WEBVTT

NOTE duration:"00:15:17.2480000"

NOTE language:en-us

NOTE Confidence: 0.8689981

00:00:00.000 --> 00:00:02.331 Thank you very much for the opportunity

NOTE Confidence: 0.8689981

00:00:02.331 --> 00:00:05.476 to tell you about the history of the VSV

NOTE Confidence: 0.8689981

00:00:05.476 --> 00:00:08.212 vaccine platform and how it was used to

NOTE Confidence: 0.8689981

00:00:08.212 --> 00:00:10.790 make the approved Ebola vaccine as required.

NOTE Confidence: 0.8689981

00:00:10.790 --> 00:00:13.086 I disclosed that I am on the Scientific

NOTE Confidence: 0.8689981

00:00:13.086 --> 00:00:15.148 Advisory Board for Carriage incorporation.

NOTE Confidence: 0.8689981

00:00:15.150 --> 00:00:17.646 My talk today is unrelated to

NOTE Confidence: 0.8689981

00:00:17.646 --> 00:00:21.108 any work at or funded by Karajan.

NOTE Confidence: 0.8689981

00:00:21.110 --> 00:00:23.285 Alright, development of an effective

NOTE Confidence: 0.8689981

00:00:23.285 --> 00:00:25.895 viral vaccine platform. The Ebola story.

NOTE Confidence: 0.8689981

00:00:25.895 --> 00:00:28.070 So the Merck Ebola vaccine.

NOTE Confidence: 0.8689981

00:00:28.070 --> 00:00:31.115 Merck Ebola vaccine is called Erve Bo.

NOTE Confidence: 0.8689981

00:00:31.120 --> 00:00:33.295 It's a recombinant VSV expressing

NOTE Confidence: 0.8689981

00:00:33.295 --> 00:00:35.470 the Zaire Ebola virus glycoprotein.

1

00:00:35.470 --> 00:00:38.080 This was fully licensed by the

00:00:38.080 --> 00:00:39.820 FDA in December 2019.

00:00:39.820 --> 00:00:43.884 It's the only vaccine based on an engineered

00:00:43.884 --> 00:00:47.117 recombinant virus that's licensed in the US.

00:00:47.120 --> 00:00:49.738 Vaccine is built on the sicular stomatitis

00:00:49.738 --> 00:00:52.590 virus or VSV vaccine platform that we

00:00:52.590 --> 00:00:55.080 developed in our laboratory at Yale.

00:00:55.080 --> 00:00:56.640 And how did this happen?

00:00:56.640 --> 00:00:58.190 It's an extremely long story.

00:00:58.190 --> 00:01:00.678 I can't really do it in 15 minutes,

00:01:00.680 --> 00:01:02.724 so I refer you to this article

00:01:02.724 --> 00:01:04.100 written by Helen brands.

00:01:04.100 --> 00:01:06.588 Well, at stat it's called against all odds.

00:01:06.590 --> 00:01:08.816 The inside story of how scientists across

00:01:08.816 --> 00:01:10.629 three continents produced any Bola vaccine.

00:01:10.630 --> 00:01:13.118 She spent at least six months on it.

NOTE Confidence: 0.8689981

00:01:13.120 --> 00:01:15.297 If you really want a good read,

NOTE Confidence: 0.8689981

00:01:15.300 --> 00:01:16.850 take a look at this.

NOTE Confidence: 0.8689981

00:01:16.850 --> 00:01:19.150 It's if you Google Hellenbrand well, Ebola

NOTE Confidence: 0.8689981

00:01:19.150 --> 00:01:22.160 vaccine will probably be your first hit.

NOTE Confidence: 0.8689981

00:01:22.160 --> 00:01:23.668 Alright, what is VSV?

NOTE Confidence: 0.8689981

00:01:23.668 --> 00:01:26.530 It's a non lethal pathogen of cattle.

NOTE Confidence: 0.8689981

00:01:26.530 --> 00:01:28.238 It causes vesicular lesions of the mouth,

NOTE Confidence: 0.8689981

00:01:28.240 --> 00:01:29.264 the tongue that eats,

NOTE Confidence: 0.8689981

00:01:29.264 --> 00:01:31.284 and the hubs and animals can't eat for

NOTE Confidence: 0.8689981

00:01:31.284 --> 00:01:33.199 a couple of weeks, but they recover.

NOTE Confidence: 0.8689981

00:01:33.199 --> 00:01:35.317 VSV grows rapidly to very high

NOTE Confidence: 0.8689981

00:01:35.317 --> 00:01:36.890 titers in tissue culture,

NOTE Confidence: 0.8689981

00:01:36.890 --> 00:01:39.626 but it's not a human pathogen.

NOTE Confidence: 0.8689981

00:01:39.630 --> 00:01:40.087 Yes,

NOTE Confidence: 0.8689981

00:01:40.087 --> 00:01:42.372 we also generates potent innate

NOTE Confidence: 0.8689981

00:01:42.372 --> 00:01:45.590 antibody and T cell based community.

NOTE Confidence: 0.8689981

00:01:45.590 --> 00:01:47.809 So it's been a favorite of molecular

NOTE Confidence: 0.8689981

00:01:47.809 --> 00:01:50.148 biologists like me and also immunologists.

NOTE Confidence: 0.82742655

00:01:54.550 --> 00:01:57.745 PSV is the prototype for the large group of

NOTE Confidence: 0.82742655

00:01:57.745 --> 00:01:59.940 Nonsegmented negative strand RNA viruses.

NOTE Confidence: 0.82742655

00:01:59.940 --> 00:02:01.480 There are numerous serious

NOTE Confidence: 0.82742655

00:02:01.480 --> 00:02:03.020 pathogens in this group.

NOTE Confidence: 0.82742655

00:02:03.020 --> 00:02:06.100 I just mentioned a couple of them here.

NOTE Confidence: 0.82742655

00:02:06.100 --> 00:02:08.030 Rabies is 90. Excuse me?

