WEBVTT

NOTE duration:"01:00:05"

NOTE recognizability:0.839

NOTE language:en-us

NOTE Confidence: 0.787334406923077

 $00:00:00.000 \rightarrow 00:00:02.072$ US online. It's my great pleasure today

NOTE Confidence: 0.787334406923077

00:00:02.072 --> 00:00:04.079 to introduce our Grand Round speaker,

NOTE Confidence: 0.787334406923077

00:00:04.080 --> 00:00:05.226 Doctor Kevin Harold.

NOTE Confidence: 0.787334406923077

00:00:05.226 --> 00:00:06.754 I've known Doctor Harold,

NOTE Confidence: 0.787334406923077

 $00:00:06.760 \longrightarrow 00:00:08.314$ it turns out, for 10 years now.

NOTE Confidence: 0.787334406923077

 $00:00:08.320 \longrightarrow 00:00:09.680$ We just figured it out.

NOTE Confidence: 0.787334406923077

 $00{:}00{:}09{.}680 \dashrightarrow 00{:}00{:}11.720$ We met at the bed side.

NOTE Confidence: 0.787334406923077

00:00:11.720 --> 00:00:13.799 And I think for the fellows in the audience,

NOTE Confidence: 0.787334406923077

 $00:00:13.800 \rightarrow 00:00:16.059$ this is a this hopefully will be a teaching

NOTE Confidence: 0.787334406923077

 $00:00:16.059 \dashrightarrow 00:00:17.916$ moment because you get a sick patient,

NOTE Confidence: 0.787334406923077

 $00{:}00{:}17.920 \dashrightarrow 00{:}00{:}19.355$ you're not sure what's wrong with him.

NOTE Confidence: 0.787334406923077

 $00{:}00{:}19.360 \dashrightarrow 00{:}00{:}20.524$ You call the expert.

NOTE Confidence: 0.787334406923077

 $00{:}00{:}20{.}524 \dashrightarrow 00{:}00{:}22{.}699$ And from that, we developed an

 $00:00:22.699 \rightarrow 00:00:24.716$ entire universe of research projects,

NOTE Confidence: 0.787334406923077

 $00{:}00{:}24.716 \dashrightarrow 00{:}00{:}27.222$ grants and so on that Doctor Harold

NOTE Confidence: 0.787334406923077

00:00:27.222 --> 00:00:29.039 will be talking about today.

NOTE Confidence: 0.787334406923077

00:00:29.040 - > 00:00:31.356 To me that exemplifies the beauty

NOTE Confidence: 0.787334406923077

 $00:00:31.356 \dashrightarrow 00:00:33.711$ of Yale University and what we're

NOTE Confidence: 0.787334406923077

 $00{:}00{:}33.711 \dashrightarrow 00{:}00{:}35.265$ about unusual clinical circumstances

NOTE Confidence: 0.787334406923077

00:00:35.265 --> 00:00:37.240 taken back to the bench,

NOTE Confidence: 0.787334406923077

00:00:37.240 --> 00:00:38.480 going back to the clinic,

NOTE Confidence: 0.787334406923077

 $00{:}00{:}38{.}480 \dashrightarrow 00{:}00{:}39{.}120$ etcetera, etcetera.

NOTE Confidence: 0.787334406923077

 $00:00:39.120 \longrightarrow 00:00:41.040$ But the best part of it

NOTE Confidence: 0.787334406923077

 $00:00:41.040 \longrightarrow 00:00:42.840$ all is the collegiality.

NOTE Confidence: 0.787334406923077

 $00:00:42.840 \longrightarrow 00:00:44.970$ So I'm just remembering my

NOTE Confidence: 0.787334406923077

00:00:44.970 -> 00:00:46.400 first after we got our funding,

NOTE Confidence: 0.787334406923077

 $00:00:46.400 \rightarrow 00:00:48.074$ the very first research meeting that

NOTE Confidence: 0.787334406923077

 $00{:}00{:}48.074 \dashrightarrow 00{:}00{:}50.177$ I had with Doctor Harold and Doctor

NOTE Confidence: 0.787334406923077

00:00:50.177 --> 00:00:52.304 Eric Murphy, who's since left Yale.

00:00:52.304 --> 00:00:54.675 Yeah, I'm not an immunologist, but they are.

NOTE Confidence: 0.787334406923077

 $00{:}00{:}54.680 \dashrightarrow 00{:}00{:}55.051$ They.

NOTE Confidence: 0.787334406923077

 $00{:}00{:}55{.}051 \dashrightarrow 00{:}00{:}56{.}906$ They both are card carrying

NOTE Confidence: 0.787334406923077

00:00:56.906 --> 00:00:58.870 immunologists and Doctor Mephre in

NOTE Confidence: 0.787334406923077

 $00:00:58.870 \dashrightarrow 00:01:00.558$ particular doesn't tolerate fools.

NOTE Confidence: 0.787334406923077

 $00:01:00.560 \rightarrow 00:01:02.555$ So I was really intimidated by this

NOTE Confidence: 0.787334406923077

00:01:02.555 --> 00:01:05.159 meeting and I had established ground rules.

NOTE Confidence: 0.787334406923077

 $00:01:05.160 \rightarrow 00:01:06.960$ I don't know if Doctor Harold remembers this.

NOTE Confidence: 0.787334406923077

 $00:01:06.960 \dashrightarrow 00:01:09.633$ We decided that this is an idiot free zone.

NOTE Confidence: 0.787334406923077

00:01:09.640 --> 00:01:10.306 We're all smart,

NOTE Confidence: 0.787334406923077

00:01:10.306 - 00:01:11.860 we can say whatever we like and

NOTE Confidence: 0.787334406923077

 $00{:}01{:}11{.}915 \dashrightarrow 00{:}01{:}13{.}397$ we never have to be embarrassed.

NOTE Confidence: 0.787334406923077

 $00{:}01{:}13{.}400 \dashrightarrow 00{:}01{:}15{.}122$ And I think that that principle

NOTE Confidence: 0.787334406923077

 $00:01:15.122 \longrightarrow 00:01:17.557$ has LED us in the last 10 years

NOTE Confidence: 0.787334406923077

 $00{:}01{:}17.557 \dashrightarrow 00{:}01{:}20.066$ because it turns out that even I had

 $00:01:20.066 \rightarrow 00:01:22.194$ something to bring to the table here.

NOTE Confidence: 0.787334406923077

 $00{:}01{:}22.200 \dashrightarrow 00{:}01{:}23.529$ So collegiality, respect,

NOTE Confidence: 0.787334406923077

 $00{:}01{:}23.529 \dashrightarrow 00{:}01{:}26.187$ creativity has led to a whole

NOTE Confidence: 0.787334406923077

 $00:01:26.187 \longrightarrow 00:01:28.845$ field that I think we've opened

NOTE Confidence: 0.787334406923077

 $00{:}01{:}28.845 \dashrightarrow 00{:}01{:}30.985$ up here in translational research

NOTE Confidence: 0.787334406923077

00:01:31.065 --> 00:01:33.695 on immune related adverse events

NOTE Confidence: 0.787334406923077

 $00:01:33.695 \longrightarrow 00:01:35.273$ for endocrine toxicities.

NOTE Confidence: 0.787334406923077

 $00{:}01{:}35{.}280 \dashrightarrow 00{:}01{:}38{.}304$ So other than this whole world Doctor

NOTE Confidence: 0.787334406923077

 $00{:}01{:}38{.}304 \dashrightarrow 00{:}01{:}41{.}165$ Harold is actually really famous for

NOTE Confidence: 0.787334406923077

 $00:01:41.165 \rightarrow 00:01:44.075$ delaying type one diabetes in kids,

NOTE Confidence: 0.787334406923077

00:01:44.080 --> 00:01:46.360 a major break
through in delivering

NOTE Confidence: 0.787334406923077

 $00:01:46.360 \longrightarrow 00:01:48.640$ CD3 antibodies to children who

NOTE Confidence: 0.787334406923077

 $00{:}01{:}48.719 \dashrightarrow 00{:}01{:}51.077$ had started to develop type one

NOTE Confidence: 0.787334406923077

 $00{:}01{:}51{.}077 \dashrightarrow 00{:}01{:}53{.}521$ diabetes giving them the anti CD3

NOTE Confidence: 0.787334406923077

 $00:01:53.521 \longrightarrow 00:01:56.192$ antibody delaying the onset of

NOTE Confidence: 0.787334406923077

 $00{:}01{:}56{.}192 \dashrightarrow 00{:}01{:}59{.}032$ full blown is let cell destruction.

- NOTE Confidence: 0.787334406923077
- $00:01:59.040 \longrightarrow 00:02:00.433$ I don't think he's going to be
- NOTE Confidence: 0.787334406923077
- $00:02:00.433 \longrightarrow 00:02:01.320$ talking about that today,
- NOTE Confidence: 0.787334406923077
- $00:02:01.320 \longrightarrow 00:02:02.682$ but today we look forward to
- NOTE Confidence: 0.787334406923077
- $00:02:02.682 \rightarrow 00:02:04.224$ listening to all the cancer related
- NOTE Confidence: 0.787334406923077
- $00{:}02{:}04{.}224 \dashrightarrow 00{:}02{:}05{.}396$ studies that he's done.
- NOTE Confidence: 0.787334406923077
- $00:02:05.400 \longrightarrow 00:02:06.680$ So without further ado,
- NOTE Confidence: 0.787334406923077
- $00:02:06.680 \rightarrow 00:02:09.160$ thank you Doctor Harold for taking the time.
- NOTE Confidence: 0.8798066
- 00:02:15.160 --> 00:02:17.380 OK, thank you very much Harriet
- NOTE Confidence: 0.8798066
- $00:02:17.380 \longrightarrow 00:02:19.280$ for that very kind introduction.
- NOTE Confidence: 0.822342689565217
- 00:02:19.280 --> 00:02:21.344 I, I, I I have to admit I I was also
- NOTE Confidence: 0.822342689565217
- $00:02:21.344 \rightarrow 00:02:22.928$ quite pleased that we were going
- NOTE Confidence: 0.822342689565217
- $00{:}02{:}22{.}928 \dashrightarrow 00{:}02{:}24{.}958$ to set up our research meeting.
- NOTE Confidence: 0.822342689565217
- $00{:}02{:}24.960 \dashrightarrow 00{:}02{:}26.370$ So there'll be no it would
- NOTE Confidence: 0.822342689565217
- $00{:}02{:}26.370 \dashrightarrow 00{:}02{:}27.640$ be an idiot free zone.
- NOTE Confidence: 0.822342689565217
- $00:02:27.640 \longrightarrow 00:02:29.400$ I I I appreciated that.
- NOTE Confidence: 0.88189794

 $00:02:31.520 \longrightarrow 00:02:36.720$ So here's my disclosures.

NOTE Confidence: 0.88189794

 $00:02:36.720 \longrightarrow 00:02:41.323$ So hopefully this is review to everyone

NOTE Confidence: 0.88189794

 $00:02:41.323 \longrightarrow 00:02:44.424$ that that basically we we live in

NOTE Confidence: 0.88189794

 $00:02:44.424 \rightarrow 00:02:46.996$ a constant immunologic equilibrium

NOTE Confidence: 0.88189794

 $00:02:46.996 \longrightarrow 00:02:49.396$ balancing lymphocyte activation

NOTE Confidence: 0.88189794

 $00{:}02{:}49{.}396 \dashrightarrow 00{:}02{:}52{.}608$ and control and the activation is

NOTE Confidence: 0.88189794

 $00:02:52.608 \dashrightarrow 00:02:55.730$ controlled by a number of Co simulatory

NOTE Confidence: 0.88189794

 $00:02:55.730 \longrightarrow 00:02:58.875$ molecules and recognition by antigen

NOTE Confidence: 0.88189794

 $00:02:58.880 \dashrightarrow 00:03:03:514$ by T cells and other immune cells.

NOTE Confidence: 0.88189794

00:03:03.520 --> 00:03:06.376 And we the the the major developments in NOTE Confidence: 0.88189794

 $00{:}03{:}06{.}376$ --> $00{:}03{:}09{.}435$ the cancer field of course are that by

NOTE Confidence: 0.88189794

00:03:09.435 --> 00:03:11.964 disrupting this balance we can develop NOTE Confidence: 0.88189794

 $00:03:11.964 \rightarrow 00:03:14.314$ effective ways of treating cancers.

NOTE Confidence: 0.88189794

 $00{:}03{:}14.320 \dashrightarrow 00{:}03{:}17.518$ And and indeed this has revolutionized

NOTE Confidence: 0.88189794

 $00{:}03{:}17.520 \dashrightarrow 00{:}03{:}20.498$ the field over the past decade and

NOTE Confidence: 0.88189794

 $00:03:20.498 \rightarrow 00:03:23.246$ it became very clear initially when

 $00:03:23.246 \rightarrow 00:03:25.669$ these agents became available for

NOTE Confidence: 0.88189794

 $00{:}03{:}25.669 \dashrightarrow 00{:}03{:}28.561$ clinical use that there were adverse

NOTE Confidence: 0.88189794

 $00{:}03{:}28{.}561 \dashrightarrow 00{:}03{:}31{.}079$ events that would occur as well

NOTE Confidence: 0.88189794

 $00:03:31.080 \rightarrow 00:03:33.365$ since the balance that prevents

NOTE Confidence: 0.88189794

 $00{:}03{:}33{.}365 \dashrightarrow 00{:}03{:}35{.}650$ us from developing autoimmunity is

NOTE Confidence: 0.88189794

 $00:03:35.724 \dashrightarrow 00:03:38.079$ controlled by the same mechanisms.

NOTE Confidence: 0.88189794

 $00{:}03{:}38{.}080 \dashrightarrow 00{:}03{:}40{.}174$ And we and it's been established

NOTE Confidence: 0.88189794

 $00:03:40.174 \longrightarrow 00:03:42.424$ for many years that even normal

NOTE Confidence: 0.88189794

 $00:03:42.424 \dashrightarrow 00:03:44.764$ patients have immune cells that are

NOTE Confidence: 0.88189794

 $00{:}03{:}44.764 \dashrightarrow 00{:}03{:}47.358$ capable of recognizing self antigens.

NOTE Confidence: 0.88189794

 $00{:}03{:}47{.}360 \dashrightarrow 00{:}03{:}49{.}985$ So by tipping this balance it's fairly

NOTE Confidence: 0.88189794

 $00:03:49.985 \dashrightarrow 00:03:53.383$ clear that one would be able to develop NOTE Confidence: 0.88189794

 $00{:}03{:}53{.}383 \dashrightarrow 00{:}03{:}55{.}578$ autoimmune diseases and that's that's

NOTE Confidence: 0.88189794

 $00:03:55.654 \dashrightarrow 00:03:58.558$ what I'm going to be talking about today. NOTE Confidence: 0.88189794

 $00:03:58.560 \dashrightarrow 00:04:01.325$ Now the endocrine organs seem to be NOTE Confidence: 0.88189794

 $\overline{7}$

00:04:01.325 --> 00:04:03.740 particularly vulnerable to immune related

NOTE Confidence: 0.88189794

 $00{:}04{:}03.740 \dashrightarrow 00{:}04{:}07.250$ adverse events with with biologic

NOTE Confidence: 0.88189794

 $00:04:07.250 \longrightarrow 00:04:09.590$ therapy particularly with checkpoint

NOTE Confidence: 0.88189794

 $00{:}04{:}09{.}590 \dashrightarrow 00{:}04{:}12{.}620$ inhibitors and you can this is from a

NOTE Confidence: 0.88189794

 $00:04:12.620 \rightarrow 00:04:15.518$ review that came out a number of years ago,

NOTE Confidence: 0.88189794

 $00:04:15.520 \longrightarrow 00:04:17.064$ but there are many,

NOTE Confidence: 0.88189794

 $00:04:17.064 \dashrightarrow 00:04:18.994$ many organs that are affected.

NOTE Confidence: 0.88189794

 $00{:}04{:}19{.}000 \dashrightarrow 00{:}04{:}21{.}592$ I've on the right side we see just the

NOTE Confidence: 0.88189794

 $00{:}04{:}21.600 \dashrightarrow 00{:}04{:}25.040$ endocrine organs that are affected.

NOTE Confidence: 0.88189794

00:04:25.040 --> 00:04:29.072 Fibroid disease is the most common and

NOTE Confidence: 0.88189794

00:04:29.072 --> 00:04:35.664 frankly can be over 15% in some series

NOTE Confidence: 0.88189794

00:04:35.664 --> 00:04:39.156 and the second most common is pituitary NOTE Confidence: 0.88189794

 $00:04:39.156 \longrightarrow 00:04:42.478$ disease that can be difficult to diagnose,

NOTE Confidence: 0.88189794

 $00:04:42.480 \dashrightarrow 00:04:44.696$ certainly important to diagnose.

NOTE Confidence: 0.88189794

 $00{:}04{:}44.696 \dashrightarrow 00{:}04{:}48.534$ And then the other endocrine organs seem

NOTE Confidence: 0.88189794

 $00:04:48.534 \rightarrow 00:04:51.464$ to be affected as well including the

 $00:04:51.464 \longrightarrow 00:04:53.528$ the insulin producing beta cells that

NOTE Confidence: 0.88189794

 $00:04:53.528 \dashrightarrow 00:04:56.159$ leads to the development of diabetes.

NOTE Confidence: 0.88189794

 $00:04:56.160 \dashrightarrow 00:04:59.600$ Now I would point out from this graph NOTE Confidence: 0.88189794

 $00:04:59.600 \longrightarrow 00:05:04.473$ that that the development of these

NOTE Confidence: 0.88189794

 $00:05:04.473 \dashrightarrow 00:05:06.939$ adverse events are most common with NOTE Confidence: 0.88189794

 $00{:}05{:}06{.}939 \dashrightarrow 00{:}05{:}08{.}812$ combination the rapies and this is going NOTE Confidence: 0.88189794

00:05:08.812 --> 00:05:10.758 to come up again in some of the data.

NOTE Confidence: 0.88189794

00:05:10.760 --> 00:05:13.904 I'm going to present to you that the

NOTE Confidence: 0.88189794

00:05:13.904 --> 00:05:18.500 combination of anti C2A4 plus anti PD

NOTE Confidence: 0.88189794

 $00:05:18.500 \dashrightarrow 00:05:22.648$ one or PDL one seems to be seems to NOTE Confidence: 0.88189794

 $00:05:22.648 \rightarrow 00:05:24.776$ impart a higher risk of developing these NOTE Confidence: 0.88189794

 $00{:}05{:}24.776$ --> $00{:}05{:}26.797$ adverse events than either agent alone.

NOTE Confidence: 0.95304476625

 $00{:}05{:}29{.}040 \dashrightarrow 00{:}05{:}31{.}840$ So the timing of them varies a bit.

NOTE Confidence: 0.95304476625

 $00{:}05{:}31.840 \dashrightarrow 00{:}05{:}35.634$ And sometimes we, as a practical matter,

NOTE Confidence: 0.95304476625

 $00{:}05{:}35{.}640 \dashrightarrow 00{:}05{:}38{.}244$ have a hard time determining whether

 $00{:}05{:}38{.}244 \dashrightarrow 00{:}05{:}41{.}986$ or not an adverse event that we may see

NOTE Confidence: 0.95304476625

 $00{:}05{:}41.986 \dashrightarrow 00{:}05{:}44.306$ is directly related to the checkpoint

NOTE Confidence: 0.95304476625

00:05:44.306 --> 00:05:46.622 inhibitor that's been given or whether NOTE Confidence: 0.95304476625

 $00:05:46.622 \rightarrow 00:05:49.118$ it was just happening by chance.

NOTE Confidence: 0.95304476625

 $00{:}05{:}49{.}120 \dashrightarrow 00{:}05{:}51{.}154$ Because some of these adverse events

NOTE Confidence: 0.95304476625

00:05:51.154 --> 00:05:53.679 such as thyroid disease or diabetes are NOTE Confidence: 0.95304476625

 $00:05:53.679 \rightarrow 00:05:55.519$ relatively common in the population,

NOTE Confidence: 0.95304476625

 $00:05:55.520 \rightarrow 00:05:58.440$ particularly in the older population.

NOTE Confidence: 0.95304476625

 $00:05:58.440 \rightarrow 00:06:00.968$ But this graph shows you the timing of NOTE Confidence: 0.95304476625

 $00{:}06{:}00{.}968 \dashrightarrow 00{:}06{:}04.144$ some of the more common adverse events. NOTE Confidence: 0.95304476625

 $00:06:04.144 \rightarrow 00:06:08.200$ You can see that hypothesitis can happen NOTE Confidence: 0.95304476625

00:06:08.200 --> 00:06:11.398 several weeks after the development after NOTE Confidence: 0.95304476625

00:06:11.398 --> 00:06:13.888 a checkpoint inhibitors are administered.

NOTE Confidence: 0.95304476625

 $00{:}06{:}13.888 \dashrightarrow 00{:}06{:}16.996$ Some of the others that are that

NOTE Confidence: 0.95304476625

 $00:06:16.996 \rightarrow 00:06:20.105$ are also quite common tend to occur

NOTE Confidence: 0.95304476625

 $00:06:20.105 \longrightarrow 00:06:22.080$ in a more acute manner.

 $00{:}06{:}22.080 \dashrightarrow 00{:}06{:}26.870$ Now as Harriet mentioned we started

NOTE Confidence: 0.95304476625

 $00{:}06{:}26.870 \dashrightarrow 00{:}06{:}30.134$ I'm going to spend most of my the rest

NOTE Confidence: 0.95304476625

 $00:06:30.134 \rightarrow 00:06:32.456$ of the talk talking about checkpoint

NOTE Confidence: 0.95304476625

 $00:06:32.456 \rightarrow 00:06:34.050$ induced autoimmune diabetes because

NOTE Confidence: 0.95304476625

00:06:34.050 --> 00:06:36.318 that's where we've done the most,

NOTE Confidence: 0.95304476625

 $00{:}06{:}36{.}320 \dashrightarrow 00{:}06{:}36{.}977$ the most work.

NOTE Confidence: 0.95304476625

00:06:36.977 --> 00:06:38.510 And let me just make it mention

NOTE Confidence: 0.95304476625

 $00:06:38.567 \longrightarrow 00:06:40.240$ one thing about some of the others.

NOTE Confidence: 0.95304476625

00:06:40.240 --> 00:06:43.500 You know I I I do want to say sort

NOTE Confidence: 0.95304476625

 $00{:}06{:}43.600 \dashrightarrow 00{:}06{:}46.402$ of up front that the mechanisms

NOTE Confidence: 0.95304476625

 $00{:}06{:}46{.}402 \dashrightarrow 00{:}06{:}49{.}126$ of some of these other checkpoint

NOTE Confidence: 0.95304476625

00:06:49.126 --> 00:06:51.775 induced endocrine adverse events are

NOTE Confidence: 0.95304476625

 $00{:}06{:}51.775 \dashrightarrow 00{:}06{:}54.120$ not very well worked out at all.

NOTE Confidence: 0.95304476625

 $00{:}06{:}54{.}120 \dashrightarrow 00{:}06{:}57{.}224$ There is really one sort of lead paper

NOTE Confidence: 0.95304476625

 $00{:}06{:}57{.}224 \dashrightarrow 00{:}06{:}59{.}702$ that described the development of

00:06:59.702 --> 00:07:01.870 autoimmune hypothesitis that talked

NOTE Confidence: 0.95304476625

00:07:01.870 --> 00:07:05.365 about expression of C of CTLA 4 on

NOTE Confidence: 0.95304476625

 $00:07:05.365 \rightarrow 00:07:07.160$ pituitary cells and suggested that

NOTE Confidence: 0.95304476625

 $00:07:07.160 \rightarrow 00:07:09.764$ what happened with anti CTLA 4 is

NOTE Confidence: 0.95304476625

 $00{:}07{:}09{.}764 \dashrightarrow 00{:}07{:}12{.}073$ that the antibodies bound to CTLA

NOTE Confidence: 0.95304476625

 $00:07:12.073 \dashrightarrow 00:07:14.305$ 4 on the pituitary fixed complement

NOTE Confidence: 0.95304476625

 $00:07:14.305 \longrightarrow 00:07:16.158$ and destroyed the cells.

NOTE Confidence: 0.95304476625

 $00:07:16.160 \rightarrow 00:07:18.400$ But if you go through the paper carefully,

NOTE Confidence: 0.95304476625

 $00{:}07{:}18{.}400 \dashrightarrow 00{:}07{:}19{.}360$ you'll see that, well,

NOTE Confidence: 0.95304476625

 $00:07:19.360 \longrightarrow 00:07:20.560$ it really wasn't sort of.

NOTE Confidence: 0.95304476625

00:07:20.560 --> 00:07:23.158 It wasn't the ACTH producing cells,

NOTE Confidence: 0.95304476625

 $00{:}07{:}23.160 \dashrightarrow 00{:}07{:}25.500$ which is a common manifestation

NOTE Confidence: 0.95304476625

00:07:25.500 --> 00:07:26.436 of hypothesitis,

NOTE Confidence: 0.95304476625

 $00{:}07{:}26.440 \dashrightarrow 00{:}07{:}28.850$ it was prolact in producing cells

NOTE Confidence: 0.95304476625

 $00:07:28.850 \dashrightarrow 00:07:31.840$ and and also TSH producing cells.

