

WEBVTT

NOTE duration:"00:11:48.2450000"

NOTE language:en-us

NOTE Confidence: 0.84344220161438

00:00:00.000 --> 00:00:02.555 I like to do is first thank

NOTE Confidence: 0.84344220161438

00:00:02.560 --> 00:00:04.000 Dean Browning organizers for

NOTE Confidence: 0.84344220161438

00:00:04.000 --> 00:00:05.392 inviting me to participate.

NOTE Confidence: 0.84344220161438

00:00:05.392 --> 00:00:07.480 I'm going to do a quick

NOTE Confidence: 0.84344220161438

00:00:07.556 --> 00:00:09.060 overview of this area.

NOTE Confidence: 0.84344220161438

00:00:09.060 --> 00:00:10.938 Some of the work that we've

NOTE Confidence: 0.84344220161438

00:00:10.938 --> 00:00:12.867 been doing here at Yale and

NOTE Confidence: 0.84344220161438

00:00:12.867 --> 00:00:14.667 also give an overview at the

NOTE Confidence: 0.84344220161438

00:00:14.667 --> 00:00:16.769 end of current approaches to

NOTE Confidence: 0.84344220161438

00:00:16.769 --> 00:00:19.154 enhancing the vaccine responses in

NOTE Confidence: 0.868290853500366

00:00:19.160 --> 00:00:21.230 older individuals. OK, so this

NOTE Confidence: 0.868290853500366

00:00:21.230 --> 00:00:23.300 is kind of our demographic

NOTE Confidence: 0.874503016471863

00:00:23.300 --> 00:00:26.124 imperative. The aging of the Post War Two

NOTE Confidence: 0.874503016471863

00:00:26.130 --> 00:00:28.362 baby boom generation in which the

NOTE Confidence: 0.874503016471863

00:00:28.362 --> 00:00:30.317 first members of this generation

NOTE Confidence: 0.874503016471863

00:00:30.317 --> 00:00:33.096 began turning 65 about 10 years ago.

NOTE Confidence: 0.874503016471863

00:00:33.100 --> 00:00:35.668 There showing the red in this US Census

NOTE Confidence: 0.874503016471863

00:00:35.668 --> 00:00:37.880 data plot with increasing age and the

NOTE Confidence: 0.874503016471863

00:00:37.880 --> 00:00:41.338 Y axis and you see how the shape of

NOTE Confidence: 0.874503016471863

00:00:41.338 --> 00:00:43.222 this population distribution changes

NOTE Confidence: 0.874503016471863

00:00:43.222 --> 00:00:45.286 substantially from 1980 to 2040,

NOTE Confidence: 0.874503016471863

00:00:45.286 --> 00:00:47.146 and it's estimated that everyday

NOTE Confidence: 0.874503016471863

00:00:47.146 --> 00:00:49.340 10,000 more members of the baby

NOTE Confidence: 0.874503016471863

00:00:49.340 --> 00:00:50.784 boom generation are turning.

NOTE Confidence: 0.874503016471863

00:00:50.784 --> 00:00:53.759 65 is going to continue until around 2013.

NOTE Confidence: 0.874503016471863

00:00:53.760 --> 00:00:55.974 By 2035, it's estimated that the

NOTE Confidence: 0.874503016471863

00:00:55.974 --> 00:00:58.560 number of adults over age 65 will

NOTE Confidence: 0.874503016471863

00:00:58.560 --> 00:01:01.038 exceed that of children for the

NOTE Confidence: 0.874503016471863

00:01:01.038 --> 00:01:03.900 first time in US history. Is

NOTE Confidence: 0.847443401813507

00:01:03.900 --> 00:01:06.917 obviously has a lot of implications for
NOTE Confidence: 0.847443401813507

00:01:06.920 --> 00:01:09.075 healthcare. Older adults are at
NOTE Confidence: 0.847443401813507

00:01:09.075 --> 00:01:11.230 increased risk for morbidity and
NOTE Confidence: 0.847443401813507

00:01:11.230 --> 00:01:12.950 mortality from infectious diseases
NOTE Confidence: 0.847443401813507

00:01:12.950 --> 00:01:15.536 and have decreased responses to vaccination
NOTE Confidence: 0.847443401813507

00:01:15.536 --> 00:01:18.120 in a typical influenza vaccine season,
NOTE Confidence: 0.847443401813507

00:01:18.120 --> 00:01:20.706 about 90% of the mortality occurs
NOTE Confidence: 0.847443401813507

00:01:20.706 --> 00:01:23.308 in older adults over age 65.
NOTE Confidence: 0.847443401813507

00:01:23.310 --> 00:01:26.166 The effectiveness of the seasonal vaccine.
NOTE Confidence: 0.847443401813507

00:01:26.170 --> 00:01:29.061 This is CDC data extending back about
NOTE Confidence: 0.847443401813507

00:01:29.061 --> 00:01:33.037 15 years and showing all comers can be
NOTE Confidence: 0.847443401813507

00:01:33.037 --> 00:01:35.682 substantially reduced in older adults,
NOTE Confidence: 0.847443401813507

00:01:35.690 --> 00:01:37.590 sometimes with vaccine efficacies
NOTE Confidence: 0.847443401813507

00:01:37.590 --> 00:01:39.965 with a lot of variability,
NOTE Confidence: 0.847443401813507

00:01:39.970 --> 00:01:42.826 but sometimes extending into the teens,
NOTE Confidence: 0.847443401813507

00:01:42.830 --> 00:01:45.680 or even worse in older individuals.

