WEBVTT

NOTE duration:"00:56:29.6640000"

NOTE language:en-us

NOTE Confidence: 0.8245773

00:00:14.880 --> 00:00:15.544 Alright everybody,

NOTE Confidence: 0.8245773

00:00:15.544 --> 00:00:17.868 I think we're going to get started.

NOTE Confidence: 0.8245773

00:00:17.870 --> 00:00:19.706 Hello and welcome I'm Lauren Tobias

NOTE Confidence: 0.8245773

00:00:19.706 --> 00:00:22.407 and I'd like to welcome you to our

NOTE Confidence: 0.8245773

00:00:22.407 --> 00:00:24.172 Yell Sleep seminar this afternoon.

NOTE Confidence: 0.8245773

00:00:24.180 --> 00:00:26.196 A few brief announcements before I turn

NOTE Confidence: 0.8245773

00:00:26.196 --> 00:00:28.601 it over to Doctor Heckman to introduce

NOTE Confidence: 0.8245773

00:00:28.601 --> 00:00:30.815 today's speaker so please feel free.

NOTE Confidence: 0.8245773

00:00:30.820 --> 00:00:32.745 Please take a moment to

NOTE Confidence: 0.8245773

00:00:32.745 --> 00:00:34.670 make sure that you're muted.

NOTE Confidence: 0.8245773

00:00:34.670 --> 00:00:36.235 In order to receive CME

NOTE Confidence: 0.8245773

00:00:36.235 --> 00:00:37.174 credit for attendance,

NOTE Confidence: 0.8245773

00:00:37.180 --> 00:00:39.684 you can see the chat room for instructions,

NOTE Confidence: 0.8245773

00:00:39.690 --> 00:00:41.601 and there's a unique idea that you

NOTE Confidence: 0.8245773

00:00:41.601 --> 00:00:44.265 can text up until 3:15 Eastern Time if

NOTE Confidence: 0.8245773

00:00:44.265 --> 00:00:46.290 you're not already registered DLC ME,

NOTE Confidence: 0.8245773

00:00:46.290 --> 00:00:48.168 you'll need to do that first.

NOTE Confidence: 0.8245773

00:00:48.170 --> 00:00:50.048 If you have any questions during

NOTE Confidence: 0.8245773

00:00:50.048 --> 00:00:51.637 the presentation, I encourage you.

NOTE Confidence: 0.8245773

00:00:51.637 --> 00:00:53.551 Thank you for the chat rooms

NOTE Confidence: 0.8245773

00:00:53.551 --> 00:00:54.450 throughout the hour,

NOTE Confidence: 0.8245773

00:00:54.450 --> 00:00:56.388 and we will also invite people

NOTE Confidence: 0.8245773

00:00:56.388 --> 00:00:58.219 to unmute themselves at the end.

NOTE Confidence: 0.8245773

00:00:58.220 --> 00:01:00.481 We do have recorded versions of these

NOTE Confidence: 0.8245773

00:01:00.481 --> 00:01:02.644 lectures that will be available on line

NOTE Confidence: 0.8245773

00:01:02.644 --> 00:01:04.920 within two weeks at the link provided.

NOTE Confidence: 0.8245773

00:01:04.920 --> 00:01:07.728 In the chat and feel free to share

NOTE Confidence: 0.8245773

00:01:07.728 --> 00:01:09.579 our announcements for this weekly

NOTE Confidence: 0.8245773

00:01:09.579 --> 00:01:11.369 lecture series to anyone else

NOTE Confidence: 0.8245773

00:01:11.369 --> 00:01:13.777 who you think may be interested,

NOTE Confidence: 0.8245773

00:01:13.780 --> 00:01:15.625 they can contact Debbie Lovejoy

NOTE Confidence: 0.8245773

00:01:15.625 --> 00:01:17.470 directly at her email address.

NOTE Confidence: 0.8245773

00:01:17.470 --> 00:01:19.941 I also want to just let everybody

NOTE Confidence: 0.8245773

00:01:19.941 --> 00:01:22.216 know that we're going to be

NOTE Confidence: 0.8245773

00:01:22.216 --> 00:01:23.740 holding our annual sleep.

NOTE Confidence: 0.8245773

00:01:23.740 --> 00:01:25.948 Yale Sleep Research Symposium on Friday,

NOTE Confidence: 0.8245773

00:01:25.950 --> 00:01:27.740 April 30th that's from 10:00

NOTE Confidence: 0.8245773

00:01:27.740 --> 00:01:29.530 o'clock in the morning until

NOTE Confidence: 0.8245773

00:01:29.601 --> 00:01:31.486 2:00 o'clock in the afternoon,

NOTE Confidence: 0.8245773

00:01:31.490 --> 00:01:33.475 and it's going to feature

NOTE Confidence: 0.8245773

00:01:33.475 --> 00:01:35.460 talks by Sam Cuna Upenn.

NOTE Confidence: 0.8245773

00:01:35.460 --> 00:01:37.756 He's going to speak about Sleep Medicine

NOTE Confidence: 0.8245773

00:01:37.756 --> 00:01:40.045 after the pandemic as well as Theresa

NOTE Confidence: 0.8245773

00:01:40.045 --> 00:01:41.911 Ward at the University of Washington.

NOTE Confidence: 0.8245773

00:01:41.920 --> 00:01:43.732 Who's going to speak about sleep

NOTE Confidence: 0.8245773

00:01:43.732 --> 00:01:44.940 health in pediatric populations

NOTE Confidence: 0.8245773

00:01:44.987 --> 00:01:46.118 with chronic conditions?

NOTE Confidence: 0.8245773

00:01:46.120 --> 00:01:48.955 So I'm going to post the link to register

NOTE Confidence: 0.8245773

00:01:48.955 --> 00:01:51.700 for this free event in the chat and

NOTE Confidence: 0.8245773

00:01:51.700 --> 00:01:54.187 please feel free to join us for that.

NOTE Confidence: 0.8245773

00:01:54.190 --> 00:01:55.522 So with that,

NOTE Confidence: 0.8245773

00:01:55.522 --> 00:01:59.500 I'll turn it over to Doctor Eric Heckman.

NOTE Confidence: 0.8245773

00:01:59.500 --> 00:02:00.817 Good afternoon everyone.

NOTE Confidence: 0.8245773

00:02:00.817 --> 00:02:03.451 I have the pleasure of introducing

NOTE Confidence: 0.8245773

00:02:03.451 --> 00:02:06.440 Jonathan Lipton today so he is joining us

NOTE Confidence: 0.8245773

00:02:06.440 --> 00:02:08.539 from Boston Children's Hospital below.

NOTE Confidence: 0.8245773

00:02:08.540 --> 00:02:10.516 Background on Doctor Lipton,

NOTE Confidence: 0.8245773

00:02:10.516 --> 00:02:13.480 he did his undergraduate at Brown

NOTE Confidence: 0.8245773

00:02:13.560 --> 00:02:16.234 followed by his MD and PhD at

NOTE Confidence: 0.8245773

00:02:16.234 --> 00:02:18.580 Albert Einstein in New York City.

NOTE Confidence: 0.8245773

00:02:18.580 --> 00:02:20.167 And following that,

NOTE Confidence: 0.8245773

00:02:20.167 --> 00:02:22.283 completed neurology training at

NOTE Confidence: 0.8245773

00:02:22.283 --> 00:02:24.317 Boston Children's Hospital as

NOTE Confidence: 0.8245773

00:02:24.317 --> 00:02:26.555 well as his sleep training both

NOTE Confidence: 0.8245773

00:02:26.555 --> 00:02:28.674 at Boston Children's and Beth

NOTE Confidence: 0.8245773

00:02:28.674 --> 00:02:30.530 Israel Deaconess Medical Center.

NOTE Confidence: 0.8245773

00:02:30.530 --> 00:02:31.414 Since then,

NOTE Confidence: 0.8245773

00:02:31.414 --> 00:02:33.624 he's continued to work at

NOTE Confidence: 0.8245773

00:02:33.624 --> 00:02:34.950 Boston Children's Hospital,

NOTE Confidence: 0.8245773

00:02:34.950 --> 00:02:37.512 as well as being an assistant

NOTE Confidence: 0.8245773

00:02:37.512 --> 00:02:39.810 professor at Harvard Medical School.

NOTE Confidence: 0.8245773

00:02:39.810 --> 00:02:42.020 He has had funded research

NOTE Confidence: 0.8245773

00:02:42.020 --> 00:02:44.230 for over a decade now.

NOTE Confidence: 0.8245773

00:02:44.230 --> 00:02:46.440 Looking into this circene Clock,

NOTE Confidence: 0.8245773

00:02:46.440 --> 00:02:48.650 an often it's overlap with

NOTE Confidence: 0.8245773

00:02:48.650 --> 00:02:49.534 neurodevelopmental disorders,

NOTE Confidence: 0.8245773

00:02:49.540 --> 00:02:52.951 I still talk about today and he has been

NOTE Confidence: 0.8245773

00:02:52.951 --> 00:02:55.442 awarded the Young Investigator Award

NOTE Confidence: 0.8245773

00:02:55.442 --> 00:02:58.478 from Sleep Research Society as well

NOTE Confidence: 0.8245773

00:02:58.562 --> 00:03:01.565 as many publications and being on the.

NOTE Confidence: 0.8245773

00:03:01.570 --> 00:03:06.645 Review Board for Sleep Advances Journal so.

NOTE Confidence: 0.8245773

00:03:06.650 --> 00:03:08.222 Doctor Lipson thank you very much

NOTE Confidence: 0.8245773

00:03:08.222 --> 00:03:09.989 for preparing for today and we all

NOTE Confidence: 0.8245773

00:03:09.989 --> 00:03:11.333 look forward to hearing from you.

NOTE Confidence: 0.84370315

00:03:12.590 --> 00:03:15.103 OK, thank you Eric and thank you

NOTE Confidence: 0.84370315

00:03:15.103 --> 00:03:17.757 for inviting me and having me today.

NOTE Confidence: 0.84370315

00:03:17.760 --> 00:03:20.712 The talk today is going to be very

NOTE Confidence: 0.84370315

00:03:20.712 --> 00:03:22.945 science heavy, so I apologize to those

NOTE Confidence: 0.84370315

00:03:22.945 --> 00:03:25.430 of you who are not that interested

NOTE Confidence: 0.84370315

00:03:25.430 --> 00:03:27.720 in in the underlying biology,

NOTE Confidence: 0.84370315

00:03:27.720 --> 00:03:30.664 but I'm going to sort of try and

NOTE Confidence: 0.84370315

00:03:30.664 --> 00:03:32.364 contextualize what we're trying to

NOTE Confidence: 0.84370315

00:03:32.364 --> 00:03:35.394 do and what I see as some of the

NOTE Confidence: 0.84370315

00:03:35.394 --> 00:03:38.046 opportunities in this very exciting field.

NOTE Confidence: 0.84370315

00:03:38.050 --> 00:03:40.962 My talk is really about the crosstalk between

NOTE Confidence: 0.84370315

00:03:40.962 --> 00:03:42.849 developmental disorders and circadian clocks,

NOTE Confidence: 0.84370315

00:03:42.850 --> 00:03:45.322 and I think that word is

NOTE Confidence: 0.84370315

00:03:45.322 --> 00:03:46.558 very important because.

NOTE Confidence: 0.84370315

00:03:46.560 --> 00:03:48.695 As I'll show you that what I've

NOTE Confidence: 0.84370315

00:03:48.695 --> 00:03:51.828 learned from my own work is that by

NOTE Confidence: 0.84370315

00:03:51.828 --> 00:03:53.118 studying developmental disorders.

NOTE Confidence: 0.84370315

00:03:53.120 --> 00:03:55.394 We've learned at by studying development

NOTE Confidence: 0.84370315

00:03:55.394 --> 00:03:56.910 disorders and circadian rhythms.

NOTE Confidence: 0.84370315

00:03:56.910 --> 00:03:58.800 We've learned something new about

NOTE Confidence: 0.84370315

00:03:58.800 --> 00:03:59.934 neurodevelopmental disorders themselves,

NOTE Confidence: 0.84370315

00:03:59.940 --> 00:04:01.404 and certain specific ones,

NOTE Confidence: 0.84370315

00:04:01.404 --> 00:04:03.234 and also we've learned new

NOTE Confidence: 0.84370315

00:04:03.234 --> 00:04:05.247 things about the circadian Clock,

NOTE Confidence: 0.84370315

00:04:05.250 --> 00:04:07.910 and so I think these these two

NOTE Confidence: 0.84370315

00:04:07.910 --> 00:04:10.180 processes are important to one another,

NOTE Confidence: 0.84370315

00:04:10.180 --> 00:04:12.826 and I think they you know we.

NOTE Confidence: 0.84370315

00:04:12.830 --> 00:04:16.508 It's an important point to make.

NOTE Confidence: 0.84370315

00:04:16.510 --> 00:04:19.300 So let me just make sure I can advance

NOTE Confidence: 0.84370315

00:04:19.300 --> 00:04:21.486 here so I have no disclosures,

NOTE Confidence: 0.84370315

00:04:21.490 --> 00:04:23.150 so get that over with.

NOTE Confidence: 0.84370315

00:04:23.150 --> 00:04:25.652 So let me dive right in and start talking

NOTE Confidence: 0.84370315

00:04:25.652 --> 00:04:28.455 to you about clocks and circadian rhythms.

NOTE Confidence: 0.84370315

00:04:28.460 --> 00:04:30.896 And obviously you understand them from the

NOTE Confidence: 0.84370315

00:04:30.896 --> 00:04:33.107 perspective of their their role in sleep,

NOTE Confidence: 0.84370315

00:04:33.110 --> 00:04:35.434 and I'm sure you see many patients

NOTE Confidence: 0.84370315

00:04:35.434 --> 00:04:36.430 with circadian disruption,

NOTE Confidence: 0.84370315

00:04:36.430 --> 00:04:39.238 so I won't spend too much time introducing

NOTE Confidence: 0.84370315

00:04:39.238 --> 00:04:41.879 the Clock and dive right in one of

NOTE Confidence: 0.84370315

00:04:41.879 --> 00:04:44.070 the real questions is you know why?

NOTE Confidence: 0.84370315

00:04:44.070 --> 00:04:45.730 Why are clocks so ubiquitous?

NOTE Confidence: 0.84370315

00:04:45.730 --> 00:04:46.052 Why?

NOTE Confidence: 0.84370315

00:04:46.052 --> 00:04:49.860 If you go to any city in Europe or any place?

NOTE Confidence: 0.84370315

00:04:49.860 --> 00:04:51.228 In the world really,

NOTE Confidence: 0.84370315

00:04:51.228 --> 00:04:54.089 you can go to the center of the

NOTE Confidence: 0.84370315

00:04:54.089 --> 00:04:56.644 town and you'll see a Clock tower

NOTE Confidence: 0.84370315

00:04:56.644 --> 00:04:58.756 o'clock in the center of town,

NOTE Confidence: 0.84370315

00:04:58.760 --> 00:05:01.608 and the reason is is because we we,

NOTE Confidence: 0.84370315

00:05:01.610 --> 00:05:03.740 we use clocks as prediction tools.

NOTE Confidence: 0.84370315

00:05:03.740 --> 00:05:05.500 The most fundamental aspect of

NOTE Confidence: 0.84370315

00:05:05.500 --> 00:05:08.008 our life on this planet is that

NOTE Confidence: 0.84370315

00:05:08.008 --> 00:05:10.042 the besides gravity maybe is that

NOTE Confidence: 0.84370315

00:05:10.042 --> 00:05:12.289 the planet rotates and it rotates,

NOTE Confidence: 0.84370315

00:05:12.290 --> 00:05:15.182 creating a 24 hour predictable and

NOTE Confidence: 0.84370315

00:05:15.182 --> 00:05:16.628 iterative geophysical oscillation.

NOTE Confidence: 0.84370315

00:05:16.630 --> 00:05:18.790 And that we experience with the

NOTE Confidence: 0.84370315

00:05:18.790 --> 00:05:20.790 light dark cycle and plants.

NOTE Confidence: 0.84370315

00:05:20.790 --> 00:05:23.230 And as you see in the middle there

NOTE Confidence: 0.84370315

00:05:23.230 --> 00:05:25.700 is the classic flowering plant,

NOTE Confidence: 0.84370315

00:05:25.700 --> 00:05:26.765 a flowering Clock.

NOTE Confidence: 0.84370315

00:05:26.765 --> 00:05:29.250 A plants are no exception to this

NOTE Confidence: 0.84370315

00:05:29.321 --> 00:05:32.147 an our entire metabolism is rooted

NOTE Confidence: 0.84370315

00:05:32.147 --> 00:05:34.396 ultimately in photosynthesis which is

NOTE Confidence: 0.84370315

00:05:34.396 --> 00:05:37.368 gated by the light dark cycle and so are we.

NOTE Confidence: 0.84370315

00:05:37.368 --> 00:05:39.992 And so I love this slide because it

NOTE Confidence: 0.84370315

00:05:39.992 --> 00:05:42.677 sort of points out just the importance

NOTE Confidence: 0.84370315

00:05:42.677 --> 00:05:45.507 of clocks to both as prediction tools

NOTE Confidence: 0.84370315

00:05:45.507 --> 00:05:48.621 and also even for our mental health so.

NOTE Confidence: 0.84370315

00:05:48.621 --> 00:05:49.103 This is,

NOTE Confidence: 0.84370315

00:05:49.103 --> 00:05:49.344 uh,

NOTE Confidence: 0.84370315

00:05:49.344 --> 00:05:52.089 this is a picture from a famous movie by

NOTE Confidence: 0.84370315

00:05:52.089 --> 00:05:54.149 Ingmar Bergman called Wild Strawberries,

NOTE Confidence: 0.84370315

00:05:54.150 --> 00:05:56.580 and it's about this older gentleman

NOTE Confidence: 0.84370315

00:05:56.580 --> 00:05:59.316 who goes to sleep and he starts

NOTE Confidence: 0.84370315

00:05:59.316 --> 00:06:01.036 to dream and wakes up.

NOTE Confidence: 0.84370315

00:06:01.040 --> 00:06:02.972 Wakes up in his hometown and looks

NOTE Confidence: 0.84370315

00:06:02.972 --> 00:06:05.345 up at the Clock tower and the Clock

NOTE Confidence: 0.84370315

00:06:05.345 --> 00:06:07.680 has no hands and this triggers a

NOTE Confidence: 0.84370315

00:06:07.680 --> 00:06:09.264 existential dilemma through which

NOTE Confidence: 0.84370315

00:06:09.264 --> 00:06:11.177 the whole movie is about.

NOTE Confidence: 0.84370315

00:06:11.177 --> 00:06:13.139 I won't get into all that,

NOTE Confidence: 0.84370315

00:06:13.140 --> 00:06:14.940 but basically it illustrates the

NOTE Confidence: 0.84370315

00:06:14.940 --> 00:06:16.740 idea that without time without

NOTE Confidence: 0.8278385

00:06:16.804 --> 00:06:19.312 a sense of time, we lose our bearings.

NOTE Confidence: 0.8278385

00:06:19.312 --> 00:06:23.300 We our sense of our our sense of context.

NOTE Confidence: 0.8278385

00:06:23.300 --> 00:06:26.396 So, circadian rhythms are the cellular

NOTE Confidence: 0.8278385

00:06:26.396 --> 00:06:29.075 mechanism that synchronizes cellular function

NOTE Confidence: 0.8278385

00:06:29.075 --> 00:06:31.760 and ultimately organismal function with

NOTE Confidence: 0.8278385

00:06:31.760 --> 00:06:34.740 this iterative oscillation of the planet,

NOTE Confidence: 0.8278385

00:06:34.740 --> 00:06:39.010 and it allows the cells of our

NOTE Confidence: 0.8278385

00:06:39.010 --> 00:06:42.219 body to anticipate the needs.

NOTE Confidence: 0.8278385

00:06:42.220 --> 00:06:45.052 Anticipate their own needs and guide

NOTE Confidence: 0.8278385

00:06:45.052 --> 00:06:47.693 animal behavior to optimize those needs

NOTE Confidence: 0.8278385

00:06:47.693 --> 00:06:50.872 as a function of time of day, and so.

NOTE Confidence: 0.8278385

00:06:50.872 --> 00:06:52.927 Because of this fundamental nature,

NOTE Confidence: 0.8278385

00:06:52.930 --> 00:06:54.990 it's probably not because of

NOTE Confidence: 0.8278385

00:06:54.990 --> 00:06:56.638 their underlying cellular basis.

NOTE Confidence: 0.8278385

00:06:56.640 --> 00:06:58.745 It's probably not that surprising

NOTE Confidence: 0.8278385

00:06:58.745 --> 00:07:01.740 that you can find circadian rhythms in

NOTE Confidence: 0.8278385

00:07:01.740 --> 00:07:04.589 pretty much all aspects of biology and

NOTE Confidence: 0.8278385

00:07:04.589 --> 00:07:06.939 certainly all aspects of our biology,

NOTE Confidence: 0.8278385

00:07:06.940 --> 00:07:09.000 including many aspects of behavior,

NOTE Confidence: 0.8278385

00:07:09.000 --> 00:07:10.335 physiological control, metabolism,

NOTE Confidence: 0.8278385

00:07:10.335 --> 00:07:13.005 and even on more molecular basis

NOTE Confidence: 0.8278385

00:07:13.005 --> 00:07:14.200 gene expression.

NOTE Confidence: 0.8278385

00:07:14.200 --> 00:07:16.517 And the reason for that is that,

NOTE Confidence: 0.8278385

00:07:16.520 --> 00:07:17.345 as I mentioned,

NOTE Confidence: 0.8278385

00:07:17.345 --> 00:07:18.995 the Clock is truly a multi

NOTE Confidence: 0.8278385

00:07:18.995 --> 00:07:20.510 scaled organizing principle.

NOTE Confidence: 0.8278385

00:07:20.510 --> 00:07:22.854 By that I mean you can see circadian

NOTE Confidence: 0.8278385

00:07:22.854 --> 00:07:24.977 rhythms at the level of the

NOTE Confidence: 0.8278385

00:07:24.977 --> 00:07:26.812 chromatin opening and closing genes,

NOTE Confidence: 0.8278385

00:07:26.820 --> 00:07:29.137 turning on and off modifications of proteins.

NOTE Confidence: 0.8278385

00:07:29.140 --> 00:07:31.132 How proteins get in and out

NOTE Confidence: 0.8278385

00:07:31.132 --> 00:07:32.128 of different organelles,

NOTE Confidence: 0.8278385

00:07:32.130 --> 00:07:33.955 you conceive circadian rhythms as

NOTE Confidence: 0.8278385

00:07:33.955 --> 00:07:35.415 they interact between different

NOTE Confidence: 0.8278385

00:07:35.415 --> 00:07:36.439 tissues of the body.

NOTE Confidence: 0.8278385

00:07:36.440 --> 00:07:37.572 And then of course,

NOTE Confidence: 0.8278385

00:07:37.572 --> 00:07:39.270 larger things like you know behavior

NOTE Confidence: 0.8278385

00:07:39.329 --> 00:07:40.873 and organization of behavior

NOTE Confidence: 0.8278385

00:07:40.873 --> 00:07:42.417 between different social groups.