NOTE Confidence: 0.95304476625

 $00:07:31.840 \longrightarrow 00:07:33.840$ So the precise mechanisms there

 $00:07:33.840 \longrightarrow 00:07:35.840$ really aren't quite so clear.

NOTE Confidence: 0.95304476625

00:07:35.840 --> 00:07:37.380 Likewise for thyroid disease.

NOTE Confidence: 0.95304476625

 $00:07:37.380 \longrightarrow 00:07:39.690$ I think it's still somewhat of

NOTE Confidence: 0.95304476625

00:07:39.758 --> 00:07:42.185 an unknown or a wide open area

NOTE Confidence: 0.95304476625

 $00{:}07{:}42.185 \dashrightarrow 00{:}07{:}44.565$ for investigation I should say to

NOTE Confidence: 0.95304476625

00:07:44.565 --> 00:07:46.119 understand the mechanisms.

NOTE Confidence: 0.95304476625

 $00{:}07{:}46.120 \dashrightarrow 00{:}07{:}48.460$ But we focused our attention on

NOTE Confidence: 0.95304476625

 $00:07:48.460 \rightarrow 00:07:50.020$ autoimmune diabetes and hopefully

NOTE Confidence: 0.95304476625

 $00{:}07{:}50.080 \dashrightarrow 00{:}07{:}52.145$ have made some inroads into

NOTE Confidence: 0.95304476625

 $00{:}07{:}52.145 \dashrightarrow 00{:}07{:}53.797$ understanding the mechanisms here.

NOTE Confidence: 0.95304476625

 $00:07:53.800 \longrightarrow 00:07:55.400$ And our work began as,

NOTE Confidence: 0.95304476625

 $00{:}07{:}55{.}400 \dashrightarrow 00{:}07{:}57{.}157$ as I I pointed out to Harriet,

NOTE Confidence: 0.95304476625

 $00:07:57.160 \longrightarrow 00:08:00.360$ if you take a look at the date on this,

NOTE Confidence: 0.95304476625

 $00{:}08{:}00{.}360 \dashrightarrow 00{:}08{:}04{.}728$ this paper almost a decade ago

NOTE Confidence: 0.95304476625

 $00:08:04.728 \longrightarrow 00:08:07.775$ when the patient #1 here was

00:08:07.775 --> 00:08:11.000 referred to me by Doctor Kluger.

NOTE Confidence: 0.95304476625

 $00{:}08{:}11.000 \dashrightarrow 00{:}08{:}16.200$ And the IT was a woman with Melanoma

NOTE Confidence: 0.95304476625

00:08:16.200 --> 00:08:20.760 who have been treated with IPI and also NOTE Confidence: 0.95304476625

 $00{:}08{:}20.760 \dashrightarrow 00{:}08{:}23.928$ had gotten nivolumab at that point and

NOTE Confidence: 0.95304476625

 $00{:}08{:}23.928 \dashrightarrow 00{:}08{:}26.040$ presented with diabetic keto acidosis.

NOTE Confidence: 0.95304476625

 $00{:}08{:}26{.}040 \dashrightarrow 00{:}08{:}28{.}714$ And you know this was quite striking.

NOTE Confidence: 0.95304476625

 $00:08:28.720 \longrightarrow 00:08:30.360$ This is someone who's 55.

NOTE Confidence: 0.95304476625

 $00:08:30.360 \rightarrow 00:08:32.040$ And then subsequently there were a

NOTE Confidence: 0.95304476625

00:08:32.040 --> 00:08:34.928 number of other cases that came from NOTE Confidence: 0.95304476625

 $00:08:34.928 \longrightarrow 00:08:39.940$ Yale of people over the age of 50 who NOTE Confidence: 0.95304476625

 $00:08:39.940 \longrightarrow 00:08:42.420$ were presenting with ketoacidosis

NOTE Confidence: 0.95304476625

 $00{:}08{:}42{.}420 \dashrightarrow 00{:}08{:}45{.}096$ often and new onset hyperglycemia.

NOTE Confidence: 0.95304476625

 $00{:}08{:}45.096 \dashrightarrow 00{:}08{:}48.691$ And this was kind of striking and

NOTE Confidence: 0.95304476625

 $00:08:48.691 \dashrightarrow 00:08:51.577$ to me it was striking because you

NOTE Confidence: 0.95304476625

 $00{:}08{:}51{.}577 \dashrightarrow 00{:}08{:}54{.}331$ know we hadn't seen it before the

NOTE Confidence: 0.95304476625

 $00{:}08{:}54{.}331 \dashrightarrow 00{:}08{:}57{.}936$ the the anti PD one drugs were new

 $00{:}08{:}57{.}936 \dashrightarrow 00{:}09{:}00{.}560$ at that time but we had had anti

NOTE Confidence: 0.8217956666666667

 $00{:}09{:}00{.}640 \dashrightarrow 00{:}09{:}03{.}680$ CTLA 4 Ipilimab for a number of years.

NOTE Confidence: 0.8217956666666667

 $00:09:03.680 \dashrightarrow 00:09:06.794$ And so that was kind of kind of striking.

NOTE Confidence: 0.8217956666666667

 $00:09:06.800 \rightarrow 00:09:09.056$ So we ended up putting these series together

NOTE Confidence: 0.8217956666666667

 $00{:}09{:}09{.}056 \dashrightarrow 00{:}09{:}11{.}201$ and this I I know I mentioned this the

NOTE Confidence: 0.8217956666666667

00:09:11.201 --> 00:09:13.607 last time I spoke but I I want to kind of

NOTE Confidence: 0.8217956666666667

 $00:09:13.607 \rightarrow 00:09:16.440$ bring this point up again particularly

NOTE Confidence: 0.8217956666666667

 $00:09:16.440 \longrightarrow 00:09:20.904$ for the trainees who are here and and

NOTE Confidence: 0.8217956666666667

 $00:09:20.904 \dashrightarrow 00:09:23.496$ the the data that we've subsequently

NOTE Confidence: 0.8217956666666667

 $00:09:23.496 \dashrightarrow 00:09:25.600$ had even makes the point even further.

NOTE Confidence: 0.8217956666666667

 $00:09:25.600 \longrightarrow 00:09:27.070$ So we we put this series

NOTE Confidence: 0.8217956666666667

 $00:09:27.070 \longrightarrow 00:09:28.440$ together and we send it in,

NOTE Confidence: 0.8217956666666667

 $00{:}09{:}28.440 \dashrightarrow 00{:}09{:}30.462$ we send it into the endocrine

NOTE Confidence: 0.8217956666666667

 $00{:}09{:}30{.}462 \dashrightarrow 00{:}09{:}31{.}473$ journals for publication.

NOTE Confidence: 0.8217956666666667

 $00:09:31.480 \longrightarrow 00:09:34.154$ And you know a lot of people,

 $00:09:34.160 \longrightarrow 00:09:35.798$ a lot of the journals or some

NOTE Confidence: 0.8217956666666667

00:09:35.798 --> 00:09:37.250 of the journals didn't weren't

NOTE Confidence: 0.8217956666666667

 $00:09:37.250 \longrightarrow 00:09:38.638$ weren't interested in it.

NOTE Confidence: 0.8217956666666667

 $00:09:38.640 \longrightarrow 00:09:40.744$ And then finally it goes to one of

NOTE Confidence: 0.8217956666666667

 $00{:}09{:}40{.}744 \dashrightarrow 00{:}09{:}42{.}252$ the leading endocrine journals and

NOTE Confidence: 0.8217956666666667

 $00:09:42.252 \rightarrow 00:09:44.787$ it's sent out for review and we get NOTE Confidence: 0.8217956666666667

 $00{:}09{:}44.787 \dashrightarrow 00{:}09{:}46.694$ comments back from the review and

NOTE Confidence: 0.8217956666666667

 $00:09:46.694 \rightarrow 00:09:49.032$ and we did a very extensive job

NOTE Confidence: 0.8217956666666667

00:09:49.032 --> 00:09:51.200 answering all the all the comments.

NOTE Confidence: 0.8217956666666667

00:09:51.200 --> 00:09:54.133 There were 12 pages of of responses NOTE Confidence: 0.8217956666666667

 $00:09:54.133 \rightarrow 00:09:58.184$ and so we sent it back and the NOTE Confidence: 0.8217956666666667

 $00:09:58.184 \rightarrow 00:10:01.352$ reviewer comes back and says well

NOTE Confidence: 0.8217956666666667

 $00:10:01.360 \longrightarrow 00:10:05.077$ if you know if this was really

NOTE Confidence: 0.8217956666666667

00:10:05.077 --> 00:10:07.631 occurring the development of of

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}07{.}631 \dashrightarrow 00{:}10{:}10{.}474$ diabetes after anti PD one we would

NOTE Confidence: 0.8217956666666667

 $00:10:10.474 \rightarrow 00:10:12.159$ have known about it already.

 $00:10:12.160 \rightarrow 00:10:14.194$ So that that was the end of that journal.

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}14.200 \dashrightarrow 00{:}10{:}17.312$ So we ended up publishing this as a

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}17{.}312 \dashrightarrow 00{:}10{:}19{.}447$ letter actually in diabetes care and

NOTE Confidence: 0.8217956666666667

 $00:10:19.447 \longrightarrow 00:10:22.440$ it is one of the most highly cited,

NOTE Confidence: 0.8217956666666667

 $00:10:22.440 \rightarrow 00:10:24.960$ certainly one of the most highly cited

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}24{.}960 \dashrightarrow 00{:}10{:}27{.}308$ papers in diabetes care that that is

NOTE Confidence: 0.8217956666666667

 $00:10:27.308 \rightarrow 00:10:29.520$ the first description of anti PD1 antibodies.

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}29{.}520 \dashrightarrow 00{:}10{:}31{.}207$ So the reason I wanted to mention

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}31.207 \dashrightarrow 00{:}10{:}33.157$ this story to you is as I'm going to,

NOTE Confidence: 0.8217956666666667

 $00:10:33.160 \longrightarrow 00:10:35.986$ as I'm going to show you later on that

NOTE Confidence: 0.8217956666666667

 $00:10:35.986 \rightarrow 00:10:38.477$ not only was the reviewer wrong in

NOTE Confidence: 0.8217956666666667

 $00:10:38.477 \rightarrow 00:10:41.560$ saying that we would have known about it,

NOTE Confidence: 0.8217956666666667

00:10:41.560 -> 00:10:43.260 but mechanistically now we know

NOTE Confidence: 0.8217956666666667

 $00:10:43.260 \longrightarrow 00:10:44.960$ why the reviewer was wrong.

NOTE Confidence: 0.8217956666666667

 $00:10:44.960 \longrightarrow 00:10:47.445$ So that's kind of nice to know

 $00:10:47.445 \longrightarrow 00:10:49.479$ why your reviewer is so wrong.

NOTE Confidence: 0.8217956666666667

 $00:10:49.480 \longrightarrow 00:10:50.232$ So what?

NOTE Confidence: 0.8217956666666667

 $00:10:50.232 \longrightarrow 00:10:51.360$ What what is,

NOTE Confidence: 0.8217956666666667

 $00:10:51.360 \longrightarrow 00:10:53.160$ what are some of the features

NOTE Confidence: 0.8217956666666667

 $00:10:53.160 \longrightarrow 00:10:55.422$ of this form of of diabetes.

NOTE Confidence: 0.8217956666666667

 $00:10:55.422 \longrightarrow 00:10:56.838$ So first of all,

NOTE Confidence: 0.8217956666666667

 $00:10:56.840 \rightarrow 00:10:59.400$ it happens relatively very acutely.

NOTE Confidence: 0.8217956666666667

 $00{:}10{:}59{.}400 \dashrightarrow 00{:}11{:}00{.}716$ Here's here's some data.

NOTE Confidence: 0.8217956666666667

 $00:11:00.716 \rightarrow 00:11:02.690$ This is coming from our colleagues

NOTE Confidence: 0.8217956666666667

 $00:11:02.754 \rightarrow 00:11:04.494$ at UCSF where we've put together

NOTE Confidence: 0.8217956666666667

 $00{:}11{:}04{.}494 \dashrightarrow 00{:}11{:}05{.}985$ patients at the two institutions

NOTE Confidence: 0.8217956666666667

 $00:11:05.985 \rightarrow 00:11:08.397$ and you can see this here are a few

NOTE Confidence: 0.8217956666666667

 $00:11:08.400 \rightarrow 00:11:10.216$ patients who developed checkpoint

NOTE Confidence: 0.8217956666666667

 $00{:}11{:}10.216 \dashrightarrow 00{:}11{:}12.486$ induced diabetes and their blood

NOTE Confidence: 0.8217956666666667

 $00:11:12.486 \rightarrow 00:11:14.980$ sugars are completely normal And then

NOTE Confidence: 0.8217956666666667

 $00:11:14.980 \longrightarrow 00:11:16.960$ dramatically there is a big spike

- NOTE Confidence: 0.8217956666666667
- $00:11:16.960 \longrightarrow 00:11:19.238$ in their in their glucose levels.
- NOTE Confidence: 0.8217956666666667
- 00:11:19.240 --> 00:11:21.298 And the other thing that's that's
- NOTE Confidence: 0.8217956666666667
- $00:11:21.298 \rightarrow 00:11:23.318$ quite interesting about that is if
- NOTE Confidence: 0.8217956666666667
- $00{:}11{:}23{.}318 \dashrightarrow 00{:}11{:}25{.}076$ you look at their endogenous beta
- NOTE Confidence: 0.8217956666666667
- $00{:}11{:}25.076$ --> $00{:}11{:}26.997$ cell function by measuring C peptide,
- NOTE Confidence: 0.8217956666666667
- $00{:}11{:}27.000 \dashrightarrow 00{:}11{:}29.124$ remember C peptide is cleaved from
- NOTE Confidence: 0.8217956666666667
- $00:11:29.124 \longrightarrow 00:11:31.256$ pro insulin when the beta cells
- NOTE Confidence: 0.8217956666666667
- $00{:}11{:}31{.}256 \dashrightarrow 00{:}11{:}33{.}510$ make insulin and it's a good measure
- NOTE Confidence: 0.8217956666666667
- $00:11:33.510 \longrightarrow 00:11:35.272$ of endogenous insulin production
- NOTE Confidence: 0.8217956666666667
- $00:11:35.272 \rightarrow 00:11:38.014$ cause the insulin you inject doesn't
- NOTE Confidence: 0.8217956666666667
- $00:11:38.014 \rightarrow 00:11:39.048$ have C peptide.
- NOTE Confidence: 0.8217956666666667
- 00:11:39.048 --> 00:11:42.360 So if you take a look at the kinetics of
- NOTE Confidence: 0.8217956666666667
- $00:11:42.360 \longrightarrow 00:11:46.320$ loss of C peptide here that it happens very,
- NOTE Confidence: 0.8217956666666667
- $00:11:46.320 \longrightarrow 00:11:47.000$ very quickly.
- NOTE Confidence: 0.8217956666666667
- 00:11:47.000 --> 00:11:49.696 In fact in one case it it happened
- NOTE Confidence: 0.8217956666666667

 $00:11:49.696 \rightarrow 00:11:51.680$ while patients were following the

NOTE Confidence: 0.8217956666666667

 $00:11:51.680 \longrightarrow 00:11:53.192$ the individual while investigators

NOTE Confidence: 0.8217956666666667

 $00{:}11{:}53{.}192 \dashrightarrow 00{:}11{:}55{.}460$ were following the individual in the NOTE Confidence: 0.81665782

 $00{:}11{:}55{.}520 \dashrightarrow 00{:}11{:}58{.}285$ hospital. And the other point about

NOTE Confidence: 0.81665782

 $00{:}11{:}58{.}285 \dashrightarrow 00{:}12{:}00{.}999$ this is patients generally go to

NOTE Confidence: 0.81665782

00:12:00.999 --> 00:12:03.727 0 or near 0 in other words levels

NOTE Confidence: 0.81665782

 $00{:}12{:}03{.}727 \dashrightarrow 00{:}12{:}06{.}479$ that are clinically insufficient.

NOTE Confidence: 0.81665782

 $00{:}12{:}06{.}480 \dashrightarrow 00{:}12{:}08{.}594$ We'll come back to that later on.

NOTE Confidence: 0.81665782

 $00{:}12{:}08.600 \dashrightarrow 00{:}12{:}12.296$ Here's a few other bits of information

NOTE Confidence: 0.81665782

 $00:12:12.296 \rightarrow 00:12:14.704$ about the demographics of patients,

NOTE Confidence: 0.81665782

 $00:12:14.704 \longrightarrow 00:12:17.392$ so you can see the age.

NOTE Confidence: 0.81665782

 $00{:}12{:}17{.}400 \dashrightarrow 00{:}12{:}21{.}896$ These are people who are older than you

NOTE Confidence: 0.81665782

 $00:12:21.896 \rightarrow 00:12:25.048$ might expect with presenting with diabetes.

NOTE Confidence: 0.81665782

00:12:25.048 --> 00:12:27.528 It generally occurs with anti

NOTE Confidence: 0.81665782

00:12:27.528 --> 00:12:29.720 PD ONE or anti PDL 1.

NOTE Confidence: 0.81665782

 $00:12:29.720 \rightarrow 00:12:34.370$ The hemoglobin A1 CS are elevated at probably

 $00:12:34.370 \rightarrow 00:12:37.280$ because of the degree of hyperglycemia.

NOTE Confidence: 0.81665782

 $00{:}12{:}37{.}280 \dashrightarrow 00{:}12{:}39{.}872$ About half of the patients are OR and

NOTE Confidence: 0.81665782

 $00{:}12{:}39{.}872 \dashrightarrow 00{:}12{:}42{.}824$ depending on the review some even even

NOTE Confidence: 0.81665782

 $00:12:42.824 \rightarrow 00:12:45.695$ higher percentage present with ketoacidosis.

NOTE Confidence: 0.81665782

00:12:45.695 --> 00:12:48.720 See peptide frequently Becomes undetectable.

NOTE Confidence: 0.81665782

 $00{:}12{:}48{.}720 \dashrightarrow 00{:}12{:}51{.}608$ The median time is about 11 weeks and

NOTE Confidence: 0.81665782

 $00:12:51.608 \rightarrow 00:12:53.849$ only about 40% of individuals are

NOTE Confidence: 0.81665782

 $00{:}12{:}53.849 \dashrightarrow 00{:}12{:}56.267$ positive for auto antibodies and this

NOTE Confidence: 0.81665782

 $00{:}12{:}56{.}267 \dashrightarrow 00{:}12{:}58{.}176$ brings up a a classification issue.

NOTE Confidence: 0.81665782

 $00{:}12{:}58{.}176$ --> $00{:}13{:}00{.}920$ Some people call this type one diabetes.

NOTE Confidence: 0.81665782

 $00{:}13{:}00{.}920 \dashrightarrow 00{:}13{:}02{.}075$ As I'm going to explain to you,

NOTE Confidence: 0.81665782

 $00{:}13{:}02.080 \dashrightarrow 00{:}13{:}04.000$ I don't think this is type one diabetes,

NOTE Confidence: 0.81665782

00:13:04.000 --> 00:13:05.760 it's autoimmune diabetes induced

NOTE Confidence: 0.81665782

 $00{:}13{:}05{.}760 \dashrightarrow 00{:}13{:}07{.}080$ by checkpoint inhibitors,

NOTE Confidence: 0.81665782

 $00{:}13{:}07{.}080 \dashrightarrow 00{:}13{:}10{.}680$ but it's very different from classic

00:13:10.680 - 00:13:14.520 spontaneous type one diabetes.

NOTE Confidence: 0.81665782

 $00{:}13{:}14{.}520 \dashrightarrow 00{:}13{:}17{.}523$ Now there is a very large proportion

NOTE Confidence: 0.81665782

 $00{:}13{:}17{.}523 \dashrightarrow 00{:}13{:}19{.}969$ of individuals who we don't talk

NOTE Confidence: 0.81665782

00:13:19.969 --> 00:13:22.482 about a lot who I think probably

NOTE Confidence: 0.81665782

 $00:13:22.562 \longrightarrow 00:13:24.278$ fall into this bucket,

NOTE Confidence: 0.81665782

00:13:24.280 --> 00:13:27.010 who are individuals who may have mild

NOTE Confidence: 0.81665782

00:13:27.010 --> 00:13:29.609 type 2 diabetes who then present

NOTE Confidence: 0.81665782

 $00{:}13{:}29{.}609 \dashrightarrow 00{:}13{:}32{.}303$ with much worsening of their glucose

NOTE Confidence: 0.81665782

 $00{:}13{:}32{.}303 \dashrightarrow 00{:}13{:}34{.}585$ control and may become may previously

NOTE Confidence: 0.81665782

 $00{:}13{:}34{.}585 \dashrightarrow 00{:}13{:}36{.}864$ have been managed with oral anti

NOTE Confidence: 0.81665782

 $00{:}13{:}36{.}864 \dashrightarrow 00{:}13{:}39{.}733$ diabetic agents and now all of a

NOTE Confidence: 0.81665782

00:13:39.733 --> 00:13:41.629 sudden may present ketoacidosis

NOTE Confidence: 0.81665782

 $00:13:41.629 \rightarrow 00:13:43.999$ or may require insulin therapy.

NOTE Confidence: 0.81665782

 $00:13:44.000 \rightarrow 00:13:47.159$ Now type 2 diabetes is a very common disease.

NOTE Confidence: 0.81665782

 $00:13:47.160 \longrightarrow 00:13:50.030$ So it may actually be that the

NOTE Confidence: 0.81665782

00:13:50.030 - 00:13:52.848 frequency of this disease is much

- NOTE Confidence: 0.81665782
- $00:13:52.848 \rightarrow 00:13:56.304$ higher than is even represented by the
- NOTE Confidence: 0.81665782
- $00:13:56.304 \rightarrow 00:13:59.348 0.2$ to 1.9% from the past reviews.
- NOTE Confidence: 0.81665782
- 00:13:59.348 --> 00:14:01.383 Now I mentioned not everybody
- NOTE Confidence: 0.81665782
- $00:14:01.383 \longrightarrow 00:14:02.960$ has autoantibodies.
- NOTE Confidence: 0.81665782
- $00:14:02.960 \longrightarrow 00:14:05.840$ Here's some examples of that.
- NOTE Confidence: 0.81665782
- 00:14:05.840 --> 00:14:07.632 Some patients, if you take a look
- NOTE Confidence: 0.81665782
- $00:14:07.632 \rightarrow 00:14:09.158$ at three patients on the bottom,
- NOTE Confidence: 0.81665782
- $00:14:09.160 \longrightarrow 00:14:10.564$ some start out negative.
- NOTE Confidence: 0.81665782
- $00:14:10.564 \rightarrow 00:14:13.064$ Each of those antibodies are one of
- NOTE Confidence: 0.81665782
- $00{:}14{:}13.064 \dashrightarrow 00{:}14{:}15.056$ the auto antibodies that we measure
- NOTE Confidence: 0.81665782
- $00{:}14{:}15.056 \dashrightarrow 00{:}14{:}16.919$ in classic type one diabetes.
- NOTE Confidence: 0.81665782
- 00:14:16.920 --> 00:14:18.800 You can see some patients start out negative,
- NOTE Confidence: 0.81665782
- 00:14:18.800 --> 00:14:19.816 become positive,
- NOTE Confidence: 0.81665782
- $00{:}14{:}19.816 \dashrightarrow 00{:}14{:}22.356$ some patients start out positive,
- NOTE Confidence: 0.81665782
- $00:14:22.360 \longrightarrow 00:14:23.308$ stay positive.
- NOTE Confidence: 0.81665782

 $00{:}14{:}23{.}308 \dashrightarrow 00{:}14{:}26{.}739$ So it varies about 40% overall are positive.

NOTE Confidence: 0.81665782

 $00:14:26.739 \rightarrow 00:14:29.840$ But the frequency of those who are positive,

NOTE Confidence: 0.81665782

 $00:14:29.840 \longrightarrow 00:14:31.752$ sorry let me go back for two or

NOTE Confidence: 0.81665782

 $00:14:31.752 \longrightarrow 00:14:32.920$ more which is what we,

NOTE Confidence: 0.81665782

 $00{:}14{:}32{.}920 \dashrightarrow 00{:}14{:}36{.}085$ which is kind of the hallmark of spontaneous

NOTE Confidence: 0.81665782

 $00{:}14{:}36.085 \dashrightarrow 00{:}14{:}39.955$ type one diabetes is relatively low.

NOTE Confidence: 0.81665782

 $00:14:39.960 \longrightarrow 00:14:42.420$ Now curiously the the alpha

NOTE Confidence: 0.81665782

 $00:14:42.420 \rightarrow 00:14:44.880$ producing cells in the islet,

NOTE Confidence: 0.81665782

 $00{:}14{:}44{.}880 \dashrightarrow 00{:}14{:}47{.}160$ remember the islet is a collection of cells,

NOTE Confidence: 0.81665782

00:14:47.160 --> 00:14:47.748 alpha cells,

NOTE Confidence: 0.81665782

00:14:47.748 --> 00:14:48.336 beta cells,

NOTE Confidence: 0.81665782

 $00{:}14{:}48{.}336 \dashrightarrow 00{:}14{:}50{.}473$ delta cells and so on that make

NOTE Confidence: 0.81665782

 $00:14:50.473 \longrightarrow 00:14:51.717$ a variety of hormones.

