WEBVTT

NOTE duration:"00:51:13.1900000"

NOTE recognizability:0.762

NOTE language:en-us

NOTE Confidence: 0.781733976363636

00:00:00.000 --> 00:00:02.576 At all to this nice, auspicious start

NOTE Confidence: 0.781733976363636

00:00:02.576 --> 00:00:07.490 of the new Grand Round series for 2023.

NOTE Confidence: 0.781733976363636

00:00:07.490 --> 00:00:10.450 And I'm happy to have Doctor David

NOTE Confidence: 0.781733976363636

00:00:10.450 --> 00:00:13.390 Hafler here is our speaker today.

NOTE Confidence: 0.781733976363636

00:00:13.390 --> 00:00:16.076 So since 2009, Doctor Heffler has

NOTE Confidence: 0.781733976363636

00:00:16.076 --> 00:00:17.798 been the William S and Lower Styles

NOTE Confidence: 0.876862086666667

00:00:17.810 --> 00:00:19.210 actually professor and chairman

NOTE Confidence: 0.876862086666667

00:00:19.210 --> 00:00:20.960 of the Department of Neurology,

NOTE Confidence: 0.666254034

00:00:20.970 --> 00:00:23.186 Professor of Immunology, Immunobiology

NOTE Confidence: 0.666254034

00:00:23.186 --> 00:00:25.160 here at Yale and his neurologist

NOTE Confidence: 0.666254034

00:00:25.160 --> 00:00:27.990 and chief of the hospital, David.

NOTE Confidence: 0.666254034

00:00:27.990 --> 00:00:30.237 He's a he's a clinical research scientist

NOTE Confidence: 0.796949021818182

00:00:30.470 --> 00:00:32.342 with an interest in understanding the

NOTE Confidence: 0.796949021818182

00:00:32.342 --> 00:00:34.260 path of pathogenesis of inflammatory

NOTE Confidence: 0.850464608571429

00:00:34.270 --> 00:00:36.158 CNS diseases by studying

NOTE Confidence: 0.850464608571429

00:00:36.158 --> 00:00:37.972 both basic properties of.

NOTE Confidence: 0.850464608571429

00:00:37.972 --> 00:00:40.120 Due to regulatory pathways in humans

NOTE Confidence: 0.850464608571429

00:00:40.120 --> 00:00:41.772 and they run this function in patients.

NOTE Confidence: 0.850464608571429

00:00:41.772 --> 00:00:44.435 But as went on, I won't show you all

NOTE Confidence: 0.850464608571429

00:00:44.435 --> 00:00:46.390 the ruminations over the 20 odd years,

NOTE Confidence: 0.850464608571429

00:00:46.390 --> 00:00:48.934 but with 47,000 patients,

NOTE Confidence: 0.850464608571429

00:00:48.934 --> 00:00:51.478 68,000 controls by identified,

NOTE Confidence: 0.850464608571429

00:00:51.480 --> 00:00:52.725 233 genetic variants,

NOTE Confidence: 0.850464608571429

00:00:52.725 --> 00:00:54.800 all these have been replicated.

NOTE Confidence: 0.850464608571429

00:00:54.800 --> 00:00:56.685 All the original ones are

NOTE Confidence: 0.850464608571429

00:00:56.685 --> 00:00:57.439 similarly replicated,

NOTE Confidence: 0.850464608571429

00:00:57.440 --> 00:01:00.458 which counts for about half the

NOTE Confidence: 0.850464608571429

00:01:00.458 --> 00:01:02.470 estimated heritability for Ms.

NOTE Confidence: 0.850464608571429

00:01:02.470 --> 00:01:03.652 So that's great.

NOTE Confidence: 0.850464608571429

00:01:03.652 --> 00:01:06.410 You can show these wonderful little figures,

NOTE Confidence: 0.850464608571429

00:01:06.410 --> 00:01:08.906 but how did the variants cause the disease?

NOTE Confidence: 0.850464608571429

00:01:08.910 --> 00:01:10.779 And I think this remains one of

NOTE Confidence: 0.850464608571429

00:01:10.779 --> 00:01:12.050 the major challenges for you,

NOTE Confidence: 0.850464608571429

00:01:12.050 --> 00:01:14.978 not modern medicine as it's relatively

NOTE Confidence: 0.850464608571429

00:01:14.978 --> 00:01:16.930 easy with these technologies.

NOTE Confidence: 0.850464608571429

00:01:16.930 --> 00:01:19.576 It wasn't so easy in 2000 where we are

NOTE Confidence: 0.850464608571429

00:01:19.576 --> 00:01:22.134 now with different aluminum athlete

NOTE Confidence: 0.850464608571429

00:01:22.134 --> 00:01:24.322 technologies to identify genetic

NOTE Confidence: 0.850464608571429

00:01:24.322 --> 00:01:26.888 variants with big patient cohorts.

NOTE Confidence: 0.850464608571429

00:01:26.890 --> 00:01:28.948 I think the challenge is how to

NOTE Confidence: 0.850464608571429

00:01:28.948 --> 00:01:30.569 go from variance to disease.

NOTE Confidence: 0.850464608571429

00:01:30.570 --> 00:01:32.070 So this is an effort.

NOTE Confidence: 0.850464608571429

00:01:32.070 --> 00:01:33.920 Collaborate effort with Alex Morrison,

NOTE Confidence: 0.850464608571429

00:01:33.920 --> 00:01:36.340 Kyle Farr and Brad Bernstein.

NOTE Confidence: 0.850464608571429

00:01:36.340 --> 00:01:38.295 We together did genetic and

NOTE Confidence: 0.850464608571429

00:01:38.295 --> 00:01:40.250 epigenetic fine mapping of autoimmune

NOTE Confidence: 0.850464608571429

00:01:40.320 --> 00:01:42.426 disease variants and these data up.

NOTE Confidence: 0.850464608571429

00:01:42.430 --> 00:01:44.740 They'll publish about 5-6 years ago.

NOTE Confidence: 0.850464608571429

00:01:44.740 --> 00:01:47.650 I think it's still hand up, pulled up.

NOTE Confidence: 0.850464608571429

00:01:47.650 --> 00:01:50.350 So what we did we turns off for a second.

NOTE Confidence: 0.850464608571429

00:01:50.350 --> 00:01:53.438 So you all know DNA goes to RNA

NOTE Confidence: 0.850464608571429

00:01:53.438 --> 00:01:55.962 goes to protein, you'll learn that.

NOTE Confidence: 0.850464608571429

00:01:55.962 --> 00:01:58.290 And so to go from DNA to RNA,

NOTE Confidence: 0.850464608571429

00:01:58.290 --> 00:02:00.411 DNA has done wine very well and

NOTE Confidence: 0.850464608571429

00:02:00.411 --> 00:02:03.040 there has to be ways so that poll

NOTE Confidence: 0.850464608571429

00:02:03.040 --> 00:02:05.472 two another enzymes can get to the

NOTE Confidence: 0.850464608571429

00:02:05.472 --> 00:02:07.590 DNA so you can have transcription.

NOTE Confidence: 0.850464608571429

00:02:07.590 --> 00:02:09.767 Well you can then use things like

NOTE Confidence: 0.850464608571429

00:02:09.770 --> 00:02:11.018 K27 installation,

NOTE Confidence: 0.850464608571429

00:02:11.018 --> 00:02:14.210 K4 methylation maps to identify where

NOTE Confidence: 0.850464608571429

00:02:14.210 --> 00:02:17.290 this open chromatid on different cell types.

NOTE Confidence: 0.850464608571429

00:02:17.290 --> 00:02:19.404 One can then take those data and

NOTE Confidence: 0.850464608571429

00:02:19.404 --> 00:02:21.399 overlay them with genetic variants,

NOTE Confidence: 0.850464608571429

00:02:21.400 --> 00:02:23.710 arguing that if a genetic variant,

NOTE Confidence: 0.850464608571429

00:02:23.710 --> 00:02:25.768 it's a region where there is

NOTE Confidence: 0.850464608571429

00:02:25.768 --> 00:02:26.797 no open chromatin,

NOTE Confidence: 0.850464608571429

00:02:26.800 --> 00:02:28.488 that variance is not going to be

NOTE Confidence: 0.850464608571429

00:02:28.488 --> 00:02:29.904 playing a role that's help with

NOTE Confidence: 0.850464608571429

00:02:29.904 --> 00:02:31.465 every place there's a genetic

NOTE Confidence: 0.850464608571429

00:02:31.465 --> 00:02:32.416 variant for chromance,

NOTE Confidence: 0.850464608571429

00:02:32.420 --> 00:02:33.052 it's open,

NOTE Confidence: 0.850464608571429

00:02:33.052 --> 00:02:35.264 then it's likely to be an influencing

NOTE Confidence: 0.850464608571429

00:02:35.264 --> 00:02:36.239 that cell type.

NOTE Confidence: 0.850464608571429

00:02:36.240 --> 00:02:38.120 That's what we did as part of the

NOTE Confidence: 0.850464608571429

00:02:38.120 --> 00:02:39.618 ENCODE project with Brad Bernstein.

NOTE Confidence: 0.850464608571429

00:02:39.620 --> 00:02:44.025 Our lab participated in generating the K27K4

NOTE Confidence: 0.850464608571429

00:02:44.025 --> 00:02:46.888 methylation maps of human immune cells and.

NOTE Confidence: 0.850464608571429

00:02:46.888 --> 00:02:48.600 We have different diseases.

NOTE Confidence: 0.850464608571429

00:02:48.600 --> 00:02:51.228 We have neurologic diseases over here.

NOTE Confidence: 0.850464608571429

00:02:51.230 --> 00:02:52.974 Here is urate levels,

NOTE Confidence: 0.850464608571429

00:02:52.974 --> 00:02:54.834 renal function, kidney disease,

NOTE Confidence: 0.850464608571429

00:02:54.834 --> 00:02:57.786 cholesterol and here the autoimmune diseases.

NOTE Confidence: 0.850464608571429

00:02:57.790 --> 00:02:59.402 We'll concentrate on Ms.

NOTE Confidence: 0.850464608571429

00:02:59.402 --> 00:03:01.417 If you look at Ms.

NOTE Confidence: 0.850464608571429

00:03:01.420 --> 00:03:03.760 We found the genetic variance,

NOTE Confidence: 0.850464608571429

00:03:03.760 --> 00:03:06.980 the P values of less than 10 to the minus 30.

NOTE Confidence: 0.850464608571429

00:03:06.980 --> 00:03:08.960 We're hitting immune cells.

NOTE Confidence: 0.850464608571429

00:03:08.960 --> 00:03:11.435 That wasn't surprising T cells.

NOTE Confidence: 0.850464608571429

00:03:11.440 --> 00:03:12.583 Macrophages T regs.

NOTE Confidence: 0.850464608571429

00:03:12.583 --> 00:03:15.250 But also what was a bit surprising

NOTE Confidence: 0.850464608571429

00:03:15.322 --> 00:03:17.440 is there were hitting B cells,

NOTE Confidence: 0.850464608571429

00:03:17.440 --> 00:03:18.960 and more so in Ms.

NOTE Confidence: 0.850464608571429

00:03:18.960 --> 00:03:20.236 most any other diseases.

NOTE Confidence: 0.850464608571429

00:03:20.236 --> 00:03:22.720 If you look at other autoimmune diseases,

NOTE Confidence: 0.850464608571429

00:03:22.720 --> 00:03:24.960 it wasn't the case,

NOTE Confidence: 0.850464608571429

00:03:24.960 --> 00:03:29.480 say for lupus and primary biliary serositis,

NOTE Confidence: 0.850464608571429

00:03:29.480 --> 00:03:31.520 suggesting that B cells play a

NOTE Confidence: 0.850464608571429

00:03:31.520 --> 00:03:33.490 critical role in the disease.

NOTE Confidence: 0.850464608571429

00:03:33.490 --> 00:03:34.220 Somewhat unfortunately,

NOTE Confidence: 0.850464608571429

00:03:34.220 --> 00:03:36.775 around the same time my dear friend

NOTE Confidence: 0.850464608571429

00:03:36.775 --> 00:03:39.288 and colleague Steve Hauser made the

NOTE Confidence: 0.850464608571429

00:03:39.288 --> 00:03:41.373 observation paper published New England.

NOTE Confidence: 0.850464608571429

00:03:41.380 --> 00:03:41.932 Channel,

NOTE Confidence: 0.850464608571429

00:03:41.932 --> 00:03:45.244 if you perform B cell depletion,

NOTE Confidence: 0.850464608571429

00:03:45.250 --> 00:03:46.640 this is the two different

NOTE Confidence: 0.850464608571429

00:03:46.640 --> 00:03:48.030 studies offer one opera 2

NOTE Confidence: 0.728758983157895

00:03:48.090 --> 00:03:50.000 compared to the standard treatment

NOTE Confidence: 0.728758983157895

00:03:50.000 --> 00:03:51.528 that time barred interferon.

NOTE Confidence: 0.728758983157895

00:03:51.530 --> 00:03:55.072 The 9897% decrease in new lesions dramatic

NOTE Confidence: 0.728758983157895

00:03:55.072 --> 00:03:57.438 effect and I would just say clinically

NOTE Confidence: 0.728758983157895

00:03:57.438 --> 00:04:00.207 will we see a patient we start them on

NOTE Confidence: 0.728758983157895

00:04:00.207 --> 00:04:02.495 B cell depletion when we have a patient

NOTE Confidence: 0.728758983157895

00:04:02.500 --> 00:04:05.308 who doesn't respond usually isn't Ms.

NOTE Confidence: 0.728758983157895

00:04:05.310 --> 00:04:07.830 that's how good that drug is right now.

NOTE Confidence: 0.728758983157895

00:04:07.830 --> 00:04:10.392 So these data fit in very

NOTE Confidence: 0.728758983157895

00:04:10.392 --> 00:04:12.100 nicely with our observation.

NOTE Confidence: 0.728758983157895

00:04:12.100 --> 00:04:14.039 All of these cells in the disease,

NOTE Confidence: 0.728758983157895

00:04:14.040 --> 00:04:16.050 but those are those in your

NOTE Confidence: 0.728758983157895

00:04:16.050 --> 00:04:17.055 biologist and neuropathologist.

NOTE Confidence: 0.728758983157895

00:04:17.060 --> 00:04:17.630 I apologize,

NOTE Confidence: 0.728758983157895

00:04:17.630 --> 00:04:19.910 we did not get hits in the brain.

NOTE Confidence: 0.799675357666667

00:04:22.360 --> 00:04:24.448 Now I will say, and I won't share Tom

NOTE Confidence: 0.799675357666667

00:04:24.448 --> 00:04:26.634 and show the data today with the paper

NOTE Confidence: 0.799675357666667

00:04:26.634 --> 00:04:28.755 that is going to be coming out in

NOTE Confidence: 0.799675357666667

00:04:28.755 --> 00:04:30.532 nature from our from our consortium,

NOTE Confidence: 0.799675357666667

00:04:30.532 --> 00:04:32.660 identifying 2 haplotypes associated

NOTE Confidence: 0.799675357666667

00:04:32.660 --> 00:04:36.500 not with the risk of developing Ms.

NOTE Confidence: 0.799675357666667

00:04:36.500 --> 00:04:37.574 but with progression.

NOTE Confidence: 0.799675357666667

00:04:37.574 --> 00:04:39.722 And these are helpful types which

NOTE Confidence: 0.799675357666667

00:04:39.722 --> 00:04:41.599 are found in neuronal cells.

NOTE Confidence: 0.799675357666667

00:04:41.600 --> 00:04:43.120 So it's a separate question

NOTE Confidence: 0.799675357666667

00:04:43.120 --> 00:04:44.640 of what causes the disease,

NOTE Confidence: 0.799675357666667

00:04:44.640 --> 00:04:46.180 what leads to disease progression.

NOTE Confidence: 0.799675357666667

00:04:46.180 --> 00:04:47.734 If you have the risk capital type,

NOTE Confidence: 0.799675357666667

00:04:47.740 --> 00:04:50.692 your likelihood of progressing

NOTE Confidence: 0.799675357666667

00:04:50.692 --> 00:04:52.906 is significantly increased.

NOTE Confidence: 0.799675357666667

00:04:52.910 --> 00:04:56.046 So how do you go from Snips

NOTE Confidence: 0.799675357666667

00:04:56.046 --> 00:04:57.416 to to functionality?

NOTE Confidence: 0.799675357666667

00:04:57.416 --> 00:05:01.144 So we found hits the enough Capital Region.

NOTE Confidence: 0.799675357666667

00:05:01.150 --> 00:05:03.598 There are part of the far paper we

NOTE Confidence: 0.799675357666667

00:05:03.598 --> 00:05:06.236 found that steps on the NF Kappa B

NOTE Confidence: 0.799675357666667

00:05:06.236 --> 00:05:08.090 binding sites across the genome.

NOTE Confidence: 0.799675357666667

00:05:08.090 --> 00:05:10.460 And there's snips happen in the

NOTE Confidence: 0.799675357666667

00:05:10.460 --> 00:05:12.250 haplotype social NF Kappa B.

NOTE Confidence: 0.799675357666667

00:05:12.250 --> 00:05:14.106 Now it's about 10 to the minus 12,

NOTE Confidence: 0.799675357666667

00:05:14.110 --> 00:05:15.930 so they're genetic variance here.

NOTE Confidence: 0.799675357666667

00:05:15.930 --> 00:05:19.450 However, the odds ratio is about 1.1,

NOTE Confidence: 0.799675357666667

00:05:19.450 --> 00:05:21.155 so not a big effect.

NOTE Confidence: 0.799675357666667

00:05:21.155 --> 00:05:22.685 So I want to show you.

NOTE Confidence: 0.799675357666667

00:05:22.690 --> 00:05:26.226 Just even though the odds ratio is low.

NOTE Confidence: 0.799675357666667

00:05:26.230 --> 00:05:27.868 It has a major biologic fact.

NOTE Confidence: 0.799675357666667

00:05:27.870 --> 00:05:32.326 In fact, about 1819% of eugenic kits Ms.

NOTE Confidence: 0.799675357666667

00:05:32.330 --> 00:05:34.922 are in the NF Capital B and the

NOTE Confidence: 0.799675357666667

00:05:34.922 --> 00:05:37.957 TNF NF Capital B signaling region.

NOTE Confidence: 0.799675357666667

00:05:37.960 --> 00:05:41.284 So this is published now 7-8 years

NOTE Confidence: 0.799675357666667

00:05:41.284 --> 00:05:43.456 ago by will housing our laboratory.

NOTE Confidence: 0.799675357666667

00:05:43.460 --> 00:05:46.148 But basically about 20% of these

NOTE Confidence: 0.799675357666667

00:05:46.148 --> 00:05:47.044 healthy subjects.

NOTE Confidence: 0.799675357666667

00:05:47.050 --> 00:05:50.746 About 20% of you here are GG's.

NOTE Confidence: 0.799675357666667

00:05:50.746 --> 00:05:52.780 Do you know enough to know who you are?