NOTE Confidence: 0.8278385

00:07:42.420 --> 00:07:44.200 Even so, it's really this.

NOTE Confidence: 0.8278385

00:07:44.200 --> 00:07:45.865 Organization principle for which you

NOTE Confidence: 0.8278385

00:07:45.865 --> 00:07:48.490 can use almost as a lens to unpack.

NOTE Confidence: 0.8278385

00:07:48.490 --> 00:07:50.646 You know this rhythmic biology that we

NOTE Confidence: 0.8278385

00:07:50.646 --> 00:07:52.582 can now unpacking multiple levels and

NOTE Confidence: 0.8278385

00:07:52.582 --> 00:07:54.496 study at multiple levels by looking

NOTE Confidence: 0.8278385

00:07:54.496 --> 00:07:56.410 at essentially the same output,

NOTE Confidence: 0.8278385

00:07:56.410 --> 00:07:58.060 which is this rhythmicity which

NOTE Confidence: 0.8278385

00:07:58.060 --> 00:07:59.710 I I find very exciting,

NOTE Confidence: 0.8278385

00:07:59.710 --> 00:08:01.858 because as someone who's interested in

NOTE Confidence: 0.8278385

00:08:01.858 --> 00:08:03.644 understanding what's the molecular basis

NOTE Confidence: 0.8278385

00:08:03.644 --> 00:08:05.468 for behavior and how that molecular

NOTE Confidence: 0.8278385

00:08:05.468 --> 00:08:06.970 basis gets disrupted in disease,

NOTE Confidence: 0.8278385

00:08:06.970 --> 00:08:08.660 the circadian Clock provides this

NOTE Confidence: 0.8278385

00:08:08.660 --> 00:08:10.666 beautiful example of how we can

NOTE Confidence: 0.8278385

00:08:10.666 --> 00:08:12.486 use this rhythmic output as a way

NOTE Confidence: 0.8278385

00:08:12.486 --> 00:08:14.230 to unpack molecular mechanisms.

NOTE Confidence: 0.8278385

00:08:14.230 --> 00:08:14.810 And also.

NOTE Confidence: 0.8278385

00:08:14.810 --> 00:08:16.840 Build them all the way up to

NOTE Confidence: 0.8278385

00:08:16.840 --> 00:08:18.727 understand how behavior is organized.

NOTE Confidence: 0.8278385

00:08:18.730 --> 00:08:20.515 So this talk is really about developmental

NOTE Confidence: 0.8278385

00:08:20.515 --> 00:08:22.234 disorders and I think it's important

NOTE Confidence: 0.8278385

00:08:22.234 --> 00:08:23.744 to realize that circadian rhythms,

NOTE Confidence: 0.8278385

00:08:23.750 --> 00:08:24.870 like all biological systems,

NOTE Confidence: 0.8278385

00:08:24.870 --> 00:08:25.150 develop.

NOTE Confidence: 0.8278385

00:08:25.150 --> 00:08:27.118 And this is from this is from a

NOTE Confidence: 0.8278385

00:08:27.118 --> 00:08:29.050 nice review paper by Seth Blackshaw,

NOTE Confidence: 0.8278385

00:08:29.050 --> 00:08:30.807 and when it is former graduate students

NOTE Confidence: 0.8278385

00:08:30.807 --> 00:08:32.535 where they talk about the development

NOTE Confidence: 0.8278385

00:08:32.535 --> 00:08:34.075 of the Super Chiasmatic nucleus,

NOTE Confidence: 0.8278385

00:08:34.080 --> 00:08:35.470 which as you guys know,

NOTE Confidence: 0.8278385

00:08:35.470 --> 00:08:36.870 is the central circadian oscillator,

NOTE Confidence: 0.8278385

00:08:36.870 --> 00:08:38.599 I just wanted to put this up

NOTE Confidence: 0.8278385

00:08:38.599 --> 00:08:40.490 to show that even before birth,

NOTE Confidence: 0.8278385

00:08:40.490 --> 00:08:42.498 so I hope you guys can see my

NOTE Confidence: 0.8278385

00:08:42.498 --> 00:08:43.840 pointer even before birth.

NOTE Confidence: 0.8278385

00:08:43.840 --> 00:08:45.786 Even there's like seven days before birth,

NOTE Confidence: 0.8278385

00:08:45.790 --> 00:08:47.855 so this is like the late trimester

NOTE Confidence: 0.8278385

00:08:47.855 --> 00:08:48.740 in a mouse.

NOTE Confidence: 0.8278385

00:08:48.740 --> 00:08:50.654 You can see circadian rhythms of

NOTE Confidence: 0.8278385

00:08:50.654 --> 00:08:52.220 oscillation in the early SCN,

NOTE Confidence: 0.8278385

00:08:52.220 --> 00:08:53.840 so circadian rhythms are becoming

NOTE Confidence: 0.8278385

00:08:53.840 --> 00:08:56.009 rhythmic in the brain very early on.

NOTE Confidence: 0.8278385

00:08:56.010 --> 00:08:58.230 We actually know very little about

NOTE Confidence: 0.8278385

00:08:58.230 --> 00:09:00.886 how those are organized and how those

NOTE Confidence: 0.8278385

00:09:00.886 --> 00:09:03.100 organized function in the early brain.

NOTE Confidence: 0.8278385

00:09:03.100 --> 00:09:06.068 This is a classic actor Graham from a

NOTE Confidence: 0.8278385

00:09:06.068 --> 00:09:08.986 from the from an old old old paper.

NOTE Confidence: 0.8278385

00:09:08.990 --> 00:09:09.792 You know,

NOTE Confidence: 0.8278385

00:09:09.792 --> 00:09:13.000 a 75 year old paper looking at circadian

NOTE Confidence: 0.8278385

00:09:13.088 --> 00:09:15.977 rhythms in a in a in a human infant,

NOTE Confidence: 0.81688106

00:09:15.980 --> 00:09:17.420 and, as you'll notice,

NOTE Confidence: 0.81688106

00:09:17.420 --> 00:09:19.220 is that the circadian oscillations

NOTE Confidence: 0.81688106

00:09:19.220 --> 00:09:21.304 of behavior are gated behavior

NOTE Confidence: 0.81688106

00:09:21.304 --> 00:09:22.960 really doesn't develop until

NOTE Confidence: 0.81688106

00:09:22.960 --> 00:09:25.177 around three to four months of age,

NOTE Confidence: 0.81688106

00:09:25.180 --> 00:09:27.196 and before that it's really much

NOTE Confidence: 0.81688106

00:09:27.196 --> 00:09:29.230 more much more poorly organized.

NOTE Confidence: 0.81688106

00:09:29.230 --> 00:09:31.135 And it's not because the

NOTE Confidence: 0.81688106

00:09:31.135 --> 00:09:33.040 underlying clocks are not there.

NOTE Confidence: 0.81688106

00:09:33.040 --> 00:09:34.588 It's probably we don't

NOTE Confidence: 0.81688106

00:09:34.588 --> 00:09:36.136 know the reason exactly,

NOTE Confidence: 0.81688106

00:09:36.140 --> 00:09:37.684 but it's probably because

NOTE Confidence: 0.81688106

00:09:37.684 --> 00:09:39.614 until this point around here,

NOTE Confidence: 0.81688106

00:09:39.620 --> 00:09:42.434 the infant is just feeding every 2-3

NOTE Confidence: 0.81688106

00:09:42.434 --> 00:09:45.847 hours and so feeding will Trump this

NOTE Confidence: 0.81688106

00:09:45.847 --> 00:09:48.492 organization of sleep wake cycles.

NOTE Confidence: 0.81688106

00:09:48.500 --> 00:09:48.917 Obviously,

NOTE Confidence: 0.81688106

00:09:48.917 --> 00:09:51.419 circadian circadian rhythms as they develop,

NOTE Confidence: 0.81688106

00:09:51.420 --> 00:09:54.339 have a huge impact on sleep architecture.

NOTE Confidence: 0.81688106

00:09:54.340 --> 00:09:56.836 Without getting too much into it,

NOTE Confidence: 0.81688106

00:09:56.840 --> 00:09:59.759 we know that so in early infants,

NOTE Confidence: 0.81688106

00:09:59.760 --> 00:10:01.424 the sleep architecture has

NOTE Confidence: 0.81688106

00:10:01.424 --> 00:10:03.504 a very rapid and frequent.

NOTE Confidence: 0.7769156

00:10:07.280 --> 00:10:08.688 Changes are changes between

NOTE Confidence: 0.7769156

00:10:08.688 --> 00:10:10.800 RAM and non REM like sleep.

NOTE Confidence: 0.7769156

00:10:10.800 --> 00:10:12.996 These become more ensconce in the

NOTE Confidence: 0.7769156

00:10:12.996 --> 00:10:15.188 child and then are really like

NOTE Confidence: 0.7769156

00:10:15.188 --> 00:10:17.484 laid down in the in the adult.

NOTE Confidence: 0.7769156

00:10:17.490 --> 00:10:19.744 As we know our as our best

NOTE Confidence: 0.7769156

00:10:19.744 --> 00:10:21.386 understanding is really that what

NOTE Confidence: 0.7769156

00:10:21.386 --> 00:10:23.507 keeps us sleep late into the night

NOTE Confidence: 0.7769156

00:10:23.507 --> 00:10:25.940 is this underlying circadian Clock,

NOTE Confidence: 0.7769156

00:10:25.940 --> 00:10:28.046 which like galvanizes our REM sleep.

NOTE Confidence: 0.7769156

00:10:28.050 --> 00:10:30.234 How that circadian Clock works in early

NOTE Confidence: 0.7769156

00:10:30.234 --> 00:10:31.920 infant to galvanise architecture,

NOTE Confidence: 0.7769156

00:10:31.920 --> 00:10:34.890 I would say at this point

NOTE Confidence: 0.7769156

00:10:34.890 --> 00:10:36.375 is completely unknown.

NOTE Confidence: 0.7769156

00:10:36.380 --> 00:10:36.932 Importantly,

NOTE Confidence: 0.7769156

00:10:36.932 --> 00:10:39.692 sleep ontogeny parallels brain ontogeny

NOTE Confidence: 0.7769156

00:10:39.692 --> 00:10:43.586 so I would refer you to this little

NOTE Confidence: 0.7769156

00:10:43.586 --> 00:10:45.986 paper that we wrote and really.

NOTE Confidence: 0.7769156

00:10:45.990 --> 00:10:47.846 The only reason I put this in here

NOTE Confidence: 0.7769156

00:10:47.846 --> 00:10:50.192 is just to remind you that sleep and

NOTE Confidence: 0.7769156

00:10:50.192 --> 00:10:51.762 circadian function is very important

NOTE Confidence: 0.7769156

00:10:51.762 --> 00:10:53.848 for the development of the brain and

NOTE Confidence: 0.7769156

00:10:53.848 --> 00:10:56.310 what we think are the development

NOTE Confidence: 0.7769156

00:10:56.310 --> 00:10:58.170 of these fundamental sculpting.

NOTE Confidence: 0.7769156

00:10:58.170 --> 00:10:59.726 Both synaptogenesis refinement and

NOTE Confidence: 0.7769156

00:10:59.726 --> 00:11:02.472 pruning of synapses that we think are

NOTE Confidence: 0.7769156

00:11:02.472 --> 00:11:04.217 essential to the normal development

NOTE Confidence: 0.7769156

00:11:04.217 --> 00:11:06.578 of human behavior and probably are

NOTE Confidence: 0.7769156

00:11:06.578 --> 00:11:08.838 contribute in many different ways

NOTE Confidence: 0.7769156

00:11:08.838 --> 00:11:10.194 to neurodevelopmental disorders.

NOTE Confidence: 0.7769156

00:11:10.200 --> 00:11:10.557 Again,

NOTE Confidence: 0.7769156

00:11:10.557 --> 00:11:13.056 the idea being here that sleep and

NOTE Confidence: 0.7769156

00:11:13.056 --> 00:11:14.669 sleep dysfunction are probably

NOTE Confidence: 0.7769156

00:11:14.669 --> 00:11:17.171 very important not just as outputs

NOTE Confidence: 0.7769156

00:11:17.171 --> 00:11:18.620 of neurodevelopmental problems,

NOTE Confidence: 0.7769156

00:11:18.620 --> 00:11:21.520 but maybe even underlying them.

NOTE Confidence: 0.7769156

00:11:21.520 --> 00:11:22.136 And again,

NOTE Confidence: 0.7769156

00:11:22.136 --> 00:11:24.292 classical work going back to you know

NOTE Confidence: 0.7769156

00:11:24.292 --> 00:11:26.372 again 30-40 years ago showing this

NOTE Confidence: 0.7769156

00:11:26.372 --> 00:11:28.890 these dramatic changes in sleep architecture.

NOTE Confidence: 0.7769156

00:11:28.890 --> 00:11:30.922 So I always talk about sleep as this

NOTE Confidence: 0.7769156

00:11:30.922 --> 00:11:33.094 one of the most developmentally

NOTE Confidence: 0.7769156

00:11:33.094 --> 00:11:34.160 regulated behaviors.

NOTE Confidence: 0.7769156

00:11:34.160 --> 00:11:36.122 And for those fellows who are

NOTE Confidence: 0.7769156

00:11:36.122 --> 00:11:38.246 listening or those people who are

NOTE Confidence: 0.7769156

00:11:38.246 --> 00:11:40.116 listening or interested in research.

NOTE Confidence: 0.7769156

00:11:40.120 --> 00:11:42.793 I think this is one of the most exciting

NOTE Confidence: 0.7769156

00:11:42.793 --> 00:11:45.390 and untapped areas of sleep research.

NOTE Confidence: 0.7769156

00:11:45.390 --> 00:11:47.420 We really know very little in general

NOTE Confidence: 0.7769156

00:11:47.420 --> 00:11:49.950 about how the mechanisms underlying sleep,

NOTE Confidence: 0.7769156

00:11:49.950 --> 00:11:50.952 sleep in development,

NOTE Confidence: 0.7769156

00:11:50.952 --> 00:11:52.956 and why Slean why sleep is

NOTE Confidence: 0.7769156

00:11:52.956 --> 00:11:54.998 so important to development.

NOTE Confidence: 0.7769156

00:11:55.000 --> 00:11:58.006 I'll skip this so sleep dysfunction

NOTE Confidence: 0.7769156

00:11:58.006 --> 00:11:59.509 and neurodevelopmental disorders

NOTE Confidence: 0.7769156

00:11:59.509 --> 00:12:02.218 are what I refer to as common

NOTE Confidence: 0.7769156

00:12:02.218 --> 00:12:04.254 bedfellows and the reason what I

NOTE Confidence: 0.7769156

00:12:04.254 --> 00:12:06.422 mean by that is that there is an

NOTE Confidence: 0.7769156

00:12:06.430 --> 00:12:07.914 incredible overlap in individuals

NOTE Confidence: 0.7769156

00:12:07.914 --> 00:12:09.398 that suffer from neurodevelopmental

NOTE Confidence: 0.7769156

00:12:09.398 --> 00:12:11.000 disorders and sleep dysfunction.

NOTE Confidence: 0.7769156

00:12:11.000 --> 00:12:15.095 I'm sure all of us who do Pediatrics have

NOTE Confidence: 0.7769156

00:12:15.095 --> 00:12:17.867 experienced this in our clinics where.

NOTE Confidence: 0.7769156

00:12:17.870 --> 00:12:19.544 Very often you'll and I experience

NOTE Confidence: 0.7769156

00:12:19.544 --> 00:12:21.900 a lot as a neurology resident.

NOTE Confidence: 0.7769156

00:12:21.900 --> 00:12:23.916 I would see patients for autism

NOTE Confidence: 0.7769156

00:12:23.916 --> 00:12:25.260 and epilepsy and diagnostics,

NOTE Confidence: 0.7769156

00:12:25.260 --> 00:12:27.294 but really what they wanted to

NOTE Confidence: 0.7769156

00:12:27.294 --> 00:12:29.689 talk about in clinic was the fact

NOTE Confidence: 0.7769156

00:12:29.689 --> 00:12:31.309 that they don't sleep out.

NOTE Confidence: 0.7769156

00:12:31.310 --> 00:12:33.638 The kids don't sleep and so you know

NOTE Confidence: 0.7769156

00:12:33.638 --> 00:12:35.811 it has a huge impact on quality

NOTE Confidence: 0.7769156

00:12:35.811 --> 00:12:38.327 of life and indeed a huge impact

NOTE Confidence: 0.7769156

00:12:38.327 --> 00:12:39.707 on underlying biology.

NOTE Confidence: 0.7769156

00:12:39.710 --> 00:12:41.385 So sleep dysfunction as most

NOTE Confidence: 0.7769156

00:12:41.385 --> 00:12:42.725 of you probably know,

NOTE Confidence: 0.7769156

00:12:42.730 --> 00:12:44.410 is associated with behavioral dyscontrol,

NOTE Confidence: 0.7769156

00:12:44.410 --> 00:12:45.418 lower seizure thresholds,

NOTE Confidence: 0.7769156

00:12:45.418 --> 00:12:46.762 mood disruption, metabolic disease,

NOTE Confidence: 0.7769156

00:12:46.762 --> 00:12:47.770 potentially even obesity,

NOTE Confidence: 0.7769156

00:12:47.770 --> 00:12:49.570 diminished quality of life measures.

NOTE Confidence: 0.7769156

00:12:49.570 --> 00:12:51.508 And obviously, we could spend many,

NOTE Confidence: 0.7769156

00:12:51.510 --> 00:12:53.460 many days discussing each of these.

NOTE Confidence: 0.7769156

00:12:53.460 --> 00:12:55.398 I don't have time for that.

NOTE Confidence: 0.7769156

00:12:55.400 --> 00:12:58.640 I want to dive into some of our actual work,

NOTE Confidence: 0.7769156

00:12:58.640 --> 00:13:01.340 but just this is a more of a reminder

NOTE Confidence: 0.7769156

00:13:01.340 --> 00:13:03.830 to you guys that this is these.

NOTE Confidence: 0.7769156

00:13:03.830 --> 00:13:04.733 These there's a.

NOTE Confidence: 0.7769156

00:13:04.733 --> 00:13:06.238 There's a potent interaction between

NOTE Confidence: 0.7769156

00:13:06.238 --> 00:13:08.038 sleep dysfunction or developmental disorders.

NOTE Confidence: 0.7769156

00:13:08.040 --> 00:13:09.660 Some of the specific examples,

NOTE Confidence: 0.84334695

00:13:09.660 --> 00:13:11.280 of course, would be autism,

NOTE Confidence: 0.84334695

00:13:11.280 --> 00:13:12.576 Fragile X syndrome, tuberculosis,

NOTE Confidence: 0.84334695

00:13:12.576 --> 00:13:13.548 complex Angelmann syndrome,

NOTE Confidence: 0.84334695

00:13:13.550 --> 00:13:14.507 many, many others.

NOTE Confidence: 0.84334695

00:13:14.507 --> 00:13:16.740 And I just wanted to raise this

NOTE Confidence: 0.84334695

00:13:16.811 --> 00:13:19.340 idea that I think what we can see by

NOTE Confidence: 0.84334695

00:13:19.340 --> 00:13:21.837 looking at animal models and even in

NOTE Confidence: 0.84334695

00:13:21.837 --> 00:13:23.970 humans with these disorders is that.

NOTE Confidence: 0.84334695

00:13:23.970 --> 00:13:25.720 The rhythmic dysfunction is often

NOTE Confidence: 0.84334695

00:13:25.720 --> 00:13:27.748 so fundamental to their clinical

NOTE Confidence: 0.84334695

00:13:27.748 --> 00:13:29.128 presentations and possibly

NOTE Confidence: 0.84334695

00:13:29.128 --> 00:13:30.968 even the disease progression.

NOTE Confidence: 0.84334695

00:13:30.970 --> 00:13:33.124 I think it bears asking the

NOTE Confidence: 0.84334695

00:13:33.124 --> 00:13:34.560 question whether these diseases

NOTE Confidence: 0.84334695

00:13:34.627 --> 00:13:36.699 are fundamentally rhythm opathy's,

NOTE Confidence: 0.84334695

00:13:36.700 --> 00:13:39.437 and I know this is a little

NOTE Confidence: 0.84334695

00:13:39.437 --> 00:13:41.200 bit of acute term,

NOTE Confidence: 0.84334695

00:13:41.200 --> 00:13:43.200 but I think it's important

NOTE Confidence: 0.84334695

00:13:43.200 --> 00:13:45.700 just to to think about that.

NOTE Confidence: 0.84334695

00:13:45.700 --> 00:13:46.966 Maybe the rhythmic,

NOTE Confidence: 0.84334695

00:13:46.966 --> 00:13:49.498 the dysrhythmias in these disorders is

NOTE Confidence: 0.84334695

00:13:49.498 --> 00:13:51.783 actually fundamental to their progression

NOTE Confidence: 0.84334695

00:13:51.783 --> 00:13:54.023 and maybe even for diagnostics.

NOTE Confidence: 0.84334695

00:13:54.030 --> 00:13:56.277 So the question is when you have

NOTE Confidence: 0.84334695

00:13:56.277 --> 00:13:57.560 these complex, multifaceted and

NOTE Confidence: 0.84334695

00:13:57.560 --> 00:13:58.520 multi factorial interactions,

NOTE Confidence: 0.84334695

00:13:58.520 --> 00:14:00.767 how do you start to unpack it?

NOTE Confidence: 0.84334695

00:14:00.770 --> 00:14:02.126 From a scientific standpoint?

NOTE Confidence: 0.84334695

00:14:02.126 --> 00:14:03.143 And obviously there's

NOTE Confidence: 0.84334695

00:14:03.143 --> 00:14:04.619 no right answer to that,

NOTE Confidence: 0.84334695

00:14:04.620 --> 00:14:06.230 so one would be you.

NOTE Confidence: 0.84334695

00:14:06.230 --> 00:14:07.490 You take the system,

NOTE Confidence: 0.84334695

00:14:07.490 --> 00:14:10.400 you take a working system and you perturb it.

NOTE Confidence: 0.84334695

00:14:10.400 --> 00:14:12.005 Another would be you studying

NOTE Confidence: 0.84334695

00:14:12.005 --> 00:14:12.968 already perturbed system.

NOTE Confidence: 0.84334695

00:14:12.970 --> 00:14:15.598 So really what I'm trying to say is you

NOTE Confidence: 0.84334695

00:14:15.598 --> 00:14:18.105 could either take like a normal animal,

NOTE Confidence: 0.84334695

00:14:18.110 --> 00:14:20.158 let's say or a normal model of a

NOTE Confidence: 0.84334695

00:14:20.158 --> 00:14:21.523 normal or typically functioning

NOTE Confidence: 0.84334695

00:14:21.523 --> 00:14:24.274 system and you can muck around with.