NOTE Confidence: 0.82742655

00:02:08.030 --> 00:02:10.718 Nearly 100% fatal measles, you know about.

NOTE Confidence: 0.82742655

00:02:10.720 --> 00:02:13.751 Ebola and Marburg are the feel of

NOTE Confidence: 0.82742655

00:02:13.751 --> 00:02:17.018 viruses and Ebola can be up to 90% fatal.

NOTE Confidence: 0.82742655

00:02:17.018 --> 00:02:19.090 They cause hemorrhagic fevers.

NOTE Confidence: 0.82742655

00:02:19.090 --> 00:02:22.086 Alright, VSV, it's a bullet shaped virus.

NOTE Confidence: 0.82742655

00:02:22.090 --> 00:02:24.535 This one favorite pictures taken

NOTE Confidence: 0.82742655

00:02:24.535 --> 00:02:26.980 by former postdoc Michael Witt.

NOTE Confidence: 0.82742655

00:02:26.980 --> 00:02:29.344 And bullet shaped particles contain the

NOTE Confidence: 0.82742655

00:02:29.344 --> 00:02:31.720 helical nucleocapsid drawn in cartoon form.

NOTE Confidence: 0.82742655

00:02:31.720 --> 00:02:34.807 Here the RNA is a negative strand shown in

NOTE Confidence: 0.82742655

00:02:34.807 --> 00:02:37.219 yellow bound to the nucleocapsid protein

NOTE Confidence: 0.82742655

00:02:37.219 --> 00:02:40.409 and because this is the negative strand,

NOTE Confidence: 0.82742655

00:02:40.410 --> 00:02:43.090 it doesn't encode protein directly.

NOTE Confidence: 0.82742655

00:02:43.090 --> 00:02:45.594 Virus has to carry a PLB race and

NOTE Confidence: 0.82742655

00:02:45.594 --> 00:02:47.640 RNA dependent RNA polymerase that

NOTE Confidence: 0.82742655

00:02:47.640 --> 00:02:49.890 was discovered by David Baltimore.

NOTE Confidence: 0.82742655

00:02:49.890 --> 00:02:52.522 He was my former mentor and I learned

NOTE Confidence: 0.82742655

00:02:52.522 --> 00:02:55.560 about VSV in his lab in between the

NOTE Confidence: 0.82742655

00:02:55.560 --> 00:02:58.388 nucleocapsid and the membrane there is a

NOTE Confidence: 0.82742655

00:02:58.388 --> 00:03:00.824 matrix protein and then the glycoprotein

NOTE Confidence: 0.82742655

00:03:00.824 --> 00:03:02.750 spikes stick through that membrane.

NOTE Confidence: 0.85417354

00:03:06.120 --> 00:03:07.179 All right, generating

5

NOTE Confidence: 0.85417354

00:03:07.179 --> 00:03:08.238 recombinant virus vaccines.

NOTE Confidence: 0.85417354

00:03:08.240 --> 00:03:10.364 Why would we ever think about

NOTE Confidence: 0.85417354

00:03:10.364 --> 00:03:11.780 doing something like that?

NOTE Confidence: 0.85417354

00:03:11.780 --> 00:03:13.957 The reason is that vaccines that are

NOTE Confidence: 0.85417354

00:03:13.957 --> 00:03:15.835 based on live attenuated viruses

NOTE Confidence: 0.85417354

00:03:15.835 --> 00:03:17.599 often induced lifelong immunity

NOTE Confidence: 0.85417354

00:03:17.599 --> 00:03:20.179 to infection after a single dose.

NOTE Confidence: 0.85417354

00:03:20.180 --> 00:03:22.100 Examples are the measles vaccine,

NOTE Confidence: 0.85417354

00:03:22.100 --> 00:03:24.020 which is about 98% effective

NOTE Confidence: 0.85417354

00:03:24.020 --> 00:03:25.940 vaccinia virus relative of smallpox,

NOTE Confidence: 0.85417354

00:03:25.940 --> 00:03:28.155 which used to eliminate that

NOTE Confidence: 0.85417354

00:03:28.155 --> 00:03:30.370 horrible disease from the Earth.

NOTE Confidence: 0.85417354

00:03:30.370 --> 00:03:31.838 And live poliovirus vaccines

NOTE Confidence: 0.85417354

00:03:31.838 --> 00:03:33.306 are also extremely effective.

NOTE Confidence: 0.85417354

00:03:33.310 --> 00:03:35.150 So in the early 1980s,

NOTE Confidence: 0.85417354

00:03:35.150 --> 00:03:36.850 researchers began to use recombinant

NOTE Confidence: 0.85417354

00:03:36.850 --> 00:03:38.550 DNA technology to generate live

NOTE Confidence: 0.85417354

00:03:38.600 --> 00:03:40.570 virus vaccines built on attenuated

NOTE Confidence: 0.85417354

00:03:40.570 --> 00:03:42.146 viruses expressing foreign antigens.

NOTE Confidence: 0.85417354

00:03:42.150 --> 00:03:44.824 The first person I heard of doing

NOTE Confidence: 0.85417354

00:03:44.824 --> 00:03:47.300 this was Bernie Moss at the NIH,

NOTE Confidence: 0.85417354

00:03:47.300 --> 00:03:50.884 and he is still working on this.

NOTE Confidence: 0.85417354

00:03:50.890 --> 00:03:53.041 So at that time we thought VSV could be

NOTE Confidence: 0.85417354

00:03:53.041 --> 00:03:55.220 an ideal recombinant vaccine system,

NOTE Confidence: 0.85417354

00:03:55.220 --> 00:03:57.418 but we had no method for recovering

NOTE Confidence: 0.85417354

00:03:57.418 --> 00:03:59.537 VSV either from DNA or RNA copies,

NOTE Confidence: 0.85417354

00:03:59.540 --> 00:04:02.081 and this is because there is no

NOTE Confidence: 0.85417354

00:04:02.081 --> 00:04:04.185 infectious RNA or DNA copy for

NOTE Confidence: 0.85417354

00:04:04.185 --> 00:04:06.362 VSP or any of the NS viruses.

