

WEBVTT

NOTE duration:"01:00:05"

NOTE recognizability:0.839

NOTE language:en-us

NOTE Confidence: 0.787334406923077

00:00:00.000 --> 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 --> 00:00:08.314 it turns out, for 10 years now.

NOTE Confidence: 0.787334406923077

00:00:08.320 --> 00:00:09.680 We just figured it out.

NOTE Confidence: 0.787334406923077

00:00:09.680 --> 00:00:11.720 We met at the bedside.

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 --> 00:00:16.059 this is a this hopefully will be a teaching

NOTE Confidence: 0.787334406923077

00:00:16.059 --> 00:00:17.916 moment because you get a sick patient,

NOTE Confidence: 0.787334406923077

00:00:17.920 --> 00:00:19.355 you're not sure what's wrong with him.

NOTE Confidence: 0.787334406923077

00:00:19.360 --> 00:00:20.524 You call the expert.

NOTE Confidence: 0.787334406923077

00:00:20.524 --> 00:00:22.699 And from that, we developed an

NOTE Confidence: 0.787334406923077

00:00:22.699 --> 00:00:24.716 entire universe of research projects,
NOTE Confidence: 0.787334406923077

00:00:24.716 --> 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 --> 00:00:33.711 of Yale University and what we're
NOTE Confidence: 0.787334406923077

00:00:33.711 --> 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 --> 00:00:39.120 etcetera, etcetera.
NOTE Confidence: 0.787334406923077

00:00:39.120 --> 00:00:41.040 But the best part of it
NOTE Confidence: 0.787334406923077

00:00:41.040 --> 00:00:42.840 all is the collegiality.
NOTE Confidence: 0.787334406923077

00:00:42.840 --> 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 --> 00:00:48.074 the very first research meeting that
NOTE Confidence: 0.787334406923077

00:00:48.074 --> 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.

NOTE Confidence: 0.787334406923077
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 --> 00:00:55.051 They.
NOTE Confidence: 0.787334406923077
00:00:55.051 --> 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 --> 00:01:00.558 particular doesn't tolerate fools.
NOTE Confidence: 0.787334406923077
00:01:00.560 --> 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 --> 00:01:06.960 I don't know if Doctor Harold remembers this.
NOTE Confidence: 0.787334406923077
00:01:06.960 --> 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 --> 00:01:13.397 we never have to be embarrassed.
NOTE Confidence: 0.787334406923077
00:01:13.400 --> 00:01:15.122 And I think that that principle
NOTE Confidence: 0.787334406923077
00:01:15.122 --> 00:01:17.557 has LED us in the last 10 years
NOTE Confidence: 0.787334406923077
00:01:17.557 --> 00:01:20.066 because it turns out that even I had
NOTE Confidence: 0.787334406923077

00:01:20.066 --> 00:01:22.194 something to bring to the table here.
NOTE Confidence: 0.787334406923077

00:01:22.200 --> 00:01:23.529 So collegiality, respect,
NOTE Confidence: 0.787334406923077

00:01:23.529 --> 00:01:26.187 creativity has led to a whole
NOTE Confidence: 0.787334406923077

00:01:26.187 --> 00:01:28.845 field that I think we've opened
NOTE Confidence: 0.787334406923077

00:01:28.845 --> 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 --> 00:01:35.273 for endocrine toxicities.
NOTE Confidence: 0.787334406923077

00:01:35.280 --> 00:01:38.304 So other than this whole world Doctor
NOTE Confidence: 0.787334406923077

00:01:38.304 --> 00:01:41.165 Harold is actually really famous for
NOTE Confidence: 0.787334406923077

00:01:41.165 --> 00:01:44.075 delaying type one diabetes in kids,
NOTE Confidence: 0.787334406923077

00:01:44.080 --> 00:01:46.360 a major breakthrough in delivering
NOTE Confidence: 0.787334406923077

00:01:46.360 --> 00:01:48.640 CD3 antibodies to children who
NOTE Confidence: 0.787334406923077

00:01:48.719 --> 00:01:51.077 had started to develop type one
NOTE Confidence: 0.787334406923077

00:01:51.077 --> 00:01:53.521 diabetes giving them the anti CD3
NOTE Confidence: 0.787334406923077

00:01:53.521 --> 00:01:56.192 antibody delaying the onset of
NOTE Confidence: 0.787334406923077

00:01:56.192 --> 00:01:59.032 full blown islet cell destruction.

NOTE Confidence: 0.787334406923077
00:01:59.040 --> 00:02:00.433 I don't think he's going to be
NOTE Confidence: 0.787334406923077
00:02:00.433 --> 00:02:01.320 talking about that today,
NOTE Confidence: 0.787334406923077
00:02:01.320 --> 00:02:02.682 but today we look forward to
NOTE Confidence: 0.787334406923077
00:02:02.682 --> 00:02:04.224 listening to all the cancer related
NOTE Confidence: 0.787334406923077
00:02:04.224 --> 00:02:05.396 studies that he's done.
NOTE Confidence: 0.787334406923077
00:02:05.400 --> 00:02:06.680 So without further ado,
NOTE Confidence: 0.787334406923077
00:02:06.680 --> 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 --> 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 --> 00:02:22.928 quite pleased that we were going
NOTE Confidence: 0.822342689565217
00:02:22.928 --> 00:02:24.958 to set up our research meeting.
NOTE Confidence: 0.822342689565217
00:02:24.960 --> 00:02:26.370 So there'll be no it would
NOTE Confidence: 0.822342689565217
00:02:26.370 --> 00:02:27.640 be an idiot free zone.
NOTE Confidence: 0.822342689565217
00:02:27.640 --> 00:02:29.400 I I I appreciated that.
NOTE Confidence: 0.88189794

00:02:31.520 --> 00:02:36.720 So here's my disclosures.
NOTE Confidence: 0.88189794

00:02:36.720 --> 00:02:41.323 So hopefully this is review to everyone
NOTE Confidence: 0.88189794

00:02:41.323 --> 00:02:44.424 that that basically we we live in
NOTE Confidence: 0.88189794

00:02:44.424 --> 00:02:46.996 a constant immunologic equilibrium
NOTE Confidence: 0.88189794

00:02:46.996 --> 00:02:49.396 balancing lymphocyte activation
NOTE Confidence: 0.88189794

00:02:49.396 --> 00:02:52.608 and control and the activation is
NOTE Confidence: 0.88189794

00:02:52.608 --> 00:02:55.730 controlled by a number of Co simulatory
NOTE Confidence: 0.88189794

00:02:55.730 --> 00:02:58.875 molecules and recognition by antigen
NOTE Confidence: 0.88189794

00:02:58.880 --> 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 --> 00:03:14.314 effective ways of treating cancers.
NOTE Confidence: 0.88189794

00:03:14.320 --> 00:03:17.518 And and indeed this has revolutionized
NOTE Confidence: 0.88189794

00:03:17.520 --> 00:03:20.498 the field over the past decade and
NOTE Confidence: 0.88189794

00:03:20.498 --> 00:03:23.246 it became very clear initially when

NOTE Confidence: 0.88189794

00:03:23.246 --> 00:03:25.669 these agents became available for

NOTE Confidence: 0.88189794

00:03:25.669 --> 00:03:28.561 clinical use that there were adverse

NOTE Confidence: 0.88189794

00:03:28.561 --> 00:03:31.079 events that would occur as well

NOTE Confidence: 0.88189794

00:03:31.080 --> 00:03:33.365 since the balance that prevents

NOTE Confidence: 0.88189794

00:03:33.365 --> 00:03:35.650 us from developing autoimmunity is

NOTE Confidence: 0.88189794

00:03:35.724 --> 00:03:38.079 controlled by the same mechanisms.

NOTE Confidence: 0.88189794

00:03:38.080 --> 00:03:40.174 And we and it's been established

NOTE Confidence: 0.88189794

00:03:40.174 --> 00:03:42.424 for many years that even normal

NOTE Confidence: 0.88189794

00:03:42.424 --> 00:03:44.764 patients have immune cells that are

NOTE Confidence: 0.88189794

00:03:44.764 --> 00:03:47.358 capable of recognizing self antigens.

NOTE Confidence: 0.88189794

00:03:47.360 --> 00:03:49.985 So by tipping this balance it's fairly

NOTE Confidence: 0.88189794

00:03:49.985 --> 00:03:53.383 clear that one would be able to develop

NOTE Confidence: 0.88189794

00:03:53.383 --> 00:03:55.578 autoimmune diseases and that's that's

NOTE Confidence: 0.88189794

00:03:55.654 --> 00:03:58.558 what I'm going to be talking about today.

NOTE Confidence: 0.88189794

00:03:58.560 --> 00:04:01.325 Now the endocrine organs seem to be

NOTE Confidence: 0.88189794

00:04:01.325 --> 00:04:03.740 particularly vulnerable to immune related
NOTE Confidence: 0.88189794

00:04:03.740 --> 00:04:07.250 adverse events with with biologic
NOTE Confidence: 0.88189794

00:04:07.250 --> 00:04:09.590 therapy particularly with checkpoint
NOTE Confidence: 0.88189794

00:04:09.590 --> 00:04:12.620 inhibitors and you can this is from a
NOTE Confidence: 0.88189794

00:04:12.620 --> 00:04:15.518 review that came out a number of years ago,
NOTE Confidence: 0.88189794

00:04:15.520 --> 00:04:17.064 but there are many,
NOTE Confidence: 0.88189794

00:04:17.064 --> 00:04:18.994 many organs that are affected.
NOTE Confidence: 0.88189794

00:04:19.000 --> 00:04:21.592 I've on the right side we see just the
NOTE Confidence: 0.88189794

00:04:21.600 --> 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 --> 00:04:42.478 disease that can be difficult to diagnose,
NOTE Confidence: 0.88189794

00:04:42.480 --> 00:04:44.696 certainly important to diagnose.
NOTE Confidence: 0.88189794

00:04:44.696 --> 00:04:48.534 And then the other endocrine organs seem
NOTE Confidence: 0.88189794

00:04:48.534 --> 00:04:51.464 to be affected as well including the

NOTE Confidence: 0.88189794

00:04:51.464 --> 00:04:53.528 the insulin producing beta cells that

NOTE Confidence: 0.88189794

00:04:53.528 --> 00:04:56.159 leads to the development of diabetes.

NOTE Confidence: 0.88189794

00:04:56.160 --> 00:04:59.600 Now I would point out from this graph

NOTE Confidence: 0.88189794

00:04:59.600 --> 00:05:04.473 that that the development of these

NOTE Confidence: 0.88189794

00:05:04.473 --> 00:05:06.939 adverse events are most common with

NOTE Confidence: 0.88189794

00:05:06.939 --> 00:05:08.812 combination therapies 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 --> 00:05:22.648 one or PDL one seems to be seems to

NOTE Confidence: 0.88189794

00:05:22.648 --> 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 --> 00:05:31.840 So the timing of them varies a bit.

NOTE Confidence: 0.95304476625

00:05:31.840 --> 00:05:35.634 And sometimes we, as a practical matter,

NOTE Confidence: 0.95304476625

00:05:35.640 --> 00:05:38.244 have a hard time determining whether

NOTE Confidence: 0.95304476625

00:05:38.244 --> 00:05:41.986 or not an adverse event that we may see

NOTE Confidence: 0.95304476625

00:05:41.986 --> 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 --> 00:05:49.118 it was just happening by chance.

NOTE Confidence: 0.95304476625

00:05:49.120 --> 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 --> 00:05:55.519 relatively common in the population,

NOTE Confidence: 0.95304476625

00:05:55.520 --> 00:05:58.440 particularly in the older population.

NOTE Confidence: 0.95304476625

00:05:58.440 --> 00:06:00.968 But this graph shows you the timing of

NOTE Confidence: 0.95304476625

00:06:00.968 --> 00:06:04.144 some of the more common adverse events.

NOTE Confidence: 0.95304476625

00:06:04.144 --> 00:06:08.200 You can see that hypothyroidism 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 --> 00:06:16.996 Some of the others that are that

NOTE Confidence: 0.95304476625

00:06:16.996 --> 00:06:20.105 are also quite common tend to occur

NOTE Confidence: 0.95304476625

00:06:20.105 --> 00:06:22.080 in a more acute manner.

NOTE Confidence: 0.95304476625

00:06:22.080 --> 00:06:26.870 Now as Harriet mentioned we started

NOTE Confidence: 0.95304476625

00:06:26.870 --> 00:06:30.134 I'm going to spend most of my the rest

NOTE Confidence: 0.95304476625

00:06:30.134 --> 00:06:32.456 of the talk talking about checkpoint

NOTE Confidence: 0.95304476625

00:06:32.456 --> 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 --> 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 --> 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 --> 00:06:46.402 of upfront that that the mechanisms

NOTE Confidence: 0.95304476625

00:06:46.402 --> 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 --> 00:06:54.120 not very well worked out at all.

NOTE Confidence: 0.95304476625

00:06:54.120 --> 00:06:57.224 There is really one sort of lead paper

NOTE Confidence: 0.95304476625

00:06:57.224 --> 00:06:59.702 that described the development of

NOTE Confidence: 0.95304476625

00:06:59.702 --> 00:07:01.870 autoimmune hypophysitis 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 --> 00:07:07.160 pituitary cells and suggested that
NOTE Confidence: 0.95304476625

00:07:07.160 --> 00:07:09.764 what happened with anti CTLA 4 is
NOTE Confidence: 0.95304476625

00:07:09.764 --> 00:07:12.073 that the antibodies bound to CTLA
NOTE Confidence: 0.95304476625

00:07:12.073 --> 00:07:14.305 4 on the pituitary fixed complement
NOTE Confidence: 0.95304476625

00:07:14.305 --> 00:07:16.158 and destroyed the cells.
NOTE Confidence: 0.95304476625

00:07:16.160 --> 00:07:18.400 But if you go through the paper carefully,
NOTE Confidence: 0.95304476625

00:07:18.400 --> 00:07:19.360 you'll see that, well,
NOTE Confidence: 0.95304476625

00:07:19.360 --> 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 --> 00:07:25.500 which is a common manifestation
NOTE Confidence: 0.95304476625

00:07:25.500 --> 00:07:26.436 of hypophysitis,
NOTE Confidence: 0.95304476625

00:07:26.440 --> 00:07:28.850 it was prolactin producing cells
NOTE Confidence: 0.95304476625

00:07:28.850 --> 00:07:31.840 and and also TSH producing cells.
NOTE Confidence: 0.95304476625

00:07:31.840 --> 00:07:33.840 So the precise mechanisms there

NOTE Confidence: 0.95304476625

00:07:33.840 --> 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 --> 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 --> 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 --> 00:07:48.460 But we focused our attention on

NOTE Confidence: 0.95304476625

00:07:48.460 --> 00:07:50.020 autoimmune diabetes and hopefully

NOTE Confidence: 0.95304476625

00:07:50.080 --> 00:07:52.145 have made some inroads into

NOTE Confidence: 0.95304476625

00:07:52.145 --> 00:07:53.797 understanding the mechanisms here.

