WEBVTT

00:00:05.380 --> 00:00:07.678 To put a historical perspective on

00:00:07.678 --> 00:00:09.800 the dramatic advances in biology,

00:00:09.800 --> 00:00:12.278 it's been during my lifetime that

00:00:12.278 --> 00:00:14.725 we learned the function of DNA as

00:00:14.725 --> 00:00:16.435 a first year student in college.

00:00:16.440 --> 00:00:19.092 In 1970, I saw a patient

00:00:19.092 --> 00:00:20.418 with multiple sclerosis,

00:00:20.420 --> 00:00:22.527 which at the time were thought to

00:00:22.527 --> 00:00:24.630 be mediated by the immune system.

00:00:24.630 --> 00:00:26.780 There were virtually no treatments

00:00:26.780 --> 00:00:28.070 I knew then.

00:00:28.070 --> 00:00:30.374 I wanted to dedicate my career

00:00:30.374 --> 00:00:32.529 to understanding the disease and

00:00:32.529 --> 00:00:34.188 discover effective treatments.

NOTE Confidence: 0.900389589090909

00:00:34.190 --> 00:00:35.975 We've come a long way since the

NOTE Confidence: 0.900389589090909

00:00:35.975 --> 00:00:37.670 two major types of immune cells,

NOTE Confidence: 0.900389589090909

00:00:37.670 --> 00:00:38.890 T cells and B cells,

NOTE Confidence: 0.900389589090909

00:00:38.890 --> 00:00:40.730 were discovered around the time

NOTE Confidence: 0.900389589090909

00:00:40.730 --> 00:00:43.250 I saw my first Ms patient.

NOTE Confidence: 0.900389589090909

00:00:43.250 --> 00:00:45.278 There is a technique allowing us

NOTE Confidence: 0.900389589090909

00:00:45.278 --> 00:00:47.033 to visualize many different immune

NOTE Confidence: 0.900389589090909

00:00:47.033 --> 00:00:48.768 cell populations in the brain.

NOTE Confidence: 0.900389589090909

00:00:48.770 --> 00:00:49.186 So, David,

NOTE Confidence: 0.900389589090909

00:00:49.186 --> 00:00:50.018 what are we looking

NOTE Confidence: 0.826476723846154

00:00:50.030 --> 00:00:52.470 at here? This is a Ms lesion and

NOTE Confidence: 0.826476723846154

00:00:52.470 --> 00:00:54.878 all of these colored objects.

NOTE Confidence: 0.826476723846154

00:00:54.880 --> 00:00:57.640 Individual cells that have different

NOTE Confidence: 0.826476723846154

00:00:57.640 --> 00:01:00.760 functions and if you zoom in.

NOTE Confidence: 0.826476723846154

00:01:00.760 --> 00:01:03.040 Like so you see, for example,

NOTE Confidence: 0.826476723846154

00:01:03.040 --> 00:01:06.218 a immune cell at cell that directs

NOTE Confidence: 0.826476723846154

00:01:06.218 --> 00:01:09.008 a scavenger cell to dibawa mile.

NOTE Confidence: 0.759757602857143

00:01:09.340 --> 00:01:11.741 In Ms Research, an important event would

NOTE Confidence: 0.759757602857143

00:01:11.741 --> 00:01:14.021 allow us to deeply characterize those

NOTE Confidence: 0.759757602857143

00:01:14.021 --> 00:01:17.190 immune T cells and B cells without bias.

NOTE Confidence: 0.759757602857143

00:01:17.190 --> 00:01:20.222 We can now use a dramatic new technology

NOTE Confidence: 0.759757602857143

00:01:20.222 --> 00:01:23.412 called single cell RNA sequencing allows us

NOTE Confidence: 0.759757602857143

00:01:23.412 --> 00:01:26.190 to interrogate each individual immune cell.

NOTE Confidence: 0.759757602857143

00:01:26.190 --> 00:01:28.836 Examining the brain itself is too invasive,

NOTE Confidence: 0.759757602857143

00:01:28.840 --> 00:01:30.821 but we can access immune cells in

NOTE Confidence: 0.759757602857143

00:01:30.821 --> 00:01:33.150 the brain by examining spinal fluid,

NOTE Confidence: 0.759757602857143

00:01:33.150 --> 00:01:34.902 the liquid around the brain and

NOTE Confidence: 0.759757602857143

00:01:34.902 --> 00:01:36.645 spinal cord that tells us what

NOTE Confidence: 0.759757602857143

00:01:36.645 --> 00:01:38.187 immune cells are in the brain.

