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DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Immune Intervention for Type 1 Diabetes, 2012–2013

Jay S. Skyler

Introduction

This chapter of the *ATTD 2013 Yearbook* reviews the key articles that have appeared between July 2012 and August 2013 in the area of immune intervention in type 1 diabetes. Also included are two studies dealing with beta-cell regeneration or replacement. The first three studies discussed deal with anti-CD3 monoclonal antibody therapy.

Teplizumab preserves C-peptide in recent-onset type 1 diabetes: 2-year results from the randomized, placebo-controlled Protege trial

Hagopian W[1], Ferry RJ Jr[2], Sherry N[3], Carlin D[4], Bonvini E[4], Johnson S[4], Stein KE[4], Koenig S[4], Daifotis AG[4], Herold KC[5], Ludvigsson J[6]; for the Protégé Trial Investigators

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Diabetes 2013 Jun 25: [Epub ahead of print]; DOI: 10/2337/db13-0236

Background

Two years ago we discussed the 1-year results of the Protégé phase 3 study using teplizumab. The primary outcome measure—a composite of the percentage of patients with insulin use of < 0.5 U/kg per day and HbA1c of < 6.5% at 1 year—was not met. However, exploratory analyses suggested that teplizumab could help preserve β-cell function—as measured by C-peptide—at 1 year, particularly in subgroups such as children. This report describes the 2-year results from this study.

Methods

Of the 516 subjects randomized, 462 completed 2 years of follow-up. Treatment was given both at study entry and 6 months later.

Results

Teplizumab (14-day full dose) reduced the loss of C-peptide mean area under curve (AUC; a prespecified secondary endpoint) at 2 years versus placebo. In analyses of subsets at entry, U.S. residents, patients with C-peptide mean AUC > 0.2 nmol/L, those randomized < 6 weeks after diagnosis, HbA1c < 7.5% (58 mmol/mol), insulin use < 0.4 U/kg/day, and ages 8–17, each had greater teplizumab-associated C-peptide preservation than their counterparts. Exogenous insulin needs tended to be reduced versus placebo. Antidrug antibodies developed in some patients without apparent change in drug efficacy. No new safety or tolerability issues were observed during year 2.

Conclusion

Anti-CD3 therapy reduced C-peptide loss and thus preserved β-cell function for 2 years.

Comment

Previous reports have shown that a short course of humanized anti-CD3 monoclonal antibody—either with teplizumab or otelixizumab—preserved β-cell function as measured by C-peptide. The Protégé study selected a different primary outcome measure—a composite of the percentage of patients with insulin use of < 0.5 U/kg/day plus HbA1c of < 6.5% at 1 year. That outcome was not met, and thus many have labeled the Protégé study a failure. Yet, in the original report, teplizumab was found to preserve β-cell function at 1 year. The current article demonstrates that this effect was maintained at 2 years. As noted in our earlier discussion of the 1-year results, there was no prior basis for the outcome measure selected. Moreover, taking two continuous variables (insulin use and HbA1c) and converting them to a single combined dichotomous variable reduces the statistical power of assessment of continuous variables. The C-peptide results, both at 1 year and at 2 years, highlight the problem. Thus, although the original primary outcome was not met, we are still learning from the Protégé study.

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Teplizumab treatment may improve C-peptide responses in participants with type 1 diabetes after the new-onset period: a randomised controlled trial

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*Diabetologia 2013; **56**: 391–400*

Background

Previous studies with anti-CD3 monoclonal antibodies have been conducted in subjects with recent-onset type 1 diabetes, generally initiated within 2–4 months from diagnosis. This study, known as the DELAY study, using teplizumab, enrolled subjects with type 1 diabetes for 4–12 months.

Methods

Fifty-eight subjects were recruited. They received a 14-day course of either intravenous teplizumab or placebo.