NOTE Confidence: 0.85417354

00:04:06.370 --> 00:04:08.380 So this was very frustrating.

NOTE Confidence: 0.85417354

00:04:08.380 --> 00:04:09.984 But finally in 1994,

NOTE Confidence: 0.85417354

00:04:09.984 --> 00:04:12.390 after over six years of failures,

NOTE Confidence: 0.85417354

00:04:12.390 --> 00:04:15.006 we were able to recover live VSV using

NOTE Confidence: 0.85417354

00:04:15.006 --> 00:04:17.059 a multi DNA transfection protocol

NOTE Confidence: 0.85417354

00:04:17.059 --> 00:04:19.705 that assembled a VSV anti genome

NOTE Confidence: 0.85417354

00:04:19.705 --> 00:04:22.320 and protein complex inside the cell

NOTE Confidence: 0.85417354

00:04:22.320 --> 00:04:25.085 bound to the VSV polymerase subunits

NOTE Confidence: 0.85417354

00:04:25.085 --> 00:04:29.075 and that got the system going.

NOTE Confidence: 0.85417354

00:04:29.080 --> 00:04:30.890 It's rather complicated if you

NOTE Confidence: 0.85417354

00:04:30.890 --> 00:04:31.976 want the details.

NOTE Confidence: 0.85417354

00:04:31.980 --> 00:04:34.647 We published this the first recovery of

NOTE Confidence: 0.85417354

00:04:34.647 --> 00:04:37.766 ESV from DNA in 1990 five 26 years ago.

NOTE Confidence: 0.85417354

00:04:37.770 --> 00:04:38.950 I can't believe it,

NOTE Confidence: 0.85417354

00:04:38.950 --> 00:04:41.111 but this opened up VSP for genetic

NOTE Confidence: 0.85417354

00:04:41.111 --> 00:04:43.037 analysis and we also noted at

NOTE Confidence: 0.85417354

00:04:43.037 --> 00:04:45.892 this time it might be possible to

NOTE Confidence: 0.85417354

00:04:45.892 --> 00:04:47.716 genetically engineer recombinant VSV

NOTE Confidence: 0.85417354

00:04:47.716 --> 00:04:49.707 is displaying foreign antigens and

NOTE Confidence: 0.85417354

00:04:49.707 --> 00:04:53.303 we might be able to use these two as

NOTE Confidence: 0.85417354

00:04:53.303 --> 00:04:55.818 vaccines protecting against other viruses.

NOTE Confidence: 0.85417354

00:04:55.820 --> 00:04:56.094 Alright,

NOTE Confidence: 0.85417354

00:04:56.094 --> 00:04:58.286 so there were major questions to be answered.

NOTE Confidence: 0.85417354

00:04:58.290 --> 00:05:00.194 We had wonderful people joining the lab.

NOTE Confidence: 0.85417354

00:05:00.200 --> 00:05:02.546 Once we had this system and.

NOTE Confidence: 0.85417354

00:05:02.550 --> 00:05:04.280 Could we express foreign genes

NOTE Confidence: 0.85417354

00:05:04.280 --> 00:05:06.388 in the VSV recombinants with the

NOTE Confidence: 0.85417354

00:05:06.388 --> 00:05:08.296 genes be stable in their comments?

NOTE Confidence: 0.85417354

00:05:08.300 --> 00:05:09.990 Could such recumbents be useful

NOTE Confidence: 0.85417354

00:05:09.990 --> 00:05:11.680 as vaccines and many viruses?

NOTE Confidence: 0.85417354

00:05:11.680 --> 00:05:14.879 Many RNA viruses? Recumbents are not stable.

NOTE Confidence: 0.85417354

00:05:14.880 --> 00:05:18.064 Alright, so we got to work on this.

NOTE Confidence: 0.85417354

00:05:18.070 --> 00:05:20.050 And found he used the conserved

NOTE Confidence: 0.85417354

00:05:20.050 --> 00:05:22.050 stop start signals that are present

NOTE Confidence: 0.85417354

00:05:22.050 --> 00:05:23.290 in the VSV genomes.

NOTE Confidence: 0.85417354

00:05:23.290 --> 00:05:25.531 Put them around a new gene stuck a new

NOTE Confidence: 0.85417354

00:05:25.531 --> 00:05:27.495 gene in all convenient restriction

NOTE Confidence: 0.85417354

00:05:27.495 --> 00:05:29.147 sites engineered into this.

NOTE Confidence: 0.85417354

00:05:29.150 --> 00:05:31.103 We could make a recombinant virus and

NOTE Confidence: 0.85417354

00:05:31.103 --> 00:05:33.590 it grew just a wild type titers and

NOTE Confidence: 0.85417354

00:05:33.590 --> 00:05:35.180 most importantly it was completely

NOTE Confidence: 0.85417354

00:05:35.242 --> 00:05:37.450 stable for at least 15 passages

NOTE Confidence: 0.85417354

00:05:37.450 --> 00:05:38.922 involving millionfold expansion at

NOTE Confidence: 0.85417354

00:05:38.930 --> 00:05:42.482 each passage. So this set to us, you know.

NOTE Confidence: 0.85417354

00:05:42.482 --> 00:05:44.764 Maybe maybe this could be a vaccine,

NOTE Confidence: 0.85417354

00:05:44.770 --> 00:05:46.606 and our first model system wasn't

NOTE Confidence: 0.85417354

00:05:46.606 --> 00:05:48.603 influenza model in mice and this

NOTE Confidence: 0.85417354

00:05:48.603 --> 00:05:49.668 was anjanette Robertson.

NOTE Confidence: 0.85417354

00:05:49.670 --> 00:05:50.464 Evelyn Kretchmar,

NOTE Confidence: 0.85417354

00:05:50.464 --> 00:05:53.243 who started this work in my lab.