NOTE Confidence: 0.84334695

00:14:24.280 --> 00:14:25.732 Sleep or muck around with molecules

NOTE Confidence: 0.84334695

00:14:25.732 --> 00:14:27.495 that you know are involved in

NOTE Confidence: 0.84334695

00:14:27.495 --> 00:14:28.617 your developmental disorders.

NOTE Confidence: 0.84334695

00:14:28.620 --> 00:14:30.524 Or you can take a newer developmental

NOTE Confidence: 0.84334695

00:14:30.524 --> 00:14:32.080 model and then study clocks.

NOTE Confidence: 0.84334695

00:14:32.080 --> 00:14:34.110 And that's really how my work started.

NOTE Confidence: 0.84334695

00:14:34.110 --> 00:14:36.028 But I think what you'll see is

NOTE Confidence: 0.84334695

00:14:36.028 --> 00:14:37.570 that it started with these.

NOTE Confidence: 0.84334695

00:14:37.570 --> 00:14:39.478 This very sort of almost naive

NOTE Confidence: 0.84334695

00:14:39.478 --> 00:14:41.479 approach and then we got into

NOTE Confidence: 0.84334695

00:14:41.479 --> 00:14:43.129 some very very deep biology.

NOTE Confidence: 0.84334695

00:14:43.130 --> 00:14:44.768 So I started this really because

NOTE Confidence: 0.84334695

00:14:44.768 --> 00:14:46.420 actually what I was a resident

NOTE Confidence: 0.84334695

00:14:46.420 --> 00:14:48.177 and I was doing my ICU rotation.

NOTE Confidence: 0.84334695

00:14:48.180 --> 00:14:49.164 I was my clinical.

NOTE Confidence: 0.84334695

00:14:49.164 --> 00:14:50.640 My clinical tending was stuff so

NOTE Confidence: 0.84334695

00:14:50.695 --> 00:14:52.319 he knew became one of my primary

NOTE Confidence: 0.84334695

00:14:52.319 --> 00:14:54.610 mentors and his focus of his lab was

NOTE Confidence: 0.84334695

00:14:54.610 --> 00:14:55.846 really understanding the underlying

NOTE Confidence: 0.84334695

00:14:55.846 --> 00:14:57.224 biology of this newer developmental

NOTE Confidence: 0.84334695

00:14:57.224 --> 00:14:58.288 syndrome called Too Brisk.

NOTE Confidence: 0.84334695

00:14:58.290 --> 00:14:59.886 Larose is complex and we were

NOTE Confidence: 0.84334695

00:14:59.886 --> 00:15:00.684 just chatting about.

NOTE Confidence: 0.84334695

00:15:00.690 --> 00:15:02.482 You know what I was going to do

NOTE Confidence: 0.84334695

00:15:02.482 --> 00:15:04.139 with my career and whatever.

NOTE Confidence: 0.84334695

00:15:04.140 --> 00:15:05.736 And I said, oh, you know,

NOTE Confidence: 0.84334695

00:15:05.740 --> 00:15:07.828 I think I'm going to study sleep and

NOTE Confidence: 0.84334695

00:15:07.828 --> 00:15:10.000 he's just set off the couple you know,

NOTE Confidence: 0.84334695

00:15:10.000 --> 00:15:11.330 kids with TSC don't sleep,

NOTE Confidence: 0.84334695

00:15:11.330 --> 00:15:12.655 they have terrible sleep problems

NOTE Confidence: 0.84334695

00:15:12.655 --> 00:15:14.602 like I didn't. I didn't know that.

NOTE Confidence: 0.84334695

00:15:14.602 --> 00:15:17.149 I never even know we don't study sleep.

NOTE Confidence: 0.84334695

00:15:17.150 --> 00:15:19.154 No one ever mentioned sleep during

NOTE Confidence: 0.84334695

00:15:19.154 --> 00:15:20.843 our clinical training 'cause we're

NOTE Confidence: 0.84334695

00:15:20.843 --> 00:15:22.887 always in the hospital taking care of.

NOTE Confidence: 0.84334695

00:15:22.890 --> 00:15:25.130 Like you know, patients who are very,

NOTE Confidence: 0.84334695

00:15:25.130 --> 00:15:29.288 very sick. So I started looking into this so.

NOTE Confidence: 0.84334695

00:15:29.290 --> 00:15:29.646 Well,

NOTE Confidence: 0.84334695

00:15:29.646 --> 00:15:32.850 I'll tell you what I'll tell you this story.

NOTE Confidence: 0.84334695

00:15:32.850 --> 00:15:34.754 So too is chlorosis to remind you

NOTE Confidence: 0.84334695

00:15:34.754 --> 00:15:36.514 guys is AutoZone will dominant

NOTE Confidence: 0.84334695

00:15:36.514 --> 00:15:38.282 or neurogenic neurogenetic and

NOTE Confidence: 0.84334695

00:15:38.282 --> 00:15:39.608 your developmental syndrome.

NOTE Confidence: 0.84334695

00:15:39.610 --> 00:15:41.390 It presents with epilepsy intellectual

NOTE Confidence: 0.84334695

00:15:41.390 --> 00:15:43.914 disability about 30 to 50% of patients

NOTE Confidence: 0.84334695

00:15:43.914 --> 00:15:46.146 have sort of classical features of

NOTE Confidence: 0.84334695

00:15:46.146 --> 00:15:48.272 autism and then very very frequently

NOTE Confidence: 0.84334695

00:15:48.272 --> 00:15:51.004 have 30 to 50% of these kids also

NOTE Confidence: 0.84334695

00:15:51.004 --> 00:15:52.428 have sleep disorders disorder.

NOTE Confidence: 0.84334695

00:15:52.430 --> 00:15:54.445 The disease is characterized by

NOTE Confidence: 0.84334695

00:15:54.445 --> 00:15:56.460 these pathognomonic tubers which you

NOTE Confidence: 0.78962356

00:15:56.527 --> 00:15:58.129 can see here on these Mris.

NOTE Confidence: 0.78962356

00:15:58.130 --> 00:16:00.250 So he's like. Areas of.

NOTE Confidence: 0.85634685

00:16:03.290 --> 00:16:05.639 In this case.

NOTE Confidence: 0.85634685

00:16:05.640 --> 00:16:07.860 Do you want me to abnormality?

NOTE Confidence: 0.85634685

00:16:07.860 --> 00:16:09.966 And it's really a disconnection syndrome

NOTE Confidence: 0.85634685

00:16:09.966 --> 00:16:12.967 and it's caused by so it causes these

NOTE Confidence: 0.85634685

00:16:12.967 --> 00:16:14.882 very abnormal white matter connections.

NOTE Confidence: 0.85634685

00:16:14.890 --> 00:16:17.850 It's caused by mutations in one or two,

NOTE Confidence: 0.85634685

00:16:17.850 --> 00:16:21.186 one of two genes, either TSC, one or TSC.

NOTE Confidence: 0.85634685

00:16:21.186 --> 00:16:23.790 2 which form a complex and just

NOTE Confidence: 0.85634685

00:16:23.886 --> 00:16:25.616 to give you an idea,

NOTE Confidence: 0.85634685

00:16:25.620 --> 00:16:28.004 there is now an appreciation that in addition

NOTE Confidence: 0.85634685

00:16:28.004 --> 00:16:30.432 to these sort of character characteristics

NOTE Confidence: 0.85634685

00:16:30.432 --> 00:16:32.642 of intellectual disability and autism,

NOTE Confidence: 0.85634685

00:16:32.650 --> 00:16:34.580 there's a whole syndrome of

NOTE Confidence: 0.85634685

00:16:34.580 --> 00:16:35.738 neuro psychiatric dysfunction.

NOTE Confidence: 0.85634685

00:16:35.740 --> 00:16:36.445 Into risk losses,

NOTE Confidence: 0.85634685

00:16:36.445 --> 00:16:38.090 which is referred to as the TSC

NOTE Confidence: 0.85634685

00:16:38.144 --> 00:16:39.200 Neuro psychiatric disorder of

NOTE Confidence: 0.85634685

00:16:39.200 --> 00:16:41.220 which sleep is one of the primary.

NOTE Confidence: 0.7803569475

00:16:43.580 --> 00:16:47.073 Symptomatology So what is the biology of

NOTE Confidence: 0.7803569475

00:16:47.073 --> 00:16:51.359 TSC and why is it so appealing to study?

NOTE Confidence: 0.7803569475

00:16:51.360 --> 00:16:53.406 So TSC is what's referred to

NOTE Confidence: 0.7803569475

00:16:53.406 --> 00:16:55.520 as an mtor opathy emptores.

NOTE Confidence: 0.7803569475

00:16:55.520 --> 00:16:57.410 The mechanistic target of rapamycin.

NOTE Confidence: 0.7803569475

00:16:57.410 --> 00:17:00.330 This is a protein kinase which is present

NOTE Confidence: 0.7803569475

00:17:00.330 --> 00:17:03.825 in all cells of the body and it is a

NOTE Confidence: 0.7803569475

00:17:03.825 --> 00:17:06.099 core regulator of nutritive status.

NOTE Confidence: 0.7803569475

00:17:06.100 --> 00:17:09.260 It basically is a decision point in all

NOTE Confidence: 0.7803569475

00:17:09.260 --> 00:17:12.529 cells about whether to grow or to not grow,

NOTE Confidence: 0.7803569475

00:17:12.530 --> 00:17:14.852 whether to break up to make

NOTE Confidence: 0.7803569475

00:17:14.852 --> 00:17:16.400 protein or break protein.

NOTE Confidence: 0.7803569475

00:17:16.400 --> 00:17:18.615 Whether to make mitochondria or

NOTE Confidence: 0.7803569475

00:17:18.615 --> 00:17:20.830 not make mitochondria and many,

NOTE Confidence: 0.7803569475

00:17:20.830 --> 00:17:22.048 many other things,

NOTE Confidence: 0.7803569475

00:17:22.048 --> 00:17:24.890 and it does so by integrating upstream

NOTE Confidence: 0.7803569475

00:17:24.963 --> 00:17:27.027 pathways that include growth,

NOTE Confidence: 0.7803569475

00:17:27.030 --> 00:17:27.916 growth factors,

NOTE Confidence: 0.7803569475

00:17:27.916 --> 00:17:31.017 nutrients such as amino acids and stress.

NOTE Confidence: 0.7803569475

00:17:31.020 --> 00:17:33.235 So changes in oxygen tension

NOTE Confidence: 0.7803569475

00:17:33.235 --> 00:17:35.007 or other other stressors,

NOTE Confidence: 0.7803569475

00:17:35.010 --> 00:17:36.598 and the TSC complex,

NOTE Confidence: 0.7803569475

00:17:36.598 --> 00:17:39.880 which is the cause of tubers chlorosis.

NOTE Confidence: 0.7803569475

00:17:39.880 --> 00:17:42.981 It's right in smack in the middle

NOTE Confidence: 0.7803569475

00:17:42.981 --> 00:17:45.696 of this cascade, and its basic

NOTE Confidence: 0.7803569475

00:17:45.696 --> 00:17:48.468 function is to suppress so block.

NOTE Confidence: 0.7803569475

00:17:48.470 --> 00:17:48.850 Amateur,

NOTE Confidence: 0.7803569475

00:17:48.850 --> 00:17:51.510 so when TSC is blocked when TC

NOTE Confidence: 0.7803569475

00:17:51.510 --> 00:17:54.380 is lost you lose this inhibition.

NOTE Confidence: 0.7803569475

00:17:54.380 --> 00:17:57.484 And mtor is high in one way of

NOTE Confidence: 0.7803569475

00:17:57.484 --> 00:18:00.709 blocking TSC is by using certain drugs,

NOTE Confidence: 0.7803569475

00:18:00.710 --> 00:18:03.236 including where how was actually originally.

NOTE Confidence: 0.7803569475

00:18:03.240 --> 00:18:05.350 This pathway is originally discovered

NOTE Confidence: 0.7803569475

00:18:05.350 --> 00:18:07.460 which is wrapping my Sonoran.

NOTE Confidence: 0.7803569475

00:18:07.460 --> 00:18:09.992 In clinical terms would be sirolimus

NOTE Confidence: 0.7803569475

00:18:09.992 --> 00:18:10.836 or everolimus.

NOTE Confidence: 0.7803569475

00:18:10.840 --> 00:18:13.336 Our raffle logs and that's where

NOTE Confidence: 0.7803569475

00:18:13.336 --> 00:18:15.480 this protein got its name.

NOTE Confidence: 0.7803569475

00:18:15.480 --> 00:18:18.490 Actually they found the drug first in.

NOTE Confidence: 0.7803569475

00:18:18.490 --> 00:18:20.352 On rapper New Ian Rappa Nui is

NOTE Confidence: 0.7803569475

00:18:20.352 --> 00:18:21.761 Easter Island in Polynesian and

NOTE Confidence: 0.7803569475

00:18:21.761 --> 00:18:23.700 they found this drug in a bunch

NOTE Confidence: 0.7803569475

00:18:23.700 --> 00:18:25.507 of bacteria and they wanted to

NOTE Confidence: 0.7803569475

00:18:25.507 --> 00:18:27.546 study with the what this drug did.

NOTE Confidence: 0.7803569475

00:18:27.546 --> 00:18:29.527 They found that it blocked cell division.

NOTE Confidence: 0.7803569475

00:18:29.530 --> 00:18:31.602 They started using it as an immune

NOTE Confidence: 0.7803569475

00:18:31.602 --> 00:18:33.076 regulator and eventually they figured

NOTE Confidence: 0.7803569475

00:18:33.076 --> 00:18:34.938 out that the way rapper Mysonne works

NOTE Confidence: 0.7803569475

00:18:34.938 --> 00:18:36.913 is by blocking mtor and that's how

NOTE Confidence: 0.7803569475

00:18:36.913 --> 00:18:38.869 the whole field started now and I

NOTE Confidence: 0.7803569475

00:18:38.869 --> 00:18:40.850 showed you here a pared down cartoon.

NOTE Confidence: 0.7803569475

00:18:40.850 --> 00:18:42.716 Mtor signaling is much more complicated

NOTE Confidence: 0.7803569475

00:18:42.716 --> 00:18:44.785 as you can imagine as all these

NOTE Confidence: 0.7803569475

00:18:44.785 --> 00:18:47.069 pathways are I won't go through all of this.

NOTE Confidence: 0.7803569475

00:18:47.070 --> 00:18:49.114 This is what a former mentor of

NOTE Confidence: 0.7803569475

00:18:49.114 --> 00:18:50.888 my often referred to as Chinese.

NOTE Confidence: 0.7803569475

00:18:50.890 --> 00:18:51.220 Well,

NOTE Confidence: 0.7803569475

00:18:51.220 --> 00:18:53.200 where you basically have hundreds of

NOTE Confidence: 0.7803569475

00:18:53.200 --> 00:18:54.779 pathways interacting with each other,

NOTE Confidence: 0.7803569475

00:18:54.780 --> 00:18:56.490 and of course any crucial homeostatic

NOTE Confidence: 0.7803569475

00:18:56.490 --> 00:18:58.555 pathway is going to be incredibly

NOTE Confidence: 0.7803569475

00:18:58.555 --> 00:18:58.989 complicated,

NOTE Confidence: 0.7803569475

00:18:58.990 --> 00:19:00.928 because even like the circadian Clock,

NOTE Confidence: 0.7803569475

00:19:00.930 --> 00:19:01.905 it's incredibly redundant.

NOTE Confidence: 0.7803569475

00:19:01.905 --> 00:19:03.530 It's built not to break,

NOTE Confidence: 0.7803569475

00:19:03.530 --> 00:19:05.468 it's built to sort of regulate,

NOTE Confidence: 0.7803569475

00:19:05.470 --> 00:19:08.386 but not fall apart, and so it has many,

NOTE Confidence: 0.7803569475

00:19:08.390 --> 00:19:10.328 many interactions and complexities to it,

NOTE Confidence: 0.7803569475

00:19:10.330 --> 00:19:12.598 which we don't have time to really

NOTE Confidence: 0.7803569475

00:19:12.598 --> 00:19:13.570 get into today.

NOTE Confidence: 0.7803569475

00:19:13.570 --> 00:19:15.796 I just wanted to point out that

NOTE Confidence: 0.7803569475

00:19:15.796 --> 00:19:17.130 as you can see,

NOTE Confidence: 0.7803569475

00:19:17.130 --> 00:19:19.015 the TSC complex sits literally

NOTE Confidence: 0.7803569475

00:19:19.015 --> 00:19:20.900 in the middle of this.

NOTE Confidence: 0.7803569475

00:19:20.900 --> 00:19:22.727 Literally, in the middle of this figure,

NOTE Confidence: 0.7803569475

00:19:22.730 --> 00:19:23.534 because it's again,

NOTE Confidence: 0.7803569475

00:19:23.534 --> 00:19:24.874 it's an integration point for

NOTE Confidence: 0.7803569475

00:19:24.874 --> 00:19:26.440 the regulation event or so when

NOTE Confidence: 0.7803569475

00:19:26.440 --> 00:19:26.930 it's dysregulated.

NOTE Confidence: 0.7803569475

00:19:26.930 --> 00:19:28.862 You can imagine all sorts of

NOTE Confidence: 0.7803569475

00:19:28.862 --> 00:19:30.690 havoc is wreaked on a cell.

NOTE Confidence: 0.7803569475

00:19:30.690 --> 00:19:32.730 So just to remind you again,

NOTE Confidence: 0.7803569475

00:19:32.730 --> 00:19:34.782 mtor basically regulates the making of

NOTE Confidence: 0.7803569475

00:19:34.782 --> 00:19:36.810 protein and the breaking of protein.

NOTE Confidence: 0.7803569475

00:19:36.810 --> 00:19:38.510 So while it's making protein,

NOTE Confidence: 0.7803569475

00:19:38.510 --> 00:19:40.550 it also is suppressing the breaking

NOTE Confidence: 0.7803569475

00:19:40.550 --> 00:19:41.230 of protein.

NOTE Confidence: 0.7803569475

00:19:41.230 --> 00:19:42.658 When mtor is inhibited,

NOTE Confidence: 0.7803569475

00:19:42.658 --> 00:19:44.800 it'll start breaking protein down and

NOTE Confidence: 0.7868047

00:19:44.859 --> 00:19:46.987 stop making it so it's sort of

NOTE Confidence: 0.7868047

00:19:46.987 --> 00:19:48.370 literally this little seesaw.

NOTE Confidence: 0.7868047

00:19:48.370 --> 00:19:50.974 So again, see styles are very appealing

NOTE Confidence: 0.7868047

00:19:50.974 --> 00:19:53.021 to people who study circadian

NOTE Confidence: 0.7868047

00:19:53.021 --> 00:19:55.589 rhythms because we like to study

NOTE Confidence: 0.7868047

00:19:55.589 --> 00:19:58.207 seesaws that oscillate with 24 hours.

NOTE Confidence: 0.7868047

00:19:58.210 --> 00:20:00.628 So there's actually pretty crummy papers

NOTE Confidence: 0.7868047

00:20:00.628 --> 00:20:03.140 on directly looking at TSC clinical,

NOTE Confidence: 0.7868047

00:20:03.140 --> 00:20:03.962 clinical, clinical,

NOTE Confidence: 0.7868047

00:20:03.962 --> 00:20:06.428 clinical dysfunction of sleep in TSC.

NOTE Confidence: 0.7868047

00:20:06.430 --> 00:20:08.901 There are a few and they show

NOTE Confidence: 0.7868047

00:20:08.901 --> 00:20:11.024 sort of fragmentation and some

NOTE Confidence: 0.7868047

00:20:11.024 --> 00:20:13.008 evidence of circadian dysfunction.

NOTE Confidence: 0.7868047

00:20:13.010 --> 00:20:14.650 Some circadian phase delay,

NOTE Confidence: 0.7868047

00:20:14.650 --> 00:20:16.290 sometimes advanced circadian rhythms.

NOTE Confidence: 0.7868047

00:20:16.290 --> 00:20:18.908 It's really a bit of a mish

NOTE Confidence: 0.7868047

00:20:18.908 --> 00:20:20.820 mosh to be honest,

NOTE Confidence: 0.7868047

00:20:20.820 --> 00:20:24.019 but there is strong evidence and certainly

NOTE Confidence: 0.7868047

00:20:24.019 --> 00:20:26.546 anecdotal evidence that sleep is a

NOTE Confidence: 0.7868047

00:20:26.546 --> 00:20:28.712 major problem for patients with TSC.

NOTE Confidence: 0.7868047

00:20:28.720 --> 00:20:31.107 I can just say as an aside,

NOTE Confidence: 0.7868047

00:20:31.110 --> 00:20:32.810 this is not scientific information,

NOTE Confidence: 0.7868047

00:20:32.810 --> 00:20:35.234 but I could just say the first time

NOTE Confidence: 0.7868047

00:20:35.234 --> 00:20:37.394 I spoke at a TS Alliance meeting

NOTE Confidence: 0.7868047

00:20:37.394 --> 00:20:40.175 and I gave a talk about sleep and

NOTE Confidence: 0.7868047

00:20:40.175 --> 00:20:42.220 these meetings are both scientific

NOTE Confidence: 0.7868047

00:20:42.220 --> 00:20:43.330 and for patients,

NOTE Confidence: 0.7868047

00:20:43.330 --> 00:20:45.940 and I can tell you that the room was

NOTE Confidence: 0.7868047

00:20:46.003 --> 00:20:48.838 completely totally jam packed to the rafters.

NOTE Confidence: 0.7868047

00:20:48.840 --> 00:20:50.545 And it's not because I

NOTE Confidence: 0.7868047

00:20:50.545 --> 00:20:51.909 was speaking about nobody,

NOTE Confidence: 0.7868047

00:20:51.910 --> 00:20:53.824 but it's because there's such desperation

NOTE Confidence: 0.7868047

00:20:53.824 --> 00:20:55.883 in this community to understand why

NOTE Confidence: 0.7868047

00:20:55.883 --> 00:20:58.049 their children sleep is so dysfunctional.

NOTE Confidence: 0.7868047

00:20:58.050 --> 00:20:59.386 So there's some evidence.

NOTE Confidence: 0.7868047

00:20:59.386 --> 00:21:01.056 When I started my work,

NOTE Confidence: 0.7868047

00:21:01.060 --> 00:21:02.890 there was already some evidence that

NOTE Confidence: 0.7868047

00:21:02.890 --> 00:21:04.786 in Drosophila and even in mouse

NOTE Confidence: 0.7868047

00:21:04.786 --> 00:21:06.646 models that are tubers process pathway,

NOTE Confidence: 0.7868047

00:21:06.650 --> 00:21:07.874 my impact circadian rhythms.

NOTE Confidence: 0.7868047

00:21:07.874 --> 00:21:09.710 I won't take you through all

NOTE Confidence: 0.7868047

00:21:09.763 --> 00:21:11.318 the complexity of this slide,

NOTE Confidence: 0.7868047

00:21:11.320 --> 00:21:13.528 but I just wanted to point out this

NOTE Confidence: 0.7868047

00:21:13.528 --> 00:21:15.785 is work done by Anita Sehgal's lab

NOTE Confidence: 0.7868047

00:21:15.785 --> 00:21:18.778 that when when you block the function of TSC,

NOTE Confidence: 0.7868047

00:21:18.780 --> 00:21:20.804 one in Clock cells in the in the

NOTE Confidence: 0.7868047

00:21:20.804 --> 00:21:22.845 flies you lose this normal gating

NOTE Confidence: 0.7868047

00:21:22.845 --> 00:21:24.685 of weight rest activity cycles.