NOTE Confidence: 0.81665782

 $00:14:51.720 \longrightarrow 00:14:55.038$ The loss of of endocrine cells,

NOTE Confidence: 0.81665782

 $00:14:55.040 \rightarrow 00:14:58.116$ this seems to be limited to the beta cells.

NOTE Confidence: 0.81665782

 $00:14:58.116 \rightarrow 00:14:59.970$ The alpha cells sitting right next

 $00{:}15{:}00{.}033 \dashrightarrow 00{:}15{:}02{.}112$ to the beta cells are unaffected and

NOTE Confidence: 0.81665782

 $00:15:02.112 \longrightarrow 00:15:04.117$ the reason for that is not clear.

NOTE Confidence: 0.81665782

 $00{:}15{:}04{.}120 \dashrightarrow 00{:}15{:}06{.}349$ But as you can see from this data

NOTE Confidence: 0.81665782

 $00{:}15{:}06{.}349 \dashrightarrow 00{:}15{:}09{.}352$ from patients that we we where we

NOTE Confidence: 0.81665782

00:15:09.352 --> 00:15:11.440 measure Glucagon here didn't seem

NOTE Confidence: 0.81665782

 $00{:}15{:}11{.}440 \dashrightarrow 00{:}15{:}15{.}019$ to make a difference in terms of

NOTE Confidence: 0.81665782

00:15:15.019 - 00:15:16.918 their Glucagon levels.

NOTE Confidence: 0.81665782

00:15:16.920 --> 00:15:18.984 Now one of the early striking

NOTE Confidence: 0.81665782

 $00:15:18.984 \longrightarrow 00:15:20.360$ findings from our series

NOTE Confidence: 0.9349334425

 $00{:}15{:}20{.}424 \dashrightarrow 00{:}15{:}23{.}007$ of patients was that a high proportion

NOTE Confidence: 0.9349334425

00:15:23.007 --> 00:15:25.696 of individuals were HLAD, R4. Now Dr.

NOTE Confidence: 0.9349334425

 $00{:}15{:}25.696 \dashrightarrow 00{:}15{:}28.682$ three and four are associated with with

NOTE Confidence: 0.9349334425

 $00{:}15{:}28.682 \dashrightarrow 00{:}15{:}31.397$ classic spontaneous type one diabetes.

NOTE Confidence: 0.9349334425

00:15:31.400 --> 00:15:33.927 But this proportion of of DR4 is

NOTE Confidence: 0.9349334425

 $00:15:33.927 \rightarrow 00:15:36.084$ strikingly high and it's higher

 $00:15:36.084 \rightarrow 00:15:38.076$ than the background population.

NOTE Confidence: 0.9349334425

 $00{:}15{:}38{.}080 \dashrightarrow 00{:}15{:}40{.}606$ And DR3, the other allele associated

NOTE Confidence: 0.9349334425

 $00:15:40.606 \rightarrow 00:15:42.290$ with spontaneous diabetes was

NOTE Confidence: 0.9349334425

 $00:15:42.357 \longrightarrow 00:15:44.077$ not increased in frequency.

NOTE Confidence: 0.9349334425

 $00{:}15{:}44.080 \dashrightarrow 00{:}15{:}46.336$ So DR4 somehow or another seems

NOTE Confidence: 0.9349334425

00:15:46.336 --> 00:15:48.432 to be important in predisposing

NOTE Confidence: 0.9349334425

 $00:15:48.432 \longrightarrow 00:15:51.760$ to the development of type of

NOTE Confidence: 0.9349334425

 $00:15:51.760 \longrightarrow 00:15:54.320$ of checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

 $00{:}15{:}54{.}320 \dashrightarrow 00{:}15{:}58{.}536$ And I want to point out this recent

NOTE Confidence: 0.9349334425

 $00{:}15{:}58{.}536$ --> $00{:}16{:}01{.}130$ observation that was originally made NOTE Confidence: 0.9349334425

00:16:01.130 --> 00:16:04.520 by Jasmine Caulfield and Lilac

NOTE Confidence: 0.9349334425

 $00:16:04.520 \rightarrow 00:16:09.240$ Eisenbud from our patients here.

NOTE Confidence: 0.9349334425

 $00:16:09.240 \longrightarrow 00:16:11.584$ And what was done is we were doing NOTE Confidence: 0.9349334425

00:16:11.584 --> 00:16:15.616 a a genome sequencing of tumors and

NOTE Confidence: 0.9349334425

00:16:15.616 --> 00:16:18.462 identified a number of mutations in

NOTE Confidence: 0.9349334425

 $00:16:18.462 \longrightarrow 00:16:20.630$ a variety of genes that seem to be

 $00:16:20.688 \longrightarrow 00:16:22.482$ associated what seemed what seemed to

NOTE Confidence: 0.9349334425

 $00:16:22.482 \longrightarrow 00:16:25.052$ be at a higher frequency in people

NOTE Confidence: 0.9349334425

 $00:16:25.052 \rightarrow 00:16:26.796$ with checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

 $00{:}16{:}26{.}800 \dashrightarrow 00{:}16{:}29{.}888$ And then we ended up going back and

NOTE Confidence: 0.9349334425

 $00{:}16{:}29.888 \dashrightarrow 00{:}16{:}32.056$ doing sequencing of of peripheral

NOTE Confidence: 0.9349334425

 $00{:}16{:}32.056 \dashrightarrow 00{:}16{:}34.642$ blood cells and finding that indeed

NOTE Confidence: 0.9349334425

 $00:16:34.642 \rightarrow 00:16:36.452$ there were germline mutations that

NOTE Confidence: 0.9349334425

 $00{:}16{:}36{.}452 \dashrightarrow 00{:}16{:}38{.}880$ seem to be associated with development

NOTE Confidence: 0.9349334425

 $00:16:38.880 \longrightarrow 00:16:40.720$ of checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

 $00:16:40.720 \longrightarrow 00:16:43.919$ And interestingly the one of the the,

NOTE Confidence: 0.9349334425

 $00:16:43.920 \rightarrow 00:16:46.350$ the highest frequency was in this

NOTE Confidence: 0.9349334425

 $00{:}16{:}46{.}350 \dashrightarrow 00{:}16{:}48{.}637$ molecule called NLRC 5 and you

NOTE Confidence: 0.9349334425

00:16:48.637 --> 00:16:50.716 can take a look on the right,

NOTE Confidence: 0.9349334425

 $00{:}16{:}50{.}720 \dashrightarrow 00{:}16{:}54{.}200$ the frequency of individuals with

NOTE Confidence: 0.9349334425

 $00:16:54.200 \longrightarrow 00:16:58.740$ NLRC 5 variants was in our series 65%.

 $00:16:58.740 \rightarrow 00:17:01.120$ Now it's not a huge series because

NOTE Confidence: 0.9349334425

 $00:17:01.120 \longrightarrow 00:17:03.438$ we don't we don't have tons of

NOTE Confidence: 0.9349334425

 $00:17:03.438 \longrightarrow 00:17:05.640$ patients we had we had 13 here.

NOTE Confidence: 0.9349334425

 $00:17:05.640 \longrightarrow 00:17:07.817$ But you can see that at least

NOTE Confidence: 0.9349334425

 $00:17:07.817 \longrightarrow 00:17:09.000$ the statistically it it,

NOTE Confidence: 0.9349334425

 $00:17:09.000 \rightarrow 00:17:12.648$ it turns out to be in a much higher

NOTE Confidence: 0.9349334425

 $00{:}17{:}12.648 \dashrightarrow 00{:}17{:}15.208$ frequency compared to those individuals

NOTE Confidence: 0.9349334425

 $00:17:15.208 \rightarrow 00:17:16.998$ without checkpoint induced diabetes

NOTE Confidence: 0.9349334425

 $00{:}17{:}16.998 \dashrightarrow 00{:}17{:}19.554$ who get the same checkpoint inhibitors.

NOTE Confidence: 0.9349334425

 $00:17:19.560 \rightarrow 00:17:23.354$ Now what's the importance of NLRC 5?

NOTE Confidence: 0.9349334425

00:17:23.360 --> 00:17:28.162 So NLRC 5 actually tends to is is is

NOTE Confidence: 0.9349334425

00:17:28.162 --> 00:17:30.780 evolved in a class one MHC antigen

NOTE Confidence: 0.9349334425

 $00:17:30.869 \longrightarrow 00:17:32.000$ presentation.

NOTE Confidence: 0.9349334425

 $00:17:32.000 \rightarrow 00:17:34.079$ I'll tell you about that in just a moment.

NOTE Confidence: 0.9349334425

 $00:17:34.080 \longrightarrow 00:17:36.951$ But you can see that it seems to be

NOTE Confidence: 0.9349334425

 $00:17:36.951 \longrightarrow 00:17:41.732$ an important molecule involved in

- NOTE Confidence: 0.9349334425
- $00{:}17{:}41.732 \dashrightarrow 00{:}17{:}46.016$ responses in in cancer patients that

00:17:46.016 --> 00:17:49.424 that methylation of NLRC 5 reduced

NOTE Confidence: 0.9349334425

 $00{:}17{:}49{.}424 \dashrightarrow 00{:}17{:}53{.}867$ NLRC 5 seems to be associated with

NOTE Confidence: 0.9349334425

00:17:53.867 --> 00:17:57.067 impaired CTL activity and clearing

NOTE Confidence: 0.9349334425

 $00:17:57.177 \longrightarrow 00:17:58.518$ of of tumors.

NOTE Confidence: 0.9349334425

 $00:17:58.520 \longrightarrow 00:18:00.962$ The its expression seems to be

NOTE Confidence: 0.9349334425

 $00{:}18{:}00{.}962 \dashrightarrow 00{:}18{:}03{.}050$ correlated with survival and in

NOTE Confidence: 0.9349334425

 $00{:}18{:}03{.}050 \dashrightarrow 00{:}18{:}05{.}360$ diabetes it's also been a associated

NOTE Confidence: 0.9349334425

 $00:18:05.360 \rightarrow 00:18:09.600$ with beta cell antigen presentation

NOTE Confidence: 0.9349334425

 $00:18:09.600 \rightarrow 00:18:11.920$ and and the interferon response.

NOTE Confidence: 0.9349334425

00:18:11.920 --> 00:18:13.720 So for example,

NOTE Confidence: 0.9349334425

00:18:13.720 --> 00:18:17.048 the NLRC knocked down beta cells

NOTE Confidence: 0.9349334425

00:18:17.048 --> 00:18:19.832 seem to have a decreased interferon

NOTE Confidence: 0.9349334425

00:18:19.832 $\operatorname{-->}$ 00:18:22.238 induced class one MHC expression

NOTE Confidence: 0.9349334425

 $00{:}18{:}22{.}240 \dashrightarrow 00{:}18{:}26{.}344$ and seems to be associated with

 $00{:}18{:}26{.}344 \dashrightarrow 00{:}18{:}29{.}080$ protection from autoimmune diabetes.

NOTE Confidence: 0.9349334425

00:18:29.080 --> 00:18:32.608 So NLRC 5 is is a regulator of Class

NOTE Confidence: 0.9349334425

00:18:32.608 --> 00:18:35.346 1 dependent antigen presentation,

NOTE Confidence: 0.9349334425

00:18:35.346 --> 00:18:40.720 much the same as the classic Class 2

NOTE Confidence: 0.81096498125

00:18:42.960 --> 00:18:46.220 transactivator. It's responsible for

NOTE Confidence: 0.81096498125

 $00{:}18{:}46{.}220 \dashrightarrow 00{:}18{:}50{.}228$ bringing peptides into the endosome NOTE Confidence: 0.81096498125

 $00{:}18{:}50{.}228 \dashrightarrow 00{:}18{:}54{.}716$ for processing and placing them on

NOTE Confidence: 0.81096498125

 $00:18:54.720 \rightarrow 00:18:57.840$ developing class one MHC molecules.

NOTE Confidence: 0.81096498125

 $00{:}18{:}57{.}840 \dashrightarrow 00{:}18{:}59{.}416$ It's expression seems to

NOTE Confidence: 0.81096498125

 $00:18:59.416 \rightarrow 00:19:01.340$ be induced by interferons,

NOTE Confidence: 0.81096498125

00:19:01.340 --> 00:19:03.560 particularly interferon gamma

NOTE Confidence: 0.81096498125

00:19:03.560 --> 00:19:06.520 through Stat 1 signalling.

NOTE Confidence: 0.81096498125

 $00:19:06.520 \longrightarrow 00:19:08.848$ So this review actually

NOTE Confidence: 0.81096498125

 $00{:}19{:}08.848 \dashrightarrow 00{:}19{:}10.594$ describes the mechanism.

NOTE Confidence: 0.81096498125

 $00:19:10.600 \rightarrow 00:19:12.994$ I'm not going to go into detail about it,

NOTE Confidence: 0.81096498125

 $00:19:13.000 \rightarrow 00:19:14.880$ but what we ended up doing and this

00:19:14.880 --> 00:19:16.719 is work that Anna Pertigato did,

NOTE Confidence: 0.81096498125

00:19:16.720 --> 00:19:19.600 we ended up looking at expression of TAP ONE,

NOTE Confidence: 0.81096498125

 $00:19:19.600 \rightarrow 00:19:22.720$ which is an important transactivator

NOTE Confidence: 0.886076019166667

 $00{:}19{:}25{.}240 \dashrightarrow 00{:}19{:}28{.}042$ that's associated with class one MHC

NOTE Confidence: 0.886076019166667

 $00{:}19{:}28.042 \dashrightarrow 00{:}19{:}31.443$ expression as well as HLAA on peripheral

NOTE Confidence: 0.886076019166667

 $00{:}19{:}31{.}443 \dashrightarrow 00{:}19{:}34{.}824$ blood cells in patients with the mutation

NOTE Confidence: 0.886076019166667

 $00:19:34.910 \longrightarrow 00:19:40.280$ or with wild type type of the NLRC 5.

NOTE Confidence: 0.886076019166667

 $00:19:40.280 \longrightarrow 00:19:43.457$ And as you can see and in patients with

NOTE Confidence: 0.886076019166667

 $00{:}19{:}43{.}457 \dashrightarrow 00{:}19{:}46{.}671$ the mutant there seems to be higher

NOTE Confidence: 0.886076019166667

 $00{:}19{:}46.671 \dashrightarrow 00{:}19{:}50.048$ expression of TAP one and actually of HLAA

NOTE Confidence: 0.886076019166667

 $00:19:50.048 \rightarrow 00:19:52.220$ although we haven't reached statistical

NOTE Confidence: 0.886076019166667

 $00{:}19{:}52{.}220 \dashrightarrow 00{:}19{:}54{.}920$ significance for the HLA molecule.

NOTE Confidence: 0.886076019166667

 $00{:}19{:}54{.}920 \dashrightarrow 00{:}19{:}58{.}385$ So it it suggests at least that there is

NOTE Confidence: 0.886076019166667

 $00{:}19{:}58{.}385 \dashrightarrow 00{:}20{:}02{.}362$ some change in expression of MHC molecules

NOTE Confidence: 0.886076019166667

 $00{:}20{:}02{.}362 \dashrightarrow 00{:}20{:}05{.}332$ or potentially presentation of peptides

 $00:20:05.332 \rightarrow 00:20:08.638$ by individuals who have this mutant.

NOTE Confidence: 0.886076019166667

00:20:08.640 --> 00:20:10.398 So to summarize these two points,

NOTE Confidence: 0.886076019166667

 $00:20:10.400 \longrightarrow 00:20:13.856$ the there seems to be evidence

NOTE Confidence: 0.886076019166667

00:20:13.856 --> 00:20:16.480 for mutations or differences.

NOTE Confidence: 0.886076019166667

 $00{:}20{:}16.480 \dashrightarrow 00{:}20{:}18.944$ In class one and Class 2 MHC molecules

NOTE Confidence: 0.886076019166667

00:20:18.944 --> 00:20:21.654 that that are associated with development

NOTE Confidence: 0.886076019166667

 $00:20:21.654 \longrightarrow 00:20:23.678$ of checkpoint induced diabetes.

NOTE Confidence: 0.886076019166667

 $00{:}20{:}23.680 \dashrightarrow 00{:}20{:}26.996$ First of all HLAD R4 is common and

NOTE Confidence: 0.886076019166667

 $00:20:26.996 \longrightarrow 00:20:29.132$ perhaps that leads to the development

NOTE Confidence: 0.886076019166667

 $00:20:29.132 \rightarrow 00:20:31.920$ of an auto autoreactive repertoire.

NOTE Confidence: 0.886076019166667

 $00{:}20{:}31{.}920 \dashrightarrow 00{:}20{:}35{.}082$ This NLRC 5 mutation also seems

NOTE Confidence: 0.886076019166667

 $00:20:35.082 \rightarrow 00:20:38.637$ to have some role in potentially

NOTE Confidence: 0.886076019166667

 $00:20:38.637 \longrightarrow 00:20:41.205$ in expression of molecules.

NOTE Confidence: 0.886076019166667

 $00{:}20{:}41.205 \dashrightarrow 00{:}20{:}44.595$ A presentation of molecules by beta

NOTE Confidence: 0.886076019166667

 $00:20:44.595 \rightarrow 00:20:48.225$ cells or even potentially in affecting

NOTE Confidence: 0.886076019166667

 $00{:}20{:}48.225 \dashrightarrow 00{:}20{:}51.514$ a subgroup of CDA positive T cells have

- NOTE Confidence: 0.886076019166667
- $00:20:51.514 \rightarrow 00:20:53.920$ been associated with immune regulation.

 $00:20:56.120 \longrightarrow 00:20:58.983$ Now the let me just raise some

NOTE Confidence: 0.8729991115

 $00:20:58.983 \rightarrow 00:21:01.456$ questions about these these two points

NOTE Confidence: 0.8729991115

 $00:21:01.456 \longrightarrow 00:21:04.158$ by make by by pointing this out.

NOTE Confidence: 0.8729991115

 $00{:}21{:}04{.}160 \dashrightarrow 00{:}21{:}07{.}022$ When we've looked at auto antigen

NOTE Confidence: 0.8729991115

 $00{:}21{:}07{.}022 \dashrightarrow 00{:}21{:}09{.}614$ reactive T cells in patients

NOTE Confidence: 0.8729991115

 $00:21:09.614 \rightarrow 00:21:12.099$ with checkpoint induced diabetes,

NOTE Confidence: 0.8729991115

 $00:21:12.099 \longrightarrow 00:21:14.842$ we've looked for auto antigen

NOTE Confidence: 0.8729991115

 $00{:}21{:}14.842 \dashrightarrow 00{:}21{:}17.368$ reactive T cells that are reactive

NOTE Confidence: 0.8729991115

 $00:21:17.368 \longrightarrow 00:21:19.480$ to conventional type one diabetes.

NOTE Confidence: 0.8729991115

00:21:19.480 --> 00:21:20.290 Auto antigens,

NOTE Confidence: 0.8729991115

 $00{:}21{:}20{.}290 \dashrightarrow 00{:}21{:}22{.}720$ we don't really find an increase.

NOTE Confidence: 0.8729991115

 $00:21:22.720 \longrightarrow 00:21:24.560$ So if you take a look at that,

NOTE Confidence: 0.8729991115

 $00{:}21{:}24{.}560 \dashrightarrow 00{:}21{:}27{.}339$ we've looked at T cells that are

NOTE Confidence: 0.8729991115

 $00:21:27.339 \rightarrow 00:21:30.099$ identified by binding to class one MHC

 $00{:}21{:}30.099 \dashrightarrow 00{:}21{:}32.343$ tetramers that are loaded with the

NOTE Confidence: 0.8729991115

 $00:21:32.426 \rightarrow 00:21:35.434$ peptides that are shown on the left side.

NOTE Confidence: 0.8729991115

 $00:21:35.440 \longrightarrow 00:21:37.631$ If you look at the frequency of

NOTE Confidence: 0.8729991115

 $00:21:37.631 \longrightarrow 00:21:39.599$ these cells on the right side

NOTE Confidence: 0.8729991115

 $00{:}21{:}39{.}600 \dashrightarrow 00{:}21{:}41{.}656$ and the individuals treated

NOTE Confidence: 0.8729991115

 $00{:}21{:}41.656 \dashrightarrow 00{:}21{:}43.198$ with checkpoint inhibitors,

NOTE Confidence: 0.8729991115

 $00:21:43.200 \rightarrow 00:21:45.034$ those who don't have diabetes or do,

NOTE Confidence: 0.8729991115

 $00:21:45.040 \rightarrow 00:21:46.388$ there's really no difference.

NOTE Confidence: 0.8729991115

00:21:46.388 --> 00:21:49.000 So it at least would suggest that the,

NOTE Confidence: 0.8729991115

 $00{:}21{:}49{.}000 \dashrightarrow 00{:}21{:}53{.}106$ the known auto antigens or recognition

NOTE Confidence: 0.8729991115

 $00{:}21{:}53.106 \dashrightarrow 00{:}21{:}55.857$ of the known auto antigens is not

NOTE Confidence: 0.8729991115

 $00:21:55.857 \rightarrow 00:21:58.141$ really increased or at least the

NOTE Confidence: 0.8729991115

00:21:58.141 --> 00:22:00.680 frequency of cells is not increased

NOTE Confidence: 0.8729991115

 $00:22:00.680 \longrightarrow 00:22:02.680$ in those individuals who are

NOTE Confidence: 0.8729991115

 $00:22:02.680 \rightarrow 00:22:03.880$ developing checkpoint inhibitors.

NOTE Confidence: 0.8729991115

00:22:03.880 --> 00:22:05.840 Let me just you know sort of say

- NOTE Confidence: 0.8729991115
- $00:22:05.840 \longrightarrow 00:22:08.318$ as a preface to this data the the,
- NOTE Confidence: 0.8729991115
- $00:22:08.320 \rightarrow 00:22:11.120$ the low hanging fruit on this was well,
- NOTE Confidence: 0.8729991115
- $00:22:11.120 \longrightarrow 00:22:13.085$ these individuals had an autoreactive
- NOTE Confidence: 0.8729991115
- 00:22:13.085 00:22:14.680 repertoire. They had Dr.
- NOTE Confidence: 0.8729991115
- $00:22:14.680 \rightarrow 00:22:17.080$ Four, we removed the checkpoint blockade.
- NOTE Confidence: 0.8729991115
- 00:22:17.080 --> 00:22:18.880 These cells just did their thing,
- NOTE Confidence: 0.8729991115
- $00:22:18.880 \longrightarrow 00:22:19.765$ don't think so.
- NOTE Confidence: 0.8729991115
- $00{:}22{:}19.765 \dashrightarrow 00{:}22{:}22.227$ It could be that there are cells that
- NOTE Confidence: 0.8729991115
- $00{:}22{:}22{.}227 \dashrightarrow 00{:}22{:}24.219$ are reactive to unknown auto antigens
- NOTE Confidence: 0.8729991115
- $00:22:24.219 \rightarrow 00:22:26.876$ and as I'll show you in just a moment,
- NOTE Confidence: 0.8729991115
- $00:22:26.880 \longrightarrow 00:22:29.490$ there is some evidence that that
- NOTE Confidence: 0.8729991115
- $00:22:29.490 \longrightarrow 00:22:32.500$ might be true, but that's not all.
- NOTE Confidence: 0.8729991115
- $00{:}22{:}32{.}500 \dashrightarrow 00{:}22{:}35{.}050$ There are also there's also evidence
- NOTE Confidence: 0.8729991115
- $00{:}22{:}35{.}128 \dashrightarrow 00{:}22{:}37{.}036$ of inflammatory lesions that or
- NOTE Confidence: 0.8729991115
- $00:22:37.036 \longrightarrow 00:22:38.353$ inflammation that's occurring
- NOTE Confidence: 0.8729991115

 $00:22:38.353 \rightarrow 00:22:41.246$ in the pancreas that may be very

NOTE Confidence: 0.8729991115

00:22:41.246 --> 00:22:42.762 important for development of

NOTE Confidence: 0.8729991115

 $00:22:42.762 \longrightarrow 00:22:44.120$ checkpoint induced diabetes.

NOTE Confidence: 0.8729991115

 $00:22:44.120 \longrightarrow 00:22:47.907$ And this actually came from from

NOTE Confidence: 0.8729991115

00:22:47.907 --> 00:22:50.242 actually a clinical observation from

NOTE Confidence: 0.8729991115

 $00{:}22{:}50{.}242 \dashrightarrow 00{:}22{:}53{.}287$ patients here in which we found that NOTE Confidence: 0.8729991115

 $00{:}22{:}53{.}287 \dashrightarrow 00{:}22{:}55{.}842$ there was an increase in amylase and

NOTE Confidence: 0.8729991115

00:22:55.921 --> 00:22:57.744 lipase in individuals who ultimately

NOTE Confidence: 0.8729991115

 $00:22:57.744 \longrightarrow 00:22:59.474$ went on to develop diabetes.

