTE Confidence: 0.912295605454545

00:13:12.666 --> 00:13:15.685 crystallized now. Even some of the
NOTE Confidence: 0.912295605454545

00:13:15.685 --> 00:13:17.880 what I called before globular.
NOTE Confidence: 0.912295605454545

00:13:17.880 --> 00:13:20.940 A garden variety, small globular proteins.
NOTE Confidence: 0.912295605454545

00:13:20.940 --> 00:13:23.270 Even some of those cannot
NOTE Confidence: 0.912295605454545

00:13:23.270 --> 00:13:25.134 be crystallized even today,
NOTE Confidence: 0.912295605454545

00:13:25.140 --> 00:13:26.772 but in addition to that I'll
NOTE Confidence: 0.912295605454545

00:13:26.772 --> 00:13:27.860 be talking about amyloids,
NOTE Confidence: 0.912295605454545

00:13:27.860 --> 00:13:32.347 which are not crystalline and not soluble.
NOTE Confidence: 0.912295605454545

00:13:32.350 --> 00:13:35.294 And the second major use of NMR is
NOTE Confidence: 0.912295605454545

00:13:35.294 --> 00:13:37.532 to study protein dynamics because
NOTE Confidence: 0.912295605454545

00:13:37.532 --> 00:13:40.829 with NMR you can see things in
NOTE Confidence: 0.912295605454545

00:13:40.915 --> 00:13:43.567 the protein that you can't see,

NOTE Confidence: 0.912295605454545

00:13:43.570 --> 00:13:46.840 oftentimes in crystallography or cryo em.

NOTE Confidence: 0.924186489

00:13:49.530 --> 00:13:53.810 Now I like to put a human face on disease.

NOTE Confidence: 0.924186489

00:13:53.810 --> 00:13:56.715 There is real suffering in disease and

NOTE Confidence: 0.924186489

00:13:56.715 --> 00:14:00.048 on the left you have the patient or

NOTE Confidence: 0.924186489

00:14:00.048 --> 00:14:03.558 gusta D 51 year old patient that was

NOTE Confidence: 0.924186489

00:14:03.558 --> 00:14:06.103 examined by Doctor Ellis Alzheimer

NOTE Confidence: 0.924186489

00:14:06.103 --> 00:14:09.570 in Frankfurt in 1901 and on the

NOTE Confidence: 0.924186489

00:14:09.570 --> 00:14:12.240 right is Doctor Alzheimer with his

NOTE Confidence: 0.924186489

00:14:12.240 --> 00:14:15.201 wife and three children and I always

NOTE Confidence: 0.924186489

00:14:15.201 --> 00:14:17.858 think that when I look at this.

NOTE Confidence: 0.924186489

00:14:17.858 --> 00:14:21.626 Woman she has this confused and

NOTE Confidence: 0.924186489

00:14:21.626 --> 00:14:25.366 forlorn expression on her face.

NOTE Confidence: 0.924186489

00:14:25.370 --> 00:14:27.806 Now as we know what Alzheimer's did,

NOTE Confidence: 0.924186489

00:14:27.810 --> 00:14:31.872 what Alzheimer did was not only studied

NOTE Confidence: 0.924186489

00:14:31.872 --> 00:14:34.464 the patient while she was alive,

NOTE Confidence: 0.924186489

00:14:34.470 --> 00:14:37.816 but studied her brain after she died
NOTE Confidence: 0.924186489

00:14:37.816 --> 00:14:42.442 of Alzheimer's disease and he used very
NOTE Confidence: 0.924186489

00:14:42.442 --> 00:14:45.634 innovative techniques of histopathology.
NOTE Confidence: 0.924186489

00:14:45.640 --> 00:14:49.462 And this is from his drawings
NOTE Confidence: 0.924186489

00:14:49.462 --> 00:14:51.373 of neurofibrillary tangles.
NOTE Confidence: 0.924186489

00:14:51.380 --> 00:14:54.053 This is I'm sure familiar to most of you,
NOTE Confidence: 0.924186489

00:14:54.060 --> 00:14:57.930 but on the top is a normal elderly brain,
NOTE Confidence: 0.924186489

00:14:57.930 --> 00:14:58.812 not quite normal,
NOTE Confidence: 0.924186489

00:14:58.812 --> 00:15:00.576 because if it were really normal
NOTE Confidence: 0.924186489

00:15:00.576 --> 00:15:02.379 it would be inside the skull,
NOTE Confidence: 0.924186489

00:15:02.380 --> 00:15:04.652 not out of it,
NOTE Confidence: 0.924186489

00:15:04.652 --> 00:15:06.724 but on the bottom Alzheimer's
NOTE Confidence: 0.924186489

00:15:06.724 --> 00:15:09.459 disease and you can see the severe
NOTE Confidence: 0.924186489

00:15:09.459 --> 00:15:11.479 cerebral atrophy when you slice
NOTE Confidence: 0.924186489

00:15:11.479 --> 00:15:13.600 it open along that plane.
NOTE Confidence: 0.924186489

00:15:13.600 --> 00:15:16.600 Here you see the atrophy better,

NOTE Confidence: 0.924186489

00:15:16.600 --> 00:15:21.190 which gives large ventral ventricles.

NOTE Confidence: 0.924186489

00:15:21.190 --> 00:15:25.258 And here are the two lesions.

NOTE Confidence: 0.924186489

00:15:25.260 --> 00:15:26.820 That Alzheimer described.

NOTE Confidence: 0.724543025

00:15:29.150 --> 00:15:32.371 Which are. Trichoplax with a

NOTE Confidence: 0.724543025

00:15:32.371 --> 00:15:34.806 dense core of beta amyloid and

NOTE Confidence: 0.724543025

00:15:34.806 --> 00:15:37.228 on the left and on the right.

NOTE Confidence: 0.724543025

00:15:37.230 --> 00:15:38.522 Neurofibrillary tangles,

NOTE Confidence: 0.724543025

00:15:38.522 --> 00:15:41.106 made mostly of Tau.

NOTE Confidence: 0.724543025

00:15:41.110 --> 00:15:42.760 Hyperphosphorylated Tau.

NOTE Confidence: 0.80596424

00:15:44.820 --> 00:15:47.070 Now beta amyloid is a

NOTE Confidence: 0.80596424

00:15:47.070 --> 00:15:49.320 series of set of proteins,

NOTE Confidence: 0.80596424

00:15:49.320 --> 00:15:53.253 most of them having 40 or 42 amino acids.

NOTE Confidence: 0.80596424

00:15:53.260 --> 00:15:54.935 Most of the proteins having

NOTE Confidence: 0.80596424

00:15:54.935 --> 00:15:56.610 40 or 42 amino acids.

NOTE Confidence: 0.80596424

00:15:56.610 --> 00:15:59.415 It is derived from sequential

NOTE Confidence: 0.80596424

00:15:59.415 --> 00:16:01.659 proteolytic processing of a
NOTE Confidence: 0.80596424

00:16:01.659 --> 00:16:04.600 single pass transmembrane protein
NOTE Confidence: 0.80596424

00:16:04.600 --> 00:16:07.648 called amyloid precursor protein.
NOTE Confidence: 0.80596424

00:16:07.648 --> 00:16:10.696 Non especially imaginative name.
NOTE Confidence: 0.80596424

00:16:10.700 --> 00:16:14.890 But I want to point out.
NOTE Confidence: 0.80596424

00:16:14.890 --> 00:16:15.680 Ben amyloid,
NOTE Confidence: 0.80596424

00:16:15.680 --> 00:16:17.976 with the failure of the some
NOTE Confidence: 0.80596424

00:16:17.976 --> 00:16:19.408 of the monoclonal antibodies
NOTE Confidence: 0.80596424

00:16:19.408 --> 00:16:21.224 and other anti amyloid drugs.
NOTE Confidence: 0.80596424

00:16:21.224 --> 00:16:23.528 People are a little bit sour
NOTE Confidence: 0.80596424

00:16:23.528 --> 00:16:25.100 about amyloid these days,
NOTE Confidence: 0.80596424

00:16:25.100 --> 00:16:27.164 but in case you go too far with
NOTE Confidence: 0.80596424

00:16:27.164 --> 00:16:29.226 that and think that amyloid has
NOTE Confidence: 0.80596424

00:16:29.226 --> 00:16:31.066 nothing bit amyloid has nothing
NOTE Confidence: 0.80596424

00:16:31.066 --> 00:16:33.320 to do with Alzheimer's disease.
NOTE Confidence: 0.80596424

00:16:33.320 --> 00:16:36.216 I include in this slide some

NOTE Confidence: 0.80596424
00:16:36.216 --> 00:16:39.478 and only some of the many point
NOTE Confidence: 0.80596424
00:16:39.478 --> 00:16:41.323 mutations within the sequence
NOTE Confidence: 0.80596424
00:16:41.323 --> 00:16:44.193 of a beta that gives rise to.
NOTE Confidence: 0.80596424
00:16:44.200 --> 00:16:47.384 Early onset familial Alzheimer's
NOTE Confidence: 0.80596424
00:16:47.384 --> 00:16:50.568 disease and related diseases.
NOTE Confidence: 0.80596424
00:16:50.570 --> 00:16:52.388 Now, once secreted,
NOTE Confidence: 0.80596424
00:16:52.388 --> 00:16:54.812 beta amyloid undergoes a
NOTE Confidence: 0.80596424
00:16:54.812 --> 00:16:57.710 process of fibril formation,
NOTE Confidence: 0.80596424
00:16:57.710 --> 00:17:00.120 and it's a process called
NOTE Confidence: 0.80596424
00:17:00.120 --> 00:17:01.084 nucleation polymerization,
NOTE Confidence: 0.80596424
00:17:01.090 --> 00:17:03.736 where it first forms a set of
NOTE Confidence: 0.80596424
00:17:03.736 --> 00:17:05.789 soluble oligomers and most people
NOTE Confidence: 0.80596424
00:17:05.789 --> 00:17:08.321 believe that these are the most
NOTE Confidence: 0.80596424
00:17:08.321 --> 00:17:10.715 toxic species and eventually you
NOTE Confidence: 0.80596424
00:17:10.715 --> 00:17:13.805 get a critical point of nucleation
NOTE Confidence: 0.80596424

00:17:13.805 --> 00:17:15.718 after which polymerization into
NOTE Confidence: 0.80596424

00:17:15.718 --> 00:17:18.322 the fibril occurs rapidly and you
NOTE Confidence: 0.80596424

00:17:18.322 --> 00:17:20.756 can follow this through a set of.
NOTE Confidence: 0.80596424

00:17:20.760 --> 00:17:23.880 A number of different simple assays.
NOTE Confidence: 0.80596424

00:17:23.880 --> 00:17:26.645 This one is thioflavin T
NOTE Confidence: 0.80596424

00:17:26.645 --> 00:17:27.693 fluorescence thioflavin.
NOTE Confidence: 0.80596424

00:17:27.693 --> 00:17:30.158 T binds to the fibril,
NOTE Confidence: 0.80596424

00:17:30.160 --> 00:17:34.273 but not much to earlier forms of the peptide.
NOTE Confidence: 0.80596424

00:17:34.280 --> 00:17:36.261 So you can see here that there's
NOTE Confidence: 0.80596424

00:17:36.261 --> 00:17:37.946 a lag period during which
NOTE Confidence: 0.80596424

00:17:37.946 --> 00:17:39.876 nothing seems to be happening.
NOTE Confidence: 0.80596424

00:17:39.880 --> 00:17:42.346 But in fact, nucleation is happening,
NOTE Confidence: 0.80596424

00:17:42.350 --> 00:17:44.474 and once that happens,
NOTE Confidence: 0.80596424

00:17:44.474 --> 00:17:46.598 thioflavin T fluorescence takes
NOTE Confidence: 0.80596424

00:17:46.598 --> 00:17:49.979 off and then the process finishes.
NOTE Confidence: 0.80596424

00:17:49.980 --> 00:17:50.485 OK,

NOTE Confidence: 0.80596424
00:17:50.485 --> 00:17:53.010 why use solid state NMR
NOTE Confidence: 0.80596424
00:17:53.010 --> 00:17:54.525 as Demetrios mentioned,
NOTE Confidence: 0.80596424
00:17:54.530 --> 00:17:56.366 this is not a simple technique.
NOTE Confidence: 0.80596424
00:17:56.370 --> 00:17:58.100 This is not high throughput.
NOTE Confidence: 0.80596424
00:17:58.100 --> 00:18:00.440 So why bother with it?
NOTE Confidence: 0.80596424
00:18:00.440 --> 00:18:02.176 Well first of all,
NOTE Confidence: 0.80596424
00:18:02.176 --> 00:18:04.346 amyloid fibrils are not crystalline,
NOTE Confidence: 0.80596424
00:18:04.350 --> 00:18:06.230 so you can't do crystallography.
NOTE Confidence: 0.80596424
00:18:06.230 --> 00:18:07.754 They are not soluble.
NOTE Confidence: 0.80596424
00:18:07.754 --> 00:18:10.040 You can't use solution anymore and.
NOTE Confidence: 0.685993334285714
00:18:12.280 --> 00:18:14.415 I will simply say that cryo EM,
NOTE Confidence: 0.685993334285714
00:18:14.420 --> 00:18:16.001 while very useful,
NOTE Confidence: 0.685993334285714
00:18:16.001 --> 00:18:18.109 has limitations as well.
NOTE Confidence: 0.685993334285714
00:18:18.110 --> 00:18:21.128 Other methods for studying amyloid have
NOTE Confidence: 0.685993334285714
00:18:21.128 --> 00:18:24.432 low resolution and even alpha folders.
NOTE Confidence: 0.685993334285714

00:18:24.432 --> 00:18:27.297 Fantastic technique as it is.
NOTE Confidence: 0.685993334285714

00:18:27.300 --> 00:18:30.204 It's absolutely brilliant but but the
NOTE Confidence: 0.685993334285714

00:18:30.204 --> 00:18:33.478 problem here is that it gives fairly
NOTE Confidence: 0.685993334285714

00:18:33.480 --> 00:18:37.100 moderate resolute levels of resolution.
NOTE Confidence: 0.685993334285714

00:18:37.100 --> 00:18:42.436 And where it falls short is on unstructured
NOTE Confidence: 0.685993334285714

00:18:42.436 --> 00:18:46.810 domains or poorly structured domains.
NOTE Confidence: 0.685993334285714

00:18:46.810 --> 00:18:50.186 So there is an important role that solid
NOTE Confidence: 0.685993334285714

00:18:50.186 --> 00:18:53.522 state NMR can fulfill because it is
NOTE Confidence: 0.685993334285714

00:18:53.522 --> 00:18:56.690 both high resolution and highly precise,
NOTE Confidence: 0.685993334285714

00:18:56.690 --> 00:18:59.910 and they're in contrast to solution NMR.
NOTE Confidence: 0.685993334285714

00:18:59.910 --> 00:19:03.070 There is no size limit of the sample,
NOTE Confidence: 0.685993334285714

00:19:03.070 --> 00:19:05.338 infinite size macroscopic size.
NOTE Confidence: 0.886621963846154

00:19:08.720 --> 00:19:10.928 Now the main kind of information
NOTE Confidence: 0.886621963846154

00:19:10.928 --> 00:19:13.838 that you get out of solid standard,
NOTE Confidence: 0.886621963846154

00:19:13.840 --> 00:19:15.428 or is interatomic distances.
NOTE Confidence: 0.886621963846154

00:19:15.428 --> 00:19:18.110 I'm not going to go into it,

NOTE Confidence: 0.886621963846154

00:19:18.110 --> 00:19:20.890 but the techniques are generally

NOTE Confidence: 0.886621963846154

00:19:20.890 --> 00:19:22.558 called dipolar recoupling,

NOTE Confidence: 0.886621963846154

00:19:22.560 --> 00:19:26.706 and the strength of the dipolar

NOTE Confidence: 0.886621963846154

00:19:26.706 --> 00:19:29.730 coupling between two spin systems,

NOTE Confidence: 0.886621963846154

00:19:29.730 --> 00:19:33.055 and we're talking about spin 1/2 nuclei.

NOTE Confidence: 0.886621963846154

00:19:33.060 --> 00:19:35.220 C13 and N15,

NOTE Confidence: 0.886621963846154

00:19:35.220 --> 00:19:38.100 either homonuclear or heteronuclear,

NOTE Confidence: 0.886621963846154

00:19:38.100 --> 00:19:39.870 the strength of the coupling.