NOTE Confidence: 0.7868047

00:21:24.690 --> 00:21:26.520 So suggested that if you block

NOTE Confidence: 0.7868047

00:21:26.520 --> 00:21:28.419 the TSC function in this case,

NOTE Confidence: 0.7868047

00:21:28.420 --> 00:21:29.122 it's TSC,

NOTE Confidence: 0.7868047

00:21:29.122 --> 00:21:31.228 one you can disrupt circadian rhythms.

NOTE Confidence: 0.7868047

00:21:31.230 --> 00:21:32.634 Around the same time,

NOTE Confidence: 0.7868047

00:21:32.634 --> 00:21:34.740 roofing Cole was working in Carlow.

NOTE Confidence: 0.7868047

00:21:34.740 --> 00:21:36.405 Britain's lab started looking at

NOTE Confidence: 0.7868047

00:21:36.405 --> 00:21:38.479 kinase kinase pathways in the Super

NOTE Confidence: 0.7868047

00:21:38.479 --> 00:21:40.249 chiasmatic nucleus and how they

NOTE Confidence: 0.7868047

00:21:40.249 --> 00:21:42.078 impact rhythmic behavior and he

NOTE Confidence: 0.7868047

00:21:42.078 --> 00:21:43.494 basically found that application

NOTE Confidence: 0.7868047

00:21:43.494 --> 00:21:45.264 of rapper Meissen could change

NOTE Confidence: 0.7868047

00:21:45.270 --> 00:21:47.030 the phase of freerunning rhythms,

NOTE Confidence: 0.7868047

00:21:47.030 --> 00:21:49.196 again suggesting that the M Tor

NOTE Confidence: 0.7868047

00:21:49.196 --> 00:21:51.381 pathway is regulating the light and

NOTE Confidence: 0.7868047

00:21:51.381 --> 00:21:53.397 then a light light sensitivity and

NOTE Confidence: 0.7868047

00:21:53.397 --> 00:21:55.161 also the underlying rhythmicity of

NOTE Confidence: 0.7868047

00:21:55.161 --> 00:21:57.909 the of the Clock and you can see

NOTE Confidence: 0.7868047

00:21:57.909 --> 00:22:00.003 here that rapper mice and causes

NOTE Confidence: 0.7868047

00:22:00.003 --> 00:22:01.890 a blockade of the normal.

NOTE Confidence: 0.7868047

00:22:01.890 --> 00:22:03.858 Phase changes that you can see

NOTE Confidence: 0.7868047

00:22:03.858 --> 00:22:04.842 impacted by light.

NOTE Confidence: 0.7868047

00:22:04.850 --> 00:22:05.116 OK,

NOTE Confidence: 0.7868047

00:22:05.116 --> 00:22:06.978 so this suggested that the M Tor

NOTE Confidence: 0.7868047

00:22:06.978 --> 00:22:08.902 pathway is required for normal

NOTE Confidence: 0.7868047

00:22:08.902 --> 00:22:09.786 circadian function,

NOTE Confidence: 0.7868047

00:22:09.790 --> 00:22:11.624 so we sought to study this in

NOTE Confidence: 0.7868047

00:22:11.624 --> 00:22:13.730 a model of tourists corrosive.

NOTE Confidence: 0.7868047

00:22:13.730 --> 00:22:16.033 So we have two two mouse models

NOTE Confidence: 0.7868047

00:22:16.033 --> 00:22:17.020 that we studied.

NOTE Confidence: 0.7868047

00:22:17.020 --> 00:22:19.568 This in first is a heterozygote model

NOTE Confidence: 0.7868047

00:22:19.568 --> 00:22:22.620 where you lose one copy of the TSC 2 gene.

NOTE Confidence: 0.7868047

00:22:22.620 --> 00:22:25.464 We have to study it this way because if

NOTE Confidence: 0.7868047

00:22:25.464 --> 00:22:28.208 you lose a both copies in an animal,

NOTE Confidence: 0.7868047

00:22:28.210 --> 00:22:30.834 its embryonic lethal and the animal will die,

NOTE Confidence: 0.7868047

00:22:30.840 --> 00:22:33.588 but the heterozygous.

NOTE Confidence: 0.7868047

00:22:33.590 --> 00:22:35.400 Survives and has various problems,

NOTE Confidence: 0.7868047

00:22:35.400 --> 00:22:36.752 including various cognitive problems

NOTE Confidence: 0.7868047

00:22:36.752 --> 00:22:38.780 and various of problems with synaptic

NOTE Confidence: 0.7868047

00:22:38.830 --> 00:22:40.108 plasticity and excitability,

NOTE Confidence: 0.7868047

00:22:40.110 --> 00:22:42.385 and to make a Long story short

NOTE Confidence: 0.7868047

00:22:42.385 --> 00:22:43.360 where we basically

NOTE Confidence: 0.81360114

00:22:43.431 --> 00:22:45.819 found is that there is a

NOTE Confidence: 0.81360114

00:22:45.819 --> 00:22:46.615 significant shortening,

NOTE Confidence: 0.81360114

00:22:46.620 --> 00:22:49.154 a free running period in these animals.

NOTE Confidence: 0.81360114

00:22:49.160 --> 00:22:52.072 So what we're looking at here is we

NOTE Confidence: 0.81360114

00:22:52.072 --> 00:22:55.267 are running so you can see the mice in

NOTE Confidence: 0.81360114

00:22:55.267 --> 00:22:57.840 train normally to a light dark cycle.

NOTE Confidence: 0.81360114

00:22:57.840 --> 00:23:00.012 I'll remind you that mice that

NOTE Confidence: 0.81360114

00:23:00.012 --> 00:23:02.152 we study are nocturnal, so there.

NOTE Confidence: 0.81360114

00:23:02.152 --> 00:23:04.574 Active in the dark and then they

NOTE Confidence: 0.81360114

00:23:04.574 --> 00:23:06.420 basically as soon as the lights

NOTE Confidence: 0.81360114

00:23:06.420 --> 00:23:08.546 come on they could be taken apps

NOTE Confidence: 0.81360114

00:23:08.546 --> 00:23:11.050 and then if you put them in darkness

NOTE Confidence: 0.81360114

00:23:11.050 --> 00:23:13.185 which will do is they you uncover

NOTE Confidence: 0.81360114

00:23:13.185 --> 00:23:14.863 the underlying rhythmicity of the

NOTE Confidence: 0.81360114

00:23:14.863 --> 00:23:16.287 free running oscillator dictated

NOTE Confidence: 0.81360114

00:23:16.287 --> 00:23:17.984 by the suprachiasmatic nucleus and

NOTE Confidence: 0.81360114

00:23:17.984 --> 00:23:18.876 the mice will run.

NOTE Confidence: 0.81360114

00:23:18.880 --> 00:23:21.064 And the reason why you see this graph

NOTE Confidence: 0.81360114

00:23:21.064 --> 00:23:23.376 sort of move this way is because

NOTE Confidence: 0.81360114

00:23:23.376 --> 00:23:25.076 the underlying periodicity of a

NOTE Confidence: 0.81360114

00:23:25.142 --> 00:23:27.326 mouse is usually less than 24 hours,

NOTE Confidence: 0.81360114

00:23:27.330 --> 00:23:29.514 at least of this strain of mouse.

NOTE Confidence: 0.81360114

00:23:29.520 --> 00:23:31.788 And so we were able to compare

NOTE Confidence: 0.81360114

00:23:31.788 --> 00:23:32.760 these these periods.

NOTE Confidence: 0.81360114

00:23:32.760 --> 00:23:34.734 Between Gina types and so we did

NOTE Confidence: 0.81360114

00:23:34.734 --> 00:23:37.019 that you can see that there's a

NOTE Confidence: 0.81360114

00:23:37.019 --> 00:23:38.739 significant shortening in the in

NOTE Confidence: 0.81360114

00:23:38.739 --> 00:23:40.029 the in the mutant,

NOTE Confidence: 0.81360114

00:23:40.030 --> 00:23:42.235 and then if we apply rappa mice

NOTE Confidence: 0.81360114

00:23:42.235 --> 00:23:43.500 and again remember Rep,

NOTE Confidence: 0.81360114

00:23:43.500 --> 00:23:45.789 my Son is going to now block

NOTE Confidence: 0.81360114

00:23:45.789 --> 00:23:47.299 the function of M Tor,

NOTE Confidence: 0.81360114

00:23:47.300 --> 00:23:49.820 so it should rescue some of these phenotypes.

NOTE Confidence: 0.81360114

00:23:49.820 --> 00:23:51.400 We were able to completely

NOTE Confidence: 0.81360114

00:23:51.400 --> 00:23:52.348 block this abnormality.

NOTE Confidence: 0.81360114

00:23:52.350 --> 00:23:54.387 We then use the more severe model

NOTE Confidence: 0.81360114

00:23:54.387 --> 00:23:55.999 and this model lacks completely

NOTE Confidence: 0.81360114

00:23:55.999 --> 00:23:58.358 knocks out one copy of this case,

NOTE Confidence: 0.81360114

00:23:58.360 --> 00:24:00.624 TSC one and I'll just mention that TSC

NOTE Confidence: 0.81360114

00:24:00.624 --> 00:24:03.157 one and TSC 2 have largely overlapping.

NOTE Confidence: 0.81360114

00:24:03.160 --> 00:24:04.500 Functions that's not entirely

NOTE Confidence: 0.81360114

00:24:04.500 --> 00:24:05.779 fair to 100% true,

NOTE Confidence: 0.81360114

00:24:05.779 --> 00:24:07.931 but we can think of them for this

NOTE Confidence: 0.81360114

00:24:07.931 --> 00:24:10.219 talk is having overlapping functions,

NOTE Confidence: 0.81360114

00:24:10.220 --> 00:24:12.523 and in this case what we did

NOTE Confidence: 0.81360114

00:24:12.523 --> 00:24:13.910 is we knocked TSC,

NOTE Confidence: 0.81360114

00:24:13.910 --> 00:24:16.052 one out of all post mitotic neurons

NOTE Confidence: 0.81360114

00:24:16.052 --> 00:24:17.940 using a synapse incread driver.

NOTE Confidence: 0.81360114

00:24:17.940 --> 00:24:19.956 So this is a transgenic animal

NOTE Confidence: 0.81360114

00:24:19.956 --> 00:24:21.300 that is expressing this.

NOTE Confidence: 0.81360114

00:24:21.300 --> 00:24:22.230 This double transgenic,

NOTE Confidence: 0.81360114

00:24:22.230 --> 00:24:24.400 and so all TSC one is lossed

NOTE Confidence: 0.81360114

00:24:24.460 --> 00:24:26.008 from post mitotic neurons.

NOTE Confidence: 0.81360114

00:24:26.010 --> 00:24:27.936 What we did is because these

NOTE Confidence: 0.81360114

00:24:27.936 --> 00:24:30.040 animals get quite sick after birth.

NOTE Confidence: 0.81360114

00:24:30.040 --> 00:24:32.134 We treated them with rapper Meissen

NOTE Confidence: 0.81360114

00:24:32.134 --> 00:24:33.530 until they reached adulthood.

NOTE Confidence: 0.81360114

00:24:33.530 --> 00:24:34.822 Enemy in the meantime,

NOTE Confidence: 0.81360114

00:24:34.822 --> 00:24:37.240 we implanted them with the data logger,

NOTE Confidence: 0.81360114

00:24:37.240 --> 00:24:39.683 so we're able to follow their temperature

NOTE Confidence: 0.81360114

00:24:39.683 --> 00:24:42.289 rhythms and to make a Long story short,

NOTE Confidence: 0.81360114

00:24:42.290 --> 00:24:44.426 we really see is that in the mutant

NOTE Confidence: 0.81360114

00:24:44.426 --> 00:24:45.906 there's a complete disruption

NOTE Confidence: 0.81360114

00:24:45.906 --> 00:24:48.106 of this rhythmicity under free

NOTE Confidence: 0.81360114

00:24:48.106 --> 00:24:50.029 running conditions when we now

NOTE Confidence: 0.81360114

00:24:50.029 --> 00:24:51.384 apply a light dark cycle,

NOTE Confidence: 0.81360114

00:24:51.390 --> 00:24:53.406 they can actually regain their rhythmicity,

NOTE Confidence: 0.81360114

00:24:53.410 --> 00:24:55.432 but it suggests that the underlying

NOTE Confidence: 0.81360114

00:24:55.432 --> 00:24:56.780 oscillations in the SCN,

NOTE Confidence: 0.81360114

00:24:56.780 --> 00:24:58.470 and potentially in their outputs,

NOTE Confidence: 0.81360114

00:24:58.470 --> 00:24:59.478 is fundamentally dysfunctional.

NOTE Confidence: 0.81360114

00:24:59.478 --> 00:25:03.158 Without TSC. Without normal mtor function.

NOTE Confidence: 0.81360114

00:25:03.160 --> 00:25:04.900 So we were really interested.

NOTE Confidence: 0.81360114

00:25:04.900 --> 00:25:07.336 Now we had this this mouse phenotype.

NOTE Confidence: 0.81360114

00:25:07.340 --> 00:25:09.629 We were really interested in sort of

NOTE Confidence: 0.81360114

00:25:09.629 --> 00:25:11.398 delving into what's the underlying

NOTE Confidence: 0.81360114

00:25:11.398 --> 00:25:13.570 biology that might underlie it and

NOTE Confidence: 0.81360114

00:25:13.570 --> 00:25:15.492 so remember, TSE is blocking mtor.

NOTE Confidence: 0.81360114

00:25:15.492 --> 00:25:17.280 We were really wondering about now

NOTE Confidence: 0.81360114

00:25:17.340 --> 00:25:19.180 what is the relationship between

NOTE Confidence: 0.81360114

00:25:19.180 --> 00:25:21.020 mtor dysfunction and the fundamental

NOTE Confidence: 0.81360114

00:25:21.073 --> 00:25:22.300 Clock mechanism itself?

NOTE Confidence: 0.81360114

00:25:22.300 --> 00:25:24.388 So again, to remind you guys,

NOTE Confidence: 0.81360114

00:25:24.390 --> 00:25:27.174 the Clock is present in all cells of

NOTE Confidence: 0.81360114

00:25:27.174 --> 00:25:29.958 the body, at least for the most part,

NOTE Confidence: 0.81360114

00:25:29.960 --> 00:25:33.182 and it is built on a negative feedback loop.

NOTE Confidence: 0.83465445

00:25:33.190 --> 00:25:35.703 Which was described by over over several

NOTE Confidence: 0.83465445

00:25:35.703 --> 00:25:38.968 decades and in 2017 was awarded the Nobel

NOTE Confidence: 0.83465445

00:25:38.968 --> 00:25:41.088 Prize for Understanding this mechanism

NOTE Confidence: 0.83465445

00:25:41.159 --> 00:25:43.375 to briefly sum it up for you guys,

NOTE Confidence: 0.83465445

00:25:43.380 --> 00:25:47.020 you have be Model 1 and this is in mammals.

NOTE Confidence: 0.83465445

00:25:47.020 --> 00:25:48.328 You have female one.

NOTE Confidence: 0.83465445

00:25:48.328 --> 00:25:50.707 In Clock they form a partnership and

NOTE Confidence: 0.83465445

00:25:50.707 --> 00:25:53.171 they bind to DNA and regulate the

NOTE Confidence: 0.83465445

00:25:53.171 --> 00:25:55.164 rhythmic expression of thousands of

NOTE Confidence: 0.83465445

00:25:55.164 --> 00:25:57.209 genes including their own inhibitors.

NOTE Confidence: 0.83465445

00:25:57.210 --> 00:25:59.639 And in this case it's the period

NOTE Confidence: 0.83465445

00:25:59.639 --> 00:26:02.199 jeans and the cryptochrome genes.

NOTE Confidence: 0.83465445

00:26:02.200 --> 00:26:04.517 Whose products go out into the cytoplasm

NOTE Confidence: 0.83465445

00:26:04.517 --> 00:26:07.170 and come back in and block the function?

NOTE Confidence: 0.83465445

00:26:07.170 --> 00:26:09.714 Have email 1:00 o'clock and so you have

NOTE Confidence: 0.83465445

00:26:09.714 --> 00:26:11.911 this iterative feedback loop that by which

NOTE Confidence: 0.83465445

00:26:11.911 --> 00:26:14.360 a system is driving its own inhibition,

NOTE Confidence: 0.83465445

00:26:14.360 --> 00:26:15.995 and that the loop itself

NOTE Confidence: 0.83465445

00:26:15.995 --> 00:26:17.303 takes about 24 hours.

NOTE Confidence: 0.83465445

00:26:17.310 --> 00:26:18.618 Now obviously this is

NOTE Confidence: 0.83465445

00:26:18.618 --> 00:26:19.599 extraordinarily pared down.

NOTE Confidence: 0.83465445

00:26:19.600 --> 00:26:20.776 It's way more complicated,

NOTE Confidence: 0.83465445

00:26:20.776 --> 00:26:23.520 and this is a slightly more detailed version,

NOTE Confidence: 0.83465445

00:26:23.520 --> 00:26:25.809 and it's even more complicated than this,

NOTE Confidence: 0.83465445

00:26:25.810 --> 00:26:27.634 but we don't have time to

NOTE Confidence: 0.83465445

00:26:27.634 --> 00:26:29.729 dive into all of that today,

NOTE Confidence: 0.83465445

00:26:29.730 --> 00:26:32.019 but I'll go back for a moment.

NOTE Confidence: 0.83465445

00:26:32.020 --> 00:26:34.141 Most of my work is really been

NOTE Confidence: 0.83465445

00:26:34.141 --> 00:26:35.620 about this single protein,

NOTE Confidence: 0.83465445

00:26:35.620 --> 00:26:38.014 bmal one because we found direct links.

NOTE Confidence: 0.83465445

00:26:38.020 --> 00:26:40.510 Between TSC dysfunction of the mtor

NOTE Confidence: 0.83465445

00:26:40.510 --> 00:26:43.468 pathway and bmal one and so I'm going

NOTE Confidence: 0.83465445

00:26:43.468 --> 00:26:46.409 to show you now all that all that data.

NOTE Confidence: 0.83465445

00:26:46.410 --> 00:26:47.340 So wide email,

NOTE Confidence: 0.83465445

00:26:47.340 --> 00:26:47.960 one email.

NOTE Confidence: 0.83465445

00:26:47.960 --> 00:26:50.327 One of the reason our it was our focus

NOTE Confidence: 0.83465445

00:26:50.327 --> 00:26:52.586 is because without the email one,

NOTE Confidence: 0.83465445

00:26:52.590 --> 00:26:54.438 you lose almost all circadian rhythmicity.

NOTE Confidence: 0.83465445

00:26:54.440 --> 00:26:56.920 So this is a female one knockout mouse.

NOTE Confidence: 0.83465445

00:26:56.920 --> 00:26:58.768 Here you have these nice ensconce

NOTE Confidence: 0.83465445

00:26:58.768 --> 00:26:59.384 circadian rhythms.

NOTE Confidence: 0.83465445

00:26:59.390 --> 00:27:01.546 That's all lost in the female knockout.

NOTE Confidence: 0.83465445

00:27:01.550 --> 00:27:03.536 Here you have cells expressing circadian

NOTE Confidence: 0.83465445

00:27:03.536 --> 00:27:05.568 Reporter without the Mail in the black.

NOTE Confidence: 0.83465445

00:27:05.570 --> 00:27:07.110 You lose those oscillations completely,

NOTE Confidence: 0.83465445

00:27:07.110 --> 00:27:09.903 so the take home message is you

NOTE Confidence: 0.83465445

00:27:09.903 --> 00:27:13.478 need to be mailed to have a rhythm.

NOTE Confidence: 0.83465445

00:27:13.480 --> 00:27:15.839 So we initially started this work by

NOTE Confidence: 0.83465445

00:27:15.839 --> 00:27:18.507 looking at TSC cells that lacked TSC 2.

NOTE Confidence: 0.83465445

00:27:18.510 --> 00:27:20.758 So we took cells that either had the

NOTE Confidence: 0.83465445

00:27:20.758 --> 00:27:23.503 gene or lack the gene completely and we

NOTE Confidence: 0.83465445

00:27:23.503 --> 00:27:25.333 just started doing some investigations

NOTE Confidence: 0.83465445

00:27:25.333 --> 00:27:28.555 and we found this is just a Western blot.

NOTE Confidence: 0.83465445

00:27:28.560 --> 00:27:30.898 So for those of you not familiar,

NOTE Confidence: 0.83465445

00:27:30.900 --> 00:27:32.976 basically the black lines represent the

NOTE Confidence: 0.83465445

00:27:32.976 --> 00:27:34.724 black smudges here represent specific

NOTE Confidence: 0.83465445

00:27:34.724 --> 00:27:36.596 proteins and don't worry about it.

NOTE Confidence: 0.83465445

00:27:36.600 --> 00:27:38.945 For those of you who are not

NOTE Confidence: 0.83465445

00:27:38.945 --> 00:27:39.950 familiar with it,

NOTE Confidence: 0.83465445

00:27:39.950 --> 00:27:42.150 don't worry about the the

NOTE Confidence: 0.83465445

00:27:42.150 --> 00:27:43.910 technique or the underlying.

NOTE Confidence: 0.83465445

00:27:43.910 --> 00:27:45.246 Looking at the plot,

NOTE Confidence: 0.83465445

00:27:45.246 --> 00:27:47.250 even I'll just type to give

NOTE Confidence: 0.83465445

00:27:47.320 --> 00:27:49.130 you the take home message,

NOTE Confidence: 0.83465445

00:27:49.130 --> 00:27:50.970 which is that females elevated

NOTE Confidence: 0.83465445

00:27:50.970 --> 00:27:53.309 so in cells that lack TSC 2,

NOTE Confidence: 0.83465445

00:27:53.310 --> 00:27:55.781 there's more female OK and in the

NOTE Confidence: 0.83465445

00:27:55.781 --> 00:27:58.565 brain you can see that in a wild

NOTE Confidence: 0.83465445

00:27:58.565 --> 00:28:01.330 type rain or normal brain we can see

NOTE Confidence: 0.83465445

00:28:01.330 --> 00:28:03.745 this rhythm of female in the cortex

NOTE Confidence: 0.83465445

00:28:03.750 --> 00:28:07.327 worth peaks around early end of the.

NOTE Confidence: 0.83465445

00:28:07.330 --> 00:28:09.986 Sleep period and then in the mutant brain.

NOTE Confidence: 0.83465445

00:28:09.990 --> 00:28:12.144 This rhythm is largely disrupted such

NOTE Confidence: 0.83465445

00:28:12.144 --> 00:28:14.966 that it's just kind of high all the time,

NOTE Confidence: 0.83465445

00:28:14.970 --> 00:28:16.470 OK?