NOTE Confidence: 0.847443401813507
00:01:45.680 --> 00:01:49.304 And we've also seen a similar effect in
NOTE Confidence: 0.847443401813507
00:01:49.304 --> 00:01:53.338 terms of mortality during the SARS Co V2.
NOTE Confidence: 0.847443401813507
00:01:53.340 --> 00:01:55.410 COVID-19 pandemic with about 80%
NOTE Confidence: 0.847443401813507
00:01:55.410 --> 00:01:58.026 mortality occurring in older adults and
NOTE Confidence: 0.847443401813507
00:01:58.026 --> 00:02:00.599 it's encouraging as on Yemen mentioned
NOTE Confidence: 0.847443401813507
00:02:00.599 --> 00:02:03.631 that the initial news seems to be good
NOTE Confidence: 0.847443401813507
00:02:03.709 --> 00:02:06.169 from some of the vaccine platforms.
NOTE Confidence: 0.847443401813507
00:02:06.170 --> 00:02:09.490 So how does age affect the immune response?
NOTE Confidence: 0.847443401813507
00:02:09.490 --> 00:02:12.423 This seems to affect all phases of
NOTE Confidence: 0.847443401813507
00:02:12.423 --> 00:02:14.990 the immune response and the adaptive
NOTE Confidence: 0.847443401813507
00:02:14.990 --> 00:02:18.180 immune system is on the Emma alluded to,
NOTE Confidence: 0.847443401813507
00:02:18.180 --> 00:02:20.250 there is decreased antibody titers
NOTE Confidence: 0.847443401813507
00:02:20.250 --> 00:02:21.078 following vaccination,
NOTE Confidence: 0.847443401813507
00:02:21.080 --> 00:02:22.752 correlating with decreased levels
NOTE Confidence: 0.847443401813507
00:02:22.752 --> 00:02:24.424 of antibody secreting cells.
NOTE Confidence: 0.847443401813507

00:02:24.430 --> 00:02:26.872 Post vaccine work from defining Bloomberg
NOTE Confidence: 0.847443401813507

00:02:26.872 --> 00:02:29.290 and Daniel Frasca is also shown.
NOTE Confidence: 0.847443401813507

00:02:29.290 --> 00:02:30.910 Decreased expression of activation
NOTE Confidence: 0.847443401813507

00:02:30.910 --> 00:02:32.125 to citing deaminase,
NOTE Confidence: 0.847443401813507

00:02:32.130 --> 00:02:34.115 an essential protein for heavy
NOTE Confidence: 0.847443401813507

00:02:34.115 --> 00:02:36.100 chain class switching and somatic
NOTE Confidence: 0.847443401813507

00:02:36.169 --> 00:02:38.061 hypermutation affecting the quality
NOTE Confidence: 0.847443401813507

00:02:38.061 --> 00:02:39.953 of the antibody response.
NOTE Confidence: 0.847443401813507

00:02:39.960 --> 00:02:41.874 The T cell compartment is dominated
NOTE Confidence: 0.847443401813507

00:02:41.874 --> 00:02:44.299 by the effects of thymic involution,
NOTE Confidence: 0.847443401813507

00:02:44.300 --> 00:02:46.834 which starts to occur in young adulthood,
NOTE Confidence: 0.847443401813507

00:02:46.840 --> 00:02:48.624 resulting in markedly decreased
NOTE Confidence: 0.847443401813507

00:02:48.624 --> 00:02:50.854 cellularity in the thymus compared
NOTE Confidence: 0.847443401813507

00:02:50.854 --> 00:02:52.787 to a thymus from a child.
NOTE Confidence: 0.847443401813507

00:02:52.790 --> 00:02:53.660 And really,
NOTE Confidence: 0.847443401813507

00:02:53.660 --> 00:02:56.270 in humans there's very little thymic

NOTE Confidence: 0.847443401813507

00:02:56.270 --> 00:02:59.026 activity to speak of in older adults,

NOTE Confidence: 0.847443401813507

00:02:59.030 --> 00:03:01.750 and the vast majority of the T slim

NOTE Confidence: 0.847443401813507

00:03:01.750 --> 00:03:03.529 partners maintain exclusively by

NOTE Confidence: 0.847443401813507

00:03:03.529 --> 00:03:06.099 homeostatic perforation in the periphery.