NOTE Confidence: 0.886621963846154

00:19:39.870 --> 00:19:44.210 Is a $1 / R^3$ relationship

NOTE Confidence: 0.886621963846154

00:19:44.210 --> 00:19:46.070 therefore exquisitely sensitive

NOTE Confidence: 0.886621963846154

00:19:46.186 --> 00:19:49.660 to interatomic distances?

NOTE Confidence: 0.886621963846154

00:19:49.660 --> 00:19:50.998 So to summarize,

NOTE Confidence: 0.886621963846154

00:19:50.998 --> 00:19:53.228 some early solid state NMR

NOTE Confidence: 0.886621963846154

00:19:53.228 --> 00:19:55.637 results that I was involved in.

NOTE Confidence: 0.886621963846154

00:19:55.640 --> 00:20:00.562 We found that a beta 10 to 35A

NOTE Confidence: 0.886621963846154

00:20:00.562 --> 00:20:04.076 beta 1 to 40 form fibrils composed
NOTE Confidence: 0.886621963846154

00:20:04.076 --> 00:20:06.339 of imperatore in register.
NOTE Confidence: 0.886621963846154

00:20:06.340 --> 00:20:08.074 Parallel beta strands,
NOTE Confidence: 0.886621963846154

00:20:08.074 --> 00:20:11.134 which was not expected and for
NOTE Confidence: 0.886621963846154

00:20:11.134 --> 00:20:13.170 awhile not believed, but now it is.
NOTE Confidence: 0.795221416666667

00:20:15.530 --> 00:20:18.128 There were two beta strands segments,
NOTE Confidence: 0.795221416666667

00:20:18.130 --> 00:20:20.870 roughly residues 16 to 22,
NOTE Confidence: 0.795221416666667

00:20:20.870 --> 00:20:23.230 and 30 to 40 residues,
NOTE Confidence: 0.795221416666667

00:20:23.230 --> 00:20:26.611 1 to 10 are disorganized residues,
NOTE Confidence: 0.795221416666667

00:20:26.611 --> 00:20:29.166 25 to 28 are structured,
NOTE Confidence: 0.795221416666667

00:20:29.170 --> 00:20:31.578 but not beta strands.
NOTE Confidence: 0.795221416666667

00:20:31.580 --> 00:20:34.695 Now continuing work in the field and
NOTE Confidence: 0.795221416666667

00:20:34.695 --> 00:20:37.324 I highlight this famous picture from
NOTE Confidence: 0.795221416666667

00:20:37.324 --> 00:20:40.650 a paper by any pet covin Rob T Co.
NOTE Confidence: 0.795221416666667

00:20:40.650 --> 00:20:43.702 Showing the structural model of a beta
NOTE Confidence: 0.795221416666667

00:20:43.702 --> 00:20:46.998 fibrils in which there are there are

NOTE Confidence: 0.795221416666667
00:20:46.998 --> 00:20:49.378 parallel in register beta strands.
NOTE Confidence: 0.795221416666667
00:20:49.380 --> 00:20:50.264 2 segments.
NOTE Confidence: 0.795221416666667
00:20:50.264 --> 00:20:52.474 Connected by a structured but
NOTE Confidence: 0.795221416666667
00:20:52.474 --> 00:20:55.309 not non beta strand segment and
NOTE Confidence: 0.795221416666667
00:20:55.309 --> 00:20:58.159 then you don't see residues one
NOTE Confidence: 0.795221416666667
00:20:58.159 --> 00:21:00.188 through 10 in the Spectra.
NOTE Confidence: 0.795221416666667
00:21:00.190 --> 00:21:03.830 So everyone said who RA the structure of
NOTE Confidence: 0.795221416666667
00:21:03.830 --> 00:21:07.070 beta amyloid fibrils is now understood.
NOTE Confidence: 0.795221416666667
00:21:07.070 --> 00:21:08.450 End of story.
NOTE Confidence: 0.795221416666667
00:21:08.450 --> 00:21:09.370 But no,
NOTE Confidence: 0.795221416666667
00:21:09.370 --> 00:21:11.290 it is not the end of the story.
NOTE Confidence: 0.795221416666667
00:21:11.290 --> 00:21:12.200 Why not?
NOTE Confidence: 0.821670853333333
00:21:15.000 --> 00:21:18.528 Well, that's because of fibril polymorphism.
NOTE Confidence: 0.821670853333333
00:21:18.530 --> 00:21:21.596 OK, and I'm going to talk now
NOTE Confidence: 0.821670853333333
00:21:21.596 --> 00:21:23.463 about fibril polymorphism and
NOTE Confidence: 0.821670853333333

00:21:23.463 --> 00:21:25.788 the structure of brain amyloid.
NOTE Confidence: 0.8216708533333333

00:21:25.790 --> 00:21:28.044 Now when you think of protein folding
NOTE Confidence: 0.8216708533333333

00:21:28.044 --> 00:21:30.848 in terms of a rugged folding landscape,
NOTE Confidence: 0.8216708533333333

00:21:30.850 --> 00:21:33.405 a polypeptide starts out its
NOTE Confidence: 0.8216708533333333

00:21:33.405 --> 00:21:36.740 life as an unstructured and
NOTE Confidence: 0.8216708533333333

00:21:36.740 --> 00:21:38.646 completely polymorphic peptide,
NOTE Confidence: 0.8216708533333333

00:21:38.646 --> 00:21:41.622 meaning that all Phi and PSI
NOTE Confidence: 0.8216708533333333

00:21:41.622 --> 00:21:43.970 torsional angles are possible,
NOTE Confidence: 0.8216708533333333

00:21:43.970 --> 00:21:46.940 and what folding consists of is
NOTE Confidence: 0.8216708533333333

00:21:46.940 --> 00:21:49.943 decreasing free energy to that own
NOTE Confidence: 0.8216708533333333

00:21:49.943 --> 00:21:52.751 lowest level by searching for the
NOTE Confidence: 0.8216708533333333

00:21:52.751 --> 00:21:55.519 perfect set of fayerence I angles.
NOTE Confidence: 0.8216708533333333

00:21:55.520 --> 00:21:58.560 Now, the reason this is a rough landscape
NOTE Confidence: 0.8216708533333333

00:21:58.560 --> 00:22:01.800 is that it that it there are certain
NOTE Confidence: 0.8216708533333333

00:22:01.800 --> 00:22:04.860 local minima kinetic traps if you will.
NOTE Confidence: 0.8216708533333333

00:22:04.860 --> 00:22:08.059 The polypeptide can get trapped in it.

NOTE Confidence: 0.8216708533333333

00:22:08.060 --> 00:22:10.636 Now I like to talk about amyloids

NOTE Confidence: 0.8216708533333333

00:22:10.636 --> 00:22:12.479 as incompetent proteins 'cause they

NOTE Confidence: 0.8216708533333333

00:22:12.479 --> 00:22:14.838 can never get to the promised land.

NOTE Confidence: 0.8216708533333333

00:22:14.840 --> 00:22:18.515 Amyloids have a Pisgah view of Palestine,

NOTE Confidence: 0.8216708533333333

00:22:18.520 --> 00:22:20.641 that is I had to bring bring

NOTE Confidence: 0.8216708533333333

00:22:20.641 --> 00:22:21.820 James Joyce into it.

NOTE Confidence: 0.8216708533333333

00:22:21.820 --> 00:22:23.948 They can get close to like Moses

NOTE Confidence: 0.8216708533333333

00:22:23.948 --> 00:22:26.139 but never reach the promised lands.

NOTE Confidence: 0.8216708533333333

00:22:26.140 --> 00:22:28.780 And for that reason,

NOTE Confidence: 0.8216708533333333

00:22:28.780 --> 00:22:32.260 amyloids retain the sum of the

NOTE Confidence: 0.8216708533333333

00:22:32.260 --> 00:22:34.420 polymorphism of the ensemble.

NOTE Confidence: 0.8216708533333333

00:22:34.420 --> 00:22:37.048 And this is again from any

NOTE Confidence: 0.8216708533333333

00:22:37.048 --> 00:22:39.120 Petkova and Rob Teeko,

NOTE Confidence: 0.8216708533333333

00:22:39.120 --> 00:22:41.214 and this is the Seminole insight

NOTE Confidence: 0.8216708533333333

00:22:41.214 --> 00:22:43.482 that I'm going to talk about

NOTE Confidence: 0.8216708533333333

00:22:43.482 --> 00:22:45.472 for thinking about getting at
NOTE Confidence: 0.8216708533333333

00:22:45.472 --> 00:22:47.719 the structure of brain amyloid.
NOTE Confidence: 0.8216708533333333

00:22:47.720 --> 00:22:49.608 This polymorphism manifests itself
NOTE Confidence: 0.8216708533333333

00:22:49.608 --> 00:22:53.178 by the fact that there are structural
NOTE Confidence: 0.8216708533333333

00:22:53.178 --> 00:22:55.810 differences depending on subtle
NOTE Confidence: 0.8216708533333333

00:22:55.810 --> 00:22:59.100 differences and fibril isation conditions.
NOTE Confidence: 0.8216708533333333

00:22:59.100 --> 00:23:02.274 The experiment here was to take
NOTE Confidence: 0.8216708533333333

00:23:02.274 --> 00:23:05.150 two identical samples of a beta.
NOTE Confidence: 0.8216708533333333

00:23:05.150 --> 00:23:06.998 Let one sit on lab bench,
NOTE Confidence: 0.8216708533333333

00:23:07.000 --> 00:23:09.485 let the other one swirl slowly on
NOTE Confidence: 0.8216708533333333

00:23:09.485 --> 00:23:12.240 a Circulator 1 cycle per second and
NOTE Confidence: 0.8216708533333333

00:23:12.240 --> 00:23:14.760 you can see in these transmission
NOTE Confidence: 0.8216708533333333

00:23:14.760 --> 00:23:17.904 pictures that the ones that were
NOTE Confidence: 0.8216708533333333

00:23:17.904 --> 00:23:20.000 quiescent have these striations.
NOTE Confidence: 0.8216708533333333

00:23:20.000 --> 00:23:21.052 These fibrils,
NOTE Confidence: 0.8216708533333333

00:23:21.052 --> 00:23:23.867 whereas the agitated ones look

NOTE Confidence: 0.8216708533333333
00:23:23.867 --> 00:23:25.988 like twisted ribbons.
NOTE Confidence: 0.8216708533333333
00:23:25.990 --> 00:23:29.340 Furthermore if you Sonic 8,
NOTE Confidence: 0.8216708533333333
00:23:29.340 --> 00:23:32.108 each of these fibrils.
NOTE Confidence: 0.8216708533333333
00:23:32.108 --> 00:23:32.800 And.
NOTE Confidence: 0.8216708533333333
00:23:32.800 --> 00:23:36.472 Then use those to seed fresh
NOTE Confidence: 0.8216708533333333
00:23:36.472 --> 00:23:38.920 solutions of a beta.
NOTE Confidence: 0.8216708533333333
00:23:38.920 --> 00:23:41.045 What you find if you'll
NOTE Confidence: 0.8216708533333333
00:23:41.045 --> 00:23:42.320 pardon this expression,
NOTE Confidence: 0.8216708533333333
00:23:42.320 --> 00:23:46.262 is that the seed Trump's the
NOTE Confidence: 0.8216708533333333
00:23:46.262 --> 00:23:48.233 fiber alization condition.
NOTE Confidence: 0.8216708533333333
00:23:48.240 --> 00:23:52.122 You get progeny fibrils that resemble
NOTE Confidence: 0.8216708533333333
00:23:52.122 --> 00:23:54.425 the seeds, not the conditions.
NOTE Confidence: 0.8216708533333333
00:23:54.425 --> 00:23:56.435 Now, what does that tell you?
NOTE Confidence: 0.8216708533333333
00:23:56.440 --> 00:23:59.513 That tells you that most of this
NOTE Confidence: 0.8216708533333333
00:23:59.513 --> 00:24:01.823 heterogeneity occurs during the process
NOTE Confidence: 0.8216708533333333

00:24:01.823 --> 00:24:04.940 of nucleation because if you provide seeds,
NOTE Confidence: 0.8216708533333333

00:24:04.940 --> 00:24:07.718 you bypass nucleation.
NOTE Confidence: 0.8216708533333333

00:24:07.720 --> 00:24:09.340 Now you can also see.
NOTE Confidence: 0.8216708533333333

00:24:09.340 --> 00:24:10.785 Differences in NMR and I'm
NOTE Confidence: 0.8216708533333333

00:24:10.785 --> 00:24:12.600 not going to go into this,
NOTE Confidence: 0.8216708533333333

00:24:12.600 --> 00:24:15.438 but these have very different structures.
NOTE Confidence: 0.8216708533333333

00:24:15.440 --> 00:24:18.290 These quiescent and agitated fibrils,
NOTE Confidence: 0.8216708533333333

00:24:18.290 --> 00:24:22.406 as determined by solid state NMR.
NOTE Confidence: 0.8216708533333333

00:24:22.410 --> 00:24:25.407 So this was the clue that we used to
NOTE Confidence: 0.8216708533333333

00:24:25.407 --> 00:24:28.859 try to get at the structure of brain
NOTE Confidence: 0.8216708533333333

00:24:28.859 --> 00:24:31.830 amyloid because you can't grow a mouse,
NOTE Confidence: 0.8216708533333333

00:24:31.830 --> 00:24:33.418 let alone a human.
NOTE Confidence: 0.8216708533333333

00:24:33.418 --> 00:24:36.390 By feeding C. 13 and N 15.
NOTE Confidence: 0.8216708533333333

00:24:36.390 --> 00:24:38.615 So what do you do?
NOTE Confidence: 0.8216708533333333

00:24:38.620 --> 00:24:39.018 Well,
NOTE Confidence: 0.8216708533333333

00:24:39.018 --> 00:24:41.804 what we did is we got brain.

NOTE Confidence: 0.821670853333333

00:24:41.810 --> 00:24:45.401 Started with brain and then from a

NOTE Confidence: 0.821670853333333

00:24:45.401 --> 00:24:48.320 patient with Alzheimer's disease and

NOTE Confidence: 0.821670853333333

00:24:48.320 --> 00:24:51.550 then isolated the amyloid biochemically.

NOTE Confidence: 0.821670853333333

00:24:51.550 --> 00:24:54.622 And then we use that as the seed

NOTE Confidence: 0.821670853333333

00:24:54.622 --> 00:24:57.808 which we put into synthetic C.

NOTE Confidence: 0.821670853333333

00:24:57.808 --> 00:25:00.948 13 and 15 beta amyloid.

NOTE Confidence: 0.821670853333333

00:25:00.950 --> 00:25:03.270 And then we can do solid state on

NOTE Confidence: 0.821670853333333

00:25:03.270 --> 00:25:05.889 the ex vivo or as I prefer to say,

NOTE Confidence: 0.821670853333333

00:25:05.890 --> 00:25:09.568 exmore 2O fibrils of a beta.

NOTE Confidence: 0.945445838571429

00:25:09.570 --> 00:25:11.929 And so we can ask the question.

NOTE Confidence: 0.945445838571429

00:25:11.930 --> 00:25:15.150 Whether the fibrils of Alzheimer's

NOTE Confidence: 0.945445838571429

00:25:15.150 --> 00:25:18.699 disease brains are quiescent or

NOTE Confidence: 0.945445838571429

00:25:18.699 --> 00:25:22.464 agitated or maybe neither one.

NOTE Confidence: 0.945445838571429

00:25:22.470 --> 00:25:25.462 Let me give you a couple of quick

NOTE Confidence: 0.945445838571429

00:25:25.462 --> 00:25:27.580 clinical vignettes here. Patient one.