NOTE Confidence: 0.799675357666667

00:05:52.780 --> 00:05:55.100 Is your homozygote for

NOTE Confidence: 0.799675357666667

00:05:55.100 --> 00:05:56.840 this particular variant?

NOTE Confidence: 0.799675357666667

00:05:56.840 --> 00:05:58.952 About 20% of you were A and the

NOTE Confidence: 0.799675357666667

00:05:58.952 --> 00:06:01.240 rest of you are had to reside in.

NOTE Confidence: 0.799675357666667

00:06:01.240 --> 00:06:02.740 If you are G,

NOTE Confidence: 0.799675357666667

00:06:02.740 --> 00:06:05.537 you have about a 20 fold increase

NOTE Confidence: 0.799675357666667

00:06:05.537 --> 00:06:07.757 in P50 NF Kappa B.

NOTE Confidence: 0.799675357666667

00:06:07.760 --> 00:06:09.674 Activity where if you're a it's

NOTE Confidence: 0.799675357666667

00:06:09.674 --> 00:06:11.639 significantly less and we every time

NOTE Confidence: 0.799675357666667

00:06:11.639 --> 00:06:13.529 we've looked at a genetic variant,

NOTE Confidence: 0.799675357666667

00:06:13.530 --> 00:06:16.026 this is what we find that the biology

NOTE Confidence: 0.799675357666667

00:06:16.026 --> 00:06:18.920 of these are quite striking and even

NOTE Confidence: 0.799675357666667

00:06:18.920 --> 00:06:22.679 though maybe 1.11 point one to the 233

NOTE Confidence: 0.799675357666667

00:06:22.679 --> 00:06:25.337 power becomes a very major effect.

NOTE Confidence: 0.834147965

00:06:28.970 --> 00:06:31.690 So in summary of the genetics big picture,

NOTE Confidence: 0.834147965

00:06:31.690 --> 00:06:33.670 the genetics of autoimmune

NOTE Confidence: 0.834147965

00:06:33.670 --> 00:06:35.650 disease dictates lower activation

NOTE Confidence: 0.834147965

00:06:35.650 --> 00:06:37.490 threshold of different cell types,

NOTE Confidence: 0.834147965

00:06:37.490 --> 00:06:40.937 including TH 17 cell B cells and T regs

NOTE Confidence: 0.834147965

00:06:40.937 --> 00:06:44.890 in the dozen or so genes we've looked at.

NOTE Confidence: 0.834147965

00:06:44.890 --> 00:06:46.976 I also say we've just started a

NOTE Confidence: 0.834147965

00:06:46.976 --> 00:06:48.650 collaboration with Steve Robbins just

NOTE Confidence: 0.834147965

00:06:48.650 --> 00:06:50.810 recruiting here from the Broad Institute.

NOTE Confidence: 0.834147965

00:06:50.810 --> 00:06:52.515 We had these wonderful techniques

NOTE Confidence: 0.834147965

00:06:52.515 --> 00:06:54.220 of looking at genetic variants

NOTE Confidence: 0.834147965

00:06:54.273 --> 00:06:55.868 and different cell types look

NOTE Confidence: 0.834147965

00:06:55.868 --> 00:06:57.463 into effect on motor function.

NOTE Confidence: 0.834147965

00:06:57.470 --> 00:06:59.584 So there are tools emerging which allows

NOTE Confidence: 0.834147965

00:06:59.584 --> 00:07:02.090 us to take a whole genome approaches.

NOTE Confidence: 0.834147965

00:07:02.090 --> 00:07:03.392 So getting back to the question

NOTE Confidence: 0.834147965

00:07:03.392 --> 00:07:04.043 I started with,

NOTE Confidence: 0.834147965

00:07:04.050 --> 00:07:06.507 you know the cause of multiple sclerosis,

NOTE Confidence: 0.834147965

00:07:06.510 --> 00:07:07.838 here's our working model.

NOTE Confidence: 0.817416687142857

00:07:09.910 --> 00:07:10.735 That's the genetically,

NOTE Confidence: 0.817416687142857

00:07:10.735 --> 00:07:13.313 as I said earlier, it's a genetically

NOTE Confidence: 0.817416687142857

00:07:13.313 --> 00:07:14.786 mediated autoimmune disease.

NOTE Confidence: 0.817416687142857

00:07:14.790 --> 00:07:17.214 It's initiating the periphery by T

NOTE Confidence: 0.817416687142857

00:07:17.214 --> 00:07:19.340 cells and macrophages that traffic

NOTE Confidence: 0.817416687142857

00:07:19.340 --> 00:07:21.545 into the central nervous system.

NOTE Confidence: 0.817416687142857

00:07:21.550 --> 00:07:24.358 So the the idea is that there are

NOTE Confidence: 0.817416687142857

00:07:24.358 --> 00:07:26.515 microbial antigens likely cross reactive

NOTE Confidence: 0.817416687142857

00:07:26.515 --> 00:07:29.275 with myelin that something happens to

NOTE Confidence: 0.817416687142857

00:07:29.275 --> 00:07:31.899 activate these antigen presenting cells.

NOTE Confidence: 0.817416687142857

00:07:31.900 --> 00:07:34.708 Probably be sales, probably EB though

NOTE Confidence: 0.817416687142857

00:07:34.708 --> 00:07:37.329 there's no biology behind that yet.

NOTE Confidence: 0.817416687142857

00:07:37.330 --> 00:07:38.998 There's expression of

NOTE Confidence: 0.817416687142857

00:07:38.998 --> 00:07:40.110 costimulatory molecules.

NOTE Confidence: 0.817416687142857

00:07:40.110 --> 00:07:41.620 We have activation of viral

NOTE Confidence: 0.817416687142857

00:07:41.620 --> 00:07:43.835 reactive T cells now we all have

NOTE Confidence: 0.817416687142857

00:07:43.835 --> 00:07:45.749 autoreactive T cells in our blood.

NOTE Confidence: 0.817416687142857

00:07:45.750 --> 00:07:47.736 I could clone mold reactive T

NOTE Confidence: 0.817416687142857

00:07:47.736 --> 00:07:49.830 cells from menu in this room.

NOTE Confidence: 0.817416687142857

00:07:49.830 --> 00:07:51.150 And a number of years ago,

NOTE Confidence: 0.817416687142857

00:07:51.150 --> 00:07:53.130 back in in the late 80s,

NOTE Confidence: 0.817416687142857

00:07:53.130 --> 00:07:55.010 we developed technologies for looking

NOTE Confidence: 0.817416687142857

00:07:55.010 --> 00:07:57.473 at autoreactive T cells were able to

NOTE Confidence: 0.817416687142857

00:07:57.473 --> 00:07:59.569 show for the first time that there are

NOTE Confidence: 0.817416687142857

00:07:59.627 --> 00:08:01.846 in fact autoreactive T cells in humans.

NOTE Confidence: 0.817416687142857

00:08:01.850 --> 00:08:04.736 Highly robust response and we identified

NOTE Confidence: 0.817416687142857

00:08:04.736 --> 00:08:07.623 a dominant epitope Amal and basic

NOTE Confidence: 0.817416687142857

00:08:07.623 --> 00:08:10.386 protein are recognized as 84102 region

NOTE Confidence: 0.817416687142857

00:08:10.386 --> 00:08:13.416 which went on to to find how it

NOTE Confidence: 0.817416687142857

00:08:13.416 --> 00:08:15.940 bounded MHC in a form post doc in the lab,

NOTE Confidence: 0.817416687142857

00:08:15.940 --> 00:08:18.736 kyouka fennick with Don Wiley went

NOTE Confidence: 0.817416687142857

00:08:18.736 --> 00:08:21.665 down to crystallize this these clones

NOTE Confidence: 0.817416687142857

00:08:21.665 --> 00:08:24.605 recognizing this epitope with the T

NOTE Confidence: 0.817416687142857

00:08:24.605 --> 00:08:28.350 cell receptor and MHC but was more.

NOTE Confidence: 0.817416687142857

00:08:28.350 --> 00:08:30.758 Interesting to me was the fact that we

NOTE Confidence: 0.817416687142857

00:08:30.758 --> 00:08:33.509 also found reactivity in healthy individuals.

NOTE Confidence: 0.817416687142857

00:08:33.510 --> 00:08:34.440 Significant reactivity

NOTE Confidence: 0.817416687142857

00:08:34.440 --> 00:08:36.765 led to decades of work.

NOTE Confidence: 0.817416687142857

00:08:36.770 --> 00:08:38.480 Why do we have autoreactive

NOTE Confidence: 0.817416687142857

00:08:38.480 --> 00:08:40.190 T cells in their circulation?

NOTE Confidence: 0.817416687142857

00:08:40.190 --> 00:08:42.126 This is work done by will count here,

NOTE Confidence: 0.817416687142857

00:08:42.130 --> 00:08:46.239 published in STM about seven years ago.

NOTE Confidence: 0.817416687142857

00:08:46.240 --> 00:08:48.075 This is principal component analysis

NOTE Confidence: 0.817416687142857

00:08:48.075 --> 00:08:51.031 looking at T cell reactivity using a T

NOTE Confidence: 0.817416687142857

00:08:51.031 --> 00:08:52.796 cell library approach against published.

NOTE Confidence: 0.817416687142857

00:08:52.800 --> 00:08:55.408 Just point out that the paper no peptide

NOTE Confidence: 0.817416687142857

00:08:55.408 --> 00:08:57.580 control anger can the myelin peptides.

NOTE Confidence: 0.817416687142857

00:08:57.580 --> 00:09:00.260 You can see that the red is Ms.

NOTE Confidence: 0.817416687142857

00:09:00.260 --> 00:09:04.382 patients that they tend to go off to GMCSF

NOTE Confidence: 0.817416687142857

00:09:04.382 --> 00:09:08.187 gamma in 17 whereas healthy individuals.

NOTE Confidence: 0.817416687142857

00:09:08.190 --> 00:09:10.332 The main reactive T cells need

NOTE Confidence: 0.817416687142857

00:09:10.332 --> 00:09:12.490 aisle 10 suppressive soda comma,

NOTE Confidence: 0.817416687142857

00:09:12.490 --> 00:09:14.410 which makes terrific sense.

NOTE Confidence: 0.817416687142857

00:09:14.410 --> 00:09:16.398 And if you do single cell cloning

NOTE Confidence: 0.817416687142857

00:09:16.398 --> 00:09:18.299 rather than the library approach,

NOTE Confidence: 0.817416687142857

00:09:18.300 --> 00:09:20.804 you can see that and help the individuals.

NOTE Confidence: 0.817416687142857

00:09:20.810 --> 00:09:23.850 They tend to make aisle 10 with single

NOTE Confidence: 0.817416687142857

00:09:23.850 --> 00:09:26.509 cell they tend they make all ten,

NOTE Confidence: 0.817416687142857

00:09:26.510 --> 00:09:27.968 that is Ms.

NOTE Confidence: 0.817416687142857

00:09:27.968 --> 00:09:30.884 patients making 17 GMCSF less gamma.

NOTE Confidence: 0.817416687142857

00:09:30.890 --> 00:09:33.361 So suggest that these aisle 10 secreting

NOTE Confidence: 0.817416687142857

00:09:33.361 --> 00:09:35.930 cells and all of us may play a role.

NOTE Confidence: 0.817416687142857

00:09:35.930 --> 00:09:38.150 For example one has damage.

NOTE Confidence: 0.817416687142857

00:09:38.150 --> 00:09:40.718 The brain stroke other factors that

NOTE Confidence: 0.817416687142857

00:09:40.718 --> 00:09:43.483 these cells may circulate into the

NOTE Confidence: 0.817416687142857

00:09:43.483 --> 00:09:45.938 nervous system involving scar formation.

NOTE Confidence: 0.817416687142857

00:09:45.940 --> 00:09:47.820 So.

NOTE Confidence: 0.817416687142857

00:09:47.820 --> 00:09:49.116 What we find is,

NOTE Confidence: 0.817416687142857

00:09:49.116 --> 00:09:50.776 so we have this situation,

NOTE Confidence: 0.817416687142857

00:09:50.780 --> 00:09:52.748 we have aisle 10 secreting cells

NOTE Confidence: 0.817416687142857

00:09:52.748 --> 00:09:53.732 in healthy individuals,

NOTE Confidence: 0.817416687142857

00:09:53.740 --> 00:09:55.686 but you also have regulatory T cells.

NOTE Confidence: 0.817416687142857

00:09:55.690 --> 00:09:58.795 Look to both TR1 and Fox V3 cells which

NOTE Confidence: 0.817416687142857

00:09:58.795 --> 00:10:01.710 are preventing this from happening.

NOTE Confidence: 0.817416687142857

00:10:01.710 --> 00:10:03.999 But multiple sclerosis is a loss of

NOTE Confidence: 0.817416687142857

00:10:03.999 --> 00:10:06.350 these Fox P3 regulatory T cells.

NOTE Confidence: 0.817416687142857

00:10:06.350 --> 00:10:09.200 I'll show you some recent unpublished

NOTE Confidence: 0.817416687142857

00:10:09.200 --> 00:10:11.510 data related to PRDM one.

NOTE Confidence: 0.817416687142857

00:10:11.510 --> 00:10:13.720 So the hypothesis is that

NOTE Confidence: 0.817416687142857

00:10:13.720 --> 00:10:15.046 in healthy individuals,

NOTE Confidence: 0.817416687142857

00:10:15.050 --> 00:10:17.858 these T regs prevent activation of

NOTE Confidence: 0.817416687142857

00:10:17.858 --> 00:10:20.030 autoreactive T cells where's Ms.

NOTE Confidence: 0.817416687142857

00:10:20.030 --> 00:10:21.056 patients are defective.

NOTE Confidence: 0.817416687142857

00:10:21.056 --> 00:10:23.450 This is work done by Dizzy Begleiten,

NOTE Confidence: 0.817416687142857

00:10:23.450 --> 00:10:24.842 Claire Batch Allen,

NOTE Confidence: 0.817416687142857

00:10:24.842 --> 00:10:27.626 published now almost 20 years ago,

NOTE Confidence: 0.81772124

00:10:27.630 --> 00:10:29.235 which was the first demonstration

NOTE Confidence: 0.81772124

00:10:29.235 --> 00:10:31.459 of T Reg dysfunction in the human.

NOTE Confidence: 0.81772124

00:10:31.460 --> 00:10:32.196 Autoimmune disease,

NOTE Confidence: 0.81772124

00:10:32.196 --> 00:10:35.140 these are all new ones that untreated Ms.

NOTE Confidence: 0.81772124

00:10:35.140 --> 00:10:37.060 patients or healthy donors and

NOTE Confidence: 0.81772124

00:10:37.060 --> 00:10:39.493 this is the presence of oppression

NOTE Confidence: 0.81772124

00:10:39.493 --> 00:10:41.663 perforation different ratios of T

NOTE Confidence: 0.81772124

00:10:41.663 --> 00:10:44.736 regs and you can see this market

NOTE Confidence: 0.81772124

00:10:44.736 --> 00:10:46.836 demolition diminish chip of Reg

NOTE Confidence: 0.81772124

00:10:46.836 --> 00:10:49.910 function in vitro in patients with Ms.

NOTE Confidence: 0.81772124

00:10:49.910 --> 00:10:52.628 and the same thing been found in type one

NOTE Confidence: 0.81772124

00:10:52.628 --> 00:10:54.599 diabetes everyone to arthritis went on

NOTE Confidence: 0.81772124

00:10:54.599 --> 00:10:57.200 to show that the T regs and patient Ms.

NOTE Confidence: 0.81772124

00:10:57.200 --> 00:10:58.915 work done by Margaret Dominguez

NOTE Confidence: 0.81772124

00:10:58.915 --> 00:11:01.530 Pierre is that these T regs and MSN.

NOTE Confidence: 0.81772124

00:11:01.530 --> 00:11:02.850 Making games that Fearon.

NOTE Confidence: 0.81772124

00:11:02.850 --> 00:11:04.500 Here we took T Reg,

NOTE Confidence: 0.81772124

00:11:04.500 --> 00:11:06.900 stimulated for four hours of PNA on a

NOTE Confidence: 0.81772124

00:11:06.900 --> 00:11:09.160 mycin and measured gamma secretion,

NOTE Confidence: 0.81772124

00:11:09.160 --> 00:11:11.572 purified populations and using

NOTE Confidence: 0.81772124

00:11:11.572 --> 00:11:12.778 sample control,

NOTE Confidence: 0.81772124

00:11:12.780 --> 00:11:15.956 aisle 17 versus gaming can see this gamma.

NOTE Confidence: 0.81772124

00:11:15.960 --> 00:11:16.905 They all express.

NOTE Confidence: 0.81772124

00:11:16.905 --> 00:11:19.530 Foxp 3 is a summary of these data

NOTE Confidence: 0.81772124

00:11:19.530 --> 00:11:21.588 that these T regs were making.

NOTE Confidence: 0.81772124

00:11:21.590 --> 00:11:21.907 Gamma,

NOTE Confidence: 0.81772124

00:11:21.907 --> 00:11:24.126 and I'll just point out I'll show

NOTE Confidence: 0.81772124

00:11:24.126 --> 00:11:26.474 a little bit in a few minutes

NOTE Confidence: 0.81772124

00:11:26.474 --> 00:11:27.794 that dysfunctional T Rex.

NOTE Confidence: 0.81772124

00:11:27.800 --> 00:11:29.912 What's happening is they go from

NOTE Confidence: 0.81772124

00:11:29.912 --> 00:11:31.730 suppressor cells to effector cells.

NOTE Confidence: 0.81772124

00:11:31.730 --> 00:11:34.430 And start making game interferon.

NOTE Confidence: 0.81772124

00:11:34.430 --> 00:11:35.225 So an Ms.

NOTE Confidence: 0.81772124

00:11:35.225 --> 00:11:37.468 is not just bad genes, not bad environment,

NOTE Confidence: 0.81772124

00:11:37.468 --> 00:11:38.998 but the bad interaction between

NOTE Confidence: 0.81772124

00:11:38.998 --> 00:11:40.450 genes and the environment.

NOTE Confidence: 0.81772124

00:11:40.450 --> 00:11:42.678 It's very interested again

NOTE Confidence: 0.81772124

00:11:42.678 --> 00:11:44.349 in environmental influences.

NOTE Confidence: 0.81772124

00:11:44.350 --> 00:11:47.024 The instance of Ms. stops at 2000,

NOTE Confidence: 0.81772124

00:11:47.030 --> 00:11:48.670 but it's continued to increase.

NOTE Confidence: 0.81772124

00:11:48.670 --> 00:11:49.040 Ms.

NOTE Confidence: 0.81772124

00:11:49.040 --> 00:11:50.890 Crohn's disease, type one diabetes,

NOTE Confidence: 0.81772124

00:11:50.890 --> 00:11:52.252 continues to increase.

NOTE Confidence: 0.81772124

00:11:52.252 --> 00:11:55.430 And of course that can't be genetics.

NOTE Confidence: 0.81772124

00:11:55.430 --> 00:11:57.990 So the pathophysiology of Ms.