NOTE Confidence: 0.95304476625

00:07:53.800 --> 00:07:55.400 And our work began as,

NOTE Confidence: 0.95304476625

00:07:55.400 --> 00:07:57.157 as I I pointed out to Harriet,

NOTE Confidence: 0.95304476625

00:07:57.160 --> 00:08:00.360 if you take a look at the date on this,

NOTE Confidence: 0.95304476625

00:08:00.360 --> 00:08:04.728 this paper almost a decade ago

NOTE Confidence: 0.95304476625

00:08:04.728 --> 00:08:07.775 when the patient #1 here was

NOTE Confidence: 0.95304476625

00:08:07.775 --> 00:08:11.000 referred to me by Doctor Kluger.
NOTE Confidence: 0.95304476625

00:08:11.000 --> 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 --> 00:08:23.928 had gotten nivolumab at that point and
NOTE Confidence: 0.95304476625

00:08:23.928 --> 00:08:26.040 presented with diabetic ketoacidosis.
NOTE Confidence: 0.95304476625

00:08:26.040 --> 00:08:28.714 And you know this was quite striking.
NOTE Confidence: 0.95304476625

00:08:28.720 --> 00:08:30.360 This is someone who's 55.
NOTE Confidence: 0.95304476625

00:08:30.360 --> 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 --> 00:08:39.940 Yale of people over the age of 50 who
NOTE Confidence: 0.95304476625

00:08:39.940 --> 00:08:42.420 were presenting with ketoacidosis
NOTE Confidence: 0.95304476625

00:08:42.420 --> 00:08:45.096 often and new onset hyperglycemia.
NOTE Confidence: 0.95304476625

00:08:45.096 --> 00:08:48.691 And this was kind of striking and
NOTE Confidence: 0.95304476625

00:08:48.691 --> 00:08:51.577 to me it was striking because you
NOTE Confidence: 0.95304476625

00:08:51.577 --> 00:08:54.331 know we hadn't seen it before the
NOTE Confidence: 0.95304476625

00:08:54.331 --> 00:08:57.936 the the anti PD one drugs were new

NOTE Confidence: 0.95304476625

00:08:57.936 --> 00:09:00.560 at that time but we had had anti

NOTE Confidence: 0.821795666666667

00:09:00.640 --> 00:09:03.680 CTLA 4 Ipilimab for a number of years.

NOTE Confidence: 0.821795666666667

00:09:03.680 --> 00:09:06.794 And so that was kind of kind of striking.

NOTE Confidence: 0.821795666666667

00:09:06.800 --> 00:09:09.056 So we ended up putting these series together

NOTE Confidence: 0.821795666666667

00:09:09.056 --> 00:09:11.201 and this I I know I mentioned this the

NOTE Confidence: 0.821795666666667

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

NOTE Confidence: 0.821795666666667

00:09:13.607 --> 00:09:16.440 bring this point up again particularly

NOTE Confidence: 0.821795666666667

00:09:16.440 --> 00:09:20.904 for the trainees who are here and and

NOTE Confidence: 0.821795666666667

00:09:20.904 --> 00:09:23.496 the the data that we've subsequently

NOTE Confidence: 0.821795666666667

00:09:23.496 --> 00:09:25.600 had even makes the point even further.

NOTE Confidence: 0.821795666666667

00:09:25.600 --> 00:09:27.070 So we we put this series

NOTE Confidence: 0.821795666666667

00:09:27.070 --> 00:09:28.440 together and we send it in,

NOTE Confidence: 0.821795666666667

00:09:28.440 --> 00:09:30.462 we send it into the endocrine

NOTE Confidence: 0.821795666666667

00:09:30.462 --> 00:09:31.473 journals for publication.

NOTE Confidence: 0.821795666666667

00:09:31.480 --> 00:09:34.154 And you know a lot of people,

NOTE Confidence: 0.821795666666667

00:09:34.160 --> 00:09:35.798 a lot of the journals or some
NOTE Confidence: 0.821795666666667

00:09:35.798 --> 00:09:37.250 of the journals didn't weren't
NOTE Confidence: 0.821795666666667

00:09:37.250 --> 00:09:38.638 weren't interested in it.
NOTE Confidence: 0.821795666666667

00:09:38.640 --> 00:09:40.744 And then finally it goes to one of
NOTE Confidence: 0.821795666666667

00:09:40.744 --> 00:09:42.252 the leading endocrine journals and
NOTE Confidence: 0.821795666666667

00:09:42.252 --> 00:09:44.787 it's sent out for review and we get
NOTE Confidence: 0.821795666666667

00:09:44.787 --> 00:09:46.694 comments back from the review and
NOTE Confidence: 0.821795666666667

00:09:46.694 --> 00:09:49.032 and we did a very extensive job
NOTE Confidence: 0.821795666666667

00:09:49.032 --> 00:09:51.200 answering all the all the comments.
NOTE Confidence: 0.821795666666667

00:09:51.200 --> 00:09:54.133 There were 12 pages of of responses
NOTE Confidence: 0.821795666666667

00:09:54.133 --> 00:09:58.184 and so we sent it back and and the
NOTE Confidence: 0.821795666666667

00:09:58.184 --> 00:10:01.352 reviewer comes back and says well
NOTE Confidence: 0.821795666666667

00:10:01.360 --> 00:10:05.077 if you know if this was really
NOTE Confidence: 0.821795666666667

00:10:05.077 --> 00:10:07.631 occurring the development of of
NOTE Confidence: 0.821795666666667

00:10:07.631 --> 00:10:10.474 diabetes after anti PD one we would
NOTE Confidence: 0.821795666666667

00:10:10.474 --> 00:10:12.159 have known about it already.

NOTE Confidence: 0.821795666666667

00:10:12.160 --> 00:10:14.194 So that that was the end of that journal.

NOTE Confidence: 0.821795666666667

00:10:14.200 --> 00:10:17.312 So we ended up publishing this as a

NOTE Confidence: 0.821795666666667

00:10:17.312 --> 00:10:19.447 letter actually in diabetes care and

NOTE Confidence: 0.821795666666667

00:10:19.447 --> 00:10:22.440 it is one of the most highly cited,

NOTE Confidence: 0.821795666666667

00:10:22.440 --> 00:10:24.960 certainly one of the most highly cited

NOTE Confidence: 0.821795666666667

00:10:24.960 --> 00:10:27.308 papers in diabetes care that that is

NOTE Confidence: 0.821795666666667

00:10:27.308 --> 00:10:29.520 the first description of anti PD1 antibodies.

NOTE Confidence: 0.821795666666667

00:10:29.520 --> 00:10:31.207 So the reason I wanted to mention

NOTE Confidence: 0.821795666666667

00:10:31.207 --> 00:10:33.157 this story to you is as I'm going to,

NOTE Confidence: 0.821795666666667

00:10:33.160 --> 00:10:35.986 as I'm going to show you later on that

NOTE Confidence: 0.821795666666667

00:10:35.986 --> 00:10:38.477 not only was the reviewer wrong in

NOTE Confidence: 0.821795666666667

00:10:38.477 --> 00:10:41.560 saying that we would have known about it,

NOTE Confidence: 0.821795666666667

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

NOTE Confidence: 0.821795666666667

00:10:43.260 --> 00:10:44.960 why the reviewer was wrong.

NOTE Confidence: 0.821795666666667

00:10:44.960 --> 00:10:47.445 So that's kind of nice to know

NOTE Confidence: 0.821795666666667

00:10:47.445 --> 00:10:49.479 why your reviewer is so wrong.
NOTE Confidence: 0.821795666666667

00:10:49.480 --> 00:10:50.232 So what?
NOTE Confidence: 0.821795666666667

00:10:50.232 --> 00:10:51.360 What what is,
NOTE Confidence: 0.821795666666667

00:10:51.360 --> 00:10:53.160 what are some of the features
NOTE Confidence: 0.821795666666667

00:10:53.160 --> 00:10:55.422 of this form of of of diabetes.
NOTE Confidence: 0.821795666666667

00:10:55.422 --> 00:10:56.838 So first of all,
NOTE Confidence: 0.821795666666667

00:10:56.840 --> 00:10:59.400 it happens relatively very acutely.
NOTE Confidence: 0.821795666666667

00:10:59.400 --> 00:11:00.716 Here's here's some data.
NOTE Confidence: 0.821795666666667

00:11:00.716 --> 00:11:02.690 This is coming from our colleagues
NOTE Confidence: 0.821795666666667

00:11:02.754 --> 00:11:04.494 at UCSF where we've put together
NOTE Confidence: 0.821795666666667

00:11:04.494 --> 00:11:05.985 patients at the two institutions
NOTE Confidence: 0.821795666666667

00:11:05.985 --> 00:11:08.397 and you can see this here are a few
NOTE Confidence: 0.821795666666667

00:11:08.400 --> 00:11:10.216 patients who developed checkpoint
NOTE Confidence: 0.821795666666667

00:11:10.216 --> 00:11:12.486 induced diabetes and their blood
NOTE Confidence: 0.821795666666667

00:11:12.486 --> 00:11:14.980 sugars are completely normal And then
NOTE Confidence: 0.821795666666667

00:11:14.980 --> 00:11:16.960 dramatically there is a big spike

NOTE Confidence: 0.821795666666667
00:11:16.960 --> 00:11:19.238 in their in their glucose levels.
NOTE Confidence: 0.821795666666667
00:11:19.240 --> 00:11:21.298 And the other thing that's that's
NOTE Confidence: 0.821795666666667
00:11:21.298 --> 00:11:23.318 quite interesting about that is if
NOTE Confidence: 0.821795666666667
00:11:23.318 --> 00:11:25.076 you look at their endogenous beta
NOTE Confidence: 0.821795666666667
00:11:25.076 --> 00:11:26.997 cell function by measuring C peptide,
NOTE Confidence: 0.821795666666667
00:11:27.000 --> 00:11:29.124 remember C peptide is cleaved from
NOTE Confidence: 0.821795666666667
00:11:29.124 --> 00:11:31.256 pro insulin when the beta cells
NOTE Confidence: 0.821795666666667
00:11:31.256 --> 00:11:33.510 make insulin and it's a good measure
NOTE Confidence: 0.821795666666667
00:11:33.510 --> 00:11:35.272 of endogenous insulin production
NOTE Confidence: 0.821795666666667
00:11:35.272 --> 00:11:38.014 cause the insulin you inject doesn't
NOTE Confidence: 0.821795666666667
00:11:38.014 --> 00:11:39.048 have C peptide.
NOTE Confidence: 0.821795666666667
00:11:39.048 --> 00:11:42.360 So if you take a look at the kinetics of
NOTE Confidence: 0.821795666666667
00:11:42.360 --> 00:11:46.320 loss of C peptide here that it happens very,
NOTE Confidence: 0.821795666666667
00:11:46.320 --> 00:11:47.000 very quickly.
NOTE Confidence: 0.821795666666667
00:11:47.000 --> 00:11:49.696 In fact in one case it it happened
NOTE Confidence: 0.821795666666667

00:11:49.696 --> 00:11:51.680 while patients were following the
NOTE Confidence: 0.821795666666667

00:11:51.680 --> 00:11:53.192 the individual while investigators
NOTE Confidence: 0.821795666666667

00:11:53.192 --> 00:11:55.460 were following the individual in the
NOTE Confidence: 0.81665782

00:11:55.520 --> 00:11:58.285 hospital. And the other point about
NOTE Confidence: 0.81665782

00:11:58.285 --> 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 --> 00:12:06.479 that are clinically insufficient.
NOTE Confidence: 0.81665782

00:12:06.480 --> 00:12:08.594 We'll come back to that later on.
NOTE Confidence: 0.81665782

00:12:08.600 --> 00:12:12.296 Here's a few other bits of information
NOTE Confidence: 0.81665782

00:12:12.296 --> 00:12:14.704 about the demographics of patients,
NOTE Confidence: 0.81665782

00:12:14.704 --> 00:12:17.392 so you can see the age.
NOTE Confidence: 0.81665782

00:12:17.400 --> 00:12:21.896 These are people who are older than you
NOTE Confidence: 0.81665782

00:12:21.896 --> 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 --> 00:12:34.370 The hemoglobin A1 CS are elevated at probably

NOTE Confidence: 0.81665782

00:12:34.370 --> 00:12:37.280 because of the degree of hyperglycemia.

NOTE Confidence: 0.81665782

00:12:37.280 --> 00:12:39.872 About half of the patients are OR and

NOTE Confidence: 0.81665782

00:12:39.872 --> 00:12:42.824 depending on the review some even even

NOTE Confidence: 0.81665782

00:12:42.824 --> 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 --> 00:12:51.608 The median time is about 11 weeks and

NOTE Confidence: 0.81665782

00:12:51.608 --> 00:12:53.849 only about 40% of individuals are

NOTE Confidence: 0.81665782

00:12:53.849 --> 00:12:56.267 positive for auto antibodies and this

NOTE Confidence: 0.81665782

00:12:56.267 --> 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 --> 00:13:02.075 As I'm going to explain to you,

NOTE Confidence: 0.81665782

00:13:02.080 --> 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 --> 00:13:07.080 by checkpoint inhibitors,

NOTE Confidence: 0.81665782

00:13:07.080 --> 00:13:10.680 but it's very different from classic

NOTE Confidence: 0.81665782

00:13:10.680 --> 00:13:14.520 spontaneous type one diabetes.
NOTE Confidence: 0.81665782

00:13:14.520 --> 00:13:17.523 Now there is a very large proportion
NOTE Confidence: 0.81665782

00:13:17.523 --> 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 --> 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 --> 00:13:32.303 with much worsening of their glucose
NOTE Confidence: 0.81665782

00:13:32.303 --> 00:13:34.585 control and may become may previously
NOTE Confidence: 0.81665782

00:13:34.585 --> 00:13:36.864 have been managed with oral anti
NOTE Confidence: 0.81665782

00:13:36.864 --> 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 --> 00:13:43.999 or may require insulin therapy.
NOTE Confidence: 0.81665782

00:13:44.000 --> 00:13:47.159 Now type 2 diabetes is a very common disease.
NOTE Confidence: 0.81665782

00:13:47.160 --> 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 --> 00:13:56.304 higher than is even represented by the

NOTE Confidence: 0.81665782

00:13:56.304 --> 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 --> 00:14:02.960 has autoantibodies.

NOTE Confidence: 0.81665782

00:14:02.960 --> 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 --> 00:14:09.158 at three patients on the bottom,

NOTE Confidence: 0.81665782

00:14:09.160 --> 00:14:10.564 some start out negative.

NOTE Confidence: 0.81665782

00:14:10.564 --> 00:14:13.064 Each of those antibodies are one of

NOTE Confidence: 0.81665782

00:14:13.064 --> 00:14:15.056 the auto antibodies that we measure

NOTE Confidence: 0.81665782

00:14:15.056 --> 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 --> 00:14:22.356 some patients start out positive,

NOTE Confidence: 0.81665782

00:14:22.360 --> 00:14:23.308 stay positive.