NOTE Confidence: 0.945445838571429

00:25:27.580 --> 00:25:31.771 It's a 72 year old woman with a tentative
NOTE Confidence: 0.945445838571429

00:25:31.771 --> 00:25:34.573 clinical diagnosis of Lewy body dementia
NOTE Confidence: 0.945445838571429

00:25:34.573 --> 00:25:37.268 and primary progressive aphasia,
NOTE Confidence: 0.945445838571429

00:25:37.270 --> 00:25:39.766 but at autopsy, that isn't what she had.
NOTE Confidence: 0.945445838571429

00:25:39.770 --> 00:25:42.434 She had mild atrophy of the
NOTE Confidence: 0.945445838571429

00:25:42.434 --> 00:25:44.210 frontal and parietal lobes,
NOTE Confidence: 0.945445838571429

00:25:44.210 --> 00:25:46.630 and neuritic abeyta plaques.
NOTE Confidence: 0.945445838571429

00:25:46.630 --> 00:25:49.655 She had diffuse amyloid and
NOTE Confidence: 0.945445838571429

00:25:49.655 --> 00:25:51.940 neurofibrillary tangles indicative.
NOTE Confidence: 0.945445838571429

00:25:51.940 --> 00:25:53.848 Of Alzheimer's disease.
NOTE Confidence: 0.945445838571429

00:25:53.848 --> 00:25:57.028 After a very extensive search,
NOTE Confidence: 0.945445838571429

00:25:57.030 --> 00:26:00.018 we were able to identify a single Lewy body.
NOTE Confidence: 0.945445838571429

00:26:00.020 --> 00:26:01.880 It says is here rare,
NOTE Confidence: 0.945445838571429

00:26:01.880 --> 00:26:03.108 but it's actually one.
NOTE Confidence: 0.94697094

00:26:05.740 --> 00:26:10.300 Now now I have immunostains, belkowski,
NOTE Confidence: 0.94697094

00:26:10.300 --> 00:26:13.498 stains and so forth showed very

NOTE Confidence: 0.94697094

00:26:13.498 --> 00:26:16.719 typical neuritic plaques in the cortex,

NOTE Confidence: 0.94697094

00:26:16.720 --> 00:26:18.676 and even more in the hippocampus.

NOTE Confidence: 0.94697094

00:26:18.680 --> 00:26:21.500 There were also neurofibrillary tangles,

NOTE Confidence: 0.94697094

00:26:21.500 --> 00:26:26.274 so this was diagnosed as Alzheimer's disease.

NOTE Confidence: 0.94697094

00:26:26.280 --> 00:26:28.998 Now, the first hint that something

NOTE Confidence: 0.94697094

00:26:28.998 --> 00:26:31.310 strange was going on here.

NOTE Confidence: 0.94697094

00:26:31.310 --> 00:26:33.810 Aside from the clinical history.

NOTE Confidence: 0.94697094

00:26:33.810 --> 00:26:37.416 Is that? When you use her

NOTE Confidence: 0.94697094

00:26:37.416 --> 00:26:40.550 brain derived amyloid to seed,

NOTE Confidence: 0.94697094

00:26:40.550 --> 00:26:43.166 you get neither of the previous

NOTE Confidence: 0.94697094

00:26:43.170 --> 00:26:45.106 morphologic patterns in transmission,

NOTE Confidence: 0.94697094

00:26:45.106 --> 00:26:48.010 and these are sort of straight,

NOTE Confidence: 0.94697094

00:26:48.010 --> 00:26:49.226 not striated,

NOTE Confidence: 0.94697094

00:26:49.226 --> 00:26:51.658 not twisted looking fibrils.

NOTE Confidence: 0.9501648333333333

00:26:54.370 --> 00:26:56.068 Now these are the solid state,

NOTE Confidence: 0.9501648333333333

00:26:56.070 --> 00:26:58.576 a couple of the solid state INNOMAR
NOTE Confidence: 0.9501648333333333

00:26:58.576 --> 00:27:01.055 Spectra that you get and I'll point
NOTE Confidence: 0.9501648333333333

00:27:01.055 --> 00:27:03.680 out a couple of things about them.
NOTE Confidence: 0.9501648333333333

00:27:03.680 --> 00:27:05.970 First, these are incredibly sharp
NOTE Confidence: 0.9501648333333333

00:27:05.970 --> 00:27:08.670 lines for a solid state NMR.
NOTE Confidence: 0.9501648333333333

00:27:08.670 --> 00:27:11.380 This makes a spectroscopist want
NOTE Confidence: 0.9501648333333333

00:27:11.380 --> 00:27:15.549 to sell of eight or other things.
NOTE Confidence: 0.9501648333333333

00:27:15.550 --> 00:27:18.583 But now let me go on to patient two.
NOTE Confidence: 0.9501648333333333

00:27:18.590 --> 00:27:21.358 This is an 85 year old woman with
NOTE Confidence: 0.9501648333333333

00:27:21.358 --> 00:27:24.124 a clinical diagnosis of probable
NOTE Confidence: 0.9501648333333333

00:27:24.124 --> 00:27:27.058 Alzheimer's disease, and at autopsy.
NOTE Confidence: 0.9501648333333333

00:27:27.058 --> 00:27:28.666 Severe Alzheimer's disease,
NOTE Confidence: 0.9501648333333333

00:27:28.670 --> 00:27:31.550 classic Alzheimer's disease, brain atrophy,
NOTE Confidence: 0.9501648333333333

00:27:31.550 --> 00:27:34.950 loss of neurons, gliosis granular,
NOTE Confidence: 0.9501648333333333

00:27:34.950 --> 00:27:38.050 vacuolar degeneration or annual bodies,
NOTE Confidence: 0.9501648333333333

00:27:38.050 --> 00:27:40.918 juridic plaques, neurofibrillary tangles,

NOTE Confidence: 0.9501648333333333

00:27:40.918 --> 00:27:43.786 the whole 9 yards.

NOTE Confidence: 0.9501648333333333

00:27:43.790 --> 00:27:47.790 But now when you see you get yet

NOTE Confidence: 0.9501648333333333

00:27:47.790 --> 00:27:50.569 another pattern in transmission.

NOTE Confidence: 0.9501648333333333

00:27:50.570 --> 00:27:52.418 These are kind of irregular fibrils.

NOTE Confidence: 0.9501648333333333

00:27:52.420 --> 00:27:54.880 They're not striated. They're not twisted.

NOTE Confidence: 0.9501648333333333

00:27:54.880 --> 00:27:56.191 They're not straight.

NOTE Confidence: 0.9501648333333333

00:27:56.191 --> 00:27:57.939 They're kind of irregular.

NOTE Confidence: 0.9501648333333333

00:27:57.940 --> 00:27:58.370 Now.

NOTE Confidence: 0.810797542727273

00:28:00.430 --> 00:28:02.869 When you do solid state in a bar of

NOTE Confidence: 0.810797542727273

00:28:02.869 --> 00:28:05.058 her brain, seated a beta fibrils,

NOTE Confidence: 0.810797542727273

00:28:05.058 --> 00:28:07.988 that's the blue and the red is what

NOTE Confidence: 0.810797542727273

00:28:07.988 --> 00:28:10.487 I showed you before from patient one.

NOTE Confidence: 0.810797542727273

00:28:10.490 --> 00:28:14.100 What you get is again a single set of sharp

NOTE Confidence: 0.810797542727273

00:28:14.193 --> 00:28:17.196 chemical shift and that says that there

NOTE Confidence: 0.810797542727273

00:28:17.196 --> 00:28:21.008 is a single predominant fibril structure.

NOTE Confidence: 0.810797542727273

00:28:21.010 --> 00:28:23.791 You get the same thing whether you see it
NOTE Confidence: 0.810797542727273

00:28:23.791 --> 00:28:26.495 with samples from the occipital lobe or
NOTE Confidence: 0.810797542727273

00:28:26.495 --> 00:28:29.010 the frontal lobe, and it's not on here,
NOTE Confidence: 0.810797542727273

00:28:29.010 --> 00:28:32.820 but also the temporal lobe.
NOTE Confidence: 0.810797542727273

00:28:32.820 --> 00:28:35.418 But the faces in both this
NOTE Confidence: 0.810797542727273

00:28:35.418 --> 00:28:38.120 is a carbon carbon spectrum.
NOTE Confidence: 0.810797542727273

00:28:38.120 --> 00:28:42.257 Same thing in a carbon nitrogen spectrum.
NOTE Confidence: 0.810797542727273

00:28:42.260 --> 00:28:45.090 Patient one and patient two
NOTE Confidence: 0.810797542727273

00:28:45.090 --> 00:28:47.354 have different chemical shifts.
NOTE Confidence: 0.810797542727273

00:28:47.360 --> 00:28:48.776 Different fibril structures.
NOTE Confidence: 0.810797542727273

00:28:48.776 --> 00:28:52.766 This is prima facie a very solid excuse.
NOTE Confidence: 0.810797542727273

00:28:52.766 --> 00:28:56.625 The pun evidence for a very different
NOTE Confidence: 0.810797542727273

00:28:56.625 --> 00:28:59.912 fibril structure and the the.
NOTE Confidence: 0.810797542727273

00:28:59.912 --> 00:29:03.320 This paper also included a structural
NOTE Confidence: 0.810797542727273

00:29:03.320 --> 00:29:06.670 model of the fibrils from patient one,
NOTE Confidence: 0.810797542727273

00:29:06.670 --> 00:29:08.158 and I'm not going to go into it.

NOTE Confidence: 0.810797542727273
00:29:08.160 --> 00:29:09.880 But bottom line here is.
NOTE Confidence: 0.810797542727273
00:29:09.880 --> 00:29:12.340 This is very different from either.
NOTE Confidence: 0.810797542727273
00:29:12.340 --> 00:29:13.118 Kind of.
NOTE Confidence: 0.810797542727273
00:29:13.118 --> 00:29:15.841 All synthetic fibril and I can tell
NOTE Confidence: 0.810797542727273
00:29:15.841 --> 00:29:18.627 you now that it's also different
NOTE Confidence: 0.810797542727273
00:29:18.627 --> 00:29:21.350 from the fibrils and patient too.
NOTE Confidence: 0.810797542727273
00:29:21.350 --> 00:29:25.436 So polymorphism and inherent property of
NOTE Confidence: 0.810797542727273
00:29:25.436 --> 00:29:29.180 all amyloid fibrils, not just a beta,
NOTE Confidence: 0.810797542727273
00:29:29.180 --> 00:29:31.730 it results from the coexistence of
NOTE Confidence: 0.810797542727273
00:29:31.813 --> 00:29:34.977 structurally diverse molecular nuclei.
NOTE Confidence: 0.810797542727273
00:29:34.980 --> 00:29:38.179 And it leads to different different patients,
NOTE Confidence: 0.810797542727273
00:29:38.180 --> 00:29:39.332 different fibrils,
NOTE Confidence: 0.810797542727273
00:29:39.332 --> 00:29:41.636 and not my work,
NOTE Confidence: 0.810797542727273
00:29:41.640 --> 00:29:44.350 but other people's work have
NOTE Confidence: 0.810797542727273
00:29:44.350 --> 00:29:45.976 identified a structure.
NOTE Confidence: 0.810797542727273

00:29:45.980 --> 00:29:48.515 Dysfunction relationship among
NOTE Confidence: 0.810797542727273

00:29:48.515 --> 00:29:51.895 patients with Alzheimer's disease.
NOTE Confidence: 0.810797542727273

00:29:51.900 --> 00:29:54.540 The surprise that I want to
NOTE Confidence: 0.810797542727273

00:29:54.540 --> 00:29:57.364 spend a moment pondering.
NOTE Confidence: 0.810797542727273

00:29:57.364 --> 00:30:01.174 Is that despite this tendency
NOTE Confidence: 0.810797542727273

00:30:01.174 --> 00:30:02.726 towards polymorphism,
NOTE Confidence: 0.810797542727273

00:30:02.730 --> 00:30:05.970 the a beta fibrils seated by
NOTE Confidence: 0.810797542727273

00:30:05.970 --> 00:30:08.162 brains from different regions of
NOTE Confidence: 0.810797542727273

00:30:08.162 --> 00:30:10.227 the brain are not polymorphic.
NOTE Confidence: 0.810797542727273

00:30:10.230 --> 00:30:12.070 You get a single structure.
NOTE Confidence: 0.810797542727273

00:30:12.070 --> 00:30:14.618 So why is that?
NOTE Confidence: 0.810797542727273

00:30:14.618 --> 00:30:17.803 Here are three possible explanation.
NOTE Confidence: 0.810797542727273

00:30:17.810 --> 00:30:20.554 The first one is that you have
NOTE Confidence: 0.810797542727273

00:30:20.560 --> 00:30:24.110 that the brain tissue environment
NOTE Confidence: 0.810797542727273

00:30:24.110 --> 00:30:27.540 permits only one nucleation process,
NOTE Confidence: 0.810797542727273

00:30:27.540 --> 00:30:30.132 but this seems kind of unlikely

NOTE Confidence: 0.810797542727273
00:30:30.132 --> 00:30:32.394 because you have different fibril
NOTE Confidence: 0.810797542727273
00:30:32.394 --> 00:30:34.530 structures in different patients.
NOTE Confidence: 0.810797542727273
00:30:34.530 --> 00:30:35.930 Why would that be different?
NOTE Confidence: 0.810797542727273
00:30:35.930 --> 00:30:36.464 Well,
NOTE Confidence: 0.810797542727273
00:30:36.464 --> 00:30:39.360 maybe there are different brain
NOTE Confidence: 0.810797542727273
00:30:39.360 --> 00:30:42.400 environments in different patients.
NOTE Confidence: 0.810797542727273
00:30:42.400 --> 00:30:45.544 Probably there are second,
NOTE Confidence: 0.810797542727273
00:30:45.544 --> 00:30:48.754 maybe fibril structures or nucleated,
NOTE Confidence: 0.810797542727273
00:30:48.754 --> 00:30:52.192 but then many of them or most of them
NOTE Confidence: 0.810797542727273
00:30:52.192 --> 00:30:55.303 are cleared by unknown or partially
NOTE Confidence: 0.810797542727273
00:30:55.303 --> 00:30:57.623 known amyloid clearance mechanisms.
NOTE Confidence: 0.810797542727273
00:30:57.630 --> 00:30:59.386 And the third possibility
NOTE Confidence: 0.810797542727273
00:30:59.386 --> 00:31:02.400 is one that I am fond of,
NOTE Confidence: 0.810797542727273
00:31:02.400 --> 00:31:04.075 though that's not this quite
NOTE Confidence: 0.810797542727273
00:31:04.075 --> 00:31:05.415 the same as evidence,
NOTE Confidence: 0.810797542727273

00:31:05.420 --> 00:31:08.284 and that is that the majority of fibrils
NOTE Confidence: 0.810797542727273

00:31:08.284 --> 00:31:11.319 present in the brains at the time of death.
NOTE Confidence: 0.810797542727273

00:31:11.320 --> 00:31:14.456 Rise from nucleation of a structure at
NOTE Confidence: 0.810797542727273

00:31:14.456 --> 00:31:17.958 a single site and then that structure.
NOTE Confidence: 0.810797542727273

00:31:17.960 --> 00:31:20.345 Spreads by fragmentation and transport
NOTE Confidence: 0.810797542727273

00:31:20.345 --> 00:31:23.551 of the fibrils from one site to
NOTE Confidence: 0.810797542727273

00:31:23.551 --> 00:31:25.765 another site in the brain where
NOTE Confidence: 0.810797542727273

00:31:25.765 --> 00:31:29.153 they can serve as seeds for growth
NOTE Confidence: 0.810797542727273

00:31:29.153 --> 00:31:31.205 of structurally identical fibrils.
NOTE Confidence: 0.810797542727273

00:31:31.210 --> 00:31:31.794 OK Sir,
NOTE Confidence: 0.810797542727273

00:31:31.794 --> 00:31:34.570 I want to talk a little more now about
NOTE Confidence: 0.810797542727273

00:31:34.570 --> 00:31:37.254 the relationship between disease
NOTE Confidence: 0.810797542727273

00:31:37.254 --> 00:31:39.938 phenotype and peptide confirmation.
NOTE Confidence: 0.950489163333333

00:31:42.410 --> 00:31:46.561 About 20 years ago we did some
NOTE Confidence: 0.950489163333333

00:31:46.561 --> 00:31:49.930 work on some of the point mutant
NOTE Confidence: 0.950489163333333