NOTE Confidence: 0.81772124

00:11:57.990 --> 00:12:00.286 will involve genetic environmental

NOTE Confidence: 0.81772124

00:12:00.286 --> 00:12:04.590 factors which lead to the immune response.

NOTE Confidence: 0.81772124

00:12:04.590 --> 00:12:09.478 So well just give background on this about.

NOTE Confidence: 0.81772124

00:12:09.480 --> 00:12:11.395 We started looking at microbiome

NOTE Confidence: 0.81772124

00:12:11.395 --> 00:12:14.559 versus TH 17 cells in the blood and

NOTE Confidence: 0.81772124

00:12:14.559 --> 00:12:16.899 we started looking at dietary history

NOTE Confidence: 0.81772124

00:12:16.899 --> 00:12:19.584 and we found that if you ate at a

NOTE Confidence: 0.81772124

00:12:19.584 --> 00:12:21.816 fast food restaurant more than twice

NOTE Confidence: 0.81772124

00:12:21.816 --> 00:12:25.080 a week you had increased dial 17 cells.

NOTE Confidence: 0.81772124

00:12:25.080 --> 00:12:26.536 Statistically significant.

NOTE Confidence: 0.81772124

00:12:26.536 --> 00:12:29.462 We said really and said,

NOTE Confidence: 0.81772124

00:12:29.462 --> 00:12:30.946 well wasn't the golden

NOTE Confidence: 0.81772124

00:12:30.946 --> 00:12:33.385 arches provide that and salt.

NOTE Confidence: 0.81772124

00:12:33.385 --> 00:12:35.800 So we did an incredibly simple experiment.

NOTE Confidence: 0.81772124

00:12:35.800 --> 00:12:38.320 This work done by Marcus Kletzel,

NOTE Confidence: 0.81772124

00:12:38.320 --> 00:12:40.366 we added salt to the culture.

NOTE Confidence: 0.81772124

00:12:40.370 --> 00:12:41.730 And the same time,

NOTE Confidence: 0.81772124

00:12:41.730 --> 00:12:44.171 my dear friend and colleague Vijay Kutru

NOTE Confidence: 0.81772124

00:12:44.171 --> 00:12:46.523 was looking at TH 17 cell induction,

NOTE Confidence: 0.81772124

00:12:46.530 --> 00:12:49.185 identified SGK one as critical

NOTE Confidence: 0.81772124

00:12:49.185 --> 00:12:51.309 inducing TH 17 cells.

NOTE Confidence: 0.81772124

00:12:51.310 --> 00:12:53.846 We are very we do lab things together.

NOTE Confidence: 0.81772124

00:12:53.850 --> 00:12:56.866 We're very closely he told that SGK one,

NOTE Confidence: 0.81772124

00:12:56.870 --> 00:12:58.676 I told him that salt and we

NOTE Confidence: 0.81772124

00:12:58.676 --> 00:13:00.249 did the papers in parallel.

NOTE Confidence: 0.81772124

00:13:00.250 --> 00:13:02.090 I'll just do a little just on terms

NOTE Confidence: 0.81772124

00:13:02.090 --> 00:13:03.987 of we couldn't have started competing

NOTE Confidence: 0.81772124

00:13:03.987 --> 00:13:06.045 who could get this out first?

NOTE Confidence: 0.81772124

00:13:06.050 --> 00:13:07.870 But we're much more clever than that.

NOTE Confidence: 0.81772124

00:13:07.870 --> 00:13:10.348 We worked in parallel, sent the papers.

NOTE Confidence: 0.81772124

00:13:10.350 --> 00:13:13.550 Back-to-back to a weekly journal.

NOTE Confidence: 0.81772124

00:13:13.550 --> 00:13:15.863 And when the editor said, well,

NOTE Confidence: 0.81772124

00:13:15.863 --> 00:13:17.354 did you know about each other's work,

NOTE Confidence: 0.81772124

00:13:17.360 --> 00:13:20.450 we said no, not really,

NOTE Confidence: 0.81772124

00:13:20.450 --> 00:13:21.938 but no one would have believed

NOTE Confidence: 0.81772124

00:13:21.938 --> 00:13:22.930 that salt did this,

NOTE Confidence: 0.81772124

00:13:22.930 --> 00:13:24.282 but having two laboratories

NOTE Confidence: 0.81772124

00:13:24.282 --> 00:13:26.698 showing the same thing at a much

NOTE Confidence: 0.81772124

00:13:26.698 --> 00:13:28.288 more credence to the work.

NOTE Confidence: 0.81772124

00:13:28.290 --> 00:13:30.514 So it was and we've gone on to

NOTE Confidence: 0.81772124

00:13:30.514 --> 00:13:33.251 look at the effect of of salt and

NOTE Confidence: 0.81772124

00:13:33.251 --> 00:13:35.353 other factors in terms of fat

NOTE Confidence: 0.81772124

00:13:35.353 --> 00:13:37.219 in terms of T Reg function.

NOTE Confidence: 0.817069043333333

00:13:37.220 --> 00:13:38.750 So I'll just show you some of these data.

NOTE Confidence: 0.817069043333333

00:13:38.750 --> 00:13:40.430 They're really quite remarkable.

NOTE Confidence: 0.817069043333333

00:13:40.430 --> 00:13:42.530 If you add 40 milliequivalents

NOTE Confidence: 0.817069043333333

00:13:42.530 --> 00:13:44.158 of salt to a culture,

NOTE Confidence: 0.817069043333333

00:13:44.160 --> 00:13:45.860 you have logarithmic increases,

NOTE Confidence: 0.817069043333333

00:13:45.860 --> 00:13:49.620 dial 17 and M RNA and and secretion.

NOTE Confidence: 0.817069043333333

00:13:49.620 --> 00:13:50.700 They may be saying yourself,

NOTE Confidence: 0.817069043333333

00:13:50.700 --> 00:13:53.601 this is artificial right concentration.

NOTE Confidence: 0.817069043333333

00:13:53.601 --> 00:13:55.540 Salt and blood is about 150,

NOTE Confidence: 0.817069043333333

00:13:55.540 --> 00:13:58.692 which is what sea water is, turns out

NOTE Confidence: 0.817069043333333

00:13:58.692 --> 00:14:02.208 the concentration of salt in tissues.

NOTE Confidence: 0.817069043333333

00:14:02.210 --> 00:14:05.186 Is higher, it's about 18190 and

NOTE Confidence: 0.817069043333333

00:14:05.186 --> 00:14:08.180 blood is a suppressive condition.

NOTE Confidence: 0.817069043333333

00:14:08.180 --> 00:14:09.884 You don't want T cells being

NOTE Confidence: 0.817069043333333

00:14:09.884 --> 00:14:11.380 activated in the peripheral blood.

NOTE Confidence: 0.817069043333333

00:14:11.380 --> 00:14:14.444 So when T cells traffic into the tissue,

NOTE Confidence: 0.817069043333333

00:14:14.450 --> 00:14:17.314 they're in the condition of leading to more

NOTE Confidence: 0.817069043333333

00:14:17.314 --> 00:14:19.470 activation which is what we were seeing.

NOTE Confidence: 0.817069043333333

00:14:19.470 --> 00:14:21.942 I also say that a recent paper by

NOTE Confidence: 0.817069043333333

00:14:21.942 --> 00:14:23.952 another group in Germany showed

NOTE Confidence: 0.817069043333333

00:14:23.952 --> 00:14:26.157 increased salt concentration using MRI

NOTE Confidence: 0.817069043333333

00:14:26.157 --> 00:14:28.750 magnets in tissue skin tissue of Ms.

NOTE Confidence: 0.817069043333333

00:14:28.750 --> 00:14:31.140 patients compared to the controls.

NOTE Confidence: 0.817069043333333

00:14:31.140 --> 00:14:32.556 So we also this work done.

NOTE Confidence: 0.817069043333333

00:14:32.560 --> 00:14:34.435 By the talented graduate student

NOTE Confidence: 0.817069043333333

00:14:34.435 --> 00:14:36.310 of the NADPH Mandatory Hernandez.

NOTE Confidence: 0.817069043333333

00:14:36.310 --> 00:14:37.913 And she showed that if you add

NOTE Confidence: 0.817069043333333

00:14:37.913 --> 00:14:38.950 salt to T regs.

NOTE Confidence: 0.817069043333333

00:14:38.950 --> 00:14:41.430 So here we have T Reg effector cells,

NOTE Confidence: 0.817069043333333

00:14:41.430 --> 00:14:43.010 we load them with a green dot at the very

NOTE Confidence: 0.817069043333333

00:14:43.051 --> 00:14:44.437 green that stimulates them not dead.

NOTE Confidence: 0.817069043333333

00:14:44.440 --> 00:14:46.176 With the dye at T regs to go

NOTE Confidence: 0.817069043333333

00:14:46.176 --> 00:14:47.130 from here to here,

NOTE Confidence: 0.817069043333333

00:14:47.130 --> 00:14:48.670 they suppress entering the cell,

NOTE Confidence: 0.817069043333333

00:14:48.670 --> 00:14:50.370 cycle through the same thing

NOTE Confidence: 0.817069043333333

00:14:50.370 --> 00:14:51.390 with sodium chloride,

NOTE Confidence: 0.817069043333333

00:14:51.390 --> 00:14:52.680 they lose functionality.

NOTE Confidence: 0.763559449444445

00:14:55.130 --> 00:14:57.842 And the mechanism, if you look at SGK

NOTE Confidence: 0.763559449444445

00:14:57.842 --> 00:15:00.839 one would solve it goes up in the T regs.

NOTE Confidence: 0.763559449444445

00:15:00.840 --> 00:15:04.017 You can knock down the SGK one with the

NOTE Confidence: 0.763559449444445

00:15:04.017 --> 00:15:07.264 short hairpin RNA and then if you look

NOTE Confidence: 0.763559449444445

00:15:07.264 --> 00:15:10.040 at function here's effective function.

NOTE Confidence: 0.763559449444445

00:15:10.040 --> 00:15:12.480 If you knockout SGK one you go from

NOTE Confidence: 0.763559449444445

00:15:12.480 --> 00:15:14.880 control to here and restore function.

NOTE Confidence: 0.763559449444445

00:15:14.880 --> 00:15:17.176 So it was happening so also inducing

NOTE Confidence: 0.763559449444445

00:15:17.176 --> 00:15:19.500 SGK one with gamma difference secretion

NOTE Confidence: 0.763559449444445

00:15:19.500 --> 00:15:22.454 and T regs leading lots of function.

NOTE Confidence: 0.763559449444445

00:15:22.460 --> 00:15:25.421 So I'm presenting to you the importance

NOTE Confidence: 0.763559449444445

00:15:25.421 --> 00:15:28.469 of SGK one as a central factor.

NOTE Confidence: 0.763559449444445

00:15:28.470 --> 00:15:30.786 And loss of T Rex function.

NOTE Confidence: 0.763559449444445

00:15:30.790 --> 00:15:32.310 So come back to that in a moment,

NOTE Confidence: 0.763559449444445

00:15:32.310 --> 00:15:34.590 one of the great surprises in my life.

NOTE Confidence: 0.763559449444445

00:15:34.590 --> 00:15:37.152 So then the question what's the

NOTE Confidence: 0.763559449444445

00:15:37.152 --> 00:15:38.433 transcriptional circuit driving

NOTE Confidence: 0.763559449444445

00:15:38.433 --> 00:15:40.144 dysfunctional foxies through positive

NOTE Confidence: 0.763559449444445

00:15:40.144 --> 00:15:42.189 regulatory T cells in autoimmunity?

NOTE Confidence: 0.763559449444445

00:15:42.190 --> 00:15:44.398 That's can we identify a master

NOTE Confidence: 0.763559449444445

00:15:44.398 --> 00:15:46.810 regulator of T cell dysfunction.

NOTE Confidence: 0.763559449444445

00:15:46.810 --> 00:15:48.623 Let me just say this is work

NOTE Confidence: 0.763559449444445

00:15:48.623 --> 00:15:49.890 done by Thomas Sabita,

NOTE Confidence: 0.763559449444445

00:15:49.890 --> 00:15:52.250 who started as a postdoc is now in the system

NOTE Confidence: 0.763559449444445

00:15:52.308 --> 00:15:54.618 professor and there's really represents his,

NOTE Confidence: 0.763559449444445

00:15:54.620 --> 00:15:55.736 his original work.

NOTE Confidence: 0.763559449444445

00:15:55.736 --> 00:15:59.007 So what we basically did was performed a

NOTE Confidence: 0.763559449444445

00:15:59.007 --> 00:16:01.407 comprehensive transcriptomic and epigenomic.

NOTE Confidence: 0.763559449444445

00:16:01.410 --> 00:16:03.242 Profiling doing bulk and

NOTE Confidence: 0.763559449444445

00:16:03.242 --> 00:16:05.532 signals of RNA seek attack.

NOTE Confidence: 0.763559449444445

00:16:05.540 --> 00:16:08.350 Seek for epigenetic regulation genome

NOTE Confidence: 0.763559449444445

00:16:08.350 --> 00:16:10.598 wide for chromatid accessibility.

NOTE Confidence: 0.763559449444445

00:16:10.600 --> 00:16:12.975 He did transcription factor footprint

NOTE Confidence: 0.763559449444445

00:16:12.975 --> 00:16:15.706 analysis and accessible chromatin regions and

NOTE Confidence: 0.763559449444445

00:16:15.706 --> 00:16:18.352 look to the E QTL effects of Automeris Lucci.

NOTE Confidence: 0.763559449444445

00:16:18.360 --> 00:16:21.078 I'll just just show data on the 1st 2:00.

NOTE Confidence: 0.763559449444445

00:16:21.080 --> 00:16:24.347 This is a whole one hour talk in itself.

NOTE Confidence: 0.763559449444445

00:16:24.350 --> 00:16:26.429 And then we did a CRISPER activation

NOTE Confidence: 0.763559449444445

00:16:26.429 --> 00:16:27.640 based validation of this.

NOTE Confidence: 0.763559449444445

00:16:27.640 --> 00:16:29.148 It's regulatory elements getting

NOTE Confidence: 0.763559449444445

00:16:29.148 --> 00:16:30.656 at the molecular mechanism.

NOTE Confidence: 0.763559449444445

00:16:30.660 --> 00:16:32.232 So it's amazing what we can

NOTE Confidence: 0.763559449444445

00:16:32.232 --> 00:16:33.560 do in human biology now.

NOTE Confidence: 0.763559449444445

00:16:33.560 --> 00:16:34.936 It's unimaginable years ago.

NOTE Confidence: 0.763559449444445

00:16:34.936 --> 00:16:37.386 So first of all let me show

NOTE Confidence: 0.763559449444445

00:16:37.386 --> 00:16:38.630 you what we found.

NOTE Confidence: 0.763559449444445

00:16:38.630 --> 00:16:41.730 Found increases in PRDM 1.

NOTE Confidence: 0.763559449444445

00:16:41.730 --> 00:16:44.346 Now for those of you who are mouse

NOTE Confidence: 0.763559449444445

00:16:44.346 --> 00:16:47.109 people who say this doesn't make sense.

NOTE Confidence: 0.763559449444445

00:16:47.110 --> 00:16:49.462 It's it's well known that PRD one

NOTE Confidence: 0.763559449444445

00:16:49.462 --> 00:16:51.268 increases T Reg function announce

NOTE Confidence: 0.763559449444445

00:16:51.268 --> 00:16:53.809 T cells and I'll show you what

NOTE Confidence: 0.763559449444445

00:16:53.809 --> 00:16:56.264 what it was and that it we found

NOTE Confidence: 0.763559449444445

00:16:56.264 --> 00:16:57.930 that it drives a dysfunctional

NOTE Confidence: 0.763559449444445

00:16:57.930 --> 00:16:59.530 sheets something like program.

NOTE Confidence: 0.763559449444445

00:16:59.530 --> 00:17:01.552 But what's happened is not the

NOTE Confidence: 0.763559449444445

00:17:01.552 --> 00:17:03.260 long form that's increased it's

NOTE Confidence: 0.763559449444445

00:17:03.260 --> 00:17:05.036 a short form which inhibits the

NOTE Confidence: 0.763559449444445

00:17:05.036 --> 00:17:07.049 long form and here's the kicker,

NOTE Confidence: 0.763559449444445

00:17:07.050 --> 00:17:10.587 it drives SGK one of all the kinases and

NOTE Confidence: 0.763559449444445

00:17:10.587 --> 00:17:13.568 proteins that could have been induced by

NOTE Confidence: 0.763559449444445

00:17:13.568 --> 00:17:17.009 the shore former PhD one it was the SGK 1.

NOTE Confidence: 0.763559449444445

00:17:17.010 --> 00:17:18.900 So let me now I showed you the results,

NOTE Confidence: 0.763559449444445

00:17:18.900 --> 00:17:20.178 let me show you the data.

NOTE Confidence: 0.763559449444445

00:17:20.180 --> 00:17:22.420 See here we looked at T Reg,

NOTE Confidence: 0.763559449444445

00:17:22.420 --> 00:17:25.892 this is doing vulgar in DC looking at

NOTE Confidence: 0.763559449444445

00:17:25.892 --> 00:17:27.902 overlapping differential expressed genes

NOTE Confidence: 0.763559449444445

00:17:27.902 --> 00:17:31.079 between memory T regs and seating for itself.

NOTE Confidence: 0.763559449444445

00:17:31.080 --> 00:17:33.612 So you can see this market

NOTE Confidence: 0.763559449444445

00:17:33.612 --> 00:17:35.300 increase in PRDM one,

NOTE Confidence: 0.763559449444445

00:17:35.300 --> 00:17:37.540 BCL 3 pin three will also regulated.

NOTE Confidence: 0.763559449444445

00:17:37.540 --> 00:17:40.699 These are all induced by PRDM one and genes

NOTE Confidence: 0.763559449444445

00:17:40.699 --> 00:17:43.817 are downregulated by PRDM one like ID 3,

NOTE Confidence: 0.763559449444445

00:17:43.820 --> 00:17:45.168 LBH were down regulated.

NOTE Confidence: 0.763559449444445

00:17:45.168 --> 00:17:47.190 So we had this increase in.

NOTE Confidence: 0.763559449444445

00:17:47.190 --> 00:17:50.799 PRDM one did a replication of the set of

NOTE Confidence: 0.763559449444445

00:17:50.799 --> 00:17:53.785 patients and showed here that the PRDM

NOTE Confidence: 0.763559449444445

00:17:53.785 --> 00:17:56.848 one is upregulated in patient with Ms.

NOTE Confidence: 0.763559449444445

00:17:56.850 --> 00:17:58.958 but again confusing because

NOTE Confidence: 0.763559449444445

00:17:58.958 --> 00:18:01.066 of the mouse data.

NOTE Confidence: 0.805132526666667

00:18:01.070 --> 00:18:02.828 It's all about mice of course,

NOTE Confidence: 0.805132526666667

00:18:02.830 --> 00:18:05.862 but then we learned that there are two

NOTE Confidence: 0.805132526666667

00:18:05.862 --> 00:18:09.125 isoforms in humans that don't exist in mice.