NOTE Confidence: 0.85417354

00:05:53.250 --> 00:05:56.026 So we made a VSV via CS5 genes,

NOTE Confidence: 0.85417354

00:05:56.030 --> 00:05:58.501 NPM giannell and we stuck in an

NOTE Confidence: 0.85417354

00:05:58.501 --> 00:06:01.650 HAG and that's the HA is the major

NOTE Confidence: 0.85417354

00:06:01.650 --> 00:06:03.254 protective antigen for flu.

NOTE Confidence: 0.85417354

00:06:03.260 --> 00:06:05.174 We made another one that's an

NOTE Confidence: 0.85417354

00:06:05.174 --> 00:06:06.982 attenuated VSV we truncate the tail

NOTE Confidence: 0.85417354

00:06:06.982 --> 00:06:08.854 of the SVG and that makes it non

NOTE Confidence: 0.83624697

00:06:08.912 --> 00:06:10.208 pathogenic. In animals.

NOTE Confidence: 0.83624697

00:06:10.208 --> 00:06:12.880 We also made a version where we take

NOTE Confidence: 0.83624697

00:06:12.958 --> 00:06:15.468 out the G and put in the HA and this

NOTE Confidence: 0.83624697

00:06:15.538 --> 00:06:17.906 is the only data that I will show.

NOTE Confidence: 0.83624697

00:06:17.910 --> 00:06:19.410 We put these into animals.

NOTE Confidence: 0.83624697

00:06:19.410 --> 00:06:21.204 This is a vaccine study is

NOTE Confidence: 0.83624697

00:06:21.204 --> 00:06:22.400 our average mouse weights.

NOTE Confidence: 0.83624697

00:06:22.400 --> 00:06:24.871 This is the time of vaccination and

NOTE Confidence: 0.83624697

00:06:24.871 --> 00:06:27.339 then the time of challenge with a

NOTE Confidence: 0.83624697

00:06:27.339 --> 00:06:30.198 lethal dose of flu is here at 35 days.

NOTE Confidence: 0.83624697

00:06:30.200 --> 00:06:32.584 And what you can see in the controls

NOTE Confidence: 0.83624697

00:06:32.584 --> 00:06:35.480 in the blue triangles is to animals

NOTE Confidence: 0.83624697

00:06:35.480 --> 00:06:37.264 that haven't been vaccinated,

NOTE Confidence: 0.83624697

00:06:37.270 --> 00:06:39.050 die within seven days.

NOTE Confidence: 0.83624697

00:06:39.050 --> 00:06:42.579 All of the vaccine animals survive just fine,

NOTE Confidence: 0.83624697

00:06:42.580 --> 00:06:44.080 not even weight loss.

NOTE Confidence: 0.83624697

00:06:44.080 --> 00:06:45.205 After the challenge,

NOTE Confidence: 0.83624697

00:06:45.210 --> 00:06:47.346 the one virus that's a little

NOTE Confidence: 0.83624697

00:06:47.346 --> 00:06:49.720 hot is the wild type virus,

NOTE Confidence: 0.83624697

00:06:49.720 --> 00:06:51.976 which causes mice to lose weight.

NOTE Confidence: 0.83624697

00:06:51.980 --> 00:06:52.512 Importantly,

NOTE Confidence: 0.83624697

00:06:52.512 --> 00:06:54.640 the influenza neutralizing antibody

NOTE Confidence: 0.83624697

00:06:54.640 --> 00:06:57.716 titers that we saw generated by

NOTE Confidence: 0.83624697

00:06:57.716 --> 00:06:59.411 these vectors were greater than

NOTE Confidence: 0.83624697

00:06:59.411 --> 00:07:02.109 one to 4001 to 20 is what you

NOTE Confidence: 0.83624697

00:07:02.109 --> 00:07:04.017 need to protect mouse from flu.

NOTE Confidence: 0.83624697

00:07:04.020 --> 00:07:05.970 Also similar number in humans,

NOTE Confidence: 0.83624697

00:07:05.970 --> 00:07:08.310 so this is 200 times what

NOTE Confidence: 0.83624697

00:07:08.310 --> 00:07:09.870 you need to protect.

NOTE Confidence: 0.83624697

00:07:09.870 --> 00:07:11.820 It was also sterilizing immunity.

NOTE Confidence: 0.83624697

00:07:11.820 --> 00:07:14.514 We couldn't detect any flu replication

NOTE Confidence: 0.83624697

00:07:14.514 --> 00:07:16.310 in these protected animals.

NOTE Confidence: 0.83624697

00:07:16.310 --> 00:07:18.445 Alright, so these are the first experiments

NOTE Confidence: 0.83624697

00:07:18.445 --> 00:07:20.299 that established VSDS as vaccine vectors.

NOTE Confidence: 0.83624697

00:07:20.300 --> 00:07:21.825 We engineered them with convenient

NOTE Confidence: 0.83624697

00:07:21.825 --> 00:07:23.680 restriction sites all over the place,

NOTE Confidence: 0.83624697

00:07:23.680 --> 00:07:25.516 so you could put in jeans

NOTE Confidence: 0.83624697

00:07:25.516 --> 00:07:26.434 in different positions.

NOTE Confidence: 0.83624697

00:07:26.440 --> 00:07:28.589 If the foreign gene encoded a membrane,

NOTE Confidence: 0.83624697

00:07:28.590 --> 00:07:30.798 protein it off and ended up in the

NOTE Confidence: 0.83624697

00:07:30.798 --> 00:07:32.578 surface of the virus particle,

NOTE Confidence: 0.83624697

00:07:32.580 --> 00:07:34.794 which is a good place to

NOTE Confidence: 0.83624697

00:07:34.794 --> 00:07:36.270 be to generate immunity.

NOTE Confidence: 0.83624697

00:07:36.270 --> 00:07:38.706 So they grew to high titers.

NOTE Confidence: 0.83624697

00:07:38.710 --> 00:07:39.865 Stable gene expression.

