US online. It’s my great pleasure today to introduce our Grand Round speaker, Doctor Kevin Harold. I’ve known Doctor Harold, it turns out, for 10 years now. We just figured it out. We met at the bedside. And I think for the fellows in the audience, this is a this hopefully will be a teaching moment because you get a sick patient, you’re not sure what’s wrong with him. You call the expert. And from that, we developed an
entire universe of research projects,

To me that exemplifies the beauty of Yale University and what we’re about unusual clinical circumstances taken back to the bench,

to the clinic,

But the best part of it all is the collegiality.

So I’m just remembering my first after we got our funding,

the very first research meeting that I had with Doctor Harold and Doctor Eric Murphy, who’s since left Yale.
Yeah, I'm not an immunologist, but they are. They both are card carrying immunologists and Doctor Mephre in particular doesn’t tolerate fools. So I was really intimidated by this meeting and I had established ground rules. We decided that this is an idiot free zone. We’re all smart, we can say whatever we like and we never have to be embarrassed. And I think that that principle has led us in the last 10 years because it turns out that even I had
something to bring to the table here.

So collegiality, respect,

creativity has led to a whole

field that I think we’ve opened

up here in translational research

on immune related adverse events

for endocrine toxicities.

So other than this whole world Doctor

Harold is actually really famous for

delaying type one diabetes in kids,

a major breakthrough in delivering

CD3 antibodies to children who

had started to develop type one

had started to develop type one diabetes giving them the anti CD3

antibody delaying the onset of

full blown islet cell destruction.
I don’t think he’s going to be talking about that today, but today we look forward to listening to all the cancer related studies that he’s done. So without further ado, thank you Doctor Harold for taking the time.

OK, thank you very much Harriet for that very kind introduction. I have to admit I was also quite pleased that we were going to set up our research meeting. So there’ll be no idiot free zone.

I appreciated that.
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 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
these agents became available for clinical use that there were adverse events that would occur as well since the balance that prevents us from developing autoimmunity is controlled by the same mechanisms. And we and it's been established for many years that even normal patients have immune cells that are capable of recognizing self antigens. So by tipping this balance it's fairly clear that one would be able to develop autoimmune diseases and that's that's what I'm going to be talking about today. Now the endocrine organs seem to be
particularly vulnerable to immune related adverse events with biologic therapy particularly with checkpoint inhibitors and you can this is from a review that came out a number of years ago, but there are many organs that are affected. I've on the right side we see just the endocrine organs that are affected. Fibroid disease is the most common and frankly can be over 15% in some series. The second most common is pituitary disease that can be difficult to diagnose, certainly important to diagnose. And then the other endocrine organs seem to be affected as well including the
the insulin producing beta cells that leads to the development of diabetes. Now I would point out from this graph that the development of these adverse events are most common with combination therapies and this is going to come up again in some of the data. I’m going to present to you that the combination of anti C2A4 plus anti PD one or PDL one seems to impart a higher risk of developing these adverse events than either agent alone. So the timing of them varies a bit. And sometimes we, as a practical matter, have a hard time determining whether
or not an adverse event that we may see is directly related to the checkpoint inhibitor that’s been given or whether it was just happening by chance. Because some of these adverse events such as thyroid disease or diabetes are relatively common in the population, particularly in the older population. But this graph shows you the timing of some of the more common adverse events. You can see that hypothesitis can happen several weeks after the development after a checkpoint inhibitors are administered. Some of the others that are also quite common tend to occur in a more acute manner.
Now as Harriet mentioned we started
I’m going to spend most of the rest of the talk talking about checkpoint
induced autoimmune diabetes because that’s where we’ve done the most,
the most work.
And let me just make it mention one thing about some of the others.
You know I do want to say sort of upfront that the mechanisms of some of these other checkpoint
induced endocrine adverse events are not very well worked out at all.
There is really one sort of lead paper that described the development of
autoimmune hypothyroidism that talked about expression of C of CTLA 4 on pituitary cells and suggested that what happened with anti CTLA 4 is that the antibodies bound to CTLA 4 on the pituitary fixed complement and destroyed the cells. But if you go through the paper carefully, it really wasn’t sort of. It wasn’t the ACTH producing cells, which is a common manifestation of hypothyroidism, it was prolactin producing cells and also TSH producing cells. So the precise mechanisms there
00:07:33.840 --> 00:07:35.840 really aren’t quite so clear.

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

00:07:37.380 --> 00:07:39.690 I think it’s still somewhat of an unknown or a wide open area for investigation I should say to understand the mechanisms.

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

00:07:42.185 --> 00:07:44.565 for investigation I should say to understand the mechanisms.