NOTE Confidence: 0.847443401813507

00:03:06.100 --> 00:03:08.774 This is obvious effects on the diversity

NOTE Confidence: 0.847443401813507

00:03:08.774 --> 00:03:11.326 of the potential diversity of the

NOTE Confidence: 0.847443401813507

00:03:11.326 --> 00:03:14.002 vaccine response or response to infections.

NOTE Confidence: 0.847443401813507

00:03:14.010 --> 00:03:15.002 In addition,

NOTE Confidence: 0.847443401813507

00:03:15.002 --> 00:03:17.482 there have been multiple signal

NOTE Confidence: 0.847443401813507

00:03:17.482 --> 00:03:19.358 transduction defects identified in

NOTE Confidence: 0.847443401813507

00:03:19.358 --> 00:03:21.278 the T cell lineages affecting the

NOTE Confidence: 0.847443401813507

00:03:21.278 --> 00:03:23.869 quality of T cell receptor signaling.

NOTE Confidence: 0.847443401813507

00:03:23.870 --> 00:03:24.664 In addition,

NOTE Confidence: 0.847443401813507

00:03:24.664 --> 00:03:26.252 alterations in other pathways

NOTE Confidence: 0.847443401813507

00:03:26.252 --> 00:03:27.840 such as adenosine sibling,

NOTE Confidence: 0.847443401813507

00:03:27.840 --> 00:03:29.830 that influence survival of memory,
NOTE Confidence: 0.847443401813507

00:03:29.830 --> 00:03:32.931 T cell populations and also the function
NOTE Confidence: 0.847443401813507

00:03:32.931 --> 00:03:36.085 of follicular helper T cells which are
NOTE Confidence: 0.847443401813507

00:03:36.085 --> 00:03:38.265 implicated in the antibody response.
NOTE Confidence: 0.847443401813507

00:03:38.270 --> 00:03:41.062 In the innate immune system there's a similar
NOTE Confidence: 0.847443401813507

00:03:41.062 --> 00:03:42.840 paradoxical chronic inflammatory state,
NOTE Confidence: 0.847443401813507

00:03:42.840 --> 00:03:44.750 termed inflammation by Claudio Franceschi.
NOTE Confidence: 0.847443401813507

00:03:44.750 --> 00:03:46.916 You'll see that in the literature
NOTE Confidence: 0.847443401813507

00:03:46.916 --> 00:03:49.233 it's not as vigorous as an
NOTE Confidence: 0.847443401813507

00:03:49.233 --> 00:03:50.837 acute reaction from infection,
NOTE Confidence: 0.847443401813507

00:03:50.840 --> 00:03:52.735 but is characterized by elevated
NOTE Confidence: 0.847443401813507

00:03:52.735 --> 00:03:55.066 levels of cytokines and acute phase
NOTE Confidence: 0.847443401813507

00:03:55.066 --> 00:03:57.316 reactants such as C reactive peptide.
NOTE Confidence: 0.847443401813507

00:03:57.320 --> 00:04:00.749 We've seen evidence of this in our own work.
NOTE Confidence: 0.847443401813507

00:04:00.750 --> 00:04:03.417 This was work done several years ago,
NOTE Confidence: 0.847443401813507

00:04:03.420 --> 00:04:05.826 and we joined forces with Ruth

NOTE Confidence: 0.847443401813507

00:04:05.826 --> 00:04:08.438 Montgomery's lab and this is data from.

NOTE Confidence: 0.847443401813507

00:04:08.440 --> 00:04:10.768 A primary human dendritic cells showing

NOTE Confidence: 0.847443401813507

00:04:10.768 --> 00:04:13.327 markedly elevated levels of pro inflammatory

NOTE Confidence: 0.847443401813507

00:04:13.327 --> 00:04:15.219 cytokine production at baseline,

NOTE Confidence: 0.847443401813507

00:04:15.220 --> 00:04:17.320 and these are levels that we

NOTE Confidence: 0.847443401813507

00:04:17.320 --> 00:04:19.350 never saw in primary dendritic

NOTE Confidence: 0.847443401813507

00:04:19.350 --> 00:04:21.578 cells from young individuals.

NOTE Confidence: 0.847443401813507

00:04:21.580 --> 00:04:23.854 And we think this chronic activation

NOTE Confidence: 0.847443401813507

00:04:23.854 --> 00:04:26.394 state contributed to an inability to

NOTE Confidence: 0.847443401813507

00:04:26.394 --> 00:04:28.784 further up regulate cytokine production.