NOTE Confidence: 0.83465445

00:28:16.470 --> 00:28:18.672 We then did this very sophisticated

NOTE Confidence: 0.83465445

00:28:18.672 --> 00:28:20.140 biochemical assay that don't

NOTE Confidence: 0.83465445

00:28:20.202 --> 00:28:21.578 worry about the details,

NOTE Confidence: 0.83465445

00:28:21.580 --> 00:28:23.728 but the details basically show that

NOTE Confidence: 0.83465445

00:28:23.728 --> 00:28:26.306 the amount of email that's being made

NOTE Confidence: 0.83465445

00:28:26.306 --> 00:28:28.812 or the bounce of protein synthesis of

NOTE Confidence: 0.8427988

00:28:28.884 --> 00:28:31.074 female is elevated about 50% when

NOTE Confidence: 0.8427988

00:28:31.074 --> 00:28:33.258 you lose the tubers grossis complex.

NOTE Confidence: 0.8427988

00:28:33.260 --> 00:28:35.450 So the idea is that without

NOTE Confidence: 0.8427988

00:28:35.450 --> 00:28:36.180 regulated interactivity,

NOTE Confidence: 0.8427988

00:28:36.180 --> 00:28:38.010 you have exuberant protein synthesis,

NOTE Confidence: 0.8427988

00:28:38.010 --> 00:28:40.481 and one of the proteins that get

NOTE Confidence: 0.8427988

00:28:40.481 --> 00:28:43.117 that gets over produced is be male,

NOTE Confidence: 0.8427988

00:28:43.120 --> 00:28:45.418 and so that was important because

NOTE Confidence: 0.8427988

00:28:45.418 --> 00:28:47.570 that could explain why we have.

NOTE Confidence: 0.8427988

00:28:47.570 --> 00:28:51.177 More bemelen these cells. OK.

NOTE Confidence: 0.8427988

00:28:51.177 --> 00:28:53.619 So yeah, so there there's more

NOTE Confidence: 0.8427988

00:28:53.619 --> 00:28:56.092 female here in the mutant than

NOTE Confidence: 0.8427988

00:28:56.092 --> 00:28:58.420 there is in the wild type.

NOTE Confidence: 0.8427988

00:28:58.420 --> 00:28:59.920 OK, so in addition,

NOTE Confidence: 0.8427988

00:28:59.920 --> 00:29:01.795 the other thing that regulates

NOTE Confidence: 0.8427988

00:29:01.795 --> 00:29:03.953 how much protein there is in a

NOTE Confidence: 0.8427988

00:29:03.953 --> 00:29:06.252 cell is it how much is produced

NOTE Confidence: 0.8427988

00:29:06.252 --> 00:29:08.430 and how much gets broken down.

NOTE Confidence: 0.8427988

00:29:08.430 --> 00:29:10.117 And we knew from work for many

NOTE Confidence: 0.8427988

00:29:10.117 --> 00:29:12.111 of many many groups that female

NOTE Confidence: 0.8427988

00:29:12.111 --> 00:29:13.727 is actually under regulated

NOTE Confidence: 0.8427988

00:29:13.727 --> 00:29:15.670 proteostasis or regulated degradation,

NOTE Confidence: 0.8427988

00:29:15.670 --> 00:29:17.700 and so we sought to understand whether

NOTE Confidence: 0.8427988

00:29:17.700 --> 00:29:19.848 or not that degradation was also

NOTE Confidence: 0.8427988

00:29:19.848 --> 00:29:21.878 disrupted in our mutant background.

NOTE Confidence: 0.8427988

00:29:21.880 --> 00:29:23.128 So very interesting, Lee.

NOTE Confidence: 0.8427988

00:29:23.128 --> 00:29:25.000 The the gene that regulates the

NOTE Confidence: 0.8427988

00:29:25.059 --> 00:29:26.571 degradation of female excitingly

NOTE Confidence: 0.8427988

00:29:26.571 --> 00:29:28.839 happens to be this ubiquitin ligase,

NOTE Confidence: 0.8427988

00:29:28.840 --> 00:29:31.122 this enzyme called UBE 3A and to

NOTE Confidence: 0.8427988

00:29:31.122 --> 00:29:33.628 those of you who are in the know,

NOTE Confidence: 0.8427988

00:29:33.630 --> 00:29:35.121 you'll know that you be 3 is

NOTE Confidence: 0.8427988

00:29:35.121 --> 00:29:37.013 thought to be the causative protein

NOTE Confidence: 0.8427988

00:29:37.013 --> 00:29:38.613 for another newer developmental

NOTE Confidence: 0.8427988

00:29:38.613 --> 00:29:40.330 syndrome called Angelmann syndrome.

NOTE Confidence: 0.8427988

00:29:40.330 --> 00:29:42.584 So already there's kind of this really

NOTE Confidence: 0.8427988

00:29:42.584 --> 00:29:44.542 from the perspective of a pediatric

NOTE Confidence: 0.8427988

00:29:44.542 --> 00:29:46.408 neurologist at there's a lot of

NOTE Confidence: 0.8427988

00:29:46.408 --> 00:29:47.978 excitement here because you know,

NOTE Confidence: 0.8427988

00:29:47.980 --> 00:29:49.852 we're starting to understand how there's

NOTE Confidence: 0.8427988

00:29:49.852 --> 00:29:52.129 two risk arose as complex through M,

NOTE Confidence: 0.8427988

00:29:52.130 --> 00:29:53.890 Tor and now we have.

NOTE Confidence: 0.8427988

00:29:53.890 --> 00:29:54.769 Investigation of the,

NOTE Confidence: 0.8427988

00:29:54.769 --> 00:29:55.062 UH,

NOTE Confidence: 0.8427988

00:29:55.062 --> 00:29:56.527 the this Clock protein is

NOTE Confidence: 0.8427988

00:29:56.527 --> 00:29:58.395 being dysregulated and we know

NOTE Confidence: 0.8427988

00:29:58.395 --> 00:30:00.295 it's also regulated by another

NOTE Confidence: 0.8427988

00:30:00.295 --> 00:30:01.609 neurodevelopmental syndrome protein.

NOTE Confidence: 0.8427988

00:30:01.610 --> 00:30:03.619 So you start to sort of imagine

NOTE Confidence: 0.8427988

00:30:03.619 --> 00:30:05.682 how the Clock can be integrating

NOTE Confidence: 0.8427988

00:30:05.682 --> 00:30:07.944 a lot of these different neural

NOTE Confidence: 0.8427988

00:30:07.944 --> 00:30:10.359 pathways that are very relevant

NOTE Confidence: 0.8427988

00:30:10.359 --> 00:30:11.838 to neurodevelopmental diseases.

NOTE Confidence: 0.8427988

00:30:11.840 --> 00:30:12.207 Interestingly,

NOTE Confidence: 0.8427988

00:30:12.207 --> 00:30:14.776 in addition to this protein that can

NOTE Confidence: 0.8427988

00:30:14.776 --> 00:30:16.860 promote the degradation of female,

NOTE Confidence: 0.8427988

00:30:16.860 --> 00:30:18.790 there also enzymes that can

NOTE Confidence: 0.8427988

00:30:18.790 --> 00:30:20.720 block the degradation of email,

NOTE Confidence: 0.8427988

00:30:20.720 --> 00:30:22.650 and they're called deubiquitinase is,

NOTE Confidence: 0.8427988

00:30:22.650 --> 00:30:25.086 and one that's been described in

NOTE Confidence: 0.8427988

00:30:25.086 --> 00:30:27.279 the literature is called USP 9X.

NOTE Confidence: 0.8427988

00:30:27.280 --> 00:30:29.849 And wouldn't you know it is also

NOTE Confidence: 0.8427988

00:30:29.849 --> 00:30:31.910 responsible for a excellent **

NOTE Confidence: 0.8427988

00:30:31.910 --> 00:30:33.638 linked intellectual disability and

NOTE Confidence: 0.8427988

00:30:33.638 --> 00:30:35.366 highly linked to synaptogenesis

NOTE Confidence: 0.8427988

00:30:35.366 --> 00:30:37.240 and fundamental synaptic function?

NOTE Confidence: 0.8427988

00:30:37.240 --> 00:30:37.584 OK,

NOTE Confidence: 0.8427988

00:30:37.584 --> 00:30:39.648 so our hypothesis was that this

NOTE Confidence: 0.8427988

00:30:39.648 --> 00:30:41.976 degradation of the Mail might be

NOTE Confidence: 0.8427988

00:30:41.976 --> 00:30:44.016 disrupted in the tubers chlorosis

NOTE Confidence: 0.8427988

00:30:44.016 --> 00:30:46.183 background where you have exuberant

NOTE Confidence: 0.8427988

00:30:46.183 --> 00:30:48.318 production and we have disrupted

NOTE Confidence: 0.8427988

00:30:48.318 --> 00:30:49.920 proteostasis in the cell.

NOTE Confidence: 0.8427988

00:30:49.920 --> 00:30:52.510 So this is the sort of fundamental

NOTE Confidence: 0.8427988

00:30:52.510 --> 00:30:55.451 seesaw now you have you be 3 driving

NOTE Confidence: 0.8427988

00:30:55.451 --> 00:30:57.753 the degradation and you have ESPN

NOTE Confidence: 0.8427988

00:30:57.753 --> 00:31:00.075 X USP 9X blocking the degradation.

NOTE Confidence: 0.8427988

00:31:00.080 --> 00:31:01.220 So first of all,

NOTE Confidence: 0.8427988

00:31:01.220 --> 00:31:03.280 don't worry about all the details here,

NOTE Confidence: 0.8427988

00:31:03.280 --> 00:31:05.215 but I'll just show you is if you do

NOTE Confidence: 0.8427988

00:31:05.215 --> 00:31:07.359 a degradation assay for bnymellon,

NOTE Confidence: 0.8427988

00:31:07.360 --> 00:31:09.100 you compare a wild type cells

NOTE Confidence: 0.8427988

00:31:09.100 --> 00:31:09.970 to mutant cells,

NOTE Confidence: 0.8427988

00:31:09.970 --> 00:31:12.535 which you can see is as the female protein

NOTE Confidence: 0.8427988

00:31:12.535 --> 00:31:14.338 degrades overtime in the wild type.

NOTE Confidence: 0.8427988

00:31:14.340 --> 00:31:16.086 It doesn't degrade in the mutant.

NOTE Confidence: 0.8427988

00:31:16.090 --> 00:31:18.120 In fact it doesn't degrade it almost.

NOTE Confidence: 0.8427988

00:31:18.120 --> 00:31:20.094 And if you do that using alive

NOTE Confidence: 0.8427988

00:31:20.094 --> 00:31:21.908 Reporter you can sort of report.

NOTE Confidence: 0.8427988

00:31:21.910 --> 00:31:23.524 They almost in real time this

NOTE Confidence: 0.8427988

00:31:23.524 --> 00:31:25.213 degradation and you can see that

NOTE Confidence: 0.8427988

00:31:25.213 --> 00:31:26.608 the decorative the half life

NOTE Confidence: 0.8427988

00:31:26.608 --> 00:31:27.445 of degradation is

NOTE Confidence: 0.81159353

00:31:27.502 --> 00:31:29.177 markedly elevated in the mutants,

NOTE Confidence: 0.81159353

00:31:29.180 --> 00:31:30.902 suggesting that there's a real problem

NOTE Confidence: 0.81159353

00:31:30.902 --> 00:31:33.130 not only with the production of email.

NOTE Confidence: 0.81159353

00:31:33.130 --> 00:31:35.888 But with the the degradation of female.

NOTE Confidence: 0.81159353

00:31:35.890 --> 00:31:38.106 And so this is a very busy slide.

NOTE Confidence: 0.81159353

00:31:38.110 --> 00:31:40.334 I won't spend too much time on it,

NOTE Confidence: 0.81159353

00:31:40.340 --> 00:31:43.556 but just to show you that basically the.

NOTE Confidence: 0.81159353

00:31:43.560 --> 00:31:45.978 We think the reason for this

NOTE Confidence: 0.81159353

00:31:45.978 --> 00:31:48.560 degradation I'll you know I'll skip

NOTE Confidence: 0.81159353

00:31:48.560 --> 00:31:51.242 all the Western blots 'cause it's

NOTE Confidence: 0.81159353

00:31:51.242 --> 00:31:53.339 probably painful is a disrupted.

NOTE Confidence: 0.81159353

00:31:53.340 --> 00:31:55.215 Disrupted balance of the Association

NOTE Confidence: 0.81159353

00:31:55.215 --> 00:31:57.410 of female with UV3A and USP,

NOTE Confidence: 0.81159353

00:31:57.410 --> 00:31:58.499 9X so affectively.

NOTE Confidence: 0.81159353

00:31:58.499 --> 00:32:01.040 More of the female is being protected

NOTE Confidence: 0.81159353

00:32:01.110 --> 00:32:03.055 from degradation so there being

NOTE Confidence: 0.81159353

00:32:03.055 --> 00:32:05.414 more produced and not enough is

NOTE Confidence: 0.81159353

00:32:05.414 --> 00:32:07.478 being degraded and that's the take

NOTE Confidence: 0.81159353

00:32:07.478 --> 00:32:09.694 home message of this of this slide

NOTE Confidence: 0.81159353

00:32:09.694 --> 00:32:12.300 we used a drug that can block this

NOTE Confidence: 0.81159353

00:32:12.300 --> 00:32:14.960 deubiquitinase so we can we can enhance

NOTE Confidence: 0.81159353

00:32:14.960 --> 00:32:17.389 the ubiquitination and doing so.

NOTE Confidence: 0.81159353

00:32:17.390 --> 00:32:20.302 We are now trying to test this in

NOTE Confidence: 0.81159353

00:32:20.302 --> 00:32:23.489 animal models of TSC to see if it can

NOTE Confidence: 0.81159353

00:32:23.489 --> 00:32:25.990 actually rescue some of the phenotypes.

NOTE Confidence: 0.81159353

00:32:25.990 --> 00:32:28.078 And I'll show you data in a moment

NOTE Confidence: 0.81159353

00:32:28.078 --> 00:32:30.021 to see why that actually might

NOTE Confidence: 0.81159353

00:32:30.021 --> 00:32:32.049 be a reasonable thing to try.

NOTE Confidence: 0.81159353

00:32:32.050 --> 00:32:33.868 So if we block USP 9X,

NOTE Confidence: 0.81159353

00:32:33.870 --> 00:32:35.082 we can completely suppress

NOTE Confidence: 0.81159353

00:32:35.082 --> 00:32:35.688 circadian amplitude.

NOTE Confidence: 0.81159353

00:32:35.690 --> 00:32:37.454 So this is like higher and

NOTE Confidence: 0.81159353

00:32:37.454 --> 00:32:39.020 higher doses of the drug.

NOTE Confidence: 0.81159353

00:32:39.020 --> 00:32:40.838 This drug that blocks USP 9X,

NOTE Confidence: 0.81159353

00:32:40.840 --> 00:32:42.350 which is now going to

NOTE Confidence: 0.81159353

00:32:42.350 --> 00:32:43.256 enhance females degradation.

NOTE Confidence: 0.81159353

00:32:43.260 --> 00:32:43.850 And remember,

NOTE Confidence: 0.81159353

00:32:43.850 --> 00:32:46.900 I told you that if you don't have the email,

NOTE Confidence: 0.81159353

00:32:46.900 --> 00:32:49.014 you're not going to have a Clock,

NOTE Confidence: 0.81159353

00:32:49.020 --> 00:32:50.838 and that's what this would support.

NOTE Confidence: 0.81159353

00:32:50.840 --> 00:32:52.658 So as you degrade the email

NOTE Confidence: 0.81159353

00:32:52.658 --> 00:32:53.870 you degrade the Clock.

NOTE Confidence: 0.81159353

00:32:53.870 --> 00:32:55.585 So that's sort of proof

NOTE Confidence: 0.81159353

00:32:55.585 --> 00:32:57.300 of principle that this is.

NOTE Confidence: 0.81159353

00:32:57.300 --> 00:32:58.785 Mechanistically sound idea.

NOTE Confidence: 0.81159353

00:32:58.785 --> 00:33:02.250 So this is really where we are

NOTE Confidence: 0.81159353

00:33:02.343 --> 00:33:04.479 at this part of the talk.

NOTE Confidence: 0.81159353

00:33:04.480 --> 00:33:07.448 We have the TSC pathway which regulates mtor.

NOTE Confidence: 0.81159353

00:33:07.450 --> 00:33:09.606 It regulates then be Mal and and

NOTE Confidence: 0.81159353

00:33:09.606 --> 00:33:11.417 the degradation of email through

NOTE Confidence: 0.81159353

00:33:11.417 --> 00:33:13.472 the relative involvement of either

NOTE Confidence: 0.81159353

00:33:13.472 --> 00:33:15.531 ubiquitin ligase or a deubiquitinase

NOTE Confidence: 0.81159353

00:33:15.531 --> 00:33:17.817 which are working in opposition to

NOTE Confidence: 0.81159353

00:33:17.817 --> 00:33:19.940 one another to balance the amount

NOTE Confidence: 0.81159353

00:33:19.940 --> 00:33:22.720 of email that you have and what we

NOTE Confidence: 0.81159353

00:33:22.720 --> 00:33:24.718 have in the TSC mutant background

NOTE Confidence: 0.81159353

00:33:24.718 --> 00:33:27.581 is we have exuberant mtor and we

NOTE Confidence: 0.81159353

00:33:27.581 --> 00:33:29.706 basically have an upregulation of

NOTE Confidence: 0.81159353

00:33:29.710 --> 00:33:32.338 the amount of email that's made.

NOTE Confidence: 0.81159353

00:33:32.340 --> 00:33:34.517 And too little of it being thrown

NOTE Confidence: 0.81159353

00:33:34.517 --> 00:33:35.450 in the trash,

NOTE Confidence: 0.81159353

00:33:35.450 --> 00:33:37.376 so there's almost like 2 problems

NOTE Confidence: 0.81159353

00:33:37.376 --> 00:33:39.646 that are being that are being sort

NOTE Confidence: 0.81159353

00:33:39.646 --> 00:33:41.494 of working in cahoots to corrupt

NOTE Confidence: 0.81159353

00:33:41.494 --> 00:33:43.322 the Clock here by just making

NOTE Confidence: 0.81159353

00:33:43.322 --> 00:33:44.772 the Mail all the time.

NOTE Confidence: 0.81159353

00:33:44.780 --> 00:33:46.335 And that's what we think

NOTE Confidence: 0.81159353

00:33:46.335 --> 00:33:47.890 is part of the phenotype.

NOTE Confidence: 0.81159353

00:33:47.890 --> 00:33:51.570 And I'll show you data to support that.

NOTE Confidence: 0.81159353

00:33:51.570 --> 00:33:51.799 OK,

NOTE Confidence: 0.81159353

00:33:51.799 --> 00:33:53.173 so you have this seesaw and

NOTE Confidence: 0.81159353

00:33:53.173 --> 00:33:54.843 the see saw is imbalanced so

NOTE Confidence: 0.81159353

00:33:54.843 --> 00:33:56.378 that there's too much female.

NOTE Confidence: 0.81159353

00:33:56.380 --> 00:33:57.664 That's basically the message.

NOTE Confidence: 0.81159353

00:33:57.664 --> 00:33:59.590 Don't worry about all the Westerns

NOTE Confidence: 0.81159353

00:33:59.640 --> 00:34:01.400 and all that other all the IPS and

NOTE Confidence: 0.81159353

00:34:01.400 --> 00:34:03.047 all these liquid in assays we do.

NOTE Confidence: 0.81159353

00:34:03.050 --> 00:34:05.202 We do all these like assays that are

NOTE Confidence: 0.81159353

00:34:05.202 --> 00:34:07.317 that take a long time to explain it.

NOTE Confidence: 0.81159353

00:34:07.320 --> 00:34:09.296 I would love to do so if those

NOTE Confidence: 0.81159353

00:34:09.296 --> 00:34:11.330 of you want to hear about it.

NOTE Confidence: 0.81159353

00:34:11.330 --> 00:34:12.926 I'm happy to talk about it,

NOTE Confidence: 0.81159353

00:34:12.930 --> 00:34:14.316 but I think from a messaging

NOTE Confidence: 0.81159353

00:34:14.316 --> 00:34:15.240 standpoint this is the

NOTE Confidence: 0.7896459

00:34:15.291 --> 00:34:16.535 message abnormal mtor abnormal

NOTE Confidence: 0.7896459

00:34:16.535 --> 00:34:19.360 amounts of email, disrupted Clock.

NOTE Confidence: 0.7896459

00:34:19.360 --> 00:34:21.610 So this is a friend of mine is a

NOTE Confidence: 0.7896459

00:34:21.610 --> 00:34:23.914 very well known artist and so she

NOTE Confidence: 0.7896459

00:34:23.914 --> 00:34:26.048 designed this for my for my lab.

NOTE Confidence: 0.7896459

00:34:26.050 --> 00:34:28.442 This is like a nice alarm Clock where

NOTE Confidence: 0.7896459

00:34:28.442 --> 00:34:30.994 you know be Mail in the shadow of TSC.

NOTE Confidence: 0.7896459

00:34:31.000 --> 00:34:32.590 Bmal is running away with the

NOTE Confidence: 0.7896459

00:34:32.590 --> 00:34:34.490 the the Clock it's causing havoc.

NOTE Confidence: 0.7896459

00:34:34.490 --> 00:34:36.527 These little guys are making a mess.

NOTE Confidence: 0.7896459

00:34:36.530 --> 00:34:39.218 OK so this is.

NOTE Confidence: 0.7896459

00:34:39.220 --> 00:34:42.410 I, for those of you hating this talk so far.

NOTE Confidence: 0.7896459

00:34:42.410 --> 00:34:44.602 I apologize 'cause this is just the tip

NOTE Confidence: 0.7896459

00:34:44.602 --> 00:34:46.879 of the iceberg because there's all.

NOTE Confidence: 0.7896459

00:34:46.880 --> 00:34:48.470 There's more. There's more details.

NOTE Confidence: 0.7896459

00:34:48.470 --> 00:34:49.750 As you might imagine,

NOTE Confidence: 0.7896459

00:34:49.750 --> 00:34:51.980 but indeed, this is a you know,

NOTE Confidence: 0.7896459

00:34:51.980 --> 00:34:52.940 with an iceberg.

NOTE Confidence: 0.7896459

00:34:52.940 --> 00:34:53.580 Of course,

NOTE Confidence: 0.7896459

00:34:53.580 --> 00:34:55.170 there's this whole underlying biology,

NOTE Confidence: 0.7896459

00:34:55.170 --> 00:34:57.714 and there's a lot more here to unpack,

NOTE Confidence: 0.7896459

00:34:57.720 --> 00:34:59.320 and I'll show you another.

NOTE Confidence: 0.7896459

00:34:59.320 --> 00:35:00.910 Another wrinkle to this story,

NOTE Confidence: 0.7896459

00:35:00.910 --> 00:35:02.510 which I think is interesting.