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

00:07:46.120 --> 00:07:48.460 But we focused our attention on autoimmune diabetes and hopefully have made some inroads into understanding the mechanisms here.

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

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

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

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

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

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

00:08:00.360 --> 00:08:04.728 when the patient #1 here was
referred to me by Doctor Kluger.

And the IT was a woman with Melanoma who have been treated with IPI and also had gotten nivolumab at that point and presented with diabetic ketoacidosis. And you know this was quite striking. This is someone who’s 55. And then subsequently there were a number of other cases that came from Yale of people over the age of 50 who were presenting with ketoacidosis and new onset hyperglycemia. And this was kind of striking and to me it was striking because you know we hadn’t seen it before the anti PD one drugs were new.
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 Ipilimumab 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,
a lot of the journals or some of the journals didn’t weren’t interested in it. And then finally it goes to one of the leading endocrine journals and it’s sent out for review and we get comments back from the review and we did a very extensive job answering all the comments. There were 12 pages of responses and so we sent it back and the reviewer comes back and says well if you know if this was really occurring the development of diabetes after anti PD one we would have known about it already.
So that was the end of that journal. We ended up publishing this as a letter actually in diabetes care and it is one of the most highly cited, certainly one of the most highly cited papers in diabetes care that is the first description of anti PD1 antibodies. So the reason I wanted to mention this story to you is as I’m going to show you later on that not only was the reviewer wrong in saying that we would have known about it, but mechanistically now we know why the reviewer was wrong. So that’s kind of nice to know.
why your reviewer is so wrong.

So what?

What are some of the features of this form of diabetes.

So first of all, it happens relatively very acutely.

Here’s some data.

This is coming from our colleagues at UCSF where we’ve put together patients at the two institutions and you can see this here are a few patients who developed checkpoint induced diabetes and their blood sugars are completely normal And then dramatically there is a big spike
00:11:16.960 --> 00:11:19.238 in their glucose levels.

And the other thing that’s quite interesting about that is if you look at their endogenous beta cell function by measuring C peptide, remember C peptide is cleaved from pro insulin when the beta cells make insulin and it’s a good measure of endogenous insulin production. Cause the insulin you inject doesn’t have C peptide. So if you take a look at the kinetics of loss of C peptide here that it happens very quickly. In fact in one case it happened very quickly.
while patients were following the individual while investigators were following the individual in the hospital. And the other point about this is patients generally go to 0 or near 0 in other words levels that are clinically insufficient. We'll come back to that later on. Here's a few other bits of information about the demographics of patients, so you can see the age. These are people who are older than you might expect with presenting with diabetes. It generally occurs with anti PD ONE or anti PDL 1. The hemoglobin A1 CS are elevated at probably
because of the degree of hyperglycemia.

About half of the patients are OR and depending on the review some even even higher percentage present with ketoacidosis.

See peptide frequently becomes undetectable.

The median time is about 11 weeks and only about 40% of individuals are positive for auto antibodies and this brings up a classification issue.

Some people call this type one diabetes.

As I’m going to explain to you,

I don’t think this is type one diabetes, it’s autoimmune diabetes induced by checkpoint inhibitors,

but it’s very different from classic
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
higher than is even represented by the 0.2 to 1.9% from the past reviews.

Now I mentioned not everybody has autoantibodies. Here’s some examples of that.

Some patients, if you take a look at three patients on the bottom, some start out negative, each of those antibodies are one of the auto antibodies that we measure in classic type one diabetes. You can see some patients start out negative, become positive, some patients start out positive, stay positive.
So it varies about 40% overall are positive. But the frequency of those who are positive,
which is what we, which is kind of the hallmark of spontaneous type one diabetes is relatively low. The loss of endocrine cells, this seems to be limited to the beta cells.

Now curiously the alpha producing cells in the islet, remember the islet is a collection of cells, delta cells and so on that make a variety of hormones. The loss of endocrine cells, this seems to be limited to the beta cells. The alpha cells sitting right next
to the beta cells are unaffected and the reason for that is not clear. But as you can see from this data from patients that we measure Glucagon here didn’t seem to make a difference in terms of their Glucagon levels. Now one of the early striking findings from our series of patients was that a high proportion of individuals were HLAD, R4. Now Dr. three and four are associated with classic spontaneous type one diabetes. But this proportion of DR4 is strikingly high and it’s higher.
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 Lilac Eisenbud from our patients here.
NOTE Confidence: 0.9349334425

00:16:04.520 --> 00:16:09.240 And what was done is we were doing
NOTE Confidence: 0.9349334425

00:16:09.240 --> 00:16:11.584 a genome sequencing of tumors and
NOTE Confidence: 0.9349334425

