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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Changing Treatment Paradigms in Type 1 Diabetes: Role of Anti-CD3 Targeted Therapy -- Anti-CD3 Monoclonal Antibodies to Prevent/Delay Onset of Type 1 Diabetes

[Slide: Program Intro Slide]

Dr. Herold:
[Slide: Title and Faculty] My name is Kevan Herold, and I'm a Professor of Immunobiology and Internal Medicine at Yale University. Today we'll be talking about anti-CD3 antibodies to prevent or delay type 1 diabetes. Joining me on this program is Dr. Stephen Gitelman, who is Professor of Pediatrics at the University of California, San Francisco, and Director of the UCSF Pediatric Diabetes Program. Steve?

Dr. Gitelman:
Thank you Kevan. It's a pleasure to be here with everyone today, and to talk about the excitement we have in the field of altering the course of type 1 diabetes. [Slide: Prevention vs Intervention] I'm going to set the stage on the progress that we've made over the past few decades, and focus on thoughts about prevention versus intervention after the onset of clinical type 1 diabetes.

[Slide: Altering the Course of T1D] This is a reconfiguration model that George Eisenbarth first showed about 50 years ago, which outlines still a lot of our current thinking about progression from someone who might be at risk for type 1 to actual clinical disease. And, we know that those who are destined to develop type 1 have genetic risks; a lot of this is borne in the HLA locus, but there are actually over 50 different regions in the genome now associated with risks for type 1. So, this genetic risk synergizing with one or more environmental factorsstarts to push you down this cascade towards type 1 diabetes. We can now track this with activation of the autoimmune response with up to five different anti-islet autoantibodies, and then you'll progress through a stage where beta-cell function starts to decline, and then you approach new-onset clinical disease where you present, of course, with hyperglycemia with or without ketoacidosis, and inevitable loss of beta cells over time.

So, this paradigm opens up some thoughts about where we might intervene in this process. We can think about primary prevention as an intervention before the onset of autoimmunity, secondary prevention when autoimmunity has taken hold but before the development of clinical disease or shortly after the onset of clinical disease, where we try and prolong the honeymoon phase. And, one further point I'll make here is there's also a concept of stages of disease, and this will come up when Kevan talks about prevention trials. So, we refer to stage one, where there's the presence of two or more autoantibodies and these people are destined to eventually develop type 1 diabetes. Stage two is the presence of the autoantibodies with some abnormalities in response to an oral glucose tolerance test but prior to frank clinical diabetes. Stage three is what you're used to thinking of as the clinical onset of diabetes.

Let's talk for a minute about potential interventions at these different stages. [Slide: Primary] So again, primary prevention is for those at genetic risk but not yet any evidence of autoimmunity. So, you could have a positive family history for type 1, coupled with genetic risk, and there are different ways to define this now. We can certainly look at higher risk HLA haplotypes or their genetic risk scores. And, some potential examples of primary prevention could include an attempt to avoid obesity, vaccination against infectious diseases that might be linked with the onset of type 1, use of probiotics to alter the microbiome, a gluten-free diet and efforts with vitamin D supplementation. I should also stress, perhaps the best study in this space has been to address the question of whether avoidance of

cow's milk will prevent the onset of type 1. That study, unfortunately, called TRIGR, did not.

[Slide: Secondary] Let's move now downstream to secondary prevention. Remember, this is for people who have the presence of autoantibodies with or without evidence of beta cell dysfunction. And, in prior decades, we've spent a lot of time and energy trying to conduct well-powered, large, long-term studies to try and prevent the onset of diabetes. One agent that we've used a great deal is insulin because that's one of the earliest things that your immune system responds against. And, we've given insulin in a variety of ways – orally, inhaled, intranasal, parenteral. There was also a study with nicotinamide, as well as another antigen, glutamate decarboxylase. So, all of these studies had strong preclinical rationale. As I mentioned, they were well-designed, well-conducted, well-powered studies, but unfortunately, they were all negative. And, one of the reasons we're talking today is the news in this field is not all negative. Kevan is going to share some experience with the anti-CD3 monoclonal antibody teplizumab in the prevention effort, and I won't address that further in my comments.