00:31:49.930 --> 00:31:52.528 forms of beta amyloid and this

NOTE Confidence: 0.9504891633333333
00:31:52.528 --> 00:31:54.887 one is the D23 and mutation.
NOTE Confidence: 0.9504891633333333
00:31:54.887 --> 00:31:57.182 It's also called the Iowa
NOTE Confidence: 0.9504891633333333
00:31:57.182 --> 00:31:59.250 mutation and beta amyloid.
NOTE Confidence: 0.9504891633333333
00:31:59.250 --> 00:32:01.435 With this mutation forms fibrils
NOTE Confidence: 0.9504891633333333
00:32:01.435 --> 00:32:04.402 about 1000 fold faster than wild type
NOTE Confidence: 0.9504891633333333
00:32:04.402 --> 00:32:06.852 a data so it's a market difference
NOTE Confidence: 0.9504891633333333
00:32:06.852 --> 00:32:09.482 but the other interesting difference
NOTE Confidence: 0.9504891633333333
00:32:09.482 --> 00:32:12.237 or the main interesting difference.
NOTE Confidence: 0.9504891633333333
00:32:12.240 --> 00:32:16.200 Is that people with this mutation in a
NOTE Confidence: 0.9504891633333333
00:32:16.200 --> 00:32:20.670 beta have a different clinical phenotype?
NOTE Confidence: 0.9504891633333333
00:32:20.670 --> 00:32:23.640 People with wild type a day
NOTE Confidence: 0.9504891633333333
00:32:23.640 --> 00:32:26.110 to get neuritic plaques and.
NOTE Confidence: 0.9504891633333333
00:32:26.110 --> 00:32:28.990 Cerebral amyloid angiopathy is
NOTE Confidence: 0.9504891633333333
00:32:28.990 --> 00:32:31.870 a partially overlapping set.
NOTE Confidence: 0.9504891633333333
00:32:31.870 --> 00:32:34.575 Most people with Alzheimer's disease
NOTE Confidence: 0.9504891633333333

00:32:34.575 --> 00:32:38.610 and neuritic plaques have some level of
NOTE Confidence: 0.9504891633333333

00:32:38.610 --> 00:32:41.090 cerebral cerebral amyloid angiopathy,
NOTE Confidence: 0.9504891633333333

00:32:41.090 --> 00:32:43.470 but now, in the case of D.
NOTE Confidence: 0.9504891633333333

00:32:43.470 --> 00:32:46.998 23 and a beta, it's the other way around.
NOTE Confidence: 0.729143146

00:32:49.260 --> 00:32:53.420 The vacante cerebral amyloid angiopathy,
NOTE Confidence: 0.729143146

00:32:53.420 --> 00:32:55.674 and they mostly die of hemorrhagic stroke.
NOTE Confidence: 0.729143146

00:32:55.680 --> 00:32:57.855 And yes, they have parenchymal
NOTE Confidence: 0.729143146

00:32:57.855 --> 00:32:59.595 deposition of a beta,
NOTE Confidence: 0.729143146

00:32:59.600 --> 00:33:01.576 but a lot of it is in the
NOTE Confidence: 0.729143146

00:33:01.576 --> 00:33:03.579 form of diffuse deposition.
NOTE Confidence: 0.729143146

00:33:03.580 --> 00:33:05.820 There are compact plaques, too,
NOTE Confidence: 0.729143146

00:33:05.820 --> 00:33:08.088 but a lot of it is diffuse.
NOTE Confidence: 0.729143146

00:33:08.090 --> 00:33:09.986 Now we did some solid state in tomorrow
NOTE Confidence: 0.729143146

00:33:09.986 --> 00:33:11.716 work that I'm not going to go into,
NOTE Confidence: 0.729143146

00:33:11.720 --> 00:33:13.840 but again to give you the bottom line,
NOTE Confidence: 0.729143146

00:33:13.840 --> 00:33:18.883 whereas wild type a beta gives you parallel.

NOTE Confidence: 0.729143146

00:33:18.883 --> 00:33:21.046 Enregistrer beta sheets.

NOTE Confidence: 0.729143146

00:33:21.050 --> 00:33:24.170 Hey Beta D 23 N forms,

NOTE Confidence: 0.729143146

00:33:24.170 --> 00:33:26.828 antiparallel beta sheets Now this is,

NOTE Confidence: 0.729143146

00:33:26.830 --> 00:33:30.008 it turns out is a metastable intermediate.

NOTE Confidence: 0.729143146

00:33:30.010 --> 00:33:35.440 If you do repeated citing the there is

NOTE Confidence: 0.729143146

00:33:35.440 --> 00:33:38.440 polymorphism and eventually the more stable

NOTE Confidence: 0.729143146

00:33:38.440 --> 00:33:41.558 parallel and register beta sheets win out.

NOTE Confidence: 0.729143146

00:33:41.560 --> 00:33:44.290 But for a long time you get

NOTE Confidence: 0.729143146

00:33:44.290 --> 00:33:47.240 antiparallel beta sheets so there is a

NOTE Confidence: 0.729143146

00:33:47.240 --> 00:33:49.365 structural difference there for sure.

NOTE Confidence: 0.729143146

00:33:49.370 --> 00:33:52.090 So to investigate this further,

NOTE Confidence: 0.729143146

00:33:52.090 --> 00:33:55.602 we have done some studies in which we

NOTE Confidence: 0.729143146

00:33:55.602 --> 00:33:58.900 start again with brain of people who

NOTE Confidence: 0.729143146

00:33:58.900 --> 00:34:02.415 have died of of Alzheimer's disease and

NOTE Confidence: 0.729143146

00:34:02.415 --> 00:34:05.703 or see a cerebral amyloid angiopathy.

NOTE Confidence: 0.729143146

00:34:05.710 --> 00:34:08.998 And we now we isolate either
NOTE Confidence: 0.729143146

00:34:08.998 --> 00:34:11.190 parenchyma with neuritic plaques.
NOTE Confidence: 0.729143146

00:34:11.190 --> 00:34:14.670 Or blood vessels from leptomeninges.
NOTE Confidence: 0.729143146

00:34:14.670 --> 00:34:18.147 Now it is true that of course brain
NOTE Confidence: 0.729143146

00:34:18.147 --> 00:34:20.229 parenchyma has a small amount of
NOTE Confidence: 0.729143146

00:34:20.229 --> 00:34:22.780 blood vessels, but as it turns out,
NOTE Confidence: 0.729143146

00:34:22.780 --> 00:34:26.380 you don't really see the the patterns
NOTE Confidence: 0.729143146

00:34:26.380 --> 00:34:29.075 in NMR and other techniques that you
NOTE Confidence: 0.729143146

00:34:29.075 --> 00:34:31.638 get from the blood vessel source.
NOTE Confidence: 0.729143146

00:34:31.640 --> 00:34:32.682 But anyway,
NOTE Confidence: 0.729143146

00:34:32.682 --> 00:34:36.329 you do the same kind of procedure.
NOTE Confidence: 0.729143146

00:34:36.330 --> 00:34:38.815 We harvest the amyloid biochemically
NOTE Confidence: 0.729143146

00:34:38.815 --> 00:34:41.930 we added to synthetic peptides with
NOTE Confidence: 0.729143146

00:34:41.930 --> 00:34:44.126 the appropriate isotopic labels.
NOTE Confidence: 0.729143146

00:34:44.130 --> 00:34:49.670 We get replicate fibrils of of that.
NOTE Confidence: 0.729143146

00:34:49.670 --> 00:34:53.590 We can now study by solid state NMR.

NOTE Confidence: 0.729143146

00:34:53.590 --> 00:34:55.830 Now we did a series of patients.

NOTE Confidence: 0.729143146

00:34:55.830 --> 00:34:57.438 I'm not going to go through each one,

NOTE Confidence: 0.729143146

00:34:57.440 --> 00:34:59.442 but I'm going to show you for

NOTE Confidence: 0.729143146

00:34:59.442 --> 00:35:01.210 the point of illustration.

NOTE Confidence: 0.729143146

00:35:01.210 --> 00:35:04.514 Patient one who is a woman who

NOTE Confidence: 0.729143146

00:35:04.514 --> 00:35:06.766 had both Alzheimer's disease

NOTE Confidence: 0.729143146

00:35:06.766 --> 00:35:09.726 and cerebral amyloid angiopathy,

NOTE Confidence: 0.729143146

00:35:09.730 --> 00:35:12.820 and these are the carbon carbon

NOTE Confidence: 0.729143146

00:35:12.820 --> 00:35:15.470 Spectra on the left in blue,

NOTE Confidence: 0.729143146

00:35:15.470 --> 00:35:17.582 and I'll use this color scheme

NOTE Confidence: 0.729143146

00:35:17.582 --> 00:35:19.550 throughout is the vascular amyloid.

NOTE Confidence: 0.729143146

00:35:19.550 --> 00:35:21.968 On the right is parenchymal amyloid

NOTE Confidence: 0.729143146

00:35:21.970 --> 00:35:23.758 and what the next slide shows.

NOTE Confidence: 0.729143146

00:35:23.760 --> 00:35:27.547 Is some of the chemical shift differences.

NOTE Confidence: 0.729143146

00:35:27.550 --> 00:35:30.242 There are significant chemical

NOTE Confidence: 0.729143146

00:35:30.242 --> 00:35:32.934 shift statistically and otherwise

NOTE Confidence: 0.729143146

00:35:32.934 --> 00:35:35.402 significant differences at many sites

NOTE Confidence: 0.729143146

00:35:35.402 --> 00:35:37.646 between these two kinds of amyloid.

NOTE Confidence: 0.895495762857143

00:35:40.220 --> 00:35:42.446 And if you look at the particular

NOTE Confidence: 0.895495762857143

00:35:42.446 --> 00:35:44.698 sites these are in the beta sheets.

NOTE Confidence: 0.844140216363636

00:35:48.480 --> 00:35:51.392 And we also did X ray diffraction and

NOTE Confidence: 0.844140216363636

00:35:51.392 --> 00:35:54.194 just to summarize this this work,

NOTE Confidence: 0.844140216363636

00:35:54.194 --> 00:35:57.120 you can see that in some patients

NOTE Confidence: 0.844140216363636

00:35:57.206 --> 00:35:59.435 the blue line, the blue line and the

NOTE Confidence: 0.844140216363636

00:35:59.435 --> 00:36:01.220 red line are more or less the same,

NOTE Confidence: 0.844140216363636

00:36:01.220 --> 00:36:04.052 but in some the blue is much higher

NOTE Confidence: 0.844140216363636

00:36:04.052 --> 00:36:06.685 and that would indicate a higher

NOTE Confidence: 0.844140216363636

00:36:06.685 --> 00:36:09.439 degree of structural order in the

NOTE Confidence: 0.844140216363636

00:36:09.526 --> 00:36:12.586 vascular than the parenchymal fibrils.

NOTE Confidence: 0.844140216363636

00:36:12.590 --> 00:36:17.665 OK, so that's another story we have

NOTE Confidence: 0.844140216363636

00:36:17.670 --> 00:36:20.966 vascular versus neuritic plaque,

NOTE Confidence: 0.844140216363636
00:36:20.966 --> 00:36:23.546 amyloid and different fibril structures.
NOTE Confidence: 0.844140216363636
00:36:23.546 --> 00:36:27.220 Now I want to show another little vignette
NOTE Confidence: 0.844140216363636
00:36:27.220 --> 00:36:30.118 about polymorphism and amyloid and start
NOTE Confidence: 0.844140216363636
00:36:30.118 --> 00:36:35.316 with the with the question why R&PDAPP mice?
NOTE Confidence: 0.844140216363636
00:36:35.316 --> 00:36:37.528 Demented or very demented,
NOTE Confidence: 0.844140216363636
00:36:37.530 --> 00:36:39.726 why don't they have a lot
NOTE Confidence: 0.844140216363636
00:36:39.726 --> 00:36:40.824 of neurological deficit?
NOTE Confidence: 0.844140216363636
00:36:40.830 --> 00:36:42.660 Now there's a lot of reasons
NOTE Confidence: 0.844140216363636
00:36:42.660 --> 00:36:44.150 why that might be so.
NOTE Confidence: 0.844140216363636
00:36:44.150 --> 00:36:46.526 And of course there are many,
NOTE Confidence: 0.844140216363636
00:36:46.530 --> 00:36:49.650 many differences between mice and humans,
NOTE Confidence: 0.844140216363636
00:36:49.650 --> 00:36:51.930 and sometimes people forget that,
NOTE Confidence: 0.844140216363636
00:36:51.930 --> 00:36:53.163 but they shouldn't.
NOTE Confidence: 0.844140216363636
00:36:53.163 --> 00:36:55.629 But I'm going to give you
NOTE Confidence: 0.844140216363636
00:36:55.629 --> 00:36:57.550 one more possibility.
NOTE Confidence: 0.844140216363636

00:36:57.550 --> 00:37:00.466 This mouse is one of the earliest models of
NOTE Confidence: 0.844140216363636

00:37:00.470 --> 00:37:02.306 Paul's mouse models of Alzheimer's disease.
NOTE Confidence: 0.844140216363636

00:37:02.310 --> 00:37:04.446 They overexpress one particular
NOTE Confidence: 0.844140216363636

00:37:04.446 --> 00:37:07.650 movement form of the eight PP,
NOTE Confidence: 0.844140216363636

00:37:07.650 --> 00:37:11.076 which is the Indiana mutant form of it.
NOTE Confidence: 0.844140216363636

00:37:11.076 --> 00:37:12.524 By about four months,
NOTE Confidence: 0.844140216363636

00:37:12.530 --> 00:37:14.696 they start to get cognitive defects,
NOTE Confidence: 0.844140216363636

00:37:14.700 --> 00:37:17.696 but they're really not all that severe.
NOTE Confidence: 0.844140216363636

00:37:17.700 --> 00:37:20.262 In spite of that, they have basically
NOTE Confidence: 0.844140216363636

00:37:20.262 --> 00:37:22.340 amyloid coming out of their ears.
NOTE Confidence: 0.844140216363636

00:37:22.340 --> 00:37:23.700 Enormous extracellular,
NOTE Confidence: 0.844140216363636

00:37:23.700 --> 00:37:28.460 a beta deposition and some other lesions.
NOTE Confidence: 0.844140216363636

00:37:28.460 --> 00:37:31.136 They also have tell the effects.
NOTE Confidence: 0.844140216363636

00:37:31.140 --> 00:37:33.640 Oh Hyperfest 4 later.
NOTE Confidence: 0.65359455

00:37:36.460 --> 00:37:41.936 Tell defects. So the question we're asking
NOTE Confidence: 0.65359455

00:37:41.936 --> 00:37:45.872 them is what kind of fibrils is there a

NOTE Confidence: 0.65359455

00:37:45.872 --> 00:37:48.296 difference in the fibril structure that

NOTE Confidence: 0.65359455

00:37:48.296 --> 00:37:51.020 leads to differences in pathogenesis?

NOTE Confidence: 0.65359455

00:37:51.020 --> 00:37:53.576 This is from the paper of Riley ET al,

NOTE Confidence: 0.65359455

00:37:53.580 --> 00:37:55.554 just to show you just how much

NOTE Confidence: 0.65359455

00:37:55.554 --> 00:37:57.852 Emma Lloyd there is in their mouse

NOTE Confidence: 0.65359455

00:37:57.852 --> 00:38:01.300 hippocampus and other areas as well.

NOTE Confidence: 0.65359455

00:38:01.300 --> 00:38:04.980 OK, so if you compare.

NOTE Confidence: 0.65359455

00:38:04.980 --> 00:38:08.010 Human and mouse a beta.

NOTE Confidence: 0.65359455

00:38:08.010 --> 00:38:13.056 There are three structural amino acid

NOTE Confidence: 0.65359455

00:38:13.056 --> 00:38:17.780 point differences in the sequence.

NOTE Confidence: 0.65359455

00:38:17.780 --> 00:38:20.308 And this is a third species I was

NOTE Confidence: 0.65359455

00:38:20.308 --> 00:38:22.797 attracted to it for the obvious reason,

NOTE Confidence: 0.65359455

00:38:22.800 --> 00:38:25.537 but it stands for naked mole rat,

NOTE Confidence: 0.65359455

00:38:25.540 --> 00:38:31.090 not nuclear magnetic resonance and.

NOTE Confidence: 0.65359455

00:38:31.090 --> 00:38:35.520 There's a picture of it. Uhm?