00:16:11.584 --> 00:16:15.616 identified a number of mutations in
NOTE Confidence: 0.9349334425

00:16:15.616 --> 00:16:18.462 a variety of genes that seem to be
NOTE Confidence: 0.9349334425

00:16:18.462 --> 00:16:20.630
00:16:20.688 --> 00:16:22.482 associated what seemed what seemed to
be at a higher frequency in people
00:16:22.482 --> 00:16:25.052 And then we ended up going back and
00:16:25.052 --> 00:16:29.888 doing sequencing of peripheral
00:16:29.888 --> 00:16:32.056 blood cells and finding that indeed
00:16:32.056 --> 00:16:34.642 there were germline mutations that
00:16:34.642 --> 00:16:36.452 seem to be associated with development
00:16:36.452 --> 00:16:38.880 And interestingly the one of the highest frequency was in this
00:16:38.880 --> 00:16:40.720 molecule called NLRC 5
00:16:40.720 --> 00:16:43.919 can take a look on the right,
00:16:43.920 --> 00:16:46.350 the frequency of individuals with
00:16:46.350 --> 00:16:48.637 NLRC 5 variants was in our series 65%.
Now it’s not a huge series because we don’t have tons of patients. We had 13 here. But you can see that statistically, it turns out to be in a much higher frequency compared to those individuals without checkpoint induced diabetes. Now what’s the importance of NLRC 5? So NLRC 5 actually tends to be evolved in a class one MHC antigen.
00:17:41.732 --> 00:17:46.016 responses in cancer patients that
00:17:46.016 --> 00:17:49.424 methylation of NLRC 5 reduced
00:17:49.424 --> 00:17:53.867 NLRC 5 seems to be associated with
00:17:53.867 --> 00:17:57.067 impaired CTL activity and clearing
00:17:57.177 --> 00:17:58.518 tumors.
00:17:58.520 --> 00:18:00.962 The its expression seems to be
00:18:00.962 --> 00:18:03.050 correlated with survival and in
00:18:03.050 --> 00:18:05.360 diabetes it’s also been associated
00:18:05.360 --> 00:18:09.600 with beta cell antigen presentation
00:18:09.600 --> 00:18:11.920 and the interferon response.
00:18:11.920 --> 00:18:13.720 So for example,
00:18:13.720 --> 00:18:17.048 the NLRC knocked down beta cells
00:18:17.048 --> 00:18:19.832 seem to have a decreased interferon
00:18:19.832 --> 00:18:22.238 induced class one MHC expression
00:18:22.240 --> 00:18:26.344 and seems to be associated with
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 1 dependent antigen presentation,
NOTE Confidence: 0.9349334425
00:18:32.608 --> 00:18:40.720 much the same as the classic Class 2 transactivator. It’s responsible for
NOTE Confidence: 0.81096498125
00:18:42.960 --> 00:18:46.220 bringing peptides into the endosome
NOTE Confidence: 0.81096498125
00:18:50.228 --> 00:18:54.716 for processing and placing them on developing class one MHC molecules.
NOTE Confidence: 0.81096498125
00:18:57.840 --> 00:18:59.416 It’s expression seems to be induced by interferons,
NOTE Confidence: 0.81096498125
00:19:01.340 --> 00:19:03.560 particularly interferon gamma
NOTE Confidence: 0.81096498125
00:19:06.520 --> 00:19:08.848 So this review actually 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
00:19:14.880 --> 00:19:16.719 is work that Anna Pertigato did,

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

00:19:19.600 --> 00:19:22.720 which is an important transactivator

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

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

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

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

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

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

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

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

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

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

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

00:20:02.362 --> 00:20:05.332 or potentially presentation of peptides
by individuals who have this mutant.

So to summarize these two points, the there seems to be evidence for mutations or differences. In class one and Class 2 MHC molecules that are associated with development of checkpoint induced diabetes.

First of all HLAD R4 is common and perhaps that leads to the development of an auto autoreactive repertoire. This NLRC 5 mutation also seems to have some role in potentially in expression of molecules. A presentation of molecules by beta cells or even potentially in affecting a subgroup of CDA positive T cells have
been associated with immune regulation.

Now let me just raise some questions about these two points by making this point.