NOTE Confidence: 0.759757602857143

00:01:38.190 --> 00:01:40.794 We extract spinal fluid from a patient

NOTE Confidence: 0.759757602857143

00:01:40.794 --> 00:01:43.165 using a Spinal Tap by inserting

NOTE Confidence: 0.759757602857143

00:01:43.165 --> 00:01:45.130 a needle between the vertebrae

NOTE Confidence: 0.759757602857143

00:01:45.130 --> 00:01:47.470 and then collecting the fluid.

NOTE Confidence: 0.759757602857143

00:01:47.470 --> 00:01:48.142 Once extracted,

NOTE Confidence: 0.759757602857143

00:01:48.142 --> 00:01:50.830 the spinal fluid is rushed to the lab,

NOTE Confidence: 0.759757602857143

00:01:50.830 --> 00:01:53.110 where it's spun down to collect the cells,

NOTE Confidence: 0.759757602857143

00:01:53.110 --> 00:01:55.096 then brought to the 10X machine.

NOTE Confidence: 0.7884652875

00:01:58.530 --> 00:02:01.378 We encapsulate each single T cell into a

NOTE Confidence: 0.7884652875

00:02:01.378 --> 00:02:03.411 functionalized gel B that's barcoded and

NOTE Confidence: 0.7884652875

00:02:03.411 --> 00:02:05.854 mixed with enzymes and oils to create

NOTE Confidence: 0.7884652875

00:02:05.854 --> 00:02:08.018 single cell microdroplets, or gems.

NOTE Confidence: 0.7884652875

00:02:08.018 --> 00:02:10.022 We then perform a chemical reaction

NOTE Confidence: 0.7884652875

00:02:10.022 --> 00:02:12.139 to amplify the nucleic acid that

NOTE Confidence: 0.7884652875

00:02:12.139 --> 00:02:14.215 codes for proteins that define each

NOTE Confidence: 0.7884652875

00:02:14.282 --> 00:02:16.346 cell type to learn their function.

NOTE Confidence: 0.7884652875

00:02:16.350 --> 00:02:18.828 The elegance of the technology is that

NOTE Confidence: 0.7884652875

00:02:18.828 --> 00:02:20.784 we can identify cellular subtypes

NOTE Confidence: 0.7884652875

00:02:20.784 --> 00:02:23.244 and rare cells with little bias,

NOTE Confidence: 0.7884652875

00:02:23.250 --> 00:02:25.674 giving a big picture of the

NOTE Confidence: 0.7884652875

00:02:25.674 --> 00:02:27.290 biology underlying the disease.

NOTE Confidence: 0.7884652875

00:02:27.290 --> 00:02:30.908 This is what? We have discovered.

NOTE Confidence: 0.7884652875

00:02:30.910 --> 00:02:32.793 Here we have a snapshot of the

NOTE Confidence: 0.7884652875

00:02:32.793 --> 00:02:34.650 different and mean populations and the

NOTE Confidence: 0.7884652875

00:02:34.650 --> 00:02:36.630 spinal fluid of a healthy subject,

NOTE Confidence: 0.7884652875

00:02:36.630 --> 00:02:37.923 the blue dots,

NOTE Confidence: 0.7884652875

00:02:37.923 --> 00:02:39.647 each representing immune cells

NOTE Confidence: 0.7884652875

00:02:39.647 --> 00:02:41.869 with RNA signatures of the blood.

NOTE Confidence: 0.7884652875

00:02:41.870 --> 00:02:44.294 The yellow dots are cells with

NOTE Confidence: 0.7884652875

00:02:44.294 --> 00:02:46.430 RNA signatures of spinal fluid.

NOTE Confidence: 0.7884652875

00:02:46.430 --> 00:02:48.750 As T cells traffic into the spinal fluid,

NOTE Confidence: 0.7884652875

00:02:48.750 --> 00:02:51.210 they transition toward RNA signature.

NOTE Confidence: 0.7884652875

00:02:51.210 --> 00:02:52.625 That's more nervous system like

NOTE Confidence: 0.7884652875

00:02:52.625 --> 00:02:53.757 which is in green.

NOTE Confidence: 0.907729982857143

00:02:55.720 --> 00:02:57.328 Armed with what happens

NOTE Confidence: 0.907729982857143

00:02:57.328 --> 00:02:58.534 in healthy subjects,

NOTE Confidence: 0.907729982857143

00:02:58.540 --> 00:03:01.036 we can now look at patients with Ms.