NOTE Confidence: 0.81665782

00:14:23.308 --> 00:14:26.739 So it varies about 40% overall are positive.
NOTE Confidence: 0.81665782

00:14:26.739 --> 00:14:29.840 But the frequency of those who are positive,
NOTE Confidence: 0.81665782

00:14:29.840 --> 00:14:31.752 sorry let me go back for two or
NOTE Confidence: 0.81665782

00:14:31.752 --> 00:14:32.920 more which is what we,
NOTE Confidence: 0.81665782

00:14:32.920 --> 00:14:36.085 which is kind of the hallmark of spontaneous
NOTE Confidence: 0.81665782

00:14:36.085 --> 00:14:39.955 type one diabetes is relatively low.
NOTE Confidence: 0.81665782

00:14:39.960 --> 00:14:42.420 Now curiously the the alpha
NOTE Confidence: 0.81665782

00:14:42.420 --> 00:14:44.880 producing cells in the islet,
NOTE Confidence: 0.81665782

00:14:44.880 --> 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 --> 00:14:50.473 delta cells and so on that make
NOTE Confidence: 0.81665782

00:14:50.473 --> 00:14:51.717 a variety of hormones.
NOTE Confidence: 0.81665782

00:14:51.720 --> 00:14:55.038 The loss of of of endocrine cells,
NOTE Confidence: 0.81665782

00:14:55.040 --> 00:14:58.116 this seems to be limited to the beta cells.
NOTE Confidence: 0.81665782

00:14:58.116 --> 00:14:59.970 The alpha cells sitting right next

NOTE Confidence: 0.81665782

00:15:00.033 --> 00:15:02.112 to the beta cells are unaffected and

NOTE Confidence: 0.81665782

00:15:02.112 --> 00:15:04.117 the reason for that is not clear.

NOTE Confidence: 0.81665782

00:15:04.120 --> 00:15:06.349 But as you can see from this data

NOTE Confidence: 0.81665782

00:15:06.349 --> 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 --> 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 --> 00:15:20.360 findings from our series

NOTE Confidence: 0.9349334425

00:15:20.424 --> 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 --> 00:15:28.682 three and four are associated with with

NOTE Confidence: 0.9349334425

00:15:28.682 --> 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 --> 00:15:36.084 strikingly high and it's higher

NOTE Confidence: 0.9349334425

00:15:36.084 --> 00:15:38.076 than the background population.

NOTE Confidence: 0.9349334425

00:15:38.080 --> 00:15:40.606 And DR3, the other allele associated

NOTE Confidence: 0.9349334425

00:15:40.606 --> 00:15:42.290 with spontaneous diabetes was

NOTE Confidence: 0.9349334425

00:15:42.357 --> 00:15:44.077 not increased in frequency.

NOTE Confidence: 0.9349334425

00:15:44.080 --> 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 --> 00:15:51.760 to the development of type of

NOTE Confidence: 0.9349334425

00:15:51.760 --> 00:15:54.320 of checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

00:15:54.320 --> 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 and Lilac

NOTE Confidence: 0.9349334425

00:16:04.520 --> 00:16:09.240 Eisenbud from our patients here.

NOTE Confidence: 0.9349334425

00:16:09.240 --> 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 --> 00:16:20.630 a variety of genes that seem to be

NOTE Confidence: 0.9349334425

00:16:20.688 --> 00:16:22.482 associated what seemed what seemed to

NOTE Confidence: 0.9349334425

00:16:22.482 --> 00:16:25.052 be at a higher frequency in people

NOTE Confidence: 0.9349334425

00:16:25.052 --> 00:16:26.796 with checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

00:16:26.800 --> 00:16:29.888 And then we ended up going back and

NOTE Confidence: 0.9349334425

00:16:29.888 --> 00:16:32.056 doing sequencing of of peripheral

NOTE Confidence: 0.9349334425

00:16:32.056 --> 00:16:34.642 blood cells and finding that indeed

NOTE Confidence: 0.9349334425

00:16:34.642 --> 00:16:36.452 there were germline mutations that

NOTE Confidence: 0.9349334425

00:16:36.452 --> 00:16:38.880 seem to be associated with development

NOTE Confidence: 0.9349334425

00:16:38.880 --> 00:16:40.720 of checkpoint induced diabetes.

NOTE Confidence: 0.9349334425

00:16:40.720 --> 00:16:43.919 And interestingly the one of the the,

NOTE Confidence: 0.9349334425

00:16:43.920 --> 00:16:46.350 the highest frequency was in this

NOTE Confidence: 0.9349334425

00:16:46.350 --> 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 --> 00:16:54.200 the frequency of individuals with

NOTE Confidence: 0.9349334425

00:16:54.200 --> 00:16:58.740 NLRC 5 variants was in our series 65%.

NOTE Confidence: 0.9349334425

00:16:58.740 --> 00:17:01.120 Now it's not a huge series because
NOTE Confidence: 0.9349334425

00:17:01.120 --> 00:17:03.438 we don't we don't have tons of
NOTE Confidence: 0.9349334425

00:17:03.438 --> 00:17:05.640 patients we had we had 13 here.
NOTE Confidence: 0.9349334425

00:17:05.640 --> 00:17:07.817 But you can see that at least
NOTE Confidence: 0.9349334425

00:17:07.817 --> 00:17:09.000 the statistically it it,
NOTE Confidence: 0.9349334425

00:17:09.000 --> 00:17:12.648 it turns out to be in a much higher
NOTE Confidence: 0.9349334425

00:17:12.648 --> 00:17:15.208 frequency compared to those individuals
NOTE Confidence: 0.9349334425

00:17:15.208 --> 00:17:16.998 without checkpoint induced diabetes
NOTE Confidence: 0.9349334425

00:17:16.998 --> 00:17:19.554 who get the same checkpoint inhibitors.
NOTE Confidence: 0.9349334425

00:17:19.560 --> 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 --> 00:17:32.000 presentation.
NOTE Confidence: 0.9349334425

00:17:32.000 --> 00:17:34.079 I'll tell you about that in just a moment.
NOTE Confidence: 0.9349334425

00:17:34.080 --> 00:17:36.951 But you can see that it seems to be
NOTE Confidence: 0.9349334425

00:17:36.951 --> 00:17:41.732 an important molecule involved in

NOTE Confidence: 0.9349334425

00:17:41.732 --> 00:17:46.016 responses in in cancer patients that

NOTE Confidence: 0.9349334425

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

NOTE Confidence: 0.9349334425

00:17:49.424 --> 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 --> 00:17:58.518 of of tumors.

NOTE Confidence: 0.9349334425

00:17:58.520 --> 00:18:00.962 The its expression seems to be

NOTE Confidence: 0.9349334425

00:18:00.962 --> 00:18:03.050 correlated with survival and in

NOTE Confidence: 0.9349334425

00:18:03.050 --> 00:18:05.360 diabetes it's also been a associated

NOTE Confidence: 0.9349334425

00:18:05.360 --> 00:18:09.600 with beta cell antigen presentation

NOTE Confidence: 0.9349334425

00:18:09.600 --> 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 --> 00:18:22.238 induced class one MHC expression

NOTE Confidence: 0.9349334425

00:18:22.240 --> 00:18:26.344 and seems to be associated with

NOTE Confidence: 0.9349334425

00:18:26.344 --> 00:18:29.080 protection from autoimmune diabetes.

NOTE Confidence: 0.9349334425

00:18:29.080 --> 00:18:32.608 So NLRC 5 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 --> 00:18:50.228 bringing peptides into the endosome

NOTE Confidence: 0.81096498125

00:18:50.228 --> 00:18:54.716 for processing and placing them on

NOTE Confidence: 0.81096498125

00:18:54.720 --> 00:18:57.840 developing class one MHC molecules.

NOTE Confidence: 0.81096498125

00:18:57.840 --> 00:18:59.416 It's expression seems to

NOTE Confidence: 0.81096498125

00:18:59.416 --> 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 --> 00:19:08.848 So this review actually

NOTE Confidence: 0.81096498125

00:19:08.848 --> 00:19:10.594 describes the mechanism.

NOTE Confidence: 0.81096498125

00:19:10.600 --> 00:19:12.994 I'm not going to go into detail about it,

NOTE Confidence: 0.81096498125

00:19:13.000 --> 00:19:14.880 but what we ended up doing and this

NOTE Confidence: 0.81096498125

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 --> 00:19:22.720 which is an important transactivator

NOTE Confidence: 0.886076019166667

00:19:25.240 --> 00:19:28.042 that's associated with class one MHC

NOTE Confidence: 0.886076019166667

00:19:28.042 --> 00:19:31.443 expression as well as HLAA on peripheral

NOTE Confidence: 0.886076019166667

00:19:31.443 --> 00:19:34.824 blood cells in patients with the mutation

NOTE Confidence: 0.886076019166667

00:19:34.910 --> 00:19:40.280 or with wild type type of the NLRC 5.

NOTE Confidence: 0.886076019166667

00:19:40.280 --> 00:19:43.457 And as you can see and in patients with

NOTE Confidence: 0.886076019166667

00:19:43.457 --> 00:19:46.671 the mutant there seems to be higher

NOTE Confidence: 0.886076019166667

00:19:46.671 --> 00:19:50.048 expression of TAP one and actually of HLAA

NOTE Confidence: 0.886076019166667

00:19:50.048 --> 00:19:52.220 although we haven't reached statistical

NOTE Confidence: 0.886076019166667

00:19:52.220 --> 00:19:54.920 significance for the HLA molecule.

NOTE Confidence: 0.886076019166667

00:19:54.920 --> 00:19:58.385 So it it suggests at least that there is

NOTE Confidence: 0.886076019166667

00:19:58.385 --> 00:20:02.362 some change in expression of MHC molecules

NOTE Confidence: 0.886076019166667

00:20:02.362 --> 00:20:05.332 or potentially presentation of peptides

NOTE Confidence: 0.886076019166667

00:20:05.332 --> 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 --> 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 --> 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 --> 00:20:23.678 of checkpoint induced diabetes.
NOTE Confidence: 0.886076019166667

00:20:23.680 --> 00:20:26.996 First of all HLAD R4 is common and
NOTE Confidence: 0.886076019166667

00:20:26.996 --> 00:20:29.132 perhaps that leads to the development
NOTE Confidence: 0.886076019166667

00:20:29.132 --> 00:20:31.920 of an auto autoreactive repertoire.
NOTE Confidence: 0.886076019166667

00:20:31.920 --> 00:20:35.082 This NLRC 5 mutation also seems
NOTE Confidence: 0.886076019166667

00:20:35.082 --> 00:20:38.637 to have some role in potentially
NOTE Confidence: 0.886076019166667

00:20:38.637 --> 00:20:41.205 in expression of molecules.
NOTE Confidence: 0.886076019166667

00:20:41.205 --> 00:20:44.595 A presentation of molecules by beta
NOTE Confidence: 0.886076019166667

00:20:44.595 --> 00:20:48.225 cells or even potentially in affecting
NOTE Confidence: 0.886076019166667

00:20:48.225 --> 00:20:51.514 a subgroup of CDA positive T cells have

NOTE Confidence: 0.886076019166667
00:20:51.514 --> 00:20:53.920 been associated with immune regulation.
NOTE Confidence: 0.8729991115
00:20:56.120 --> 00:20:58.983 Now the let me just raise some
NOTE Confidence: 0.8729991115
00:20:58.983 --> 00:21:01.456 questions about these these two points
NOTE Confidence: 0.8729991115
00:21:01.456 --> 00:21:04.158 by make by by pointing this out.
NOTE Confidence: 0.8729991115
00:21:04.160 --> 00:21:07.022 When we've looked at auto antigen
NOTE Confidence: 0.8729991115
00:21:07.022 --> 00:21:09.614 reactive T cells in patients
NOTE Confidence: 0.8729991115
00:21:09.614 --> 00:21:12.099 with checkpoint induced diabetes,
NOTE Confidence: 0.8729991115
00:21:12.099 --> 00:21:14.842 we've looked for auto antigen
NOTE Confidence: 0.8729991115
00:21:14.842 --> 00:21:17.368 reactive T cells that are reactive
NOTE Confidence: 0.8729991115
00:21:17.368 --> 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 --> 00:21:22.720 we don't really find an increase.
NOTE Confidence: 0.8729991115
00:21:22.720 --> 00:21:24.560 So if you take a look at that,
NOTE Confidence: 0.8729991115
00:21:24.560 --> 00:21:27.339 we've looked at T cells that are
NOTE Confidence: 0.8729991115
00:21:27.339 --> 00:21:30.099 identified by binding to class one MHC
NOTE Confidence: 0.8729991115

00:21:30.099 --> 00:21:32.343 tetramers that are loaded with the
NOTE Confidence: 0.8729991115

00:21:32.426 --> 00:21:35.434 peptides that are shown on the left side.
NOTE Confidence: 0.8729991115

00:21:35.440 --> 00:21:37.631 If you look at the frequency of
NOTE Confidence: 0.8729991115

00:21:37.631 --> 00:21:39.599 these cells on the right side
NOTE Confidence: 0.8729991115

00:21:39.600 --> 00:21:41.656 and the individuals treated
NOTE Confidence: 0.8729991115

00:21:41.656 --> 00:21:43.198 with checkpoint inhibitors,
NOTE Confidence: 0.8729991115

00:21:43.200 --> 00:21:45.034 those who don't have diabetes or do,
NOTE Confidence: 0.8729991115

00:21:45.040 --> 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 --> 00:21:53.106 the known auto antigens or recognition
NOTE Confidence: 0.8729991115

00:21:53.106 --> 00:21:55.857 of the known auto antigens is not
NOTE Confidence: 0.8729991115

00:21:55.857 --> 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 --> 00:22:02.680 in those individuals who are
NOTE Confidence: 0.8729991115

00:22:02.680 --> 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 --> 00:22:08.318 as a preface to this data the the,

NOTE Confidence: 0.8729991115

00:22:08.320 --> 00:22:11.120 the low hanging fruit on this was well,

NOTE Confidence: 0.8729991115

00:22:11.120 --> 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 --> 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 --> 00:22:19.765 don't think so.

NOTE Confidence: 0.8729991115

00:22:19.765 --> 00:22:22.227 It could be that there are cells that

NOTE Confidence: 0.8729991115

00:22:22.227 --> 00:22:24.219 are reactive to unknown auto antigens

NOTE Confidence: 0.8729991115

00:22:24.219 --> 00:22:26.876 and as I'll show you in just a moment,

NOTE Confidence: 0.8729991115

00:22:26.880 --> 00:22:29.490 there is some evidence that that

NOTE Confidence: 0.8729991115

00:22:29.490 --> 00:22:32.500 might be true, but that's not all.