When we've looked at auto-antigen reactive T cells in patients with checkpoint induced diabetes, we've looked for auto-antigen reactive T cells that are reactive to conventional type one diabetes. We don’t really find an increase. So if you take a look at that, we've looked at T cells that are identified by binding to class one MHC
tetramers that are loaded with the peptides that are shown on the left side. If you look at the frequency of these cells on the right side and the individuals treated with checkpoint inhibitors, those who don’t have diabetes or do, there’s really no difference. So it at least would suggest that the frequency of cells is not increased in those individuals who are developing checkpoint inhibitors.
as a preface to this data the the,
the low hanging fruit on this was well,
these individuals had an autoreactive
repertoire. They had Dr.
Four, we removed the checkpoint blockade.
These cells just did their thing,
don’t think so.
It could be that there are cells that
are reactive to unknown auto antigens
and as I’ll show you in just a moment,
there is some evidence that that
might be true, but that’s not all.
There are also there’s also evidence
of inflammatory lesions that or
inflammation that’s occurring
in the pancreas that may be very important for development of checkpoint induced diabetes. And this actually came from a clinical observation from patients here in which we found that there was an increase in amylase and lipase in individuals who ultimately went on to develop diabetes. They don’t develop clinical pancreatitis. But here we’re looking at the amylase and lipase level on one individual who is who develops checkpoint induced diabetes and you can see the lipase on the left bumps and then red is when they developed diabetes.
and the amylase bumps and then red

is when they developed diabetes.

If you look at our entire series

and look at the relative levels

of lipacer amylase on the bottom,

you can see that the that that

both are elevated prior to the

development of diabetes.

Now interestingly it prompted us

what well like what’s

to look at what well like what’s

actually happening in the pancreas.

They were not symptomatic and so we

ended up looking at CT scans that

fortunately we had from before and

after individuals presented with diabetes.
And what we found if you take a look at the CTS and on the top here is the red arrow identifies the pancreas. The there actually seem to be shrinkage of the pancreas in individuals who went on to develop checkpoint induced diabetes. So it’s suggested that there is more than just a direct attack on beta cells that there may actually be a broader attack in a broader inflammatory response in the pancreas. And unfortunately one of our patients died as soon after they had developed checkpoint induced diabetes.

But we had the opportunity to take a look at their pancreas by immunohistic
chemistry and this is what we found.

You can see that there are plenty of CD45 positive immune cells that are infiltrating the islets and that are infiltrating the pancreas.

They are not just in the islets and in fact many of them are outside of the islets, as you can see by standing for insulin on the right.

And there are both CD4 and CD8 positive cells.

Chromagranin identifies the endocrine cells.

They’re infiltrating the islets and they’re outside of the islets.

And if you look at cytokines that
are present in the pancreas,

we find both interferon gamma and TNF.

And interestingly,

one of the other findings from this immunohistochemical analysis is PDL

one was actually induced on beta cells in and on the other endocrine cells in this patient who died with a checkpoint induced diabetes.

We thought that PDL one was actually protective against diabetes.

So what’s going on here?

So let me just make the point and again this is work that Anna Pertigato has done that indeed inflammatory mediators,
particularly gamma interferon will induce PDL One on beta cells.

There is an interferon response element in the promoter of PDL One and as you can see by looking but by flow interferon gamma. This is human beta cells.

Interferon gamma and interferon gamma with TNF induce expression of PDL One on beta cells and it seems to be dependent through signaling by gamma interferon because if you give rexolitinib to block Jack signaling through Stat One, you can inhibit the expression of PDL One.
Now there was good evidence for the importance of PDL 1 in development of autoimmune diabetes and most of this work came originally from Arlene Sharp. The work that I'm showing on the left is from a paper of hers a number of actually 20 years ago now that showed if you knock PDL one out of this susceptible mouse strain NOD that the mice spontaneously developed diabetes at a very young age. Furthermore, if you gave anti CD3 antibody to mice that spontaneously developed diabetes at a very young age.
diabetes and induced remission
with the anti CD3 antibody,
if you gave anti PD one or anti PDL one,
this is work by Jeff Bluestone
and Brian Fife On the right side,
the mice immediately redeveloped diabetes.
So this work suggested that PDL one
had a critical role in maintaining
non development of diabetes in
a susceptible host.
And here are some additional studies
from Arlene’s lab that showed
if you took wild type cells,
transferred them into APDL 1
knockout or a wild type
NOTE Confidence: 0.865200372631579
host if you put them into the knockout recipient, which is on the left side in the open circles, mice rapidly developed diabetes whereas they didn’t at the same rate if you put them into the wild type recipient. And it also was shown in her work that the importance of PDL One was indeed on the islets. But if she transplanted PDL 1 deficient beta cells into either wild type or knockout mice, which is shown on the on the right, the PDL 1 knockout islets were more rapidly killed compared to wild type eyelids. So PDL one seems to have some unique
features that’s important in in protecting against autoimmune diabetes.