NOTE Confidence: 0.83624697

00:07:39.865 --> 00:07:42.175 We could accommodate over 4 kilobases

NOTE Confidence: 0.83624697

00:07:42.175 --> 00:07:44.799 of foreign genes in multiple positions.

NOTE Confidence: 0.83624697

00:07:44.800 --> 00:07:46.830 Strong antibody CT cell responses.

NOTE Confidence: 0.83624697

00:07:46.830 --> 00:07:48.450 An importantly there was

NOTE Confidence: 0.83624697

00:07:48.450 --> 00:07:50.070 no pre existing immunity.

NOTE Confidence: 0.83624697

00:07:50.070 --> 00:07:51.288 No significant community

NOTE Confidence: 0.83624697

00:07:51.288 --> 00:07:53.318 to the vector in humans.

NOTE Confidence: 0.83624697

00:07:53.320 --> 00:07:53.760 Alright.

NOTE Confidence: 0.83624697

00:07:53.760 --> 00:07:55.960 Another important point was that

NOTE Confidence: 0.83624697

00:07:55.960 --> 00:07:59.008 we found this is a paper in 1999.

NOTE Confidence: 0.83624697

00:07:59.010 --> 00:08:01.350 You're going to actually replace

NOTE Confidence: 0.83624697

00:08:01.350 --> 00:08:05.219 the VSV G with a very distantly.

NOTE Confidence: 0.83624697

00:08:05.220 --> 00:08:07.260 Very foreign glycoprotein from a

NOTE Confidence: 0.83624697

00:08:07.260 --> 00:08:09.980 retrovirus from HIV and now you have.

NOTE Confidence: 0.83624697

00:08:09.980 --> 00:08:13.228 You can make a VSV which has the

NOTE Confidence: 0.83624697

00:08:13.228 --> 00:08:16.432 HIV coat and shows the specificity

NOTE Confidence: 0.83624697

00:08:16.432 --> 00:08:19.292 of infection that HIV has.

NOTE Confidence: 0.83624697

00:08:19.300 --> 00:08:19.678 Alright.

NOTE Confidence: 0.83624697

00:08:19.678 --> 00:08:22.324 So the first brick that we put

NOTE Confidence: 0.83624697

00:08:22.324 --> 00:08:24.672 on the foundation was that

NOTE Confidence: 0.83624697

00:08:24.672 --> 00:08:27.187 for influenza virus later on,

NOTE Confidence: 0.83624697

00:08:27.190 --> 00:08:27.542 Gen.

NOTE Confidence: 0.83624697

00:08:27.542 --> 00:08:29.654 Schwartz and others in my lab

NOTE Confidence: 0.83624697

00:08:29.654 --> 00:08:32.050 went on to study avian flu,

NOTE Confidence: 0.83624697

00:08:32.050 --> 00:08:35.034 which we thought might be the next pandemic,

NOTE Confidence: 0.83624697

00:08:35.040 --> 00:08:36.910 and it still could be.

NOTE Confidence: 0.83624697

00:08:36.910 --> 00:08:39.410 We studied respiratory syncytial virus.

NOTE Confidence: 0.83624697

00:08:39.410 --> 00:08:42.000 Our major focus was HIV aids using

NOTE Confidence: 0.83624697

00:08:42.000 --> 00:08:44.847 Sivs and Shift models in monkeys and

NOTE Confidence: 0.83624697

00:08:44.847 --> 00:08:47.337 this led to clinical trials which

NOTE Confidence: 0.83624697

00:08:47.417 --> 00:08:49.905 I don't have time to go into now.

NOTE Confidence: 0.83624697

00:08:49.910 --> 00:08:53.590 We also worked on SARS.

NOTE Confidence: 0.83624697

00:08:53.590 --> 00:08:56.070 But by the time we had these vectors,

NOTE Confidence: 0.83624697

00:08:56.070 --> 00:08:57.310 SARS was illuminated through

NOTE Confidence: 0.83624697

00:08:57.310 --> 00:08:58.240 public health measures.

NOTE Confidence: 0.83624697

00:08:58.240 --> 00:08:59.480 Papilloma virus plague chicken,

NOTE Confidence: 0.83624697

00:08:59.480 --> 00:09:00.440 gunia, Zika, nipah.

NOTE Confidence: 0.83624697

00:09:00.440 --> 00:09:02.715 These are all all these things in

NOTE Confidence: 0.83624697

00:09:02.715 --> 00:09:04.826 green are examples of ones that we

NOTE Confidence: 0.83624697

00:09:04.826 --> 00:09:07.230 where we made the factors in our lab,

NOTE Confidence: 0.83624697

00:09:07.230 --> 00:09:07.563 and.

NOTE Confidence: 0.83624697

00:09:07.563 --> 00:09:09.894 They were often tested in other labs

NOTE Confidence: 0.83624697

00:09:09.894 --> 00:09:12.547 where they could work with the pathogens,

NOTE Confidence: 0.83624697

00:09:12.550 --> 00:09:14.440 but what about what about Ebola?

NOTE Confidence: 0.83624697

00:09:14.440 --> 00:09:15.985 These examples in white are

NOTE Confidence: 0.83624697

00:09:15.985 --> 00:09:17.530 examples of studies where we

NOTE Confidence: 0.8141519

00:09:17.590 --> 00:09:19.795 simply sent the vectors to other people.

NOTE Confidence: 0.8141519

00:09:19.800 --> 00:09:22.560 We couldn't work on Ebola and Marburg at

NOTE Confidence: 0.8141519

00:09:22.560 --> 00:09:25.627 Yale we didn't have facilities for that.

NOTE Confidence: 0.8141519

00:09:25.630 --> 00:09:28.258 So we sent these out to hundreds of labs,

NOTE Confidence: 0.8141519

00:09:28.260 --> 00:09:29.676 including labs in Europe.