NOTE Confidence: 0.805132526666667

00:18:09.130 --> 00:18:11.979 Dry nosed mammals do not express a

NOTE Confidence: 0.805132526666667

00:18:11.979 --> 00:18:15.540 short form of PRDM one and so the

NOTE Confidence: 0.805132526666667

00:18:15.540 --> 00:18:17.790 short form the dominant negative.

NOTE Confidence: 0.805132526666667

00:18:17.790 --> 00:18:20.149 When we looked in normal cell types,

NOTE Confidence: 0.805132526666667

00:18:20.150 --> 00:18:22.678 we found that the short form is what's

NOTE Confidence: 0.805132526666667

00:18:22.678 --> 00:18:24.330 expression memory cells and T regs,

NOTE Confidence: 0.805132526666667

00:18:24.330 --> 00:18:26.920 but not in B cells.

NOTE Confidence: 0.805132526666667

00:18:26.920 --> 00:18:28.803 So then we looked at the short

NOTE Confidence: 0.805132526666667

00:18:28.803 --> 00:18:30.339 former period you want by PCR,

NOTE Confidence: 0.805132526666667

00:18:30.340 --> 00:18:31.925 and indeed it's this short

NOTE Confidence: 0.805132526666667

00:18:31.925 --> 00:18:33.193 form that's increased NS,

NOTE Confidence: 0.805132526666667

00:18:33.200 --> 00:18:35.908 not the long form.

NOTE Confidence: 0.805132526666667

00:18:35.910 --> 00:18:38.175 And we rapidly perform Western

NOTE Confidence: 0.805132526666667

00:18:38.175 --> 00:18:40.938 blotting to show that indeed the

NOTE Confidence: 0.805132526666667

00:18:40.938 --> 00:18:43.048 short form is what's induced.

NOTE Confidence: 0.805132526666667

00:18:43.050 --> 00:18:45.858 We then looked at the data sets in

NOTE Confidence: 0.805132526666667

00:18:45.858 --> 00:18:48.103 particular set by oted all that's

NOTE Confidence: 0.805132526666667

00:18:48.103 --> 00:18:50.514 published in cell and we found that

NOTE Confidence: 0.805132526666667

00:18:50.514 --> 00:18:53.504 the PRD one isoform PRD one is also

NOTE Confidence: 0.805132526666667

00:18:53.504 --> 00:18:55.889 increased in most autoimmune diseases.

NOTE Confidence: 0.805132526666667

00:18:55.890 --> 00:18:58.653 So appears to be a common regulator of in

NOTE Confidence: 0.805132526666667

00:18:58.653 --> 00:19:01.967 T regs among different autoimmune diseases.

NOTE Confidence: 0.805132526666667

00:19:01.970 --> 00:19:03.902 And of course PRD one drives the

NOTE Confidence: 0.805132526666667

00:19:03.902 --> 00:19:05.966 blimp one and we looked at blimp

NOTE Confidence: 0.805132526666667

00:19:05.966 --> 00:19:08.052 one expression and MST regs it was

NOTE Confidence: 0.805132526666667

00:19:08.052 --> 00:19:09.886 in and it was it was increased.

NOTE Confidence: 0.805132526666667

00:19:09.890 --> 00:19:13.060 So it wasn't memory T Rex and memory T Rex.

NOTE Confidence: 0.805132526666667

00:19:13.060 --> 00:19:15.755 By flow. By both PCR and flow.

NOTE Confidence: 0.72634748

00:19:17.930 --> 00:19:19.885 So then here's the experiment

NOTE Confidence: 0.72634748

00:19:19.885 --> 00:19:22.242 where we transfected PRD one into

NOTE Confidence: 0.72634748

00:19:22.242 --> 00:19:24.210 T regs and integer cat cells.

NOTE Confidence: 0.72634748

00:19:24.210 --> 00:19:27.261 We have the induction of SGK one and here's

NOTE Confidence: 0.72634748

00:19:27.261 --> 00:19:29.707 measuring SGK one and primary union T Rex.

NOTE Confidence: 0.72634748

00:19:29.710 --> 00:19:31.490 See this? When we overexpressed

NOTE Confidence: 0.72634748

00:19:31.490 --> 00:19:33.690 the short form of T regs,

NOTE Confidence: 0.72634748

00:19:33.690 --> 00:19:38.594 you had an increase in SGK one expression.

NOTE Confidence: 0.72634748

00:19:38.600 --> 00:19:40.230 And then if you go in and do all the

NOTE Confidence: 0.72634748

00:19:40.275 --> 00:19:42.078 other experiments, not get SGK one,

NOTE Confidence: 0.72634748

00:19:42.078 --> 00:19:44.846 you lose the loss of T rate function but the

NOTE Confidence: 0.72634748

00:19:44.846 --> 00:19:47.630 short form in T Rex become dysfunctional.

NOTE Confidence: 0.72634748

00:19:47.630 --> 00:19:49.950 The whole story came together.

NOTE Confidence: 0.72634748

00:19:49.950 --> 00:19:52.461 So this suggests to us that the short form

NOTE Confidence: 0.72634748

00:19:52.461 --> 00:19:55.367 of PD one may be critical in different

NOTE Confidence: 0.72634748

00:19:55.367 --> 00:19:57.769 autoimmune diseases and driving dysfunction.

NOTE Confidence: 0.72634748

00:19:57.770 --> 00:19:59.989 And again we believe it's related to

NOTE Confidence: 0.72634748

00:19:59.989 --> 00:20:02.602 salt and to genetic factors that will

NOTE Confidence: 0.72634748

00:20:02.602 --> 00:20:05.417 show the data particular CD toward the

NOTE Confidence: 0.72634748

00:20:05.417 --> 00:20:09.730 genetic variant in CD28 who drives a P1.

NOTE Confidence: 0.72634748

00:20:09.730 --> 00:20:12.894 Now switch gears and show some public,

NOTE Confidence: 0.72634748

00:20:12.900 --> 00:20:14.915 recently published work looking at

NOTE Confidence: 0.72634748

00:20:14.915 --> 00:20:17.296 T cell traffic between blood and

NOTE Confidence: 0.72634748

00:20:17.296 --> 00:20:19.368 the CNS and the single cell work.

NOTE Confidence: 0.72634748

00:20:19.370 --> 00:20:19.721 So.

NOTE Confidence: 0.72634748

00:20:19.721 --> 00:20:22.880 T cell traffic into the CNS is very tightly

NOTE Confidence: 0.72634748

00:20:22.956 --> 00:20:25.332 regulated and CXCR 3 positive cells

NOTE Confidence: 0.72634748

00:20:25.332 --> 00:20:28.410 are the ones that get into the brain,

NOTE Confidence: 0.72634748

00:20:28.410 --> 00:20:30.362 crossing the correct plexus

NOTE Confidence: 0.72634748

00:20:30.362 --> 00:20:31.826 near great interest,

NOTE Confidence: 0.72634748

00:20:31.830 --> 00:20:33.570 and they get into the brain.

NOTE Confidence: 0.72634748

00:20:33.570 --> 00:20:36.027 And what I'll show you is a T cells

NOTE Confidence: 0.72634748

00:20:36.027 --> 00:20:38.452 in the central nervous system are

NOTE Confidence: 0.72634748

00:20:38.452 --> 00:20:41.070 CXCR 3 positive and express Tibet

NOTE Confidence: 0.72634748

00:20:41.070 --> 00:20:42.906 and make gamma interferon.

NOTE Confidence: 0.72634748

00:20:42.910 --> 00:20:45.255 We believe that this relates to the

NOTE Confidence: 0.72634748

00:20:45.255 --> 00:20:47.111 fundamental observation by the late

NOTE Confidence: 0.72634748

00:20:47.111 --> 00:20:49.481 Ben Barris that astrocytes are driving

NOTE Confidence: 0.72634748

00:20:49.481 --> 00:20:50.869 homeostatic communication would not.

NOTE Confidence: 0.72634748

00:20:50.870 --> 00:20:53.942 This is Michael Glee up but also are

NOTE Confidence: 0.72634748

00:20:53.942 --> 00:20:56.033 driving through secretion of cholesterol

NOTE Confidence: 0.72634748

00:20:56.033 --> 00:20:59.364 and TGF beta are driving this T bet

NOTE Confidence: 0.72634748

00:20:59.364 --> 00:21:01.849 induction that isn't the T cells go

NOTE Confidence: 0.72634748

00:21:01.849 --> 00:21:04.076 into the nervous system then they'll

NOTE Confidence: 0.72634748

00:21:04.076 --> 00:21:07.030 you in the brain drives this function.

NOTE Confidence: 0.72634748

00:21:07.030 --> 00:21:09.018 So give them on the knowledge of

NOTE Confidence: 0.72634748

00:21:09.018 --> 00:21:10.950 particular genre pop or Lotto submitter.

NOTE Confidence: 0.72634748

00:21:10.950 --> 00:21:14.142 Our Krishnaswamy and David Vandyke and Lee

NOTE Confidence: 0.72634748

00:21:14.142 --> 00:21:17.109 sang together did this worker with us.

NOTE Confidence: 0.72634748

00:21:17.110 --> 00:21:19.510 And basically we took spinal

NOTE Confidence: 0.72634748

00:21:19.510 --> 00:21:21.430 fluid group of patients,

NOTE Confidence: 0.72634748

00:21:21.430 --> 00:21:25.006 isolated the spinal fluid homonuclear cells,

NOTE Confidence: 0.72634748

00:21:25.010 --> 00:21:27.698 perform 10X the usual way that

NOTE Confidence: 0.72634748

00:21:27.698 --> 00:21:29.890 most you're familiar with now.

NOTE Confidence: 0.72634748

00:21:29.890 --> 00:21:33.670 And then we perform this on 6 healthy donors,

NOTE Confidence: 0.72634748

00:21:33.670 --> 00:21:36.394 get the bed in the moment, 5 patient with Ms.

NOTE Confidence: 0.72634748

00:21:36.394 --> 00:21:38.650 And looked at over 100,000 cells

NOTE Confidence: 0.72634748

00:21:38.725 --> 00:21:40.790 into 50,000 T cell receptor.

NOTE Confidence: 0.72634748

00:21:40.790 --> 00:21:43.221 Now does show high level summary

NOTE Confidence: 0.72634748

00:21:43.221 --> 00:21:46.326 of the of this work.

NOTE Confidence: 0.72634748

00:21:46.330 --> 00:21:47.830 So first in terms of blood

NOTE Confidence: 0.72634748

00:21:47.830 --> 00:21:48.580 versus spinal fluid,

NOTE Confidence: 0.72634748

00:21:48.580 --> 00:21:51.282 what we found wasn't surprising that the

NOTE Confidence: 0.72634748

00:21:51.282 --> 00:21:53.765 majority of cells in the spinal fluid

NOTE Confidence: 0.72634748

00:21:53.765 --> 00:21:56.180 or T cells what we observed before.

NOTE Confidence: 0.72634748

00:21:56.180 --> 00:21:58.259 So we started first bikes adding a

NOTE Confidence: 0.72634748

00:21:58.259 --> 00:22:00.178 spinal fluid from patients with Ms.

NOTE Confidence: 0.72634748

00:22:00.180 --> 00:22:01.548 right blood spinal fluid.

NOTE Confidence: 0.72634748

00:22:01.548 --> 00:22:04.540 We found the spinal fluid was very inflamed.

NOTE Confidence: 0.72634748

00:22:04.540 --> 00:22:06.948 I love this picture and we're sitting

NOTE Confidence: 0.72634748

00:22:06.948 --> 00:22:09.009 at the immunology repeat this change

NOTE Confidence: 0.72634748

00:22:09.009 --> 00:22:11.582 that we need to do controls goes that

NOTE Confidence: 0.72634748

00:22:11.582 --> 00:22:14.003 means we have to do spinal taps on age

NOTE Confidence: 0.72634748

00:22:14.010 --> 00:22:17.292 match 20 something year old students

NOTE Confidence: 0.72634748

00:22:17.292 --> 00:22:20.470 to do that. So Full disclosure.

NOTE Confidence: 0.72634748

00:22:20.470 --> 00:22:25.148 I do not know who would spinal taps, I said.

NOTE Confidence: 0.72634748

00:22:25.148 --> 00:22:27.100 I do not want to know because I

NOTE Confidence: 0.901740950555556

00:22:27.163 --> 00:22:28.945 do not want to be accused

NOTE Confidence: 0.901740950555556

00:22:28.945 --> 00:22:30.078 of coercion, collusion.

NOTE Confidence: 0.901740950555556

00:22:30.078 --> 00:22:33.306 So only Jenna knows who volunteered.

NOTE Confidence: 0.901740950555556

00:22:33.310 --> 00:22:34.646 They're all de identified.

NOTE Confidence: 0.901740950555556

00:22:34.646 --> 00:22:37.478 But at the I acknowledge all these wonderful

NOTE Confidence: 0.901740950555556

00:22:37.478 --> 00:22:39.758 students who had Spinal Tap stuff.

NOTE Confidence: 0.901740950555556

00:22:39.760 --> 00:22:42.415 So these cells acquire an

NOTE Confidence: 0.901740950555556

00:22:42.415 --> 00:22:43.477 inflammatory signature.

NOTE Confidence: 0.901740950555556

00:22:43.480 --> 00:22:46.196 So just quickly the menu now fate

NOTE Confidence: 0.901740950555556

00:22:46.196 --> 00:22:48.389 where the cell progression of

NOTE Confidence: 0.901740950555556

00:22:48.389 --> 00:22:51.233 blood and CSF release fate maps.

NOTE Confidence: 0.901740950555556

00:22:51.240 --> 00:22:52.160 This is a fading out.

NOTE Confidence: 0.901740950555556

00:22:52.160 --> 00:22:54.848 The red is blood, the blue is CSF

NOTE Confidence: 0.901740950555556

00:22:54.848 --> 00:22:57.680 via very different characteristics.

NOTE Confidence: 0.901740950555556

00:22:57.680 --> 00:23:00.008 They sense potential of heat diffusion,

NOTE Confidence: 0.901740950555556

00:23:00.010 --> 00:23:02.940 if any based transition embedding.

NOTE Confidence: 0.901740950555556

00:23:02.940 --> 00:23:05.460 I love the words they come up with and

NOTE Confidence: 0.901740950555556

00:23:05.460 --> 00:23:07.920 that world, but it's a way of looking at it.

NOTE Confidence: 0.901740950555556

00:23:07.920 --> 00:23:10.184 Unsupervised visualization that looks

NOTE Confidence: 0.901740950555556

00:23:10.184 --> 00:23:13.580 at geometric distance between data points.

NOTE Confidence: 0.901740950555556

00:23:13.580 --> 00:23:15.155 So here's the original tissue

NOTE Confidence: 0.901740950555556

00:23:15.155 --> 00:23:16.415 on the fate map.

NOTE Confidence: 0.901740950555556

00:23:16.420 --> 00:23:17.660 We can define the CD.

NOTE Confidence: 0.901740950555556

00:23:17.660 --> 00:23:20.000 8 cells are here,

NOTE Confidence: 0.901740950555556

00:23:20.000 --> 00:23:22.340 CD4 cells are here.

NOTE Confidence: 0.901740950555556

00:23:22.340 --> 00:23:24.436 And we were able to describe we took

NOTE Confidence: 0.901740950555556

00:23:24.436 --> 00:23:26.083 the top 10 differential expressed

NOTE Confidence: 0.901740950555556

00:23:26.083 --> 00:23:28.547 genes in each cluster and to find

NOTE Confidence: 0.901740950555556

00:23:28.610 --> 00:23:30.638 different populations naive cells,

NOTE Confidence: 0.901740950555556

00:23:30.640 --> 00:23:31.574 naive CD4,

NOTE Confidence: 0.901740950555556

00:23:31.574 --> 00:23:34.376 CD 8 and really three different

NOTE Confidence: 0.901740950555556

00:23:34.376 --> 00:23:36.835 populations CSF cell we called CSF

NOTE Confidence: 0.901740950555556

00:23:36.835 --> 00:23:41.080 1/2 and three in memory CD8 cells.

NOTE Confidence: 0.901740950555556

00:23:41.080 --> 00:23:43.747 So one could do something very interesting,

NOTE Confidence: 0.901740950555556

00:23:43.750 --> 00:23:45.964 which is looking at the continuum

NOTE Confidence: 0.901740950555556

00:23:45.964 --> 00:23:47.890 between blood and spinal fluid,

NOTE Confidence: 0.901740950555556

00:23:47.890 --> 00:23:50.626 getting back to the point of how T

NOTE Confidence: 0.901740950555556

00:23:50.626 --> 00:23:53.208 cells change function going to tissue.

NOTE Confidence: 0.901740950555556

00:23:53.210 --> 00:23:55.562 So we merge the fate to fusion

NOTE Confidence: 0.901740950555556

00:23:55.562 --> 00:23:57.410 operator with the original identity

NOTE Confidence: 0.901740950555556

00:23:57.410 --> 00:24:00.490 of itself come up with a tissue score

NOTE Confidence: 0.901740950555556

00:24:00.490 --> 00:24:02.410 which is basically the probability

NOTE Confidence: 0.901740950555556

00:24:02.410 --> 00:24:04.659 of transitioning from one form to

NOTE Confidence: 0.901740950555556

00:24:04.659 --> 00:24:06.606 another in a random walk and you

NOTE Confidence: 0.901740950555556

00:24:06.606 --> 00:24:08.762 can see the Tisha score that their

NOTE Confidence: 0.901740950555556

00:24:08.762 --> 00:24:10.687 cells are very blood like over

NOTE Confidence: 0.901740950555556

00:24:10.687 --> 00:24:12.800 here CD4CD8 cells in transition

NOTE Confidence: 0.901740950555556

00:24:12.800 --> 00:24:15.500 and cells is very CSF like.

NOTE Confidence: 0.851845215

00:24:17.720 --> 00:24:20.520 And so I did have a reality test.

NOTE Confidence: 0.851845215

00:24:20.520 --> 00:24:21.780 Ensuring that tissue

NOTE Confidence: 0.851845215

00:24:21.780 --> 00:24:23.460 score captures no biology.

NOTE Confidence: 0.851845215

00:24:23.460 --> 00:24:26.904 ITG Force is the LA4CD49D and

NOTE Confidence: 0.851845215

00:24:26.904 --> 00:24:28.414 requires this T cell traffic

NOTE Confidence: 0.851845215

00:24:28.414 --> 00:24:30.200 into the into nervous system.

NOTE Confidence: 0.851845215

00:24:30.200 --> 00:24:31.820 It's a treatment for Ms.

NOTE Confidence: 0.851845215

00:24:31.820 --> 00:24:34.756 blocking T cell traffic and you can see

NOTE Confidence: 0.851845215

00:24:34.756 --> 00:24:37.938 that it's expressed predominantly in the T

NOTE Confidence: 0.851845215

00:24:37.938 --> 00:24:41.151 cells and transition CSL against the XR3,

NOTE Confidence: 0.851845215

00:24:41.151 --> 00:24:43.336 KEMA concord and fatty cell

NOTE Confidence: 0.851845215

00:24:43.336 --> 00:24:44.990 entry predominant expressed.