Now we did some additional studies looking comparing anti PDL one and anti CTE 4 because let me go back to that paper in that letter in 2015 and the comments from the reviewer that pointed out, well if this was really important we would have known about it. And if you take a look at the
Mouse data here and this has been reproduced in other labs, anti CTLA 4 doesn’t do this seems to be unique for anti PDL 1. And so we did some studies to try to identify what’s different about anti PDL one and anti CTLA 4 in induction of diabetes and I’m going to go through the data fairly quickly. We did this by performing single cell RNA seq on infiltrating cells and islet cells from mice that had received either of these checkpoint inhibitors. And let me first point out that in the presence that when these susceptible mice and OD mice are given anti C24,
there are cells that infiltrate the islets.

It’s not that they don’t develop insulitis, it’s just that they don’t develop diabetes.

They don’t go on and kill, kill the beta cells.

So first of all, when we look at immune cells that are infiltrating the islets,

you can see there is a difference.

If you take a look at panel D in the MELD analysis,

there’s a difference in CDAT cells that are infiltrating the islets when

the when the mice are treated with anti PDL 1 compared to anti cetal A4.
And there are a number of genes that are differentially expressed including some of the ones that you might expect such as T cell Interferon, Gamma Granzyme B and even PDL one as we would have predicted, as well as Perfran and the volcano plot showing you the differences in expression in the CDA T cells as shown in the bottom. Now what about the cells that are infiltrating the eyelids? Are they the same? Maybe they’re different. And this is the data that we have to date. And fortunately I can’t go into this and more with more granularity.
except to point out that yes, they are different. They are not the same cells that are being driven to the eyelids in when with the two different checkpoint inhibitors. If you just take a look at the frequency of various clonotypes you can see with anti PDL one in mice that do develop diabetes, there seems to be a relative selection of particular clonotypes compared to the anti C2E4 treated mice. Now macrophages also seem to be different for reasons that we don’t completely understand.
But you can see that they express PDL one, they themselves express PDL one. They produce CXCL 10, which is important in recruiting cells to the islets, as well as Stat 1 indicating they’ve been looking at interferon gamma. Work from Emil Yunanoway’s lab had actually pointed out that these cells seem to be the critically important cells for initiating checkpoint induced diabetes in this model. Now in addition there are changes in beta cells.
of PDL one in human beta cells that were treated with interferon gamma. And indeed if we looked at genes that are differentially expressed with interferon gamma, you can see that there are a whole lot of genes that have some immune response properties. Now the reason that we think this is important is because seeing inflammatory when beta cells see inflammatory cytokines, they make a number of important immune ligands such as CXCL 9, CXCL 10 important for recruiting.
cells to the islets and as well as increase expression of class one.

MHC when we looked at this again is with human cells.

When we looked at other features of human islets exposed to gamma interferon, we found that actually there was induction of FAS suggesting that indeed that cytokine might induce a killing of beta cells.

And if you take a look at impanel E you can see that in the PDL expressing cells we we find this morphology suggesting the cells are actually dying.

And indeed if we look at at
00:34:08.120 --> 00:34:10.640 the percentage of dead beta cells

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

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

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

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

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

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

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

00:34:28.999 --> 00:34:32.797 of a unique subgroup of beta cells.

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

00:34:36.280 --> 00:34:37.260 the fate,

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

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

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

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

NOTE Confidence: 0.9614282
with anti cetal E4 or anti PDL one
and then this unique a cluster
of beta cells that seems to be
uniquely found in anti PDL one.
The main beta cells express the same
log in so they just showed you with
human beta cells CXCL 10 PDL one.
Class one MHC goes up stat
one is signaling and trail is
actually increased as well.
But in the unique beta
cells there’s also changes,
including reduced expression
of a number of the beta cell
identity genes such as NTX 6.1,
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
what can we do about it.

So let me point out that in follow up work that we did to try to figure out could we based on this knowledge stop the development of checkpoint induced diabetes.

We first tested whether anti cytokine antibodies might be able to do that.

And I've shown you already the critical role of interferon gamma and potentially TNF in development of checkpoint induced diabetes at least in mice and evidence in humans that both of these cytokines were present in the pancreas of an individual who died with checkpoint induced diabetes.
What happens if you neutralize those cytokines?

And you can see in the top here if you gave the combination of anti PDL, interferon gamma and anti TNF to mice treated with anti PDL one, you could indeed prevent the development of checkpoint induced diabetes in the mice. Furthermore, if you blocked a little further downstream with a Jack inhibitor and this is an ongoing collaboration with folks at Pfizer.
and with two new Jack inhibitors, the identities of which we don’t know except we know they’re different. But as you can see Jack inhibitor 1 looks pretty good in terms of developing preventing the development of checkpoint induced diabetes. So to summarize what I’ve just told then what we think is there’s actually an inflammatory cycle that’s going on between immune cells and beta cells that leads to the development of a checkpoint induced diabetes in response to interferon gamma. Beta cells in turn make a number of immune regulatory molecules.
that recruit other immune cells, activate immune cells leads to increased production of inflammatory cytokines particularly interferon gamma. It leads to expression of PDL one. When you block PDL 1 you seem to block the stop signal in immune cells that otherwise would cause them to leave the eyelid and the immune cells then are there in the eyelid and capable of going on and killing the insulin producing cells so and killing beta cells. So what is, is there anything we can take home from
00:38:43.294 --> 00:38:45.484 this in terms of treating patients?