NOTE Confidence: 0.907729982857143

00:03:01.040 --> 00:03:02.240 The lighter the color,

NOTE Confidence: 0.907729982857143

00:03:02.240 --> 00:03:03.440 the more the difference.

NOTE Confidence: 0.907729982857143

00:03:03.440 --> 00:03:05.164 Here we've identified the

NOTE Confidence: 0.907729982857143

00:03:05.164 --> 00:03:06.457 fundamental gene signatures

NOTE Confidence: 0.907729982857143

00:03:06.457 --> 00:03:08.469 that are different in patients

NOTE Confidence: 0.75188609631579

00:03:08.480 --> 00:03:11.222 with Ms an environmental event like

NOTE Confidence: 0.75188609631579

00:03:11.222 --> 00:03:13.847 an infection by common virus such

NOTE Confidence: 0.75188609631579

00:03:13.847 --> 00:03:16.360 as Epstein Barr virus or E BV,

NOTE Confidence: 0.75188609631579

00:03:16.360 --> 00:03:19.150 may lead to the activation of

NOTE Confidence: 0.75188609631579

00:03:19.150 --> 00:03:21.620 autoreactive T cells recognizing myelin.

NOTE Confidence: 0.75188609631579

00:03:21.620 --> 00:03:23.280 These activated T cells that

NOTE Confidence: 0.75188609631579

00:03:23.280 --> 00:03:25.290 migrate into the brain where they.

NOTE Confidence: 0.75188609631579

00:03:25.290 --> 00:03:26.582 Cause inflammation.

NOTE Confidence: 0.75188609631579

00:03:26.582 --> 00:03:29.812 Blocking their migration with monoclonal

NOTE Confidence: 0.75188609631579

00:03:29.812 --> 00:03:31.750 antibodies markedly decreases.

NOTE Confidence: 0.75188609631579

00:03:31.750 --> 00:03:32.936 Ms attacks.

NOTE Confidence: 0.75188609631579

00:03:32.936 --> 00:03:35.308 Multiple sclerosis is a

NOTE Confidence: 0.75188609631579

00:03:35.308 --> 00:03:37.087 genetically mediated disease.

NOTE Confidence: 0.75188609631579

00:03:37.090 --> 00:03:40.870 We've identified 233 common genetic variants,

NOTE Confidence: 0.75188609631579

00:03:40.870 --> 00:03:42.950 each with a small effect on disease risk,

NOTE Confidence: 0.75188609631579

00:03:42.950 --> 00:03:45.128 but together lead to the disease.

NOTE Confidence: 0.75188609631579

00:03:45.130 --> 00:03:46.985 Majority of these common variants

NOTE Confidence: 0.75188609631579

00:03:46.985 --> 00:03:48.840 are controlling immune function and

NOTE Confidence: 0.75188609631579

00:03:48.897 --> 00:03:51.027 together contribute to a lower threshold

NOTE Confidence: 0.75188609631579

00:03:51.027 --> 00:03:52.880 for activating the immune system.

NOTE Confidence: 0.75188609631579

00:03:52.880 --> 00:03:55.295 It appears that B cells are critical.

NOTE Confidence: 0.75188609631579

00:03:55.300 --> 00:03:57.210 The activation of T cells.

00:03:57.210 --> 00:03:59.808 Perhaps related to the EBV virus,

00:03:59.810 --> 00:04:01.430 which infects B cells.

00:04:01.430 --> 00:04:03.860 Now the bleeding B cells also

00:04:03.946 --> 00:04:06.706 has a dramatic effect on stopping

00:04:06.706 --> 00:04:08.546 attacks in early disease.

00:04:08.550 --> 00:04:10.790 Here the monoclonal antibody is

00:04:10.790 --> 00:04:13.990 given to a patient every six months.

00:04:13.990 --> 00:04:16.223 We're now engaged in a clinical trial

00:04:16.223 --> 00:04:18.731 using B cell depletion at the very

00:04:18.731 --> 00:04:20.951 early stages of disease before there

00:04:21.024 --> 00:04:23.068 are any clinical manifestations.

00:04:23.070 --> 00:04:25.184 What advances that have been made since

00:04:25.184 --> 00:04:28.359 I saw my first patient with Ms Back in 1970.

00:04:28.359 --> 00:04:30.942 Back then we didn't know if the

00:04:30.942 --> 00:04:32.679 brain inflammation was secondary.