NOTE Confidence: 0.8141519

00:09:29.676 --> 00:09:32.370 And we sent to a lab actually

NOTE Confidence: 0.8141519

00:09:32.370 --> 00:09:34.810 at the University of Marburg,

NOTE Confidence: 0.8141519

00:09:34.810 --> 00:09:36.390 Hans Dieter, Clanks lab.

NOTE Confidence: 0.8141519

00:09:36.390 --> 00:09:38.365 We sent the vectors there,

00:09:38.370 --> 00:09:39.946 Anna guy there Heinz,

00:09:39.946 --> 00:09:41.916 Feldmann was making these recombinants,

00:09:41.920 --> 00:09:43.895 and then Hines moved to

00:09:43.895 --> 00:09:45.870 Canada to their BL4 lab,

00:09:45.870 --> 00:09:48.576 where he could do studies using

00:09:48.576 --> 00:09:50.927 the Ebola and Marburg vectors

00:09:50.927 --> 00:09:53.197 built on RV SV platform.

00:09:53.200 --> 00:09:55.060 And his paper the 1st paper.

00:09:55.060 --> 00:09:56.920 They did small animal studies first.

00:09:56.920 --> 00:09:59.400 The 1st paper in Monkeys is shown here.

00:09:59.400 --> 00:10:00.180 Nature Meadow.

00:10:00.180 --> 00:10:00.960 In 2005,

00:10:00.960 --> 00:10:03.300 so they made these recombinant VSV's

00:10:03.368 --> 00:10:05.136 expressing the Ebola glycoprotein

00:10:05.136 --> 00:10:07.788 or the Marburg single IM injection

00:10:07.857 --> 00:10:09.222 completely protective immune

NOTE Confidence: 0.8141519

00:10:09.222 --> 00:10:11.042 response and most importantly

NOTE Confidence: 0.8141519

00:10:11.042 --> 00:10:13.898 they had no evidence of Ebola or

NOTE Confidence: 0.8141519

00:10:13.898 --> 00:10:16.130 Marburg replication in any of the

NOTE Confidence: 0.8141519

00:10:16.204 --> 00:10:18.548 protected animals after challenge,

NOTE Confidence: 0.8141519

00:10:18.550 --> 00:10:20.878 so sterilizing immunity apparently.

NOTE Confidence: 0.8141519

00:10:20.878 --> 00:10:21.460 Alright,

NOTE Confidence: 0.8141519

00:10:21.460 --> 00:10:24.022 so how did the VSV Ebola

NOTE Confidence: 0.8141519

00:10:24.022 --> 00:10:25.730 vaccine get to Africa?

NOTE Confidence: 0.8141519

00:10:25.730 --> 00:10:26.066 Well,

NOTE Confidence: 0.8141519

00:10:26.066 --> 00:10:28.754 I wasn't really involved in any of this.

NOTE Confidence: 0.8141519

00:10:28.760 --> 00:10:31.040 I've read about it in in the public

NOTE Confidence: 0.8141519

00:10:31.040 --> 00:10:33.016 press and I've read it Mountain

NOTE Confidence: 0.8141519

00:10:33.016 --> 00:10:35.026 Helens article and I'm going to

NOTE Confidence: 0.8141519

00:10:35.098 --> 00:10:37.188 summarize this just very briefly,

NOTE Confidence: 0.8141519

00:10:37.190 --> 00:10:38.534 so the Canadian Government

NOTE Confidence: 0.8141519

00:10:38.534 --> 00:10:40.214 patented the VSV Ebola vaccine,

NOTE Confidence: 0.8141519

00:10:40.220 --> 00:10:42.579 but they found no market for it.

NOTE Confidence: 0.8141519

00:10:42.580 --> 00:10:44.310 Canada then sold the vaccine

NOTE Confidence: 0.8141519

00:10:44.310 --> 00:10:46.619 rights to a small company in Iowa,

NOTE Confidence: 0.8141519

00:10:46.620 --> 00:10:47.968 and they apparently didn't

NOTE Confidence: 0.8141519

00:10:47.968 --> 00:10:49.316 do anything with it.

NOTE Confidence: 0.8141519

00:10:49.320 --> 00:10:51.651 Then in 2014 there was this major

NOTE Confidence: 0.8141519

00:10:51.651 --> 00:10:53.700 outbreak of Ebola in West Africa.

NOTE Confidence: 0.8141519

00:10:53.700 --> 00:10:55.740 Thousands of people were dying.

NOTE Confidence: 0.8141519

00:10:55.740 --> 00:10:57.295 Cases were being imported into

NOTE Confidence: 0.8141519

00:10:57.295 --> 00:10:59.540 the US and to other countries.

NOTE Confidence: 0.8141519

00:10:59.540 --> 00:11:01.682 It was a real panic situation and

NOTE Confidence: 0.8141519

00:11:01.682 --> 00:11:03.806 because the VSV Ebola vaccine had

NOTE Confidence: 0.8141519

00:11:03.806 --> 00:11:05.711 been tested extensively in monkeys

NOTE Confidence: 0.8141519

00:11:05.711 --> 00:11:08.156 and also in one exposed lab worker,

NOTE Confidence: 0.8141519

00:11:08.160 --> 00:11:09.890 it was a reasonable candidate.

NOTE Confidence: 0.8141519

00:11:09.890 --> 00:11:11.600 This is actually important right

NOTE Confidence: 0.8141519

00:11:11.600 --> 00:11:14.066 here that they used it in somebody

NOTE Confidence: 0.8141519

00:11:14.066 --> 00:11:16.118 who had been exposed because they

NOTE Confidence: 0.8141519

00:11:16.118 --> 00:11:18.217 knew that the ESV Ebola vaccine

NOTE Confidence: 0.8141519

00:11:18.217 --> 00:11:20.233 worked in monkeys even after the

NOTE Confidence: 0.8141519

00:11:20.240 --> 00:11:21.960 monkeys were exposed to Ebola.

NOTE Confidence: 0.8141519

00:11:21.960 --> 00:11:24.030 At least up to 24 hours.