[Slide: Tertiary] Finally, we can talk about tertiary prevention. Remember, this is the onset of clinical disease where the effort is to prolong the honeymoon phase, to preserve that 10 to 40 percent of beta-cell mass that may still be remaining. And, over time, hopefully this may lead to a delay in the complications of type 1 diabetes, as well as, of course, reduce exogenous insulin needs and allow better glycemic control. The efforts in this arena really started in the '80s with a series of clinical trials, many of which were conducted with cyclosporin, which of course is a broad immunosuppressant. This actually worked, but the challenges with this approach is not everyone responds, it requires continuous treatment, and of course there are potential risks and toxicities from this approach. Nonetheless, as the field has evolved, we've realized that there are more refined approaches with immunomodulatory agents that allow us to get in and potentially alter the course of type 1.

[Slide: Immunopathogenesis] And, our thoughts about this axis have evolved over time as well. So as you look at this paradigm here, potentially autoreactive naive T cells that escape thymic selection get activated in the peripheral circulation and become autoreactive or T effector cells that traffic to the islets and destroy the islets. So, the thought is, is there a way to come in and target any aspects of this axis and alter the course of disease? And, we're here today, of course, because there's great hope on this front. [Slide: Immunopathogenesis, cont'd] In the blue boxes are agents that have been successful in phase II new-onset studies. So, well-powered studies that have met their primary endpoint. We don't have time to talk about the whole host of agents here, but we're going to focus in on this approach with the anti-CD3 monoclonal antibodies and teplizumab.

[Slide: Prior Studies] Just a quick overview of anti-CD3 before I turn it over to Kevan, who will talk in more detail. These efforts were really launched in the nineties, looking of course first in a preclinical model of type 1 diabetes, the non-obese diabetic mouse, and the powerful observations from Lucienne Chatenoud and Kevan's work with Jeff Bluestone is that a short-term treatment with anti-CD3 monoclonal antibody can reverse diabetes and lead to lasting remission. So, this led to a series of clinical studies, phase I, II and now III, with two different monoclonal antibodies – teplizumab and otelixizumab – and these results have shown that we can indeed preserve beta-cell function out to 24 months and in some cases beyond from the initiation of treatment. And so, this has really been quite a powerful observation and very exciting. [Slide: Prior Studies cont'd] The results suggest that those who are younger seem to do better, along with those who had better glycemic control at the time the treatment was initiated, and this is thought to be an offering of treatment to those who are at an earlier stage of type 1 diabetes.

Just a quick thought on one of the compounds, otelixizumab. There's been concerns that with the higher doses initially used with this drug that treated subjects had Epstein Barr virus reactivation response in some patients. So, that's a Phase III study where the investigators used a 20-fold lower dose of drug. It was safe, but unfortunately, it wasn't effective in preserving beta-cell function. I'm not currently aware of follow-up studies with this agent at this point in time. However, there have been a series of further studies now with teplizumab. There's an ongoing phase III study in new-onset type 1 diabetes for those 8 to 17 years old, and there's an interesting combination trial using teplizumab with a modified Lactococcus that expresses pro-insulin and interleukin-10.

[Slide: Will Intervention Earlier…] And so, with that, there are a number of questions that can come up, of course, but one of the questions in the field is it's great that we've had this success at this new onset phase of things, but what about trying to come in earlier and prevent type 1 diabetes? Will it be effective there? Will it be even more effective that what we've observed in our new onset studies? So, I'll stop there and turn it over to Kevan.

Dr. Herold:
Thanks very much, Steve. I will be talking about teplizumab, one anti-CD3 antibody – and the delay or prevention of type 1 diabetes. [Herold Slide: Title Slide] So, let me first begin by a very brief review of the role of the CD3 surface molecule in T-cell signaling and what the anti-CD3 antibodies actually do.