00:38:45.484 --> 00:38:48.858 And let me just start by mentioning

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

00:38:53.324 --> 00:38:57.234 another letter in diabetes care

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

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

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

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

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

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

00:39:11.277 --> 00:39:13.515 patients who are going to develop

00:39:13.582 --> 00:39:15.862 checkpoint induced diabetes who already

00:39:15.862 --> 00:39:18.624 may have pre-existing type 2 diabetes.

00:39:18.624 --> 00:39:21.390 And that’s the explanation I’m going

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

So this is an individual with pre-existing type 2 diabetes had much worsening glucose control. You can see with a hemoglobin A1C of 11.6% but did have detectable beta cell function. The C peptide was 993 which is you know plenty respectable and was also auto anybody positive. So they believe that this patient had immune mediated diabetes. They gave the patient infliximab, the anti TNF antibody and as you can see the glucose is improved. The hemoglobin A1C came down and so that was
that seemed to be very impressive to those investigators.

The patient had been treated with insulin.

They stopped the insulin.

Now since we saw that, we’ve also treated a few patients here and I want to mention this work that’s been ongoing by Noam and Anna for treating patients who’ve developed checkpoint induced diabetes with infliximab.

Let me show you 2 cases.

This patient had a history of type 2 diabetes like the previous one that I showed you and presented with very very high glucoses and the the
hемoglobin A1C in the past had been a fairly reasonable and the patient had not been treated with insulin. There was a bump in the amylase and light paves just as I showed you in one of the first slides. And then the glucose became markedly elevated and as you can see the patient received 3 doses of infliximab. And if you take a look at the response curves and in terms of the C peptide, it actually did seem to these are random C peptides. I should point out the C peptide did seem to improve after the
patient was treated with infliximab
and the glucose was also better.
Now these are, these are anecdotal,
these are not performed in a rigorous endocrine setting where we're actually stimulating beta cell function.
But nonetheless and I think from the patient’s point of view, the fact that he was able to get off of insulin and his hemoglobin A1 CS were subsequently improved is is clinically meaningful.
Here’s another case.
This individual with metastatic Melanoma was treated with EPI and Nevo and had adverse events
including uveitis and diarrhea that have been treated with steroids and hyperglycemia was noted at cycle 21. There was no prior history of diabetes in this patient and previous hemoglobin A1 CS have been normal. This patient again presented with a very elevated hemoglobin A1C and the glucose was also quite elevated. This patient did not have evidence of ketoacidosis whereas the previous patient that I showed you did. And remember that ketoacidosis is a sign of substantial insulin deficiency. This patient was auto antibody negative.
So here we’re looking at the random C peptide levels, one of them is stimulated, the last one that was just done a few days ago and the glucose levels improve probably with the medical care of the patient received but the C peptide also seemed to be pretty substantial. This is markedly different than what I showed you in one of the first slides where the C peptides pretty much go to undetectable in the majority of patients who present with checkpoint induced diabetes and do so fairly rapidly.
So to conclude adverse events are not infrequent with checkpoint inhibitors. In fact I would change that to say adverse events are common with checkpoint inhibitors. Most common is thyroid disease and hypotesitis but diabetes also occurs in about 1% of checkpoint inhibitor treated patients. Now one thing I should mention is for patients and you know we see them. Thanks to all of you in our clinic. But for the patients this is a difficult disease.
I mean you know it’s it, it, it’s a lot different when a 12 year old presents with. It’s not that the disease is easy for a 12 year old, but it’s even more cumbersome for a 65 or 75 year old who now has become insulin deficient. Completely dependent on exogenous insulin for maintaining metabolic control. So it is quite a burden for patients. So preventing the disease would obviously be would result in very significant improvements in quality of life. It’s most common in patients treated with anti PD one or anti PDL 1.
antibodies and in patients or HLAD R4. Still a lot of work needs to go on to understand what is the significance of DL DDR4 or the significance of NLRC 5. But it nonetheless suggests that there is some change or some difference in these patients in presentation of either class one or Class 2 or both. MHC presented antigens, pancreatic inflammation is frequent prior to the development of checkpoint induced diabetes. Curiously, PDL one’s expressed on beta cells. And I think we have to conclude that in spite of expressing PDL.
One on beta cells and in spite of showing its extraordinary protective effect in animal models of disease that when you give a checkpoint, when the checkpoint inhibitor is given that protective, that protective blockade is gone. And even afterwards PDL one expression is no longer able to stop the development of diabetes. And I think the identification of mechanism suggest have suggested a therapeutic strategy inhibition of inflammatory mediators may potentially halt progression of diabetes and beta cell loss with checkpoint.
induced diabetes and a short acting inhibitor potentially Jack inhibitors would warrant some further testing.