NOTE Confidence: 0.8729991115

 $00{:}22{:}59{.}480 \dashrightarrow 00{:}23{:}02{.}480$ They don't develop clinical pancreatitis.

NOTE Confidence: 0.8729991115

00:23:02.480 --> 00:23:05.378 But here we're looking at the amylase

NOTE Confidence: 0.8729991115

 $00{:}23{:}05{.}378$ --> $00{:}23{:}07{.}915$ and lip ase level on one individual

NOTE Confidence: 0.8729991115

 $00{:}23{:}07{.}915 \dashrightarrow 00{:}23{:}09{.}816$ who is who develops checkpoint

NOTE Confidence: 0.8729991115

 $00{:}23{:}09{.}816 \dashrightarrow 00{:}23{:}12{.}404$ induced diabetes and you can see the

NOTE Confidence: 0.8729991115

 $00:23:12.404 \longrightarrow 00:23:14.357$ lipase on the left bumps and then

NOTE Confidence: 0.8729991115

 $00:23:14.357 \rightarrow 00:23:16.475$ red is when they developed diabetes
00:23:16.475 -> 00:23:19.080 and the amylase bumps and then red

NOTE Confidence: 0.8729991115

00:23:19.080 - 00:23:20.880 is when they developed diabetes.

NOTE Confidence: 0.8729991115

00:23:20.880 --> 00:23:25.598 If you look at our entire series

NOTE Confidence: 0.8729991115

 $00:23:25.600 \rightarrow 00:23:28.205$ and look at the relative levels

NOTE Confidence: 0.8729991115

00:23:28.205 --> 00:23:30.635 of lipacer amylase on the bottom,

NOTE Confidence: 0.8729991115

 $00{:}23{:}30{.}640 \dashrightarrow 00{:}23{:}33{.}188$ you can see that the that that

NOTE Confidence: 0.8729991115

 $00:23:33.188 \longrightarrow 00:23:35.499$ both are elevated prior to the

NOTE Confidence: 0.8729991115

 $00:23:35.499 \longrightarrow 00:23:37.410$ development of of diabetes.

NOTE Confidence: 0.8729991115

 $00{:}23{:}37{.}410 \dashrightarrow 00{:}23{:}39{.}335$ Now interestingly it prompted us

NOTE Confidence: 0.8729991115

 $00:23:39.335 \longrightarrow 00:23:42.300$ to look at what well like what's

NOTE Confidence: 0.8729991115

 $00{:}23{:}42{.}300 \dashrightarrow 00{:}23{:}44{.}475$ actually happening in the pancreas.

NOTE Confidence: 0.8729991115

 $00{:}23{:}44{.}480 \dashrightarrow 00{:}23{:}48{.}490$ They were not symptomatic and so we

NOTE Confidence: 0.8729991115

 $00{:}23{:}48{.}490 \dashrightarrow 00{:}23{:}51{.}080$ ended up looking at CT scans that

NOTE Confidence: 0.8729991115

 $00{:}23{:}51{.}080 \dashrightarrow 00{:}23{:}54{.}740$ fortunately we had from before and

NOTE Confidence: 0.8729991115

 $00{:}23{:}54{.}740 \dashrightarrow 00{:}23{:}57{.}106$ after individuals presented with diabetes.

 $00:23:57.106 \longrightarrow 00:24:00.355$ And what we found if you take a look

NOTE Confidence: 0.8729991115

00:24:00.355 --> 00:24:03.176 at the CTS and on the on the top here

NOTE Confidence: 0.8729991115

 $00{:}24{:}03{.}176$ --> $00{:}24{:}06{.}232$ is the the red arrow identifies the pancreas. NOTE Confidence: 0.8729991115

 $00:24:06.240 \rightarrow 00:24:08.816$ The there actually seem to be shrinkage NOTE Confidence: 0.8729991115

 $00{:}24{:}08.816 \dashrightarrow 00{:}24{:}11.816$ of the pancreas in individuals who went

NOTE Confidence: 0.8729991115

 $00{:}24{:}11.816 \dashrightarrow 00{:}24{:}14.632$ on to develop checkpoint induced diabetes.

NOTE Confidence: 0.8729991115

 $00{:}24{:}14.632 \dashrightarrow 00{:}24{:}17.880$ So it's suggested that there is more

NOTE Confidence: 0.854538988666666

00:24:17.957 --> 00:24:20.456 than just a direct attack on beta

NOTE Confidence: 0.854538988666666

00:24:20.456 --> 00:24:22.606 cells that there may actually be

NOTE Confidence: 0.854538988666666

 $00{:}24{:}22.606 \dashrightarrow 00{:}24{:}24.951$ a broader attack in a a broader

NOTE Confidence: 0.854538988666666

 $00:24:24.960 \rightarrow 00:24:27.880$ inflammatory response in the pancreas.

NOTE Confidence: 0.854538988666666

00:24:27.880 --> 00:24:31.066 And unfortunately one of our patients

NOTE Confidence: 0.854538988666666

 $00{:}24{:}31.066 \dashrightarrow 00{:}24{:}33.706$ died as soon after they had developed

NOTE Confidence: 0.8545389886666666

 $00:24:33.706 \longrightarrow 00:24:34.759$ checkpoint induced diabetes.

NOTE Confidence: 0.854538988666666

 $00{:}24{:}34{.}760 \dashrightarrow 00{:}24{:}36{.}856$ But we had the opportunity to take a

NOTE Confidence: 0.854538988666666

 $00:24:36.856 \rightarrow 00:24:38.872$ look at their pancreas by immunohistic

00:24:38.872 - 00:24:41.440 chemistry and this is what we found.

NOTE Confidence: 0.854538988666666

 $00:24:41.440 \longrightarrow 00:24:43.302$ You can see that there are plenty

NOTE Confidence: 0.854538988666666

 $00:24:43.302 \longrightarrow 00:24:45.797$ of CD 45 positive immune cells that

NOTE Confidence: 0.854538988666666

 $00:24:45.797 \rightarrow 00:24:47.837$ are infiltrating the islets and

NOTE Confidence: 0.854538988666666

 $00:24:47.840 \rightarrow 00:24:49.600$ that are infiltrating the pancreas.

NOTE Confidence: 0.854538988666666

 $00{:}24{:}49{.}600 \dashrightarrow 00{:}24{:}51{.}796$ They are not just in the islets and in

NOTE Confidence: 0.854538988666666

 $00:24:51.796 \rightarrow 00:24:54.318$ fact many of them are outside of the islets,

NOTE Confidence: 0.854538988666666

 $00:24:54.320 \longrightarrow 00:24:55.976$ as you can see by standing

NOTE Confidence: 0.854538988666666

 $00:24:55.976 \longrightarrow 00:24:57.520$ for insulin on the right.

NOTE Confidence: 0.854538988666666

 $00{:}24{:}57{.}520 \dashrightarrow 00{:}25{:}00{.}052$ And there are both CD4 and

NOTE Confidence: 0.854538988666666

 $00:25:00.052 \rightarrow 00:25:01.318$ CD8 positive cells.

NOTE Confidence: 0.854538988666666

 $00:25:01.320 \rightarrow 00:25:05.400$ Chromagranin identifies the endocrine cells.

NOTE Confidence: 0.854538988666666

 $00{:}25{:}05{.}400 \dashrightarrow 00{:}25{:}06{.}936$ They're infiltrating the islets

NOTE Confidence: 0.854538988666666

 $00{:}25{:}06{.}936 \dashrightarrow 00{:}25{:}09{.}240$ and they're outside of the islets.

NOTE Confidence: 0.854538988666666

 $00:25:09.240 \longrightarrow 00:25:12.425$ And if you look at cytokines that

 $00:25:12.425 \longrightarrow 00:25:15.119$ are present in the pancreas,

NOTE Confidence: 0.854538988666666

 $00:25:15.120 \rightarrow 00:25:18.879$ we find both interferon gamma and TNF.

NOTE Confidence: 0.854538988666666

00:25:18.880 --> 00:25:19.986 And interestingly,

NOTE Confidence: 0.854538988666666

 $00:25:19.986 \longrightarrow 00:25:24.417$ one of the other findings from this

NOTE Confidence: 0.854538988666666

 $00:25:24.417 \rightarrow 00:25:27.373$ immunohistochemical analysis is PDL

NOTE Confidence: 0.854538988666666

 $00{:}25{:}27{.}373 \dashrightarrow 00{:}25{:}31{.}200$ one was actually induced on beta

NOTE Confidence: 0.854538988666666

 $00{:}25{:}31{.}200 \dashrightarrow 00{:}25{:}34{.}075$ cells in and on the other endocrine

NOTE Confidence: 0.854538988666666

 $00{:}25{:}34.075 \dashrightarrow 00{:}25{:}36.511$ cells in this patient who died

NOTE Confidence: 0.854538988666666

 $00:25:36.511 \rightarrow 00:25:38.916$ with a checkpoint induced diabetes.

NOTE Confidence: 0.854538988666666

 $00:25:38.920 \longrightarrow 00:25:40.840$ Now that's a little weird.

NOTE Confidence: 0.854538988666666

 $00:25:40.840 \rightarrow 00:25:44.445$ We thought that PDL one was actually

NOTE Confidence: 0.854538988666666

 $00:25:44.445 \longrightarrow 00:25:46.050$ protective against diabetes.

NOTE Confidence: 0.8545389886666666

 $00:25:46.050 \rightarrow 00:25:49.320$ So what what's going on here?

NOTE Confidence: 0.854538988666666

 $00:25:49.320 \rightarrow 00:25:52.209$ So let me just make the point and again

NOTE Confidence: 0.854538988666666

 $00{:}25{:}52{.}209 \dashrightarrow 00{:}25{:}54{.}950$ this is work that Anna Pertigato has

NOTE Confidence: 0.854538988666666

 $00:25:54.950 \rightarrow 00:25:57.162$ done that indeed inflammatory mediators,

- NOTE Confidence: 0.854538988666666
- 00:25:57.162 --> 00:25:58.725 particularly gamma interferon
- NOTE Confidence: 0.854538988666666
- 00:25:58.725 --> 00:26:02.159 will induce PDL One on beta cells.
- NOTE Confidence: 0.854538988666666
- $00{:}26{:}02{.}160 \dashrightarrow 00{:}26{:}04{.}285$ There is a interferon response
- NOTE Confidence: 0.854538988666666
- 00:26:04.285 --> 00:26:06.789 element in the promoter of PDL
- NOTE Confidence: 0.854538988666666
- 00:26:06.789 --> 00:26:09.229 one and as you can see by looking
- NOTE Confidence: 0.854538988666666
- $00:26:09.229 \rightarrow 00:26:11.480$ but by flow interferon gamma.
- NOTE Confidence: 0.854538988666666
- $00:26:11.480 \longrightarrow 00:26:13.320$ This is human beta cells.
- NOTE Confidence: 0.854538988666666
- $00{:}26{:}13.320 \dashrightarrow 00{:}26{:}16.546$ Interferon gamma and interferon
- NOTE Confidence: 0.854538988666666
- $00{:}26{:}16.546 \dashrightarrow 00{:}26{:}19.102$ gamma with TNF induce expression of
- NOTE Confidence: 0.854538988666666
- $00{:}26{:}19{.}102 \dashrightarrow 00{:}26{:}22{.}591$ PDL one on beta cells and it seems
- NOTE Confidence: 0.854538988666666
- $00:26:22.591 \rightarrow 00:26:24.721$ to be dependent through signaling
- NOTE Confidence: 0.854538988666666
- 00:26:24.801 --> 00:26:27.303 by gamma interferon because if you
- NOTE Confidence: 0.854538988666666
- 00:26:27.303 --> 00:26:31.696 give rexolitinib to block Jack
- NOTE Confidence: 0.854538988666666
- $00:26:31.696 \rightarrow 00:26:34.160$ signaling through Stat One,
- NOTE Confidence: 0.854538988666666
- $00{:}26{:}34.160 \dashrightarrow 00{:}26{:}38.880$ you can inhibit the expression of PDL one.
- NOTE Confidence: 0.854538988666666

 $00:26:38.880 \rightarrow 00:26:41.974$ Now there was good evidence for the

NOTE Confidence: 0.854538988666666

 $00{:}26{:}41{.}974 \dashrightarrow 00{:}26{:}45{.}255$ importance of PDL 1 in development of

NOTE Confidence: 0.854538988666666

 $00{:}26{:}45{.}255 \dashrightarrow 00{:}26{:}48{.}057$ autoimmune diabetes and most of this NOTE Confidence: 0.854538988666666

 $00:26:48.145 \rightarrow 00:26:51.397$ work came originally from Arlene Sharp.

NOTE Confidence: 0.854538988666666

 $00{:}26{:}51{.}400 \dashrightarrow 00{:}26{:}54{.}848$ And the the work that I'm I'm showing

NOTE Confidence: 0.854538988666666

 $00:26:54.848 \longrightarrow 00:26:58.558$ on the left is from a paper of hers

NOTE Confidence: 0.854538988666666

 $00:26:58.560 \longrightarrow 00:27:00.779$ a number of actually 20 years ago

NOTE Confidence: 0.854538988666666

 $00{:}27{:}00{.}779 \dashrightarrow 00{:}27{:}03{.}098$ now that showed if you knock PDL one

NOTE Confidence: 0.854538988666666

 $00{:}27{:}03.098 \dashrightarrow 00{:}27{:}06.360$ out of this susceptible mouse strain

NOTE Confidence: 0.854538988666666

 $00:27:06.360 \rightarrow 00:27:08.676$ NOD that the mice spontaneously

NOTE Confidence: 0.854538988666666

 $00{:}27{:}08.676$ --> $00{:}27{:}11.600$ developed diabetes at a very young age.

NOTE Confidence: 0.854538988666666

 $00:27:11.600 \rightarrow 00:27:14.935$ And the Histology is shown in

NOTE Confidence: 0.854538988666666

 $00{:}27{:}14.935 \dashrightarrow 00{:}27{:}15.760$ the middle here.

NOTE Confidence: 0.854538988666666

00:27:15.760 --> 00:27:16.202 Furthermore,

NOTE Confidence: 0.854538988666666

 $00{:}27{:}16{.}202 \dashrightarrow 00{:}27{:}19{.}296$ if you gave anti CD3 antibody to

NOTE Confidence: 0.854538988666666

 $00:27:19.296 \rightarrow 00:27:21.981$ mice that spontaneously developed

- NOTE Confidence: 0.854538988666666
- $00{:}27{:}21.981 \dashrightarrow 00{:}27{:}24.265$ diabetes and induced remission
- NOTE Confidence: 0.854538988666666
- $00:27:24.265 \longrightarrow 00:27:26.640$ with the anti CD3 antibody,
- NOTE Confidence: 0.854538988666666
- 00:27:26.640 --> 00:27:30.360 if you gave anti PD one or anti PDL one,
- NOTE Confidence: 0.854538988666666
- $00:27:30.360 \longrightarrow 00:27:32.034$ this is work by Jeff Bluestone
- NOTE Confidence: 0.854538988666666
- 00:27:32.034 --> 00:27:34.078 and Brian Fife On the right side,
- NOTE Confidence: 0.854538988666666
- $00:27:34.080 \longrightarrow 00:27:37.240$ the mice immediately redeveloped diabetes.
- NOTE Confidence: 0.854538988666666
- $00:27:37.240 \longrightarrow 00:27:40.516$ So this work suggested that PDL one
- NOTE Confidence: 0.854538988666666
- 00:27:40.516 --> 00:27:43.798 had a critical role in maintaining
- NOTE Confidence: 0.854538988666666
- $00:27:43.800 \longrightarrow 00:27:45.850$ non development of diabetes in
- NOTE Confidence: 0.854538988666666
- $00:27:45.850 \longrightarrow 00:27:47.080$ a susceptible host.
- NOTE Confidence: 0.854538988666666
- $00{:}27{:}47.080 \dashrightarrow 00{:}27{:}50.090$ And here are some additional studies
- NOTE Confidence: 0.854538988666666
- $00{:}27{:}50{.}090 \dashrightarrow 00{:}27{:}52{.}860$ from Arlene's lab that showed
- NOTE Confidence: 0.854538988666666
- $00:27:52.860 \longrightarrow 00:27:54.600$ if you took wild type cells,
- NOTE Confidence: 0.854538988666666
- 00:27:54.600 --> 00:27:56.750 transferred them into APDL 1
- NOTE Confidence: 0.854538988666666
- $00{:}27{:}56{.}750 \dashrightarrow 00{:}27{:}58{.}900$ knock out or a wild type
- NOTE Confidence: 0.865200372631579

 $00:27:58.985 \longrightarrow 00:28:02.135$ host if you put them into the

NOTE Confidence: 0.865200372631579

00:28:02.135 --> 00:28:03.676 knockout recipient, which is on

NOTE Confidence: 0.865200372631579

 $00:28:03.676 \rightarrow 00:28:05.160$ the left side in the open circles,

NOTE Confidence: 0.865200372631579

 $00:28:05.160 \rightarrow 00:28:06.960$ mice rapidly developed diabetes whereas

NOTE Confidence: 0.865200372631579

 $00{:}28{:}06{.}960 \dashrightarrow 00{:}28{:}09{.}678$ they didn't at the same rate if you

NOTE Confidence: 0.865200372631579

 $00{:}28{:}09{.}678$ --> $00{:}28{:}11{.}680$ put them into the wild type recipient.

NOTE Confidence: 0.865200372631579

 $00:28:11.680 \longrightarrow 00:28:13.948$ And it also was shown in her

NOTE Confidence: 0.865200372631579

 $00:28:13.948 \rightarrow 00:28:16.214$ work that the importance of PDL

NOTE Confidence: 0.865200372631579

 $00{:}28{:}16{.}214 \dashrightarrow 00{:}28{:}18{.}632$ One was indeed on the islets.

NOTE Confidence: 0.865200372631579

 $00{:}28{:}18.640 \dashrightarrow 00{:}28{:}21.790$ Because if she transplanted PDL 1

NOTE Confidence: 0.865200372631579

 $00{:}28{:}21.790 \dashrightarrow 00{:}28{:}24.484$ deficient beta cells into either

NOTE Confidence: 0.865200372631579

00:28:24.484 --> 00:28:26.760 wild type or knockout mice,

NOTE Confidence: 0.865200372631579

 $00:28:26.760 \longrightarrow 00:28:29.000$ which is shown on the on the right,

NOTE Confidence: 0.865200372631579

 $00{:}28{:}29{.}000 \dashrightarrow 00{:}28{:}32{.}892$ the PDL 1 knockout is lets were more

NOTE Confidence: 0.865200372631579

 $00:28:32.892 \rightarrow 00:28:37.520$ rapidly killed compared to wild type eyelids.

NOTE Confidence: 0.865200372631579

 $00:28:37.520 \longrightarrow 00:28:40.160$ So PDL one seems to have some unique

- NOTE Confidence: 0.89180748
- $00:28:42.960 \longrightarrow 00:28:45.735$ features that's important in in

 $00{:}28{:}45.735 \dashrightarrow 00{:}28{:}47.955$ protecting against autoimmune diabetes.

NOTE Confidence: 0.89180748

 $00{:}28{:}47{.}960 \dashrightarrow 00{:}28{:}51{.}142$ Now we did some additional studies

NOTE Confidence: 0.89180748

 $00{:}28{:}51{.}142 \dashrightarrow 00{:}28{:}53{.}914$ look comparing anti PDL one and

NOTE Confidence: 0.89180748

00:28:53.914 --> 00:28:57.395 anti CTE 4 because let me go back

NOTE Confidence: 0.89180748

 $00{:}28{:}57{.}395 \dashrightarrow 00{:}29{:}00{.}257$ to that paper in that that letter

NOTE Confidence: 0.89180748

 $00{:}29{:}00{.}257 \dashrightarrow 00{:}29{:}03{.}190$ in 2015 and and the comments from

NOTE Confidence: 0.89180748

 $00:29:03.274 \rightarrow 00:29:05.039$ the reviewer that pointed out,

NOTE Confidence: 0.89180748

 $00:29:05.039 \rightarrow 00:29:06.557$ well if this was really important

NOTE Confidence: 0.89180748

00:29:06.557 --> 00:29:08.080 we would have known about it.

NOTE Confidence: 0.89180748

 $00{:}29{:}08.080 \dashrightarrow 00{:}29{:}10.774$ Well that reviewer was completely wrong

NOTE Confidence: 0.89180748

 $00{:}29{:}10.774 \dashrightarrow 00{:}29{:}13.089$ because indeed the only checkpoint

NOTE Confidence: 0.89180748

 $00{:}29{:}13.089 \dashrightarrow 00{:}29{:}15.299$ inhibitor that was available prior

NOTE Confidence: 0.89180748

 $00{:}29{:}15{.}299 \dashrightarrow 00{:}29{:}17{.}999$ to that time was anti CTLA 4.

NOTE Confidence: 0.89180748

 $00:29:18.000 \longrightarrow 00:29:20.184$ And if you take a look at the

 $00:29:20.184 \rightarrow 00:29:22.380$ mouse data here and this has been

NOTE Confidence: 0.89180748

00:29:22.380 --> 00:29:23.680 reproduced in other labs,

NOTE Confidence: 0.89180748

00:29:23.680 --> 00:29:26.935 anti CTLA 4 doesn't do this seems

NOTE Confidence: 0.89180748

 $00:29:26.935 \longrightarrow 00:29:29.957$ to be unique for anti PDL 1.

NOTE Confidence: 0.89180748

 $00{:}29{:}29{.}960 \dashrightarrow 00{:}29{:}32{.}888$ And so we did some studies to to

NOTE Confidence: 0.89180748

00:29:32.888 --> 00:29:35.910 try to identify what's different

NOTE Confidence: 0.89180748

00:29:35.910 --> 00:29:40.792 about anti PDL one and anti CTLA 4IN

NOTE Confidence: 0.89180748

 $00{:}29{:}40.792 \dashrightarrow 00{:}29{:}44.474$ induction of diabetes and I'm going to

NOTE Confidence: 0.89180748

 $00{:}29{:}44.474 \dashrightarrow 00{:}29{:}46.273$ go through the the data fairly quickly. NOTE Confidence: 0.89180748

 $00:29:46.280 \dashrightarrow 00:29:50.224$ We did this by performing single cell

NOTE Confidence: 0.89180748

 $00{:}29{:}50{.}224 \dashrightarrow 00{:}29{:}56{.}280$ RNA seq on infiltrating cells and

NOTE Confidence: 0.89180748

 $00:29:56.280 \longrightarrow 00:29:59.717$ is let cells from mice that had received NOTE Confidence: 0.89180748

 $00:29:59.720 \rightarrow 00:30:02.040$ either of these checkpoint inhibitors.

NOTE Confidence: 0.89180748

 $00{:}30{:}02{.}040 \dashrightarrow 00{:}30{:}05{.}181$ And let me first point out that in the

NOTE Confidence: 0.89180748

 $00:30:05.181 \rightarrow 00:30:07.571$ presence that when when these susceptible NOTE Confidence: 0.89180748

 $00:30:07.571 \rightarrow 00:30:10.690$ mice and OD mice are given anti C24,

- NOTE Confidence: 0.89180748
- $00:30:10.690 \dashrightarrow 00:30:13.000$ there are cells that infiltrate the islets.

 $00{:}30{:}13.000 \dashrightarrow 00{:}30{:}15.800$ It's not that they don't develop insulitis,

NOTE Confidence: 0.89180748

 $00:30:15.800 \rightarrow 00:30:17.956$ it's just that they don't develop diabetes.

NOTE Confidence: 0.89180748

 $00:30:17.960 \longrightarrow 00:30:19.880$ They don't go on and kill,

NOTE Confidence: 0.89180748

 $00:30:19.880 \longrightarrow 00:30:21.340$ kill the beta cells.

NOTE Confidence: 0.89180748

 $00:30:21.340 \longrightarrow 00:30:22.800$ So first of all,

NOTE Confidence: 0.89180748

 $00:30:22.800 \rightarrow 00:30:25.820$ when we look at and when we look at immune

NOTE Confidence: 0.89180748

 $00{:}30{:}25.820 \dashrightarrow 00{:}30{:}27.920$ cells that are infiltrating the islets,

NOTE Confidence: 0.89180748

 $00{:}30{:}27{.}920 \dashrightarrow 00{:}30{:}29{.}754$ you can see there is a difference.

NOTE Confidence: 0.89180748

 $00:30:29.760 \longrightarrow 00:30:32.140$ If you take a look at panel

NOTE Confidence: 0.89180748

 $00{:}30{:}32{.}140 \dashrightarrow 00{:}30{:}34{.}148$ D in the MELD analysis,

NOTE Confidence: 0.89180748

 $00{:}30{:}34.148 \dashrightarrow 00{:}30{:}36.420$ there's a difference in CDAT cells

NOTE Confidence: 0.89180748

 $00:30:36.420 \rightarrow 00:30:38.460$ that are infiltrating the islets when

NOTE Confidence: 0.89180748

 $00{:}30{:}38{.}460 \dashrightarrow 00{:}30{:}40{.}722$ the when the mice are treated with

NOTE Confidence: 0.89180748

 $00{:}30{:}40.722 \dashrightarrow 00{:}30{:}43.079$ anti PDL 1 compared to anti cetal A4.