NOTE Confidence: 0.851845215

00:24:44.990 --> 00:24:47.478 It's expressed only really

NOTE Confidence: 0.851845215

00:24:47.478 --> 00:24:50.580 in PCNSL CR7 Express 9 T.

NOTE Confidence: 0.851845215

00:24:50.580 --> 00:24:52.530 So she excluded from the brain

NOTE Confidence: 0.851845215

00:24:52.530 --> 00:24:55.307 and you can see that it's almost

NOTE Confidence: 0.851845215

00:24:55.307 --> 00:24:57.647 exclusively in the peripheral blood.

NOTE Confidence: 0.851845215

00:24:57.650 --> 00:24:59.305 So we've found nine clusters

NOTE Confidence: 0.851845215

00:24:59.305 --> 00:25:01.430 of T cells and spinal fluid.

NOTE Confidence: 0.851845215

00:25:01.430 --> 00:25:04.022 We use the gene expressions imputed

NOTE Confidence: 0.851845215

00:25:04.022 --> 00:25:06.301 with something called magic because

NOTE Confidence: 0.851845215

00:25:06.301 --> 00:25:08.701 basically looked at gene expression

NOTE Confidence: 0.851845215

00:25:08.701 --> 00:25:11.310 across the gene expression patterns.

NOTE Confidence: 0.851845215

00:25:11.310 --> 00:25:12.858 You see different patterns

NOTE Confidence: 0.851845215

00:25:12.858 --> 00:25:14.406 across different tissue scores.

NOTE Confidence: 0.851845215

00:25:14.410 --> 00:25:14.655 Again,

NOTE Confidence: 0.851845215

00:25:14.655 --> 00:25:16.370 all the details in the paper have

NOTE Confidence: 0.851845215

00:25:16.370 --> 00:25:18.419 the 9 clusters and I want to start

NOTE Confidence: 0.851845215

00:25:18.419 --> 00:25:20.105 with the teach one cluster and

NOTE Confidence: 0.851845215

00:25:20.105 --> 00:25:21.665 think about single cell data.

NOTE Confidence: 0.851845215

00:25:21.670 --> 00:25:23.345 There's so many things you

NOTE Confidence: 0.851845215

00:25:23.345 --> 00:25:24.685 can explore with it.

NOTE Confidence: 0.851845215

00:25:24.690 --> 00:25:25.590 So to me,

NOTE Confidence: 0.851845215

00:25:25.590 --> 00:25:27.390 I find a few interesting stories,

NOTE Confidence: 0.851845215

00:25:27.390 --> 00:25:28.512 validate them biologically,

NOTE Confidence: 0.851845215

00:25:28.512 --> 00:25:31.130 get the data out in the literature,

NOTE Confidence: 0.851845215

00:25:31.130 --> 00:25:33.074 and I've been so pleased by how many

NOTE Confidence: 0.851845215

00:25:33.074 --> 00:25:35.077 others have taken our data and use

NOTE Confidence: 0.851845215

00:25:35.077 --> 00:25:36.542 it for really important experiment.

NOTE Confidence: 0.851845215

00:25:36.550 --> 00:25:38.110 That's what we're trying to do.

NOTE Confidence: 0.851845215

00:25:38.110 --> 00:25:41.470 So even treat bothers TH1 cluster.

NOTE Confidence: 0.851845215

00:25:41.470 --> 00:25:44.150 So if you look at the TH with the CD

NOTE Confidence: 0.851845215

00:25:44.227 --> 00:25:46.907 four cells to different populations,

NOTE Confidence: 0.851845215

00:25:46.910 --> 00:25:49.330 the CSF 3 populations particular

NOTE Confidence: 0.851845215

00:25:49.330 --> 00:25:52.215 and high amounts of gabito Ferrum

NOTE Confidence: 0.851845215

00:25:52.215 --> 00:25:54.465 tibets CXCR 3 run 3 stat.

NOTE Confidence: 0.851845215

00:25:54.470 --> 00:25:57.170 4, so an aisle 12 receptor,

NOTE Confidence: 0.851845215

00:25:57.170 --> 00:26:00.425 another CD4 population of tissue

NOTE Confidence: 0.851845215

00:26:00.425 --> 00:26:03.486 resident markers like lag 3CD-69

NOTE Confidence: 0.851845215

00:26:03.486 --> 00:26:05.766 and PRDM 1 interestingly enough

NOTE Confidence: 0.851845215

00:26:05.766 --> 00:26:08.350 and markets have soda toxicity,

NOTE Confidence: 0.851845215

00:26:08.350 --> 00:26:10.050 a grandson and grandson K,

NOTE Confidence: 0.851845215

00:26:10.050 --> 00:26:11.538 which is interesting.

NOTE Confidence: 0.851845215

00:26:11.538 --> 00:26:14.018 Colleague Michael Brenner at Harvard

NOTE Confidence: 0.851845215

00:26:14.018 --> 00:26:15.927 recently identified grandson Kay

NOTE Confidence: 0.851845215

00:26:15.927 --> 00:26:18.057 as being involved in complement

NOTE Confidence: 0.851845215

00:26:18.057 --> 00:26:20.254 deposition and finally CDA population

NOTE Confidence: 0.851845215

00:26:20.254 --> 00:26:22.389 markets at tissue residence and,

NOTE Confidence: 0.851845215

00:26:22.390 --> 00:26:25.798 not surprising cytotoxicity.

NOTE Confidence: 0.851845215

00:26:25.800 --> 00:26:27.858 So to summarize a lot of data,

NOTE Confidence: 0.851845215

00:26:27.860 --> 00:26:30.860 what do we find in the blood cells

NOTE Confidence: 0.851845215

00:26:30.860 --> 00:26:33.217 excluded from entering the CSF and

NOTE Confidence: 0.851845215

00:26:33.217 --> 00:26:36.037 we found cells that are rich for

NOTE Confidence: 0.851845215

00:26:36.037 --> 00:26:38.247 for traits necessary for entry

NOTE Confidence: 0.851845215

00:26:38.247 --> 00:26:41.101 and then finally markers for CSF

NOTE Confidence: 0.851845215

00:26:41.101 --> 00:26:43.636 entry and tissue dependent changes.

NOTE Confidence: 0.851845215

00:26:43.640 --> 00:26:46.587 So in CSF we found gamma interferon

NOTE Confidence: 0.851845215

00:26:46.587 --> 00:26:48.570 signature rest in T cells,

NOTE Confidence: 0.851845215

00:26:48.570 --> 00:26:49.772 cholesterol homeostasis,

NOTE Confidence: 0.851845215

00:26:49.772 --> 00:26:52.777 TGIF beta pathway and these

NOTE Confidence: 0.851845215

00:26:52.777 --> 00:26:54.977 cohabitated receptors will get

NOTE Confidence: 0.851845215

00:26:54.977 --> 00:26:56.867 to that in just a moment.

NOTE Confidence: 0.851845215

00:26:56.870 --> 00:26:57.810 So then the question is,

NOTE Confidence: 0.851845215

00:26:57.810 --> 00:27:00.102 do we actually see gamma difference

NOTE Confidence: 0.851845215

00:27:00.102 --> 00:27:02.570 creating T cells from spinal fluid?

NOTE Confidence: 0.851845215

00:27:02.570 --> 00:27:05.104 So first we looked at PPD one.

NOTE Confidence: 0.851845215

00:27:05.110 --> 00:27:07.651 So this is from another three healthy

NOTE Confidence: 0.851845215

00:27:07.651 --> 00:27:09.890 subjects looking at blood versus CSF.

NOTE Confidence: 0.851845215

00:27:09.890 --> 00:27:11.406 This is no stimulation,

NOTE Confidence: 0.851845215

00:27:11.406 --> 00:27:14.453 4 hours of stimulation with PM out of

NOTE Confidence: 0.851845215

00:27:14.453 --> 00:27:17.296 mice and see this market expression of PD1.

NOTE Confidence: 0.851845215

00:27:17.296 --> 00:27:19.612 And see itself compared to blood

NOTE Confidence: 0.851845215

00:27:19.612 --> 00:27:21.629 with stimulation goes even higher.

NOTE Confidence: 0.851845215

00:27:21.630 --> 00:27:24.654 So there is very high expression of this

NOTE Confidence: 0.851845215

00:27:24.654 --> 00:27:27.586 Co inhibitory stepter in spinal fluid cells.

NOTE Confidence: 0.851845215

00:27:27.590 --> 00:27:29.306 We then looked at that together,

NOTE Confidence: 0.851845215

00:27:29.310 --> 00:27:31.330 interferon response with blood and

NOTE Confidence: 0.851845215

00:27:31.330 --> 00:27:34.490 you can see this major gamma signature

NOTE Confidence: 0.851845215

00:27:34.490 --> 00:27:36.775 recapitulating what we found with

NOTE Confidence: 0.851845215

00:27:36.775 --> 00:27:39.840 the RNC data and compared to blood.

NOTE Confidence: 0.742978355

00:27:39.840 --> 00:27:41.970 So this is major gamma signature

NOTE Confidence: 0.742978355

00:27:41.970 --> 00:27:44.409 and T cells from spinal fluid.

NOTE Confidence: 0.742978355

00:27:44.410 --> 00:27:45.860 I'll show you another experiment

NOTE Confidence: 0.742978355

00:27:45.860 --> 00:27:47.020 which I found interesting.

NOTE Confidence: 0.742978355

00:27:47.020 --> 00:27:48.200 This is work we've done.

NOTE Confidence: 0.742978355

00:27:48.200 --> 00:27:51.152 We did looking at PD1 glioblastoma

NOTE Confidence: 0.742978355

00:27:51.152 --> 00:27:54.348 and basically we took the PD1 high,

NOTE Confidence: 0.742978355

00:27:54.350 --> 00:27:55.188 PD1 intermediate,

NOTE Confidence: 0.742978355

00:27:55.188 --> 00:27:58.121 PD one negative and total T cells

NOTE Confidence: 0.742978355

00:27:58.121 --> 00:28:00.309 stimulated them and not surprisingly

NOTE Confidence: 0.742978355

00:28:00.310 --> 00:28:03.846 PD1 high cells do not enter cell cycle.

NOTE Confidence: 0.742978355

00:28:03.850 --> 00:28:06.839 But they did make gamuts to pharon.

NOTE Confidence: 0.742978355

00:28:06.840 --> 00:28:10.410 3% to 50 to over 50%.

NOTE Confidence: 0.742978355

00:28:10.410 --> 00:28:12.734 So it suggests to us it's phenocopies,

NOTE Confidence: 0.742978355

00:28:12.740 --> 00:28:14.336 what we see in the brain,

NOTE Confidence: 0.742978355

00:28:14.340 --> 00:28:15.380 the cells in the brain,

NOTE Confidence: 0.742978355

00:28:15.380 --> 00:28:17.912 they're condition in the brain have

NOTE Confidence: 0.742978355

00:28:17.912 --> 00:28:20.055 high amounts of combinatory molecules

NOTE Confidence: 0.742978355

00:28:20.055 --> 00:28:22.729 that make gaming jefferon and we wonder

NOTE Confidence: 0.742978355

00:28:22.729 --> 00:28:25.239 is this what immune privilege is?

NOTE Confidence: 0.742978355

00:28:25.240 --> 00:28:27.010 Is that what if you privilege

NOTE Confidence: 0.742978355

00:28:27.010 --> 00:28:27.895 the high expression?

NOTE Confidence: 0.742978355

00:28:27.900 --> 00:28:30.658 Comunitar molecules can enter the cell cycle,

NOTE Confidence: 0.742978355

00:28:30.660 --> 00:28:32.960 but they are functional.

NOTE Confidence: 0.742978355

00:28:32.960 --> 00:28:34.616 So now we know normal spot on the floor.

NOTE Confidence: 0.742978355

00:28:34.620 --> 00:28:36.404 What about multiple sclerosis?

NOTE Confidence: 0.742978355

00:28:36.404 --> 00:28:38.634 Did the single cell analysis

NOTE Confidence: 0.742978355

00:28:38.634 --> 00:28:40.997 say looking at the populations

NOTE Confidence: 0.742978355

00:28:41.000 --> 00:28:42.850 between healthy blood and Ms.

NOTE Confidence: 0.742978355

00:28:42.850 --> 00:28:43.996 or no difference?

NOTE Confidence: 0.742978355

00:28:43.996 --> 00:28:44.760 Not surprising.

NOTE Confidence: 0.742978355

00:28:44.760 --> 00:28:47.856 We never found any differences before.

NOTE Confidence: 0.742978355

00:28:47.860 --> 00:28:49.420 But if we look at log fold changes,

NOTE Confidence: 0.742978355

00:28:49.420 --> 00:28:51.076 I'll just highlight some of them

NOTE Confidence: 0.742978355

00:28:51.076 --> 00:28:52.861 were just beginning to work out

NOTE Confidence: 0.742978355

00:28:52.861 --> 00:28:54.436 what these different factors being.

NOTE Confidence: 0.742978355

00:28:54.440 --> 00:28:56.084 We're intrigued by mallet.

NOTE Confidence: 0.742978355

00:28:56.084 --> 00:28:58.550 Mallet one which is involved in

NOTE Confidence: 0.742978355

00:28:58.629 --> 00:29:00.793 gene expression and epigenetic

NOTE Confidence: 0.742978355

00:29:00.793 --> 00:29:02.957 modulation of gene expression.

NOTE Confidence: 0.742978355

00:29:02.960 --> 00:29:06.747 We found I 32 it's a pro

NOTE Confidence: 0.742978355

00:29:06.747 --> 00:29:08.370 inflammatory cytokine induces

NOTE Confidence: 0.742978355

00:29:08.480 --> 00:29:11.390 TNF alpha associated with Ms.

NOTE Confidence: 0.742978355

00:29:11.390 --> 00:29:15.750 And we found June a part of the AP1 bonding.

NOTE Confidence: 0.742978355

00:29:15.750 --> 00:29:17.120 I won't show all these

NOTE Confidence: 0.742978355

00:29:17.120 --> 00:29:18.490 dates to talk in itself,

NOTE Confidence: 0.742978355

00:29:18.490 --> 00:29:20.038 but we looked at healthy Ms.

NOTE Confidence: 0.742978355

00:29:20.040 --> 00:29:23.988 versus non expanded versus expanded itself.

NOTE Confidence: 0.742978355

00:29:23.990 --> 00:29:26.014 It's tremendous clonal expansion

NOTE Confidence: 0.742978355

00:29:26.014 --> 00:29:29.302 these cells and again looking at

NOTE Confidence: 0.742978355

00:29:29.302 --> 00:29:31.574 the different populations within

NOTE Confidence: 0.742978355

00:29:31.574 --> 00:29:34.222 the aisle 32AP1 and there was

NOTE Confidence: 0.742978355

00:29:34.222 --> 00:29:36.490 more distinct in the clone expand

NOTE Confidence: 0.742978355

00:29:36.571 --> 00:29:38.930 itself both in CD4 and CD8 cells.

NOTE Confidence: 0.742978355

00:29:38.930 --> 00:29:40.664 I think the next decade will

NOTE Confidence: 0.742978355

00:29:40.664 --> 00:29:41.820 be taking these various.

NOTE Confidence: 0.742978355

00:29:41.820 --> 00:29:44.070 A fact is we found replicating

NOTE Confidence: 0.742978355

00:29:44.070 --> 00:29:46.420 them by protein and then seeing

NOTE Confidence: 0.742978355

00:29:46.420 --> 00:29:48.350 how they involved in Ms.

NOTE Confidence: 0.742978355

00:29:48.350 --> 00:29:48.694 induction.

NOTE Confidence: 0.742978355

00:29:48.694 --> 00:29:51.790 But this is really a road map as genetics

NOTE Confidence: 0.742978355

00:29:51.859 --> 00:29:54.819 work road map for what drives and drives

NOTE Confidence: 0.742978355

00:29:54.819 --> 00:29:56.889 autoimmunity in the nervous system.

NOTE Confidence: 0.742978355

00:29:56.890 --> 00:29:57.454 And of course,

NOTE Confidence: 0.742978355

00:29:57.454 --> 00:29:58.206 what about the brain?

NOTE Confidence: 0.742978355

00:29:58.210 --> 00:30:02.158 I couldn't resist being a pathology group.

NOTE Confidence: 0.742978355

00:30:02.160 --> 00:30:04.750 So here we did characterize T cells

NOTE Confidence: 0.742978355

00:30:04.750 --> 00:30:07.577 in normal human brain prank them up

NOTE Confidence: 0.742978355

00:30:07.577 --> 00:30:09.480 here different cluster patients.

NOTE Confidence: 0.742978355

00:30:09.480 --> 00:30:13.089 Some of these involve fresh RNC from

NOTE Confidence: 0.742978355

00:30:13.089 --> 00:30:15.987 brain that provided by Jack Intel

NOTE Confidence: 0.742978355

00:30:15.987 --> 00:30:18.556 doing epilepsy surgery and here

NOTE Confidence: 0.742978355

00:30:18.556 --> 00:30:20.780 are the T cells over here at the

NOTE Confidence: 0.742978355

00:30:20.856 --> 00:30:22.738 very end and different populations.

NOTE Confidence: 0.742978355

00:30:22.738 --> 00:30:24.522 While summarizing here we're

NOTE Confidence: 0.742978355

00:30:24.522 --> 00:30:27.139 looking at the tissue residence and

NOTE Confidence: 0.742978355

00:30:27.139 --> 00:30:29.551 functional gene expression and T cell

NOTE Confidence: 0.742978355

00:30:29.551 --> 00:30:31.869 with normal brain prank comma and.

NOTE Confidence: 0.742978355

00:30:31.870 --> 00:30:32.652 You know,

NOTE Confidence: 0.742978355

00:30:32.652 --> 00:30:34.998 I mentioned we saw this game

NOTE Confidence: 0.742978355

00:30:34.998 --> 00:30:35.780 interferon signature.

NOTE Confidence: 0.742978355

00:30:35.780 --> 00:30:39.260 In the spinal fluid and we see here

NOTE Confidence: 0.742978355

00:30:39.260 --> 00:30:42.490 in the brain this is RNA seek up

NOTE Confidence: 0.742978355

00:30:42.490 --> 00:30:44.590 T cells right out of the brain.

NOTE Confidence: 0.742978355

00:30:44.590 --> 00:30:47.152 Here is with Duke seek his major

NOTE Confidence: 0.742978355

00:30:47.152 --> 00:30:48.250 gaming different signature.

NOTE Confidence: 0.742978355

00:30:48.250 --> 00:30:50.966 So these data indicate that the gamma

NOTE Confidence: 0.742978355

00:30:50.966 --> 00:30:53.428 different signature is there in the brain.