NOTE Confidence: 0.847443401813507

00:04:28.790 --> 00:04:30.910 Appan encounter of a new

NOTE Confidence: 0.847443401813507

00:04:30.910 --> 00:04:32.606 pathogen or vac steam,

NOTE Confidence: 0.847443401813507

00:04:32.610 --> 00:04:35.570 so we model this by doing ex vivo

NOTE Confidence: 0.847443401813507

00:04:35.570 --> 00:04:38.209 toll like receptor stimulation.

NOTE Confidence: 0.847443401813507

00:04:38.210 --> 00:04:40.610 And pretty much across the board,

NOTE Confidence: 0.847443401813507

00:04:40.610 --> 00:04:42.150 you'll see decreased cytokine
NOTE Confidence: 0.847443401813507

00:04:42.150 --> 00:04:44.460 production is cohort of about 100
NOTE Confidence: 0.827477276325226

00:04:44.528 --> 00:04:46.483 young and older individuals following
NOTE Confidence: 0.827477276325226

00:04:46.483 --> 00:04:48.918 X people simulation and we have
NOTE Confidence: 0.827477276325226

00:04:48.918 --> 00:04:51.378 similar data for the TLR induced
NOTE Confidence: 0.827477276325226

00:04:51.378 --> 00:04:53.010 upregulation of costimulatory proteins.
NOTE Confidence: 0.827477276325226

00:04:53.010 --> 00:04:55.010 Now the mechanisms for this
NOTE Confidence: 0.827477276325226

00:04:55.010 --> 00:04:56.210 we're still investigating.
NOTE Confidence: 0.827477276325226

00:04:56.210 --> 00:04:57.930 I think it's multifactorial.
NOTE Confidence: 0.827477276325226

00:04:57.930 --> 00:05:01.310 One area that we think may play a
NOTE Confidence: 0.827477276325226

00:05:01.310 --> 00:05:03.802 role is the UP regulation in self.
NOTE Confidence: 0.827477276325226

00:05:03.810 --> 00:05:06.210 Some older adults of anti inflammatory
NOTE Confidence: 0.827477276325226

00:05:06.210 --> 00:05:08.220 cytokines and you see this.
NOTE Confidence: 0.827477276325226

00:05:08.220 --> 00:05:09.804 Shown in this slide.
NOTE Confidence: 0.827477276325226

00:05:09.804 --> 00:05:11.784 This is work from Sebastian
NOTE Confidence: 0.827477276325226

00:05:11.784 --> 00:05:13.959 Mohanty in the lab showing that.

NOTE Confidence: 0.827477276325226

00:05:13.960 --> 00:05:15.672 In monocytes evaluated following

NOTE Confidence: 0.827477276325226

00:05:15.672 --> 00:05:17.384 influenza vaccination that day,

NOTE Confidence: 0.827477276325226

00:05:17.390 --> 00:05:19.340 two 728 there's a substantial

NOTE Confidence: 0.827477276325226

00:05:19.340 --> 00:05:21.844 elevation and out ten production and

NOTE Confidence: 0.827477276325226

00:05:21.844 --> 00:05:24.259 anti-inflammatory cytokine in the mileage.

NOTE Confidence: 0.827477276325226

00:05:24.260 --> 00:05:26.405 The boss is ultimately focused

NOTE Confidence: 0.827477276325226

00:05:26.405 --> 00:05:28.550 on a negative regulator valve.

NOTE Confidence: 0.827477276325226

00:05:28.550 --> 00:05:30.690 Ten production, called Dust blonde.

NOTE Confidence: 0.827477276325226

00:05:30.690 --> 00:05:33.264 This is a map kinase phosphatase

NOTE Confidence: 0.827477276325226

00:05:33.264 --> 00:05:34.980 and showed that dust.

NOTE Confidence: 0.827477276325226

00:05:34.980 --> 00:05:36.812 One phosphorylation was downregulated

NOTE Confidence: 0.827477276325226

00:05:36.812 --> 00:05:39.102 in monocytes and older adults

NOTE Confidence: 0.827477276325226

00:05:39.102 --> 00:05:41.158 and is provided with potential

NOTE Confidence: 0.827477276325226

00:05:41.158 --> 00:05:43.444 mechanism to explain or at least

NOTE Confidence: 0.827477276325226

00:05:43.512 --> 00:05:45.707 a contributing factor to impaired.

NOTE Confidence: 0.827477276325226

00:05:45.710 --> 00:05:48.188 Innate immune responses in older individuals.

NOTE Confidence: 0.827477276325226

00:05:48.190 --> 00:05:50.250 Now we've been very fortunate.