 $00:30:43.080 \rightarrow 00:30:45.608$ And there are a number of genes that NOTE Confidence: 0.89180748 00:30:45.608 --> 00:30:47.010 are differentially expressed including NOTE Confidence: 0.89180748 $00{:}30{:}47.010 \dashrightarrow 00{:}30{:}49.700$ some of the the ones that you might NOTE Confidence: 0.89180748 00:30:49.700 --> 00:30:53.910 expect such as as Tea Bed Interferon, NOTE Confidence: 0.89180748 $00{:}30{:}53{.}910 \dashrightarrow 00{:}30{:}57{.}118$ Gamma Granzyme B and even PDL one NOTE Confidence: 0.89180748 $00:30:57.118 \rightarrow 00:31:00.040$ as as we would have predicted, NOTE Confidence: 0.89180748 $00:31:00.040 \dashrightarrow 00:31:03.215$ as well as Perfran and the volcano NOTE Confidence: 0.89180748 $00:31:03.215 \rightarrow 00:31:05.090$ plot showing you the differences NOTE Confidence: 0.89180748 $00{:}31{:}05{.}090 \dashrightarrow 00{:}31{:}07{.}640$ in expression in the CDA T cells NOTE Confidence: 0.89180748 $00:31:07.640 \longrightarrow 00:31:09.640$ as shown in the bottom. NOTE Confidence: 0.89180748 $00:31:09.640 \longrightarrow 00:31:11.392$ Now what about the cells that NOTE Confidence: 0.89180748 $00:31:11.392 \rightarrow 00:31:12.560$ are infiltrating the eyelids? NOTE Confidence: 0.89180748 $00:31:12.560 \rightarrow 00:31:15.556$ Are they the same? Maybe they're different. NOTE Confidence: 0.89180748 $00:31:15.560 \rightarrow 00:31:18.160$ And this is the data that we have to date. NOTE Confidence: 0.89180748 00:31:18.160 --> 00:31:20.800 And fortunately I can't go into NOTE Confidence: 0.89180748 $00:31:20.800 \rightarrow 00:31:23.251$ this and more with more granularity

- NOTE Confidence: 0.89180748
- $00:31:23.251 \rightarrow 00:31:25.513$ except to point out that yes,

 $00:31:25.520 \rightarrow 00:31:26.450$ they are different.

NOTE Confidence: 0.89180748

 $00:31:26.450 \longrightarrow 00:31:28.971$ They are not the same cells that are

NOTE Confidence: 0.89180748

 $00:31:28.971 \rightarrow 00:31:30.973$ being driven to the eyelids in when

NOTE Confidence: 0.89180748

 $00:31:30.973 \rightarrow 00:31:33.758$ with the two different checkpoint inhibitors.

NOTE Confidence: 0.89180748

 $00:31:33.760 \longrightarrow 00:31:36.112$ If you just take a look at the

NOTE Confidence: 0.89180748

 $00:31:36.112 \rightarrow 00:31:37.465$ frequency of various clonotypes

NOTE Confidence: 0.89180748

 $00{:}31{:}37{.}465 \dashrightarrow 00{:}31{:}40{.}249$ you can see with anti PDL one in

NOTE Confidence: 0.89180748

 $00{:}31{:}40{.}326 \dashrightarrow 00{:}31{:}42{.}720$ mice that that do develop diabetes,

NOTE Confidence: 0.89180748

 $00{:}31{:}42.720 \dashrightarrow 00{:}31{:}46.626$ there seems to be a relative selection

NOTE Confidence: 0.89180748

 $00{:}31{:}46.626 \dashrightarrow 00{:}31{:}48.831$ of particular clonotypes compared

NOTE Confidence: 0.89180748

 $00{:}31{:}48{.}831 \dashrightarrow 00{:}31{:}52{.}920$ to the anti C2E4 treated mice.

NOTE Confidence: 0.89180748

 $00{:}31{:}52{.}920 \dashrightarrow 00{:}31{:}56{.}016$ Now macrophages also seem to be

NOTE Confidence: 0.89180748

 $00{:}31{:}56.016 \dashrightarrow 00{:}31{:}58.512$ different for reasons that we

NOTE Confidence: 0.89180748

 $00:31:58.512 \dashrightarrow 00:32:00.240$ we don't completely understand.

 $00:32:00.240 \longrightarrow 00:32:04.200$ But you can see that they they express

NOTE Confidence: 0.712054261428571

 $00:32:06.280 \dashrightarrow 00:32:09.234$ PDL one, they themselves express PDL one.

NOTE Confidence: 0.712054261428571

 $00:32:09.240 \longrightarrow 00:32:12.376$ They produce CXCL 10, which is important NOTE Confidence: 0.712054261428571

 $00:32:12.376 \rightarrow 00:32:14.839$ in recruiting cells to the islets,

NOTE Confidence: 0.712054261428571

 $00:32:14.840 \longrightarrow 00:32:17.822$ as well as Stat 1 indicating they've

NOTE Confidence: 0.712054261428571

 $00{:}32{:}17.822 \dashrightarrow 00{:}32{:}20.680$ they've been looking at interferon gamma.

NOTE Confidence: 0.712054261428571

 $00:32:20.680 \rightarrow 00:32:23.040$ And this is interesting because

NOTE Confidence: 0.712054261428571

 $00{:}32{:}23.040 \dashrightarrow 00{:}32{:}25.572$ work from Emil Yunanoway's lab had

NOTE Confidence: 0.712054261428571

 $00{:}32{:}25{.}572 \dashrightarrow 00{:}32{:}28{.}159$ actually pointed out that these cells

NOTE Confidence: 0.712054261428571

 $00:32:28.159 \rightarrow 00:32:30.637$ seem to be the critically important

NOTE Confidence: 0.712054261428571

 $00:32:30.640 \longrightarrow 00:32:33.040$ cells for initiating checkpoint

NOTE Confidence: 0.712054261428571

 $00:32:33.040 \longrightarrow 00:32:35.878$ induced diabetes in in this model.

NOTE Confidence: 0.9614282

 $00{:}32{:}38{.}040 \dashrightarrow 00{:}32{:}41{.}948$ Now in addition there are there

NOTE Confidence: 0.9614282

 $00:32:41.948 \longrightarrow 00:32:44.036$ there are changes in beta cells.

NOTE Confidence: 0.9614282

 $00:32:44.040 \rightarrow 00:32:46.490$ I showed you already in humans that

NOTE Confidence: 0.9614282

 $00{:}32{:}46{.}490 \dashrightarrow 00{:}32{:}49{.}015$ that we found that there was induction

- NOTE Confidence: 0.9614282
- $00{:}32{:}49.015 \dashrightarrow 00{:}32{:}52.129$ of PDL one in human beta cells that

 $00{:}32{:}52{.}129 \dashrightarrow 00{:}32{:}54{.}474$ were treated with interferon gamma.

NOTE Confidence: 0.9614282

 $00:32:54.480 \longrightarrow 00:32:56.562$ And indeed if we looked at

NOTE Confidence: 0.9614282

 $00:32:56.562 \longrightarrow 00:32:57.950$ genes that are differentially

NOTE Confidence: 0.9614282

 $00{:}32{:}58.015 \dashrightarrow 00{:}32{:}59.999$ expressed with interferon gamma,

NOTE Confidence: 0.9614282

 $00{:}33{:}00{.}000 \dashrightarrow 00{:}33{:}02{.}079$ you can see that there are a

NOTE Confidence: 0.9614282

 $00:33:02.079 \longrightarrow 00:33:04.531$ whole lot of genes that have

NOTE Confidence: 0.9614282

 $00:33:04.531 \rightarrow 00:33:06.515$ some immune response properties.

NOTE Confidence: 0.9614282

 $00{:}33{:}06{.}520 \dashrightarrow 00{:}33{:}08{.}548$ Now the reason that we think

NOTE Confidence: 0.9614282

 $00{:}33{:}08{.}548 \dashrightarrow 00{:}33{:}10{.}520$ this is important is because

NOTE Confidence: 0.9614282

 $00:33:10.520 \dashrightarrow 00:33:12.700$ seeing inflammatory when beta

NOTE Confidence: 0.9614282

00:33:12.700 --> 00:33:14.880 cells see inflammatory cytokines,

NOTE Confidence: 0.9614282

 $00{:}33{:}14.880 \dashrightarrow 00{:}33{:}18.120$ they make a number of important NOTE Confidence: 0.9614282

00:33:18.120 --> 00:33:21.080 immune ligands such as CXCL 9,

NOTE Confidence: 0.9614282

 $00{:}33{:}21.080 \dashrightarrow 00{:}33{:}24.320$ CXCL 10 important for recruiting

 $00:33:24.320 \longrightarrow 00:33:28.696$ cells to the islets and as well as

NOTE Confidence: 0.9614282

 $00{:}33{:}28.696 \dashrightarrow 00{:}33{:}31.160$ increase expression of of class one.

NOTE Confidence: 0.9614282

 $00{:}33{:}31{.}160 \dashrightarrow 00{:}33{:}35{.}052$ MHC when we looked at this again

NOTE Confidence: 0.9614282

 $00:33:35.052 \rightarrow 00:33:36.356$ is with human cells.

NOTE Confidence: 0.9614282

 $00{:}33{:}36{.}360 \dashrightarrow 00{:}33{:}38{.}985$ When we looked at other features of

NOTE Confidence: 0.9614282

 $00:33:38.985 \rightarrow 00:33:41.518$ human islets exposed to gamma interferon,

NOTE Confidence: 0.9614282

 $00:33:41.520 \longrightarrow 00:33:43.250$ we found that actually there

NOTE Confidence: 0.9614282

00:33:43.250 --> 00:33:45.188 was induction of FAS suggesting

NOTE Confidence: 0.9614282

 $00{:}33{:}45.188 \dashrightarrow 00{:}33{:}47.928$ that indeed that cytokine might

NOTE Confidence: 0.9614282

 $00:33:47.928 \rightarrow 00:33:50.880$ induce a killing of beta cells.

NOTE Confidence: 0.9614282

00:33:50.880 --> 00:33:54.504 And if you take a look at impanel

NOTE Confidence: 0.9614282

 $00:33:54.504 \dashrightarrow 00:33:57.800$ E you you can see that in the PDL

NOTE Confidence: 0.9614282

00:33:57.800 - 00:34:00.644 1 expressing cells we we find

NOTE Confidence: 0.9614282

 $00{:}34{:}00{.}644 \dashrightarrow 00{:}34{:}02{.}726$ this morphology suggesting the cells

NOTE Confidence: 0.9614282

 $00:34:02.726 \longrightarrow 00:34:04.874$ are are are are actually dying.

NOTE Confidence: 0.9614282

 $00:34:04.880 \longrightarrow 00:34:08.120$ And indeed if if we look at at

- NOTE Confidence: 0.9614282
- $00:34:08.120 \longrightarrow 00:34:10.640$ the percentage of dead beta cells

00:34:10.640 --> 00:34:13.520 in panel D it is much higher with

NOTE Confidence: 0.9614282

 $00{:}34{:}13{.}520 \dashrightarrow 00{:}34{:}16{.}002$ cells that are cultured with

NOTE Confidence: 0.9614282

 $00:34:16.002 \rightarrow 00:34:18.576$ interferon gamma back to the mice.

NOTE Confidence: 0.9614282

 $00{:}34{:}18{.}576 \dashrightarrow 00{:}34{:}21{.}215$ Now when we look at beta cells

NOTE Confidence: 0.9614282

 $00{:}34{:}21{.}215 \dashrightarrow 00{:}34{:}23{.}478$ in the mice in site two,

NOTE Confidence: 0.9614282

 $00{:}34{:}23{.}478 \dashrightarrow 00{:}34{:}26{.}257$ there are a number of differences in

NOTE Confidence: 0.9614282

 $00:34:26.257 \rightarrow 00:34:28.999$ in in them including the development

NOTE Confidence: 0.9614282

 $00{:}34{:}28{.}999 \dashrightarrow 00{:}34{:}32{.}797$ of a unique subgroup of of beta cells.

NOTE Confidence: 0.9614282

00:34:32.800 --> 00:34:36.280 If you take a look at panel C,

NOTE Confidence: 0.9614282

 $00:34:36.280 \longrightarrow 00:34:37.260$ the fate,

NOTE Confidence: 0.9614282

 $00{:}34{:}37{.}260 \dashrightarrow 00{:}34{:}40{.}200$ the fate diagram here shows you

NOTE Confidence: 0.9614282

 $00:34:40.200 \longrightarrow 00:34:42.520$ 2 populations of beta cells.

NOTE Confidence: 0.9614282

 $00{:}34{:}42{.}520 \dashrightarrow 00{:}34{:}44{.}458$ The the standard beta cells

NOTE Confidence: 0.9614282

 $00{:}34{:}44{.}458 \dashrightarrow 00{:}34{:}46{.}746$ that you can see in mice treated

00:34:46.746 --> 00:34:49.307 with anti cetal E4 or anti PDL one NOTE Confidence: 0.9614282 00:34:49.307 --> 00:34:51.302 and then this unique a cluster NOTE Confidence: 0.9614282 $00:34:51.302 \longrightarrow 00:34:53.759$ of beta cells that seems to be NOTE Confidence: 0.9614282 $00:34:53.759 \rightarrow 00:34:55.758$ uniquely found in anti PDL one. NOTE Confidence: 0.9614282 $00:34:55.760 \rightarrow 00:34:58.336$ The main beta cells express the same NOTE Confidence: 0.9614282 $00{:}34{:}58{.}336 \dashrightarrow 00{:}35{:}01{.}520$ log in so they just showed you with NOTE Confidence: 0.9614282 00:35:01.520 --> 00:35:04.240 human beta cells CXCL 10 PDL one. NOTE Confidence: 0.9614282 00:35:04.240 --> 00:35:06.214 Class one MHC goes up stat NOTE Confidence: 0.9614282 $00{:}35{:}06{.}214 \dashrightarrow 00{:}35{:}08{.}440$ one is signaling and trail is NOTE Confidence: 0.9614282 $00:35:08.440 \rightarrow 00:35:10.120$ actually increased as well. NOTE Confidence: 0.9614282 $00:35:10.120 \longrightarrow 00:35:12.495$ But in the unique beta NOTE Confidence: 0.9614282 $00{:}35{:}12.495 \dashrightarrow 00{:}35{:}14.395$ cells there's also changes, NOTE Confidence: 0.9614282 00:35:14.400 --> 00:35:15.921 including reduced expression NOTE Confidence: 0.9614282 $00:35:15.921 \longrightarrow 00:35:19.470$ of a number of the beta cell NOTE Confidence: 0.9614282 00:35:19.562 --> 00:35:23.060 identity genes such as NTX 6.1, NOTE Confidence: 0.9614282 $00:35:23.060 \rightarrow 00:35:25.106$ Maffe of course,

- NOTE Confidence: 0.9614282
- $00:35:25.106 \dashrightarrow 00:35:27.636$ insulin and and chromogram.

 $00:35:27.640 \longrightarrow 00:35:29.168$ So it's what this,

NOTE Confidence: 0.9614282

 $00:35:29.168 \rightarrow 00:35:31.460$ what this finding suggests is work

NOTE Confidence: 0.9614282

 $00:35:31.532 \longrightarrow 00:35:33.866$ that we've done in other models

NOTE Confidence: 0.9614282

 $00{:}35{:}33{.}866 \dashrightarrow 00{:}35{:}36{.}000$ of diabetes that there is some

NOTE Confidence: 0.927789400833333

 $00{:}35{:}38{.}560 \dashrightarrow 00{:}35{:}41{.}493$ pathway leading to be ta cell survival in

NOTE Confidence: 0.927789400833333

 $00:35:41.493 \longrightarrow 00:35:44.400$ the presence of checkpoint inhibitors

NOTE Confidence: 0.927789400833333

 $00{:}35{:}44{.}400 \dashrightarrow 00{:}35{:}48{.}272$ that that seems to be turned on when

NOTE Confidence: 0.927789400833333

 $00{:}35{:}48.272 \dashrightarrow 00{:}35{:}51.260$ these drugs are given. All right.

NOTE Confidence: 0.927789400833333

 $00:35:51.260 \dashrightarrow 00:35:54.444$ So that's that's kind of where things are

NOTE Confidence: 0.927789400833333

 $00:35:54.444 \rightarrow 00:35:56.760$ in terms of what's going on in the islet,

NOTE Confidence: 0.927789400833333

 $00{:}35{:}56.760 \dashrightarrow 00{:}36{:}00.072$ what how human beta cells respond

NOTE Confidence: 0.927789400833333

 $00:36:00.072 \rightarrow 00:36:02.280$ similarly to inflammatory mediators.

NOTE Confidence: 0.927789400833333

 $00:36:02.280 \longrightarrow 00:36:04.278$ So what what is, what is,

NOTE Confidence: 0.927789400833333

 $00:36:04.280 \longrightarrow 00:36:06.794$ what's the point of that and

 $00:36:06.794 \longrightarrow 00:36:07.958$ what can we do about it.

NOTE Confidence: 0.927789400833333

 $00{:}36{:}07{.}960 \dashrightarrow 00{:}36{:}13{.}725$ So let me point out that in follow

NOTE Confidence: 0.927789400833333

 $00{:}36{:}13.725 \dashrightarrow 00{:}36{:}16.781$ up work that that we did to try to

NOTE Confidence: 0.927789400833333

 $00:36:16.781 \longrightarrow 00:36:18.790$ figure out could we based on this

NOTE Confidence: 0.927789400833333

 $00:36:18.859 \rightarrow 00:36:20.927$ knowledge stop the development

NOTE Confidence: 0.927789400833333

 $00{:}36{:}20{.}927 \dashrightarrow 00{:}36{:}22{.}995$ of checkpoint induced diabetes.

NOTE Confidence: 0.927789400833333

 $00{:}36{:}23.000 \dashrightarrow 00{:}36{:}25.634$ We first tested whether anti cytokine

NOTE Confidence: 0.927789400833333

 $00:36:25.634 \rightarrow 00:36:28.238$ antibodies might be able to do that.

NOTE Confidence: 0.927789400833333

00:36:28.240 --> 00:36:30.826 And I've shown you already the

NOTE Confidence: 0.927789400833333

00:36:30.826 --> 00:36:33.457 critical role of interferon gamma and NOTE Confidence: 0.927789400833333

00:36:33.457 --> 00:36:35.742 potentially TNF in development of NOTE Confidence: 0.927789400833333

 $00:36:35.742 \rightarrow 00:36:37.975$ checkpoint induced diabetes at least

NOTE Confidence: 0.927789400833333

00:36:37.975 --> 00:36:40.278 in mice and evidence in humans that NOTE Confidence: 0.927789400833333

 $00{:}36{:}40{.}278 \dashrightarrow 00{:}36{:}42{.}653$ both of these cytokines were present

NOTE Confidence: 0.927789400833333

 $00{:}36{:}42.653 \dashrightarrow 00{:}36{:}45.486$ in the pancreas of an individual who

NOTE Confidence: 0.927789400833333

 $00:36:45.486 \dashrightarrow 00:36:47.316$ died with checkpoint induced diabetes.

 $00:36:47.320 \longrightarrow 00:36:49.630$ What happens if you neutralize

NOTE Confidence: 0.927789400833333

 $00:36:49.630 \longrightarrow 00:36:50.554$ those cytokines?

NOTE Confidence: 0.927789400833333

 $00:36:50.560 \rightarrow 00:36:53.660$ And you can see in the on the top here

NOTE Confidence: 0.927789400833333

 $00:36:53.742 \rightarrow 00:36:57.168$ that if you gave the combination of

NOTE Confidence: 0.927789400833333

 $00{:}36{:}57{.}168 \dashrightarrow 00{:}37{:}00{.}464$ anti PDL interferon gamma and anti TNF

NOTE Confidence: 0.927789400833333

00:37:00.464 --> 00:37:03.400 to mice treated with anti PDL one,

NOTE Confidence: 0.927789400833333

 $00:37:03.400 \longrightarrow 00:37:06.034$ you could indeed prevent the development

NOTE Confidence: 0.927789400833333

 $00:37:06.034 \rightarrow 00:37:08.598$ of checkpoint induced diabetes in the mice.

NOTE Confidence: 0.927789400833333

00:37:08.600 --> 00:37:09.021 Furthermore,

NOTE Confidence: 0.927789400833333

 $00:37:09.021 \rightarrow 00:37:11.968$ if you blocked a little further downstream

NOTE Confidence: 0.927789400833333

00:37:11.968 --> 00:37:14.920 with a Jack inhibitor and this is,

NOTE Confidence: 0.927789400833333

00:37:14.920 --> 00:37:17.000 I'm sorry, this says Jack inhibitor 1,

NOTE Confidence: 0.927789400833333

 $00{:}37{:}17.000 \dashrightarrow 00{:}37{:}18.962$ Jack inhibitor 2 and I should

NOTE Confidence: 0.927789400833333

 $00{:}37{:}18.962 \dashrightarrow 00{:}37{:}21.289$ just mention this is an ongoing

NOTE Confidence: 0.927789400833333

 $00{:}37{:}21.289 \dashrightarrow 00{:}37{:}23.506$ collaboration with folks at Pfizer

00:37:23.506 --> 00:37:26.038 and with two new Jack inhibitors,

NOTE Confidence: 0.927789400833333

 $00{:}37{:}26.040 \dashrightarrow 00{:}37{:}27.741$ The identities of which we don't know

NOTE Confidence: 0.927789400833333

 $00:37:27.741 \rightarrow 00:37:29.360$ except we know they're different.

NOTE Confidence: 0.927789400833333

00:37:29.360 --> 00:37:31.968 But as you can see Jack inhibitor 1

NOTE Confidence: 0.927789400833333

 $00:37:31.968 \rightarrow 00:37:34.600$ looks pretty good in terms of developing,

NOTE Confidence: 0.927789400833333

 $00{:}37{:}34.600 \dashrightarrow 00{:}37{:}37.616$ preventing the development of

NOTE Confidence: 0.927789400833333

00:37:37.616 --> 00:37:39.878 checkpoint induced diabetes.

NOTE Confidence: 0.927789400833333

 $00:37:39.880 \rightarrow 00:37:42.106$ So to summarize what I've just told

NOTE Confidence: 0.927789400833333

 $00:37:42.106 \longrightarrow 00:37:44.769$ you then what we think is there's

NOTE Confidence: 0.927789400833333

 $00:37:44.769 \rightarrow 00:37:46.814$ actually an inflammatory cycle that's

NOTE Confidence: 0.927789400833333

 $00{:}37{:}46.814 \dashrightarrow 00{:}37{:}49.325$ going on between immune cells and beta

NOTE Confidence: 0.927789400833333

 $00:37:49.325 \rightarrow 00:37:51.580$ cells that leads to the development

NOTE Confidence: 0.927789400833333

00:37:51.580 --> 00:37:54.280 of of a checkpoint induced diabetes

NOTE Confidence: 0.927789400833333

 $00:37:54.280 \rightarrow 00:37:56.679$ in response to interferon gamma.

NOTE Confidence: 0.927789400833333

 $00{:}37{:}56.680 \dashrightarrow 00{:}37{:}59.753$ Beta cells in turn make a number

NOTE Confidence: 0.927789400833333

00:37:59.753 --> 00:38:01.738 of immune regulatory molecules

 $00:38:01.738 \longrightarrow 00:38:04.638$ that recruit other immune cells,

NOTE Confidence: 0.927789400833333

 $00{:}38{:}04.640 \dashrightarrow 00{:}38{:}08.780$ activate immune cells leads to increased

NOTE Confidence: 0.927789400833333

00:38:08.780 --> 00:38:11.536 production of inflammatory cytokines

NOTE Confidence: 0.927789400833333

 $00:38:11.536 \rightarrow 00:38:13.600$ particularly interferon gamma.

NOTE Confidence: 0.927789400833333

 $00:38:13.600 \dashrightarrow 00:38:16.274$ It leads to expression of PDL one.

NOTE Confidence: 0.927789400833333

00:38:16.280 --> 00:38:20.088 When you block PDL 1 you seem to

NOTE Confidence: 0.927789400833333

 $00:38:20.088 \rightarrow 00:38:23.670$ block the stop signal in immune cells

NOTE Confidence: 0.927789400833333

 $00:38:23.670 \longrightarrow 00:38:26.420$ that otherwise would would cause

NOTE Confidence: 0.927789400833333

 $00:38:26.518 \dashrightarrow 00:38:28.920$ them to leave the eyelid and and

NOTE Confidence: 0.927789400833333

 $00{:}38{:}28{.}920 \dashrightarrow 00{:}38{:}31{.}415$ the immune cells then are there in

NOTE Confidence: 0.927789400833333

 $00:38:31.415 \longrightarrow 00:38:33.732$ the eyelid and capable of going on

NOTE Confidence: 0.927789400833333

 $00{:}38{:}33{.}732 \dashrightarrow 00{:}38{:}36{.}106$ and killing the insulin producing

NOTE Confidence: 0.927789400833333

 $00:38:36.106 \dashrightarrow 00:38:39.558$ cells so and and killing beta cells.