NOTE Confidence: 0.7896459

00:35:02.510 --> 00:35:04.724 So the next part of the story is how

NOTE Confidence: 0.7896459

00:35:04.724 --> 00:35:06.076 studying tubers chlorosis actually

NOTE Confidence: 0.7896459

00:35:06.076 --> 00:35:07.826 taught us something new about

NOTE Confidence: 0.7896459

00:35:07.826 --> 00:35:09.839 what the circadian clocks doing.

NOTE Confidence: 0.7896459

00:35:09.840 --> 00:35:11.850 What I've shown you so far.

NOTE Confidence: 0.7896459

00:35:11.850 --> 00:35:13.656 Is how the Clock is disrupted in

NOTE Confidence: 0.7896459

00:35:13.656 --> 00:35:15.729 a model of TSC and now what I'm

NOTE Confidence: 0.7896459

00:35:15.729 --> 00:35:17.702 going to show you is based on

NOTE Confidence: 0.7896459

00:35:17.702 --> 00:35:19.387 those those findings and thinking

NOTE Confidence: 0.7896459

00:35:19.387 --> 00:35:21.255 a little more deeply about what

NOTE Confidence: 0.7896459

00:35:21.255 --> 00:35:22.680 we actually were showing here.

NOTE Confidence: 0.7896459

00:35:22.680 --> 00:35:24.984 We were able to find something new about

NOTE Confidence: 0.7896459

00:35:24.984 --> 00:35:26.957 the circadian Clock and an actual show.

NOTE Confidence: 0.7896459

00:35:26.960 --> 00:35:28.670 You some new data from my

NOTE Confidence: 0.7896459

00:35:28.670 --> 00:35:29.810 lab that shows something.

NOTE Confidence: 0.7896459

00:35:29.810 --> 00:35:32.288 I think it's really, really interesting.

NOTE Confidence: 0.7896459

00:35:32.290 --> 00:35:34.160 So again to remind you,

NOTE Confidence: 0.7896459

00:35:34.160 --> 00:35:36.398 the mtor pathway is is this

NOTE Confidence: 0.7896459

00:35:36.398 --> 00:35:37.890 crucial regulator of growth,

NOTE Confidence: 0.7896459

00:35:37.890 --> 00:35:40.438 and it's disrupted in TSC and one

NOTE Confidence: 0.7896459

00:35:40.438 --> 00:35:43.477 of the main things that M Tor does.

NOTE Confidence: 0.7896459

00:35:43.480 --> 00:35:45.718 It regulates growth through making protein,

NOTE Confidence: 0.7896459

00:35:45.720 --> 00:35:48.564 and so we thought a lot about if if

NOTE Confidence: 0.7896459

00:35:48.564 --> 00:35:50.201 emptores dysregulating bmal couldn't

NOTE Confidence: 0.7896459

00:35:50.201 --> 00:35:53.550 be doing so by what it usually does,

NOTE Confidence: 0.7896459

00:35:53.550 --> 00:35:55.420 which is by phosphorylating proteins,

NOTE Confidence: 0.7896459

00:35:55.420 --> 00:35:56.491 it's a kainic,

NOTE Confidence: 0.7896459

00:35:56.491 --> 00:35:57.919 so kindly phosphorylates proteins

NOTE Confidence: 0.7896459

00:35:57.919 --> 00:36:00.270 and one of the core regulators,

NOTE Confidence: 0.7896459

00:36:00.270 --> 00:36:02.979 or one of the core outputs rather.

NOTE Confidence: 0.7896459

00:36:02.980 --> 00:36:05.476 Event or is this Chinese called

NOTE Confidence: 0.7896459

00:36:05.476 --> 00:36:07.605 S6K1 and S6K1 phosphorylates many

NOTE Confidence: 0.7896459

00:36:07.605 --> 00:36:09.580 translation factors and to summarize

NOTE Confidence: 0.7896459

00:36:09.580 --> 00:36:12.480 six years of my life in one slide.

NOTE Confidence: 0.7896459

00:36:12.480 --> 00:36:15.252 What we found is we found that

NOTE Confidence: 0.7896459

00:36:15.252 --> 00:36:16.440 S6K1 phosphorylates female,

NOTE Confidence: 0.7896459

00:36:16.440 --> 00:36:18.816 so the Mail is a substrate

NOTE Confidence: 0.7896459

00:36:18.816 --> 00:36:20.400 of the mtor pathway.

NOTE Confidence: 0.7896459

00:36:20.400 --> 00:36:22.776 So not only is mtor regulating

NOTE Confidence: 0.7896459

00:36:22.776 --> 00:36:24.360 the production of email,

NOTE Confidence: 0.7896459

00:36:24.360 --> 00:36:26.736 and not only is it regulating

NOTE Confidence: 0.7896459

00:36:26.736 --> 00:36:28.320 the degradation of email,

NOTE Confidence: 0.7896459

00:36:28.320 --> 00:36:30.395 it's actually modulating the email

NOTE Confidence: 0.7896459

00:36:30.395 --> 00:36:33.270 itself through this S6K1 and also other.

NOTE Confidence: 0.7896459

00:36:33.270 --> 00:36:35.030 One other kinase as well,

NOTE Confidence: 0.7896459

00:36:35.030 --> 00:36:37.178 but it it it basically phosphorylating

NOTE Confidence: 0.7896459

00:36:37.178 --> 00:36:39.344 this protein and what it does

NOTE Confidence: 0.7896459

00:36:39.344 --> 00:36:41.009 is the phosphorylation of bmal,

NOTE Confidence: 0.7896459

00:36:41.010 --> 00:36:43.098 then mediates be males interaction with

NOTE Confidence: 0.7896459

00:36:43.098 --> 00:36:44.890 the protein synthesis machinery itself.

NOTE Confidence: 0.7896459

00:36:44.890 --> 00:36:46.418 So remember, be males,

NOTE Confidence: 0.7896459

00:36:46.418 --> 00:36:47.946 a transcription factor that

NOTE Confidence: 0.7896459

00:36:47.946 --> 00:36:50.256 spends most of its life in the

NOTE Confidence: 0.7896459

00:36:50.256 --> 00:36:52.539 nucleus and it's been studied as a

NOTE Confidence: 0.7896459

00:36:52.539 --> 00:36:54.389 transcription factor for two decades.

NOTE Confidence: 0.7896459

00:36:54.390 --> 00:36:56.861 So this was a little bit of

NOTE Confidence: 0.7896459

00:36:56.861 --> 00:36:58.260 heresy to sort of,

NOTE Confidence: 0.7896459

00:36:58.260 --> 00:37:00.040 start proposing that a Clock

NOTE Confidence: 0.7896459

00:37:00.040 --> 00:37:02.555 transcription factor has this role in a

NOTE Confidence: 0.7896459

00:37:02.555 --> 00:37:04.250 fundamental process in the cytoplasm,

NOTE Confidence: 0.7896459

00:37:04.250 --> 00:37:05.150 namely.

NOTE Confidence: 0.7896459

00:37:05.150 --> 00:37:06.950 Protein synthesis.

NOTE Confidence: 0.7896459

00:37:06.950 --> 00:37:09.638 And so to make a Long story short,

NOTE Confidence: 0.8405372

00:37:09.640 --> 00:37:12.055 we found that female interacts with this

NOTE Confidence: 0.8405372

00:37:12.055 --> 00:37:14.010 whole translation machinery in the cytoplasm,

NOTE Confidence: 0.8405372

00:37:14.010 --> 00:37:15.615 and these are just like

NOTE Confidence: 0.8405372

00:37:15.615 --> 00:37:16.578 immunoprecipitations showing like

NOTE Confidence: 0.8405372

00:37:16.578 --> 00:37:17.700 individual translational regulators.

NOTE Confidence: 0.8405372

00:37:17.700 --> 00:37:19.380 So this whole initiation complexes,

NOTE Confidence: 0.8405372

00:37:19.380 --> 00:37:21.438 which you probably learned in biochemistry

NOTE Confidence: 0.8405372

00:37:21.438 --> 00:37:23.409 and we're very happy to forget,

NOTE Confidence: 0.8405372

00:37:23.410 --> 00:37:25.090 but are very important in

NOTE Confidence: 0.8405372

00:37:25.090 --> 00:37:26.434 the production of protein.

NOTE Confidence: 0.8405372

00:37:26.440 --> 00:37:28.702 We found that female can actually

NOTE Confidence: 0.8405372

00:37:28.702 --> 00:37:30.551 associate with those proteins both

NOTE Confidence: 0.8405372

00:37:30.551 --> 00:37:32.490 in cells and in liver and brain,

NOTE Confidence: 0.8405372

00:37:32.490 --> 00:37:34.290 and we found actually that it

NOTE Confidence: 0.8405372

00:37:34.290 --> 00:37:36.850 can do so in a rhythmic manner,

NOTE Confidence: 0.8405372

00:37:36.850 --> 00:37:38.266 so females Association.

NOTE Confidence: 0.8405372

00:37:38.266 --> 00:37:40.626 With the translation machinery actually

NOTE Confidence: 0.8405372

00:37:40.626 --> 00:37:42.910 demonstrates just circadian oscillation.

NOTE Confidence: 0.8405372

00:37:42.910 --> 00:37:43.342 And.

NOTE Confidence: 0.8405372

00:37:43.342 --> 00:37:45.934 What the important part of this

NOTE Confidence: 0.8405372

00:37:45.934 --> 00:37:48.399 graph is really just to show,

NOTE Confidence: 0.8405372

00:37:48.400 --> 00:37:50.086 So what you're looking at here

NOTE Confidence: 0.8405372

00:37:50.086 --> 00:37:52.129 is the interaction of female with

NOTE Confidence: 0.8405372

00:37:52.129 --> 00:37:53.857 these different translation factors.

NOTE Confidence: 0.8405372

00:37:53.860 --> 00:37:56.247 So everywhere you see this black band,

NOTE Confidence: 0.8405372

00:37:56.250 --> 00:37:58.110 you're saying that the female is

NOTE Confidence: 0.8405372

00:37:58.110 --> 00:38:00.160 actually pulling down this protein when

NOTE Confidence: 0.8405372

00:38:00.160 --> 00:38:02.040 we mutated that phosphorylation site,

NOTE Confidence: 0.8405372

00:38:02.040 --> 00:38:04.086 so that one single amino acid

NOTE Confidence: 0.8405372

00:38:04.086 --> 00:38:05.450 where mtor phosphorylates it.

NOTE Confidence: 0.8405372

00:38:05.450 --> 00:38:07.496 If we mutate that site so

NOTE Confidence: 0.8405372

00:38:07.496 --> 00:38:08.860 it can't get phosphorylated,

NOTE Confidence: 0.8405372

00:38:08.860 --> 00:38:10.570 none of these proteins interact,

NOTE Confidence: 0.8405372

00:38:10.570 --> 00:38:12.724 so now none of the translation

NOTE Confidence: 0.8405372

00:38:12.724 --> 00:38:14.660 machinery can interact with female.

NOTE Confidence: 0.8405372

00:38:14.660 --> 00:38:16.683 And when we add the Mou into

NOTE Confidence: 0.8405372

00:38:16.683 --> 00:38:19.063 cells and look at the amount of

NOTE Confidence: 0.8405372

00:38:19.063 --> 00:38:20.507 protein that's being made,

NOTE Confidence: 0.8405372

00:38:20.510 --> 00:38:22.140 the more bmal you add,

NOTE Confidence: 0.8405372

00:38:22.140 --> 00:38:23.760 the more protein you make.

NOTE Confidence: 0.8405372

00:38:23.760 --> 00:38:26.360 But if you make this single point mutation,

NOTE Confidence: 0.8405372

00:38:26.360 --> 00:38:26.960 nothing happens.

NOTE Confidence: 0.8405372

00:38:26.960 --> 00:38:29.360 You can add as much as you want

NOTE Confidence: 0.8405372

00:38:29.430 --> 00:38:31.560 and you'll never get more protein.

NOTE Confidence: 0.8405372

00:38:31.560 --> 00:38:33.250 So this basically nominated this

NOTE Confidence: 0.8405372

00:38:33.250 --> 00:38:35.300 transcription factor in the Clock as

NOTE Confidence: 0.8405372

00:38:35.300 --> 00:38:37.414 a translation factor as a regulator of

NOTE Confidence: 0.8405372

00:38:37.414 --> 00:38:39.357 protein synthesis through the mtor pathway.

NOTE Confidence: 0.8405372

00:38:39.360 --> 00:38:42.267 And this is showing if we now take cells

NOTE Confidence: 0.8405372

00:38:42.267 --> 00:38:44.868 and we synchronize them in a dish.

NOTE Confidence: 0.8405372

00:38:44.870 --> 00:38:46.748 We can actually see a rhythm.

NOTE Confidence: 0.8405372

00:38:46.750 --> 00:38:48.310 This is every four hours.

NOTE Confidence: 0.8405372

00:38:48.310 --> 00:38:50.494 We can see a rhythm of high,

NOTE Confidence: 0.8405372

00:38:50.500 --> 00:38:50.804 low,

NOTE Confidence: 0.8405372

00:38:50.804 --> 00:38:52.324 high low protein synthesis that

NOTE Confidence: 0.8405372

00:38:52.324 --> 00:38:53.950 where we lose by email.

NOTE Confidence: 0.8405372

00:38:53.950 --> 00:38:55.624 You can see there's this rhythm

NOTE Confidence: 0.8405372

00:38:55.624 --> 00:38:57.661 but it starts to degrade by the

NOTE Confidence: 0.8405372

00:38:57.661 --> 00:38:59.656 2nd cycle so it can't maintain the

NOTE Confidence: 0.8405372

00:38:59.719 --> 00:39:01.251 oscillation without having female

NOTE Confidence: 0.8405372

00:39:01.251 --> 00:39:02.400 in the cell.

NOTE Confidence: 0.8405372

00:39:02.400 --> 00:39:04.518 To get this phosphorylation signal to

NOTE Confidence: 0.8405372

00:39:04.518 --> 00:39:07.739 tell it to make protein at the right time.

NOTE Confidence: 0.8405372

00:39:07.740 --> 00:39:09.370 So that's summarized here and

NOTE Confidence: 0.8405372

00:39:09.370 --> 00:39:11.480 I just want to say again,

NOTE Confidence: 0.8405372

00:39:11.480 --> 00:39:14.248 this is 5 1/2 years of work that

NOTE Confidence: 0.8405372

00:39:14.248 --> 00:39:16.238 I'm summarizing in in 20 seconds.

NOTE Confidence: 0.8405372

00:39:16.240 --> 00:39:17.968 But the point I wanted to make is

NOTE Confidence: 0.8405372

00:39:17.968 --> 00:39:19.694 that the email is this critical

NOTE Confidence: 0.8405372

00:39:19.694 --> 00:39:21.548 component of the circadian Clock that

NOTE Confidence: 0.8405372

00:39:21.604 --> 00:39:23.239 undergoes rhythmic phosphorylation

NOTE Confidence: 0.8405372

00:39:23.239 --> 00:39:25.419 Association with translation machinery,

NOTE Confidence: 0.8405372

00:39:25.420 --> 00:39:27.604 and in so doing contributes to an

NOTE Confidence: 0.8405372

00:39:27.604 --> 00:39:29.160 oscillation in protein synthesis.

NOTE Confidence: 0.8405372

00:39:29.160 --> 00:39:31.512 So we learn something new about

NOTE Confidence: 0.8405372

00:39:31.512 --> 00:39:34.053 the Clock from starting with this

NOTE Confidence: 0.8405372

00:39:34.053 --> 00:39:35.857 clinical question about TSC.

NOTE Confidence: 0.8405372

00:39:35.860 --> 00:39:37.988 So now what I'm going to show you

NOTE Confidence: 0.8405372

00:39:37.988 --> 00:39:40.085 is just a couple of pieces of

NOTE Confidence: 0.8405372

00:39:40.085 --> 00:39:41.866 data where we now asked, OK,

NOTE Confidence: 0.8405372

00:39:41.866 --> 00:39:43.296 well this protein gets phosphorylated.

NOTE Confidence: 0.8405372

00:39:43.300 --> 00:39:45.580 What does that mean? What does it do?

NOTE Confidence: 0.8405372

00:39:45.580 --> 00:39:47.296 Does it do anything like that?

NOTE Confidence: 0.8405372

00:39:47.300 --> 00:39:49.703 When I showed you all this stuff is in

NOTE Confidence: 0.8405372

00:39:49.703 --> 00:39:52.155 cells and and cell lines in cell culture,

NOTE Confidence: 0.8405372

00:39:52.160 --> 00:39:53.540 does this thing actually do

NOTE Confidence: 0.8405372

00:39:53.540 --> 00:39:55.310 anything in the in the brain?

NOTE Confidence: 0.8405372

00:39:55.310 --> 00:39:57.880 And this is new work from my lab and because

NOTE Confidence: 0.83106023

00:39:57.944 --> 00:40:00.456 of the function of female in the cytoplasm,

NOTE Confidence: 0.83106023

00:40:00.460 --> 00:40:02.170 we started looking at neurons neurons.

NOTE Confidence: 0.83106023

00:40:02.170 --> 00:40:03.634 As you know, are these incredibly

NOTE Confidence: 0.83106023

00:40:03.634 --> 00:40:04.610 beautiful nuclei with these

NOTE Confidence: 0.83106023

00:40:04.657 --> 00:40:05.938 incredibly elaborated cytoplasm.

NOTE Confidence: 0.83106023

00:40:05.940 --> 00:40:07.876 And the cytoplasm is where I would argue

NOTE Confidence: 0.83106023

00:40:07.876 --> 00:40:09.927 alot of the interesting stuff happens.

NOTE Confidence: 0.83106023

00:40:09.930 --> 00:40:12.140 You have all the synaptic

NOTE Confidence: 0.83106023

00:40:12.140 --> 00:40:13.466 connections and synaptic.

NOTE Confidence: 0.83106023

00:40:13.470 --> 00:40:15.325 Transmission and also the the

NOTE Confidence: 0.83106023

00:40:15.325 --> 00:40:17.180 interaction of cells with one

NOTE Confidence: 0.83106023

00:40:17.247 --> 00:40:19.669 another and for a variety of reasons

NOTE Confidence: 0.83106023

00:40:19.669 --> 00:40:21.588 we started looking at the mound,

NOTE Confidence: 0.83106023

00:40:21.590 --> 00:40:23.345 the cytoplasm and what we've

NOTE Confidence: 0.83106023

00:40:23.345 --> 00:40:25.470 discovered since this work is work,

NOTE Confidence: 0.83106023

00:40:25.470 --> 00:40:27.468 we're about to send out for

NOTE Confidence: 0.83106023

00:40:27.468 --> 00:40:28.800 publication is we discovered

NOTE Confidence: 0.83106023

00:40:28.864 --> 00:40:30.769 that female is actually present,

NOTE Confidence: 0.83106023

00:40:30.770 --> 00:40:32.530 not just in the cytoplasm,

NOTE Confidence: 0.83106023

00:40:32.530 --> 00:40:34.721 But actually act synapses and so all

NOTE Confidence: 0.83106023

00:40:34.721 --> 00:40:36.930 these white dots that you see here

NOTE Confidence: 0.83106023

00:40:36.930 --> 00:40:38.736 in the hippocampus with the mouse

NOTE Confidence: 0.83106023

00:40:38.804 --> 00:40:41.004 are actually places where female

NOTE Confidence: 0.83106023

00:40:41.004 --> 00:40:42.764 colocalizes with defined synapses,

NOTE Confidence: 0.83106023

00:40:42.770 --> 00:40:45.020 and we found that the phosphorylated

NOTE Confidence: 0.83106023

00:40:45.020 --> 00:40:47.668 form of the protein does so as well,

NOTE Confidence: 0.83106023

00:40:47.670 --> 00:40:50.310 and this is looking at females

NOTE Confidence: 0.83106023

00:40:50.310 --> 00:40:52.070 colocalization with synapses in

NOTE Confidence: 0.83106023

00:40:52.146 --> 00:40:54.486 in hippocampal neurons in a dish.

NOTE Confidence: 0.83106023

00:40:54.490 --> 00:40:56.392 We also did this by looking

NOTE Confidence: 0.83106023

00:40:56.392 --> 00:40:57.343 at the ultrastructure,

NOTE Confidence: 0.83106023

00:40:57.350 --> 00:40:59.252 so in this case we used

NOTE Confidence: 0.83106023

00:40:59.252 --> 00:41:00.203 immunogold to basically,

NOTE Confidence: 0.83106023

00:41:00.210 --> 00:41:02.436 which uses a gold particle that's later,

NOTE Confidence: 0.83106023

00:41:02.440 --> 00:41:04.030 that's connected to an antibody,

NOTE Confidence: 0.83106023

00:41:04.030 --> 00:41:05.615 and in this case the

NOTE Confidence: 0.83106023

00:41:05.615 --> 00:41:06.883 antibody is against female,

NOTE Confidence: 0.83106023

00:41:06.890 --> 00:41:09.158 and then you can penetrate mouse tissue

NOTE Confidence: 0.83106023

00:41:09.158 --> 00:41:11.530 or any any any any tissue that you

NOTE Confidence: 0.83106023

00:41:11.530 --> 00:41:14.326 can do this in an and would you then

NOTE Confidence: 0.83106023

00:41:14.326 --> 00:41:16.426 do is by doing electron microscopy.

NOTE Confidence: 0.83106023

00:41:16.430 --> 00:41:19.049 You can look at the Indian Gold label as

NOTE Confidence: 0.83106023

00:41:19.049 --> 00:41:21.750 a way of seeing the female molecules and

NOTE Confidence: 0.83106023

00:41:21.750 --> 00:41:24.840 so we can see here is that these fuzzy.

NOTE Confidence: 0.83106023

00:41:24.840 --> 00:41:26.388 Fuzzy shapes here are actual synapses.

NOTE Confidence: 0.83106023

00:41:26.390 --> 00:41:27.438 That's the postsynaptic density

NOTE Confidence: 0.83106023

00:41:27.438 --> 00:41:29.010 in the presynaptic side where you

NOTE Confidence: 0.83106023

00:41:29.051 --> 00:41:30.256 can see the synaptic vesicles,

NOTE Confidence: 0.83106023

00:41:30.260 --> 00:41:31.926 and once you'll notice is that there's

NOTE Confidence: 0.83106023

00:41:31.926 --> 00:41:33.510 lots of female at these presynaptic

NOTE Confidence: 0.83106023

00:41:33.510 --> 00:41:35.154 vesicles and this is the knockout,

NOTE Confidence: 0.83106023

00:41:35.160 --> 00:41:36.642 just to show that the antibody

NOTE Confidence: 0.83106023

00:41:36.642 --> 00:41:38.000 is specific to be melon,

NOTE Confidence: 0.83106023

00:41:38.000 --> 00:41:40.076 not just labeling some garbage in

NOTE Confidence: 0.83106023

00:41:40.076 --> 00:41:42.789 the in the in the in the brain.

NOTE Confidence: 0.83106023

00:41:42.790 --> 00:41:43.161 Uhm?