NOTE Confidence: 0.742978355

00:30:53.430 --> 00:30:55.734 Speculate at the end what that

NOTE Confidence: 0.742978355

00:30:55.734 --> 00:30:58.390 might be doing also Joe work from

NOTE Confidence: 0.742978355

00:30:58.390 --> 00:31:00.640 Tomo samita done with Andrew Wang

NOTE Confidence: 0.614207617333333

00:31:00.720 --> 00:31:03.250 out loud that's predominant humans,

NOTE Confidence: 0.614207617333333

00:31:03.250 --> 00:31:05.578 we do mice, we work with vice people.

NOTE Confidence: 0.614207617333333

00:31:05.580 --> 00:31:08.020 And this is data from a few months ago and

NOTE Confidence: 0.614207617333333

00:31:08.079 --> 00:31:10.515 she's getting barrage of write her thesis.

NOTE Confidence: 0.614207617333333

00:31:10.520 --> 00:31:13.373 But basically we wanted to look at T cells

NOTE Confidence: 0.614207617333333

00:31:13.373 --> 00:31:15.619 isolated directly from the house brain.

NOTE Confidence: 0.614207617333333

00:31:15.620 --> 00:31:17.378 So we saw this in humans.

NOTE Confidence: 0.614207617333333

00:31:17.380 --> 00:31:20.377 The question is to see it in mouse brain.

NOTE Confidence: 0.614207617333333

00:31:20.380 --> 00:31:23.068 And so here we're looking at T cells

NOTE Confidence: 0.614207617333333

00:31:23.068 --> 00:31:25.299 isolated directly from parenchymal tissue.

NOTE Confidence: 0.614207617333333

00:31:25.300 --> 00:31:26.665 We wash out the vessels

NOTE Confidence: 0.614207617333333

00:31:26.665 --> 00:31:27.757 and work with HomeGoods.

NOTE Confidence: 0.614207617333333

00:31:27.760 --> 00:31:29.260 Lander suggests he T cells

NOTE Confidence: 0.614207617333333

00:31:29.260 --> 00:31:31.020 are in the prank him up.

NOTE Confidence: 0.614207617333333

00:31:31.020 --> 00:31:35.580 He's gamma to Fearon on the X axis.

NOTE Confidence: 0.614207617333333

00:31:35.580 --> 00:31:38.370 Case in the CD three you can see this

NOTE Confidence: 0.614207617333333

00:31:38.370 --> 00:31:40.739 prominent cabinet different signature in

NOTE Confidence: 0.614207617333333

00:31:40.740 --> 00:31:43.503 CD4CD8 cells as we saw in the brain with

NOTE Confidence: 0.614207617333333

00:31:43.503 --> 00:31:46.888 40% that cells are making game interferon.

NOTE Confidence: 0.614207617333333

00:31:46.890 --> 00:31:48.150 You can see this here,

NOTE Confidence: 0.614207617333333

00:31:48.150 --> 00:31:49.790 but you don't see it,

NOTE Confidence: 0.614207617333333

00:31:49.790 --> 00:31:51.446 you don't see it in the

NOTE Confidence: 0.614207617333333

00:31:51.446 --> 00:31:52.550 in the peripheral blood,

NOTE Confidence: 0.614207617333333

00:31:52.550 --> 00:31:54.990 you only see it in the nervous system.

NOTE Confidence: 0.614207617333333

00:31:54.990 --> 00:31:57.366 So it suggests that these Gavin

NOTE Confidence: 0.614207617333333

00:31:57.366 --> 00:31:59.402 difference between T cells are

NOTE Confidence: 0.614207617333333

00:31:59.402 --> 00:32:02.090 physiologic and won't show that the data.

NOTE Confidence: 0.614207617333333

00:32:02.090 --> 00:32:04.338 But if you put if you do this

NOTE Confidence: 0.614207617333333

00:32:04.338 --> 00:32:05.589 experiments and germ free.

NOTE Confidence: 0.614207617333333

00:32:05.590 --> 00:32:07.978 Animals work done with Noah Palm,

NOTE Confidence: 0.614207617333333

00:32:07.980 --> 00:32:09.820 they don't make these cells.

NOTE Confidence: 0.614207617333333

00:32:09.820 --> 00:32:12.358 These gamma different secreting T cells

NOTE Confidence: 0.614207617333333

00:32:12.358 --> 00:32:14.854 are being driven by gut microbiome

NOTE Confidence: 0.614207617333333

00:32:14.854 --> 00:32:17.416 and if you label these T cells.

NOTE Confidence: 0.614207617333333

00:32:17.420 --> 00:32:19.796 In the gut with the dye that turns

NOTE Confidence: 0.614207617333333

00:32:19.796 --> 00:32:21.919 color with the fluorescent probe,

NOTE Confidence: 0.614207617333333

00:32:21.920 --> 00:32:24.136 you can show that all these cells in

NOTE Confidence: 0.614207617333333

00:32:24.136 --> 00:32:26.198 the brain are coming from the gut,

NOTE Confidence: 0.614207617333333

00:32:26.200 --> 00:32:29.116 similar to what BJ's Country did.

NOTE Confidence: 0.614207617333333

00:32:29.120 --> 00:32:30.476 And E model.

NOTE Confidence: 0.614207617333333

00:32:30.476 --> 00:32:32.736 But this is normal Physiology,

NOTE Confidence: 0.614207617333333

00:32:32.740 --> 00:32:35.611 so we can speculate why is it that T

NOTE Confidence: 0.614207617333333

00:32:35.611 --> 00:32:38.520 cells in normal central nervous system?

NOTE Confidence: 0.614207617333333

00:32:38.520 --> 00:32:39.800 Our country from the cotton

NOTE Confidence: 0.614207617333333

00:32:39.800 --> 00:32:41.080 what are they doing there?

NOTE Confidence: 0.614207617333333

00:32:41.080 --> 00:32:43.558 Nature doesn't do this for no reason.

NOTE Confidence: 0.614207617333333

00:32:43.560 --> 00:32:45.618 I'm sort of speculate that maybe at

NOTE Confidence: 0.614207617333333

00:32:45.618 --> 00:32:47.839 night when you have the lymphatics and

NOTE Confidence: 0.614207617333333

00:32:47.839 --> 00:32:50.612 you clean your brain out these T cells

NOTE Confidence: 0.614207617333333

00:32:50.612 --> 00:32:52.617 that surfing along secreting gamma

NOTE Confidence: 0.614207617333333

00:32:52.617 --> 00:32:54.216 influencing the microglia experiments

NOTE Confidence: 0.614207617333333

00:32:54.216 --> 00:32:56.988 were battery to begin it's to look

NOTE Confidence: 0.614207617333333

00:32:56.988 --> 00:32:59.983 at Tibet gamma knockouts to see what

NOTE Confidence: 0.614207617333333

00:32:59.983 --> 00:33:03.028 happens to synaptic pruning and what it

NOTE Confidence: 0.614207617333333

00:33:03.028 --> 00:33:05.695 does to the microglia influencing the

NOTE Confidence: 0.614207617333333

00:33:05.695 --> 00:33:08.470 neuronal excellent interactions and by.

NOTE Confidence: 0.614207617333333

00:33:08.470 --> 00:33:09.298 In summary,

NOTE Confidence: 0.614207617333333

00:33:09.298 --> 00:33:10.540 so is there.

NOTE Confidence: 0.614207617333333

00:33:10.540 --> 00:33:12.945 Is there glial tea sub

NOTE Confidence: 0.614207617333333

00:33:12.945 --> 00:33:13.907 communications circuits?

NOTE Confidence: 0.614207617333333

00:33:13.910 --> 00:33:15.375 This is again from light

NOTE Confidence: 0.614207617333333

00:33:15.375 --> 00:33:16.547 Ben Barris sowing TGF.

NOTE Confidence: 0.614207617333333

00:33:16.550 --> 00:33:19.898 Beta and cholesterol drove these together.

NOTE Confidence: 0.614207617333333

00:33:19.900 --> 00:33:21.570 And after I drive TJF,

NOTE Confidence: 0.614207617333333

00:33:21.570 --> 00:33:23.706 painting classes are required for my

NOTE Confidence: 0.614207617333333

00:33:23.706 --> 00:33:26.094 survival and these sizeable factors are

NOTE Confidence: 0.614207617333333

00:33:26.094 --> 00:33:28.359 produced by astrocytes including cholesterol,

NOTE Confidence: 0.614207617333333

00:33:28.360 --> 00:33:30.778 lipoprotein which are found in CSF.

NOTE Confidence: 0.614207617333333

00:33:30.780 --> 00:33:33.093 I won't show the data but if you take

NOTE Confidence: 0.614207617333333

00:33:33.093 --> 00:33:35.702 spinal fluid or cholesterol and TGF beta,

NOTE Confidence: 0.614207617333333

00:33:35.702 --> 00:33:37.198 it drives gamma interferon

NOTE Confidence: 0.614207617333333

00:33:37.198 --> 00:33:39.138 almost as much as Isle 12.

NOTE Confidence: 0.614207617333333

00:33:39.140 --> 00:33:41.737 So we think the cholesterol in the

NOTE Confidence: 0.614207617333333

00:33:41.737 --> 00:33:44.209 brain brains what mainly cholesterol

NOTE Confidence: 0.614207617333333

00:33:44.210 --> 00:33:47.372 is driving this gamma driving this

NOTE Confidence: 0.614207617333333

00:33:47.372 --> 00:33:49.490 gamma and what it's unknown function.

NOTE Confidence: 0.614207617333333

00:33:49.490 --> 00:33:52.000 Gamma interferon in the CNS.

NOTE Confidence: 0.614207617333333

00:33:52.000 --> 00:33:54.808 It's known to involve in chemical

NOTE Confidence: 0.614207617333333

00:33:54.808 --> 00:33:56.212 production record Plexus.

NOTE Confidence: 0.614207617333333

00:33:56.220 --> 00:33:58.088 Gamma has known neuroprotective

NOTE Confidence: 0.614207617333333

00:33:58.088 --> 00:33:59.956 function like glutamate clearance,

NOTE Confidence: 0.614207617333333

00:33:59.960 --> 00:34:01.386 neuronal survival.

NOTE Confidence: 0.614207617333333

00:34:01.386 --> 00:34:04.238 We speculate synaptic pruning

NOTE Confidence: 0.614207617333333

00:34:04.240 --> 00:34:06.214 and work done by Yoni Kipness

NOTE Confidence: 0.614207617333333

00:34:06.214 --> 00:34:08.499 published a few years ago in nature.

NOTE Confidence: 0.740374574

00:34:08.500 --> 00:34:11.660 So if you knock out gamma to Ferron in mice,

NOTE Confidence: 0.740374574

00:34:11.660 --> 00:34:12.533 they developed depression.

NOTE Confidence: 0.740374574

00:34:12.533 --> 00:34:14.279 How do you measure depression mice?

NOTE Confidence: 0.740374574

00:34:14.280 --> 00:34:17.176 I don't know, but they clearly had changes

NOTE Confidence: 0.740374574

00:34:17.176 --> 00:34:19.918 in behavior until they meet them working.

NOTE Confidence: 0.740374574

00:34:19.920 --> 00:34:21.846 That with a number of individuals

NOTE Confidence: 0.740374574

00:34:21.846 --> 00:34:23.424 and psychiatry department I can

NOTE Confidence: 0.740374574

00:34:23.424 --> 00:34:25.320 tell you that if you put animals the

NOTE Confidence: 0.740374574

00:34:25.320 --> 00:34:27.057 germ free environment and get rid

NOTE Confidence: 0.740374574

00:34:27.057 --> 00:34:28.900 of these games to creating cells

NOTE Confidence: 0.740374574

00:34:28.900 --> 00:34:30.850 that market changes in behavior.

NOTE Confidence: 0.740374574

00:34:30.850 --> 00:34:33.310 So it is psychiatrist one field,

NOTE Confidence: 0.740374574

00:34:33.310 --> 00:34:34.182 neurologist another.

NOTE Confidence: 0.740374574

00:34:34.182 --> 00:34:36.798 But what's beginning to happen feels

NOTE Confidence: 0.740374574

00:34:36.798 --> 00:34:38.803 are colliding of course centered

NOTE Confidence: 0.740374574

00:34:38.803 --> 00:34:40.939 around their inflammation but to me

NOTE Confidence: 0.740374574

00:34:40.939 --> 00:34:43.006 the normal Physiology the discovery

NOTE Confidence: 0.740374574

00:34:43.006 --> 00:34:45.472 of gamma difference between T cells

NOTE Confidence: 0.740374574

00:34:45.480 --> 00:34:47.784 that are normal Physiology which arose

NOTE Confidence: 0.740374574

00:34:47.784 --> 00:34:49.940 from studying disease is actually.

NOTE Confidence: 0.740374574

00:34:49.940 --> 00:34:51.242 More interestingly enough,

NOTE Confidence: 0.740374574

00:34:51.242 --> 00:34:54.280 observations please to how how things work.

NOTE Confidence: 0.792448911071429

00:34:56.330 --> 00:34:58.100 And one other experiment again which

NOTE Confidence: 0.792448911071429

00:34:58.100 --> 00:35:00.604 I didn't show the data for is you can

NOTE Confidence: 0.792448911071429

00:35:00.604 --> 00:35:02.493 ask the question well what if he's

NOTE Confidence: 0.792448911071429

00:35:02.493 --> 00:35:04.215 teased cell receptor as a barcode?

NOTE Confidence: 0.792448911071429

00:35:04.220 --> 00:35:07.132 To look at this identical T cell

NOTE Confidence: 0.792448911071429

00:35:07.132 --> 00:35:09.950 in spinal fluid versus the blood.

NOTE Confidence: 0.792448911071429

00:35:09.950 --> 00:35:12.188 Does it change or is there

NOTE Confidence: 0.792448911071429

00:35:12.188 --> 00:35:13.307 a selective migration?

NOTE Confidence: 0.792448911071429

00:35:13.310 --> 00:35:15.390 The answer is it changes.

NOTE Confidence: 0.792448911071429

00:35:15.390 --> 00:35:18.118 The T cells in the blood that share

NOTE Confidence: 0.792448911071429

00:35:18.118 --> 00:35:20.854 the same T cell receptor sequence with

NOTE Confidence: 0.792448911071429

00:35:20.854 --> 00:35:24.073 cells in the CSF have very different

NOTE Confidence: 0.792448911071429

00:35:24.073 --> 00:35:26.397 characteristics the CSF cells.

NOTE Confidence: 0.792448911071429

00:35:26.400 --> 00:35:29.039 Have the gamma signature and other PD.

NOTE Confidence: 0.792448911071429

00:35:29.040 --> 00:35:30.745 One signature with the identical

NOTE Confidence: 0.792448911071429

00:35:30.745 --> 00:35:33.269 T cell in the blood does not

NOTE Confidence: 0.792448911071429

00:35:33.269 --> 00:35:34.757 have markets knife cells,

NOTE Confidence: 0.792448911071429

00:35:34.760 --> 00:35:36.872 so this provides strong evidence that

NOTE Confidence: 0.792448911071429

00:35:36.872 --> 00:35:39.377 what's happening as the T cells migrate

NOTE Confidence: 0.792448911071429

00:35:39.377 --> 00:35:41.107 into the central nervous system,

NOTE Confidence: 0.792448911071429

00:35:41.110 --> 00:35:44.090 they're acquiring these phenotypes.

NOTE Confidence: 0.792448911071429

00:35:44.090 --> 00:35:45.422 So in summary,

NOTE Confidence: 0.792448911071429

00:35:45.422 --> 00:35:47.642 all immune disorders are complex

NOTE Confidence: 0.792448911071429

00:35:47.642 --> 00:35:49.976 complex genetic diseases where genetic

NOTE Confidence: 0.792448911071429

00:35:49.976 --> 00:35:52.394 variants mapped to the immune system

NOTE Confidence: 0.792448911071429

00:35:52.394 --> 00:35:55.036 in MSB cells drive the inflamed

NOTE Confidence: 0.792448911071429

00:35:55.036 --> 00:35:57.236 Mon reactive CD4 cells instead.

NOTE Confidence: 0.792448911071429

00:35:57.240 --> 00:35:59.886 Let me just comment on EB for a moment.

NOTE Confidence: 0.792448911071429

00:35:59.890 --> 00:36:02.488 May have heard that beautiful paper

NOTE Confidence: 0.792448911071429

00:36:02.488 --> 00:36:04.548 by Alberto Mascaro clearly showing

NOTE Confidence: 0.792448911071429

00:36:04.548 --> 00:36:07.580 that if you are a he looked at

NOTE Confidence: 0.792448911071429

00:36:07.671 --> 00:36:10.226 1,000,000 recruits in the army.

NOTE Confidence: 0.792448911071429

00:36:10.230 --> 00:36:12.270 Identified individuals are EB

NOTE Confidence: 0.792448911071429

00:36:12.270 --> 00:36:13.800 negative and follow.

NOTE Confidence: 0.792448911071429

00:36:13.800 --> 00:36:16.482 Deerfield their light chains come CPK

NOTE Confidence: 0.792448911071429

00:36:16.482 --> 00:36:19.505 the brain shows brain damage and he

NOTE Confidence: 0.792448911071429

00:36:19.505 --> 00:36:22.207 showed that the on the serial samples

NOTE Confidence: 0.792448911071429

00:36:22.287 --> 00:36:24.884 they collected that when NFL went up

NOTE Confidence: 0.792448911071429

00:36:24.884 --> 00:36:28.100 in the serum followed by diagnosis of Ms.

NOTE Confidence: 0.792448911071429

00:36:28.100 --> 00:36:30.680 it was 49 and 50 ton

NOTE Confidence: 0.792448911071429

00:36:30.680 --> 00:36:32.400 preceded by EB infection.

NOTE Confidence: 0.792448911071429

00:36:32.400 --> 00:36:33.940 You have to look at a million

NOTE Confidence: 0.792448911071429

00:36:33.940 --> 00:36:34.900 people to find that.

NOTE Confidence: 0.792448911071429

00:36:34.900 --> 00:36:36.775 But incredibly provocative

NOTE Confidence: 0.792448911071429

00:36:36.775 --> 00:36:39.900 data that's EV trigger Ms.

NOTE Confidence: 0.792448911071429

00:36:39.900 --> 00:36:41.559 what's the experiment we need to do.

NOTE Confidence: 0.792448911071429

00:36:41.560 --> 00:36:43.948 There's one key experiment.

NOTE Confidence: 0.792448911071429

00:36:43.950 --> 00:36:45.790 Which we're working on,

NOTE Confidence: 0.792448911071429

00:36:45.790 --> 00:36:49.040 which is to vaccinate patients at risk.

NOTE Confidence: 0.792448911071429

00:36:49.040 --> 00:36:52.808 So there's no EV vaccine out there now?