NOTE Confidence: 0.8141519

00:11:24.030 --> 00:11:26.100 They could protect with this vaccine,

NOTE Confidence: 0.8141519

00:11:26.100 --> 00:11:27.584 so it's a very.

NOTE Confidence: 0.8141519

00:11:27.584 --> 00:11:29.068 Fast response that protects.

NOTE Confidence: 0.8141519

00:11:29.070 --> 00:11:30.750 So Merck bought the vaccine,

NOTE Confidence: 0.8141519

00:11:30.750 --> 00:11:31.761 started producing it,

NOTE Confidence: 0.8141519

00:11:31.761 --> 00:11:33.109 and organized clinical trials,

NOTE Confidence: 0.8141519

00:11:33.110 --> 00:11:35.132 and there are many people involved

NOTE Confidence: 0.8141519

00:11:35.132 --> 00:11:36.143 in clinical trials.

00:11:36.150 --> 00:11:38.166 I don't know any of them.

00:11:38.170 --> 00:11:40.529 Merck ship the vaccine to West Africa,

00:11:40.530 --> 00:11:42.972 where it was used for clinical

00:11:42.972 --> 00:11:44.600 trials in the field.

00:11:44.600 --> 00:11:46.730 And here's the paper on this.

00:11:46.730 --> 00:11:49.215 This was published in Lancet in 2015.

00:11:49.220 --> 00:11:50.990 Single dose VSV Ebola vaccine

00:11:50.990 --> 00:11:52.765 was 100% effective and this

00:11:52.765 --> 00:11:54.540 was a ring vaccination study.

00:11:54.540 --> 00:11:55.960 It's an interesting way

00:11:55.960 --> 00:11:58.090 of doing it in the field,

00:11:58.090 --> 00:12:00.118 but in the case where they

00:12:00.118 --> 00:12:02.000 got the vaccine in early,

00:12:02.000 --> 00:12:04.478 they protected everybody around in the ring.

00:12:04.480 --> 00:12:06.944 In the case where they got the

00:12:06.944 --> 00:12:08.739 vaccine and later they had,

NOTE Confidence: 0.8141519

00:12:08.740 --> 00:12:10.624 I think 16 infections.

NOTE Confidence: 0.8141519

00:12:10.624 --> 00:12:12.066 So anyway, look,

NOTE Confidence: 0.8141519

00:12:12.066 --> 00:12:14.546 looked really good and it

NOTE Confidence: 0.8141519

00:12:14.546 --> 00:12:16.920 continues to be used so.

NOTE Confidence: 0.8141519

00:12:16.920 --> 00:12:18.153 Just to summarize,

NOTE Confidence: 0.8141519

00:12:18.153 --> 00:12:20.208 the Merck VSV Ebola vaccine,

NOTE Confidence: 0.8141519

00:12:20.210 --> 00:12:22.315 fully licensed by the European

NOTE Confidence: 0.8141519

00:12:22.315 --> 00:12:24.420 Commission and by the FDA

NOTE Confidence: 0.85490096

00:12:24.497 --> 00:12:27.128 and late 2019. It's also been

NOTE Confidence: 0.85490096

00:12:27.128 --> 00:12:29.758 licensed in eight African countries.

NOTE Confidence: 0.85490096

00:12:29.760 --> 00:12:31.360 Over 350,000 people have been

NOTE Confidence: 0.85490096

00:12:31.360 --> 00:12:33.450 vaccinated with the VSV Ebola vaccine,

NOTE Confidence: 0.85490096

00:12:33.450 --> 00:12:35.796 and there are stockpiles that I

NOTE Confidence: 0.85490096

00:12:35.796 --> 00:12:38.749 think are even much larger than that.

NOTE Confidence: 0.85490096

00:12:38.750 --> 00:12:40.905 Antibodies are the major correlate

NOTE Confidence: 0.85490096

00:12:40.905 --> 00:12:43.525 of protection and they persist for

NOTE Confidence: 0.85490096

00:12:43.525 --> 00:12:45.859 at least two years after vaccination,

NOTE Confidence: 0.85490096

00:12:45.860 --> 00:12:49.304 and it's really exciting to see our

NOTE Confidence: 0.85490096

00:12:49.304 --> 00:12:52.370 basic vaccine vector work go this far.

NOTE Confidence: 0.85490096

00:12:52.370 --> 00:12:54.323 Alright, normally at this point I would

NOTE Confidence: 0.85490096

00:12:54.323 --> 00:12:56.593 have a slide thanking all of the people

NOTE Confidence: 0.85490096

00:12:56.593 --> 00:12:58.827 who got involved in this work in my lab.

NOTE Confidence: 0.85490096

00:12:58.830 --> 00:12:59.810 All of our collaborators,

NOTE Confidence: 0.85490096

00:12:59.810 --> 00:13:02.492 but it would just be too many and I would

NOTE Confidence: 0.85490096

00:13:02.492 --> 00:13:03.937 leave out somebody really important.

NOTE Confidence: 0.85490096

00:13:03.940 --> 00:13:06.284 Then there are also all the people who

NOTE Confidence: 0.85490096

00:13:06.284 --> 00:13:08.880 took the vaccine and out into the field.

NOTE Confidence: 0.85490096

00:13:08.880 --> 00:13:09.746 In Africa,

NOTE Confidence: 0.85490096

00:13:09.746 --> 00:13:11.478 working under dangerous conditions,

NOTE Confidence: 0.85490096

00:13:11.480 --> 00:13:13.820 especially most recently in the

NOTE Confidence: 0.85490096

00:13:13.820 --> 00:13:16.585 Democratic Republic of the Congo and

NOTE Confidence: 0.85490096

00:13:16.585 --> 00:13:19.726 now we've got covid. On top of that.

NOTE Confidence: 0.85490096

00:13:19.726 --> 00:13:21.610 Alright, so?