NOTE Confidence: 0.83106023

00:41:43.161 --> 00:41:43.532 OK,

NOTE Confidence: 0.83106023

00:41:43.532 --> 00:41:46.500 I think I am running short on time,

NOTE Confidence: 0.83106023

00:41:46.500 --> 00:41:48.552 so I'm going to skip that so we so

NOTE Confidence: 0.83106023

00:41:48.552 --> 00:41:50.760 in order to study what this thing,

NOTE Confidence: 0.83106023

00:41:50.760 --> 00:41:52.356 what this phosphorylation system is doing,

NOTE Confidence: 0.83106023

00:41:52.360 --> 00:41:53.950 we made a mouse using CRISPR.

NOTE Confidence: 0.83106023

00:41:53.950 --> 00:41:57.040 So we knocked out this single.

NOTE Confidence: 0.83106023

00:41:57.040 --> 00:41:58.986 We know that we made a change

NOTE Confidence: 0.83106023

00:41:58.986 --> 00:42:00.660 in the single amino acids,

NOTE Confidence: 0.83106023

00:42:00.660 --> 00:42:02.568 so the protein cannot get phosphorylated

NOTE Confidence: 0.83106023

00:42:02.568 --> 00:42:04.590 and consistent with our work in cells.

NOTE Confidence: 0.83106023

00:42:04.590 --> 00:42:06.396 We found that the phosphorylation had no

NOTE Confidence: 0.83106023

00:42:06.396 --> 00:42:07.911 effect on the transcriptional oscillation

NOTE Confidence: 0.83106023

00:42:07.911 --> 00:42:10.326 in circadian rhythms and as a result,

NOTE Confidence: 0.83106023

00:42:10.330 --> 00:42:12.591 circadian behavior as driven by the Super

NOTE Confidence: 0.83106023

00:42:12.591 --> 00:42:14.249 chiasmatic nucleus seems to be normal.

NOTE Confidence: 0.83106023

00:42:14.250 --> 00:42:16.062 So here you can see like

NOTE Confidence: 0.83106023

00:42:16.062 --> 00:42:17.270 the free running period.

NOTE Confidence: 0.83106023

00:42:17.270 --> 00:42:18.780 I didn't show the quantification,

NOTE Confidence: 0.83106023

00:42:18.780 --> 00:42:20.866 but there's no difference between a cohort

NOTE Confidence: 0.83106023

00:42:20.866 --> 00:42:23.009 of wild type and of mutant animals,

NOTE Confidence: 0.83106023

00:42:23.010 --> 00:42:25.124 so this was not surprising to us.

NOTE Confidence: 0.83106023

00:42:25.130 --> 00:42:26.382 We weren't really expecting

NOTE Confidence: 0.83106023

00:42:26.382 --> 00:42:27.947 to see a global change.

NOTE Confidence: 0.83106023

00:42:27.950 --> 00:42:29.090 In circadian behavior,

NOTE Confidence: 0.83106023

00:42:29.090 --> 00:42:31.750 but it got interesting is we started

NOTE Confidence: 0.83106023

00:42:31.823 --> 00:42:33.468 to delve into the neurobiology

NOTE Confidence: 0.83106023

00:42:33.468 --> 00:42:35.890 and there's a lot on this slide,

NOTE Confidence: 0.83106023

00:42:35.890 --> 00:42:38.778 so I'm just going to summarize it quickly.

NOTE Confidence: 0.83106023

00:42:38.780 --> 00:42:39.099 Basically,

NOTE Confidence: 0.83106023

00:42:39.099 --> 00:42:41.332 what we found is that in mutant

NOTE Confidence: 0.83106023

00:42:41.332 --> 00:42:41.970 animals that

NOTE Confidence: 0.8213236

00:42:42.031 --> 00:42:43.827 lack this phosphorylation site,

NOTE Confidence: 0.8213236

00:42:43.830 --> 00:42:45.912 they reduce the amount of neurotransmitter

NOTE Confidence: 0.8213236

00:42:45.912 --> 00:42:48.170 that they can release in hippocampus,

NOTE Confidence: 0.8213236

00:42:48.170 --> 00:42:50.330 and they have evidence of presynaptic

NOTE Confidence: 0.8213236

00:42:50.330 --> 00:42:52.550 dysfunction, which this is an asset

NOTE Confidence: 0.8213236

00:42:52.550 --> 00:42:54.410 that basically measures the probability

NOTE Confidence: 0.8213236

00:42:54.470 --> 00:42:56.570 of release and a a increased increased

NOTE Confidence: 0.8213236

00:42:56.570 --> 00:42:58.730 dip here is basically effective.

NOTE Confidence: 0.8213236

00:42:58.730 --> 00:43:01.130 Of a impaired release of neurotransmitter,

NOTE Confidence: 0.8213236

00:43:01.130 --> 00:43:03.902 there's no change in the actual synapse

NOTE Confidence: 0.8213236

00:43:03.902 --> 00:43:06.727 number between the wildtype in the mutant,

NOTE Confidence: 0.8213236

00:43:06.730 --> 00:43:09.130 yet the network dysfunction in these

NOTE Confidence: 0.8213236

00:43:09.130 --> 00:43:10.730 animals is very dysfunctional,

NOTE Confidence: 0.8213236

00:43:10.730 --> 00:43:13.794 so this is long term potentiation where you

NOTE Confidence: 0.8213236

00:43:13.794 --> 00:43:17.529 use a stimulation to see how long can they.

NOTE Confidence: 0.8213236

00:43:17.530 --> 00:43:19.138 A network maintain dysfunction,

NOTE Confidence: 0.8213236

00:43:19.138 --> 00:43:21.550 and what you can see is

NOTE Confidence: 0.8213236

00:43:21.628 --> 00:43:23.528 that it can maintain that.

NOTE Confidence: 0.8213236

00:43:23.530 --> 00:43:25.930 Maintain the signature of of potentiation.

NOTE Confidence: 0.8213236

00:43:25.930 --> 00:43:28.828 It just does so much lower level.

NOTE Confidence: 0.8213236

00:43:28.830 --> 00:43:31.788 We think because it's not releasing

NOTE Confidence: 0.8213236

00:43:31.788 --> 00:43:33.267 as many vesicles.

NOTE Confidence: 0.8213236

00:43:33.270 --> 00:43:35.280 And this is the interesting part

NOTE Confidence: 0.8213236

00:43:35.280 --> 00:43:38.230 that I I hope will make some sense.

NOTE Confidence: 0.8213236

00:43:38.230 --> 00:43:40.000 Well, we found as though,

NOTE Confidence: 0.8213236

00:43:40.000 --> 00:43:42.070 even though there's no change in

NOTE Confidence: 0.8213236

00:43:42.070 --> 00:43:44.240 the global rhythm of the animal,

NOTE Confidence: 0.8213236

00:43:44.240 --> 00:43:46.750 we found that there is a a a loss of

NOTE Confidence: 0.8213236

00:43:46.825 --> 00:43:49.197 the synaptic vesicle accumulation.

NOTE Confidence: 0.8213236

00:43:49.200 --> 00:43:51.592 So in wild type animals we see that

NOTE Confidence: 0.8213236

00:43:51.592 --> 00:43:54.465 there is a diurnal change in the number

NOTE Confidence: 0.8213236

00:43:54.465 --> 00:43:56.770 of synaptic vesicles we actually counted

NOTE Confidence: 0.8213236

00:43:56.770 --> 00:43:59.437 by hand over 85,000 vesicles from 40

NOTE Confidence: 0.8213236

00:43:59.437 --> 00:44:01.590 to 50 micrographs from different animals,

NOTE Confidence: 0.8213236

00:44:01.590 --> 00:44:05.260 so we are very sure about this data we spent.

NOTE Confidence: 0.8213236

00:44:05.260 --> 00:44:07.018 Many months are counting this and

NOTE Confidence: 0.8213236

00:44:07.018 --> 00:44:09.289 what we see is that there's a

NOTE Confidence: 0.8213236

00:44:09.289 --> 00:44:11.004 diagonal difference in the amount

NOTE Confidence: 0.8213236

00:44:11.004 --> 00:44:13.275 and the number of vesicles that's

NOTE Confidence: 0.8213236

00:44:13.275 --> 00:44:15.180 completely lost in our mutant.

NOTE Confidence: 0.8213236

00:44:15.180 --> 00:44:17.232 So even though the mutants have

NOTE Confidence: 0.8213236

00:44:17.232 --> 00:44:18.600 normal global circadian rhythms,

NOTE Confidence: 0.8213236

00:44:18.600 --> 00:44:19.644 they lose this.

NOTE Confidence: 0.8213236

00:44:19.644 --> 00:44:22.482 What we're calling a local rhythm at the

NOTE Confidence: 0.8213236

00:44:22.482 --> 00:44:25.434 level of the synapse and the key question is,

NOTE Confidence: 0.8213236

00:44:25.440 --> 00:44:28.056 does this mean anything if you know the

NOTE Confidence: 0.8213236

00:44:28.056 --> 00:44:29.880 global circadian behavior is normal?

NOTE Confidence: 0.8213236

00:44:29.880 --> 00:44:31.248 What about other behaviors?

NOTE Confidence: 0.8213236

00:44:31.248 --> 00:44:32.274 So we don't.

NOTE Confidence: 0.8213236

00:44:32.280 --> 00:44:34.555 We put these mice through a battery

NOTE Confidence: 0.8213236

00:44:34.555 --> 00:44:36.150 of different cognitive behaviors.

NOTE Confidence: 0.8213236

00:44:36.150 --> 00:44:38.544 And what's really interesting is that they

NOTE Confidence: 0.8213236

00:44:38.544 --> 00:44:41.463 seem to have a relatively specific defect

NOTE Confidence: 0.8213236

00:44:41.463 --> 00:44:43.743 defect in hippocampal related memory,

NOTE Confidence: 0.8213236

00:44:43.750 --> 00:44:46.053 so this is just showing that the

NOTE Confidence: 0.8213236

00:44:46.053 --> 00:44:48.880 mice do not remember the context in

NOTE Confidence: 0.8213236

00:44:48.880 --> 00:44:51.085 which they've been been delivered

NOTE Confidence: 0.8213236

00:44:51.085 --> 00:44:52.948 a a paired stimulus.

NOTE Confidence: 0.8213236

00:44:52.950 --> 00:44:55.350 So this is a classical measurement

NOTE Confidence: 0.8213236

00:44:55.350 --> 00:44:56.550 for hippocampal memory,

NOTE Confidence: 0.8213236

00:44:56.550 --> 00:44:59.224 and these mice are very dysfunctional in

NOTE Confidence: 0.8213236

00:44:59.224 --> 00:45:02.300 this in this regard, and it actually,

NOTE Confidence: 0.8213236

00:45:02.300 --> 00:45:04.550 this is correlated very nicely

NOTE Confidence: 0.8213236

00:45:04.550 --> 00:45:06.320 with this change in.

NOTE Confidence: 0.8213236

00:45:06.320 --> 00:45:08.030 In the amount of potentiation,

NOTE Confidence: 0.8213236

00:45:08.030 --> 00:45:09.740 because these are often connected

NOTE Confidence: 0.8213236

00:45:09.740 --> 00:45:10.766 to each other,

NOTE Confidence: 0.8213236

00:45:10.770 --> 00:45:12.482 the other Physiology connected

NOTE Confidence: 0.8213236

00:45:12.482 --> 00:45:14.194 to the behavior OK?

NOTE Confidence: 0.8213236

00:45:14.200 --> 00:45:16.713 So I've told you a lot of

NOTE Confidence: 0.8213236

00:45:16.713 --> 00:45:18.580 different things and which is.

NOTE Confidence: 0.8213236

00:45:18.580 --> 00:45:21.084 This is sort of like the word salad

NOTE Confidence: 0.8213236

00:45:21.084 --> 00:45:23.657 of my my professional life and I'll

NOTE Confidence: 0.8213236

00:45:23.657 --> 00:45:26.979 just show you a two more quick things.

NOTE Confidence: 0.8213236

00:45:26.980 --> 00:45:28.800 So again, just to reiterate,

NOTE Confidence: 0.8213236

00:45:28.800 --> 00:45:31.341 we found that the TSC to risk

NOTE Confidence: 0.8213236

00:45:31.341 --> 00:45:32.820 LAROSA'S pathway regulates mtor,

NOTE Confidence: 0.8213236

00:45:32.820 --> 00:45:34.640 and in so doing it,

NOTE Confidence: 0.8213236

00:45:34.640 --> 00:45:36.152 dis regulates circadian rhythms.

NOTE Confidence: 0.8213236

00:45:36.152 --> 00:45:38.042 But we think by disrupting

NOTE Confidence: 0.8213236

00:45:38.042 --> 00:45:39.748 the function of the Mail,

NOTE Confidence: 0.8213236

00:45:39.750 --> 00:45:42.670 and it does so by over phosphorylating it,

NOTE Confidence: 0.8213236

00:45:42.670 --> 00:45:44.590 producing too much of it.

NOTE Confidence: 0.8213236

00:45:44.590 --> 00:45:46.190 And disrupting its proteostasis.

NOTE Confidence: 0.8213236

00:45:46.190 --> 00:45:50.019 And we think this has a disruption of both.

NOTE Confidence: 0.77490693

00:45:50.020 --> 00:45:52.110 Has stands to disrupt both

NOTE Confidence: 0.77490693

00:45:52.110 --> 00:45:53.364 global circadian dynamics.

NOTE Confidence: 0.77490693

00:45:53.370 --> 00:45:55.782 If there's enough disruption of mtor

NOTE Confidence: 0.77490693

00:45:55.782 --> 00:45:57.970 and potentially even local circuit,

NOTE Confidence: 0.77490693

00:45:57.970 --> 00:46:00.435 local synaptic rhythms through this

NOTE Confidence: 0.77490693

00:46:00.435 --> 00:46:01.914 phosphorylation mechanism and.

NOTE Confidence: 0.77490693

00:46:01.920 --> 00:46:04.412 I think some of you might be

NOTE Confidence: 0.77490693

00:46:04.412 --> 00:46:07.036 wondering if what I told you is true.

NOTE Confidence: 0.77490693

00:46:07.040 --> 00:46:09.080 Then one question is as well.

NOTE Confidence: 0.77490693

00:46:09.080 --> 00:46:12.149 If the email is high in models of tubers,

NOTE Confidence: 0.77490693

00:46:12.150 --> 00:46:14.196 sclerosis, and models of TSC loss,

NOTE Confidence: 0.77490693

00:46:14.200 --> 00:46:16.240 what happens if we lowered email?

NOTE Confidence: 0.77490693

00:46:16.240 --> 00:46:18.298 Can we make a difference on these

NOTE Confidence: 0.77490693

00:46:18.298 --> 00:46:20.767 mikes and the answer is yes remarkably

NOTE Confidence: 0.77490693

00:46:20.767 --> 00:46:23.053 so with regard to circadian rhythms,

NOTE Confidence: 0.77490693

00:46:23.060 --> 00:46:25.447 we found that in our mouse model,

NOTE Confidence: 0.77490693

00:46:25.450 --> 00:46:28.178 not only do they have a period defect,

NOTE Confidence: 0.77490693

00:46:28.180 --> 00:46:30.560 but they have this jet lagged effect.

NOTE Confidence: 0.77490693

00:46:30.560 --> 00:46:32.370 So the the mutant animals.

NOTE Confidence: 0.77490693

00:46:32.370 --> 00:46:34.866 Respond to a period shift much more rapidly,

NOTE Confidence: 0.77490693

00:46:34.870 --> 00:46:36.435 almost like an arrow that's

NOTE Confidence: 0.77490693

00:46:36.435 --> 00:46:37.687 been pulled too tight,

NOTE Confidence: 0.77490693

00:46:37.690 --> 00:46:40.194 and when we lower the amount of email,

NOTE Confidence: 0.77490693

00:46:40.200 --> 00:46:42.084 so this is a little counter

NOTE Confidence: 0.77490693

00:46:42.084 --> 00:46:43.706 intuitive because I told you

NOTE Confidence: 0.77490693

00:46:43.706 --> 00:46:45.518 you need the email for o'clock,

NOTE Confidence: 0.77490693

00:46:45.520 --> 00:46:48.016 but you need the right amount of email,

NOTE Confidence: 0.77490693

00:46:48.020 --> 00:46:50.516 so if you lower one copy of email,

NOTE Confidence: 0.77490693

00:46:50.520 --> 00:46:53.340 we could entirely rescue this phenotype.

NOTE Confidence: 0.77490693

00:46:53.340 --> 00:46:53.667 Similarly,

NOTE Confidence: 0.77490693

00:46:53.667 --> 00:46:55.956 we were able to rescue the free

NOTE Confidence: 0.77490693

00:46:55.956 --> 00:46:57.719 running period that I showed you

NOTE Confidence: 0.77490693

00:46:57.719 --> 00:46:59.650 in the very beginning of the talk.

NOTE Confidence: 0.77490693

00:46:59.650 --> 00:47:01.306 In the in the other model,

NOTE Confidence: 0.77490693

00:47:01.310 --> 00:47:02.700 and this is still preliminary,

NOTE Confidence: 0.77490693

00:47:02.700 --> 00:47:04.639 but we are starting to believe it.

NOTE Confidence: 0.77490693

00:47:04.640 --> 00:47:06.474 If you have this model that I

NOTE Confidence: 0.77490693

00:47:06.474 --> 00:47:08.464 showed you where you knock TSC one

NOTE Confidence: 0.77490693

00:47:08.464 --> 00:47:10.174 out of all post mitotic neurons.

NOTE Confidence: 0.77490693

00:47:10.180 --> 00:47:12.910 These animals shown here will die.

NOTE Confidence: 0.77490693

00:47:12.910 --> 00:47:15.214 And this is the control both for the

NOTE Confidence: 0.77490693

00:47:15.214 --> 00:47:17.694 crian the flocks strain, so they don't.

NOTE Confidence: 0.77490693

00:47:17.694 --> 00:47:18.648 They live normalized.

NOTE Confidence: 0.77490693

00:47:18.650 --> 00:47:20.890 If we knock be mild down in.

NOTE Confidence: 0.77490693

00:47:20.890 --> 00:47:21.850 In that background,

NOTE Confidence: 0.77490693

00:47:21.850 --> 00:47:24.390 we can extend the life span almost 50%.

NOTE Confidence: 0.77490693

00:47:24.390 --> 00:47:25.990 We don't know why exactly,

NOTE Confidence: 0.77490693

00:47:25.990 --> 00:47:27.580 but we know we can.

NOTE Confidence: 0.77490693

00:47:27.580 --> 00:47:29.692 And this again is consistent with

NOTE Confidence: 0.77490693

00:47:29.692 --> 00:47:32.834 the idea that email is one of the key

NOTE Confidence: 0.77490693

00:47:32.834 --> 00:47:35.100 downstream regulators of the TSC pathway.

NOTE Confidence: 0.77490693

00:47:35.100 --> 00:47:35.487 OK,

NOTE Confidence: 0.77490693

00:47:35.487 --> 00:47:37.422 so summary tuberculosis mouse models

NOTE Confidence: 0.77490693

00:47:37.422 --> 00:47:38.970 demonstrate abnormal circadian rhythms,

NOTE Confidence: 0.77490693

00:47:38.970 --> 00:47:40.872 which we think is related to

NOTE Confidence: 0.77490693

00:47:40.872 --> 00:47:42.755 a defective balance of female

NOTE Confidence: 0.77490693

00:47:42.755 --> 00:47:44.390 translation and degradation.

NOTE Confidence: 0.77490693

00:47:44.390 --> 00:47:46.320 That ESC pathway regulates circadian

NOTE Confidence: 0.77490693

00:47:46.320 --> 00:47:48.650 rhythms of protein synthesis in cells.

NOTE Confidence: 0.77490693

00:47:48.650 --> 00:47:50.450 We think through the phosphorylation

NOTE Confidence: 0.77490693

00:47:50.450 --> 00:47:52.725 of the male and female phosphorylation

NOTE Confidence: 0.77490693

00:47:52.725 --> 00:47:55.609 in data that we haven't published yet.

NOTE Confidence: 0.77490693

00:47:55.610 --> 00:47:57.550 We're about to send out.

NOTE Confidence: 0.77490693

00:47:57.550 --> 00:47:59.800 We think we've identified a novel

NOTE Confidence: 0.77490693

00:47:59.800 --> 00:48:02.783 role for the local control of synaptic

NOTE Confidence: 0.77490693

00:48:02.783 --> 00:48:05.128 function by the circadian Clock.

NOTE Confidence: 0.77490693

00:48:05.130 --> 00:48:07.050 And the important thing is that

NOTE Confidence: 0.77490693

00:48:07.050 --> 00:48:09.743 the Clock might be a point of

NOTE Confidence: 0.77490693

00:48:09.743 --> 00:48:11.535 convergence between multiple pathways.

NOTE Confidence: 0.77490693

00:48:11.540 --> 00:48:12.246 So remember,

NOTE Confidence: 0.77490693

00:48:12.246 --> 00:48:14.717 I told you that TSC is causing

NOTE Confidence: 0.77490693

00:48:14.717 --> 00:48:16.439 dysregulation o'clock through bmal,

NOTE Confidence: 0.77490693

00:48:16.440 --> 00:48:18.252 but females being regulated by other

NOTE Confidence: 0.77490693

00:48:18.252 --> 00:48:20.067 proteins that are also responsible

NOTE Confidence: 0.77490693

00:48:20.067 --> 00:48:21.720 for neurodegenerative syndrome,

NOTE Confidence: 0.77490693

00:48:21.720 --> 00:48:23.052 neurodevelopmental syndromes that

NOTE Confidence: 0.77490693

00:48:23.052 --> 00:48:25.272 have differences but overlap with

NOTE Confidence: 0.77490693

00:48:25.272 --> 00:48:27.640 TSC and so it becomes an exciting

NOTE Confidence: 0.77490693

00:48:27.640 --> 00:48:30.292 idea to start to think of the Clock

NOTE Confidence: 0.77490693

00:48:30.292 --> 00:48:32.632 as a capacitor for these different

NOTE Confidence: 0.77490693

00:48:32.632 --> 00:48:33.466 neurodevelopmental syndromes,

NOTE Confidence: 0.77490693

00:48:33.466 --> 00:48:35.210 almost like a common.

NOTE Confidence: 0.77490693

00:48:35.210 --> 00:48:37.502 Like a final common pathway that

NOTE Confidence: 0.77490693

00:48:37.502 --> 00:48:38.648 we can target.