NOTE Confidence: 0.927789400833333

 $00{:}38{:}39{.}560 \dashrightarrow 00{:}38{:}40{.}565$ So what is,

NOTE Confidence: 0.927789400833333

 $00{:}38{:}40{.}565 \dashrightarrow 00{:}38{:}43{.}294$ is there anything we can take home from

 $00:38:43.294 \rightarrow 00:38:45.484$ this in terms of treating patients?

NOTE Confidence: 0.927789400833333

 $00:38:45.484 \rightarrow 00:38:48.858$ And let me just start by mentioning

NOTE Confidence: 0.927789400833333

00:38:48.858 --> 00:38:53.324 this patient that was again another NOTE Confidence: 0.927789400833333

 $00:38:53.324 \rightarrow 00:38:57.234$ another letter in diabetes care

NOTE Confidence: 0.927789400833333

 $00:38:57.240 \dashrightarrow 00:39:00.320$ that was treated in Switzerland.

NOTE Confidence: 0.927789400833333

 $00:39:00.320 \longrightarrow 00:39:02.378$ This is a patient who had presented NOTE Confidence: 0.927789400833333

 $00:39:02.378 \longrightarrow 00:39:04.587$ with type 2 diabetes and let me go

NOTE Confidence: 0.927789400833333

 $00:39{:}04.587 \dashrightarrow 00{:}39{:}06.720$ back to a point I made earlier.

NOTE Confidence: 0.927789400833333

 $00:39:06.720 \rightarrow 00:39:08.813$ Type 2 diabetes is a common disease

NOTE Confidence: 0.927789400833333

 $00{:}39{:}08{.}813 \dashrightarrow 00{:}39{:}11{.}277$ and so it follows that there are

NOTE Confidence: 0.927789400833333

 $00:39{:}11.277 \dashrightarrow 00{:}39{:}13.515$ patients who are going to develop

NOTE Confidence: 0.878915246296296

00:39:13.582 --> 00:39:15.862 checkpoint induced diabetes who already

NOTE Confidence: 0.878915246296296

 $00:39:15.862 \rightarrow 00:39:18.624$ may have pre-existing type 2 diabetes.

NOTE Confidence: 0.878915246296296

 $00:39:18.624 \rightarrow 00:39:21.390$ And that's the explanation I'm going

NOTE Confidence: 0.878915246296296

 $00:39:21.464 \longrightarrow 00:39:24.032$ to give you for for this this case

NOTE Confidence: 0.878915246296296

 $00:39:24.032 \rightarrow 00:39:26.384$ report that appeared in the literature.

- NOTE Confidence: 0.878915246296296
- $00:39:26.384 \dashrightarrow 00:39:29.240$ So this is an individual with pre
- NOTE Confidence: 0.878915246296296
- 00:39:29.240 --> 00:39:32.380 pre-existing type 2 diabetes had
- NOTE Confidence: 0.878915246296296
- $00:39:32.380 \longrightarrow 00:39:34.592$ much worsening glucose control.
- NOTE Confidence: 0.878915246296296
- $00:39:34.592 \rightarrow 00:39:38.880$ You can see with a hemoglobin A1C of 11.6%
- NOTE Confidence: 0.878915246296296
- $00:39:38.880 \rightarrow 00:39:42.240$ but did have detectable beta cell function.
- NOTE Confidence: 0.878915246296296
- $00:39:42.240 \longrightarrow 00:39:45.278$ The C peptide was 993 which is
- NOTE Confidence: 0.878915246296296
- $00:39:45.278 \rightarrow 00:39:48.126$ you know plenty respectable and
- NOTE Confidence: 0.878915246296296
- $00:39:48.126 \rightarrow 00:39:50.156$ was also auto anybody positive.
- NOTE Confidence: 0.878915246296296
- 00:39:50.160 00:39:52.284 So they believe that this patient
- NOTE Confidence: 0.878915246296296
- $00:39:52.284 \rightarrow 00:39:54.005$ had immune mediated diabetes.
- NOTE Confidence: 0.878915246296296
- $00:39:54.005 \rightarrow 00:39:56.280$ They gave the patient infliximab,
- NOTE Confidence: 0.878915246296296
- $00:39:56.280 \dashrightarrow 00:39:59.512$ the anti TNF antibody and as you can
- NOTE Confidence: 0.878915246296296
- $00:39:59.512 \dashrightarrow 00:40:02.600$ see the the glucose is improved.
- NOTE Confidence: 0.878915246296296
- 00:40:02.600 --> 00:40:05.400 The hemoglobin A1C came down
- NOTE Confidence: 0.878915246296296
- $00{:}40{:}05{.}400 \dashrightarrow 00{:}40{:}06{.}760$ and so that was
- NOTE Confidence: 0.86068467

 $00:40:08.800 \rightarrow 00:40:10.852$ that seemed to be very impressive

NOTE Confidence: 0.86068467

 $00{:}40{:}10.852 \dashrightarrow 00{:}40{:}11.878$ to those investigators.

NOTE Confidence: 0.86068467

 $00:40:11.880 \longrightarrow 00:40:13.238$ The patient had been treated with insulin.

NOTE Confidence: 0.86068467

 $00:40:13.240 \longrightarrow 00:40:14.856$ They stopped the insulin.

NOTE Confidence: 0.86068467

 $00{:}40{:}14.856 \dashrightarrow 00{:}40{:}16.876$ Now since we saw that,

NOTE Confidence: 0.86068467

 $00{:}40{:}16.880 \dashrightarrow 00{:}40{:}19.400$ we've also treated a few patients

NOTE Confidence: 0.86068467

 $00{:}40{:}19{.}400 \dashrightarrow 00{:}40{:}22{.}512$ here and I want to mention this

NOTE Confidence: 0.86068467

 $00:40:22.512 \rightarrow 00:40:25.188$ work that's been ongoing by Noam

NOTE Confidence: 0.86068467

 $00{:}40{:}25.188 \dashrightarrow 00{:}40{:}27.964$ and Anna for treating patients

NOTE Confidence: 0.86068467

 $00{:}40{:}27{.}964 \dashrightarrow 00{:}40{:}30{.}288$ here who've developed checkpoint

NOTE Confidence: 0.86068467

 $00{:}40{:}30{.}288 \dashrightarrow 00{:}40{:}32{.}759$ induced diabetes with infliximab.

NOTE Confidence: 0.86068467

 $00:40:32.760 \longrightarrow 00:40:36.120$ Let me show you 2 cases.

NOTE Confidence: 0.86068467

 $00{:}40{:}36{.}120 \dashrightarrow 00{:}40{:}39{.}179$ This patient had a history of type

NOTE Confidence: 0.86068467

 $00:40:39.179 \longrightarrow 00:40:41.572$ 2 diabetes like the previous one

NOTE Confidence: 0.86068467

 $00{:}40{:}41{.}572 \dashrightarrow 00{:}40{:}44{.}771$ that I showed you and presented with

NOTE Confidence: 0.86068467

 $00:40:44.771 \longrightarrow 00:40:49.360$ very very high glucoses and the the

 $00:40:49.360 \longrightarrow 00:40:52.430$ hemoglobin A1C in the past had been

NOTE Confidence: 0.86068467

 $00:40:52.430 \rightarrow 00:40:54.433$ a fairly reasonable and the patient

NOTE Confidence: 0.86068467

 $00{:}40{:}54{.}433 \dashrightarrow 00{:}40{:}56{.}755$ had not been treated with insulin.

NOTE Confidence: 0.86068467

 $00{:}40{:}56.760 \dashrightarrow 00{:}40{:}59.476$ There was a bump in the amylase

NOTE Confidence: 0.86068467

 $00:40:59.476 \longrightarrow 00:41:01.484$ and light paves just as I showed

NOTE Confidence: 0.86068467

 $00:41:01.484 \rightarrow 00:41:03.560$ you in in one of the first slides.

NOTE Confidence: 0.86068467

 $00:41:03.560 \rightarrow 00:41:05.708$ And then the glucose became markedly

NOTE Confidence: 0.86068467

 $00:41:05.708 \longrightarrow 00:41:08.282$ elevated and as you can see the

NOTE Confidence: 0.86068467

 $00{:}41{:}08.282 \dashrightarrow 00{:}41{:}10.592$ patient received 3 doses of infliximab.

NOTE Confidence: 0.86068467

00:41:10.592 --> 00:41:13.888 And if you take a look at the response

NOTE Confidence: 0.86068467

 $00{:}41{:}13.888 \dashrightarrow 00{:}41{:}16.192$ curves and in terms of the C peptide,

NOTE Confidence: 0.86068467

 $00{:}41{:}16{.}200 \dashrightarrow 00{:}41{:}17{.}904$ it actually did seem to these

NOTE Confidence: 0.86068467

00:41:17.904 --> 00:41:19.040 are random C peptides.

NOTE Confidence: 0.86068467

00:41:19.040 --> 00:41:20.986 I should point out the C peptide

NOTE Confidence: 0.86068467

 $00{:}41{:}20.986 \dashrightarrow 00{:}41{:}23.039$ did seem to improve after the

 $00:41:23.039 \rightarrow 00:41:24.964$ patient was treated with infliximab

NOTE Confidence: 0.86068467

 $00{:}41{:}24{.}964 \dashrightarrow 00{:}41{:}27{.}319$ and the glucose was also better.

NOTE Confidence: 0.86068467

 $00:41:27.320 \longrightarrow 00:41:30.518$ Now these are, these are anecdotal,

NOTE Confidence: 0.86068467

 $00{:}41{:}30{.}520 \dashrightarrow 00{:}41{:}33{.}754$ these are not performed in a rigorous

NOTE Confidence: 0.86068467

 $00{:}41{:}33.760 \dashrightarrow 00{:}41{:}35.935$ endocrine setting where we're actually

NOTE Confidence: 0.86068467

 $00{:}41{:}35{.}935 \dashrightarrow 00{:}41{:}37.675$ stimulating beta cell function.

NOTE Confidence: 0.86068467

 $00{:}41{:}37.680 \dashrightarrow 00{:}41{:}39.276$ But nonetheless and I think from

NOTE Confidence: 0.86068467

 $00:41:39.276 \longrightarrow 00:41:40.640$ the patient's point of view,

NOTE Confidence: 0.86068467

00:41:40.640 --> 00:41:42.808 the fact that he was able to get

NOTE Confidence: 0.86068467

 $00{:}41{:}42.808 \dashrightarrow 00{:}41{:}44.896$ off of insulin and his hemoglobin

NOTE Confidence: 0.86068467

00:41:44.896 --> 00:41:47.372 A1 CS were subsequently improved

NOTE Confidence: 0.86068467

 $00:41:47.372 \longrightarrow 00:41:50.116$ is is clinically meaningful.

NOTE Confidence: 0.86068467

 $00{:}41{:}50{.}120 \dashrightarrow 00{:}41{:}52{.}136$ Here's another case.

NOTE Confidence: 0.86068467

 $00{:}41{:}52{.}136 \dashrightarrow 00{:}41{:}54{.}572$ This individual with metastatic

NOTE Confidence: 0.86068467

 $00{:}41{:}54{.}572 \dashrightarrow 00{:}41{:}57{.}302$ Melanoma was treated with EPI

NOTE Confidence: 0.86068467

 $00{:}41{:}57{.}302 \dashrightarrow 00{:}42{:}00{.}404$ and Nevo and had adverse events

 $00:42:00.404 \rightarrow 00:42:02.909$ including uveitis and diarrhea that

NOTE Confidence: 0.86068467

 $00{:}42{:}02{.}909 \dashrightarrow 00{:}42{:}06{.}142$ have been treated with steroids and

NOTE Confidence: 0.86068467

 $00:42:06.142 \longrightarrow 00:42:09.634$ hyperglycemia was noted at cycle 21.

NOTE Confidence: 0.86068467

 $00:42:09.640 \longrightarrow 00:42:11.884$ There was no prior history of

NOTE Confidence: 0.86068467

 $00{:}42{:}11{.}884$ --> $00{:}42{:}14{.}272$ diabetes in this patient and previous

NOTE Confidence: 0.86068467

00:42:14.272 --> 00:42:16.714 hemoglobin A1 CS have been normal.

NOTE Confidence: 0.86068467

 $00{:}42{:}16.720 \dashrightarrow 00{:}42{:}19.200$ This patient again presented with

NOTE Confidence: 0.86068467

 $00:42:19.200 \longrightarrow 00:42:21.858$ a very elevated hemoglobin A1C and

NOTE Confidence: 0.86068467

 $00{:}42{:}21.858 \dashrightarrow 00{:}42{:}24.920$ the glucose was also quite elevated.

NOTE Confidence: 0.86068467

 $00{:}42{:}24{.}920 \dashrightarrow 00{:}42{:}27{.}164$ This patient did not have evidence

NOTE Confidence: 0.86068467

 $00{:}42{:}27.164 \dashrightarrow 00{:}42{:}29.061$ of ketoacidosis whereas the previous

NOTE Confidence: 0.86068467

 $00{:}42{:}29.061 \dashrightarrow 00{:}42{:}31.077$ patient that I showed you did.

NOTE Confidence: 0.86068467

00:42:31.080 --> 00:42:34.200 And remember that ketoacidosis is a

NOTE Confidence: 0.86068467

 $00{:}42{:}34{.}200 \dashrightarrow 00{:}42{:}37{.}359$ sign of of substantial insulin deficiency.

NOTE Confidence: 0.86068467

 $00{:}42{:}37{.}359 \dashrightarrow 00{:}42{:}40{.}557$ This patient was auto antibody negative.

 $00:42:40.560 \longrightarrow 00:42:43.200$ So here we're looking at the

NOTE Confidence: 0.86068467

00:42:43.200 --> 00:42:44.692 random C peptide levels,

NOTE Confidence: 0.86068467

 $00:42:44.692 \longrightarrow 00:42:46.557$ one of them is stimulated,

NOTE Confidence: 0.86068467

 $00:42:46.560 \longrightarrow 00:42:48.952$ the last one that was just done a

NOTE Confidence: 0.86068467

 $00:42:48.952 \rightarrow 00:42:51.293$ few days ago and the glucose levels

NOTE Confidence: 0.86068467

 $00{:}42{:}51{.}293 \dashrightarrow 00{:}42{:}54{.}269$ and you can see that the glucose did

NOTE Confidence: 0.86068467

 $00{:}42{:}54{.}269 \dashrightarrow 00{:}42{:}56{.}375$ improve probably with the medical care

NOTE Confidence: 0.86068467

 $00{:}42{:}56{.}375 \dashrightarrow 00{:}42{:}58{.}796$ of the patient received but the C

NOTE Confidence: 0.86068467

 $00:42:58.796 \rightarrow 00:43:01.113$ peptide also seemed to be pretty substantial.

NOTE Confidence: 0.86068467

 $00{:}43{:}01{.}120 \dashrightarrow 00{:}43{:}03{.}178$ This is markedly different than what

NOTE Confidence: 0.86068467

 $00:43:03.178 \longrightarrow 00:43:05.966$ I showed you in in in one of the

NOTE Confidence: 0.86068467

 $00{:}43{:}05{.}966 \dashrightarrow 00{:}43{:}07{.}815$ first slides where the C peptides

NOTE Confidence: 0.86068467

 $00{:}43{:}07{.}815 \dashrightarrow 00{:}43{:}10{.}472$ pretty much go to undetectable in

NOTE Confidence: 0.86068467

 $00{:}43{:}10.472 \dashrightarrow 00{:}43{:}13.544$ in the majority of patients who

NOTE Confidence: 0.86068467

 $00{:}43{:}13{.}544 \dashrightarrow 00{:}43{:}15{.}700$ present with checkpoint induced

NOTE Confidence: 0.86068467

00:43:15.700 --> 00:43:18.874 diabetes and do so fairly rapidly.

- NOTE Confidence: 0.86068467
- $00{:}43{:}18.880 \dashrightarrow 00{:}43{:}21.260$ So to conclude adverse events are not

 $00{:}43{:}21.260 \dashrightarrow 00{:}43{:}22.920$ infrequent with checkpoint inhibitors.

NOTE Confidence: 0.86068467

 $00:43:22.920 \longrightarrow 00:43:25.173$ In fact I would change that to

NOTE Confidence: 0.86068467

 $00{:}43{:}25{.}173 \dashrightarrow 00{:}43{:}27{.}038$ say adverse events are common

NOTE Confidence: 0.86068467

 $00:43:27.038 \longrightarrow 00:43:28.157$ with checkpoint inhibitors.

NOTE Confidence: 0.86068467

 $00:43:28.160 \longrightarrow 00:43:30.525$ Most common is thyroid disease

NOTE Confidence: 0.86068467

00:43:30.525 --> 00:43:32.417 and hypothesitis but diabetes

NOTE Confidence: 0.86068467

00:43:32.417 --> 00:43:34.277 also occurs in about 1%

NOTE Confidence: 0.67271843625

 $00{:}43{:}34{.}280 \dashrightarrow 00{:}43{:}37{.}005$ of checkpoint induce a checkpoint

NOTE Confidence: 0.67271843625

 $00:43:37.005 \longrightarrow 00:43:38.640$ inhibitor treated patients.

NOTE Confidence: 0.67271843625

00:43:38.640 --> 00:43:41.800 Now one thing I should mention is for

NOTE Confidence: 0.67271843625

 $00{:}43{:}41{.}800 \dashrightarrow 00{:}43{:}44{.}516$ patients and you know we see them.

NOTE Confidence: 0.67271843625

 $00:43:44.520 \longrightarrow 00:43:47.005$ Thanks to all of you in our clinic.

NOTE Confidence: 0.67271843625

 $00{:}43{:}47.005 \dashrightarrow 00{:}43{:}48.480$ But for the patients this

NOTE Confidence: 0.67271843625

 $00:43:48.480 \longrightarrow 00:43:50.319$ is a difficult disease.

00:43:50.320 --> 00:43:52.206 I mean you know it's it, it,

NOTE Confidence: 0.67271843625

 $00{:}43{:}52.206 \dashrightarrow 00{:}43{:}54.760$ it's a lot different when a

NOTE Confidence: 0.67271843625

 $00{:}43{:}54{.}760 \dashrightarrow 00{:}43{:}56{.}360$ 12 year old presents with.

NOTE Confidence: 0.67271843625

 $00{:}43{:}56{.}360 \dashrightarrow 00{:}43{:}57{.}535$ It's not that the disease

NOTE Confidence: 0.67271843625

 $00:43:57.535 \longrightarrow 00:43:59.279$ is easy for a 12 year old,

NOTE Confidence: 0.67271843625

00:43:59.280 --> 00:44:00.885 but it's even more cumbersome

NOTE Confidence: 0.67271843625

 $00:44:00.885 \longrightarrow 00:44:04.240$ for a 65 or 75 year old who now

NOTE Confidence: 0.67271843625

00:44:04.240 --> 00:44:05.916 has become insulin deficient,

NOTE Confidence: 0.67271843625

 $00:44:05.920 \rightarrow 00:44:09.160$ completely dependent on exogenous insulin

NOTE Confidence: 0.67271843625

 $00:44:09.160 \rightarrow 00:44:11.752$ for maintaining metabolic control.

NOTE Confidence: 0.67271843625

 $00{:}44{:}11.760 \dashrightarrow 00{:}44{:}15.120$ So it is quite a burden for patients.

NOTE Confidence: 0.67271843625

 $00:44:15.120 \rightarrow 00:44:18.102$ So preventing the disease would obviously

NOTE Confidence: 0.67271843625

 $00{:}44{:}18{.}102 \dashrightarrow 00{:}44{:}20{.}640$ be would result in very significant

NOTE Confidence: 0.67271843625

 $00{:}44{:}20.640 \dashrightarrow 00{:}44{:}22.680$ improvements in quality of life.

NOTE Confidence: 0.67271843625

 $00{:}44{:}22.680 \dashrightarrow 00{:}44{:}24.840$ It's most common in patients treated

NOTE Confidence: 0.67271843625

 $00{:}44{:}24{.}840 \dashrightarrow 00{:}44{:}27{.}654$ with anti PD one or anti PDL 1

 $00:44:27.654 \rightarrow 00:44:29.900$ antibodies and in patients or HLAD R4.

NOTE Confidence: 0.67271843625

 $00:44:29.900 \longrightarrow 00:44:33.318$ Still a lot of work needs to go on to

NOTE Confidence: 0.67271843625

 $00{:}44{:}33{.}318$ --> $00{:}44{:}35{.}880$ understand what is the significance of

NOTE Confidence: 0.67271843625

 $00:44:35.880 \rightarrow 00:44:40.200$ DL DDR4 or the significance of NLRC 5.

NOTE Confidence: 0.67271843625

 $00:44:40.200 \rightarrow 00:44:42.624$ But it nonetheless suggests that there

NOTE Confidence: 0.67271843625

 $00:44:42.624 \rightarrow 00:44:45.606$ is some some change or some difference

NOTE Confidence: 0.67271843625

 $00:44:45.606 \rightarrow 00:44:48.198$ in these patients in presentation of

NOTE Confidence: 0.67271843625

 $00{:}44{:}48.198 \dashrightarrow 00{:}44{:}50.716$ either class one or Class 2 or both.

NOTE Confidence: 0.67271843625

 $00{:}44{:}50{.}720$ --> $00{:}44{:}53{.}240$ MHC presented antigens,

NOTE Confidence: 0.67271843625

 $00:44:53.240 \longrightarrow 00:44:56.600$ pancreatic inflammation is is

NOTE Confidence: 0.67271843625

 $00{:}44{:}56.600 \dashrightarrow 00{:}44{:}59.340$ frequent prior to the development

NOTE Confidence: 0.67271843625

 $00{:}44{:}59{.}340 \dashrightarrow 00{:}45{:}01{.}240$ of checkpoint induced diabetes.

NOTE Confidence: 0.67271843625

 $00:45:01.240 \rightarrow 00:45:04.040$ Curiously, PDL one's expressed on beta cells.

NOTE Confidence: 0.67271843625

 $00{:}45{:}04{.}040 \dashrightarrow 00{:}45{:}06{.}238$ And I think we have to conclude

NOTE Confidence: 0.67271843625

 $00{:}45{:}06{.}238 \dashrightarrow 00{:}45{:}08{.}256$ that in spite of expressing PDL

 $00:45:08.256 \longrightarrow 00:45:11.132$ One on beta cells and in spite of

NOTE Confidence: 0.67271843625

 $00{:}45{:}11{.}132 \dashrightarrow 00{:}45{:}12{.}972$ showing its extraordinary protective

NOTE Confidence: 0.67271843625

 $00{:}45{:}12.972 \dashrightarrow 00{:}45{:}15.874$ effect in animal models of disease

NOTE Confidence: 0.67271843625

 $00:45:15.874 \rightarrow 00:45:19.438$ that when you give a checkpoint,

NOTE Confidence: 0.67271843625

 $00{:}45{:}19{.}440 \dashrightarrow 00{:}45{:}21{.}320$ when the checkpoint inhibitor

NOTE Confidence: 0.67271843625

 $00:45:21.320 \longrightarrow 00:45:23.200$ is given that protective,

NOTE Confidence: 0.67271843625

 $00:45:23.200 \rightarrow 00:45:26.280$ that protective blockade is gone.

NOTE Confidence: 0.67271843625

 $00{:}45{:}26.280 \dashrightarrow 00{:}45{:}30.232$ And even afterwards PDL one

NOTE Confidence: 0.67271843625

 $00{:}45{:}30{.}232 \dashrightarrow 00{:}45{:}33{.}040$ expression is no longer able to

NOTE Confidence: 0.67271843625

 $00{:}45{:}33.040 \dashrightarrow 00{:}45{:}35.240$ stop the development of diabetes.

NOTE Confidence: 0.67271843625

 $00{:}45{:}35{.}240 \dashrightarrow 00{:}45{:}37{.}712$ And I think the identification of

NOTE Confidence: 0.67271843625

 $00{:}45{:}37{.}712 \dashrightarrow 00{:}45{:}39{.}884$ mechanism suggest have suggested a

NOTE Confidence: 0.67271843625

 $00:45:39.884 \rightarrow 00:45:41.760$ the rapeutic strategy inhibition of

NOTE Confidence: 0.67271843625

 $00:45:41.760 \rightarrow 00:45:43.680$ inflammatory mediators may potentially

NOTE Confidence: 0.67271843625

 $00:45:43.680 \longrightarrow 00:45:46.023$ halt progression of diabetes and

NOTE Confidence: 0.67271843625

 $00:45:46.023 \longrightarrow 00:45:47.803$ beta cell loss with checkpoint

 $00{:}45{:}47.803 \dashrightarrow 00{:}45{:}51.010$ induced diabetes and a short acting

NOTE Confidence: 0.67271843625

 $00:45:51.010 \longrightarrow 00:45:53.290$ inhibitor potentially Jack inhibitors

NOTE Confidence: 0.67271843625

 $00:45:53.290 \rightarrow 00:45:56.277$ would warrant some further testing.