NOTE Confidence: 0.827477276325226

00:05:50.250 --> 00:05:52.995 Go to be one center in the niht IDs

NOTE Confidence: 0.827477276325226

00:05:52.995 --> 00:05:55.618 Human Immunology Project Consortium,

NOTE Confidence: 0.827477276325226

00:05:55.620 --> 00:05:58.924 where one center of nine on a country

NOTE Confidence: 0.827477276325226

00:05:58.924 --> 00:06:01.950 where in our second cycle of funding

NOTE Confidence: 0.827477276325226

00:06:01.950 --> 00:06:05.307 were led by a David and Ruth as

NOTE Confidence: 0.827477276325226

00:06:05.307 --> 00:06:08.394 the peas and the purpose of the Hip

NOTE Confidence: 0.827477276325226

00:06:08.394 --> 00:06:10.698 See consortium is to evaluate or

NOTE Confidence: 0.827477276325226

00:06:10.698 --> 00:06:12.560 understand human immune responses,

NOTE Confidence: 0.827477276325226

00:06:12.560 --> 00:06:14.212 particularly under conditions of

NOTE Confidence: 0.827477276325226

00:06:14.212 --> 00:06:16.277 perturbation by infections or vaccines.

NOTE Confidence: 0.827477276325226

00:06:16.280 --> 00:06:18.004 And as an example,

NOTE Confidence: 0.827477276325226

00:06:18.004 --> 00:06:20.159 we recently published an assessment.

NOTE Confidence: 0.827477276325226

00:06:20.160 --> 00:06:22.799 I think the largest assessment of the

NOTE Confidence: 0.827477276325226

00:06:22.799 --> 00:06:26.190 effects of age on influenza vaccine response,

NOTE Confidence: 0.827477276325226
00:06:26.190 --> 00:06:28.345 evaluating signatures over a 5
NOTE Confidence: 0.827477276325226
00:06:28.345 --> 00:06:30.500 / 5 consecutive vaccine seasons,
NOTE Confidence: 0.827477276325226
00:06:30.500 --> 00:06:33.080 and these were about 135 young
NOTE Confidence: 0.827477276325226
00:06:33.155 --> 00:06:35.585 and older adults stratified into
NOTE Confidence: 0.827477276325226
00:06:35.585 --> 00:06:37.529 individuals with very strong.
NOTE Confidence: 0.827477276325226
00:06:37.530 --> 00:06:40.110 Or weak or absent antibody responses
NOTE Confidence: 0.827477276325226
00:06:40.110 --> 00:06:40.970 to vaccination.
NOTE Confidence: 0.827477276325226
00:06:40.970 --> 00:06:43.040 One of the signatures that emerge
NOTE Confidence: 0.827477276325226
00:06:43.040 --> 00:06:45.737 from this work is a mitochondrial
NOTE Confidence: 0.827477276325226
00:06:45.737 --> 00:06:46.987 Biogenesis signature.
NOTE Confidence: 0.827477276325226
00:06:46.990 --> 00:06:49.140 Kind of linking metabolic function
NOTE Confidence: 0.827477276325226
00:06:49.140 --> 00:06:50.430 to immune response.
NOTE Confidence: 0.827477276325226
00:06:50.430 --> 00:06:52.752 We validated this at the protein
NOTE Confidence: 0.827477276325226
00:06:52.752 --> 00:06:54.786 level evaluating two nuclear encoded
NOTE Confidence: 0.827477276325226
00:06:54.786 --> 00:06:57.264 mitochondrial protein GHB 60 and a
NOTE Confidence: 0.827477276325226

00:06:57.264 --> 00:06:59.460 component of succinate dehydrogenase.
NOTE Confidence: 0.827477276325226

00:06:59.460 --> 00:07:02.040 If one looks at responders versus
NOTE Confidence: 0.827477276325226

00:07:02.040 --> 00:07:03.760 nonresponders that day seven,
NOTE Confidence: 0.827477276325226

00:07:03.760 --> 00:07:05.775 there were significant differences in
NOTE Confidence: 0.827477276325226

00:07:05.775 --> 00:07:08.560 the protein expression in young individuals.
NOTE Confidence: 0.827477276325226

00:07:08.560 --> 00:07:11.452 And more extensive differences in one
NOTE Confidence: 0.827477276325226

00:07:11.452 --> 00:07:14.037 looked at older vaccine responders
NOTE Confidence: 0.827477276325226

00:07:14.037 --> 00:07:16.922 compared to nonresponders at all
NOTE Confidence: 0.827477276325226

00:07:16.922 --> 00:07:19.230 time points post vaccination.
NOTE Confidence: 0.827477276325226

00:07:19.230 --> 00:07:19.601 However,
NOTE Confidence: 0.827477276325226

00:07:19.601 --> 00:07:21.456 there's a lot of heterogeneity
NOTE Confidence: 0.827477276325226

00:07:21.456 --> 00:07:24.178 in that we saw in this response,
NOTE Confidence: 0.827477276325226

00:07:24.180 --> 00:07:26.840 so this is work done in collaboration
NOTE Confidence: 0.827477276325226

00:07:26.840 --> 00:07:28.370 with Steve Kleinstein Slab,
NOTE Confidence: 0.827477276325226