NOTE Confidence: 0.77490693

00:48:38.650 --> 00:48:40.449 And so this is mainly for the

NOTE Confidence: 0.77490693

00:48:40.449 --> 00:48:42.215 trainees to say that I just wanted

NOTE Confidence: 0.77490693

00:48:42.215 --> 00:48:44.480 to sort of put put you through again,

NOTE Confidence: 0.77490693

00:48:44.480 --> 00:48:46.120 sort of the the arc of this part

NOTE Confidence: 0.77490693

00:48:46.120 --> 00:48:46.530 of my

NOTE Confidence: 0.82182735

00:48:46.589 --> 00:48:48.503 my professional life is really I

NOTE Confidence: 0.82182735

00:48:48.503 --> 00:48:50.093 started with this critical question

NOTE Confidence: 0.82182735

00:48:50.093 --> 00:48:52.165 that came out of a rotation and we

NOTE Confidence: 0.82182735

00:48:52.165 --> 00:48:54.164 went to an animal model of cellular

NOTE Confidence: 0.82182735

00:48:54.164 --> 00:48:55.907 model and behavioral analysis and into

NOTE Confidence: 0.82182735

00:48:55.907 --> 00:48:57.521 the cell biology and the signaling

NOTE Confidence: 0.82182735

00:48:57.521 --> 00:48:59.471 pathways and that took us to this novel

NOTE Confidence: 0.82182735

00:48:59.471 --> 00:49:01.175 by calling not novel ideas about what

NOTE Confidence: 0.82182735

00:49:01.175 --> 00:49:03.030 the Clock might be might be doing,

NOTE Confidence: 0.82182735

00:49:03.030 --> 00:49:04.927 and even the breath of what the

NOTE Confidence: 0.82182735

00:49:04.927 --> 00:49:06.478 clocks functions are in the brain.

NOTE Confidence: 0.82182735

00:49:06.480 --> 00:49:08.148 And so we've now come back.

NOTE Confidence: 0.82182735

00:49:08.150 --> 00:49:10.350 Circle and really the ultimate

NOTE Confidence: 0.82182735

00:49:10.350 --> 00:49:12.110 goal for this work,

NOTE Confidence: 0.82182735

00:49:12.110 --> 00:49:15.036 is to find ways to use this

NOTE Confidence: 0.82182735

00:49:15.036 --> 00:49:16.950 system to improve sleep,

NOTE Confidence: 0.82182735

00:49:16.950 --> 00:49:20.373 but also to maybe even mitigate underlying

NOTE Confidence: 0.82182735

00:49:20.373 --> 00:49:22.470 causes of neurodevelopmental disease.

NOTE Confidence: 0.82182735

00:49:22.470 --> 00:49:25.676 So we have lots of future questions.

NOTE Confidence: 0.82182735

00:49:25.680 --> 00:49:27.044 Babies up here, yeah?

NOTE Confidence: 0.82182735

00:49:27.044 --> 00:49:29.807 Happy to look at and then of course

NOTE Confidence: 0.82182735

00:49:29.807 --> 00:49:32.359 I have to thank all the people who

NOTE Confidence: 0.82182735

00:49:32.439 --> 00:49:34.903 did the work so members of my lab,

NOTE Confidence: 0.82182735

00:49:34.910 --> 00:49:36.686 former members of my lab and

NOTE Confidence: 0.82182735

00:49:36.686 --> 00:49:37.278 my collaborators,

NOTE Confidence: 0.82182735

00:49:37.280 --> 00:49:38.765 Alex Rundberg is Sasha Memori

NOTE Confidence: 0.82182735

00:49:38.765 --> 00:49:40.250 and members of their lab.

NOTE Confidence: 0.82182735

00:49:40.250 --> 00:49:42.474 And then of course my my friend and

NOTE Confidence: 0.82182735

00:49:42.474 --> 00:49:43.520 colleague Peter Society,

NOTE Confidence: 0.82182735

00:49:43.520 --> 00:49:43.859 Southwestern,

NOTE Confidence: 0.82182735

00:49:43.859 --> 00:49:46.571 my former mentor stuff to him for a

NOTE Confidence: 0.82182735

00:49:46.571 --> 00:49:48.771 lot of the work I showed was done

NOTE Confidence: 0.82182735

00:49:48.771 --> 00:49:50.950 when I was a postdoc in his lab,

NOTE Confidence: 0.82182735

00:49:50.950 --> 00:49:52.987 and of course all of our funding

NOTE Confidence: 0.82182735

00:49:52.987 --> 00:49:54.511 throughout which none of this

NOTE Confidence: 0.82182735

00:49:54.511 --> 00:49:55.695 would have ever happened.

NOTE Confidence: 0.82182735

00:49:55.700 --> 00:49:55.996 OK,

NOTE Confidence: 0.82182735

00:49:55.996 --> 00:49:57.180 thank you so much.

NOTE Confidence: 0.86628914

00:50:06.070 --> 00:50:07.430 Thank you Jonathan very

NOTE Confidence: 0.86628914

00:50:07.430 --> 00:50:08.790 much that was fascinating.

NOTE Confidence: 0.86628914

00:50:08.790 --> 00:50:10.830 I'll open the floor for any

NOTE Confidence: 0.86628914

00:50:10.830 --> 00:50:12.190 questions anyone may have.

NOTE Confidence: 0.7996008

00:50:14.670 --> 00:50:16.138 Have a question? Jonathan

NOTE Confidence: 0.7996008

00:50:16.140 --> 00:50:18.336 can you hear me? Yep yeah.

NOTE Confidence: 0.7996008

00:50:18.340 --> 00:50:20.538 So what happens if you give

NOTE Confidence: 0.7996008

00:50:20.540 --> 00:50:23.816 certain limits to healthy mouse like?

NOTE Confidence: 0.7996008

00:50:23.820 --> 00:50:25.140 Does it change anything?

NOTE Confidence: 0.7964723

00:50:26.540 --> 00:50:29.580 Well, well, so so.

NOTE Confidence: 0.7964723

00:50:29.580 --> 00:50:32.814 Now in 2010, and even before that,

NOTE Confidence: 0.7964723

00:50:32.820 --> 00:50:35.538 roofing cows showed that rapper myosin

NOTE Confidence: 0.7964723

00:50:35.538 --> 00:50:38.379 can block light induced phase shifts.

NOTE Confidence: 0.7964723

00:50:38.380 --> 00:50:41.614 So and that came out of work,

NOTE Confidence: 0.7964723

00:50:41.620 --> 00:50:43.472 showing that light actually

NOTE Confidence: 0.7964723

00:50:43.472 --> 00:50:46.250 induced mtor activity in the SCN.

NOTE Confidence: 0.7964723

00:50:46.250 --> 00:50:49.028 So first they showed that light

NOTE Confidence: 0.7964723

00:50:49.028 --> 00:50:50.880 can actually potentiates mtor,

NOTE Confidence: 0.7964723

00:50:50.880 --> 00:50:53.125 and then they basically showed

NOTE Confidence: 0.7964723

00:50:53.125 --> 00:50:56.924 that if you time if you time rappa

NOTE Confidence: 0.7964723

00:50:56.924 --> 00:50:59.852 mice into different points in the.

NOTE Confidence: 0.7964723

00:50:59.860 --> 00:51:01.725 Circadian Clock, you can effectively

NOTE Confidence: 0.7964723

00:51:01.725 --> 00:51:03.590 block the effect of light,

NOTE Confidence: 0.7964723

00:51:03.590 --> 00:51:05.455 so the take home message

NOTE Confidence: 0.7964723

00:51:05.455 --> 00:51:08.440 would be that REPL, mison.

NOTE Confidence: 0.7964723

00:51:08.440 --> 00:51:09.900 By itself can potentially

NOTE Confidence: 0.7964723

00:51:09.900 --> 00:51:10.995 impair phase shifts,

NOTE Confidence: 0.7964723

00:51:11.000 --> 00:51:13.166 and it might be consistent with

NOTE Confidence: 0.7964723

00:51:13.166 --> 00:51:15.740 what we see with the TSC model,

NOTE Confidence: 0.7964723

00:51:15.740 --> 00:51:18.148 where we see very rapid phase shifts

NOTE Confidence: 0.7964723

00:51:18.148 --> 00:51:20.120 with emptoris sort of exuberance.

NOTE Confidence: 0.8089371

00:51:22.530 --> 00:51:23.688 So could it?

NOTE Confidence: 0.8089371

00:51:23.690 --> 00:51:27.425 Could it possibly be of benefit if there is

NOTE Confidence: 0.8089371

00:51:27.425 --> 00:51:30.908 too rapid a phase shift? Like it could be

NOTE Confidence: 0.7710173

00:51:30.910 --> 00:51:32.968 only problem is of course rapper myosin

NOTE Confidence: 0.7710173

00:51:32.968 --> 00:51:35.172 has so many so many effects, right?

NOTE Confidence: 0.7710173

00:51:35.172 --> 00:51:37.566 So it's a little hard to make

NOTE Confidence: 0.7710173

00:51:37.566 --> 00:51:39.550 the argument that you're going

NOTE Confidence: 0.7710173

00:51:39.550 --> 00:51:41.600 to use recognizing for sleep.

NOTE Confidence: 0.7710173

00:51:41.600 --> 00:51:43.574 By itself, I don't think anyone would.

NOTE Confidence: 0.7710173

00:51:43.580 --> 00:51:44.692 Would would do that,

NOTE Confidence: 0.7710173

00:51:44.692 --> 00:51:47.538 but I think it's part of the reason why we.

NOTE Confidence: 0.7710173

00:51:47.540 --> 00:51:48.955 I mean, it's really part

NOTE Confidence: 0.7710173

00:51:48.955 --> 00:51:50.370 of the reason we want.

NOTE Confidence: 0.7710173

00:51:50.370 --> 00:51:52.274 We want to do our work is

NOTE Confidence: 0.7710173

00:51:52.274 --> 00:51:54.024 because we're hoping to be able

NOTE Confidence: 0.7710173

00:51:54.024 --> 00:51:55.469 to identify things that can.

NOTE Confidence: 0.7710173

00:51:55.470 --> 00:51:57.726 You know if sleep is the main problem,

NOTE Confidence: 0.7710173

00:51:57.730 --> 00:51:59.764 we want to be able to sort of target

NOTE Confidence: 0.7710173

00:51:59.764 --> 00:52:02.101 that without affecting like all the 3000

NOTE Confidence: 0.7710173

00:52:02.101 --> 00:52:04.518 other things that emptores doing so you know,

NOTE Confidence: 0.7710173

00:52:04.520 --> 00:52:05.652 you know recognizing is

NOTE Confidence: 0.7710173

00:52:05.652 --> 00:52:06.784 well tolerated in general,

NOTE Confidence: 0.7710173

00:52:06.790 --> 00:52:08.452 but it isn't immune suppressant and

NOTE Confidence: 0.7710173

00:52:08.452 --> 00:52:10.469 it can have lots of side effects,

NOTE Confidence: 0.7710173

00:52:10.470 --> 00:52:13.350 so it's probably not like the best sleep.

NOTE Confidence: 0.7710173

00:52:13.350 --> 00:52:13.778 Sleep modulator.

NOTE Confidence: 0.7710173

00:52:13.778 --> 00:52:14.848 You know what I mean?

NOTE Confidence: 0.86049986

00:52:15.760 --> 00:52:18.760 I was thinking of non 24 because it.

NOTE Confidence: 0.86049986

00:52:18.760 --> 00:52:22.028 Goes diving out. Maybe it'll have at least. I

NOTE Confidence: 0.8306253

00:52:22.030 --> 00:52:23.478 think that's an interesting.

NOTE Confidence: 0.8306253

00:52:23.478 --> 00:52:24.926 That's an interesting idea.

NOTE Confidence: 0.8306253

00:52:24.930 --> 00:52:27.464 I mean, maybe, maybe not REPL Meissen,

NOTE Confidence: 0.8306253

00:52:27.470 --> 00:52:29.588 but maybe something something that you

NOTE Confidence: 0.8306253

00:52:29.588 --> 00:52:31.796 know could target this mechanism that

NOTE Confidence: 0.8306253

00:52:31.796 --> 00:52:34.010 that that that would be interesting.

NOTE Confidence: 0.79624856

00:52:35.560 --> 00:52:36.862 You don't think you could find some

NOTE Confidence: 0.79624856

00:52:36.862 --> 00:52:38.038 teenager that would take rapper mice,

NOTE Confidence: 0.79624856

00:52:38.040 --> 00:52:39.186 and if they can play their

NOTE Confidence: 0.79624856

00:52:39.186 --> 00:52:41.990 video games later at night.

NOTE Confidence: 0.79624856

00:52:41.990 --> 00:52:43.650 I was actually going to similar

NOTE Confidence: 0.79624856

00:52:43.650 --> 00:52:45.030 question that meaning is there.

NOTE Confidence: 0.79624856

00:52:45.030 --> 00:52:47.040 Is there any?

NOTE Confidence: 0.79624856

00:52:47.040 --> 00:52:49.098 Evidence that people who are on

NOTE Confidence: 0.79624856

00:52:49.098 --> 00:52:50.470 mtor inhibitors have increased

NOTE Confidence: 0.79624856

00:52:50.532 --> 00:52:51.639 problems with sleep.

NOTE Confidence: 0.79624856

00:52:51.640 --> 00:52:52.699 Yeah, we don't

NOTE Confidence: 0.8142073

00:52:52.700 --> 00:52:55.874 really know. Honestly, it really is

NOTE Confidence: 0.8142073

00:52:55.874 --> 00:52:58.560 something I've wondered about a lot.

NOTE Confidence: 0.8142073

00:52:58.560 --> 00:53:00.032 We we don't know.

NOTE Confidence: 0.8142073

00:53:00.032 --> 00:53:03.339 I mean, one thing that seems to be true,

NOTE Confidence: 0.8142073

00:53:03.340 --> 00:53:05.180 which is that patients with

NOTE Confidence: 0.8142073

00:53:05.180 --> 00:53:07.020 that there have been trials.

NOTE Confidence: 0.8142073

00:53:07.020 --> 00:53:09.114 Now for using like sirolimus and

NOTE Confidence: 0.8142073

00:53:09.114 --> 00:53:11.359 everolimus in NTSC and the primary

NOTE Confidence: 0.8142073

00:53:11.359 --> 00:53:13.276 outcomes have been, you know,

NOTE Confidence: 0.8142073

00:53:13.276 --> 00:53:16.220 sort of a mixed bag a little bit.

NOTE Confidence: 0.8142073

00:53:16.220 --> 00:53:18.060 They haven't measured sleep directly,

NOTE Confidence: 0.8142073

00:53:18.060 --> 00:53:21.546 but from what I understand anecdotally.

NOTE Confidence: 0.8142073

00:53:21.550 --> 00:53:24.226 I think he paid patients generally

NOTE Confidence: 0.8142073

00:53:24.226 --> 00:53:27.818 feel better so he could again be like.

NOTE Confidence: 0.8142073

00:53:27.820 --> 00:53:29.668 You know it could again be

NOTE Confidence: 0.8142073

00:53:29.668 --> 00:53:31.469 in in the setting of TSC.

NOTE Confidence: 0.8142073

00:53:31.470 --> 00:53:32.990 You're kind of normalizing things.

NOTE Confidence: 0.8142073

00:53:32.990 --> 00:53:34.845 I think the question becomes in a

NOTE Confidence: 0.8142073

00:53:34.845 --> 00:53:36.410 setting where you're taking rappa

NOTE Confidence: 0.8142073

00:53:36.410 --> 00:53:37.850 Meissen for another indication.

NOTE Confidence: 0.8142073

00:53:37.850 --> 00:53:39.050 It's really different question,

NOTE Confidence: 0.8142073

00:53:39.050 --> 00:53:40.250 because then you're potentially

NOTE Confidence: 0.8142073

00:53:40.250 --> 00:53:41.200 suppressing it already.

NOTE Confidence: 0.8142073

00:53:41.200 --> 00:53:42.280 Normal baseline of M,

NOTE Confidence: 0.8142073

00:53:42.280 --> 00:53:45.179 Tor and I think if I had to say one

NOTE Confidence: 0.8142073

00:53:45.179 --> 00:53:47.580 message is that with anything in biology,

NOTE Confidence: 0.8142073

00:53:47.580 --> 00:53:49.398 and especially with any homeostatic pathway,

NOTE Confidence: 0.8142073

00:53:49.400 --> 00:53:51.528 you don't want to have too much.

NOTE Confidence: 0.8142073

00:53:51.530 --> 00:53:53.258 You don't want too little and

NOTE Confidence: 0.8142073

00:53:53.258 --> 00:53:55.419 it's the same thing with M Tor

NOTE Confidence: 0.8142073

00:53:55.419 --> 00:53:56.999 over exuberant or causes cancer.

NOTE Confidence: 0.8142073

00:53:57.000 --> 00:53:58.986 Lack of mtor called his death.

NOTE Confidence: 0.8142073

00:53:58.990 --> 00:54:00.712 So it's like you know you you

NOTE Confidence: 0.8142073

00:54:00.712 --> 00:54:02.630 you you don't want to have you

NOTE Confidence: 0.8142073

00:54:02.630 --> 00:54:04.030 know no protein being made.

NOTE Confidence: 0.8142073

00:54:04.030 --> 00:54:05.661 You also don't want too much being

NOTE Confidence: 0.8142073

00:54:05.661 --> 00:54:07.209 made and that's a simplification.

NOTE Confidence: 0.8142073

00:54:07.210 --> 00:54:09.338 But the idea is that these all these

NOTE Confidence: 0.8142073

00:54:09.338 --> 00:54:10.917 homeostatic systems have to be regulated,

NOTE Confidence: 0.8142073

00:54:10.920 --> 00:54:13.040 and I think this is exactly the message.

NOTE Confidence: 0.8142073

00:54:13.040 --> 00:54:14.630 This is a message from the

NOTE Confidence: 0.8142073

00:54:14.630 --> 00:54:15.950 Clock world as well, right?

NOTE Confidence: 0.7072729

00:54:25.670 --> 00:54:31.313 What happens to these mice as they get older?

NOTE Confidence: 0.7072729

00:54:31.320 --> 00:54:33.380 Mike, yes mice. They're hitting

NOTE Confidence: 0.7072729

00:54:33.380 --> 00:54:36.320 hitters like us as they get older.

NOTE Confidence: 0.85091525

00:54:37.680 --> 00:54:39.498 So I actually don't know about,

NOTE Confidence: 0.85091525

00:54:39.500 --> 00:54:41.150 you know whether they have like

NOTE Confidence: 0.85091525

00:54:41.150 --> 00:54:42.830 clearly like age dependent phenotypes.

NOTE Confidence: 0.85091525

00:54:42.830 --> 00:54:44.582 Most of the work has been

NOTE Confidence: 0.85091525

00:54:44.582 --> 00:54:46.160 done and like you know,

NOTE Confidence: 0.85091525

00:54:46.160 --> 00:54:49.526 young Ish or like sort of.

NOTE Confidence: 0.85091525

00:54:49.530 --> 00:54:52.368 Middle of adulthood.

NOTE Confidence: 0.85091525

00:54:52.370 --> 00:54:53.936 There's certainly a lot of work

NOTE Confidence: 0.85091525

00:54:53.936 --> 00:54:56.008 showing that in the more severe models,

NOTE Confidence: 0.85091525

00:54:56.010 --> 00:54:57.410 there are critical periods of

NOTE Confidence: 0.85091525

00:54:57.410 --> 00:54:58.250 intervention during development,

NOTE Confidence: 0.85091525

00:54:58.250 --> 00:55:00.042 which is sort of the opposite of your

NOTE Confidence: 0.85091525

00:55:00.042 --> 00:55:01.379 question to definitely like critical

NOTE Confidence: 0.85091525

00:55:01.379 --> 00:55:03.053 periods during which you know TST

NOTE Confidence: 0.85091525

00:55:03.053 --> 00:55:04.399 is probably misshaping cortical

NOTE Confidence: 0.85091525

00:55:04.399 --> 00:55:06.089 circuits and things like that.

NOTE Confidence: 0.85091525

00:55:06.090 --> 00:55:08.316 So there are points where you

NOTE Confidence: 0.85091525

00:55:08.316 --> 00:55:10.745 have to intervene or before which

NOTE Confidence: 0.85091525

00:55:10.745 --> 00:55:12.477 you have to intervene.

NOTE Confidence: 0.85091525

00:55:12.480 --> 00:55:14.766 With regard to like long-term phenotypes,

NOTE Confidence: 0.85091525

00:55:14.770 --> 00:55:16.680 to be honest, I'm not.

NOTE Confidence: 0.85091525

00:55:16.680 --> 00:55:20.180 I'm not really sure. I mean,

NOTE Confidence: 0.85091525

00:55:20.180 --> 00:55:21.920 one might imagine with over exuberant,

NOTE Confidence: 0.85091525

00:55:21.920 --> 00:55:25.256 or that you would have a.

NOTE Confidence: 0.85091525

00:55:25.260 --> 00:55:26.152 You know,

NOTE Confidence: 0.85091525

00:55:26.152 --> 00:55:27.490 potentially shorten lifespan.

NOTE Confidence: 0.85091525

00:55:27.490 --> 00:55:30.374 There's a lot of evidence that showing

NOTE Confidence: 0.85091525

00:55:30.374 --> 00:55:33.268 that mtor suppression prolongs prolongs life,

NOTE Confidence: 0.85091525

00:55:33.270 --> 00:55:35.050 probably by regulating caloric,

NOTE Confidence: 0.85091525

00:55:35.050 --> 00:55:35.940 you know,

NOTE Confidence: 0.85091525

00:55:35.940 --> 00:55:38.530 by regulating the amount of

NOTE Confidence: 0.85091525

00:55:38.530 --> 00:55:40.602 oxidative stress that's produced

NOTE Confidence: 0.85091525

00:55:40.602 --> 00:55:42.479 from the turnover of.

NOTE Confidence: 0.85091525

00:55:42.480 --> 00:55:44.040 Biomolecules basically.

NOTE Confidence: 0.8467998

00:55:50.910 --> 00:55:52.080 Any other questions?

NOTE Confidence: 0.8457988

00:55:55.410 --> 00:55:58.226 I'll just if there are no other questions.

NOTE Confidence: 0.8457988

00:55:58.230 --> 00:56:01.078 I'll just chime in just to let folks

NOTE Confidence: 0.8457988

00:56:01.078 --> 00:56:03.878 know what our talk is for next week.

NOTE Confidence: 0.8457988

00:56:03.880 --> 00:56:06.368 So we're going to be hearing from Dennis

NOTE Confidence: 0.8457988

00:56:06.368 --> 00:56:09.045 Wang from Kaiser who's going to be

NOTE Confidence: 0.8457988

00:56:09.045 --> 00:56:10.944 thinking about automation, big data,

NOTE Confidence: 0.8457988

00:56:10.944 --> 00:56:12.704 and artificial intelligence in the

NOTE Confidence: 0.8457988

00:56:12.704 --> 00:56:14.510 management of obstructive sleep apnea

NOTE Confidence: 0.8457988

00:56:14.510 --> 00:56:16.235 for future and current implications.

NOTE Confidence: 0.8457988

00:56:16.240 --> 00:56:19.846 So please join us for that.

NOTE Confidence: 0.8457988

00:56:19.850 --> 00:56:21.638 Thanks everybody, have a great week.

NOTE Confidence: 0.8457988

00:56:21.640 --> 00:56:23.810 Thank you, thank you Jonathan.

NOTE Confidence: 0.8457988

00:56:23.810 --> 00:56:24.660 Thanks everybody.