NOTE Confidence: 0.67271843625

 $00:45:56.280 \rightarrow 00:45:58.200$ One last one last comment,

NOTE Confidence: 0.67271843625

 $00:45:58.200 \longrightarrow 00:45:59.992$ let me mention that you know I

NOTE Confidence: 0.67271843625

 $00{:}45{:}59{.}992 \dashrightarrow 00{:}46{:}01{.}996$ think one of the interesting things

NOTE Confidence: 0.67271843625

 $00{:}46{:}01{.}996 \dashrightarrow 00{:}46{:}04{.}348$ about all of the adverse checkpoint

NOTE Confidence: 0.67271843625

 $00:46:04.348 \longrightarrow 00:46:05.879$ induced adverse events is,

NOTE Confidence: 0.67271843625

 $00:46:05.880 \rightarrow 00:46:08.400$ is it a feature of the checkpoint inhibitor,

NOTE Confidence: 0.67271843625

 $00{:}46{:}08{.}400 \dashrightarrow 00{:}46{:}10{.}656$ a feature of the tissue or a feature

NOTE Confidence: 0.67271843625

 $00{:}46{:}10.656 \dashrightarrow 00{:}46{:}13.320$ of the patients or all three of these.

NOTE Confidence: 0.67271843625

 $00{:}46{:}13.320 \dashrightarrow 00{:}46{:}15.920$ And let me just point out this work

NOTE Confidence: 0.67271843625

00:46:15.920 $\operatorname{-->}$ 00:46:18.936 from Jackie Mann in our group who

NOTE Confidence: 0.67271843625

00:46:18.936 --> 00:46:21.456 looked at checkpoint inhibitor induced

NOTE Confidence: 0.67271843625

 $00{:}46{:}21{.}456 \dashrightarrow 00{:}46{:}25{.}000$ colitis and she did this by single cell RNAC.

 $00{:}46{:}25.000 \dashrightarrow 00{:}46{:}27.838$ This work was published fairly recently,

NOTE Confidence: 0.67271843625

 $00{:}46{:}27.840 \dashrightarrow 00{:}46{:}30.441$ but let me point out that a number of

NOTE Confidence: 0.67271843625

00:46:30.441 --> 00:46:32.970 the molecules that I just told you

NOTE Confidence: 0.67271843625

 $00{:}46{:}32{.}970$ --> $00{:}46{:}35{.}780$ about being found in the pancreas of

NOTE Confidence: 0.67271843625

 $00{:}46{:}35{.}780 \dashrightarrow 00{:}46{:}37{.}935$ checkpoint induced diabetes can also

NOTE Confidence: 0.67271843625

 $00{:}46{:}37{.}935 \dashrightarrow 00{:}46{:}41{.}040$ be found in patients who develop colitis,

NOTE Confidence: 0.67271843625

00:46:41.040 --> 00:46:44.134 suggesting that we might even think about

NOTE Confidence: 0.67271843625

 $00:46:44.134 \rightarrow 00:46:47.560$ a broader use of of various inhibitors,

NOTE Confidence: 0.67271843625

 $00{:}46{:}47{.}560 \dashrightarrow 00{:}46{:}48{.}530$ not inhibitors.

NOTE Confidence: 0.67271843625

 $00{:}46{:}48{.}530 \dashrightarrow 00{:}46{:}51{.}460$ Obviously that would prevent the anti

NOTE Confidence: 0.67271843625

 $00:46:51.460 \rightarrow 00:46:54.375$ tumor effect of the checkpoint inhibitors,

NOTE Confidence: 0.67271843625

00:46:54.375 -> 00:46:56.450 but might be given sequentially

NOTE Confidence: 0.67271843625

 $00{:}46{:}56{.}450 \dashrightarrow 00{:}46{:}59{.}583$ after the anti tumor effects of the

NOTE Confidence: 0.67271843625

 $00{:}46{:}59{.}583 \dashrightarrow 00{:}47{:}02{.}659$ checkpoint inhibitors and that might

NOTE Confidence: 0.67271843625

 $00:47:02.659 \rightarrow 00:47:06.612$ be rapidly tapered in the event that

NOTE Confidence: 0.67271843625

 $00{:}47{:}06.612 \dashrightarrow 00{:}47{:}08.877$ further cancer the rapy is needed.
- NOTE Confidence: 0.914448272857143
- $00:47:08.880 \longrightarrow 00:47:10.280$ So I'm going to close with that.
- NOTE Confidence: 0.914448272857143
- 00:47:10.280 --> 00:47:13.120 I want to thank a number of individuals,
- NOTE Confidence: 0.914448272857143
- 00:47:13.120 --> 00:47:15.544 particularly Harriet, who's been,
- NOTE Confidence: 0.914448272857143
- $00:47:15.544 \rightarrow 00:47:19.436$ you know, a colleague for a decade now,
- NOTE Confidence: 0.914448272857143
- $00{:}47{:}19{.}440 \dashrightarrow 00{:}47{:}21{.}624$ and a number of individuals in
- NOTE Confidence: 0.914448272857143
- $00:47:21.624 \longrightarrow 00:47:23.650$ her group who've I've had the
- NOTE Confidence: 0.914448272857143
- $00:47:23.650 \longrightarrow 00:47:25.200$ good fortune of working with.
- NOTE Confidence: 0.914448272857143
- $00{:}47{:}25.200 \dashrightarrow 00{:}47{:}27.960$ As well, I want to mention
- NOTE Confidence: 0.3145552
- $00:47:30.440 \longrightarrow 00:47:33.419$ Lalak's work on identifying
- NOTE Confidence: 0.3145552
- $00{:}47{:}33{.}419 \dashrightarrow 00{:}47{:}35{.}370$ the LLRC 5 mutations.
- NOTE Confidence: 0.3145552
- 00:47:35.370 --> 00:47:37.400 I showed you some of Jackie's work.
- NOTE Confidence: 0.3145552
- 00:47:37.400 --> 00:47:40.916 Nolan is continuing this work with
- NOTE Confidence: 0.3145552
- 00:47:40.916 --> 00:47:43.614 particularly with giving with the
- NOTE Confidence: 0.3145552
- $00{:}47{:}43.614 \dashrightarrow 00{:}47{:}45.949$ NLRC 5 mutations and the rapies
- NOTE Confidence: 0.3145552
- $00:47:45.949 \longrightarrow 00:47:48.120$ of checkpoint induced diabetes.
- NOTE Confidence: 0.3145552

- $00:47:48.120 \longrightarrow 00:47:49.560$ Anna Perdigata did a lot of,
- NOTE Confidence: 0.3145552
- $00:47:49.560 \longrightarrow 00:47:51.678$ did actually all of the work,
- NOTE Confidence: 0.3145552
- $00{:}47{:}51{.}680 \dashrightarrow 00{:}47{:}54{.}000$ the single cell work with the mouse models
- NOTE Confidence: 0.3145552
- 00:47:54.000 00:47:56.394 and it's continuing to go on to do that.
- NOTE Confidence: 0.3145552
- $00{:}47{:}56{.}400 \dashrightarrow 00{:}48{:}00{.}042$ And we have colleagues at UCSF and funding
- NOTE Confidence: 0.3145552
- $00{:}48{:}00{.}042 \dashrightarrow 00{:}48{:}03{.}480$ you can see on the right side here.
- NOTE Confidence: 0.3145552
- $00{:}48{:}03{.}480 \dashrightarrow 00{:}48{:}04{.}950$ So I'll stop there and I'm
- NOTE Confidence: 0.3145552
- $00:48:04.950 \longrightarrow 00:48:06.520$ happy to answer any questions.
- NOTE Confidence: 0.840739008571428
- 00:48:13.720 --> 00:48:15.890 Thank you, Kevin for a
- NOTE Confidence: 0.840739008571428
- 00:48:15.890 00:48:17.240 wonderful presentation. Kurt,
- NOTE Confidence: 0.97329267
- $00:48:22.570 \longrightarrow 00:48:23.450$ thank you for an excellent
- NOTE Confidence: 0.929915654
- $00{:}48{:}23{.}450 \dashrightarrow 00{:}48{:}24{.}930$ talk. I wanted to ask,
- NOTE Confidence: 0.929915654
- 00:48:24.930 --> 00:48:26.484 so LRC 5 is a little bit
- NOTE Confidence: 0.625720556
- $00:48:26.690 \rightarrow 00:48:28.570$ kind of superficially counter intuitive
- NOTE Confidence: 0.625720556
- $00:48:28.570 \longrightarrow 00:48:29.530$ in terms of germline mutation.
- NOTE Confidence: 0.625720556
- $00:48:29.530 \longrightarrow 00:48:30.800$ I was wondering if there was a

- NOTE Confidence: 0.625720556
- $00:48:30.800 \longrightarrow 00:48:32.050$ role in central tolerance and

NOTE Confidence: 0.80699388

00:48:32.050 --> 00:48:33.980 if you saw increased checkpoint

NOTE Confidence: 0.80699388

 $00:48:33.980 \longrightarrow 00:48:35.570$ inhibitor autoimmunity in

NOTE Confidence: 0.80699388

 $00{:}48{:}35{.}570 \dashrightarrow 00{:}48{:}37{.}610$ hypothesitis or hypothyroidism.

NOTE Confidence: 0.771907615

 $00{:}48{:}41{.}280 \dashrightarrow 00{:}48{:}43{.}280$ I'm sorry I I missed the second part.

NOTE Confidence: 0.771907615

00:48:43.280 --> 00:48:45.464 I, I, I, I, I understood your

NOTE Confidence: 0.771907615

 $00{:}48{:}45{.}464 \dashrightarrow 00{:}48{:}46{.}752$ question about central tolerance

NOTE Confidence: 0.771907615

 $00:48:46.752 \longrightarrow 00:48:48.796$ but so and so whether you saw

NOTE Confidence: 0.771907615

 $00{:}48{:}48{.}800 \dashrightarrow 00{:}48{:}51{.}820$ rather than an LRC 5 mutations,

NOTE Confidence: 0.771907615

 $00:48:51.820 \longrightarrow 00:48:54.733$ germline ingest type one diabetes

NOTE Confidence: 0.771907615

 $00{:}48{:}54{.}733 \dashrightarrow 00{:}48{:}56{.}839$ or well check one inhibitor diabetes

NOTE Confidence: 0.6369411675

 $00{:}48{:}56{.}840 \dashrightarrow 00{:}48{:}57{.}840$ or whether also intra,

NOTE Confidence: 0.81279564125

00:48:59.840 --> 00:49:02.590 I think that's still somewhat

NOTE Confidence: 0.81279564125

 $00{:}49{:}02{.}590 \dashrightarrow 00{:}49{:}04{.}880$ of a ongoing question.

NOTE Confidence: 0.95789525

00:49:07.280 --> 00:49:10.800 I think it's unlikely Harriet may have a

NOTE Confidence: 0.95789525

 $00:49:10.800 \rightarrow 00:49:12.480$ thought as to whether it's more likely.

NOTE Confidence: 0.78725771777778

00:49:12.680 --> 00:49:15.155 Yeah, I can Norm can answer it as well.

NOTE Confidence: 0.78725771777778

 $00{:}49{:}15.160 \dashrightarrow 00{:}49{:}17.936$ So we have looked in at NLRC 5

NOTE Confidence: 0.78725771777778

 $00:49:17.936 \rightarrow 00:49:20.639$ SNPs in other other toxicity,

NOTE Confidence: 0.78725771777778

 $00:49:20.640 \longrightarrow 00:49:23.656$ it seems to be higher as well in

NOTE Confidence: 0.78725771777778

 $00{:}49{:}23.656 \dashrightarrow 00{:}49{:}25.096$ hypothesitis but not colitis.

NOTE Confidence: 0.78725771777778

 $00:49:25.096 \longrightarrow 00:49:27.960$ That's as far as we know so far.

NOTE Confidence: 0.78725771777778

 $00:49:27.960 \longrightarrow 00:49:29.626$ But the statistics are they're

NOTE Confidence: 0.78725771777778

 $00:49:29.626 \longrightarrow 00:49:30.756$ not this numbers are small.

NOTE Confidence: 0.78725771777778

 $00:49:30.760 \longrightarrow 00:49:31.924$ Still, that's exactly what

NOTE Confidence: 0.78725771777778

00:49:31.924 --> 00:49:33.280 Norm is working on right now.

NOTE Confidence: 0.83181655

00:49:46.160 --> 00:49:48.240 Yeah. I mean it could be

NOTE Confidence: 0.687196584545454

00:49:48.240 --> 00:49:51.271 the only. So I I I think

NOTE Confidence: 0.687196584545454

 $00:49:51.271 \longrightarrow 00:49:53.520$ that's an interesting question.

NOTE Confidence: 0.687196584545454

 $00:49:53.520 \longrightarrow 00:49:54.830$ But you're taking us back

NOTE Confidence: 0.687196584545454

 $00:49:54.830 \rightarrow 00:49:55.878$ to the original model.

NOTE Confidence: 0.687196584545454

 $00:49:55.880 \rightarrow 00:50:00.200$ These patients had a repertoire ready to go.

NOTE Confidence: 0.687196584545454

 $00:50:00.200 \longrightarrow 00:50:01.880$ And look, it could be right.

NOTE Confidence: 0.687196584545454

 $00:50:01.880 \longrightarrow 00:50:03.662$ I mean just because we don't

NOTE Confidence: 0.687196584545454

 $00:50:03.662 \rightarrow 00:50:05.298$ see the usual suspects doesn't

NOTE Confidence: 0.687196584545454

 $00:50:05.298 \rightarrow 00:50:07.238$ mean that there aren't suspects.

NOTE Confidence: 0.687196584545454

 $00:50:07.240 \dashrightarrow 00:50:08.680$ Kevin, that was an amazing lecture.

NOTE Confidence: 0.687196584545454

 $00:50:08.680 \longrightarrow 00:50:11.070$ It it reminds me of 2015 or earlier when

NOTE Confidence: 0.687196584545454

 $00:50:11.070 \rightarrow 00:50:12.855$ we first started using these agents

NOTE Confidence: 0.687196584545454

 $00:50:12.855 \rightarrow 00:50:14.760$ and we're seeing wonderful responses.

NOTE Confidence: 0.687196584545454

00:50:14.760 --> 00:50:16.080 And you know patients with lung

NOTE Confidence: 0.687196584545454

 $00:50:16.080 \longrightarrow 00:50:17.400$ cancers and others would have these

NOTE Confidence: 0.687196584545454

 $00{:}50{:}17{.}400 \dashrightarrow 00{:}50{:}19{.}110$ problems and you know they'd be

NOTE Confidence: 0.687196584545454

 $00{:}50{:}19{.}110 \dashrightarrow 00{:}50{:}20{.}370$ on the throughout the hospital and

NOTE Confidence: 0.687196584545454

 $00{:}50{:}20{.}370 \dashrightarrow 00{:}50{:}21{.}779$ they wouldn't get the care they

NOTE Confidence: 0.687196584545454

 $00{:}50{:}21.779 \dashrightarrow 00{:}50{:}22.929$ needed because no one recognized

NOTE Confidence: 0.687196584545454

 $00:50:22.972 \rightarrow 00:50:24.062$ that these toxicities were were

NOTE Confidence: 0.687196584545454

 $00:50:24.062 \rightarrow 00:50:25.720$ part of this even though they were

NOTE Confidence: 0.687196584545454

 $00:50:25.720 \rightarrow 00:50:27.120$ benefiting from the therapy.

NOTE Confidence: 0.687196584545454

 $00:50:27.120 \rightarrow 00:50:29.120$ I have a two-part question for you and

NOTE Confidence: 0.687196584545454

00:50:29.120 --> 00:50:30.700 you you now know who's at most risk,

NOTE Confidence: 0.687196584545454

 $00{:}50{:}30{.}700 \dashrightarrow 00{:}50{:}32{.}760$ you have the NLR, other other risk factors.

NOTE Confidence: 0.687196584545454

 $00:50:32.760 \longrightarrow 00:50:35.920$ So my first question would be 1,

NOTE Confidence: 0.687196584545454

 $00:50:35.920 \longrightarrow 00:50:37.780$ would you treat prophylactically or

NOTE Confidence: 0.687196584545454

 $00:50:37.780 \longrightarrow 00:50:40.372$ or would you wait until they develop

NOTE Confidence: 0.687196584545454

 $00:50:40.372 \longrightarrow 00:50:42.800$ the toxicity to to start treating

NOTE Confidence: 0.687196584545454

 $00{:}50{:}42.800 \dashrightarrow 00{:}50{:}44.312$ And then the second would be you see

NOTE Confidence: 0.687196584545454

 $00{:}50{:}44{.}312 \dashrightarrow 00{:}50{:}46{.}370$ that the activity against the cancer

NOTE Confidence: 0.687196584545454

 $00:50:46.370 \longrightarrow 00:50:47.960$ is is increased in the patients

NOTE Confidence: 0.687196584545454

 $00{:}50{:}47.960 \dashrightarrow 00{:}50{:}49.559$ that have these abnormalities.

NOTE Confidence: 0.687196584545454

 $00:50:49.560 \longrightarrow 00:50:50.848$ Yeah that's a let.

NOTE Confidence: 0.687196584545454

 $00{:}50{:}50{.}848 \dashrightarrow 00{:}50{:}52{.}780$ Let me address the second question

- NOTE Confidence: 0.687196584545454
- $00:50:52.843 \rightarrow 00:50:55.177$ first because there is some literature
- NOTE Confidence: 0.687196584545454
- $00{:}50{:}55{.}177 \dashrightarrow 00{:}50{:}57{.}135$ suggesting that those who develop
- NOTE Confidence: 0.687196584545454
- $00{:}50{:}57{.}135 \dashrightarrow 00{:}50{:}59{.}175$ these adverse events do better in
- NOTE Confidence: 0.687196584545454
- $00{:}50{:}59{.}175 \dashrightarrow 00{:}51{:}01.672$ terms of their anti cancer activity and
- NOTE Confidence: 0.687196584545454
- $00:51:01.672 \rightarrow 00:51:04.480$ indeed our patients did well in general,
- NOTE Confidence: 0.687196584545454
- $00{:}51{:}04{.}480 \dashrightarrow 00{:}51{:}06{.}916$ but there is a publication for sure
- NOTE Confidence: 0.687196584545454
- $00:51:06.916 \rightarrow 00:51:08.924$ suggesting that those who develop
- NOTE Confidence: 0.687196584545454
- $00:51:08.924 \rightarrow 00:51:10.716$ hypothesitis had better outcomes
- NOTE Confidence: 0.687196584545454
- $00:51:10.720 \longrightarrow 00:51:13.280$ in patients with Melanoma.
- NOTE Confidence: 0.687196584545454
- 00:51:13.280 --> 00:51:13.920 So,
- NOTE Confidence: 0.687196584545454
- $00:51:13.920 \dashrightarrow 00:51:17.288$ so I'm not certain but I think it's
- NOTE Confidence: 0.687196584545454
- 00:51:17.288 --> 00:51:19.600 certainly not a negative thing
- NOTE Confidence: 0.687196584545454
- $00{:}51{:}19.600 \dashrightarrow 00{:}51{:}22.276$ in terms of the cancer response
- NOTE Confidence: 0.687196584545454
- $00:51:22.280 \longrightarrow 00:51:23.360$ and it may look it may,
- NOTE Confidence: 0.687196584545454
- 00:51:23.360 --> 00:51:25.754 I mean just because you don't develop
- NOTE Confidence: 0.687196584545454

 $00:51:25.760 \rightarrow 00:51:27.540$ toxicities doesn't mean you can't

NOTE Confidence: 0.687196584545454

 $00{:}51{:}27{.}540 \dashrightarrow 00{:}51{:}29{.}320$ do well with checkpoint inhibitors.

NOTE Confidence: 0.687196584545454

 $00{:}51{:}29{.}320 \dashrightarrow 00{:}51{:}31{.}800$ So in terms of when I would treat

NOTE Confidence: 0.687196584545454

 $00:51:31.800 \longrightarrow 00:51:34.383$ if I if if we knew how to

NOTE Confidence: 0.687196584545454

00:51:34.383 --> 00:51:36.878 treat type autoimmune diabetes,

NOTE Confidence: 0.687196584545454

 $00{:}51{:}36{.}880 \dashrightarrow 00{:}51{:}38{.}452$ if we knew what the antigens

NOTE Confidence: 0.687196584545454

 $00:51:38.452 \rightarrow 00:51:39.238$ were for example,

NOTE Confidence: 0.687196584545454

 $00:51:39.240 \longrightarrow 00:51:41.634$ we could we could dream about coming

NOTE Confidence: 0.687196584545454

 $00:51:41.634 \rightarrow 00:51:44.802$ up with some sort of antigen specific

NOTE Confidence: 0.687196584545454

 $00{:}51{:}44{.}802 \dashrightarrow 00{:}51{:}46{.}712$ prophylactic therapy and give that

NOTE Confidence: 0.687196584545454

 $00:51:46.712 \rightarrow 00:51:48.800$ before we give the checkpoint inhibitor.

NOTE Confidence: 0.687196584545454

 $00:51:48.800 \longrightarrow 00:51:49.706$ At this point,

NOTE Confidence: 0.687196584545454

 $00:51:49.706 \longrightarrow 00:51:51.518$ I don't think we have that.

NOTE Confidence: 0.687196584545454

 $00:51:51.520 \rightarrow 00:51:54.220$ And so my suggestion would be

NOTE Confidence: 0.687196584545454

 $00:51:54.220 \rightarrow 00:51:55.862$ to carefully follow patients,

NOTE Confidence: 0.687196584545454

 $00:51:55.862 \rightarrow 00:51:58.088$ look for the signs that identify

- NOTE Confidence: 0.687196584545454
- $00:51:58.088 \rightarrow 00:52:00.313$ those who are at risk of developing
- NOTE Confidence: 0.687196584545454
- $00{:}52{:}00{.}313 \dashrightarrow 00{:}52{:}02{.}549$ it and then when is appropriate in
- NOTE Confidence: 0.687196584545454
- $00{:}52{:}02{.}549 \dashrightarrow 00{:}52{:}04{.}830$ terms of the cancer therapy strategy,
- NOTE Confidence: 0.687196584545454
- $00:52:04.830 \longrightarrow 00:52:07.560$ if if it's possible come in with
- NOTE Confidence: 0.687196584545454
- $00{:}52{:}07{.}560 \dashrightarrow 00{:}52{:}09{.}880$ some short term inhibitor. Thanks.
- NOTE Confidence: 0.792301511666667
- 00:52:13.360 --> 00:52:15.440 Thanks, Kevin. Dr. Wagner.
- NOTE Confidence: 0.7923015116666667
- 00:52:15.440 --> 00:52:18.960 And then just just great talk,
- NOTE Confidence: 0.792301511666667
- $00:52:18.960 \rightarrow 00:52:21.080$ just a couple of simple questions.
- NOTE Confidence: 0.7923015116666667
- $00:52:21.080 \rightarrow 00:52:23.360$ Are there gender differences in toxicity?
- NOTE Confidence: 0.9163537
- $00:52:26.800 \rightarrow 00:52:27.360$ We
- NOTE Confidence: 0.929516157142857
- $00{:}52{:}29.600 \dashrightarrow 00{:}52{:}32.274$ not that we had seen in diabetes.
- NOTE Confidence: 0.929516157142857
- $00{:}52{:}32{.}280 \dashrightarrow 00{:}52{:}34{.}239$ Not significantly different.
- NOTE Confidence: 0.8302601148
- $00:52:35.160 \longrightarrow 00:52:35.958$ Harry looks puzzled.
- NOTE Confidence: 0.8302601148
- $00{:}52{:}35{.}958 \dashrightarrow 00{:}52{:}37{.}820$ Why I would ask that only because
- NOTE Confidence: 0.8302601148
- $00{:}52{:}37{.}873 \dashrightarrow 00{:}52{:}39{.}153$ autoimmune disease is so much
- NOTE Confidence: 0.8302601148

 $00:52:39.153 \rightarrow 00:52:40.733$ more common in is more common

NOTE Confidence: 0.8302601148

00:52:40.733 --> 00:52:42.240 in women than men. Yeah. We

NOTE Confidence: 0.6828273

 $00:52:44.760 \longrightarrow 00:52:46.640$ didn't find that we we'd

NOTE Confidence: 0.764676322222222

 $00{:}52{:}46{.}640 \dashrightarrow 00{:}52{:}47{.}936$ love. Yeah. The only the only

NOTE Confidence: 0.764676322222222

 $00{:}52{:}47{.}936 \dashrightarrow 00{:}52{:}49{.}599$ thing I could say is type one

NOTE Confidence: 0.764676322222222

 $00:52:49.599 \rightarrow 00:52:50.839$ diabetes is not really general.

NOTE Confidence: 0.49742869

 $00{:}52{:}50{.}840 \dashrightarrow 00{:}52{:}53{.}440$ No, I I realized that, but

NOTE Confidence: 0.598270838333333

 $00:52:53.440 \longrightarrow 00:52:57.120$ this isn't type 1 to obvious and

NOTE Confidence: 0.598270838333333

 $00:52:57.120 \longrightarrow 00:52:59.238$ and this is for either of you.