[Slide: CD3 Cell Surface Marker] CD3 is a cell surface marker. It's a complex of a number of different protein chains that are found on the surfaces of CD4+ and CD8+ T cells. It's a protein complex that has four distinct chains and it associates with the T-cell receptor

alpha/beta chain. The T cell-receptor alpha and beta chain are responsible for recognizing their antigens, the targets of the T cell, that is presented by the major histocompatibility complex. For CD8+ T cells, these antigens, these peptides, are presented by class I MHC, whereas for CD4 cells, these are presented by class II MHC. The T cells are activated by binding to that MHC antigen complex, and the T cell then will make cytokines, and it will proliferate. The CD3 molecule, therefore, is essential for the signaling capacity of the T cell, and the signaling cascade that then follows. The T cell itself is activated, it makes cytokines that will affect other T cells, and the entire process gets amplified greatly.

[Slide: CD3 and TCR]

Dr. Herold:
On this slide, we look at the interactions between the CD3 complex and its targets, the MHC class II molecules with an antigen, peptidesin its binding groove. In this case, we're looking at the interaction of a CD4+ T cell that, as I mentioned already, recognizes antigen presented by class II MHC molecules. So, you can see the various components to the CD3 complex. They include epsilon, delta and the zeta chains, and those are all responsible for signaling of the T cell when the alpha and beta chains, the T cell receptor, interacts with the MHC molecule that is presenting in the antigen. Now, the CD4 molecule, which is found, of course on CD4+ T cells, gets involved in this interaction and is responsible for phosphorylation of the zeta chain, which is required for T cell activation.

[Slide: Anti-CD3 mAbs] Now, the anti-CD3 antibodies that have been tested in type 1 diabetes induce a partial agonist signal to T cells through the CD3 complex. What do I mean by that? In the diagram that we just discussed, if you give a full-blown signal to the T-cell receptor by presenting the antigen in the context of the MHC molecules with all of the signaling that is involved in standard T cell receptor signaling, the T cells get quite excited, they make a lot of cytokines, and we recognize the production of cytokines clinically as a cytokine release syndrome if many T cells are activated. In contrast, the modified anti-CD3 antibodies, which bind to the CD3 epsilon chain, deliver a much weaker signal to the T cell, a so-called partial agonist signal. Now, I think it's important to recognize that the T cell receptor signaling is not an on/off switch. Weak agonists have different effects than very strong agonists. And eventually, that is going to play out into how we think the drug may actually be working. It appears as though the effect of the anti-CD3 antibody is greater on CD8+ T cells than CD4+ T cells, for reasons that are not completely clear.

[Slide: Teplizumab] Here's a diagram that shows you this anti-CD3 antibody, teplizumab. This is a humanized anti-CD3 antibody, and there are mutations in the Fc portion, the heavy chain, of the immunoglobulin in which the amino acids at position 234 and 235 have been changed to alanines. This eliminates the binding of the anti-CD3 antibody to an Fc receptor that is found on many different cells. And, by eliminating the Fc receptor binding, the same robust activation of T cells does not occur that otherwise would happen if you had Fc receptor binding. It greatly reduces the toxicity associated with a molecule that perhaps some of you will remember called OKT3, and we also think it changes its mechanism of action. In clinical studies in type 1 diabetes, it's been shown that treatment with this monoclonal antibody can improve beta-cell function in those with new-onset type 1 diabetes. And, as I'm going to show, you even reduce the risk of progressing to overt type 1 diabetes.

[Slide: Other Investigational…] Before I mention the results of the teplizumab trial, let me point out that there are a number of other investigational agents that have been tested in type 1 diabetes, and some of these have been very effective, and others have not. For example, on the left side, Dr. Gitelman mentioned otelixizumab and indeed, that's another anti-CD3 antibody, similar mechanism of action of teplizumab, but also showed efficacy in patients with new-onset diabetes. An anti-CD20 antibody that binds to CD20 that's found on B cells was effective, and anti-IL-1 antibody, canakinumab, was not effective. That neutralizes the cytokine IL-1beta. However, recently it was shown that an antibody against TNF-alpha, golimumab, showed the ability to delay the progression of type 1 diabetes in individuals with new-onset disease. Dr. Gitelman and I, with Dr. Bluestone, have done studies to look at the ability of regulatory T cells, cells that are able to modulate immune responses to prevent the progression of diabetes, and that work is still ongoing.