00:07:28.370 --> 00:07:31.930 where I think it's complex and the reasons.
NOTE Confidence: 0.827477276325226

00:07:31.930 --> 00:07:33.820 Euro excellent or poor responder

NOTE Confidence: 0.827477276325226
00:07:33.820 --> 00:07:36.127 seem to largely differ or diverge
NOTE Confidence: 0.827477276325226
00:07:36.127 --> 00:07:37.852 dependent on whether you were
NOTE Confidence: 0.827477276325226
00:07:37.852 --> 00:07:40.089 older or in the young group.
NOTE Confidence: 0.827477276325226
00:07:40.090 --> 00:07:41.945 There was one area where
NOTE Confidence: 0.827477276325226
00:07:41.945 --> 00:07:43.429 there was some commonality.
NOTE Confidence: 0.827477276325226
00:07:43.430 --> 00:07:45.656 Is is this gene cluster C,
NOTE Confidence: 0.827477276325226
00:07:45.660 --> 00:07:48.332 which seemed to be shared between young and
NOTE Confidence: 0.827477276325226
00:07:48.332 --> 00:07:50.848 older adults and being downregulated today.
NOTE Confidence: 0.827477276325226
00:07:50.850 --> 00:07:51.750 28 post vaccine.
NOTE Confidence: 0.827477276325226
00:07:51.750 --> 00:07:54.398 It was enriched for a lot of immunological
NOTE Confidence: 0.827477276325226
00:07:54.398 --> 00:07:56.788 pathways and had three jeans.
NOTE Confidence: 0.827477276325226
00:07:56.790 --> 00:07:57.125 OK,
NOTE Confidence: 0.827477276325226
00:07:57.125 --> 00:07:59.470 McConnell again and the same dust one
NOTE Confidence: 0.827477276325226
00:07:59.470 --> 00:08:02.049 protein I mentioned or Gina mentioned.
NOTE Confidence: 0.827477276325226
00:08:02.050 --> 00:08:02.370 Earlier,
NOTE Confidence: 0.827477276325226

00:08:02.370 --> 00:08:04.610 along with another member of the family,
NOTE Confidence: 0.827477276325226

00:08:04.610 --> 00:08:06.353 this seemed to be shared in a
NOTE Confidence: 0.827477276325226

00:08:06.353 --> 00:08:08.450 kind of a regulatory capacity,
NOTE Confidence: 0.827477276325226

00:08:08.450 --> 00:08:11.660 and we think the source of this is at least
NOTE Confidence: 0.832725465297699

00:08:11.735 --> 00:08:14.210 in part T cells, be cause we saw
NOTE Confidence: 0.832725465297699

00:08:14.210 --> 00:08:15.810 a similar downregulation at 8:20.
NOTE Confidence: 0.832725465297699

00:08:15.810 --> 00:08:18.170 Eighteen purified T cell populations.
NOTE Confidence: 0.832725465297699

00:08:18.170 --> 00:08:20.630 So we finish by briefly discussing
NOTE Confidence: 0.832725465297699

00:08:20.630 --> 00:08:22.270 the current approaches for
NOTE Confidence: 0.832725465297699

00:08:22.346 --> 00:08:24.701 augmenting and responses in older
NOTE Confidence: 0.832725465297699

00:08:24.701 --> 00:08:26.585 adults for influenza vaccine.
NOTE Confidence: 0.832725465297699

00:08:26.590 --> 00:08:28.800 The high dose vaccines available.
NOTE Confidence: 0.832725465297699

00:08:28.800 --> 00:08:31.030 This is essentially preparation is
NOTE Confidence: 0.832725465297699

00:08:31.030 --> 00:08:33.860 four times the dose of hemagglutinin
NOTE Confidence: 0.832725465297699

00:08:33.860 --> 00:08:36.950 is in the standard dose vaccine.
NOTE Confidence: 0.832725465297699

00:08:36.950 --> 00:08:39.175 There is now a quadrivalent

NOTE Confidence: 0.832725465297699

00:08:39.175 --> 00:08:41.400 preparation that is in use.

NOTE Confidence: 0.832725465297699

00:08:41.400 --> 00:08:43.812 This was the original phase three

NOTE Confidence: 0.832725465297699

00:08:43.812 --> 00:08:47.190 trial led by Kip Talbot at Vanderbilt,

NOTE Confidence: 0.832725465297699

00:08:47.190 --> 00:08:49.926 then rolled over 30,000 individuals and

NOTE Confidence: 0.832725465297699

00:08:49.926 --> 00:08:52.622 found a modest relative reduction of

NOTE Confidence: 0.832725465297699

00:08:52.622 --> 00:08:55.056 about 24% in laboratory confirmed influenza,

NOTE Confidence: 0.832725465297699

00:08:55.056 --> 00:08:58.310 and this is all evaluating older individuals.