NOTE Confidence: 0.65359455

00:38:35.520 --> 00:38:37.592 You can see that when you fiber
NOTE Confidence: 0.65359455

00:38:37.592 --> 00:38:39.080 allies these three peptides,
NOTE Confidence: 0.65359455

00:38:39.080 --> 00:38:40.460 we made it, we made fibers.
NOTE Confidence: 0.65359455

00:38:40.460 --> 00:38:42.784 We did transmission again and right off
NOTE Confidence: 0.65359455

00:38:42.784 --> 00:38:45.533 the bat you can see that there are under
NOTE Confidence: 0.65359455

00:38:45.533 --> 00:38:48.419 a given set of fibril isation conditions.
NOTE Confidence: 0.65359455

00:38:48.420 --> 00:38:50.655 You get fibrils with rather
NOTE Confidence: 0.65359455

00:38:50.655 --> 00:38:51.549 different morphology.
NOTE Confidence: 0.65359455

00:38:51.550 --> 00:38:54.682 Here you see these fluoride striations
NOTE Confidence: 0.65359455

00:38:54.682 --> 00:38:57.906 in human a beta 40 twists mostly
NOTE Confidence: 0.65359455

00:38:57.906 --> 00:39:00.867 in the nick and Mallrat a beta
NOTE Confidence: 0.65359455

00:39:00.867 --> 00:39:03.963 40 and this kind of mixed with a
NOTE Confidence: 0.65359455

00:39:03.963 --> 00:39:06.330 lot of very thin fibrils.
NOTE Confidence: 0.65359455

00:39:06.330 --> 00:39:10.026 In a beta mouse, a beta 40.
NOTE Confidence: 0.65359455

00:39:10.030 --> 00:39:12.886 The reason for including the naked mole
NOTE Confidence: 0.65359455

00:39:12.886 --> 00:39:18.498 rat is that it is the longest lived rodent.

NOTE Confidence: 0.65359455

00:39:18.500 --> 00:39:22.815 It is insensitive to pain and it is

NOTE Confidence: 0.65359455

00:39:22.815 --> 00:39:25.040 supposedly resistant to the effects

NOTE Confidence: 0.65359455

00:39:25.040 --> 00:39:28.609 of a beta and Alzheimer's disease.

NOTE Confidence: 0.65359455

00:39:28.610 --> 00:39:31.746 I say this is a story that

NOTE Confidence: 0.65359455

00:39:31.746 --> 00:39:33.090 is still developing.

NOTE Confidence: 0.65359455

00:39:33.090 --> 00:39:33.521 OK,

NOTE Confidence: 0.65359455

00:39:33.521 --> 00:39:34.814 in any case,

NOTE Confidence: 0.65359455

00:39:34.814 --> 00:39:38.458 if you now take the mouse and human

NOTE Confidence: 0.65359455

00:39:38.458 --> 00:39:42.242 a beta and you compare them and this

NOTE Confidence: 0.65359455

00:39:42.344 --> 00:39:44.968 is data that's hot off the presses,

NOTE Confidence: 0.65359455

00:39:44.970 --> 00:39:47.578 so I don't have a structure for this,

NOTE Confidence: 0.65359455

00:39:47.580 --> 00:39:48.480 it is coming,

NOTE Confidence: 0.65359455

00:39:48.480 --> 00:39:50.280 but I think it's pretty clear

NOTE Confidence: 0.65359455

00:39:50.280 --> 00:39:52.976 that there are going to be major

NOTE Confidence: 0.65359455

00:39:52.976 --> 00:39:54.140 structural differences between

NOTE Confidence: 0.65359455

00:39:54.140 --> 00:39:56.470 the Hughes human and mouse a beta,

NOTE Confidence: 0.65359455

00:39:56.470 --> 00:40:00.960 despite having been fibril eisd

NOTE Confidence: 0.65359455

00:40:00.960 --> 00:40:03.654 under identical conditions.

NOTE Confidence: 0.65359455

00:40:03.660 --> 00:40:05.924 And this slide to show up a closeup

NOTE Confidence: 0.65359455

00:40:05.924 --> 00:40:08.200 of 1 region of the spectrum.

NOTE Confidence: 0.65359455

00:40:08.200 --> 00:40:11.063 If you look at the upper right

NOTE Confidence: 0.65359455

00:40:11.063 --> 00:40:12.290 of this spectrum.

NOTE Confidence: 0.65359455

00:40:12.290 --> 00:40:15.398 This is an alanine peak for what it for,

NOTE Confidence: 0.65359455

00:40:15.398 --> 00:40:17.322 what it matters, but there's a.

NOTE Confidence: 0.65359455

00:40:17.322 --> 00:40:20.010 There's a big difference in this region

NOTE Confidence: 0.65359455

00:40:20.083 --> 00:40:22.995 as well with leucine and glutamine peaks,

NOTE Confidence: 0.65359455

00:40:23.000 --> 00:40:25.208 so a big difference as well.

NOTE Confidence: 0.65359455

00:40:25.210 --> 00:40:27.022 So we're in the process of

NOTE Confidence: 0.65359455

00:40:27.022 --> 00:40:27.928 doing the assignment.

NOTE Confidence: 0.65359455

00:40:27.930 --> 00:40:29.022 I'm not absolutely sure

NOTE Confidence: 0.65359455

00:40:29.022 --> 00:40:30.114 about the assignments yet,

NOTE Confidence: 0.65359455

00:40:30.120 --> 00:40:32.808 but this is very exciting research.

NOTE Confidence: 0.65359455

00:40:32.810 --> 00:40:35.630 That is work in progress.

NOTE Confidence: 0.65359455

00:40:35.630 --> 00:40:35.899 OK,

NOTE Confidence: 0.65359455

00:40:35.899 --> 00:40:38.051 in the last few minutes of the talk

NOTE Confidence: 0.65359455

00:40:38.051 --> 00:40:40.185 I'm going to switch and talk about

NOTE Confidence: 0.65359455

00:40:40.185 --> 00:40:42.579 the other story I mentioned earlier,

NOTE Confidence: 0.65359455

00:40:42.580 --> 00:40:45.550 which is how NMR can be used to study that.

NOTE Confidence: 0.65359455

00:40:45.550 --> 00:40:48.712 And I'm the dynamics of proteins

NOTE Confidence: 0.65359455

00:40:48.712 --> 00:40:51.446 in particular of occluding and

NOTE Confidence: 0.65359455

00:40:51.446 --> 00:40:53.590 it's alpha helical bundle.

NOTE Confidence: 0.65359455

00:40:53.590 --> 00:40:55.966 The reason for interest in this

NOTE Confidence: 0.65359455

00:40:55.966 --> 00:40:59.253 is that this is a tight junction

NOTE Confidence: 0.65359455

00:40:59.253 --> 00:41:01.948 protein in which one particular

NOTE Confidence: 0.65359455

00:41:01.948 --> 00:41:04.035 residue residue serine 408,

NOTE Confidence: 0.65359455

00:41:04.035 --> 00:41:06.110 seems to be very important.

NOTE Confidence: 0.65359455

00:41:06.110 --> 00:41:10.000 In regulating tight junction function.
NOTE Confidence: 0.65359455

00:41:10.000 --> 00:41:12.835 Now this is from a paper by
NOTE Confidence: 0.65359455

00:41:12.835 --> 00:41:15.220 David Raleigh and Jerry Turner
NOTE Confidence: 0.65359455

00:41:15.220 --> 00:41:17.932 collaborator in this work,
NOTE Confidence: 0.65359455

00:41:17.932 --> 00:41:19.690 and I'm not going to go
NOTE Confidence: 0.65359455

00:41:19.690 --> 00:41:20.554 through their whole model.
NOTE Confidence: 0.981117268571429

00:41:20.560 --> 00:41:23.199 They have tons and tons of data.
NOTE Confidence: 0.981117268571429

00:41:23.200 --> 00:41:24.700 Beautiful data on this,
NOTE Confidence: 0.981117268571429

00:41:24.700 --> 00:41:27.439 except I'll point out one part of it.
NOTE Confidence: 0.981117268571429

00:41:27.440 --> 00:41:32.528 And that is that sehring 508 of occluding.
NOTE Confidence: 0.981117268571429

00:41:32.530 --> 00:41:35.280 Can be phosphorylated or not.
NOTE Confidence: 0.981117268571429

00:41:35.280 --> 00:41:37.920 It gets phosphorylated by CK2 and
NOTE Confidence: 0.981117268571429

00:41:37.920 --> 00:41:41.245 if it is not phosphorylated it
NOTE Confidence: 0.981117268571429

00:41:41.245 --> 00:41:48.777 binds zielone and and that makes the
NOTE Confidence: 0.981117268571429

00:41:48.777 --> 00:41:51.012 the tight junction more permeable
NOTE Confidence: 0.981117268571429

00:41:51.012 --> 00:41:54.259 to water and ions so you get

NOTE Confidence: 0.981117268571429
00:41:54.259 --> 00:41:56.544 leakage across the tight junction.
NOTE Confidence: 0.942382691818182
00:41:58.820 --> 00:42:00.896 Now we wanted to investigate the
NOTE Confidence: 0.942382691818182
00:42:00.896 --> 00:42:03.000 structural basis for this difference,
NOTE Confidence: 0.942382691818182
00:42:03.000 --> 00:42:04.810 and as I'll show you,
NOTE Confidence: 0.942382691818182
00:42:04.810 --> 00:42:06.800 there's a big problem here.
NOTE Confidence: 0.942382691818182
00:42:06.800 --> 00:42:10.296 This slide won't go into it in detail,
NOTE Confidence: 0.942382691818182
00:42:10.300 --> 00:42:13.666 but let me go back here.
NOTE Confidence: 0.942382691818182
00:42:13.670 --> 00:42:17.513 This slide shows that occludin has a
NOTE Confidence: 0.942382691818182
00:42:17.513 --> 00:42:20.190 membrane spanning region for membrane
NOTE Confidence: 0.942382691818182
00:42:20.190 --> 00:42:23.466 spanning helices and then it has a
NOTE Confidence: 0.942382691818182
00:42:23.466 --> 00:42:26.998 tail that is cytosolic or cytoplasmic.
NOTE Confidence: 0.942382691818182
00:42:27.000 --> 00:42:31.158 Now this slide shows the evolutionary
NOTE Confidence: 0.942382691818182
00:42:31.158 --> 00:42:34.825 conservation of occludin in its
NOTE Confidence: 0.942382691818182
00:42:34.825 --> 00:42:38.662 cytoplasmic domain and it is 100%
NOTE Confidence: 0.942382691818182
00:42:38.662 --> 00:42:40.934 identical throughout mammalian evolution,
NOTE Confidence: 0.942382691818182

00:42:40.940 --> 00:42:43.617 and he and greater than 90%

NOTE Confidence: 0.942382691818182

00:42:43.617 --> 00:42:45.228 conserved in birds,

NOTE Confidence: 0.942382691818182

00:42:45.228 --> 00:42:46.839 amphibians and fish.

NOTE Confidence: 0.942382691818182

00:42:46.840 --> 00:42:49.948 And that's absolutely true at this

NOTE Confidence: 0.942382691818182

00:42:49.948 --> 00:42:51.502 critical sehning 408.

NOTE Confidence: 0.884304182857143

00:42:53.620 --> 00:42:56.938 Now here's the problem. Here is a.

NOTE Confidence: 0.884304182857143

00:42:56.940 --> 00:42:59.826 Here is a crystal structure done

NOTE Confidence: 0.884304182857143

00:42:59.826 --> 00:43:04.750 by Arnon levy of the helical of the

NOTE Confidence: 0.884304182857143

00:43:04.750 --> 00:43:07.534 cytoplasmic portion of occludin.

NOTE Confidence: 0.884304182857143

00:43:07.540 --> 00:43:08.420 And as you can see,

NOTE Confidence: 0.884304182857143

00:43:08.420 --> 00:43:12.140 it consistently 3A helical bundle.

NOTE Confidence: 0.884304182857143

00:43:12.140 --> 00:43:15.080 But what I will point out is the in terminus,

NOTE Confidence: 0.884304182857143

00:43:15.080 --> 00:43:18.392 in which many of the residues are not seen.

NOTE Confidence: 0.884304182857143

00:43:18.400 --> 00:43:21.039 In fact, there's about 30 residues that

NOTE Confidence: 0.884304182857143

00:43:21.039 --> 00:43:24.058 are not seen in the crystal structure.

NOTE Confidence: 0.884304182857143

00:43:24.060 --> 00:43:26.288 So here's the problem.

NOTE Confidence: 0.884304182857143
00:43:26.288 --> 00:43:29.073 You have sehning 408 phosphorylation.
NOTE Confidence: 0.884304182857143
00:43:29.080 --> 00:43:31.580 It's crucial for physiological
NOTE Confidence: 0.884304182857143
00:43:31.580 --> 00:43:34.705 function of the tight junction.
NOTE Confidence: 0.884304182857143
00:43:34.710 --> 00:43:38.185 This region is extremely well
NOTE Confidence: 0.884304182857143
00:43:38.185 --> 00:43:39.575 conserved evolutionarily,
NOTE Confidence: 0.884304182857143
00:43:39.580 --> 00:43:42.286 but especially the unstructured domain with
NOTE Confidence: 0.884304182857143
00:43:42.286 --> 00:43:45.700 serine 408 and the surrounding residues,
NOTE Confidence: 0.884304182857143
00:43:45.700 --> 00:43:48.325 and yet sehning 408 is not seen
NOTE Confidence: 0.884304182857143
00:43:48.325 --> 00:43:50.752 in the crystal structure. Why?
NOTE Confidence: 0.884304182857143
00:43:50.752 --> 00:43:53.566 Because it is in an unstructured domain.
NOTE Confidence: 0.884304182857143
00:43:53.570 --> 00:43:57.467 So how do we make sense of this conundrum?
NOTE Confidence: 0.884304182857143
00:43:57.470 --> 00:43:59.696 Well, we made a group of peptides
NOTE Confidence: 0.884304182857143
00:43:59.696 --> 00:44:02.053 and I'm only going to focus on
NOTE Confidence: 0.884304182857143
00:44:02.053 --> 00:44:03.708 the first three of those,
NOTE Confidence: 0.884304182857143
00:44:03.710 --> 00:44:06.111 and I'm going to use a little
NOTE Confidence: 0.884304182857143

00:44:06.111 --> 00:44:07.590 bit of shorthand here.
NOTE Confidence: 0.884304182857143

00:44:07.590 --> 00:44:11.082 Occluding A has a searing 408
NOTE Confidence: 0.884304182857143

00:44:11.082 --> 00:44:13.410 substituted by an alanine,
NOTE Confidence: 0.884304182857143

00:44:13.410 --> 00:44:17.832 so it's like the D phospho amino acid
NOTE Confidence: 0.884304182857143

00:44:17.832 --> 00:44:23.208 serine and occludin with a D at position 408.
NOTE Confidence: 0.884304182857143

00:44:23.210 --> 00:44:26.999 I'll call it occlusion D or occlusion 408 D.
NOTE Confidence: 0.884304182857143

00:44:27.000 --> 00:44:29.112 And so this is now the same length
NOTE Confidence: 0.884304182857143

00:44:29.112 --> 00:44:31.251 as the protein that was used
NOTE Confidence: 0.884304182857143

00:44:31.251 --> 00:44:32.795 for the crystal structure.
NOTE Confidence: 0.884304182857143

00:44:32.800 --> 00:44:35.180 But with this point mutation
NOTE Confidence: 0.884304182857143

00:44:35.180 --> 00:44:37.828 now this third construct.
NOTE Confidence: 0.884304182857143

00:44:37.828 --> 00:44:42.958 Lops off the part that isn't seen in the
NOTE Confidence: 0.884304182857143

00:44:42.958 --> 00:44:46.470 crystal structure and is unstructured.
NOTE Confidence: 0.884304182857143

00:44:46.470 --> 00:44:47.031 Now,
NOTE Confidence: 0.884304182857143

00:44:47.031 --> 00:44:50.397 if you express this in acoli,
NOTE Confidence: 0.884304182857143

00:44:50.400 --> 00:44:53.670 you get alpha helical structure and

NOTE Confidence: 0.884304182857143
00:44:53.670 --> 00:44:58.930 it's the same in both A&D and if you
NOTE Confidence: 0.884304182857143
00:44:58.930 --> 00:45:01.130 look at the one with just the helical
NOTE Confidence: 0.884304182857143
00:45:01.195 --> 00:45:03.570 bundle the unstructured domain lopped
NOTE Confidence: 0.884304182857143
00:45:03.570 --> 00:45:05.945 off slightly higher helical percentage
NOTE Confidence: 0.884304182857143
00:45:06.011 --> 00:45:07.946 because you've lopped off this,
NOTE Confidence: 0.884304182857143
00:45:07.950 --> 00:45:09.162 the unstructured domain.
NOTE Confidence: 0.884304182857143
00:45:09.162 --> 00:45:10.778 But other than that,
NOTE Confidence: 0.884304182857143
00:45:10.780 --> 00:45:14.972 these proteins look to have at this low
NOTE Confidence: 0.884304182857143
00:45:14.972 --> 00:45:18.358 resolution level very similar structures.
NOTE Confidence: 0.884304182857143
00:45:18.360 --> 00:45:21.008 Now this is a.
NOTE Confidence: 0.884304182857143
00:45:21.010 --> 00:45:23.260 This is like in HSQC,
NOTE Confidence: 0.884304182857143
00:45:23.260 --> 00:45:27.054 except because the protein is very elongated.
NOTE Confidence: 0.884304182857143
00:45:27.060 --> 00:45:29.680 We used a technique called.
NOTE Confidence: 0.884304182857143
00:45:29.680 --> 00:45:32.386 And trozzi, but it's basically gives
NOTE Confidence: 0.884304182857143
00:45:32.386 --> 00:45:35.530 you the same kind of information.
NOTE Confidence: 0.884304182857143