NOTE Confidence: 0.792448911071429

00:36:52.810 --> 00:36:55.033 Ohh Danner GSK have one and I'm on a

NOTE Confidence: 0.792448911071429

00:36:55.033 --> 00:36:56.763 group of devices trying to convince

NOTE Confidence: 0.792448911071429

00:36:56.763 --> 00:36:59.159 GSK to do a subset with the clinical

NOTE Confidence: 0.792448911071429

00:36:59.159 --> 00:37:00.995 trial patients at risk that we

NOTE Confidence: 0.792448911071429

00:37:00.995 --> 00:37:02.950 can vaccinate and prevent disease

NOTE Confidence: 0.792448911071429

00:37:02.950 --> 00:37:05.410 as we prevented SP with measles

NOTE Confidence: 0.792448911071429

00:37:05.481 --> 00:37:07.836 vaccination that be the defendant

NOTE Confidence: 0.792448911071429

00:37:07.836 --> 00:37:09.720 rather definitive evidence we've

NOTE Confidence: 0.792448911071429

00:37:09.720 --> 00:37:12.154 not been able to find any biology

NOTE Confidence: 0.792448911071429

00:37:12.154 --> 00:37:14.868 B we've looked in the brain of Ms.

NOTE Confidence: 0.792448911071429

00:37:14.868 --> 00:37:16.678 patient just interviewing our graduate

NOTE Confidence: 0.792448911071429

00:37:16.678 --> 00:37:18.595 student he said you haven't published

NOTE Confidence: 0.792448911071429

00:37:18.595 --> 00:37:21.047 much on EV why haven't you go we've

NOTE Confidence: 0.792448911071429

00:37:21.047 --> 00:37:22.847 been looking we haven't found any.

NOTE Confidence: 0.792448911071429

00:37:22.850 --> 00:37:25.195 In your own publishing that data right.

NOTE Confidence: 0.792448911071429

00:37:25.200 --> 00:37:27.727 But what we have your IRB approval

NOTE Confidence: 0.792448911071429

00:37:27.727 --> 00:37:30.640 to do now and start shortly it's

NOTE Confidence: 0.792448911071429

00:37:30.640 --> 00:37:32.825 a do tonsil aspirates it,

NOTE Confidence: 0.792448911071429

00:37:32.830 --> 00:37:34.320 wants it in this patience.

NOTE Confidence: 0.792448911071429

00:37:34.320 --> 00:37:36.918 EB lives in the nasal pharynx.

NOTE Confidence: 0.792448911071429

00:37:36.920 --> 00:37:38.866 Then you have any ideas how to

NOTE Confidence: 0.792448911071429

00:37:38.866 --> 00:37:41.233 do this but we do singles RDC can

NOTE Confidence: 0.792448911071429

00:37:41.233 --> 00:37:43.363 do CV expression so we can fund

NOTE Confidence: 0.792448911071429

00:37:43.363 --> 00:37:45.477 the EB signature we once and Ms.

NOTE Confidence: 0.792448911071429

00:37:45.480 --> 00:37:47.232 patients but of course there may

NOTE Confidence: 0.792448911071429

00:37:47.232 --> 00:37:49.340 be gone by the time we do it.

NOTE Confidence: 0.792448911071429

00:37:49.340 --> 00:37:51.710 So once again summary of the

NOTE Confidence: 0.792448911071429

00:37:51.710 --> 00:37:52.895 talk autoimmune disorders.

NOTE Confidence: 0.792448911071429

00:37:52.900 --> 00:37:55.900 Particular mass or complex genetic diseases,

NOTE Confidence: 0.792448911071429

00:37:55.900 --> 00:37:57.870 genetic variance mapped to the

NOTE Confidence: 0.792448911071429

00:37:57.870 --> 00:37:59.840 immune system and MSB cells.

NOTE Confidence: 0.792448911071429

00:37:59.840 --> 00:38:01.178 We believe Dr.

NOTE Confidence: 0.792448911071429

00:38:01.178 --> 00:38:04.710 Inflame months specific CD4 cells in the CNS.

NOTE Confidence: 0.792448911071429

00:38:04.710 --> 00:38:06.530 Also mentioned that we're doing

NOTE Confidence: 0.792448911071429

00:38:06.530 --> 00:38:08.350 single cell RNA sequencing pre

NOTE Confidence: 0.7626621584

00:38:08.416 --> 00:38:10.061 post treatment THC stated about

NOTE Confidence: 0.7626621584

00:38:10.061 --> 00:38:12.116 two weeks all we've been spending

NOTE Confidence: 0.7626621584

00:38:12.116 --> 00:38:14.198 now year analyzing the data but

NOTE Confidence: 0.7626621584

00:38:14.198 --> 00:38:16.196 the most promising we're seeing

NOTE Confidence: 0.7626621584

00:38:16.196 --> 00:38:18.586 would be cell depletion myeloid,

NOTE Confidence: 0.7626621584

00:38:18.590 --> 00:38:22.060 express myeloid, induction of TNF.

NOTE Confidence: 0.7626621584

00:38:22.060 --> 00:38:24.034 You might say, are you kidding me?

NOTE Confidence: 0.7626621584

00:38:24.040 --> 00:38:26.504 It's working by inducing

NOTE Confidence: 0.7626621584

00:38:26.504 --> 00:38:27.736 inflammatory cytokine.

NOTE Confidence: 0.7626621584

00:38:27.740 --> 00:38:30.240 But go back to the clinical trial,

NOTE Confidence: 0.7626621584

00:38:30.240 --> 00:38:31.852 anti TNF makes Ms.

NOTE Confidence: 0.7626621584

00:38:31.852 --> 00:38:34.620 work works great in IBD and RA.

NOTE Confidence: 0.7626621584

00:38:34.620 --> 00:38:37.217 So the data is now suggesting that

NOTE Confidence: 0.7626621584

00:38:37.217 --> 00:38:40.047 TNF induced by the B cell depletion

NOTE Confidence: 0.7626621584

00:38:40.047 --> 00:38:42.501 is leading to TNF secretion which

NOTE Confidence: 0.7626621584

00:38:42.582 --> 00:38:44.777 then induces increased T Reg

NOTE Confidence: 0.7626621584

00:38:44.777 --> 00:38:46.972 function with TNFR 2 receptor

NOTE Confidence: 0.7626621584

00:38:46.980 --> 00:38:48.560 doing the single cell analysis.

NOTE Confidence: 0.7626621584

00:38:48.560 --> 00:38:50.990 So we'll see where that goes.

NOTE Confidence: 0.7626621584

00:38:50.990 --> 00:38:52.810 Yeah I showed you the T cell

NOTE Confidence: 0.7626621584

00:38:52.810 --> 00:38:54.252 traffic between blood and spinal

NOTE Confidence: 0.7626621584

00:38:54.252 --> 00:38:55.762 fluid and brain tightly regulated

NOTE Confidence: 0.7626621584

00:38:55.762 --> 00:38:57.504 showed the TH one signature and

NOTE Confidence: 0.7626621584

00:38:57.504 --> 00:38:59.324 that the blood and sees that for

NOTE Confidence: 0.7626621584

00:38:59.330 --> 00:39:00.701 functionally different indicating

NOTE Confidence: 0.7626621584

00:39:00.701 --> 00:39:03.443 the CNS shapes homeostatic T cell

NOTE Confidence: 0.7626621584

00:39:03.443 --> 00:39:05.442 states that happens all the tissues

NOTE Confidence: 0.7626621584

00:39:05.442 --> 00:39:07.729 at T cell center in the tissues.

NOTE Confidence: 0.7626621584

00:39:07.730 --> 00:39:09.038 This is phenotypic difference

NOTE Confidence: 0.7626621584

00:39:09.038 --> 00:39:11.000 in healthy and masks and control

NOTE Confidence: 0.7626621584

00:39:11.059 --> 00:39:12.854 particularly more expanded cells and

NOTE Confidence: 0.7626621584

00:39:12.854 --> 00:39:14.954 we're beginning to explore what these

NOTE Confidence: 0.7626621584

00:39:14.954 --> 00:39:16.938 are what they mean and this help us

NOTE Confidence: 0.7626621584

00:39:16.938 --> 00:39:18.514 teach one signature seen healthy

NOTE Confidence: 0.7626621584

00:39:18.514 --> 00:39:20.810 brain and of course with the PRT.

NOTE Confidence: 0.7626621584

00:39:20.810 --> 00:39:23.498 And positive teabags think we may have

NOTE Confidence: 0.7626621584

00:39:23.498 --> 00:39:25.464 identified a major transcriptional

NOTE Confidence: 0.7626621584

00:39:25.464 --> 00:39:27.690 factor driving autoimmunity.

NOTE Confidence: 0.7626621584

00:39:27.690 --> 00:39:31.319 So let me end by thanking I I put

NOTE Confidence: 0.7626621584

00:39:31.319 --> 00:39:34.634 here the members of the lab who made

NOTE Confidence: 0.7626621584

00:39:34.634 --> 00:39:37.169 major contributions work Jenna Pappalardo,

NOTE Confidence: 0.7626621584

00:39:37.170 --> 00:39:40.047 who is now out in West Coast,

NOTE Confidence: 0.7626621584

00:39:40.050 --> 00:39:40.960 an industry.

NOTE Confidence: 0.7626621584

00:39:40.960 --> 00:39:43.235 Tomo, who's assistant professor Tomia,

NOTE Confidence: 0.7626621584

00:39:43.240 --> 00:39:44.076 graduate student,

NOTE Confidence: 0.7626621584

00:39:44.076 --> 00:39:45.748 please thank assistant professor

NOTE Confidence: 0.7626621584

00:39:45.748 --> 00:39:47.002 in our department.

NOTE Confidence: 0.7626621584

00:39:47.010 --> 00:39:49.413 Others in the lab now is the former lab

NOTE Confidence: 0.7626621584

00:39:49.413 --> 00:39:51.838 members who contributed the work I discussed.

NOTE Confidence: 0.7626621584

00:39:51.840 --> 00:39:52.244 Today,

NOTE Confidence: 0.7626621584

00:39:52.244 --> 00:39:55.072 Matt Lincoln and the PRD one projects

NOTE Confidence: 0.7626621584

00:39:55.072 --> 00:39:56.713 computational Margot who did the

NOTE Confidence: 0.7626621584

00:39:56.713 --> 00:39:58.498 work with the TH1 T Rex phone

NOTE Confidence: 0.7626621584

00:39:58.562 --> 00:40:00.532 contact and the Center colleagues

NOTE Confidence: 0.7626621584

00:40:00.532 --> 00:40:02.108 of the Broad Institute.

NOTE Confidence: 0.7626621584

00:40:02.110 --> 00:40:03.990 In particular Brad Bernstein

NOTE Confidence: 0.7626621584

00:40:03.990 --> 00:40:04.930 analyst Kellison,

NOTE Confidence: 0.7626621584

00:40:04.930 --> 00:40:06.730 Chuck Epstein who worked with us,

NOTE Confidence: 0.7626621584

00:40:06.730 --> 00:40:08.610 the PRD one project collaborators

NOTE Confidence: 0.7626621584

00:40:08.610 --> 00:40:11.678 at the MI Year in Yale Genetics and

NOTE Confidence: 0.7626621584

00:40:11.678 --> 00:40:14.261 Marcelo and Yang who we feel are

NOTE Confidence: 0.7626621584

00:40:14.337 --> 00:40:17.067 part of our Neuro inflammation group.

NOTE Confidence: 0.7626621584

00:40:17.070 --> 00:40:19.102 So thank you for your time and just

NOTE Confidence: 0.7626621584

00:40:19.102 --> 00:40:20.774 say here's my e-mail and here's

NOTE Confidence: 0.7626621584

00:40:20.774 --> 00:40:22.154 our last picture of our.

NOTE Confidence: 0.7626621584

00:40:22.160 --> 00:40:22.440 Ms.

NOTE Confidence: 0.7626621584

00:40:22.440 --> 00:40:24.680 Group if we have a lot of meetings

NOTE Confidence: 0.7626621584

00:40:24.680 --> 00:40:27.414 every week, all winter, not really.

NOTE Confidence: 0.7626621584

00:40:27.414 --> 00:40:28.446 But anyway,

NOTE Confidence: 0.7626621584

00:40:28.450 --> 00:40:29.488 thank you for giving me the

NOTE Confidence: 0.7626621584

00:40:29.488 --> 00:40:30.180 opportunity to talk to.

NOTE Confidence: 0.7626621584

00:40:30.180 --> 00:40:30.950 I really appreciate it.

NOTE Confidence: 0.88935668625

00:40:42.510 --> 00:40:46.118 So do we know who's in the chat?

NOTE Confidence: 0.88935668625

00:40:46.120 --> 00:40:48.766 That is OK. Good story here.

NOTE Confidence: 0.891316055

00:40:54.920 --> 00:40:55.870 OK, question.

NOTE Confidence: 0.840520132857143

00:40:58.100 --> 00:41:00.564 Thank you for a great thank you.

NOTE Confidence: 0.840520132857143

00:41:00.570 --> 00:41:02.420 What about this are those? Who

NOTE Confidence: 0.865935815

00:41:04.750 --> 00:41:05.210 are they?

NOTE Confidence: 0.63591128

00:41:11.130 --> 00:41:13.410 You should ask.

NOTE Confidence: 0.63591128

00:41:13.410 --> 00:41:18.180 Unable to defrag the hard problem.

NOTE Confidence: 0.63591128

00:41:18.180 --> 00:41:19.148 Here's how to approach.

NOTE Confidence: 0.63591128

00:41:19.148 --> 00:41:20.358 Do you have a collaboration?

NOTE Confidence: 0.18896529

00:41:22.950 --> 00:41:26.780 Change. And what we're doing is we're

NOTE Confidence: 0.18896529

00:41:26.780 --> 00:41:28.758 taking the T cell receptor, thousands of

NOTE Confidence: 0.766415126842105

00:41:28.770 --> 00:41:30.990 T cell receptors, popping them into

NOTE Confidence: 0.766415126842105

00:41:30.990 --> 00:41:33.267 reporter cell lines and then using

NOTE Confidence: 0.766415126842105

00:41:33.267 --> 00:41:35.808 antigen libraries see what they react to.

NOTE Confidence: 0.766415126842105

00:41:35.810 --> 00:41:39.242 We're also have tetramers loaded with

NOTE Confidence: 0.766415126842105

00:41:39.242 --> 00:41:41.530 different peptide libraries barcoded.

NOTE Confidence: 0.766415126842105

00:41:41.530 --> 00:41:43.196 We do single cell and pull them

NOTE Confidence: 0.766415126842105

00:41:43.196 --> 00:41:44.906 out and see what they're reacting

NOTE Confidence: 0.766415126842105

00:41:44.906 --> 00:41:46.432 with so far, guess what?

NOTE Confidence: 0.766415126842105

00:41:46.432 --> 00:41:48.178 Answer we're finding the spinal fluid

NOTE Confidence: 0.766415126842105

00:41:48.178 --> 00:41:49.900 across different patient, anything else?

NOTE Confidence: 0.24135157

00:41:52.330 --> 00:41:56.170 Beebe. Whether it's primarily I

NOTE Confidence: 0.24135157

00:41:56.170 --> 00:41:58.400 don't know but we also see that the

NOTE Confidence: 0.24135157

00:41:58.400 --> 00:42:00.042 activity and what we're doing you

NOTE Confidence: 0.24135157

00:42:00.042 --> 00:42:01.786 know we can I can tell you that

NOTE Confidence: 0.24135157

00:42:01.786 --> 00:42:03.590 team cell rachamim based approach

NOTE Confidence: 0.24135157

00:42:03.590 --> 00:42:05.536 that's and tells me one thing right.

NOTE Confidence: 0.24135157

00:42:05.536 --> 00:42:08.120 So you'd like non hypothetical need

NOTE Confidence: 0.24135157

00:42:08.120 --> 00:42:09.995 approaches so we're halfway in the

NOTE Confidence: 0.24135157

00:42:09.995 --> 00:42:11.675 project and hopefully hear so the

NOTE Confidence: 0.24135157

00:42:11.675 --> 00:42:13.418 better idea to do the same thing

NOTE Confidence: 0.24135157

00:42:13.418 --> 00:42:15.217 with cancer antigens or they'll know

NOTE Confidence: 0.24135157

00:42:15.220 --> 00:42:17.860 and guess what they're recognizing.

NOTE Confidence: 0.24135157

00:42:17.860 --> 00:42:19.080 Don't just rent apart.

NOTE Confidence: 0.39766955

00:42:24.490 --> 00:42:27.010 The train.

NOTE Confidence: 0.61007991

00:42:30.760 --> 00:42:31.669 Yeah, the traffic.

NOTE Confidence: 0.483998476666667

00:42:35.690 --> 00:42:36.569 Of the possible.

NOTE Confidence: 0.4093337

00:42:40.610 --> 00:42:41.160 Requires.

NOTE Confidence: 0.54116213

00:42:47.780 --> 00:42:48.210 Or.

NOTE Confidence: 0.65118932

00:42:50.270 --> 00:42:50.850 Stop it.

NOTE Confidence: 0.64863056

00:42:56.380 --> 00:42:56.750 Sure.

NOTE Confidence: 0.742292938

00:43:06.870 --> 00:43:10.170 What happens with the message? All Star.

NOTE Confidence: 0.595268977142857

00:43:19.220 --> 00:43:24.680 K1 did not qualify. In the South. So.

NOTE Confidence: 0.7548707

00:43:27.400 --> 00:43:29.870 But since it's increased solid,

NOTE Confidence: 0.7548707

00:43:29.870 --> 00:43:32.408 expect to see it. But you know.

NOTE Confidence: 0.8120597

00:43:35.410 --> 00:43:35.790 And then?

NOTE Confidence: 0.676597346666667

00:43:38.340 --> 00:43:40.730 And yes, it's laughing.

NOTE Confidence: 0.4112627

00:43:42.870 --> 00:43:43.320 Disease.

NOTE Confidence: 0.5244426225

00:43:45.390 --> 00:43:48.386 That's where we had she is thought

NOTE Confidence: 0.5244426225

00:43:48.386 --> 00:43:50.254 to subtractive stuff because

NOTE Confidence: 0.5244426225

00:43:50.254 --> 00:43:53.960 these papers the post office.

NOTE Confidence: 0.5244426225

00:43:53.960 --> 00:43:56.968 How much is that?

NOTE Confidence: 0.5244426225

00:43:56.970 --> 00:43:59.038 That there's whereas I think

NOTE Confidence: 0.5244426225

00:43:59.038 --> 00:44:01.600 we have a good working model

NOTE Confidence: 0.5244426225

00:44:01.600 --> 00:44:03.952 for relaxing the EMS not yet to

NOTE Confidence: 0.5244426225

00:44:03.952 --> 00:44:06.277 discover but a good model I have

NOTE Confidence: 0.820201316666667

00:44:06.290 --> 00:44:09.668 no idea where cost of progressive.

NOTE Confidence: 0.820201316666667

00:44:09.670 --> 00:44:10.810 Before we had trees

NOTE Confidence: 0.7182784825

00:44:10.820 --> 00:44:12.080 that will be 50%.

NOTE Confidence: 0.75895238625

00:44:14.890 --> 00:44:17.915 Now the most important question

NOTE Confidence: 0.75895238625

00:44:17.915 --> 00:44:20.758 here is that we have a plan.

NOTE Confidence: 0.60247827

00:44:22.840 --> 00:44:23.270 Question.

NOTE Confidence: 0.694367625

00:44:25.740 --> 00:44:26.290 The station.