NOTE Confidence: 0.85490096

00:13:21.610 --> 00:13:24.578 We don't have any format for questions here,

NOTE Confidence: 0.85490096

00:13:24.580 --> 00:13:26.638 but there's obviously there must be

NOTE Confidence: 0.85490096

00:13:26.638 --> 00:13:29.030 a question in some people's minds.

NOTE Confidence: 0.85490096

00:13:29.030 --> 00:13:32.806 What about a VSV SARS Co V2 vaccine?

NOTE Confidence: 0.85490096

00:13:32.810 --> 00:13:33.194 Alright,

NOTE Confidence: 0.85490096

00:13:33.194 --> 00:13:35.498 well I was already semi retired

NOTE Confidence: 0.85490096

00:13:35.498 --> 00:13:37.787 and beginning to close down my

NOTE Confidence: 0.85490096

00:13:37.787 --> 00:13:39.557 lab as the pandemic emerged,

NOTE Confidence: 0.85490096

00:13:39.560 --> 00:13:41.810 but with support and encouragement from

NOTE Confidence: 0.85490096

00:13:41.810 --> 00:13:45.620 Chen Liu, our new chair of Pathology.

NOTE Confidence: 0.85490096

00:13:45.620 --> 00:13:49.650 Timber yard bensky began this collaboration

NOTE Confidence: 0.85490096

00:13:49.650 --> 00:13:52.380 with Craig Wyland's lab to make VSV SARS,

NOTE Confidence: 0.85490096

00:13:52.380 --> 00:13:54.767 two Spike Suda types and also recombinants.

NOTE Confidence: 0.85490096

00:13:54.770 --> 00:13:56.470 And we've made the pseudotyped.

NOTE Confidence: 0.85490096

00:13:56.470 --> 00:13:59.020 The Recumbents have been more problematic

NOTE Confidence: 0.85490096

00:13:59.020 --> 00:14:01.459 'cause they don't grow very well.

NOTE Confidence: 0.85490096

00:14:01.460 --> 00:14:02.438 In the meantime,

NOTE Confidence: 0.85490096

00:14:02.438 --> 00:14:04.068 it became clear very quickly

NOTE Confidence: 0.85490096

00:14:04.068 --> 00:14:06.002 through the Grapevine and preprint

NOTE Confidence: 0.85490096

00:14:06.002 --> 00:14:08.032 servers that major laboratories in

NOTE Confidence: 0.85490096

00:14:08.032 --> 00:14:10.169 companies had already made VSV SARS.

NOTE Confidence: 0.85490096

00:14:10.170 --> 00:14:12.348 Two spiker comments they had initiated

NOTE Confidence: 0.85490096

00:14:12.348 --> 00:14:14.445 animal studies, and these were.

NOTE Confidence: 0.85490096

00:14:14.445 --> 00:14:16.720 These were looking very good.

NOTE Confidence: 0.85490096

00:14:16.720 --> 00:14:18.915 So Merck has initiated Phase

NOTE Confidence: 0.85490096

00:14:18.915 --> 00:14:21.668 one clinical trials with the VSV

NOTE Confidence: 0.85490096

00:14:21.668 --> 00:14:23.576 stars to spike recombinant.

NOTE Confidence: 0.85490096

00:14:23.580 --> 00:14:25.536 They haven't really published on this,

NOTE Confidence: 0.85490096

00:14:25.540 --> 00:14:27.514 but often big companies don't publish

NOTE Confidence: 0.85490096

00:14:27.514 --> 00:14:29.223 the Israel Institute for Biological

NOTE Confidence: 0.85490096

00:14:29.223 --> 00:14:30.918 Research is also doing clinical

NOTE Confidence: 0.85490096

00:14:30.918 --> 00:14:32.970 trials with a similar recombinant.

NOTE Confidence: 0.85490096

00:14:32.970 --> 00:14:35.412 And they have published on that

NOTE Confidence: 0.85490096

00:14:35.412 --> 00:14:37.040 in a hamster model,

NOTE Confidence: 0.85490096

00:14:37.040 --> 00:14:39.075 where it appears to give

NOTE Confidence: 0.85490096

00:14:39.075 --> 00:14:39.889 sterilizing protection.

NOTE Confidence: 0.85490096

00:14:39.890 --> 00:14:42.954 So I hope the vaccines that are already

NOTE Confidence: 0.85490096

00:14:42.954 --> 00:14:46.512 in use or in phase three trials will

NOTE Confidence: 0.85490096

00:14:46.512 --> 00:14:49.570 be sufficient to control this pandemic.

NOTE Confidence: 0.85490096

00:14:49.570 --> 00:14:51.758 You know we've got.

NOTE Confidence: 0.85490096

00:14:51.760 --> 00:14:53.350 We've got the M RNA vaccines

NOTE Confidence: 0.85490096

00:14:53.350 --> 00:14:54.790 that look really good there.

NOTE Confidence: 0.85490096

00:14:54.790 --> 00:14:57.968 It seems to be in short supply.

NOTE Confidence: 0.85490096

00:14:57.970 --> 00:14:59.402 The various adenovirus vectors

NOTE Confidence: 0.85490096

00:14:59.402 --> 00:15:00.476 are extremely good.

NOTE Confidence: 0.85490096

00:15:00.480 --> 00:15:02.724 Their protein vaccines in the pipeline

NOTE Confidence: 0.85490096

00:15:02.724 --> 00:15:05.130 and they are likely to work also,

NOTE Confidence: 0.85490096

00:15:05.130 --> 00:15:07.278 but if these are not sufficient,

NOTE Confidence: 0.85490096

00:15:07.280 --> 00:15:09.428 I think of ESV based SARS.

NOTE Confidence: 0.85490096

00:15:09.430 --> 00:15:12.118 Two vaccine is likely to be an

NOTE Confidence: 0.85490096

00:15:12.118 --> 00:15:13.940 effective single dose vaccine.

NOTE Confidence: 0.85490096

00:15:13.940 --> 00:15:17.243 Then I will stop there and say thank you.