00:45:35.530 --> 00:45:37.698 But what this show is first of all,
NOTE Confidence: 0.884304182857143

00:45:37.700 --> 00:45:40.130 on the left you see red and blue and
NOTE Confidence: 0.884304182857143

00:45:40.130 --> 00:45:42.317 most of the peaks are overlapped.
NOTE Confidence: 0.884304182857143

00:45:42.320 --> 00:45:43.520 And this is a clue.
NOTE Confidence: 0.884304182857143

00:45:43.520 --> 00:45:45.024 Danae and occludin D.
NOTE Confidence: 0.884304182857143

00:45:45.024 --> 00:45:48.147 And with this tells you that is that
NOTE Confidence: 0.884304182857143

00:45:48.147 --> 00:45:50.898 even on the very fine structural level,
NOTE Confidence: 0.884304182857143

00:45:50.900 --> 00:45:53.576 these proteins have very similar structures,
NOTE Confidence: 0.884304182857143

00:45:53.580 --> 00:45:56.140 though not quite identical.
NOTE Confidence: 0.884304182857143

00:45:56.140 --> 00:45:58.754 Now, if you compare, on the other hand,
NOTE Confidence: 0.884304182857143

00:45:58.760 --> 00:45:59.280 occludin.
NOTE Confidence: 0.884304182857143

00:45:59.280 --> 00:45:59.800 D.
NOTE Confidence: 0.884304182857143

00:45:59.800 --> 00:46:03.440 You can also do occluding a same
NOTE Confidence: 0.884304182857143

00:46:03.440 --> 00:46:06.066 answer if you compare occlusion
NOTE Confidence: 0.884304182857143

00:46:06.066 --> 00:46:08.752 D with the Helix only occluding.
NOTE Confidence: 0.884304182857143

00:46:08.752 --> 00:46:12.395 Now you see a lot of places where red

NOTE Confidence: 0.884304182857143
00:46:12.395 --> 00:46:15.209 and green do not overlap very well,
NOTE Confidence: 0.884304182857143
00:46:15.210 --> 00:46:18.040 so this bespeaks large differences
NOTE Confidence: 0.884304182857143
00:46:18.040 --> 00:46:22.030 of some kind in the structure.
NOTE Confidence: 0.884304182857143
00:46:22.030 --> 00:46:23.465 And you can put some numbers on.
NOTE Confidence: 0.884304182857143
00:46:23.470 --> 00:46:26.206 It won't go through the details of it,
NOTE Confidence: 0.884304182857143
00:46:26.210 --> 00:46:28.928 but what I want to point out is the
NOTE Confidence: 0.884304182857143
00:46:28.928 --> 00:46:30.607 difference in the Y axis scale.
NOTE Confidence: 0.884304182857143
00:46:30.610 --> 00:46:32.710 If you compare A&D on top,
NOTE Confidence: 0.884304182857143
00:46:32.710 --> 00:46:34.570 these are tiny numbers,
NOTE Confidence: 0.884304182857143
00:46:34.570 --> 00:46:38.610 whereas if you compare in this case
NOTE Confidence: 0.884304182857143
00:46:38.610 --> 00:46:42.570 D with the Helix only version,
NOTE Confidence: 0.905753026
00:46:42.570 --> 00:46:44.418 you can see that these numbers are
NOTE Confidence: 0.905753026
00:46:44.418 --> 00:46:46.740 sometimes quite large, almost one PPM.
NOTE Confidence: 0.910917138333333
00:46:48.900 --> 00:46:52.326 Now to get at this further, we used a
NOTE Confidence: 0.910917138333333
00:46:52.326 --> 00:46:56.092 technique that was developed by Marius
NOTE Confidence: 0.910917138333333

00:46:56.092 --> 00:47:00.544 Floor and Nicholas Fousey which is called.
NOTE Confidence: 0.9109171383333333

00:47:00.550 --> 00:47:05.296 Oh, which is called paramagnetic relaxation
NOTE Confidence: 0.9109171383333333

00:47:05.296 --> 00:47:07.805 enhancement and basically what you do
NOTE Confidence: 0.9109171383333333

00:47:07.805 --> 00:47:10.916 here is you put an electron spin label
NOTE Confidence: 0.9109171383333333

00:47:10.916 --> 00:47:13.975 on a cysteine by a disulfide bridge.
NOTE Confidence: 0.9109171383333333

00:47:13.980 --> 00:47:16.549 So you're making mutation at a particular
NOTE Confidence: 0.9109171383333333

00:47:16.549 --> 00:47:18.990 site in amino acid for assisting,
NOTE Confidence: 0.9109171383333333

00:47:18.990 --> 00:47:22.026 and then that electron spin causes
NOTE Confidence: 0.9109171383333333

00:47:22.026 --> 00:47:25.320 rapid relaxation of a nuclear spin.
NOTE Confidence: 0.9109171383333333

00:47:25.320 --> 00:47:30.192 Now the readout for that is that if the.
NOTE Confidence: 0.9109171383333333

00:47:30.192 --> 00:47:33.524 Electron Spin label is close to the
NOTE Confidence: 0.9109171383333333

00:47:33.524 --> 00:47:36.710 nuclear spin that you're looking at.
NOTE Confidence: 0.9109171383333333

00:47:36.710 --> 00:47:38.330 You see, broadening of the peak,
NOTE Confidence: 0.9109171383333333

00:47:38.330 --> 00:47:41.192 it gets less intense due to
NOTE Confidence: 0.9109171383333333

00:47:41.192 --> 00:47:42.623 the paramagnetic label,
NOTE Confidence: 0.9109171383333333

00:47:42.630 --> 00:47:44.845 so you see decreased peak

NOTE Confidence: 0.910917138333333
00:47:44.845 --> 00:47:46.617 volume and peak height.
NOTE Confidence: 0.858288247272727
00:47:48.890 --> 00:47:51.900 OK, now I was going to tell you two types
NOTE Confidence: 0.858288247272727
00:47:51.983 --> 00:47:55.688 of PRE experiments we did on occludin.
NOTE Confidence: 0.858288247272727
00:47:55.690 --> 00:47:57.657 The first kind and the first kind.
NOTE Confidence: 0.858288247272727
00:47:57.660 --> 00:48:01.890 We took the the the two,
NOTE Confidence: 0.858288247272727
00:48:01.890 --> 00:48:05.052 the two versions of the protein
NOTE Confidence: 0.858288247272727
00:48:05.052 --> 00:48:07.652 with the unstructured domain and
NOTE Confidence: 0.858288247272727
00:48:07.652 --> 00:48:10.417 now we put a label on either
NOTE Confidence: 0.858288247272727
00:48:10.417 --> 00:48:13.148 cysteine 409 which occurs naturally
NOTE Confidence: 0.858288247272727
00:48:13.148 --> 00:48:16.223 in the peptide very conveniently,
NOTE Confidence: 0.858288247272727
00:48:16.230 --> 00:48:18.534 or we mutated the.
NOTE Confidence: 0.858288247272727
00:48:18.534 --> 00:48:21.414 End terminal alanine to assisting
NOTE Confidence: 0.858288247272727
00:48:21.420 --> 00:48:23.956 now this is I'm going to call this
NOTE Confidence: 0.858288247272727
00:48:23.956 --> 00:48:25.452 insist because the unstructured
NOTE Confidence: 0.858288247272727
00:48:25.452 --> 00:48:27.822 domain is attached to the helical
NOTE Confidence: 0.858288247272727

00:48:27.822 --> 00:48:30.041 bundle and this arrow indicates
NOTE Confidence: 0.858288247272727

00:48:30.041 --> 00:48:32.759 roughly where the little way the
NOTE Confidence: 0.858288247272727

00:48:32.759 --> 00:48:35.340 crystallographic structure ends.
NOTE Confidence: 0.858288247272727

00:48:35.340 --> 00:48:37.698 Now the second time that experiments,
NOTE Confidence: 0.858288247272727

00:48:37.700 --> 00:48:42.433 we take a free peptide and we lay,
NOTE Confidence: 0.858288247272727

00:48:42.433 --> 00:48:46.219 and it's either the peptide containing
NOTE Confidence: 0.858288247272727

00:48:46.220 --> 00:48:51.044 S 4088 or S408D and then we attach the
NOTE Confidence: 0.858288247272727

00:48:51.044 --> 00:48:54.373 paramagnetic spin label to cysteine
NOTE Confidence: 0.858288247272727

00:48:54.373 --> 00:48:57.420 409 and naturally occurring, assisting,
NOTE Confidence: 0.858288247272727

00:48:57.420 --> 00:49:00.505 and now we add it to the occluding,
NOTE Confidence: 0.858288247272727

00:49:00.505 --> 00:49:01.635 in which.
NOTE Confidence: 0.858288247272727

00:49:01.635 --> 00:49:05.590 **** be Helix only version of occlusion.
NOTE Confidence: 0.87096644875

00:49:08.310 --> 00:49:11.614 No, I'm just wanna give you the
NOTE Confidence: 0.87096644875

00:49:11.614 --> 00:49:15.078 gross outlines of what we see and if
NOTE Confidence: 0.87096644875

00:49:15.078 --> 00:49:18.046 you look at the overall pattern on
NOTE Confidence: 0.87096644875

00:49:18.046 --> 00:49:21.006 the left of the Paramedic Clinic,

NOTE Confidence: 0.87096644875

00:49:21.006 --> 00:49:25.206 label is at 16509 on the right.

NOTE Confidence: 0.87096644875

00:49:25.206 --> 00:49:28.698 At 8383C you can see that the two

NOTE Confidence: 0.87096644875

00:49:28.698 --> 00:49:31.342 valleys whoops that the two valleys

NOTE Confidence: 0.87096644875

00:49:31.342 --> 00:49:34.036 here are at very different places.

NOTE Confidence: 0.87096644875

00:49:34.040 --> 00:49:37.280 Then then in on the right side picture.

NOTE Confidence: 0.87096644875

00:49:37.280 --> 00:49:40.440 So through mapping like this,

NOTE Confidence: 0.87096644875

00:49:40.440 --> 00:49:43.588 we think that C 409 is roughly

NOTE Confidence: 0.87096644875

00:49:43.588 --> 00:49:45.430 where it's shown in this cartoon

NOTE Confidence: 0.87096644875

00:49:45.501 --> 00:49:47.120 on the bottom, whereas

NOTE Confidence: 0.864888431428571

00:49:50.000 --> 00:49:51.946 A383C is roughly at where you see

NOTE Confidence: 0.864888431428571

00:49:51.946 --> 00:49:54.240 it in this picture on the bottom.

NOTE Confidence: 0.864888431428571

00:49:54.240 --> 00:49:56.826 So basically we're mapping the location

NOTE Confidence: 0.864888431428571

00:49:56.826 --> 00:50:00.110 of residues in the unstructured domain.

NOTE Confidence: 0.904584300833333

00:50:02.490 --> 00:50:04.608 And this is the experiment intrans

NOTE Confidence: 0.904584300833333

00:50:04.608 --> 00:50:07.888 where you get a small difference D

NOTE Confidence: 0.904584300833333

00:50:07.888 --> 00:50:12.750 slightly more than a four for the
NOTE Confidence: 0.9045843008333333

00:50:12.750 --> 00:50:17.860 binding of the peptide to the Helix.
NOTE Confidence: 0.9045843008333333

00:50:17.860 --> 00:50:20.524 Only version of the peptide of the protein.
NOTE Confidence: 0.9045843008333333

00:50:20.530 --> 00:50:23.850 Now I have to say that it really
NOTE Confidence: 0.9045843008333333

00:50:23.850 --> 00:50:26.701 wasn't known before this that the
NOTE Confidence: 0.9045843008333333

00:50:26.701 --> 00:50:30.140 peptide would bind to the Helix only.
NOTE Confidence: 0.9045843008333333

00:50:30.140 --> 00:50:33.175 Protein, but we confirmed that
NOTE Confidence: 0.9045843008333333

00:50:33.175 --> 00:50:36.142 by doing affinity measurements
NOTE Confidence: 0.9045843008333333

00:50:36.142 --> 00:50:38.770 by microscale thermophoresis,
NOTE Confidence: 0.9045843008333333

00:50:38.770 --> 00:50:41.906 there is in fact about a six fold
NOTE Confidence: 0.9045843008333333

00:50:41.906 --> 00:50:45.553 difference of affinity phospho S 408
NOTE Confidence: 0.9045843008333333

00:50:45.553 --> 00:50:49.044 higher than D phospho 408, and this,
NOTE Confidence: 0.9045843008333333

00:50:49.044 --> 00:50:51.686 by the way, is the phosphorylated,
NOTE Confidence: 0.9045843008333333

00:50:51.686 --> 00:50:54.294 not the phospho mimetic.
NOTE Confidence: 0.9045843008333333

00:50:54.300 --> 00:50:56.946 Now the other thing that is
NOTE Confidence: 0.9045843008333333

00:50:56.946 --> 00:50:58.269 physiologically very important.

NOTE Confidence: 0.87900090375
00:51:01.240 --> 00:51:04.061 Is that this does lead to a
NOTE Confidence: 0.87900090375
00:51:04.061 --> 00:51:06.402 difference of affinity for the
NOTE Confidence: 0.87900090375
00:51:06.402 --> 00:51:08.498 molecular partner of occluding,
NOTE Confidence: 0.87900090375
00:51:08.500 --> 00:51:12.154 which is 01, and as you can see here,
NOTE Confidence: 0.87900090375
00:51:12.160 --> 00:51:15.736 as predicted by the physiological data,
NOTE Confidence: 0.87900090375
00:51:15.740 --> 00:51:19.620 the S 4088 binds with about a two
NOTE Confidence: 0.87900090375
00:51:19.620 --> 00:51:23.610 fold higher affinity than AS408D.
NOTE Confidence: 0.87900090375
00:51:23.610 --> 00:51:26.550 No, the conclusions.
NOTE Confidence: 0.87900090375
00:51:26.550 --> 00:51:29.749 First, NMR can help us understand disease,
NOTE Confidence: 0.87900090375
00:51:29.750 --> 00:51:32.330 and I've given you some diverse
NOTE Confidence: 0.87900090375
00:51:32.330 --> 00:51:34.880 vignettes to demonstrate that first
NOTE Confidence: 0.87900090375
00:51:34.880 --> 00:51:37.430 there is a structure dysfunction
NOTE Confidence: 0.87900090375
00:51:37.510 --> 00:51:40.078 relationship between amyloid structure
NOTE Confidence: 0.87900090375
00:51:40.078 --> 00:51:43.288 and the Alzheimer's disease phenotype.
NOTE Confidence: 0.87900090375
00:51:43.290 --> 00:51:46.594 This is shown by patient one versus patient.
NOTE Confidence: 0.87900090375

00:51:46.600 --> 00:51:49.835 Two Riddick plaques versus vascular
NOTE Confidence: 0.87900090375

00:51:49.835 --> 00:51:53.862 amyloid mouse versus human amyloid second.
NOTE Confidence: 0.87900090375

00:51:53.862 --> 00:51:56.726 This is important because.
NOTE Confidence: 0.87900090375

00:51:56.730 --> 00:51:59.992 Amyloid a genic peptides can Co fiber
NOTE Confidence: 0.87900090375

00:51:59.992 --> 00:52:03.600 allies as well as Co precipitate.
NOTE Confidence: 0.87900090375

00:52:03.600 --> 00:52:04.075 Alright,
NOTE Confidence: 0.87900090375

00:52:04.075 --> 00:52:07.875 a beta and a synuclein I didn't mention,
NOTE Confidence: 0.87900090375

00:52:07.880 --> 00:52:11.121 but we also did stains for Alpha's
NOTE Confidence: 0.87900090375

00:52:11.121 --> 00:52:13.648 nucleus and this was present in some
NOTE Confidence: 0.87900090375

00:52:13.648 --> 00:52:16.320 places in patient one and there are
NOTE Confidence: 0.87900090375

00:52:16.320 --> 00:52:18.600 probably many more examples of this,
NOTE Confidence: 0.87900090375

00:52:18.600 --> 00:52:21.016 so we all know that there are more
NOTE Confidence: 0.87900090375

00:52:21.016 --> 00:52:23.128 things in heaven and earth than
NOTE Confidence: 0.87900090375

00:52:23.128 --> 00:52:25.156 are dreamt of in our philosophy.
NOTE Confidence: 0.87900090375

00:52:25.160 --> 00:52:27.700 Alzheimer's disease is not just
NOTE Confidence: 0.87900090375

00:52:27.700 --> 00:52:29.881 amyloid period yet there is

NOTE Confidence: 0.87900090375

00:52:29.881 --> 00:52:32.590 amyloid involved in it in a way.