NOTE Confidence: 0.8729991115

00:22:32.500 --> 00:22:35.050 There are also there's also evidence

NOTE Confidence: 0.8729991115

00:22:35.128 --> 00:22:37.036 of inflammatory lesions that or

NOTE Confidence: 0.8729991115

00:22:37.036 --> 00:22:38.353 inflammation that's occurring

NOTE Confidence: 0.8729991115

00:22:38.353 --> 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 --> 00:22:44.120 checkpoint induced diabetes.
NOTE Confidence: 0.8729991115

00:22:44.120 --> 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 --> 00:22:53.287 patients here in which we found that
NOTE Confidence: 0.8729991115

00:22:53.287 --> 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 --> 00:22:59.474 went on to develop diabetes.
NOTE Confidence: 0.8729991115

00:22:59.480 --> 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 lipase level on one individual
NOTE Confidence: 0.8729991115

00:23:07.915 --> 00:23:09.816 who is who develops checkpoint
NOTE Confidence: 0.8729991115

00:23:09.816 --> 00:23:12.404 induced diabetes and you can see the
NOTE Confidence: 0.8729991115

00:23:12.404 --> 00:23:14.357 lipase on the left bumps and then
NOTE Confidence: 0.8729991115

00:23:14.357 --> 00:23:16.475 red is when they developed diabetes

NOTE Confidence: 0.8729991115

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 --> 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 --> 00:23:33.188 you can see that the that that

NOTE Confidence: 0.8729991115

00:23:33.188 --> 00:23:35.499 both are elevated prior to the

NOTE Confidence: 0.8729991115

00:23:35.499 --> 00:23:37.410 development of of of diabetes.

NOTE Confidence: 0.8729991115

00:23:37.410 --> 00:23:39.335 Now interestingly it prompted us

NOTE Confidence: 0.8729991115

00:23:39.335 --> 00:23:42.300 to look at what well like what's

NOTE Confidence: 0.8729991115

00:23:42.300 --> 00:23:44.475 actually happening in the pancreas.

NOTE Confidence: 0.8729991115

00:23:44.480 --> 00:23:48.490 They were not symptomatic and so we

NOTE Confidence: 0.8729991115

00:23:48.490 --> 00:23:51.080 ended up looking at CT scans that

NOTE Confidence: 0.8729991115

00:23:51.080 --> 00:23:54.740 fortunately we had from before and

NOTE Confidence: 0.8729991115

00:23:54.740 --> 00:23:57.106 after individuals presented with diabetes.

NOTE Confidence: 0.8729991115

00:23:57.106 --> 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 --> 00:24:08.816 The there actually seem to be shrinkage
NOTE Confidence: 0.8729991115

00:24:08.816 --> 00:24:11.816 of the pancreas in individuals who went
NOTE Confidence: 0.8729991115

00:24:11.816 --> 00:24:14.632 on to develop checkpoint induced diabetes.
NOTE Confidence: 0.8729991115

00:24:14.632 --> 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 --> 00:24:24.951 a broader attack in a a broader
NOTE Confidence: 0.854538988666666

00:24:24.960 --> 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 --> 00:24:33.706 died as soon after they had developed
NOTE Confidence: 0.854538988666666

00:24:33.706 --> 00:24:34.759 checkpoint induced diabetes.
NOTE Confidence: 0.854538988666666

00:24:34.760 --> 00:24:36.856 But we had the opportunity to take a
NOTE Confidence: 0.854538988666666

00:24:36.856 --> 00:24:38.872 look at their pancreas by immunohistic

NOTE Confidence: 0.854538988666666

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

NOTE Confidence: 0.854538988666666

00:24:41.440 --> 00:24:43.302 You can see that there are plenty

NOTE Confidence: 0.854538988666666

00:24:43.302 --> 00:24:45.797 of CD 45 positive immune cells that

NOTE Confidence: 0.854538988666666

00:24:45.797 --> 00:24:47.837 are infiltrating the islets and

NOTE Confidence: 0.854538988666666

00:24:47.840 --> 00:24:49.600 that are infiltrating the pancreas.

NOTE Confidence: 0.854538988666666

00:24:49.600 --> 00:24:51.796 They are not just in the islets and in

NOTE Confidence: 0.854538988666666

00:24:51.796 --> 00:24:54.318 fact many of them are outside of the islets,

NOTE Confidence: 0.854538988666666

00:24:54.320 --> 00:24:55.976 as you can see by standing

NOTE Confidence: 0.854538988666666

00:24:55.976 --> 00:24:57.520 for insulin on the right.

NOTE Confidence: 0.854538988666666

00:24:57.520 --> 00:25:00.052 And there are both CD4 and

NOTE Confidence: 0.854538988666666

00:25:00.052 --> 00:25:01.318 CD8 positive cells.

NOTE Confidence: 0.854538988666666

00:25:01.320 --> 00:25:05.400 Chromagranin identifies the endocrine cells.

NOTE Confidence: 0.854538988666666

00:25:05.400 --> 00:25:06.936 They're infiltrating the islets

NOTE Confidence: 0.854538988666666

00:25:06.936 --> 00:25:09.240 and they're outside of the islets.

NOTE Confidence: 0.854538988666666

00:25:09.240 --> 00:25:12.425 And if you look at cytokines that

NOTE Confidence: 0.854538988666666

00:25:12.425 --> 00:25:15.119 are present in the pancreas,
NOTE Confidence: 0.8545389886666666

00:25:15.120 --> 00:25:18.879 we find both interferon gamma and TNF.
NOTE Confidence: 0.8545389886666666

00:25:18.880 --> 00:25:19.986 And interestingly,
NOTE Confidence: 0.8545389886666666

00:25:19.986 --> 00:25:24.417 one of the other findings from this
NOTE Confidence: 0.8545389886666666

00:25:24.417 --> 00:25:27.373 immunohistochemical analysis is PDL
NOTE Confidence: 0.8545389886666666

00:25:27.373 --> 00:25:31.200 one was actually induced on beta
NOTE Confidence: 0.8545389886666666

00:25:31.200 --> 00:25:34.075 cells in and on the other endocrine
NOTE Confidence: 0.8545389886666666

00:25:34.075 --> 00:25:36.511 cells in this patient who died
NOTE Confidence: 0.8545389886666666

00:25:36.511 --> 00:25:38.916 with a checkpoint induced diabetes.
NOTE Confidence: 0.8545389886666666

00:25:38.920 --> 00:25:40.840 Now that's a little weird.
NOTE Confidence: 0.8545389886666666

00:25:40.840 --> 00:25:44.445 We thought that PDL one was actually
NOTE Confidence: 0.8545389886666666

00:25:44.445 --> 00:25:46.050 protective against diabetes.
NOTE Confidence: 0.8545389886666666

00:25:46.050 --> 00:25:49.320 So what what's going on here?
NOTE Confidence: 0.8545389886666666

00:25:49.320 --> 00:25:52.209 So let me just make the point and again
NOTE Confidence: 0.8545389886666666

00:25:52.209 --> 00:25:54.950 this is work that Anna Pertigato has
NOTE Confidence: 0.8545389886666666

00:25:54.950 --> 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 --> 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 --> 00:26:11.480 but by flow interferon gamma.

NOTE Confidence: 0.854538988666666

00:26:11.480 --> 00:26:13.320 This is human beta cells.

NOTE Confidence: 0.854538988666666

00:26:13.320 --> 00:26:16.546 Interferon gamma and interferon

NOTE Confidence: 0.854538988666666

00:26:16.546 --> 00:26:19.102 gamma with TNF induce expression of

NOTE Confidence: 0.854538988666666

00:26:19.102 --> 00:26:22.591 PDL one on beta cells and it seems

NOTE Confidence: 0.854538988666666

00:26:22.591 --> 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 --> 00:26:34.160 signaling through Stat One,

NOTE Confidence: 0.854538988666666

00:26:34.160 --> 00:26:38.880 you can inhibit the expression of PDL one.

NOTE Confidence: 0.854538988666666

00:26:38.880 --> 00:26:41.974 Now there was good evidence for the
NOTE Confidence: 0.854538988666666

00:26:41.974 --> 00:26:45.255 importance of PDL 1 in development of
NOTE Confidence: 0.854538988666666

00:26:45.255 --> 00:26:48.057 autoimmune diabetes and most of this
NOTE Confidence: 0.854538988666666

00:26:48.145 --> 00:26:51.397 work came originally from Arlene Sharp.
NOTE Confidence: 0.854538988666666

00:26:51.400 --> 00:26:54.848 And the the work that I'm I'm showing
NOTE Confidence: 0.854538988666666

00:26:54.848 --> 00:26:58.558 on the left is from a paper of hers
NOTE Confidence: 0.854538988666666

00:26:58.560 --> 00:27:00.779 a number of actually 20 years ago
NOTE Confidence: 0.854538988666666

00:27:00.779 --> 00:27:03.098 now that showed if you knock PDL one
NOTE Confidence: 0.854538988666666

00:27:03.098 --> 00:27:06.360 out of this susceptible mouse strain
NOTE Confidence: 0.854538988666666

00:27:06.360 --> 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 --> 00:27:14.935 And the the Histology is shown in
NOTE Confidence: 0.854538988666666

00:27:14.935 --> 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 --> 00:27:19.296 if you gave anti CD3 antibody to
NOTE Confidence: 0.854538988666666

00:27:19.296 --> 00:27:21.981 mice that spontaneously developed

NOTE Confidence: 0.854538988666666

00:27:21.981 --> 00:27:24.265 diabetes and induced remission

NOTE Confidence: 0.854538988666666

00:27:24.265 --> 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 --> 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 --> 00:27:37.240 the mice immediately redeveloped diabetes.

NOTE Confidence: 0.854538988666666

00:27:37.240 --> 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 --> 00:27:45.850 non development of diabetes in

NOTE Confidence: 0.854538988666666

00:27:45.850 --> 00:27:47.080 a susceptible host.

NOTE Confidence: 0.854538988666666

00:27:47.080 --> 00:27:50.090 And here are some additional studies

NOTE Confidence: 0.854538988666666

00:27:50.090 --> 00:27:52.860 from Arlene's lab that showed

NOTE Confidence: 0.854538988666666

00:27:52.860 --> 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 --> 00:27:58.900 knockout or a wild type

NOTE Confidence: 0.865200372631579

00:27:58.985 --> 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 --> 00:28:05.160 the left side in the open circles,
NOTE Confidence: 0.865200372631579

00:28:05.160 --> 00:28:06.960 mice rapidly developed diabetes whereas
NOTE Confidence: 0.865200372631579

00:28:06.960 --> 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 --> 00:28:13.948 And it also was shown in her
NOTE Confidence: 0.865200372631579

00:28:13.948 --> 00:28:16.214 work that the importance of PDL
NOTE Confidence: 0.865200372631579

00:28:16.214 --> 00:28:18.632 One was indeed on the islets.
NOTE Confidence: 0.865200372631579

00:28:18.640 --> 00:28:21.790 Because if she transplanted PDL 1
NOTE Confidence: 0.865200372631579

00:28:21.790 --> 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 --> 00:28:29.000 which is shown on the on the right,
NOTE Confidence: 0.865200372631579

00:28:29.000 --> 00:28:32.892 the PDL 1 knockout islets were more
NOTE Confidence: 0.865200372631579

00:28:32.892 --> 00:28:37.520 rapidly killed compared to wild type eyelids.
NOTE Confidence: 0.865200372631579

00:28:37.520 --> 00:28:40.160 So PDL one seems to have some unique

NOTE Confidence: 0.89180748

00:28:42.960 --> 00:28:45.735 features that's important in in

NOTE Confidence: 0.89180748

00:28:45.735 --> 00:28:47.955 protecting against autoimmune diabetes.

NOTE Confidence: 0.89180748

00:28:47.960 --> 00:28:51.142 Now we did some additional studies

NOTE Confidence: 0.89180748

00:28:51.142 --> 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 --> 00:29:00.257 to that paper in that that letter

NOTE Confidence: 0.89180748

00:29:00.257 --> 00:29:03.190 in 2015 and and the comments from

NOTE Confidence: 0.89180748

00:29:03.274 --> 00:29:05.039 the reviewer that pointed out,

NOTE Confidence: 0.89180748

00:29:05.039 --> 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 --> 00:29:10.774 Well that reviewer was completely wrong

NOTE Confidence: 0.89180748

00:29:10.774 --> 00:29:13.089 because indeed the only checkpoint

NOTE Confidence: 0.89180748

00:29:13.089 --> 00:29:15.299 inhibitor that was available prior

NOTE Confidence: 0.89180748

00:29:15.299 --> 00:29:17.999 to that time was anti CTLA 4.

NOTE Confidence: 0.89180748

00:29:18.000 --> 00:29:20.184 And if you take a look at the

NOTE Confidence: 0.89180748

00:29:20.184 --> 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 --> 00:29:29.957 to be unique for anti PDL 1.
NOTE Confidence: 0.89180748

00:29:29.960 --> 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 --> 00:29:44.474 induction of diabetes and I'm going to
NOTE Confidence: 0.89180748

00:29:44.474 --> 00:29:46.273 go through the the data fairly quickly.
NOTE Confidence: 0.89180748

00:29:46.280 --> 00:29:50.224 We did this by performing single cell
NOTE Confidence: 0.89180748

00:29:50.224 --> 00:29:56.280 RNA seq on infiltrating cells and
NOTE Confidence: 0.89180748

00:29:56.280 --> 00:29:59.717 islet cells from mice that had received
NOTE Confidence: 0.89180748

00:29:59.720 --> 00:30:02.040 either of these checkpoint inhibitors.
NOTE Confidence: 0.89180748

00:30:02.040 --> 00:30:05.181 And let me first point out that in the
NOTE Confidence: 0.89180748

00:30:05.181 --> 00:30:07.571 presence that when when these susceptible
NOTE Confidence: 0.89180748

00:30:07.571 --> 00:30:10.690 mice and OD mice are given anti C24,

NOTE Confidence: 0.89180748

00:30:10.690 --> 00:30:13.000 there are cells that infiltrate the islets.

NOTE Confidence: 0.89180748

00:30:13.000 --> 00:30:15.800 It's not that they don't develop insulinitis,

NOTE Confidence: 0.89180748

00:30:15.800 --> 00:30:17.956 it's just that they don't develop diabetes.

NOTE Confidence: 0.89180748

00:30:17.960 --> 00:30:19.880 They don't go on and kill,

NOTE Confidence: 0.89180748

00:30:19.880 --> 00:30:21.340 kill the beta cells.

NOTE Confidence: 0.89180748

00:30:21.340 --> 00:30:22.800 So first of all,

NOTE Confidence: 0.89180748

00:30:22.800 --> 00:30:25.820 when we look at and when we look at immune

NOTE Confidence: 0.89180748

00:30:25.820 --> 00:30:27.920 cells that are infiltrating the islets,

NOTE Confidence: 0.89180748

00:30:27.920 --> 00:30:29.754 you can see there is a difference.

NOTE Confidence: 0.89180748

00:30:29.760 --> 00:30:32.140 If you take a look at panel

NOTE Confidence: 0.89180748

00:30:32.140 --> 00:30:34.148 D in the MELD analysis,

NOTE Confidence: 0.89180748

00:30:34.148 --> 00:30:36.420 there's a difference in CDAT cells

NOTE Confidence: 0.89180748

00:30:36.420 --> 00:30:38.460 that are infiltrating the islets when

NOTE Confidence: 0.89180748

00:30:38.460 --> 00:30:40.722 the when the mice are treated with

NOTE Confidence: 0.89180748

00:30:40.722 --> 00:30:43.079 anti PDL 1 compared to anti cetel A4.