CTLA4Ig, which binds to another set of molecules, co-stimulatory molecules, that are needed for T cell activation, they've shown efficacy, as has a molecule called alefacept, or LFA3Ig, that blocks a co-stimulatory signal, CD2, on T cells. There has been work with interleukin-2 that's thought to promote regulatory T cells that has shown some interesting effects, both good and bad, so that still is a work in progress. And unfortunately, oral antigen-specific therapies still have not really had a substantial proof of concept, including oral insulin and GAD65. A polyclonal antibody that targets T cells and B cells and other cells, ATG, has shown efficacy in patients with new-onset type 1 diabetes as well.

[Slide: Phase II Trial] I'm going to tell you about the Phase II TN-10 teplizumab trial that was done by TrialNet for patients at risk for diabetes. This was a randomized, placebo-controlled trial to assess the effects of teplizumab on the onset of diabetes in 76 individuals who were over the age of 8, who were related to someone with type 1 diabetes but did not have the disease themselves. We know that they are at very high risk of developing diabetes because they had at least two islet autoantibodies, and they had some abnormality of

their glucose tolerance test. But I want to emphasize, they didn't have clinical type 1 diabetes. We knew from the evaluation of the autoantibodies and their glucose tolerance test that the risk of developing diabetes was about 75 percent over the next five years. The teplizumab was given as a single course, 14-day treatment, which consisted of 30-minute IV infusions with gradually increasing doses, which was done to decrease the adverse events related to cytokine release, and the primary endpoint of this trial was very straightforward. The question was, did people develop type 1 diabetes or not? And, if they did, how long did it take them to develop diabetes?

[Slide: 3-Year Extended] There's new data that I'm going to share with you: a follow-up of the original report from 2019 that showed that there was a two-year median delay in the time to development of type 1 diabetes in the individuals treated with teplizumab compared to placebo. With an extended follow-up with individuals, the median time to the clinical diagnosis is now approximately five years from the time that they were enrolled in the trial, as compared to two years in the placebo group. So again, let me emphasize, these individuals did not have diabetes, but we knew from their oral glucose tolerance testing and the detection of the autoantibodies that they were at very high risk. And indeed, data in the placebo group confirms that. Half of the individuals developed diabetes after about 27 months from when they were enrolled in the trial.

[Slide: Effects of Teplizumab] The updated data just published shows that the median time to development of diabetes in the drug group, as I mentioned, is approximately five years, 59.6 months, whereas it's 27 months in the placebo group, a difference of almost three years. Importantly, I want to mention that half of the individuals treated with drug still didn't have diabetes at the end of the trial. Now, we don't know what will happen to those individuals; we're continuing to follow them. But, this information does raise the point that there may be some who really have very robust responses to the anti-CD3 antibody. This is still a work in progress.

[Slide: 3-Year Extended cont'd] So, compared to placebo, teplizumab resulted in a 54 percent reduction in the risk of progressing to type 1 diabetes, which was statistically significant. Half of those treated with drug were free of type 1 diabetes at the close of the study. The C-peptide, a measure of endogenous insulin production, was also improved. Now, this is an interesting finding, I think, because although the progression to type 1 diabetes is clinically silent, the data that we have from this trial indicates that their-beta cell function, their ability to make C-peptide in response to oral glucose, when they entered the trial was still impaired compared to healthy relatives. And, it suggested that by treating with the anti-CD3, their beta-cell function improved, just like we had seen in individuals with new-onset disease. The drug is well-tolerated. The safety data are consistent with previous analyses.