NOTE Confidence: 0.942884927777778

00:52:34.880 --> 00:52:37.260 The next lesson from this is that

NOTE Confidence: 0.942884927777778

00:52:37.260 --> 00:52:39.665 when you say something is not

NOTE Confidence: 0.942884927777778

00:52:39.665 --> 00:52:41.840 seen in the crystal structure,

NOTE Confidence: 0.942884927777778

00:52:41.840 --> 00:52:44.535 that does not mean it is unimportant.

NOTE Confidence: 0.942884927777778

00:52:44.540 --> 00:52:47.552 It may still yet influence

NOTE Confidence: 0.942884927777778

00:52:47.552 --> 00:52:48.968 Physiology and biochemistry,

NOTE Confidence: 0.942884927777778

00:52:48.968 --> 00:52:53.334 so the reason for that is that we're not

NOTE Confidence: 0.942884927777778

00:52:53.334 --> 00:52:56.238 talking about protein structure along alone.

NOTE Confidence: 0.942884927777778

00:52:56.240 --> 00:53:00.308 We're also talking about protein dynamics.

NOTE Confidence: 0.942884927777778

00:53:00.310 --> 00:53:03.558 OK, now as I like to say.

NOTE Confidence: 0.942884927777778

00:53:03.560 --> 00:53:07.410 When I say I, I mean we and when I say we,

NOTE Confidence: 0.942884927777778

00:53:07.410 --> 00:53:11.630 I mean they and I wanna give a shout out to

NOTE Confidence: 0.942884927777778

00:53:11.630 --> 00:53:16.760 people who really did the work and these are.

NOTE Confidence: 0.942884927777778

00:53:16.760 --> 00:53:19.399 Past and present members of the lab,

NOTE Confidence: 0.942884927777778

00:53:19.400 --> 00:53:21.152 from left to right,
NOTE Confidence: 0.942884927777778

00:53:21.152 --> 00:53:23.780 J Pittman had tools Rivas Diva,
NOTE Confidence: 0.942884927777778

00:53:23.780 --> 00:53:25.680 Jonathan Servic,
NOTE Confidence: 0.942884927777778

00:53:25.680 --> 00:53:29.480 Bharat Venkata and Patmore.
NOTE Confidence: 0.942884927777778

00:53:29.480 --> 00:53:32.049 And I want to particularly give a
NOTE Confidence: 0.942884927777778

00:53:32.049 --> 00:53:35.229 shout out to the tools for Srivastava.
NOTE Confidence: 0.942884927777778

00:53:35.230 --> 00:53:41.392 Very talented postdoc who is a superb
NOTE Confidence: 0.942884927777778

00:53:41.392 --> 00:53:44.776 biochemist and and spectroscopist
NOTE Confidence: 0.942884927777778

00:53:44.780 --> 00:53:46.808 and this is Joe Sock Laban.
NOTE Confidence: 0.942884927777778

00:53:46.810 --> 00:53:50.668 Who as the saying goes, knows more about,
NOTE Confidence: 0.942884927777778

00:53:50.668 --> 00:53:53.298 has forgotten more about NMR
NOTE Confidence: 0.942884927777778

00:53:53.298 --> 00:53:55.950 than I will ever know?
NOTE Confidence: 0.942884927777778

00:53:55.950 --> 00:53:58.220 And now other collaborators I
NOTE Confidence: 0.942884927777778

00:53:58.220 --> 00:54:00.950 particularly want to thank Rob Tiko,
NOTE Confidence: 0.942884927777778

00:54:00.950 --> 00:54:03.242 with whom the brain seated amyloid
NOTE Confidence: 0.942884927777778

00:54:03.242 --> 00:54:05.709 work has been done and as well,

NOTE Confidence: 0.942884927777778

00:54:05.710 --> 00:54:09.450 a lot of some of the the work on the D.

NOTE Confidence: 0.942884927777778

00:54:09.450 --> 00:54:12.036 23 N Jerry Turner,

NOTE Confidence: 0.942884927777778

00:54:12.036 --> 00:54:15.357 who has been working on has been working

NOTE Confidence: 0.942884927777778

00:54:15.357 --> 00:54:17.170 on tight junctions for a long time.

NOTE Confidence: 0.942884927777778

00:54:17.170 --> 00:54:18.950 Though we're doing this work

NOTE Confidence: 0.942884927777778

00:54:18.950 --> 00:54:20.730 on occluding and he has,

NOTE Confidence: 0.942884927777778

00:54:20.730 --> 00:54:23.467 as I say, a whole system going.

NOTE Confidence: 0.942884927777778

00:54:23.470 --> 00:54:25.726 It's wonderful data.

NOTE Confidence: 0.942884927777778

00:54:25.726 --> 00:54:30.238 Joseph Orgell doing the fiber diffraction,

NOTE Confidence: 0.942884927777778

00:54:30.240 --> 00:54:33.395 the the vascular versus parenchymal

NOTE Confidence: 0.942884927777778

00:54:33.395 --> 00:54:37.367 amyloid work was done with Yoshitaka

NOTE Confidence: 0.942884927777778

00:54:37.367 --> 00:54:39.832 ISHI and Katherine Chappell.

NOTE Confidence: 0.942884927777778

00:54:39.832 --> 00:54:43.920 And I want to also mention gingelly

NOTE Confidence: 0.942884927777778

00:54:44.023 --> 00:54:47.230 you at NIH formerly working on

NOTE Confidence: 0.942884927777778

00:54:47.230 --> 00:54:50.900 the brain seating and Peter Patel.

NOTE Confidence: 0.942884927777778

00:54:50.900 --> 00:54:53.595 Great neuro pathologist in our
NOTE Confidence: 0.942884927777778

00:54:53.595 --> 00:54:56.290 department who has who has.
NOTE Confidence: 0.942884927777778

00:54:56.290 --> 00:55:00.060 Helped me enormously with his
NOTE Confidence: 0.942884927777778

00:55:00.060 --> 00:55:01.568 histopathology diagnosis.
NOTE Confidence: 0.942884927777778

00:55:01.570 --> 00:55:03.946 I like to say that science has learned
NOTE Confidence: 0.942884927777778

00:55:03.946 --> 00:55:06.344 more from the steam engine than the
NOTE Confidence: 0.942884927777778

00:55:06.344 --> 00:55:08.640 steam engine ever learned from science.
NOTE Confidence: 0.942884927777778

00:55:08.640 --> 00:55:10.890 Science has also learned more
NOTE Confidence: 0.942884927777778

00:55:10.890 --> 00:55:12.690 from disease than disease.
NOTE Confidence: 0.942884927777778

00:55:12.690 --> 00:55:14.098 Has learned from science.
NOTE Confidence: 0.396505815

00:55:17.150 --> 00:55:21.798 The aardvark my my my prediction
NOTE Confidence: 0.396505815

00:55:21.798 --> 00:55:23.624 for 2002 and I realized
NOTE Confidence: 0.396505815

00:55:23.624 --> 00:55:25.430 speaking to people in New Haven.
NOTE Confidence: 0.396505815

00:55:25.430 --> 00:55:27.968 I have to specify that the
NOTE Confidence: 0.396505815

00:55:27.968 --> 00:55:30.720 White Sox are the good socks
NOTE Confidence: 0.396505815

00:55:30.720 --> 00:55:33.156 and at that point I will stop.

NOTE Confidence: 0.5458121

00:55:34.600 --> 00:55:36.922 Right? It's good that

NOTE Confidence: 0.5458121

00:55:36.922 --> 00:55:37.938 they welcomed your lab.

NOTE Confidence: 0.5458121

00:55:37.940 --> 00:55:42.660 There must've been a nice lab outing.

NOTE Confidence: 0.5458121

00:55:42.660 --> 00:55:43.398 Any questions?

NOTE Confidence: 0.5458121

00:55:43.398 --> 00:55:45.612 I'm sure there are some questions

NOTE Confidence: 0.5458121

00:55:45.612 --> 00:55:46.980 for Doctor Meredith.

NOTE Confidence: 0.5458121

00:55:46.980 --> 00:55:47.949 Road open here.

NOTE Confidence: 0.7308325333333333

00:55:48.180 --> 00:55:50.660 Sure, I'll start. And then we'll go forward.

NOTE Confidence: 0.7308325333333333

00:55:50.660 --> 00:55:52.290 Stephen, thank you for a wonderful,

NOTE Confidence: 0.800429

00:55:52.680 --> 00:55:56.389 very clear presentation. You alluded to

NOTE Confidence: 0.922137016

00:55:56.400 --> 00:55:58.240 it at the end, although it wasn't

NOTE Confidence: 0.922137016

00:55:58.240 --> 00:56:01.088 clear when you were doing your data. If

NOTE Confidence: 0.661232094

00:56:01.330 --> 00:56:03.290 when you harvest these

NOTE Confidence: 0.661232094

00:56:03.290 --> 00:56:05.490 nucleating fibrils from real

NOTE Confidence: 0.85125144

00:56:05.500 --> 00:56:07.750 brains, whether it's mouse, human, or humans

NOTE Confidence: 0.826004796666667

00:56:07.760 --> 00:56:10.286 with different patients, they're going to
NOTE Confidence: 0.898409476666667

00:56:10.300 --> 00:56:11.920 be contaminated at a trace level,
NOTE Confidence: 0.898409476666667

00:56:11.920 --> 00:56:14.218 you won't see any NMR with other stuff.
NOTE Confidence: 0.898409476666667

00:56:14.220 --> 00:56:16.861 Almost inevitably. Do you think that
NOTE Confidence: 0.898409476666667

00:56:16.861 --> 00:56:20.078 is Co nucleating with an accounting
NOTE Confidence: 0.898409476666667

00:56:20.080 --> 00:56:22.670 for the different structures?
NOTE Confidence: 0.65925996725

00:56:22.680 --> 00:56:24.188 The different nucleation universe,
NOTE Confidence: 0.7787846075

00:56:24.200 --> 00:56:25.668 which minimum the nucleus
NOTE Confidence: 0.760856025

00:56:25.680 --> 00:56:27.048 filament finds in this.
NOTE Confidence: 0.64040661

00:56:27.750 --> 00:56:28.755 In their words, just the
NOTE Confidence: 0.64040661

00:56:28.755 --> 00:56:29.810 proteins associated with
NOTE Confidence: 0.72829385

00:56:29.810 --> 00:56:32.274 the A beta. That's really we should
NOTE Confidence: 0.72829385

00:56:32.274 --> 00:56:34.482 be looking at absolutely absolutely.
NOTE Confidence: 0.72829385

00:56:34.482 --> 00:56:37.968 I mean, we know what happens
NOTE Confidence: 0.72829385

00:56:37.970 --> 00:56:40.250 when you have pure peptide.
NOTE Confidence: 0.72829385

00:56:40.250 --> 00:56:42.504 Right now it's not the same conditions

NOTE Confidence: 0.72829385

00:56:42.504 --> 00:56:46.188 you can say, and that's true, but it is.

NOTE Confidence: 0.72829385

00:56:46.190 --> 00:56:48.710 I think it is all about what else is

NOTE Confidence: 0.72829385

00:56:48.710 --> 00:56:51.339 mixed up in that junk in the lab we refer

NOTE Confidence: 0.72829385

00:56:51.339 --> 00:56:53.866 to this affectionately as brain goo.

NOTE Confidence: 0.72829385

00:56:53.870 --> 00:56:55.956 Now what I will say is that

NOTE Confidence: 0.72829385

00:56:55.956 --> 00:56:58.259 as we do the biochemical.

NOTE Confidence: 0.72829385

00:56:58.260 --> 00:57:00.640 Purification of the amyloid.

NOTE Confidence: 0.72829385

00:57:00.640 --> 00:57:03.966 We follow the the NUCLEATING activity,

NOTE Confidence: 0.72829385

00:57:03.966 --> 00:57:07.388 where the seeding activity So what we

NOTE Confidence: 0.72829385

00:57:07.388 --> 00:57:10.580 throw away does not have seeding activity.

NOTE Confidence: 0.72829385

00:57:10.580 --> 00:57:13.184 That said, what does have seating

NOTE Confidence: 0.72829385

00:57:13.184 --> 00:57:16.660 activity is not pure, not even close.

NOTE Confidence: 0.72829385

00:57:16.660 --> 00:57:18.980 No, not even close.

NOTE Confidence: 0.72829385

00:57:18.980 --> 00:57:23.346 So you know if I live another hundred

NOTE Confidence: 0.72829385

00:57:23.346 --> 00:57:25.794 years or maybe someone else will do this,

NOTE Confidence: 0.72829385

00:57:25.800 --> 00:57:28.059 I think it would be very important to do
NOTE Confidence: 0.72829385

00:57:28.059 --> 00:57:30.637 a proteomic analysis of what else is in,
NOTE Confidence: 0.72829385

00:57:30.640 --> 00:57:31.372 you know,
NOTE Confidence: 0.72829385

00:57:31.372 --> 00:57:33.202 a fairly systematic proteomic analysis
NOTE Confidence: 0.72829385

00:57:33.202 --> 00:57:35.320 of what else is in the brain.
NOTE Confidence: 0.72829385

00:57:35.320 --> 00:57:37.944 Do we know for sure in patient one,
NOTE Confidence: 0.72829385

00:57:37.950 --> 00:57:38.704 for example,
NOTE Confidence: 0.72829385

00:57:38.704 --> 00:57:40.589 that she had this diagnosis
NOTE Confidence: 0.72829385

00:57:40.589 --> 00:57:42.360 of Lewy body disease?
NOTE Confidence: 0.72829385

00:57:42.360 --> 00:57:44.184 We know that there was at
NOTE Confidence: 0.72829385

00:57:44.184 --> 00:57:45.400 least one Lewy body,
NOTE Confidence: 0.72829385

00:57:45.400 --> 00:57:47.890 and there's alpha synuclein by immunostain.
NOTE Confidence: 0.72829385

00:57:47.890 --> 00:57:48.784 Not a lot,
NOTE Confidence: 0.72829385

00:57:48.784 --> 00:57:49.380 but some.
NOTE Confidence: 0.86042656

00:57:50.410 --> 00:57:52.422 Yeah, so can I just follow up?
NOTE Confidence: 0.86042656

00:57:52.422 --> 00:57:55.600 So why is this any different? Maybe because

NOTE Confidence: 0.926973834

00:57:55.610 --> 00:57:57.145 you can't eat it any different

NOTE Confidence: 0.926973834

00:57:57.145 --> 00:58:00.610 than a prion in nucleates formation

NOTE Confidence: 0.926973834

00:58:00.610 --> 00:58:04.060 of a pathologic. Confirmation

NOTE Confidence: 0.781973852

00:58:04.310 --> 00:58:06.435 as another friend and colleague

NOTE Confidence: 0.781973852

00:58:06.435 --> 00:58:08.560 Jim Mastriani likes to say.

NOTE Confidence: 0.837913623636364

00:58:12.260 --> 00:58:14.565 Point out that Alzheimer's disease

NOTE Confidence: 0.837913623636364

00:58:14.565 --> 00:58:17.410 has been transmitted as a prion.

NOTE Confidence: 0.837913623636364

00:58:17.410 --> 00:58:20.330 Now it probably takes a set of special

NOTE Confidence: 0.837913623636364

00:58:20.330 --> 00:58:23.500 circumstances, so don't worry too much,

NOTE Confidence: 0.837913623636364

00:58:23.500 --> 00:58:26.812 but but I think I think it can be,

NOTE Confidence: 0.837913623636364

00:58:26.820 --> 00:58:30.666 and the difference between an amyloid

NOTE Confidence: 0.837913623636364

00:58:30.666 --> 00:58:34.620 and prion is basically infectivity.