NOTE Confidence: 0.832725465297699

00:08:58.310 --> 00:09:00.535 Another approach has been to

NOTE Confidence: 0.832725465297699

00:09:00.535 --> 00:09:02.760 use a vaccine edge events.

NOTE Confidence: 0.832725465297699

00:09:02.760 --> 00:09:04.544 The other approved influenza

NOTE Confidence: 0.832725465297699

00:09:04.544 --> 00:09:07.220 vaccine preparation in the US for.

NOTE Confidence: 0.832725465297699

00:09:07.220 --> 00:09:09.896 Older adults is standard dose vaccine.

NOTE Confidence: 0.832725465297699

00:09:09.900 --> 00:09:12.130 It's aggravated with Emma 59.

NOTE Confidence: 0.832725465297699

00:09:12.130 --> 00:09:14.818 This is an agile meant as a squealing

NOTE Confidence: 0.832725465297699

00:09:14.818 --> 00:09:17.408 emotion that perhaps enhances antigen

NOTE Confidence: 0.832725465297699

00:09:17.408 --> 00:09:19.256 transport engine presentation.
NOTE Confidence: 0.832725465297699

00:09:19.260 --> 00:09:21.500 There's pretty good data for
NOTE Confidence: 0.832725465297699

00:09:21.500 --> 00:09:23.740 enhanced antibody responses in older
NOTE Confidence: 0.832725465297699

00:09:23.812 --> 00:09:25.947 adults compared to standard oh,
NOTE Confidence: 0.832725465297699

00:09:25.950 --> 00:09:26.347 Son,
NOTE Confidence: 0.832725465297699

00:09:26.347 --> 00:09:28.729 Edgerton vaccine and the hint in
NOTE Confidence: 0.832725465297699

00:09:28.729 --> 00:09:31.560 some studies that there may even be
NOTE Confidence: 0.832725465297699

00:09:31.560 --> 00:09:33.900 a more broadly based immune response
NOTE Confidence: 0.832725465297699

00:09:33.978 --> 00:09:37.188 in terms of antibody production to
NOTE Confidence: 0.832725465297699

00:09:37.188 --> 00:09:39.328 heterologous influenza vaccine strains.
NOTE Confidence: 0.832725465297699

00:09:39.330 --> 00:09:41.134 When using the agitated.
NOTE Confidence: 0.832725465297699

00:09:41.134 --> 00:09:43.840 Compared to an agent in vaccine,
NOTE Confidence: 0.832725465297699

00:09:43.840 --> 00:09:46.731 I should also comment on the management
NOTE Confidence: 0.832725465297699

00:09:46.731 --> 00:09:49.648 using the varicella zoster subunit vaccine.
NOTE Confidence: 0.832725465297699

00:09:49.650 --> 00:09:52.332 The SONB edge event used a
NOTE Confidence: 0.832725465297699

00:09:52.332 --> 00:09:53.673 combination of lipid,

NOTE Confidence: 0.832725465297699

00:09:53.680 --> 00:09:55.910 a tiller four agonist combined

NOTE Confidence: 0.832725465297699

00:09:55.910 --> 00:09:57.694 with US opponent glycoside,

NOTE Confidence: 0.832725465297699

00:09:57.700 --> 00:09:59.925 and there's really quite impressive

NOTE Confidence: 0.832725465297699

00:09:59.925 --> 00:10:02.657 vaccine efficacy that does not seem

NOTE Confidence: 0.832725465297699

00:10:02.657 --> 00:10:04.847 to be substantially age dependent,

NOTE Confidence: 0.832725465297699

00:10:04.850 --> 00:10:06.922 with almost essentially equivalent

NOTE Confidence: 0.832725465297699

00:10:06.922 --> 00:10:09.512 efficacy and individuals over age

NOTE Confidence: 0.832725465297699

00:10:09.512 --> 00:10:12.517 80 as compared to those in your 50s.

NOTE Confidence: 0.832725465297699

00:10:12.520 --> 00:10:14.662 And there's a number of vents

NOTE Confidence: 0.832725465297699

00:10:14.662 --> 00:10:15.733 are relatively small.

NOTE Confidence: 0.832725465297699

00:10:15.740 --> 00:10:16.098 Also,

NOTE Confidence: 0.832725465297699

00:10:16.098 --> 00:10:17.530 efficacy in the prevention

NOTE Confidence: 0.832725465297699

00:10:17.530 --> 00:10:18.604 of postherpetic neuralgia.

NOTE Confidence: 0.832725465297699

00:10:18.610 --> 00:10:20.746 So I think there's a promise.