NOTE Confidence: 0.89180748

00:30:43.080 --> 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 --> 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 --> 00:30:57.118 Gamma Granzyme B and even PDL one
NOTE Confidence: 0.89180748

00:30:57.118 --> 00:31:00.040 as as we would have predicted,
NOTE Confidence: 0.89180748

00:31:00.040 --> 00:31:03.215 as well as Perfran and the volcano
NOTE Confidence: 0.89180748

00:31:03.215 --> 00:31:05.090 plot showing you the differences
NOTE Confidence: 0.89180748

00:31:05.090 --> 00:31:07.640 in expression in the CDA T cells
NOTE Confidence: 0.89180748

00:31:07.640 --> 00:31:09.640 as shown in the bottom.
NOTE Confidence: 0.89180748

00:31:09.640 --> 00:31:11.392 Now what about the cells that
NOTE Confidence: 0.89180748

00:31:11.392 --> 00:31:12.560 are infiltrating the eyelids?
NOTE Confidence: 0.89180748

00:31:12.560 --> 00:31:15.556 Are they the same? Maybe they're different.
NOTE Confidence: 0.89180748

00:31:15.560 --> 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 --> 00:31:23.251 this and more with more granularity

NOTE Confidence: 0.89180748

00:31:23.251 --> 00:31:25.513 except to point out that yes,

NOTE Confidence: 0.89180748

00:31:25.520 --> 00:31:26.450 they are different.

NOTE Confidence: 0.89180748

00:31:26.450 --> 00:31:28.971 They are not the same cells that are

NOTE Confidence: 0.89180748

00:31:28.971 --> 00:31:30.973 being driven to the eyelids in when

NOTE Confidence: 0.89180748

00:31:30.973 --> 00:31:33.758 with the two different checkpoint inhibitors.

NOTE Confidence: 0.89180748

00:31:33.760 --> 00:31:36.112 If you just take a look at the

NOTE Confidence: 0.89180748

00:31:36.112 --> 00:31:37.465 frequency of various clonotypes

NOTE Confidence: 0.89180748

00:31:37.465 --> 00:31:40.249 you can see with anti PDL one in

NOTE Confidence: 0.89180748

00:31:40.326 --> 00:31:42.720 mice that that do develop diabetes,

NOTE Confidence: 0.89180748

00:31:42.720 --> 00:31:46.626 there seems to be a relative selection

NOTE Confidence: 0.89180748

00:31:46.626 --> 00:31:48.831 of particular clonotypes compared

NOTE Confidence: 0.89180748

00:31:48.831 --> 00:31:52.920 to the anti C2E4 treated mice.

NOTE Confidence: 0.89180748

00:31:52.920 --> 00:31:56.016 Now macrophages also seem to be

NOTE Confidence: 0.89180748

00:31:56.016 --> 00:31:58.512 different for reasons that we

NOTE Confidence: 0.89180748

00:31:58.512 --> 00:32:00.240 we don't completely understand.

NOTE Confidence: 0.89180748

00:32:00.240 --> 00:32:04.200 But you can see that they they express
NOTE Confidence: 0.712054261428571

00:32:06.280 --> 00:32:09.234 PDL one, they themselves express PDL one.
NOTE Confidence: 0.712054261428571

00:32:09.240 --> 00:32:12.376 They produce CXCL 10, which is important
NOTE Confidence: 0.712054261428571

00:32:12.376 --> 00:32:14.839 in recruiting cells to the islets,
NOTE Confidence: 0.712054261428571

00:32:14.840 --> 00:32:17.822 as well as Stat 1 indicating they've
NOTE Confidence: 0.712054261428571

00:32:17.822 --> 00:32:20.680 they've been looking at interferon gamma.
NOTE Confidence: 0.712054261428571

00:32:20.680 --> 00:32:23.040 And this is interesting because
NOTE Confidence: 0.712054261428571

00:32:23.040 --> 00:32:25.572 work from Emil Yunanoway's lab had
NOTE Confidence: 0.712054261428571

00:32:25.572 --> 00:32:28.159 actually pointed out that these cells
NOTE Confidence: 0.712054261428571

00:32:28.159 --> 00:32:30.637 seem to be the critically important
NOTE Confidence: 0.712054261428571

00:32:30.640 --> 00:32:33.040 cells for initiating checkpoint
NOTE Confidence: 0.712054261428571

00:32:33.040 --> 00:32:35.878 induced diabetes in in this model.
NOTE Confidence: 0.9614282

00:32:38.040 --> 00:32:41.948 Now in addition there are there
NOTE Confidence: 0.9614282

00:32:41.948 --> 00:32:44.036 there are changes in beta cells.
NOTE Confidence: 0.9614282

00:32:44.040 --> 00:32:46.490 I showed you already in humans that
NOTE Confidence: 0.9614282

00:32:46.490 --> 00:32:49.015 that we found that there was induction

NOTE Confidence: 0.9614282

00:32:49.015 --> 00:32:52.129 of PDL one in human beta cells that

NOTE Confidence: 0.9614282

00:32:52.129 --> 00:32:54.474 were treated with interferon gamma.

NOTE Confidence: 0.9614282

00:32:54.480 --> 00:32:56.562 And indeed if we looked at

NOTE Confidence: 0.9614282

00:32:56.562 --> 00:32:57.950 genes that are differentially

NOTE Confidence: 0.9614282

00:32:58.015 --> 00:32:59.999 expressed with interferon gamma,

NOTE Confidence: 0.9614282

00:33:00.000 --> 00:33:02.079 you can see that there are a

NOTE Confidence: 0.9614282

00:33:02.079 --> 00:33:04.531 whole lot of genes that have

NOTE Confidence: 0.9614282

00:33:04.531 --> 00:33:06.515 some immune response properties.

NOTE Confidence: 0.9614282

00:33:06.520 --> 00:33:08.548 Now the reason that we think

NOTE Confidence: 0.9614282

00:33:08.548 --> 00:33:10.520 this is important is because

NOTE Confidence: 0.9614282

00:33:10.520 --> 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 --> 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 --> 00:33:24.320 CXCL 10 important for recruiting

NOTE Confidence: 0.9614282

00:33:24.320 --> 00:33:28.696 cells to the islets and as well as
NOTE Confidence: 0.9614282

00:33:28.696 --> 00:33:31.160 increase expression of of of class one.
NOTE Confidence: 0.9614282

00:33:31.160 --> 00:33:35.052 MHC when we looked at this again
NOTE Confidence: 0.9614282

00:33:35.052 --> 00:33:36.356 is with human cells.
NOTE Confidence: 0.9614282

00:33:36.360 --> 00:33:38.985 When we looked at other features of
NOTE Confidence: 0.9614282

00:33:38.985 --> 00:33:41.518 human islets exposed to gamma interferon,
NOTE Confidence: 0.9614282

00:33:41.520 --> 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 --> 00:33:47.928 that indeed that cytokine might
NOTE Confidence: 0.9614282

00:33:47.928 --> 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 --> 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 we find
NOTE Confidence: 0.9614282

00:34:00.644 --> 00:34:02.726 this morphology suggesting the cells
NOTE Confidence: 0.9614282

00:34:02.726 --> 00:34:04.874 are are are actually dying.
NOTE Confidence: 0.9614282

00:34:04.880 --> 00:34:08.120 And indeed if if we look at at

NOTE Confidence: 0.9614282

00:34:08.120 --> 00:34:10.640 the percentage of dead beta cells

NOTE Confidence: 0.9614282

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

NOTE Confidence: 0.9614282

00:34:13.520 --> 00:34:16.002 cells that are cultured with

NOTE Confidence: 0.9614282

00:34:16.002 --> 00:34:18.576 interferon gamma back to the mice.

NOTE Confidence: 0.9614282

00:34:18.576 --> 00:34:21.215 Now when we look at beta cells

NOTE Confidence: 0.9614282

00:34:21.215 --> 00:34:23.478 in the mice in site two,

NOTE Confidence: 0.9614282

00:34:23.478 --> 00:34:26.257 there are a number of differences in

NOTE Confidence: 0.9614282

00:34:26.257 --> 00:34:28.999 in in them including the development

NOTE Confidence: 0.9614282

00:34:28.999 --> 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 --> 00:34:37.260 the fate,

NOTE Confidence: 0.9614282

00:34:37.260 --> 00:34:40.200 the fate diagram here shows you

NOTE Confidence: 0.9614282

00:34:40.200 --> 00:34:42.520 2 populations of beta cells.

NOTE Confidence: 0.9614282

00:34:42.520 --> 00:34:44.458 The the the standard beta cells

NOTE Confidence: 0.9614282

00:34:44.458 --> 00:34:46.746 that you can see in mice treated

NOTE Confidence: 0.9614282

00:34:46.746 --> 00:34:49.307 with anti cetel 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 --> 00:34:53.759 of beta cells that seems to be

NOTE Confidence: 0.9614282

00:34:53.759 --> 00:34:55.758 uniquely found in anti PDL one.

NOTE Confidence: 0.9614282

00:34:55.760 --> 00:34:58.336 The main beta cells express the same

NOTE Confidence: 0.9614282

00:34:58.336 --> 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 --> 00:35:08.440 one is signaling and trail is

NOTE Confidence: 0.9614282

00:35:08.440 --> 00:35:10.120 actually increased as well.

NOTE Confidence: 0.9614282

00:35:10.120 --> 00:35:12.495 But in the unique beta

NOTE Confidence: 0.9614282

00:35:12.495 --> 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 --> 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 --> 00:35:25.106 Maffe of course,

NOTE Confidence: 0.9614282

00:35:25.106 --> 00:35:27.636 insulin and and and chromogram.

NOTE Confidence: 0.9614282

00:35:27.640 --> 00:35:29.168 So it's what this,

NOTE Confidence: 0.9614282

00:35:29.168 --> 00:35:31.460 what this finding suggests is work

NOTE Confidence: 0.9614282

00:35:31.532 --> 00:35:33.866 that we've done in other models

NOTE Confidence: 0.9614282

00:35:33.866 --> 00:35:36.000 of diabetes that there is some

NOTE Confidence: 0.927789400833333

00:35:38.560 --> 00:35:41.493 pathway leading to beta cell survival in

NOTE Confidence: 0.927789400833333

00:35:41.493 --> 00:35:44.400 the presence of checkpoint inhibitors

NOTE Confidence: 0.927789400833333

00:35:44.400 --> 00:35:48.272 that that seems to be turned on when

NOTE Confidence: 0.927789400833333

00:35:48.272 --> 00:35:51.260 these drugs are given. All right.

NOTE Confidence: 0.927789400833333

00:35:51.260 --> 00:35:54.444 So that's that's kind of where things are

NOTE Confidence: 0.927789400833333

00:35:54.444 --> 00:35:56.760 in terms of what's going on in the islet,

NOTE Confidence: 0.927789400833333

00:35:56.760 --> 00:36:00.072 what how human beta cells respond

NOTE Confidence: 0.927789400833333

00:36:00.072 --> 00:36:02.280 similarly to inflammatory mediators.

NOTE Confidence: 0.927789400833333

00:36:02.280 --> 00:36:04.278 So what what is, what is,

NOTE Confidence: 0.927789400833333

00:36:04.280 --> 00:36:06.794 what's the point of that and

NOTE Confidence: 0.927789400833333

00:36:06.794 --> 00:36:07.958 what can we do about it.
NOTE Confidence: 0.927789400833333

00:36:07.960 --> 00:36:13.725 So let me point out that in follow
NOTE Confidence: 0.927789400833333

00:36:13.725 --> 00:36:16.781 up work that that we did to try to
NOTE Confidence: 0.927789400833333

00:36:16.781 --> 00:36:18.790 figure out could we based on this
NOTE Confidence: 0.927789400833333

00:36:18.859 --> 00:36:20.927 knowledge stop the development
NOTE Confidence: 0.927789400833333

00:36:20.927 --> 00:36:22.995 of checkpoint induced diabetes.
NOTE Confidence: 0.927789400833333

00:36:23.000 --> 00:36:25.634 We first tested whether anti cytokine
NOTE Confidence: 0.927789400833333

00:36:25.634 --> 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 --> 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 --> 00:36:42.653 both of these cytokines were present
NOTE Confidence: 0.927789400833333

00:36:42.653 --> 00:36:45.486 in the pancreas of an individual who
NOTE Confidence: 0.927789400833333

00:36:45.486 --> 00:36:47.316 died with checkpoint induced diabetes.

NOTE Confidence: 0.927789400833333
00:36:47.320 --> 00:36:49.630 What happens if you neutralize
NOTE Confidence: 0.927789400833333
00:36:49.630 --> 00:36:50.554 those cytokines?
NOTE Confidence: 0.927789400833333
00:36:50.560 --> 00:36:53.660 And you can see in the on the top here
NOTE Confidence: 0.927789400833333
00:36:53.742 --> 00:36:57.168 that if you gave the combination of
NOTE Confidence: 0.927789400833333
00:36:57.168 --> 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 --> 00:37:06.034 you could indeed prevent the development
NOTE Confidence: 0.927789400833333
00:37:06.034 --> 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 --> 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 --> 00:37:18.962 Jack inhibitor 2 and I should
NOTE Confidence: 0.927789400833333
00:37:18.962 --> 00:37:21.289 just mention this is an ongoing
NOTE Confidence: 0.927789400833333
00:37:21.289 --> 00:37:23.506 collaboration with folks at Pfizer
NOTE Confidence: 0.927789400833333

00:37:23.506 --> 00:37:26.038 and with two new Jack inhibitors,
NOTE Confidence: 0.927789400833333

00:37:26.040 --> 00:37:27.741 The identities of which we don't know
NOTE Confidence: 0.927789400833333

00:37:27.741 --> 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 --> 00:37:34.600 looks pretty good in terms of developing,
NOTE Confidence: 0.927789400833333

00:37:34.600 --> 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 --> 00:37:42.106 So to summarize what I've just told
NOTE Confidence: 0.927789400833333

00:37:42.106 --> 00:37:44.769 you then what we think is there's
NOTE Confidence: 0.927789400833333

00:37:44.769 --> 00:37:46.814 actually an inflammatory cycle that's
NOTE Confidence: 0.927789400833333

00:37:46.814 --> 00:37:49.325 going on between immune cells and beta
NOTE Confidence: 0.927789400833333

00:37:49.325 --> 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 --> 00:37:56.679 in response to interferon gamma.
NOTE Confidence: 0.927789400833333

00:37:56.680 --> 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

NOTE Confidence: 0.927789400833333

00:38:01.738 --> 00:38:04.638 that recruit other immune cells,

NOTE Confidence: 0.927789400833333

00:38:04.640 --> 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 --> 00:38:13.600 particularly interferon gamma.

NOTE Confidence: 0.927789400833333

00:38:13.600 --> 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 --> 00:38:23.670 block the stop signal in immune cells

NOTE Confidence: 0.927789400833333

00:38:23.670 --> 00:38:26.420 that otherwise would would cause

NOTE Confidence: 0.927789400833333

00:38:26.518 --> 00:38:28.920 them to leave the eyelid and and

NOTE Confidence: 0.927789400833333

00:38:28.920 --> 00:38:31.415 the immune cells then are there in

NOTE Confidence: 0.927789400833333

00:38:31.415 --> 00:38:33.732 the eyelid and capable of going on

NOTE Confidence: 0.927789400833333

00:38:33.732 --> 00:38:36.106 and killing the insulin producing

NOTE Confidence: 0.927789400833333

00:38:36.106 --> 00:38:39.558 cells so and and killing beta cells.