NOTE Confidence: 0.44306989

00:44:28.900 --> 00:44:31.000 Progressive disease.

NOTE Confidence: 0.44306989

00:44:31.000 --> 00:44:33.604 But that's a major question by suspected

NOTE Confidence: 0.44306989

00:44:33.604 --> 00:44:36.056 to be progressive disease cells stay

NOTE Confidence: 0.44306989

00:44:36.056 --> 00:44:38.912 there trapped in the back and forth

NOTE Confidence: 0.44306989

00:44:38.912 --> 00:44:41.638 that we might see on the sausage.

NOTE Confidence: 0.44306989

00:44:41.640 --> 00:44:43.176 Is it really correct?

NOTE Confidence: 0.44306989

00:44:43.176 --> 00:44:44.712 That's terrific questions and

NOTE Confidence: 0.44306989

00:44:44.712 --> 00:44:48.288 we'll go back and then you have to.

NOTE Confidence: 0.44306989

00:44:48.290 --> 00:44:50.888 The second version.

NOTE Confidence: 0.44306989

00:44:50.890 --> 00:44:52.980 This is really interesting people,

NOTE Confidence: 0.44306989

00:44:52.980 --> 00:44:55.710 normal people have T cells are going.

NOTE Confidence: 0.44306989

00:44:55.710 --> 00:44:58.740 They're making their gambling responsibly.

NOTE Confidence: 0.78697665125

00:45:02.200 --> 00:45:07.000 Yeah, So what are the time scales involved?

NOTE Confidence: 0.78697665125

00:45:07.000 --> 00:45:08.844 T cell recognizes something

NOTE Confidence: 0.78697665125

00:45:08.844 --> 00:45:10.227 that wasn't changed.

NOTE Confidence: 0.78697665125

00:45:10.230 --> 00:45:12.340 You might not know, obviously, but you.

NOTE Confidence: 0.78697665125

00:45:12.340 --> 00:45:14.560 Visioning that it's terms of making

NOTE Confidence: 0.78697665125

00:45:14.560 --> 00:45:16.320 a change there and then having

NOTE Confidence: 0.78697665125

00:45:16.320 --> 00:45:18.880 some response back afterwards,

NOTE Confidence: 0.78697665125

00:45:18.880 --> 00:45:20.560 well, I I could do it my side.

NOTE Confidence: 0.734211706

00:45:23.700 --> 00:45:25.550 New brand. I can get

NOTE Confidence: 0.734211706

00:45:25.550 --> 00:45:27.400 spinal fluid but drain it.

NOTE Confidence: 0.56005221

00:45:28.890 --> 00:45:30.075 But now that it's very

NOTE Confidence: 0.56005221

00:45:30.075 --> 00:45:31.249 radically so, it happens. If

NOTE Confidence: 0.69304979

00:45:31.260 --> 00:45:34.374 we so pre, we don't see them at

NOTE Confidence: 0.69304979

00:45:34.374 --> 00:45:37.200 the time of reading when you start

NOTE Confidence: 0.685592616

00:45:37.210 --> 00:45:38.522 acquiring the microphone and

NOTE Confidence: 0.685592616

00:45:38.522 --> 00:45:40.490 that's when we started seeing it.

NOTE Confidence: 0.685592616

00:45:40.490 --> 00:45:41.598 That happens very quickly.

NOTE Confidence: 0.685592616

00:45:41.598 --> 00:45:42.706 So we label them,

NOTE Confidence: 0.685592616

00:45:42.710 --> 00:45:43.950 I can answer that question.

NOTE Confidence: 0.685592616

00:45:43.950 --> 00:45:46.560 We might label them in

NOTE Confidence: 0.685592616

00:45:46.560 --> 00:45:49.170 the gut within 2-3 days.

NOTE Confidence: 0.685592616

00:45:49.170 --> 00:45:50.836 So, so the experiment I did as

NOTE Confidence: 0.783097523333333

00:45:50.850 --> 00:45:52.788 as a postdoc.

NOTE Confidence: 0.783097523333333

00:45:52.790 --> 00:45:54.245 The terrific experiment.

NOTE Confidence: 0.783097523333333

00:45:54.245 --> 00:45:56.670 There's some new thing called

NOTE Confidence: 0.783097523333333

00:45:56.670 --> 00:45:58.089 monoclonal antibodies and we

NOTE Confidence: 0.783097523333333

00:45:58.090 --> 00:45:59.308 want to put them into people.

NOTE Confidence: 0.783097523333333

00:45:59.310 --> 00:46:00.140 No one has really done

NOTE Confidence: 0.794155941428571

00:46:00.150 --> 00:46:02.670 that yet. So we're kind of cowboy.

NOTE Confidence: 0.794155941428571

00:46:02.670 --> 00:46:07.720 Please stop the recording now. So I've got 5.

NOTE Confidence: 0.849884606

00:46:08.510 --> 00:46:09.870 So what we did was

NOTE Confidence: 0.716579526666667

00:46:10.360 --> 00:46:11.350 we had invited.

NOTE Confidence: 0.7498658075

00:46:15.420 --> 00:46:17.876 Two and I did it with my 5.

NOTE Confidence: 0.63013353

00:46:21.120 --> 00:46:24.140 Make these. And we said, Gee,

NOTE Confidence: 0.63013353

00:46:24.140 --> 00:46:27.340 if we don't find material across state lines,

NOTE Confidence: 0.63013353

00:46:27.340 --> 00:46:29.380 that would be Massachusetts.

NOTE Confidence: 0.63013353

00:46:29.380 --> 00:46:32.440 You don't need that TA approval.

NOTE Confidence: 0.63013353

00:46:32.440 --> 00:46:34.890 That now, but you know IRB approval.

NOTE Confidence: 0.840586293333333

00:46:35.060 --> 00:46:37.163 So we're very careful what we did,

NOTE Confidence: 0.840586293333333

00:46:37.163 --> 00:46:38.694 we had RV approval and what

NOTE Confidence: 0.840586293333333

00:46:38.694 --> 00:46:40.790 we do and so we injected.

NOTE Confidence: 0.728172209090909

00:46:43.130 --> 00:46:45.874 And to our patients and we showed

NOTE Confidence: 0.728172209090909

00:46:45.874 --> 00:46:47.620 that major biological effects

NOTE Confidence: 0.58900646425

00:46:48.410 --> 00:46:49.858 but they're now sanctified

NOTE Confidence: 0.686966116666667

00:46:49.870 --> 00:46:52.096 after one child human anti mouse

NOTE Confidence: 0.5612157172

00:46:52.110 --> 00:46:54.400 antibody would deactivate them. So

NOTE Confidence: 0.73392724

00:46:54.610 --> 00:46:55.640 we only had to make.

NOTE Confidence: 0.4347557692

00:46:57.800 --> 00:47:01.940 But 11 experiments that anti CD 2

NOTE Confidence: 0.4347557692

00:47:01.940 --> 00:47:04.264 N IG23 coded all the T cell but

NOTE Confidence: 0.4347557692

00:47:04.264 --> 00:47:06.316 did not cross into the central

NOTE Confidence: 0.4347557692

00:47:06.316 --> 00:47:08.200 nervous system showed that.

NOTE Confidence: 0.4347557692

00:47:08.200 --> 00:47:09.932 So I would do this thing.

NOTE Confidence: 0.4347557692

00:47:09.932 --> 00:47:13.449 That's a new call, Microsoft you guys.

NOTE Confidence: 0.4347557692

00:47:13.450 --> 00:47:14.905 There was one solicitation to

NOTE Confidence: 0.4347557692

00:47:14.905 --> 00:47:16.360 Harvard Medical School at the

NOTE Confidence: 0.4347557692

00:47:16.413 --> 00:47:18.614 time and I did the first thing

NOTE Confidence: 0.4347557692

00:47:18.614 --> 00:47:19.950 pretreatment did with respondent.

NOTE Confidence: 0.4347557692

00:47:19.950 --> 00:47:23.086 Few days respond that did the same thing.

NOTE Confidence: 0.4347557692

00:47:23.090 --> 00:47:25.435 We got anti mouse and everything but.

NOTE Confidence: 0.4347557692

00:47:25.440 --> 00:47:28.198 Then we did this that it's standing

NOTE Confidence: 0.4347557692

00:47:28.198 --> 00:47:30.491 after the treatment and majority of

NOTE Confidence: 0.4347557692

00:47:30.491 --> 00:47:33.190 cells lit off the coat anti mass and

NOTE Confidence: 0.820641488

00:47:31.860 --> 00:47:33.180 said what's going on here? Let's just

NOTE Confidence: 0.78438866

00:47:33.190 --> 00:47:36.538 screw it up again.

NOTE Confidence: 0.78438866

00:47:36.540 --> 00:47:38.562 Oh my God they're covered with

NOTE Confidence: 0.78438866

00:47:38.562 --> 00:47:40.134 antibody with mouse antibody.

NOTE Confidence: 0.78438866

00:47:40.134 --> 00:47:42.890 So we use this way of labeling all

NOTE Confidence: 0.78438866

00:47:42.890 --> 00:47:45.535 the peripheral blood T cell and that's

NOTE Confidence: 0.78438866

00:47:45.535 --> 00:47:48.210 being traffic into the CNS policy.

NOTE Confidence: 0.78438866

00:47:48.210 --> 00:47:49.622 And because everyone looked

NOTE Confidence: 0.78438866

00:47:49.622 --> 00:47:51.387 at the blood brain barrier,

NOTE Confidence: 0.78438866

00:47:51.390 --> 00:47:55.526 80% of the cells traffic within three days.

NOTE Confidence: 0.78438866

00:47:55.530 --> 00:47:56.200 How did they do it?

NOTE Confidence: 0.562511566666667

00:47:58.570 --> 00:48:00.250 Found the entry right before crossing.

NOTE Confidence: 0.657706014

00:48:01.230 --> 00:48:02.500 Well, because when we took

NOTE Confidence: 0.691355185

00:48:02.870 --> 00:48:05.450 that we couldn't find the party even though.

NOTE Confidence: 0.68694216

00:48:09.770 --> 00:48:10.130 No.

NOTE Confidence: 0.610505545555556

00:48:12.650 --> 00:48:15.760 Now that doesn't listen all

NOTE Confidence: 0.610505545555556

00:48:15.760 --> 00:48:18.248 the circulating T cells.

NOTE Confidence: 0.590843675

00:48:23.140 --> 00:48:26.153 Invite them. So it's suggested

NOTE Confidence: 0.590843675

00:48:26.153 --> 00:48:27.508 you can follow the connection.

NOTE Confidence: 0.7627134175

00:48:29.990 --> 00:48:33.048 So it's suggested and that nice people

NOTE Confidence: 0.7627134175

00:48:33.050 --> 00:48:35.990 have gone to replicate that more output.

NOTE Confidence: 0.7627134175

00:48:35.990 --> 00:48:38.623 So the traffic of T cells from the blood

NOTE Confidence: 0.7627134175

00:48:38.623 --> 00:48:41.530 to the nervous system side is very fast.

NOTE Confidence: 0.7627134175

00:48:41.530 --> 00:48:43.409 And I think it's continuing this intro data,

NOTE Confidence: 0.7627134175

00:48:43.410 --> 00:48:45.185 but there are three different

NOTE Confidence: 0.7627134175

00:48:45.185 --> 00:48:46.996 scenes of population in CSF.

NOTE Confidence: 0.7627134175

00:48:46.996 --> 00:48:49.698 One and three are about basically residents.

NOTE Confidence: 0.7627134175

00:48:49.700 --> 00:48:53.627 LCF 2 looks like sales and traffic,

NOTE Confidence: 0.7627134175

00:48:53.630 --> 00:48:56.628 so one opposition doesn't have CD-69

NOTE Confidence: 0.7627134175

00:48:56.630 --> 00:48:58.076 was like a population is garden.

NOTE Confidence: 0.737587758333333

00:48:59.440 --> 00:49:03.030 We have a question in chat. Yes, yeah.

NOTE Confidence: 0.737587758333333

00:49:03.030 --> 00:49:04.550 What's the concordance of Ms.

NOTE Confidence: 0.737587758333333

00:49:04.550 --> 00:49:05.525 and identical twins?

NOTE Confidence: 0.737587758333333

00:49:05.525 --> 00:49:06.900 That might be a good group in

NOTE Confidence: 0.737587758333333

00:49:06.900 --> 00:49:08.538 which to consider prophylaxis.

NOTE Confidence: 0.737587758333333

00:49:08.540 --> 00:49:10.069 And a second related question,

NOTE Confidence: 0.737587758333333

00:49:10.070 --> 00:49:11.138 is there any handle on what

NOTE Confidence: 0.737587758333333

00:49:11.138 --> 00:49:13.430 causes spontaneous remission?

NOTE Confidence: 0.737587758333333

00:49:13.430 --> 00:49:15.230 And by these days goes untreated,

NOTE Confidence: 0.737587758333333

00:49:15.230 --> 00:49:16.798 Nope, no one goes and I want to

NOTE Confidence: 0.737587758333333

00:49:16.798 --> 00:49:18.230 comes to Yelp goes untreated.

NOTE Confidence: 0.737587758333333

00:49:18.230 --> 00:49:19.342 Well occasionally they don't

NOTE Confidence: 0.737587758333333

00:49:19.342 --> 00:49:21.010 want to do a patient want.

NOTE Confidence: 0.737587758333333

00:49:21.010 --> 00:49:23.206 So the answer Jeff is about

NOTE Confidence: 0.737587758333333

00:49:23.210 --> 00:49:25.359 3040% and yes that would be a

NOTE Confidence: 0.737587758333333

00:49:25.359 --> 00:49:27.204 great group to consider for

NOTE Confidence: 0.737587758333333

00:49:27.204 --> 00:49:29.766 prophylaxis but it's a small number,

NOTE Confidence: 0.737587758333333

00:49:29.770 --> 00:49:30.954 it's two small numbers.

NOTE Confidence: 0.737587758333333

00:49:30.954 --> 00:49:33.120 So what we're doing in the Rs

NOTE Confidence: 0.737587758333333

00:49:33.120 --> 00:49:34.750 study is developing the tools

NOTE Confidence: 0.737587758333333

00:49:34.750 --> 00:49:36.505 to develop to identify average

NOTE Confidence: 0.737587758333333

00:49:36.505 --> 00:49:38.069 patients of intake first.

NOTE Confidence: 0.737587758333333

00:49:38.070 --> 00:49:40.725 So the question is what is the incident Ms.

NOTE Confidence: 0.737587758333333

00:49:40.730 --> 00:49:42.728 in daughters of patients with Ms.

NOTE Confidence: 0.737587758333333

00:49:42.730 --> 00:49:43.993 about one in.

NOTE Confidence: 0.737587758333333

00:49:43.993 --> 00:49:46.924 30 It's quite high and we can do

NOTE Confidence: 0.737587758333333

00:49:46.924 --> 00:49:48.479 polygenic risk score and increase

NOTE Confidence: 0.737587758333333

00:49:48.479 --> 00:49:50.930 it even more so and then we can

NOTE Confidence: 0.737587758333333

00:49:50.930 --> 00:49:53.355 use NFL we were fully light chains

NOTE Confidence: 0.737587758333333

00:49:53.355 --> 00:49:56.267 to follow them so that's why I'm

NOTE Confidence: 0.737587758333333

00:49:56.267 --> 00:49:58.730 proposing GSK first as a subset take

NOTE Confidence: 0.737587758333333

00:49:58.730 --> 00:50:00.770 5000 and first degree relatives

NOTE Confidence: 0.737587758333333

00:50:00.770 --> 00:50:03.265 children at risk before they become

NOTE Confidence: 0.737587758333333

00:50:03.265 --> 00:50:05.170 EB positive seriously follow them

NOTE Confidence: 0.737587758333333

00:50:05.170 --> 00:50:08.502 with NFL NFL go up MRI them I think

NOTE Confidence: 0.737587758333333

00:50:08.502 --> 00:50:10.237 that's attractable study to do.

NOTE Confidence: 0.737587758333333

00:50:10.240 --> 00:50:11.906 That's how we're going to try to

NOTE Confidence: 0.737587758333333

00:50:11.906 --> 00:50:13.679 do it will cause spontaneous.

NOTE Confidence: 0.737587758333333

00:50:13.680 --> 00:50:15.410 So what So what relapse,

NOTE Confidence: 0.737587758333333

00:50:15.410 --> 00:50:17.050 it's a really good question.

NOTE Confidence: 0.737587758333333

00:50:17.050 --> 00:50:18.586 What happens I think in Ms.

NOTE Confidence: 0.737587758333333

00:50:18.590 --> 00:50:21.026 is that it's there's an acute

NOTE Confidence: 0.737587758333333

00:50:21.026 --> 00:50:23.134 event there's the attacks occur

NOTE Confidence: 0.737587758333333

00:50:23.134 --> 00:50:25.570 very quickly within a day within

NOTE Confidence: 0.737587758333333

00:50:25.570 --> 00:50:27.350 forty 2448 hours they come on,

NOTE Confidence: 0.737587758333333

00:50:27.350 --> 00:50:29.828 it's T cell trafficking into the CNS.

NOTE Confidence: 0.737587758333333

00:50:29.830 --> 00:50:32.320 There is Dima that breakdown,

NOTE Confidence: 0.737587758333333

00:50:32.320 --> 00:50:33.862 the barbarian barrier,

NOTE Confidence: 0.737587758333333

00:50:33.862 --> 00:50:34.890 gadolinium enhancement.

NOTE Confidence: 0.737587758333333

00:50:34.890 --> 00:50:37.332 I think it's the edema that's

NOTE Confidence: 0.737587758333333

00:50:37.332 --> 00:50:38.960 causing neurologic symptoms with

NOTE Confidence: 0.737587758333333

00:50:39.028 --> 00:50:40.668 time there is retraction,

NOTE Confidence: 0.737587758333333

00:50:40.670 --> 00:50:41.474 edema goes away,

NOTE Confidence: 0.737587758333333

00:50:41.474 --> 00:50:43.082 the blood brain barrier is closed

NOTE Confidence: 0.737587758333333

00:50:43.082 --> 00:50:44.997 and rather than having a big lesion.

NOTE Confidence: 0.737587758333333

00:50:45.000 --> 00:50:46.420 With a tiny scar,

NOTE Confidence: 0.737587758333333

00:50:46.420 --> 00:50:48.550 like it's just just normal Physiology

NOTE Confidence: 0.737587758333333

00:50:48.614 --> 00:50:50.546 of of the lesions resolving as

NOTE Confidence: 0.737587758333333

00:50:50.546 --> 00:50:52.344 edema goes away and steroids

NOTE Confidence: 0.737587758333333

00:50:52.344 --> 00:50:54.096 makes that happen faster.

NOTE Confidence: 0.737587758333333

00:50:54.100 --> 00:50:55.340 I think that's what's happening.

NOTE Confidence: 0.774260875

00:50:58.350 --> 00:51:01.400 That one. Alright.

NOTE Confidence: 0.842704594285714

00:51:01.590 --> 00:51:03.676 Well, thank you very much to David.