[Slide: Ongoing Phase III] I want to close with this trial that is ongoing. This is the PROTECT study, which is going to be testing whether teplizumab would attenuate the loss of beta-cell function in individuals with new-onset diabetes. These are individuals diagnosed with clinical type 1 diabetes. Dr. Gitelman already brought up this idea that perhaps we need to intervene very early, and that's exactly what's happening in the PROTECT study. And, he also mentioned that perhaps children may have the more robust responses to the drug, and that also is being tested in this study. So, it is testing whether two 12-day courses of the drug in individuals between 8 and 17 will attenuate the loss of beta-cell function. The total study duration for each participant is going to be up to 86 weeks, and the study is estimated to be completed in May of 2022. As I mentioned to you, the primary objective is to determine whether the drug would attenuate the loss of beta-cell function, and there are a number of secondary objectives as well to determine the clinical impact of the drug treatment.

So, I will stop there and open this for some discussion. I'm joined by Dr. Gitelman again, and Steve, I wonder where are we going to go with this exciting data? I think it's fair to make the point that insulin is kind of a band-aid for type 1 diabetes. It keeps people alive, It's not a disease-modifying therapy, as we like to refer to in rheumatologic disease. But where are we going next? What are your thoughts? Is this something that individuals in practice should be considering? And then, of course, what's the next scientific steps that we should be talking about?

Dr. Gitelman:
Well, first of all, I think we're all very excited to be at this point because although we've figured out how to screen and predict for risk for type 1, we haven't had a successful prevention trial until the study that you just described, and that's really, I think, a game changer for the field, and has us very excited about thinking about next steps. So, I think we could go a lot of different directions with the discussion. I think one issue to remind everyone about is in this study, we focused on people who had a relative with type 1. And that's because we know that the other family members are going to be at 10- to 15-fold higher risk for disease. But, 90 percent of new onset type 1 is in people without an affected family member. So, I think one thing that this does is really force us now to think about the general population. Are there effective ways to screen the general population same risk as people who have relatives with type 1? And, can we now pivot to screen the general population and try and head off or at least delay, if not block, the progression to type 1? So, that effort is rolling out in countries around the world, of course in the United States as well, with some ongoing efforts with TrialNet and Juvenile Diabetes Research Foundation. And so, I think there's going to be a lot of interest there. But I'll put the question back to you. We've got this observation at what we call stage two with a single course of teplizumab. What should the next studies be? What do you think?

Dr. Herold:
So it's interesting because we know from the stage two data that those individuals were indeed progressing. I mean, the stage two is really an intermediate point between stage one and stage three that we call clinical diabetes, and we know that during that period of time, there was active beta cell killing going on. And, the question is, would this work in the primary prevention type of setting that you mentioned, if we identified, for example, individuals at high genetic risk? You know, it's speculation at this point. My own feeling is I don't think so. I think actually, the best approach may be to be targeting individuals where we know that they are progressing to diabetes. On the other hand, that still leaves open the idea that we—perhaps, since we have the ability to identify people at earlier stages, need to think about therapies that could be introduced earlier. Now, I think it's worth testing teplizumab in an earlier stage. And the other point, of course, is what about the very young children, where the disease has been increasing? That's been well-documented in Europe and in the United States, and we still don't have anything to offer very young children. So, I think these are all questions that can be answered and probably those are the next steps.

And then lastly, I showed the data about the median time to the development of diabetes, but remember, the median is half the people. Half the people develop diabetes before that time, and half the people didn't develop diabetes before that time. What should we do for those where maybe we need to come in with a second agent? Or, maybe we need to treat again, or maybe there's a different type of an approach that's needed in some individuals. So, I think identifying in whom the drug is most likely to work, and if we find out that it's not likely to work, think about perhaps a combination, perhaps a different agent, or maybe re-treatment is the answer. I don't know yet. But these are all answerable questions.

Dr. Gitelman:
And then we can see where that leaves us. I think everything you've outlined -- those are very exciting questions. And so, I think the good news is, we have a lot of exciting work ahead of us, and it's going to be very exciting to try and build on this initial observation and see how we can make changes in type 1. But I share your enthusiasm and lots of important directions for us to pursue now.

Dr. Herold:
Thanks Dr. Gitelman. I think that was a very informative session, gave us a lot to think about that's been done, and a lot to think about going forward.