NOTE Confidence: 0.927789400833333

00:38:39.560 --> 00:38:40.565 So what is,

NOTE Confidence: 0.927789400833333

00:38:40.565 --> 00:38:43.294 is there anything we can take home from

NOTE Confidence: 0.927789400833333

00:38:43.294 --> 00:38:45.484 this in terms of treating patients?
NOTE Confidence: 0.927789400833333

00:38:45.484 --> 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 --> 00:38:57.234 another letter in diabetes care
NOTE Confidence: 0.927789400833333

00:38:57.240 --> 00:39:00.320 that was treated in Switzerland.
NOTE Confidence: 0.927789400833333

00:39:00.320 --> 00:39:02.378 This is a patient who had presented
NOTE Confidence: 0.927789400833333

00:39:02.378 --> 00:39:04.587 with type 2 diabetes and let me go
NOTE Confidence: 0.927789400833333

00:39:04.587 --> 00:39:06.720 back to a point I made earlier.
NOTE Confidence: 0.927789400833333

00:39:06.720 --> 00:39:08.813 Type 2 diabetes is a common disease
NOTE Confidence: 0.927789400833333

00:39:08.813 --> 00:39:11.277 and so it follows that there are
NOTE Confidence: 0.927789400833333

00:39:11.277 --> 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 --> 00:39:18.624 may have pre-existing type 2 diabetes.
NOTE Confidence: 0.878915246296296

00:39:18.624 --> 00:39:21.390 And that's the explanation I'm going
NOTE Confidence: 0.878915246296296

00:39:21.464 --> 00:39:24.032 to give you for for this this case
NOTE Confidence: 0.878915246296296

00:39:24.032 --> 00:39:26.384 report that appeared in the literature.

NOTE Confidence: 0.878915246296296
00:39:26.384 --> 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 --> 00:39:34.592 much worsening glucose control.
NOTE Confidence: 0.878915246296296
00:39:34.592 --> 00:39:38.880 You can see with a hemoglobin A1C of 11.6%
NOTE Confidence: 0.878915246296296
00:39:38.880 --> 00:39:42.240 but did have detectable beta cell function.
NOTE Confidence: 0.878915246296296
00:39:42.240 --> 00:39:45.278 The C peptide was 993 which is
NOTE Confidence: 0.878915246296296
00:39:45.278 --> 00:39:48.126 you know plenty respectable and
NOTE Confidence: 0.878915246296296
00:39:48.126 --> 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 --> 00:39:54.005 had immune mediated diabetes.
NOTE Confidence: 0.878915246296296
00:39:54.005 --> 00:39:56.280 They gave the patient infliximab,
NOTE Confidence: 0.878915246296296
00:39:56.280 --> 00:39:59.512 the anti TNF antibody and as you can
NOTE Confidence: 0.878915246296296
00:39:59.512 --> 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 --> 00:40:06.760 and so that was
NOTE Confidence: 0.86068467

00:40:08.800 --> 00:40:10.852 that seemed to be very impressive
NOTE Confidence: 0.86068467

00:40:10.852 --> 00:40:11.878 to those investigators.
NOTE Confidence: 0.86068467

00:40:11.880 --> 00:40:13.238 The patient had been treated with insulin.
NOTE Confidence: 0.86068467

00:40:13.240 --> 00:40:14.856 They stopped the insulin.
NOTE Confidence: 0.86068467

00:40:14.856 --> 00:40:16.876 Now since we saw that,
NOTE Confidence: 0.86068467

00:40:16.880 --> 00:40:19.400 we've also treated a few patients
NOTE Confidence: 0.86068467

00:40:19.400 --> 00:40:22.512 here and I want to mention this
NOTE Confidence: 0.86068467

00:40:22.512 --> 00:40:25.188 work that's been ongoing by Noam
NOTE Confidence: 0.86068467

00:40:25.188 --> 00:40:27.964 and Anna for treating patients
NOTE Confidence: 0.86068467

00:40:27.964 --> 00:40:30.288 here who've developed checkpoint
NOTE Confidence: 0.86068467

00:40:30.288 --> 00:40:32.759 induced diabetes with infliximab.
NOTE Confidence: 0.86068467

00:40:32.760 --> 00:40:36.120 Let me show you 2 cases.
NOTE Confidence: 0.86068467

00:40:36.120 --> 00:40:39.179 This patient had a history of type
NOTE Confidence: 0.86068467

00:40:39.179 --> 00:40:41.572 2 diabetes like the previous one
NOTE Confidence: 0.86068467

00:40:41.572 --> 00:40:44.771 that I showed you and presented with
NOTE Confidence: 0.86068467

00:40:44.771 --> 00:40:49.360 very very high glucoses and the the

NOTE Confidence: 0.86068467

00:40:49.360 --> 00:40:52.430 hemoglobin A1C in the past had been

NOTE Confidence: 0.86068467

00:40:52.430 --> 00:40:54.433 a fairly reasonable and the patient

NOTE Confidence: 0.86068467

00:40:54.433 --> 00:40:56.755 had not been treated with insulin.

NOTE Confidence: 0.86068467

00:40:56.760 --> 00:40:59.476 There was a bump in the amylase

NOTE Confidence: 0.86068467

00:40:59.476 --> 00:41:01.484 and light paves just as I showed

NOTE Confidence: 0.86068467

00:41:01.484 --> 00:41:03.560 you in in one of the first slides.

NOTE Confidence: 0.86068467

00:41:03.560 --> 00:41:05.708 And then the glucose became markedly

NOTE Confidence: 0.86068467

00:41:05.708 --> 00:41:08.282 elevated and as you can see the

NOTE Confidence: 0.86068467

00:41:08.282 --> 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 --> 00:41:16.192 curves and in terms of the C peptide,

NOTE Confidence: 0.86068467

00:41:16.200 --> 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 --> 00:41:23.039 did seem to improve after the

NOTE Confidence: 0.86068467

00:41:23.039 --> 00:41:24.964 patient was treated with infliximab
NOTE Confidence: 0.86068467

00:41:24.964 --> 00:41:27.319 and the glucose was also better.
NOTE Confidence: 0.86068467

00:41:27.320 --> 00:41:30.518 Now these are, these are anecdotal,
NOTE Confidence: 0.86068467

00:41:30.520 --> 00:41:33.754 these are not performed in a rigorous
NOTE Confidence: 0.86068467

00:41:33.760 --> 00:41:35.935 endocrine setting where we're actually
NOTE Confidence: 0.86068467

00:41:35.935 --> 00:41:37.675 stimulating beta cell function.
NOTE Confidence: 0.86068467

00:41:37.680 --> 00:41:39.276 But nonetheless and I think from
NOTE Confidence: 0.86068467

00:41:39.276 --> 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 --> 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 --> 00:41:50.116 is is clinically meaningful.
NOTE Confidence: 0.86068467

00:41:50.120 --> 00:41:52.136 Here's another case.
NOTE Confidence: 0.86068467

00:41:52.136 --> 00:41:54.572 This individual with metastatic
NOTE Confidence: 0.86068467

00:41:54.572 --> 00:41:57.302 Melanoma was treated with EPI
NOTE Confidence: 0.86068467

00:41:57.302 --> 00:42:00.404 and Nevo and had adverse events

NOTE Confidence: 0.86068467

00:42:00.404 --> 00:42:02.909 including uveitis and diarrhea that

NOTE Confidence: 0.86068467

00:42:02.909 --> 00:42:06.142 have been treated with steroids and

NOTE Confidence: 0.86068467

00:42:06.142 --> 00:42:09.634 hyperglycemia was noted at cycle 21.

NOTE Confidence: 0.86068467

00:42:09.640 --> 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 --> 00:42:19.200 This patient again presented with

NOTE Confidence: 0.86068467

00:42:19.200 --> 00:42:21.858 a very elevated hemoglobin A1C and

NOTE Confidence: 0.86068467

00:42:21.858 --> 00:42:24.920 the glucose was also quite elevated.

NOTE Confidence: 0.86068467

00:42:24.920 --> 00:42:27.164 This patient did not have evidence

NOTE Confidence: 0.86068467

00:42:27.164 --> 00:42:29.061 of ketoacidosis whereas the previous

NOTE Confidence: 0.86068467

00:42:29.061 --> 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 --> 00:42:37.359 sign of of substantial insulin deficiency.

NOTE Confidence: 0.86068467

00:42:37.359 --> 00:42:40.557 This patient was auto antibody negative.

NOTE Confidence: 0.86068467

00:42:40.560 --> 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 --> 00:42:46.557 one of them is stimulated,
NOTE Confidence: 0.86068467

00:42:46.560 --> 00:42:48.952 the last one that was just done a
NOTE Confidence: 0.86068467

00:42:48.952 --> 00:42:51.293 few days ago and the glucose levels
NOTE Confidence: 0.86068467

00:42:51.293 --> 00:42:54.269 and you can see that the glucose did
NOTE Confidence: 0.86068467

00:42:54.269 --> 00:42:56.375 improve probably with the medical care
NOTE Confidence: 0.86068467

00:42:56.375 --> 00:42:58.796 of the patient received but the C
NOTE Confidence: 0.86068467

00:42:58.796 --> 00:43:01.113 peptide also seemed to be pretty substantial.
NOTE Confidence: 0.86068467

00:43:01.120 --> 00:43:03.178 This is markedly different than what
NOTE Confidence: 0.86068467

00:43:03.178 --> 00:43:05.966 I showed you in in in one of the
NOTE Confidence: 0.86068467

00:43:05.966 --> 00:43:07.815 first slides where the C peptides
NOTE Confidence: 0.86068467

00:43:07.815 --> 00:43:10.472 pretty much go to undetectable in
NOTE Confidence: 0.86068467

00:43:10.472 --> 00:43:13.544 in the majority of patients who
NOTE Confidence: 0.86068467

00:43:13.544 --> 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 --> 00:43:21.260 So to conclude adverse events are not

NOTE Confidence: 0.86068467

00:43:21.260 --> 00:43:22.920 infrequent with checkpoint inhibitors.

NOTE Confidence: 0.86068467

00:43:22.920 --> 00:43:25.173 In fact I would change that to

NOTE Confidence: 0.86068467

00:43:25.173 --> 00:43:27.038 say adverse events are common

NOTE Confidence: 0.86068467

00:43:27.038 --> 00:43:28.157 with checkpoint inhibitors.

NOTE Confidence: 0.86068467

00:43:28.160 --> 00:43:30.525 Most common is thyroid disease

NOTE Confidence: 0.86068467

00:43:30.525 --> 00:43:32.417 and hypophysitis 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 --> 00:43:37.005 of checkpoint induce a checkpoint

NOTE Confidence: 0.67271843625

00:43:37.005 --> 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 --> 00:43:44.516 patients and you know we see them.

NOTE Confidence: 0.67271843625

00:43:44.520 --> 00:43:47.005 Thanks to all of you in our clinic.

NOTE Confidence: 0.67271843625

00:43:47.005 --> 00:43:48.480 But for the patients this

NOTE Confidence: 0.67271843625

00:43:48.480 --> 00:43:50.319 is a difficult disease.

NOTE Confidence: 0.67271843625

00:43:50.320 --> 00:43:52.206 I mean you know it's it, it,
NOTE Confidence: 0.67271843625

00:43:52.206 --> 00:43:54.760 it's a lot different when a
NOTE Confidence: 0.67271843625

00:43:54.760 --> 00:43:56.360 12 year old presents with.
NOTE Confidence: 0.67271843625

00:43:56.360 --> 00:43:57.535 It's not that the disease
NOTE Confidence: 0.67271843625

00:43:57.535 --> 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 --> 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 --> 00:44:09.160 completely dependent on exogenous insulin
NOTE Confidence: 0.67271843625

00:44:09.160 --> 00:44:11.752 for maintaining metabolic control.
NOTE Confidence: 0.67271843625

00:44:11.760 --> 00:44:15.120 So it is quite a burden for patients.
NOTE Confidence: 0.67271843625

00:44:15.120 --> 00:44:18.102 So preventing the disease would obviously
NOTE Confidence: 0.67271843625

00:44:18.102 --> 00:44:20.640 be would result in very significant
NOTE Confidence: 0.67271843625

00:44:20.640 --> 00:44:22.680 improvements in quality of life.
NOTE Confidence: 0.67271843625

00:44:22.680 --> 00:44:24.840 It's most common in patients treated
NOTE Confidence: 0.67271843625

00:44:24.840 --> 00:44:27.654 with anti PD one or anti PDL 1

NOTE Confidence: 0.67271843625

00:44:27.654 --> 00:44:29.900 antibodies and in patients or HLAD R4.

NOTE Confidence: 0.67271843625

00:44:29.900 --> 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 --> 00:44:40.200 DL DDR4 or the significance of NLRC 5.

NOTE Confidence: 0.67271843625

00:44:40.200 --> 00:44:42.624 But it nonetheless suggests that there

NOTE Confidence: 0.67271843625

00:44:42.624 --> 00:44:45.606 is some some change or some difference

NOTE Confidence: 0.67271843625

00:44:45.606 --> 00:44:48.198 in these patients in presentation of

NOTE Confidence: 0.67271843625

00:44:48.198 --> 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 --> 00:44:56.600 pancreatic inflammation is is

NOTE Confidence: 0.67271843625

00:44:56.600 --> 00:44:59.340 frequent prior to the development

NOTE Confidence: 0.67271843625

00:44:59.340 --> 00:45:01.240 of checkpoint induced diabetes.

NOTE Confidence: 0.67271843625

00:45:01.240 --> 00:45:04.040 Curiously, PDL one's expressed on beta cells.

NOTE Confidence: 0.67271843625

00:45:04.040 --> 00:45:06.238 And I think we have to conclude

NOTE Confidence: 0.67271843625

00:45:06.238 --> 00:45:08.256 that in spite of expressing PDL

NOTE Confidence: 0.67271843625

00:45:08.256 --> 00:45:11.132 One on beta cells and in spite of
NOTE Confidence: 0.67271843625

00:45:11.132 --> 00:45:12.972 showing its extraordinary protective
NOTE Confidence: 0.67271843625

00:45:12.972 --> 00:45:15.874 effect in animal models of disease
NOTE Confidence: 0.67271843625

00:45:15.874 --> 00:45:19.438 that when you give a checkpoint,
NOTE Confidence: 0.67271843625

00:45:19.440 --> 00:45:21.320 when the checkpoint inhibitor
NOTE Confidence: 0.67271843625

00:45:21.320 --> 00:45:23.200 is given that protective,
NOTE Confidence: 0.67271843625

00:45:23.200 --> 00:45:26.280 that protective blockade is gone.
NOTE Confidence: 0.67271843625

00:45:26.280 --> 00:45:30.232 And even afterwards PDL one
NOTE Confidence: 0.67271843625

00:45:30.232 --> 00:45:33.040 expression is no longer able to
NOTE Confidence: 0.67271843625

00:45:33.040 --> 00:45:35.240 stop the development of diabetes.
NOTE Confidence: 0.67271843625

00:45:35.240 --> 00:45:37.712 And I think the identification of
NOTE Confidence: 0.67271843625

00:45:37.712 --> 00:45:39.884 mechanism suggest have suggested a
NOTE Confidence: 0.67271843625

00:45:39.884 --> 00:45:41.760 therapeutic strategy inhibition of
NOTE Confidence: 0.67271843625

00:45:41.760 --> 00:45:43.680 inflammatory mediators may potentially
NOTE Confidence: 0.67271843625

00:45:43.680 --> 00:45:46.023 halt progression of diabetes and
NOTE Confidence: 0.67271843625

00:45:46.023 --> 00:45:47.803 beta cell loss with checkpoint

NOTE Confidence: 0.67271843625

00:45:47.803 --> 00:45:51.010 induced diabetes and a short acting

NOTE Confidence: 0.67271843625

00:45:51.010 --> 00:45:53.290 inhibitor potentially Jack inhibitors

NOTE Confidence: 0.67271843625

00:45:53.290 --> 00:45:56.277 would warrant some further testing.