One last comment, let me mention that you know I think one of the interesting things about all of the adverse checkpoint induced adverse events is, is it a feature of the checkpoint inhibitor, a feature of the tissue or a feature of the patients or all three of these. And let me just point out this work from Jackie Mann in our group who looked at checkpoint inhibitor induced colitis and she did this by single cell RNAC.
This work was published fairly recently, but let me point out that a number of the molecules that I just told you about being found in the pancreas of checkpoint induced diabetes can also be found in patients who develop colitis, suggesting that we might even think about a broader use of various inhibitors, not inhibitors. Obviously that would prevent the anti tumor effect of the checkpoint inhibitors, but might be given sequentially after the anti tumor effects of the checkpoint inhibitors and that might be rapidly tapered in the event that further cancer therapy is needed.
So I’m going to close with that. I want to thank a number of individuals, particularly Harriet, who’s been a colleague for a decade now, and a number of individuals in her group who’ve I’ve had the good fortune of working with. As well, I want to mention Lalak’s work on identifying the LLRC 5 mutations. I showed you some of Jackie’s work. Nolan is continuing this work with particularly with giving with the NLRC 5 mutations and therapies of checkpoint induced diabetes.
Anna Perdigata did a lot of, did actually all of the work, the single cell work with the mouse models and it’s continuing to go on to do that. And we have colleagues at UCSF and funding. You can see on the right side here. So I’ll stop there and I’m happy to answer any questions.
role in central tolerance and

if you saw increased checkpoint

inhibitor autoimmunity in

hypothesitis or hypothyroidism.

I'm sorry I I missed the second part.

I understood your

question about central tolerance

but so and so whether you saw

rather than an LRC 5 mutations,

germline ingest type one diabetes

or well check one inhibitor diabetes

or whether also intra,

I think that’s still somewhat

of a ongoing question.

I think it’s unlikely Harriet may have a
thought as to whether it’s more likely.

Yeah, I can Norm can answer it as well.

So we have looked in at NLRC 5 SNPs in other other toxicity.

It seems to be higher as well in hypothesitis but not colitis.

That’s as far as we know so far.

But the statistics are they’re not this numbers are small.

Still, that’s exactly what Norm is working on right now.

Yeah. I mean it could be

Still, that’s an interesting question.

But you’re taking us back to the original model.
These patients had a repertoire ready to go. And look, it could be right. I mean just because we don’t see the usual suspects doesn’t mean that there aren’t suspects. Kevin, that was an amazing lecture. It reminds me of 2015 or earlier when we first started using these agents and we’re seeing wonderful responses. And you know patients with lung cancers and others would have these problems and you know they’d be throughout the hospital and they wouldn’t get the care they needed because no one recognized
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 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
first because there is some literature suggesting that those who develop these adverse events do better in terms of their anti cancer activity and indeed our patients did well in general, but there is a publication for sure suggesting that those who develop hypothesitis had better outcomes in patients with Melanoma. So, so I'm not certain but I think it's certainly not a negative thing in terms of the cancer response and it may look it may, I mean just because you don't develop
toxicities doesn’t mean you can’t do well with checkpoint inhibitors. So in terms of when I would treat if we knew how to treat type autoimmune diabetes, if we knew what the antigens were for example, we could dream about coming up with some sort of antigen specific prophylactic therapy and give that before we give the checkpoint inhibitor. At this point, I don’t think we have that. And so my suggestion would be to carefully follow patients, look for the signs that identify
those who are at risk of developing it and then when is appropriate in terms of the cancer therapy strategy, if it’s possible come in with some short term inhibitor. Thanks. Thanks, Kevin. Dr. Wagner. And then just great talk, just a couple of simple questions. Are there gender differences in toxicity? We not that we had seen in diabetes. Not significantly different. Harry looks puzzled. Why I would ask that only because autoimmune disease is so much.
more common in women than men. Yeah. We didn’t find that we’d love. Yeah. The only thing I could say is type one diabetes is not really general.