NOTE Confidence: 0.941466585714286

 $00:52:59.640 \longrightarrow 00:53:02.352$ I mean do you think that that clinicians

NOTE Confidence: 0.941466585714286

 $00:53:02.352 \rightarrow 00:53:06.960$ really have a sense of how abrupt the

NOTE Confidence: 0.941466585714286

 $00:53:06.960 \longrightarrow 00:53:10.000$ onset is of of diabetes in this

NOTE Confidence: 0.941466585714286

 $00:53:10.090 \rightarrow 00:53:12.880$ situation and are looking for it.

NOTE Confidence: 0.941466585714286

00:53:12.880 - 00:53:14.644 I mean because you know it's

NOTE Confidence: 0.941466585714286

00:53:14.644 --> 00:53:16.120 happening not at week two,

NOTE Confidence: 0.941466585714286

 $00:53:16.120 \rightarrow 00:53:19.158$ it's happening at week six or eight.

- NOTE Confidence: 0.941466585714286
- 00:53:19.160 00:53:22.240 The presentation is very acute.
- NOTE Confidence: 0.941466585714286
- 00:53:22.240 --> 00:53:23.700 I mean you know there are some
- NOTE Confidence: 0.941466585714286
- $00:53:23.700 \longrightarrow 00:53:25.344$ number of people out there as
- NOTE Confidence: 0.941466585714286
- $00{:}53{:}25{.}344 \dashrightarrow 00{:}53{:}26{.}904$ these the rapies are used more and
- NOTE Confidence: 0.941466585714286
- $00:53:26.904 \rightarrow 00:53:28.360$ more we're going to die from this.
- NOTE Confidence: 0.941466585714286
- $00:53:28.360 \longrightarrow 00:53:30.520$ So there have been deaths,
- NOTE Confidence: 0.941466585714286
- $00:53:30.520 \longrightarrow 00:53:32.785$ there will be deaths where
- NOTE Confidence: 0.941466585714286
- $00:53:32.785 \rightarrow 00:53:36.192$ there isn't sufficient there,
- NOTE Confidence: 0.941466585714286
- $00:53:36.192 \rightarrow 00:53:38.400$ there isn't sufficient insight.
- NOTE Confidence: 0.941466585714286
- 00:53:38.400 -> 00:53:40.206 The cup, the two patients that we
- NOTE Confidence: 0.941466585714286
- $00:53:40.206 \rightarrow 00:53:41.836$ haven't showed that we were able to
- NOTE Confidence: 0.941466585714286
- $00:53:41.836 \rightarrow 00:53:43.399$ give the TNF that was just chance.
- NOTE Confidence: 0.941466585714286
- $00{:}53{:}43{.}399 \dashrightarrow 00{:}53{:}45{.}170$ The first one was in hospital because
- NOTE Confidence: 0.941466585714286
- $00{:}53{:}45{.}226 \dashrightarrow 00{:}53{:}47{.}102$ of colitis or something else and that's
- NOTE Confidence: 0.941466585714286
- $00{:}53{:}47.102 \dashrightarrow 00{:}53{:}48.798$ when they noticed the ship going up.
- NOTE Confidence: 0.941466585714286

 $00:53:48.800 \longrightarrow 00:53:50.480$ The second one is an EMT and

NOTE Confidence: 0.941466585714286

 $00:53:50.480 \longrightarrow 00:53:52.028$ he he noted his only party,

NOTE Confidence: 0.941466585714286

 $00:53:52.028 \longrightarrow 00:53:53.363$ that's it called a million

NOTE Confidence: 0.941466585714286

 $00:53:53.363 \rightarrow 00:53:54.680$ started checking his glucose.

NOTE Confidence: 0.941466585714286

 $00{:}53{:}54{.}680 \dashrightarrow 00{:}53{:}56{.}558$ But there there's not sufficient awareness.

NOTE Confidence: 0.840468102666666

 $00{:}53{:}57{.}440 \dashrightarrow 00{:}53{:}58{.}934$ Yeah. The but the other sort

NOTE Confidence: 0.840468102666666

 $00:53:58.934 \longrightarrow 00:54:00.638$ of take home point from that is

NOTE Confidence: 0.840468102666666

 $00:54:00.638 \rightarrow 00:54:02.157$ you need to be aware of this

NOTE Confidence: 0.840468102666666

 $00{:}54{:}02{.}215 \dashrightarrow 00{:}54{:}04{.}217$ acutely because I showed you the C

NOTE Confidence: 0.840468102666666

 $00:54:04.217 \rightarrow 00:54:06.380$ peptide levels when it goes to 0,

NOTE Confidence: 0.840468102666666

 $00:54:06.380 \longrightarrow 00:54:07.680$ there's no turning back.

NOTE Confidence: 0.840468102666666

00:54:07.680 --> 00:54:10.515 So I think close surveillance was important.

NOTE Confidence: 0.82001626

 $00{:}54{:}13.400 \dashrightarrow 00{:}54{:}13.680$ Yeah.

NOTE Confidence: 0.893244745

00:54:15.480 --> 00:54:18.648 Well, I can tell you that I don't

NOTE Confidence: 0.893244745

 $00{:}54{:}18.648 \dashrightarrow 00{:}54{:}20.120$ educate patients, you know so, so look

NOTE Confidence: 0.716728292

 $00:54:23.200 \rightarrow 00:54:23.880$ for these kinds of things.

- NOTE Confidence: 0.716728292
- 00:54:23.880 --> 00:54:24.914 Can I just a quick, very,

NOTE Confidence: 0.716728292

00:54:24.914 --> 00:54:26.096 very interesting data,

NOTE Confidence: 0.716728292

00:54:26.096 --> 00:54:27.278 Two quick questions.

NOTE Confidence: 0.716728292

00:54:27.280 --> 00:54:30.640 One for the germline NLCR 5 mutations,

NOTE Confidence: 0.716728292

 $00:54:30.640 \longrightarrow 00:54:31.560$ you may have said this,

NOTE Confidence: 0.716728292

 $00{:}54{:}31{.}560 \dashrightarrow 00{:}54{:}34{.}825$ but are those associated with

NOTE Confidence: 0.716728292

 $00{:}54{:}34.825 \dashrightarrow 00{:}54{:}36.784$ standard classic autoimmune

NOTE Confidence: 0.716728292

 $00:54:36.784 \rightarrow 00:54:38.760$ diet type one diabetes as well?

NOTE Confidence: 0.716728292

 $00:54:38.760 \longrightarrow 00:54:40.359$ Yeah, there there's,

NOTE Confidence: 0.716728292

 $00{:}54{:}40{.}359 \dashrightarrow 00{:}54{:}44{.}090$ there's that one paper from Dejo Isrich

NOTE Confidence: 0.716728292

 $00:54:44.186 \rightarrow 00:54:48.238$ suggesting that the answer is no not really,

NOTE Confidence: 0.716728292

 $00{:}54{:}48{.}240 \dashrightarrow 00{:}54{:}50{.}436$ not one of the important players.

NOTE Confidence: 0.716728292

 $00{:}54{:}50{.}440 \dashrightarrow 00{:}54{:}52{.}491$ None the less though seems to be

NOTE Confidence: 0.716728292

 $00{:}54{:}52{.}491 \dashrightarrow 00{:}54{:}54{.}663$ important and it it can affect

NOTE Confidence: 0.716728292

 $00:54:54.663 \rightarrow 00:54:56.718$ antigenicity and development of diabetes.

NOTE Confidence: 0.716728292

 $00{:}54{:}56{.}720 \dashrightarrow 00{:}54{:}58{.}196$ And and did you go back so you made

NOTE Confidence: 0.716728292

00:54:58.196 - 00:54:59.836 a comment early that you know the,

NOTE Confidence: 0.716728292

 $00:54:59.840 \rightarrow 00:55:03.844$ the, the, the, the,

NOTE Confidence: 0.716728292

 $00:55:03.844 \rightarrow 00:55:07.076$ the 40% of the patients who have autoimmune,

NOTE Confidence: 0.716728292

 $00:55:07.080 \rightarrow 00:55:09.120$ who have auto antibodies to to,

NOTE Confidence: 0.716728292

 $00:55:09.120 \longrightarrow 00:55:10.760$ to, to the islet cells.

NOTE Confidence: 0.648686158571429

 $00:55:13.280 \longrightarrow 00:55:15.135$ There's only relatively it was

NOTE Confidence: 0.648686158571429

 $00:55:15.135 \longrightarrow 00:55:16.720$ only 40% as opposed to all of them.

NOTE Confidence: 0.648686158571429

 $00{:}55{:}16.720 \dashrightarrow 00{:}55{:}17.875$ And that was one of the reasons

NOTE Confidence: 0.648686158571429

00:55:17.875 - 00:55:18.760 why this looked like this,

NOTE Confidence: 0.648686158571429

 $00:55:18.760 \longrightarrow 00:55:21.560$ one of your conclusions why this was

NOTE Confidence: 0.648686158571429

 $00{:}55{:}21.560 \dashrightarrow 00{:}55{:}23.274$ different than standard, you know,

NOTE Confidence: 0.648686158571429

 $00:55:23.274 \rightarrow 00:55:25.330$ type one diabetes did when you went back

NOTE Confidence: 0.648686158571429

 $00:55:25.383 \rightarrow 00:55:27.357$ and you started looking at all these

NOTE Confidence: 0.648686158571429

 $00:55:27.357 \rightarrow 00:55:29.239$ mechanisms in your patient population,

NOTE Confidence: 0.648686158571429

 $00{:}55{:}29{.}240 \dashrightarrow 00{:}55{:}31{.}496$ did you, did you look at the difference

- NOTE Confidence: 0.648686158571429
- $00{:}55{:}31{.}496 \dashrightarrow 00{:}55{:}33{.}415$ in those patients who had auto
- NOTE Confidence: 0.648686158571429
- 00:55:33.415 --> 00:55:35.353 antibodies and those who did not,
- NOTE Confidence: 0.648686158571429
- $00:55:35.360 \dashrightarrow 00:55:39.200$ You know, yeah it's interesting point.
- NOTE Confidence: 0.648686158571429
- $00:55:39.200 \longrightarrow 00:55:42.185$ No, to my knowledge,
- NOTE Confidence: 0.648686158571429
- $00{:}55{:}42.185 \dashrightarrow 00{:}55{:}45.035$ I don't think we've done that.
- NOTE Confidence: 0.648686158571429
- $00:55:45.040 \dashrightarrow 00:55:47.360$ That's an interesting point way to kind of.
- NOTE Confidence: 0.648686158571429
- 00:55:47.360 --> 00:55:47.760 Yeah, yeah.
- NOTE Confidence: 0.648686158571429
- $00:55:47.760 \rightarrow 00:55:49.332$ Yeah, confirm this here,
- NOTE Confidence: 0.648686158571429
- $00:55:49.332 \longrightarrow 00:55:50.118$ this hypothesis.
- NOTE Confidence: 0.648686158571429
- $00:55:50.120 \rightarrow 00:55:50.266$ Yeah.
- NOTE Confidence: 0.648686158571429
- $00{:}55{:}50{.}266 \dashrightarrow 00{:}55{:}50{.}558$ So we
- NOTE Confidence: 0.896271925
- $00{:}55{:}51{.}840 \dashrightarrow 00{:}55{:}53{.}640$ have a couple of online questions.
- NOTE Confidence: 0.896271925
- $00:55:53.640 \rightarrow 00:55:55.340$ Oh, oh comments that would be
- NOTE Confidence: 0.896271925
- $00{:}55{:}55{.}340 \dashrightarrow 00{:}55{:}56{.}920$ easy for you to look at it there.
- NOTE Confidence: 0.862695698
- $00:55:56.920 \rightarrow 00:56:00.840$ OK. Anna has a comment.
- NOTE Confidence: 0.862695698

 $00:56:00.840 \rightarrow 00:56:03.030$ It'd be helpful to monitor blood NOTE Confidence: 0.862695698 $00{:}56{:}03.030 \dashrightarrow 00{:}56{:}05.020$ glucose more carefully in patients NOTE Confidence: 0.862695698 $00{:}56{:}05{.}020 \dashrightarrow 00{:}56{:}07{.}978$ who have lip ase elevation and in some NOTE Confidence: 0.862695698 $00:56:07.978 \rightarrow 00:56:10.208$ patients there's mild elevation in NOTE Confidence: 0.862695698 $00:56:10.208 \rightarrow 00:56:12.639$ glucose before severe presentation. NOTE Confidence: 0.862695698 $00:56:12.640 \longrightarrow 00:56:14.555$ So monitoring them more more NOTE Confidence: 0.862695698 $00:56:14.555 \rightarrow 00:56:17.000$ carefully may be valuable that that's, NOTE Confidence: 0.862695698 00:56:17.000 - 00:56:19.040 yeah, a very good point. NOTE Confidence: 0.862695698 $00{:}56{:}19{.}040 \dashrightarrow 00{:}56{:}21{.}170$ And then there's a question about NOTE Confidence: 0.862695698 $00:56:21.170 \rightarrow 00:56:22.855$ racial differences in in toxicity, NOTE Confidence: 0.862695698 $00{:}56{:}22.855 \dashrightarrow 00{:}56{:}24.480$ not that I know of NOTE Confidence: 0.910353418 00:56:28.560 --> 00:56:31.456 most. Yeah, I think we, I think that's right. NOTE Confidence: 0.910353418 00:56:31.456 --> 00:56:33.760 Most of our patients are Caucasian. NOTE Confidence: 0.6970684 00:56:36.440 --> 00:56:38.678 Yeah. Time for two. NOTE Confidence: 0.604493355 00:56:38.720 --> 00:56:39.960 Oh, what are we going to do here? NOTE Confidence: 0.604493355 00:56:39.960 --> 00:56:41.927 You see you should have sent your

- NOTE Confidence: 0.604493355
- $00:56:41.927 \rightarrow 00:56:44.788$ paper to the New England Journal to the
- NOTE Confidence: 0.604493355
- $00{:}56{:}44.788 \dashrightarrow 00{:}56{:}46.360$ clinical oncology inside the diabetes.
- NOTE Confidence: 0.7047284125
- 00:56:46.960 --> 00:56:47.640 That's right. That's right.
- NOTE Confidence: 0.840401586
- 00:56:53.040 00:56:54.622 That was an amazing talk. Thank you.
- NOTE Confidence: 0.840401586
- $00:56:54.622 \longrightarrow 00:56:56.799$ I had a question about the the,
- NOTE Confidence: 0.840401586
- $00:56:56.800 \longrightarrow 00:56:59.840$ the lipase elevation occurring before
- NOTE Confidence: 0.840401586
- $00:56:59.840 \longrightarrow 00:57:02.996$ the onset of diabetes as well.
- NOTE Confidence: 0.840401586
- $00:57:03.000 \longrightarrow 00:57:04.285$ You showed that it's it's
- NOTE Confidence: 0.840401586
- $00:57:04.285 \longrightarrow 00:57:05.313$ common that that occurs,
- NOTE Confidence: 0.840401586
- 00:57:05.320 --> 00:57:07.408 but did you look at patients
- NOTE Confidence: 0.840401586
- $00:57:07.408 \longrightarrow 00:57:09.288$ that have lipase elevations and
- NOTE Confidence: 0.840401586
- $00:57:09.288 \dashrightarrow 00:57:11.198$ how often they develop diabetes.
- NOTE Confidence: 0.840401586
- $00:57:11.200 \longrightarrow 00:57:12.512$ We don't routinely follow
- NOTE Confidence: 0.840401586
- $00{:}57{:}12{.}512$ --> $00{:}57{:}14{.}152$ amyloc
in lipase in patients but
- NOTE Confidence: 0.840401586
- $00{:}57{:}14.152 \dashrightarrow 00{:}57{:}15.436$ occasionally on clinical trials we
- NOTE Confidence: 0.840401586

 $00:57:15.436 \longrightarrow 00:57:17.120$ do we are required to look at it.

NOTE Confidence: 0.840401586

 $00:57:17.120 \longrightarrow 00:57:19.456$ And so that may be it would be

NOTE Confidence: 0.840401586

 $00{:}57{:}19{.}456 \dashrightarrow 00{:}57{:}21{.}072$ interesting to see is it common

NOTE Confidence: 0.840401586

00:57:21.072 --> 00:57:23.559 that it it is pre occurring or or

NOTE Confidence: 0.906680966

 $00:57:24.200 \longrightarrow 00:57:25.640$ that's a very good point.

NOTE Confidence: 0.906680966

00:57:25.640 --> 00:57:27.796 I I don't believe we've done the

NOTE Confidence: 0.906680966

00:57:27.796 --> 00:57:29.408 analysis that way unless area

NOTE Confidence: 0.906680966

 $00:57:29.408 \longrightarrow 00:57:31.144$ to know them you or Anna you

NOTE Confidence: 0.906680966

 $00:57:31.144 \longrightarrow 00:57:33.157$ know of of doing it differently.

NOTE Confidence: 0.906680966

 $00{:}57{:}33.160 \dashrightarrow 00{:}57{:}34.216$ It's an interesting approach

NOTE Confidence: 0.906680966

 $00:57:34.216 \longrightarrow 00:57:35.800$ because we use the a lipase

NOTE Confidence: 0.815012178846154

 $00{:}57{:}36{.}120 \dashrightarrow 00{:}57{:}37{.}807$ elevated or not often but when we

NOTE Confidence: 0.815012178846154

 $00:57:37.807 \dashrightarrow 00:57:39.293$ see elevated amylase or lipase and

NOTE Confidence: 0.815012178846154

 $00:57:39.293 \rightarrow 00:57:40.715$ patients are asymptomatic we we just

NOTE Confidence: 0.815012178846154

 $00:57:40.715 \longrightarrow 00:57:42.516$ we don't really do anything about it.

NOTE Confidence: 0.815012178846154

 $00:57:42.520 \longrightarrow 00:57:43.352$ We just watch them.

- NOTE Confidence: 0.815012178846154
- $00:57:43.352 \rightarrow 00:57:45.408$ But if you knew that had a higher
- NOTE Confidence: 0.815012178846154
- 00:57:45.408 --> 00:57:46.678 incidence of going to diabetes,
- NOTE Confidence: 0.815012178846154
- $00:57:46.680 \rightarrow 00:57:48.675$ maybe that's a population you could treat.
- NOTE Confidence: 0.27943775
- $00{:}57{:}51{.}840 \dashrightarrow 00{:}57{:}52{.}200$ Yes.
- NOTE Confidence: 0.895023865
- 00:57:59.080 --> 00:58:03.358 Hello, I'm relatively new to immunobiology,
- NOTE Confidence: 0.895023865
- $00{:}58{:}03{.}360 \dashrightarrow 00{:}58{:}05{.}106$ but I had a question about
- NOTE Confidence: 0.895023865
- 00:58:05.106 --> 00:58:07.565 the slide where you showed the
- NOTE Confidence: 0.895023865
- $00:58:07.565 \rightarrow 00:58:09.121$ immunohistochemistry results and
- NOTE Confidence: 0.895023865
- 00:58:09.121 --> 00:58:11.689 you said that you saw signal or you
- NOTE Confidence: 0.895023865
- $00:58:11.689 \rightarrow 00:58:14.478$ saw standing outside of the eyelids.
- NOTE Confidence: 0.895023865
- 00:58:14.480 --> 00:58:16.489 And I was wondering if you could
- NOTE Confidence: 0.895023865
- $00{:}58{:}16{.}489 \dashrightarrow 00{:}58{:}17{.}720$ further explain the significance
- NOTE Confidence: 0.895023865
- $00{:}58{:}17.720 \dashrightarrow 00{:}58{:}19.630$ on why you were excited about
- NOTE Confidence: 0.895023865
- $00{:}58{:}19.630 \dashrightarrow 00{:}58{:}21.640$ them being outside of the islets.
- NOTE Confidence: 0.7785898346666667
- 00:58:21.960 --> 00:58:24.272 Oh yeah, look, I would have been more
- NOTE Confidence: 0.778589834666667

 $00:58:24.272 \rightarrow 00:58:26.598$ excited if they were inside the islets.

NOTE Confidence: 0.7785898346666667

 $00{:}58{:}26.600 \dashrightarrow 00{:}58{:}32.044$ But the I think I think the point from

NOTE Confidence: 0.778589834666667

 $00:58:32.044 \rightarrow 00:58:35.693$ that is that this is not just there's

NOTE Confidence: 0.7785898346666667

 $00:58:35.693 \rightarrow 00:58:39.558$ a broader inflammatory response and

NOTE Confidence: 0.778589834666667

 $00{:}58{:}39{.}560 \dashrightarrow 00{:}58{:}42{.}812$ our assumption is that the islets

NOTE Confidence: 0.7785898346666667

 $00{:}58{:}42.812 \dashrightarrow 00{:}58{:}46.999$ cells can see the soluble mediators.

NOTE Confidence: 0.778589834666667

00:58:47.000 --> 00:58:49.830 So I I think you know we at least in

NOTE Confidence: 0.778589834666667

 $00:58:49.916 \longrightarrow 00:58:52.506$ the type one diabetes field we tend

NOTE Confidence: 0.778589834666667

 $00:58:52.506 \dashrightarrow 00:58:55.629$ to think of you know single T cell

NOTE Confidence: 0.7785898346666667

 $00{:}58{:}55{.}629 \dashrightarrow 00{:}58{:}58{.}276$ clone going into the islet hitting a

NOTE Confidence: 0.7785898346666667

00:58:58.276 --> 00:59:01.140 single target and I think this is this

NOTE Confidence: 0.7785898346666667

 $00:59:01.220 \rightarrow 00:59:03.760$ is a bigger inflammatory response.

NOTE Confidence: 0.7785898346666667

 $00:59:03.760 \longrightarrow 00:59:04.280$ Thank you.

NOTE Confidence: 0.7785898346666667

 $00:59:04.280 \longrightarrow 00:59:06.016$ And I think that's why the lipase

NOTE Confidence: 0.7785898346666667

 $00:59:06.016 \longrightarrow 00:59:07.200$ and amylase are elevated.

NOTE Confidence: 0.775977063333333

00:59:10.280 --> 00:59:11.552 I have, I have many questions

- NOTE Confidence: 0.775977063333333
- 00:59:11.552 --> 00:59:12.800 but I'll I'll just ask you.
- NOTE Confidence: 0.775977063333333
- 00:59:12.800 --> 00:59:15.520 Had you mentioned or you
- NOTE Confidence: 0.70661166
- $00{:}59{:}15{.}520 \dashrightarrow 00{:}59{:}17{.}720$ had referred to the potential
- NOTE Confidence: 0.70661166
- $00:59:17.720 \longrightarrow 00:59:19.720$ implication of regulatory
- NOTE Confidence: 0.793536518181818
- $00{:}59{:}19{.}720 \dashrightarrow 00{:}59{:}22{.}378$ CDAT cells and was wondering in
- NOTE Confidence: 0.793536518181818
- $00:59:22.378 \dashrightarrow 00:59:24.520$ your comparison between anti PD1,
- NOTE Confidence: 0.793536518181818
- 00:59:24.520 --> 00:59:28.320 anti CTLA 4 differences, did you see any,
- NOTE Confidence: 0.793536518181818
- $00:59:28.320 \longrightarrow 00:59:30.300$ no differences, haven't seen it.
- NOTE Confidence: 0.793536518181818
- $00:59:30.300 \longrightarrow 00:59:32.600$ And then have you also,
- NOTE Confidence: 0.728210011428572
- $00:59:30.880 \longrightarrow 00:59:31.650$ but we're going to look
- NOTE Confidence: 0.728210011428572
- $00:59:31.650 \longrightarrow 00:59:32.600$ for it, you know if there
- NOTE Confidence: 0.7376229775
- $00:59:32.600 \rightarrow 00:59:36.440$ are any differences in HLAC allotypes
- NOTE Confidence: 0.7376229775
- $00{:}59{:}36{.}440 \dashrightarrow 00{:}59{:}40{.}040$ or HLAU or non canonical MHC.
- NOTE Confidence: 0.957117892
- $00{:}59{:}42.200 \dashrightarrow 00{:}59{:}43.960$ That's a good question
- NOTE Confidence: 0.957117892
- 00:59:43.960 00:59:46.600 and not that I know of,
- NOTE Confidence: 0.957117892

00:59:46.600 --> 00:59:50.510 but that certainly is something NOTE Confidence: 0.95711789200:59:50.510 --> 00:59:55.158 worth doing EG and yeah, NOTE Confidence: 0.95711789200:59:55.160 --> 00:59:56.520 yeah, for the yeah, NOTE Confidence: 0.95711789200:59:56.520 --> 00:59:57.920 for the Kurds probably the NOTE Confidence: 0.898911042500:59:58.040 --> 00:59:59.720 C and EI think. NOTE Confidence: 0.778593301:00:01.800 --> 01:00:03.864 Yeah. Kevin, thank you so NOTE Confidence: 0.7785933

 $01:00:03.864 \longrightarrow 01:00:04.994$ much for a wonderful talk.