NOTE Confidence: 0.67271843625

00:45:56.280 --> 00:45:58.200 One last one last comment,

NOTE Confidence: 0.67271843625

00:45:58.200 --> 00:45:59.992 let me mention that you know I

NOTE Confidence: 0.67271843625

00:45:59.992 --> 00:46:01.996 think one of the interesting things

NOTE Confidence: 0.67271843625

00:46:01.996 --> 00:46:04.348 about all of the adverse checkpoint

NOTE Confidence: 0.67271843625

00:46:04.348 --> 00:46:05.879 induced adverse events is,

NOTE Confidence: 0.67271843625

00:46:05.880 --> 00:46:08.400 is it a feature of the checkpoint inhibitor,

NOTE Confidence: 0.67271843625

00:46:08.400 --> 00:46:10.656 a feature of the tissue or a feature

NOTE Confidence: 0.67271843625

00:46:10.656 --> 00:46:13.320 of the patients or all three of these.

NOTE Confidence: 0.67271843625

00:46:13.320 --> 00:46:15.920 And let me just point out this work

NOTE Confidence: 0.67271843625

00:46:15.920 --> 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 --> 00:46:25.000 colitis and she did this by single cell RNAC.

NOTE Confidence: 0.67271843625

00:46:25.000 --> 00:46:27.838 This work was published fairly recently,
NOTE Confidence: 0.67271843625

00:46:27.840 --> 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 --> 00:46:37.935 checkpoint induced diabetes can also
NOTE Confidence: 0.67271843625

00:46:37.935 --> 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 --> 00:46:47.560 a broader use of of various inhibitors,
NOTE Confidence: 0.67271843625

00:46:47.560 --> 00:46:48.530 not inhibitors.
NOTE Confidence: 0.67271843625

00:46:48.530 --> 00:46:51.460 Obviously that would prevent the anti
NOTE Confidence: 0.67271843625

00:46:51.460 --> 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 --> 00:46:59.583 after the anti tumor effects of the
NOTE Confidence: 0.67271843625

00:46:59.583 --> 00:47:02.659 checkpoint inhibitors and that might
NOTE Confidence: 0.67271843625

00:47:02.659 --> 00:47:06.612 be rapidly tapered in the event that
NOTE Confidence: 0.67271843625

00:47:06.612 --> 00:47:08.877 further cancer therapy is needed.

NOTE Confidence: 0.914448272857143

00:47:08.880 --> 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 --> 00:47:19.436 you know, a colleague for a decade now,

NOTE Confidence: 0.914448272857143

00:47:19.440 --> 00:47:21.624 and a number of individuals in

NOTE Confidence: 0.914448272857143

00:47:21.624 --> 00:47:23.650 her group who've I've had the

NOTE Confidence: 0.914448272857143

00:47:23.650 --> 00:47:25.200 good fortune of working with.

NOTE Confidence: 0.914448272857143

00:47:25.200 --> 00:47:27.960 As well, I want to mention

NOTE Confidence: 0.3145552

00:47:30.440 --> 00:47:33.419 Lalak's work on identifying

NOTE Confidence: 0.3145552

00:47:33.419 --> 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 --> 00:47:45.949 NLRC 5 mutations and therapies

NOTE Confidence: 0.3145552

00:47:45.949 --> 00:47:48.120 of checkpoint induced diabetes.

NOTE Confidence: 0.3145552

00:47:48.120 --> 00:47:49.560 Anna Perdigata did a lot of,
NOTE Confidence: 0.3145552

00:47:49.560 --> 00:47:51.678 did actually all of the work,
NOTE Confidence: 0.3145552

00:47:51.680 --> 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 --> 00:48:00.042 And we have colleagues at UCSF and funding
NOTE Confidence: 0.3145552

00:48:00.042 --> 00:48:03.480 you can see on the right side here.
NOTE Confidence: 0.3145552

00:48:03.480 --> 00:48:04.950 So I'll stop there and I'm
NOTE Confidence: 0.3145552

00:48:04.950 --> 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 --> 00:48:23.450 thank you for an excellent
NOTE Confidence: 0.929915654

00:48:23.450 --> 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 --> 00:48:28.570 kind of superficially counter intuitive
NOTE Confidence: 0.625720556

00:48:28.570 --> 00:48:29.530 in terms of germline mutation.
NOTE Confidence: 0.625720556

00:48:29.530 --> 00:48:30.800 I was wondering if there was a

NOTE Confidence: 0.625720556

00:48:30.800 --> 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 --> 00:48:35.570 inhibitor autoimmunity in

NOTE Confidence: 0.80699388

00:48:35.570 --> 00:48:37.610 hypothesitis or hypothyroidism.

NOTE Confidence: 0.771907615

00:48:41.280 --> 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 --> 00:48:46.752 question about central tolerance

NOTE Confidence: 0.771907615

00:48:46.752 --> 00:48:48.796 but so and so whether you saw

NOTE Confidence: 0.771907615

00:48:48.800 --> 00:48:51.820 rather than an LRC 5 mutations,

NOTE Confidence: 0.771907615

00:48:51.820 --> 00:48:54.733 germline ingest type one diabetes

NOTE Confidence: 0.771907615

00:48:54.733 --> 00:48:56.839 or well check one inhibitor diabetes

NOTE Confidence: 0.6369411675

00:48:56.840 --> 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 --> 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 --> 00:49:12.480 thought as to whether it's more likely.
NOTE Confidence: 0.787257717777778

00:49:12.680 --> 00:49:15.155 Yeah, I can Norm can answer it as well.
NOTE Confidence: 0.787257717777778

00:49:15.160 --> 00:49:17.936 So we have looked in at NLRC 5
NOTE Confidence: 0.787257717777778

00:49:17.936 --> 00:49:20.639 SNPs in other other toxicity,
NOTE Confidence: 0.787257717777778

00:49:20.640 --> 00:49:23.656 it seems to be higher as well in
NOTE Confidence: 0.787257717777778

00:49:23.656 --> 00:49:25.096 hypothesitis but not colitis.
NOTE Confidence: 0.787257717777778

00:49:25.096 --> 00:49:27.960 That's as far as we know so far.
NOTE Confidence: 0.787257717777778

00:49:27.960 --> 00:49:29.626 But the statistics are they're
NOTE Confidence: 0.787257717777778

00:49:29.626 --> 00:49:30.756 not this numbers are small.
NOTE Confidence: 0.787257717777778

00:49:30.760 --> 00:49:31.924 Still, that's exactly what
NOTE Confidence: 0.787257717777778

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 --> 00:49:53.520 that's an interesting question.
NOTE Confidence: 0.687196584545454

00:49:53.520 --> 00:49:54.830 But you're taking us back
NOTE Confidence: 0.687196584545454

00:49:54.830 --> 00:49:55.878 to the original model.

NOTE Confidence: 0.687196584545454

00:49:55.880 --> 00:50:00.200 These patients had a repertoire ready to go.

NOTE Confidence: 0.687196584545454

00:50:00.200 --> 00:50:01.880 And look, it could be right.

NOTE Confidence: 0.687196584545454

00:50:01.880 --> 00:50:03.662 I mean just because we don't

NOTE Confidence: 0.687196584545454

00:50:03.662 --> 00:50:05.298 see the usual suspects doesn't

NOTE Confidence: 0.687196584545454

00:50:05.298 --> 00:50:07.238 mean that there aren't suspects.

NOTE Confidence: 0.687196584545454

00:50:07.240 --> 00:50:08.680 Kevin, that was an amazing lecture.

NOTE Confidence: 0.687196584545454

00:50:08.680 --> 00:50:11.070 It it reminds me of 2015 or earlier when

NOTE Confidence: 0.687196584545454

00:50:11.070 --> 00:50:12.855 we first started using these agents

NOTE Confidence: 0.687196584545454

00:50:12.855 --> 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 --> 00:50:17.400 cancers and others would have these

NOTE Confidence: 0.687196584545454

00:50:17.400 --> 00:50:19.110 problems and you know they'd be

NOTE Confidence: 0.687196584545454

00:50:19.110 --> 00:50:20.370 on the throughout the hospital and

NOTE Confidence: 0.687196584545454

00:50:20.370 --> 00:50:21.779 they wouldn't get the care they

NOTE Confidence: 0.687196584545454

00:50:21.779 --> 00:50:22.929 needed because no one recognized

NOTE Confidence: 0.687196584545454

00:50:22.972 --> 00:50:24.062 that these toxicities were were
NOTE Confidence: 0.687196584545454

00:50:24.062 --> 00:50:25.720 part of this even though they were
NOTE Confidence: 0.687196584545454

00:50:25.720 --> 00:50:27.120 benefiting from the the therapy.
NOTE Confidence: 0.687196584545454

00:50:27.120 --> 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 --> 00:50:32.760 you have the NLR, other other risk factors.
NOTE Confidence: 0.687196584545454

00:50:32.760 --> 00:50:35.920 So my first question would be 1,
NOTE Confidence: 0.687196584545454

00:50:35.920 --> 00:50:37.780 would you treat prophylactically or
NOTE Confidence: 0.687196584545454

00:50:37.780 --> 00:50:40.372 or would you wait until they develop
NOTE Confidence: 0.687196584545454

00:50:40.372 --> 00:50:42.800 the toxicity to to start treating
NOTE Confidence: 0.687196584545454

00:50:42.800 --> 00:50:44.312 And then the second would be you see
NOTE Confidence: 0.687196584545454

00:50:44.312 --> 00:50:46.370 that the activity against the cancer
NOTE Confidence: 0.687196584545454

00:50:46.370 --> 00:50:47.960 is is increased in the patients
NOTE Confidence: 0.687196584545454

00:50:47.960 --> 00:50:49.559 that have these abnormalities.
NOTE Confidence: 0.687196584545454

00:50:49.560 --> 00:50:50.848 Yeah that's a let.
NOTE Confidence: 0.687196584545454

00:50:50.848 --> 00:50:52.780 Let me address the second question

NOTE Confidence: 0.687196584545454

00:50:52.843 --> 00:50:55.177 first because there is some literature

NOTE Confidence: 0.687196584545454

00:50:55.177 --> 00:50:57.135 suggesting that those who develop

NOTE Confidence: 0.687196584545454

00:50:57.135 --> 00:50:59.175 these adverse events do better in

NOTE Confidence: 0.687196584545454

00:50:59.175 --> 00:51:01.672 terms of their anti cancer activity and

NOTE Confidence: 0.687196584545454

00:51:01.672 --> 00:51:04.480 indeed our patients did well in general,

NOTE Confidence: 0.687196584545454

00:51:04.480 --> 00:51:06.916 but there is a publication for sure

NOTE Confidence: 0.687196584545454

00:51:06.916 --> 00:51:08.924 suggesting that those who develop

NOTE Confidence: 0.687196584545454

00:51:08.924 --> 00:51:10.716 hypothesitis had better outcomes

NOTE Confidence: 0.687196584545454

00:51:10.720 --> 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 --> 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 --> 00:51:22.276 in terms of the cancer response

NOTE Confidence: 0.687196584545454

00:51:22.280 --> 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 --> 00:51:27.540 toxicities doesn't mean you can't
NOTE Confidence: 0.687196584545454

00:51:27.540 --> 00:51:29.320 do well with checkpoint inhibitors.
NOTE Confidence: 0.687196584545454

00:51:29.320 --> 00:51:31.800 So in terms of when I would treat
NOTE Confidence: 0.687196584545454

00:51:31.800 --> 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 --> 00:51:38.452 if we knew what the antigens
NOTE Confidence: 0.687196584545454

00:51:38.452 --> 00:51:39.238 were for example,
NOTE Confidence: 0.687196584545454

00:51:39.240 --> 00:51:41.634 we could we could dream about coming
NOTE Confidence: 0.687196584545454

00:51:41.634 --> 00:51:44.802 up with some sort of antigen specific
NOTE Confidence: 0.687196584545454

00:51:44.802 --> 00:51:46.712 prophylactic therapy and give that
NOTE Confidence: 0.687196584545454

00:51:46.712 --> 00:51:48.800 before we give the checkpoint inhibitor.
NOTE Confidence: 0.687196584545454

00:51:48.800 --> 00:51:49.706 At this point,
NOTE Confidence: 0.687196584545454

00:51:49.706 --> 00:51:51.518 I don't think we have that.
NOTE Confidence: 0.687196584545454

00:51:51.520 --> 00:51:54.220 And so my suggestion would be
NOTE Confidence: 0.687196584545454

00:51:54.220 --> 00:51:55.862 to carefully follow patients,
NOTE Confidence: 0.687196584545454

00:51:55.862 --> 00:51:58.088 look for the signs that identify

NOTE Confidence: 0.687196584545454

00:51:58.088 --> 00:52:00.313 those who are at risk of developing

NOTE Confidence: 0.687196584545454

00:52:00.313 --> 00:52:02.549 it and then when is appropriate in

NOTE Confidence: 0.687196584545454

00:52:02.549 --> 00:52:04.830 terms of the cancer therapy strategy,

NOTE Confidence: 0.687196584545454

00:52:04.830 --> 00:52:07.560 if it's possible come in with

NOTE Confidence: 0.687196584545454

00:52:07.560 --> 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: 0.792301511666667

00:52:15.440 --> 00:52:18.960 And then just just great talk,

NOTE Confidence: 0.792301511666667

00:52:18.960 --> 00:52:21.080 just a couple of simple questions.

NOTE Confidence: 0.792301511666667

00:52:21.080 --> 00:52:23.360 Are there gender differences in toxicity?

NOTE Confidence: 0.9163537

00:52:26.800 --> 00:52:27.360 We

NOTE Confidence: 0.929516157142857

00:52:29.600 --> 00:52:32.274 not that we had seen in diabetes.

NOTE Confidence: 0.929516157142857

00:52:32.280 --> 00:52:34.239 Not significantly different.

NOTE Confidence: 0.8302601148

00:52:35.160 --> 00:52:35.958 Harry looks puzzled.