No, I realized that, but this isn’t type 1 to obvious and this is for either of you. I mean do you think that that clinicians really have a sense of how abrupt the onset is of of diabetes in this situation and are looking for it. I mean because you know it’s happening not at week two, it’s happening at week six or eight.
The presentation is very acute. I mean you know there are some number of people out there as these therapies are used more and more we're going to die from this. So there have been deaths, there will be deaths where there isn't sufficient there, there isn't sufficient insight. The cup, the two patients that we haven't showed that we were able to give the TNF that was just chance. The first one was in hospital because of colitis or something else and that's when they noticed the ship going up.
The second one is an EMT and he noted his only party, that's it called a million started checking his glucose. But there there's not sufficient awareness. Yeah. The but the other sort of take home point from that is you need to be aware of this acutely because I showed you the C peptide levels when it goes to 0, there's no turning back. So I think close surveillance was important. Yeah. I can tell you that I don’t educate patients, you know so, so look for these kinds of things.
Can I just a quick, very, very interesting data, Two quick questions. One for the germline NLCR 5 mutations, you may have said this, but are those associated with standard classic autoimmune diet type one diabetes as well? Yeah, there’s, there’s that one paper from Dejo Isrich there’s that one paper from Dejo Isrich suggesting that the answer is no not really, not one of the important players. None the though seems to be important and it it can affect antigenicity and development of diabetes.
And did you go back so you made a comment early that you know the, the, the, the 40% of the patients who have autoimmune, who have auto antibodies to to, to the islet cells. There's only relatively it was only 40% as opposed to all of them. And that was one of the reasons why this looked like this, why this was different than standard, you know, type one diabetes did when you went back and you started looking at all these mechanisms in your patient population, did you, did you look at the difference.
in those patients who had auto antibodies and those who did not, you know, yeah it’s interesting point. No, to my knowledge, I don’t think we’ve done that. That’s an interesting point way to kind of. Yeah. So we have a couple of online questions. Yeah, confirm this here, this hypothesis. Yeah. So we have a couple of online questions. Oh, oh comments that would be easy for you to look at it there. OK. Anna has a comment.
It’d be helpful to monitor blood glucose more carefully in patients who have lipase elevation and in some patients there’s mild elevation in glucose before severe presentation. So monitoring them more carefully may be valuable. Yeah, a very good point.

And then there’s a question about racial differences in toxicity. Most of our patients are Caucasian. Yeah, I think we, I think that’s right. Most of our patients are Caucasian. 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: 0.7047284125
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 --> 00:57:02.996 the lipase elevation occurring before
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

89
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.
But if you knew that that had a higher incidence of going to diabetes, maybe that’s a population you could treat.

Hello, I’m relatively new to immunobiology, but I had a question about the slide where you showed the immunohistochemistry results and you said that you saw signal or you saw standing outside of the eyelids. And I was wondering if you could further explain the significance on why you were excited about them being outside of the islets.
00:58:24.272 --> 00:58:26.598 excited if they were inside the islets.
00:58:26.600 --> 00:58:32.044 But the I think I think the point from
00:58:32.044 --> 00:58:35.693 that is that this is not just there’s
00:58:35.693 --> 00:58:39.558 a broader inflammatory response and
00:58:39.560 --> 00:58:42.812 our assumption is that the islets
00:58:42.812 --> 00:58:46.999 cells can see the soluble mediators.
00:58:47.000 --> 00:58:49.830 So I I think you know we at least in
00:58:49.916 --> 00:59:02.506 the type one diabetes field we tend
00:59:01.220 --> 00:59:03.760 to think of you know single T cell
00:59:01.140 --> 00:59:04.280 to think of you know single T cell
00:59:03.760 --> 00:59:04.280 Thank you.
00:59:04.280 --> 00:59:06.016 And I think that’s why the lipase
00:59:06.016 --> 00:59:07.200 and amylase are elevated.
00:59:10.280 --> 00:59:11.552 I have, I have many questions
but I'll just ask you. Had you mentioned or you had referred to the potential implication of regulatory CD4 T cells and was wondering in your comparison between anti PD1, anti CTLA 4 differences, did you see any, no differences, haven’t seen it. And then have you also, but we’re going to look for it, you know if there are any differences in HLAC allotypes or HLAU or non canonical MHC. That’s a good question and not that I know of.
but that certainly is something
NOTE Confidence: 0.957117892
worth doing EG and yeah,
NOTE Confidence: 0.957117892
yeah, for the yeah,
NOTE Confidence: 0.957117892
for the Kurds probably the
NOTE Confidence: 0.8989110425
C and EI think.
NOTE Confidence: 0.7785933
Yeah. Kevin, thank you so
NOTE Confidence: 0.7785933
much for a wonderful talk.