NOTE Confidence: 0.75188609631579

00:04:32.680 --> 00:04:35.424 Or causing Ms we now know the

NOTE Confidence: 0.75188609631579

00:04:35.424 --> 00:04:37.620 inflammation is causing the disease

NOTE Confidence: 0.75188609631579

00:04:37.620 --> 00:04:39.985 as immune modulation has dramatic

NOTE Confidence: 0.75188609631579

00:04:39.985 --> 00:04:42.370 effects on disease progression.

NOTE Confidence: 0.75188609631579

00:04:42.370 --> 00:04:44.200 We now know a significant number

NOTE Confidence: 0.75188609631579

00:04:44.200 --> 00:04:46.029 of the genes that cause Ms.

NOTE Confidence: 0.75188609631579

00:04:46.030 --> 00:04:48.030 They directly implicate the immune

NOTE Confidence: 0.75188609631579

00:04:48.030 --> 00:04:50.030 system in initiating the disease.

NOTE Confidence: 0.75188609631579

00:04:50.030 --> 00:04:50.780 Most importantly,

NOTE Confidence: 0.75188609631579

00:04:50.780 --> 00:04:53.405 in 1970 we had no treatments for

NOTE Confidence: 0.75188609631579

00:04:53.405 --> 00:04:56.084 Ms Now we have highly effective

NOTE Confidence: 0.75188609631579

00:04:56.084 --> 00:04:58.670 treatments that stop disease flare ups.

NOTE Confidence: 0.75188609631579

00:04:58.670 --> 00:05:00.966 Do we know the cause of Ms while

NOTE Confidence: 0.75188609631579

00:05:00.966 --> 00:05:03.269 science does not truly prove causality.

NOTE Confidence: 0.75188609631579

00:05:03.270 --> 00:05:05.496 Would make models that are constantly

NOTE Confidence: 0.75188609631579

00:05:05.496 --> 00:05:08.060 refined and tested by clinical trials.

NOTE Confidence: 0.75188609631579

00:05:08.060 --> 00:05:10.460 These models provide the most

NOTE Confidence: 0.75188609631579

00:05:10.460 --> 00:05:12.380 convincing evidence for causality.

NOTE Confidence: 0.75188609631579

00:05:12.380 --> 00:05:14.578 While we have a good working model

NOTE Confidence: 0.75188609631579

00:05:14.578 --> 00:05:16.220 for early relapsing mitting Ms,

NOTE Confidence: 0.75188609631579

00:05:16.220 --> 00:05:18.416 we have little insight into the

NOTE Confidence: 0.75188609631579

00:05:18.416 --> 00:05:20.470 progressive phase of the disease.

NOTE Confidence: 0.75188609631579

00:05:20.470 --> 00:05:22.744 We also don't know yet whether

NOTE Confidence: 0.75188609631579

00:05:22.744 --> 00:05:24.775 early treatment would be cell

NOTE Confidence: 0.75188609631579

00:05:24.775 --> 00:05:26.539 depletion prevents evolution to

NOTE Confidence: 0.75188609631579

00:05:26.539 --> 00:05:28.744 the progressive form of Ms.

NOTE Confidence: 0.75188609631579

00:05:28.750 --> 00:05:31.270 However, our examination of spinal fluid,

NOTE Confidence: 0.75188609631579

00:05:31.270 --> 00:05:33.325 these powerful new single cell

NOTE Confidence: 0.75188609631579

00:05:33.325 --> 00:05:34.558 technologies has revealed

NOTE Confidence: 0.75188609631579

00:05:34.558 --> 00:05:36.145 previously unknown pathways found

NOTE Confidence: 0.75188609631579

00:05:36.145 --> 00:05:37.900 in the infiltrating immune cells

NOTE Confidence: 0.75188609631579

00:05:37.900 --> 00:05:39.669 that are causing the disease.

NOTE Confidence: 0.75188609631579

00:05:39.670 --> 00:05:42.630 It will take years to put these new

NOTE Confidence: 0.75188609631579

00:05:42.630 --> 00:05:45.366 experiments into a more refined model of Ms,

NOTE Confidence: 0.75188609631579

00:05:45.370 --> 00:05:47.638 but this is an incredibly exciting time

NOTE Confidence: 0.75188609631579

00:05:47.638 --> 00:05:50.485 in the study of this disease and of neuro.

NOTE Confidence: 0.75188609631579

00:05:50.490 --> 00:05:51.370 Degeneration.