NOTE Confidence: 0.8302601148

00:52:35.958 --> 00:52:37.820 Why I would ask that only because

NOTE Confidence: 0.8302601148

00:52:37.873 --> 00:52:39.153 autoimmune disease is so much

NOTE Confidence: 0.8302601148

00:52:39.153 --> 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 --> 00:52:46.640 didn't find that we we'd
NOTE Confidence: 0.764676322222222

00:52:46.640 --> 00:52:47.936 love. Yeah. The only the only
NOTE Confidence: 0.764676322222222

00:52:47.936 --> 00:52:49.599 thing I could say is type one
NOTE Confidence: 0.764676322222222

00:52:49.599 --> 00:52:50.839 diabetes is not really general.
NOTE Confidence: 0.49742869

00:52:50.840 --> 00:52:53.440 No, I I realized that, but
NOTE Confidence: 0.598270838333333

00:52:53.440 --> 00:52:57.120 this isn't type 1 to obvious and
NOTE Confidence: 0.598270838333333

00:52:57.120 --> 00:52:59.238 and this is for either of you.
NOTE Confidence: 0.941466585714286

00:52:59.640 --> 00:53:02.352 I mean do you think that that clinicians
NOTE Confidence: 0.941466585714286

00:53:02.352 --> 00:53:06.960 really have a sense of how abrupt the
NOTE Confidence: 0.941466585714286

00:53:06.960 --> 00:53:10.000 onset is of of of diabetes in this
NOTE Confidence: 0.941466585714286

00:53:10.090 --> 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 --> 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 --> 00:53:25.344 number of people out there as

NOTE Confidence: 0.941466585714286

00:53:25.344 --> 00:53:26.904 these therapies are used more and

NOTE Confidence: 0.941466585714286

00:53:26.904 --> 00:53:28.360 more we're going to die from this.

NOTE Confidence: 0.941466585714286

00:53:28.360 --> 00:53:30.520 So there have been deaths,

NOTE Confidence: 0.941466585714286

00:53:30.520 --> 00:53:32.785 there will be deaths where

NOTE Confidence: 0.941466585714286

00:53:32.785 --> 00:53:36.192 there isn't sufficient there,

NOTE Confidence: 0.941466585714286

00:53:36.192 --> 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 --> 00:53:41.836 haven't showed that we were able to

NOTE Confidence: 0.941466585714286

00:53:41.836 --> 00:53:43.399 give the TNF that was just chance.

NOTE Confidence: 0.941466585714286

00:53:43.399 --> 00:53:45.170 The first one was in hospital because

NOTE Confidence: 0.941466585714286

00:53:45.226 --> 00:53:47.102 of colitis or something else and that's

NOTE Confidence: 0.941466585714286

00:53:47.102 --> 00:53:48.798 when they noticed the ship going up.

NOTE Confidence: 0.941466585714286

00:53:48.800 --> 00:53:50.480 The second one is an EMT and
NOTE Confidence: 0.941466585714286

00:53:50.480 --> 00:53:52.028 he he noted his only party,
NOTE Confidence: 0.941466585714286

00:53:52.028 --> 00:53:53.363 that's it called a million
NOTE Confidence: 0.941466585714286

00:53:53.363 --> 00:53:54.680 started checking his glucose.
NOTE Confidence: 0.941466585714286

00:53:54.680 --> 00:53:56.558 But there there's not sufficient awareness.
NOTE Confidence: 0.840468102666666

00:53:57.440 --> 00:53:58.934 Yeah. The but the other sort
NOTE Confidence: 0.840468102666666

00:53:58.934 --> 00:54:00.638 of take home point from that is
NOTE Confidence: 0.840468102666666

00:54:00.638 --> 00:54:02.157 you need to be aware of this
NOTE Confidence: 0.840468102666666

00:54:02.215 --> 00:54:04.217 acutely because I showed you the C
NOTE Confidence: 0.840468102666666

00:54:04.217 --> 00:54:06.380 peptide levels when it goes to 0,
NOTE Confidence: 0.840468102666666

00:54:06.380 --> 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 --> 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 --> 00:54:20.120 educate patients, you know so, so look
NOTE Confidence: 0.716728292

00:54:23.200 --> 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 --> 00:54:31.560 you may have said this,
NOTE Confidence: 0.716728292
00:54:31.560 --> 00:54:34.825 but are those associated with
NOTE Confidence: 0.716728292
00:54:34.825 --> 00:54:36.784 standard classic autoimmune
NOTE Confidence: 0.716728292
00:54:36.784 --> 00:54:38.760 diet type one diabetes as well?
NOTE Confidence: 0.716728292
00:54:38.760 --> 00:54:40.359 Yeah, there there's,
NOTE Confidence: 0.716728292
00:54:40.359 --> 00:54:44.090 there's that one paper from Dejo Isrich
NOTE Confidence: 0.716728292
00:54:44.186 --> 00:54:48.238 suggesting that the answer is no not really,
NOTE Confidence: 0.716728292
00:54:48.240 --> 00:54:50.436 not one of the important players.
NOTE Confidence: 0.716728292
00:54:50.440 --> 00:54:52.491 None the less though seems to be
NOTE Confidence: 0.716728292
00:54:52.491 --> 00:54:54.663 important and it it can affect
NOTE Confidence: 0.716728292
00:54:54.663 --> 00:54:56.718 antigenicity and development of diabetes.
NOTE Confidence: 0.716728292

00:54:56.720 --> 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 --> 00:55:03.844 the, the, the, the,
NOTE Confidence: 0.716728292

00:55:03.844 --> 00:55:07.076 the 40% of the patients who have autoimmune,
NOTE Confidence: 0.716728292

00:55:07.080 --> 00:55:09.120 who have auto antibodies to to,
NOTE Confidence: 0.716728292

00:55:09.120 --> 00:55:10.760 to, to the islet cells.
NOTE Confidence: 0.648686158571429

00:55:13.280 --> 00:55:15.135 There's only relatively it was
NOTE Confidence: 0.648686158571429

00:55:15.135 --> 00:55:16.720 only 40% as opposed to all of them.
NOTE Confidence: 0.648686158571429

00:55:16.720 --> 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 --> 00:55:21.560 one of your conclusions why this was
NOTE Confidence: 0.648686158571429

00:55:21.560 --> 00:55:23.274 different than standard, you know,
NOTE Confidence: 0.648686158571429

00:55:23.274 --> 00:55:25.330 type one diabetes did when you went back
NOTE Confidence: 0.648686158571429

00:55:25.383 --> 00:55:27.357 and you started looking at all these
NOTE Confidence: 0.648686158571429

00:55:27.357 --> 00:55:29.239 mechanisms in your patient population,
NOTE Confidence: 0.648686158571429

00:55:29.240 --> 00:55:31.496 did you, did you look at the difference

NOTE Confidence: 0.648686158571429
00:55:31.496 --> 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 --> 00:55:39.200 You know, yeah it's interesting point.
NOTE Confidence: 0.648686158571429
00:55:39.200 --> 00:55:42.185 No, to my knowledge,
NOTE Confidence: 0.648686158571429
00:55:42.185 --> 00:55:45.035 I don't think we've done that.
NOTE Confidence: 0.648686158571429
00:55:45.040 --> 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 --> 00:55:49.332 Yeah, confirm this here,
NOTE Confidence: 0.648686158571429
00:55:49.332 --> 00:55:50.118 this hypothesis.
NOTE Confidence: 0.648686158571429
00:55:50.120 --> 00:55:50.266 Yeah.
NOTE Confidence: 0.648686158571429
00:55:50.266 --> 00:55:50.558 So we
NOTE Confidence: 0.896271925
00:55:51.840 --> 00:55:53.640 have a couple of online questions.
NOTE Confidence: 0.896271925
00:55:53.640 --> 00:55:55.340 Oh, oh comments that would be
NOTE Confidence: 0.896271925
00:55:55.340 --> 00:55:56.920 easy for you to look at it there.
NOTE Confidence: 0.862695698
00:55:56.920 --> 00:56:00.840 OK. Anna has a comment.
NOTE Confidence: 0.862695698

00:56:00.840 --> 00:56:03.030 It'd be helpful to monitor blood
NOTE Confidence: 0.862695698

00:56:03.030 --> 00:56:05.020 glucose more carefully in patients
NOTE Confidence: 0.862695698

00:56:05.020 --> 00:56:07.978 who have lipase elevation and in some
NOTE Confidence: 0.862695698

00:56:07.978 --> 00:56:10.208 patients there's mild elevation in
NOTE Confidence: 0.862695698

00:56:10.208 --> 00:56:12.639 glucose before severe presentation.
NOTE Confidence: 0.862695698

00:56:12.640 --> 00:56:14.555 So monitoring them more more
NOTE Confidence: 0.862695698

00:56:14.555 --> 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 --> 00:56:21.170 And then there's a question about
NOTE Confidence: 0.862695698

00:56:21.170 --> 00:56:22.855 racial differences in in toxicity,
NOTE Confidence: 0.862695698

00:56:22.855 --> 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 --> 00:56:44.788 paper to the New England Journal to the

NOTE Confidence: 0.604493355

00:56:44.788 --> 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 --> 00:56:56.799 I had a question about the the,

NOTE Confidence: 0.840401586

00:56:56.800 --> 00:56:59.840 the lipase elevation occurring before

NOTE Confidence: 0.840401586

00:56:59.840 --> 00:57:02.996 the onset of diabetes as well.

NOTE Confidence: 0.840401586

00:57:03.000 --> 00:57:04.285 You showed that it's it's

NOTE Confidence: 0.840401586

00:57:04.285 --> 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 --> 00:57:09.288 that have lipase elevations and

NOTE Confidence: 0.840401586

00:57:09.288 --> 00:57:11.198 how often they develop diabetes.

NOTE Confidence: 0.840401586

00:57:11.200 --> 00:57:12.512 We don't routinely follow

NOTE Confidence: 0.840401586

00:57:12.512 --> 00:57:14.152 amylocin lipase in patients but

NOTE Confidence: 0.840401586

00:57:14.152 --> 00:57:15.436 occasionally on clinical trials we

NOTE Confidence: 0.840401586

00:57:15.436 --> 00:57:17.120 do we are required to look at it.

NOTE Confidence: 0.840401586

00:57:17.120 --> 00:57:19.456 And so that may be it would be

NOTE Confidence: 0.840401586

00:57:19.456 --> 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 it is pre occurring or or

NOTE Confidence: 0.906680966

00:57:24.200 --> 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 --> 00:57:31.144 to know them you or Anna you

NOTE Confidence: 0.906680966

00:57:31.144 --> 00:57:33.157 know of of doing it differently.

NOTE Confidence: 0.906680966

00:57:33.160 --> 00:57:34.216 It's an interesting approach

NOTE Confidence: 0.906680966

00:57:34.216 --> 00:57:35.800 because we use the a lipase

NOTE Confidence: 0.815012178846154

00:57:36.120 --> 00:57:37.807 elevated or not often but when we

NOTE Confidence: 0.815012178846154

00:57:37.807 --> 00:57:39.293 see elevated amylase or lipase and

NOTE Confidence: 0.815012178846154

00:57:39.293 --> 00:57:40.715 patients are asymptomatic we we just

NOTE Confidence: 0.815012178846154

00:57:40.715 --> 00:57:42.516 we don't really do anything about it.

NOTE Confidence: 0.815012178846154

00:57:42.520 --> 00:57:43.352 We just watch them.

NOTE Confidence: 0.815012178846154

00:57:43.352 --> 00:57:45.408 But if you knew that 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 --> 00:57:48.675 maybe that's a population you could treat.

NOTE Confidence: 0.27943775

00:57:51.840 --> 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 --> 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 --> 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 --> 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 --> 00:58:17.720 further explain the significance

NOTE Confidence: 0.895023865

00:58:17.720 --> 00:58:19.630 on why you were excited about

NOTE Confidence: 0.895023865

00:58:19.630 --> 00:58:21.640 them being outside of the islets.

NOTE Confidence: 0.778589834666667

00:58:21.960 --> 00:58:24.272 Oh yeah, look, I would have been more

NOTE Confidence: 0.778589834666667

00:58:24.272 --> 00:58:26.598 excited if they were inside the islets.
NOTE Confidence: 0.778589834666667

00:58:26.600 --> 00:58:32.044 But the I think I think the point from
NOTE Confidence: 0.778589834666667

00:58:32.044 --> 00:58:35.693 that is that this is not just there's
NOTE Confidence: 0.778589834666667

00:58:35.693 --> 00:58:39.558 a broader inflammatory response and
NOTE Confidence: 0.778589834666667

00:58:39.560 --> 00:58:42.812 our assumption is that the islets
NOTE Confidence: 0.778589834666667

00:58:42.812 --> 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 --> 00:58:52.506 the type one diabetes field we tend
NOTE Confidence: 0.778589834666667

00:58:52.506 --> 00:58:55.629 to think of you know single T cell
NOTE Confidence: 0.778589834666667

00:58:55.629 --> 00:58:58.276 clone going into the islet hitting a
NOTE Confidence: 0.778589834666667

00:58:58.276 --> 00:59:01.140 single target and I think this is this
NOTE Confidence: 0.778589834666667

00:59:01.220 --> 00:59:03.760 is a bigger inflammatory response.
NOTE Confidence: 0.778589834666667

00:59:03.760 --> 00:59:04.280 Thank you.
NOTE Confidence: 0.778589834666667

00:59:04.280 --> 00:59:06.016 And I think that's why the lipase
NOTE Confidence: 0.778589834666667

00:59:06.016 --> 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: 0.7759770633333333
00:59:11.552 --> 00:59:12.800 but I'll I'll just ask you.
NOTE Confidence: 0.7759770633333333
00:59:12.800 --> 00:59:15.520 Had you mentioned or you
NOTE Confidence: 0.70661166
00:59:15.520 --> 00:59:17.720 had referred to the potential
NOTE Confidence: 0.70661166
00:59:17.720 --> 00:59:19.720 implication of regulatory
NOTE Confidence: 0.793536518181818
00:59:19.720 --> 00:59:22.378 CDAT cells and was wondering in
NOTE Confidence: 0.793536518181818
00:59:22.378 --> 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 --> 00:59:30.300 no differences, haven't seen it.
NOTE Confidence: 0.793536518181818
00:59:30.300 --> 00:59:32.600 And then have you also,
NOTE Confidence: 0.728210011428572
00:59:30.880 --> 00:59:31.650 but we're going to look
NOTE Confidence: 0.728210011428572
00:59:31.650 --> 00:59:32.600 for it, you know if there
NOTE Confidence: 0.7376229775
00:59:32.600 --> 00:59:36.440 are any differences in HLAC allotypes
NOTE Confidence: 0.7376229775
00:59:36.440 --> 00:59:40.040 or HLAU or non canonical MHC.
NOTE Confidence: 0.957117892
00:59:42.200 --> 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: 0.957117892

00:59:50.510 --> 00:59:55.158 worth doing EG and yeah,

NOTE Confidence: 0.957117892

00:59:55.160 --> 00:59:56.520 yeah, for the yeah,

NOTE Confidence: 0.957117892

00:59:56.520 --> 00:59:57.920 for the Kurds probably the

NOTE Confidence: 0.8989110425

00:59:58.040 --> 00:59:59.720 C and EI think.

NOTE Confidence: 0.7785933

01:00:01.800 --> 01:00:03.864 Yeah. Kevin, thank you so

NOTE Confidence: 0.7785933

01:00:03.864 --> 01:00:04.994 much for a wonderful talk.