NOTE Confidence: 0.832725465297699

00:10:20.750 --> 00:10:22.899 Therefore the use of agents to try

NOTE Confidence: 0.832725465297699

00:10:22.899 --> 00:10:25.080 to overcome the limitations of age
NOTE Confidence: 0.832725465297699

00:10:25.080 --> 00:10:27.474 in vaccines and a closeout mentioned
NOTE Confidence: 0.832725465297699

00:10:27.474 --> 00:10:29.349 something that's in the pipeline,
NOTE Confidence: 0.832725465297699

00:10:29.350 --> 00:10:30.064 somewhat surprising,
NOTE Confidence: 0.832725465297699

00:10:30.064 --> 00:10:32.206 and we can talk about it.
NOTE Confidence: 0.832725465297699

00:10:32.210 --> 00:10:34.716 The use of M Tor inhibitors for
NOTE Confidence: 0.832725465297699

00:10:34.716 --> 00:10:35.790 augmenting immune responses,
NOTE Confidence: 0.832725465297699

00:10:35.790 --> 00:10:37.937 as many of you know, mtor,
NOTE Confidence: 0.832725465297699

00:10:37.937 --> 00:10:40.793 in addition in terms of low dose rapamycin,
NOTE Confidence: 0.832725465297699

00:10:40.800 --> 00:10:42.640 has been used in animal.
NOTE Confidence: 0.832725465297699

00:10:42.640 --> 00:10:44.970 Model systems mooring systems to
NOTE Confidence: 0.832725465297699

00:10:44.970 --> 00:10:47.843 increase lifespan it probably does is
NOTE Confidence: 0.832725465297699

00:10:47.843 --> 00:10:50.645 by mimicking effects of caloric restriction,
NOTE Confidence: 0.832725465297699

00:10:50.650 --> 00:10:53.639 but this is work from restore Bio
NOTE Confidence: 0.832725465297699

00:10:53.639 --> 00:10:56.553 and Joan Mannix Group that have
NOTE Confidence: 0.832725465297699

00:10:56.553 --> 00:10:59.637 used two inhibitors of 1 downstream

NOTE Confidence: 0.832725465297699

00:10:59.637 --> 00:11:02.509 pathway event or torque one to

NOTE Confidence: 0.832725465297699

00:11:02.509 --> 00:11:05.190 show in all older individuals that

NOTE Confidence: 0.832725465297699

00:11:05.190 --> 00:11:07.650 use of both of these inhibitors

NOTE Confidence: 0.832725465297699

00:11:07.650 --> 00:11:09.483 resulted in increased antibody

NOTE Confidence: 0.832725465297699

00:11:09.483 --> 00:11:12.103 responses following in Saint BENS

NOTE Confidence: 0.832725465297699

00:11:12.103 --> 00:11:14.199 influenza vaccination and also.

NOTE Confidence: 0.832725465297699

00:11:14.200 --> 00:11:14.527 Surprisingly,

NOTE Confidence: 0.832725465297699

00:11:14.527 --> 00:11:16.489 six week course of these inhibitors

NOTE Confidence: 0.832725465297699

00:11:16.489 --> 00:11:18.302 resulted in a significant decrease

NOTE Confidence: 0.832725465297699

00:11:18.302 --> 00:11:19.842 in restaurant tract infections

NOTE Confidence: 0.832725465297699

00:11:19.842 --> 00:11:21.800 observed over one year period.

NOTE Confidence: 0.832725465297699

00:11:21.800 --> 00:11:23.635 So someone paradox too unsurprising

NOTE Confidence: 0.832725465297699

00:11:23.635 --> 00:11:25.877 to think of the biology of

NOTE Confidence: 0.832725465297699

00:11:25.877 --> 00:11:27.587 what mtor inhibition is doing,

NOTE Confidence: 0.832725465297699

00:11:27.590 --> 00:11:29.660 but it's something I think to

NOTE Confidence: 0.832725465297699

00:11:29.660 --> 00:11:31.939 keep in mind for the future.

NOTE Confidence: 0.832725465297699

00:11:31.940 --> 00:11:33.077 And with that,

NOTE Confidence: 0.832725465297699

00:11:33.077 --> 00:11:35.351 I'll thank all of our great

NOTE Confidence: 0.832725465297699

00:11:35.351 --> 00:11:36.340 collaborators at Yale.

NOTE Confidence: 0.832725465297699

00:11:36.340 --> 00:11:37.910 Many of which I mentioned.

NOTE Confidence: 0.832725465297699

00:11:37.910 --> 00:11:39.848 Also like to mention our long-term

NOTE Confidence: 0.832725465297699

00:11:39.848 --> 00:11:41.140 collaboration with the Claude

NOTE Confidence: 0.859437823295593

00:11:41.197 --> 00:11:43.249 Pepper Center at Yale, and wanted to

NOTE Confidence: 0.859437823295593

00:11:43.249 --> 00:11:44.814 thank everyone for your attention.

NOTE Confidence: 0.859437823295593

00:11:44.820 --> 00:11:48.240 And thank you for inviting me.