NOTE Confidence: 0.837913623636364

00:58:34.620 --> 00:58:38.100 Data fibrils have very low infectivity.

NOTE Confidence: 0.837913623636364

00:58:38.100 --> 00:58:41.790 They don't go through the GI tract very well.

NOTE Confidence: 0.837913623636364

00:58:41.790 --> 00:58:43.770 Attempts to transmit it that way.

NOTE Confidence: 0.837913623636364

00:58:43.770 --> 00:58:46.134 I think I've not been particularly
NOTE Confidence: 0.837913623636364

00:58:46.134 --> 00:58:47.928 successful, and the other thing that happens.
NOTE Confidence: 0.837913623636364

00:58:47.930 --> 00:58:50.192 You know that how we got
NOTE Confidence: 0.837913623636364

00:58:50.192 --> 00:58:51.323 these monoclonal antibodies?
NOTE Confidence: 0.837913623636364

00:58:51.330 --> 00:58:53.538 Is someone tried to transmit this
NOTE Confidence: 0.837913623636364

00:58:53.538 --> 00:58:56.490 as prion and got an immune response?
NOTE Confidence: 0.837913623636364

00:58:56.490 --> 00:58:59.838 So I think in the case of a beta,
NOTE Confidence: 0.837913623636364

00:58:59.840 --> 00:59:02.705 maybe the immune response partially
NOTE Confidence: 0.837913623636364

00:59:02.705 --> 00:59:05.570 opposes transmission as a prion,
NOTE Confidence: 0.837913623636364

00:59:05.570 --> 00:59:06.605 but that's speculation.
NOTE Confidence: 0.837913623636364

00:59:06.605 --> 00:59:07.985 I don't really know.
NOTE Confidence: 0.837913623636364

00:59:07.990 --> 00:59:09.496 I think it can be transmitted.
NOTE Confidence: 0.54086554

00:59:11.020 --> 00:59:13.008 Not to say on this right, of course,
NOTE Confidence: 0.54086554

00:59:13.008 --> 00:59:15.200 and I I think the question John was
NOTE Confidence: 0.54086554

00:59:15.262 --> 00:59:17.614 really great because I think that most
NOTE Confidence: 0.54086554

00:59:17.614 --> 00:59:19.918 people don't know that what's injected

NOTE Confidence: 0.54086554

00:59:19.918 --> 00:59:22.479 as prion fibrils are actually not pure

NOTE Confidence: 0.54086554

00:59:22.480 --> 00:59:23.880 and they have many things in them.

NOTE Confidence: 0.54086554

00:59:23.880 --> 00:59:25.040 So the second thing,

NOTE Confidence: 0.54086554

00:59:25.040 --> 00:59:27.399 just I'll make my comment about my strone.

NOTE Confidence: 0.54086554

00:59:27.400 --> 00:59:29.976 I actually do those kinds of experiments

NOTE Confidence: 0.54086554

00:59:29.976 --> 00:59:32.723 and I'm allowed data is not infection that

NOTE Confidence: 0.54086554

00:59:32.723 --> 00:59:35.790 says that any kind of what you would call

NOTE Confidence: 0.54086554

00:59:35.790 --> 00:59:38.317 apprion or infectious agent of TSS is.

NOTE Confidence: 0.54086554

00:59:38.317 --> 00:59:40.699 That is, it doesn't seriously transmit.

NOTE Confidence: 0.54086554

00:59:40.700 --> 00:59:42.260 If you put a lot of it into a brain.

NOTE Confidence: 0.54086554

00:59:42.260 --> 00:59:43.930 The animal. That's very sick.

NOTE Confidence: 0.54086554

00:59:43.930 --> 00:59:45.043 It may seed,

NOTE Confidence: 0.54086554

00:59:45.043 --> 00:59:48.300 but it doesn't transmit to a new animal.

NOTE Confidence: 0.54086554

00:59:48.300 --> 00:59:51.378 OK, so that is that is an important point,

NOTE Confidence: 0.54086554

00:59:51.380 --> 00:59:53.225 but what I would like to ask you because

NOTE Confidence: 0.54086554

00:59:53.225 --> 00:59:54.849 I thought your your presentation
NOTE Confidence: 0.54086554

00:59:54.849 --> 00:59:56.559 was great and very illuminating.
NOTE Confidence: 0.54086554

00:59:56.560 --> 00:59:58.130 Very instructive for me about
NOTE Confidence: 0.54086554

00:59:58.130 --> 01:00:00.543 fibroids and how you look at them is
NOTE Confidence: 0.54086554

01:00:00.543 --> 01:00:03.298 if you wanted to think about what
NOTE Confidence: 0.54086554

01:00:03.298 --> 01:00:06.231 makes a a beta amyloid of let's
NOTE Confidence: 0.54086554

01:00:06.231 --> 01:00:09.197 say a prion protein infectious.
NOTE Confidence: 0.54086554

01:00:09.200 --> 01:00:11.209 What would the structure be and what
NOTE Confidence: 0.54086554

01:00:11.209 --> 01:00:13.451 would happen if you found that something
NOTE Confidence: 0.54086554

01:00:13.451 --> 01:00:15.437 that had a very different structure
NOTE Confidence: 0.54086554

01:00:15.497 --> 01:00:18.006 from let's say an infected lymph node?
NOTE Confidence: 0.54086554

01:00:18.006 --> 01:00:21.956 Actually did gave the exact same types of
NOTE Confidence: 0.54086554

01:00:21.956 --> 01:00:24.488 transmission and strain characteristics,
NOTE Confidence: 0.54086554

01:00:24.490 --> 01:00:26.674 which are different which are only
NOTE Confidence: 0.54086554

01:00:26.674 --> 01:00:28.932 for that particular agent and not
NOTE Confidence: 0.54086554

01:00:28.932 --> 01:00:30.782 for something that makes something

NOTE Confidence: 0.54086554
01:00:30.782 --> 01:00:32.614 very similar with a different strain.
NOTE Confidence: 0.54086554
01:00:32.614 --> 01:00:35.027 So I really want to know your inside
NOTE Confidence: 0.54086554
01:00:35.027 --> 01:00:37.217 is what would make an amyloid
NOTE Confidence: 0.54086554
01:00:37.217 --> 01:00:37.947 infectious structurally.
NOTE Confidence: 0.812500338333333
01:00:40.470 --> 01:00:42.430 Well, I can give you a short
NOTE Confidence: 0.812500338333333
01:00:42.430 --> 01:00:44.180 answer in a long answer.
NOTE Confidence: 0.812500338333333
01:00:44.180 --> 01:00:47.966 The short answer is. No idea.
NOTE Confidence: 0.812500338333333
01:00:47.970 --> 01:00:52.064 The longest somewhat longer answer is it it.
NOTE Confidence: 0.812500338333333
01:00:52.064 --> 01:00:54.434 First of all, it needs to be.
NOTE Confidence: 0.812500338333333
01:00:54.434 --> 01:00:56.730 I mean, I think you're talking about
NOTE Confidence: 0.812500338333333
01:00:56.730 --> 01:00:58.870 the route of entry into the brain.
NOTE Confidence: 0.812500338333333
01:00:58.870 --> 01:01:01.338 That's the first thing.
NOTE Confidence: 0.812500338333333
01:01:01.340 --> 01:01:04.175 Why is it that a prion can?
NOTE Confidence: 0.812500338333333
01:01:04.180 --> 01:01:05.580 I mean a real prion?
NOTE Confidence: 0.812500338333333
01:01:05.580 --> 01:01:07.996 And I agree with you that being amyloid
NOTE Confidence: 0.812500338333333

01:01:07.996 --> 01:01:11.170 is it's under some circumstances it can be
NOTE Confidence: 0.8125003383333333

01:01:11.170 --> 01:01:13.710 transmitted from one animal to another,
NOTE Confidence: 0.8125003383333333

01:01:13.710 --> 01:01:15.348 but you have to sort of squirt
NOTE Confidence: 0.8125003383333333

01:01:15.348 --> 01:01:16.600 it directly into the brain,
NOTE Confidence: 0.8125003383333333

01:01:16.600 --> 01:01:19.714 which is not the case for a real prion.
NOTE Confidence: 0.8125003383333333

01:01:19.720 --> 01:01:22.478 But I think you know somehow the
NOTE Confidence: 0.8125003383333333

01:01:22.478 --> 01:01:26.972 prion has to be picked up by the by.
NOTE Confidence: 0.8125003383333333

01:01:26.972 --> 01:01:28.420 For example,
NOTE Confidence: 0.8125003383333333

01:01:28.420 --> 01:01:30.780 the dendritic cells in the
NOTE Confidence: 0.8125003383333333

01:01:30.780 --> 01:01:32.668 nose or the oropharynx.
NOTE Confidence: 0.8125003383333333

01:01:32.670 --> 01:01:34.735 And then hitch a ride on the
NOTE Confidence: 0.8125003383333333

01:01:34.735 --> 01:01:36.270 trigeminal nerve into the brain.
NOTE Confidence: 0.8125003383333333

01:01:36.270 --> 01:01:37.950 Or maybe be able to go through
NOTE Confidence: 0.8125003383333333

01:01:37.950 --> 01:01:39.408 other routes in the GI track.
NOTE Confidence: 0.8125003383333333

01:01:39.410 --> 01:01:41.608 I don't really know how it occurs,
NOTE Confidence: 0.8125003383333333

01:01:41.610 --> 01:01:41.940 but

NOTE Confidence: 0.869369025714286
01:01:42.450 --> 01:01:44.354 goes by blood. It goes by white
NOTE Confidence: 0.869369025714286
01:01:44.354 --> 01:01:46.358 blood cells as shown in the 1970s.
NOTE Confidence: 0.89769656
01:01:47.670 --> 01:01:50.050 I think you know this is not
NOTE Confidence: 0.89769656
01:01:50.050 --> 01:01:51.520 necessarily a structural thing.
NOTE Confidence: 0.89769656
01:01:51.520 --> 01:01:55.657 This could be a receptor ligand interaction.
NOTE Confidence: 0.89769656
01:01:55.660 --> 01:01:58.978 I suspect that the different prion strains
NOTE Confidence: 0.89769656
01:01:58.978 --> 01:02:03.164 and of course there are strains of prions
NOTE Confidence: 0.89769656
01:02:03.164 --> 01:02:06.556 that depends on the the differences
NOTE Confidence: 0.89769656
01:02:06.556 --> 01:02:10.630 among them have a lot to do with.
NOTE Confidence: 0.89769656
01:02:10.630 --> 01:02:13.666 How the beta sheets are arranged?
NOTE Confidence: 0.89769656
01:02:13.670 --> 01:02:18.089 In other words, if you do limit digests of.
NOTE Confidence: 0.89769656
01:02:18.090 --> 01:02:22.820 The, let's say the GSS, prion versus.
NOTE Confidence: 0.89769656
01:02:22.820 --> 01:02:24.640 Yakub kreutzfeldt prions you
NOTE Confidence: 0.89769656
01:02:24.640 --> 01:02:26.460 get different limit digest.
NOTE Confidence: 0.89769656
01:02:26.460 --> 01:02:30.766 It suggests that different that they're
NOTE Confidence: 0.89769656

01:02:30.766 --> 01:02:32.922 at different locations of the beta sheets

NOTE Confidence: 0.89769656

01:02:32.922 --> 01:02:35.099 and therefore different relationships.

NOTE Confidence: 0.89769656

01:02:35.100 --> 01:02:36.570 3 dimensional relationships

NOTE Confidence: 0.89769656

01:02:36.570 --> 01:02:38.530 among the beta sheets,

NOTE Confidence: 0.89769656

01:02:38.530 --> 01:02:40.714 and that would be really nice to know.

NOTE Confidence: 0.89769656

01:02:40.720 --> 01:02:41.632 I mean,

NOTE Confidence: 0.89769656

01:02:41.632 --> 01:02:44.656 if you get the different prion strains,

NOTE Confidence: 0.89769656

01:02:44.656 --> 01:02:47.140 and I know vittle sure of

NOTE Confidence: 0.89769656

01:02:47.219 --> 01:02:49.289 it is doing work like this.

NOTE Confidence: 0.89769656

01:02:49.290 --> 01:02:51.410 For example in cervid prions

NOTE Confidence: 0.89769656

01:02:51.410 --> 01:02:53.530 and other kinds of prions.

NOTE Confidence: 0.89769656

01:02:53.530 --> 01:02:55.217 So I think that would be very

NOTE Confidence: 0.89769656

01:02:55.217 --> 01:02:56.907 important to know and I'll bet

NOTE Confidence: 0.89769656

01:02:56.907 --> 01:02:58.422 that the different strains have

NOTE Confidence: 0.89769656

01:02:58.422 --> 01:03:00.059 different beta sheet arrangements.

NOTE Confidence: 0.7706685633333333

01:03:00.690 --> 01:03:03.462 Actually, the digests are the same

NOTE Confidence: 0.7706685633333333

01:03:03.462 --> 01:03:06.125 in the organ, but they're very

NOTE Confidence: 0.7706685633333333

01:03:06.125 --> 01:03:08.250 different in the peripheral tissues,

NOTE Confidence: 0.7706685633333333

01:03:08.250 --> 01:03:10.258 so it depends on the organ that they're

NOTE Confidence: 0.7706685633333333

01:03:10.258 --> 01:03:12.629 in and that does not reflect the strain.

NOTE Confidence: 0.9359780725

01:03:14.120 --> 01:03:15.704 Well, in that case I really don't know.

NOTE Confidence: 0.923980479375

01:03:16.350 --> 01:03:18.430 I just I. I sometimes think that there's

NOTE Confidence: 0.923980479375

01:03:18.430 --> 01:03:20.877 a lot of popular notions that are said,

NOTE Confidence: 0.923980479375

01:03:20.880 --> 01:03:23.080 and I really think your stuff is interesting,

NOTE Confidence: 0.923980479375

01:03:23.080 --> 01:03:24.851 and I think the structural stuff is

NOTE Confidence: 0.923980479375

01:03:24.851 --> 01:03:26.350 really interesting and I'm very happy

NOTE Confidence: 0.923980479375

01:03:26.350 --> 01:03:27.967 that you said that there's other stuff

NOTE Confidence: 0.923980479375

01:03:28.015 --> 01:03:29.497 when you isolate stuff from brain,

NOTE Confidence: 0.923980479375

01:03:29.500 --> 01:03:31.666 because most people don't know that.

NOTE Confidence: 0.919285575

01:03:33.110 --> 01:03:34.772 I don't know why they don't

NOTE Confidence: 0.919285575

01:03:34.772 --> 01:03:36.635 know that all you have to do

NOTE Confidence: 0.919285575

01:03:36.635 --> 01:03:38.809 is look at it and it's brown.
NOTE Confidence: 0.919285575

01:03:38.810 --> 01:03:40.902 It's not white and fluffy
NOTE Confidence: 0.919285575

01:03:40.902 --> 01:03:42.278 like a synthetic peptide.
NOTE Confidence: 0.925392654166667

01:03:44.030 --> 01:03:45.572 Great, well listen, I think we've
NOTE Confidence: 0.925392654166667

01:03:45.572 --> 01:03:47.159 gone a little bit over time,
NOTE Confidence: 0.925392654166667

01:03:47.160 --> 01:03:50.190 but I want to thank Steve and for for
NOTE Confidence: 0.925392654166667

01:03:50.190 --> 01:03:52.230 sharing his work with us and I want
NOTE Confidence: 0.925392654166667

01:03:52.292 --> 01:03:54.532 to thank you for all your questions
NOTE Confidence: 0.925392654166667

01:03:54.532 --> 01:03:56.269 and your attention to his talk.
NOTE Confidence: 0.925392654166667

01:03:56.270 --> 01:03:59.730 Very grateful to you all.
NOTE Confidence: 0.925392654166667

01:03:59.730 --> 01:04:01.416 Take care everyone and we'll see
NOTE Confidence: 0.925392654166667

01:04:01.416 --> 01:04:03.329 you next week for grand rounds.
NOTE Confidence: 0.925392654166667

01:04:03.330 --> 01:04:06.879 Steve stay warm out there in Chicago.
NOTE Confidence: 0.925392654166667

01:04:06.880 --> 01:04:07.788 I'll see you soon.
NOTE Confidence: 0.7098075975

01:04:08.540 --> 01:04:11.320 See you bye bye Many thanks,
NOTE Confidence: 0.7098075975

01:04:11.320 --> 01:04:14.540 thank you, thank you. Thank you.