Results

The primary outcome analysis showed a 21.7% higher C-peptide response in the teplizumab-treated group (0.45 vs. 0.371; difference, 0.059 [95% CI 0.006, 0.115] nmol/L) ($p=0.03$), when corrected for baseline imbalances in HbA1c levels, the C-peptide levels in the teplizumab-treated group were 17.7% higher (0.44 vs. 0.378; difference, 0.049 [95% CI 0, 0.108] nmol/L, $p=0.09$). A greater proportion of placebo-treated participants lost detectable C-peptide responses at 12 months ($p=0.03$). The teplizumab group required less exogenous insulin ($p<0.001$), but treatment differences in HbA1c levels were not observed. Teplizumab was well tolerated. A subgroup analysis showed that treatment benefits were larger in younger individuals and those with HbA1c <6.5% at entry. Subjects enrolled between 4 and 8 months after diagnosis showed better effect than those enrolled between 9 and 12 months after diagnosis.

Conclusion

The secondary outcomes suggest that anti-CD3 therapy reduced C-peptide loss and thus preserved β-cell even when therapy was initiated after the recent-onset period. However, the magnitude of the effect is less than during the recent-onset period. The analyses identified age and HbA1c as characteristics that may identify participants most likely to respond to drug treatment.

Comment

This study initiated therapy with anti-CD3 at a later time point after diagnosis than has been done in previous studies. Treatment may reduce the decline of C-peptide in patients with established disease of up to 1-year duration. Nonetheless, subjects did better if enrollment occurred between a 4- and 8-month duration of type 1 diabetes. Given the success with anti-CD3 in recent-onset type 1 diabetes, this study indicates that if one is a bit late in initiating therapy, then there is still likely to be benefit, particularly if the HbA1c is well controlled. This gives clinicians more time to offer this treatment to potential subjects.

Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders

Herold KC[1], Gitelman SE[6], Ehlers MR[2], Gottlieb PA[7], Greenbaum CJ[8], Hagopian W[9], Boyle KD[5], Keyes-Elstein L[5], Aggarwal S[4], Phippard D[4], Sayre PH[2], McNamara J[3], Bluestone JA[6]; the AbATE Study Team

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Diabetes 2013 July 8: [Epub ahead of print]; DOI: 10.2337/db-0345

Background

This study, known as ABATE, looked at whether two courses of teplizumab (at entry and 1 year later) could help preserve β-cell function—as measured by C-peptide—at 2 years. The other goal of the study was to identify characteristics of responders.

Methods

Fifty-two subjects were randomized. The active group received a 14-day course of teplizumab both at study entry and 12 months later. The comparison group was randomized but did not receive placebo. The primary outcome was at 2 years.

Results

In the intention to treat analysis of the primary endpoint, teplizumab-treated patients had a reduced decline in C-peptide at 2 years [mean (95% CI), −0.28 (−0.36, −0.20) nmol/L vs. control, −0.46 (−0.57, −0.35) nmol/L; $p=0.002$], a 75% improvement. In a *post hoc* analysis, clinical responders (identified by having maintained C-peptide better than the randomized comparison group at 24 months) were found to have metabolic (lower HbA1c and less insulin use) and immunologic

features (lower frequency of CD4+ CCR4+ memory and naïve T cells, CD4+ CCR6+-naïve CD4+ T cells, naïve CCR4+ CD8+ T cells, and IFNγ-producing CD8+ T cells at baseline, and a higher number of activated CD8+ terminally differentiated effector and CD8+ effector-memory T cells) that distinguished this group from nonresponders to teplizumab.

Conclusion

Anti-CD3 therapy reduced C-peptide loss and thus preserved β-cell function for 2 years.

Comment

In this study, although the overall response showed significant improvement in retention of C-peptide, the most interesting aspect was the identification of two groups of subjects—responders and nonresponders. Responders constituted 45% of the subjects treated with anti-CD3. The responders maintained beta-cell function for 2 years, whereas the nonresponders lost beta-cell function at a rate similar to the control group. It is not known why some subjects respond and others fail to respond. Nonetheless, the lower HbA1c levels and lower insulin doses in responders imply that these individuals may have had a milder disease or be earlier in the course of the disease. This reinforces the notion that therapy with anti-CD3 should be as early as possible in the disease process. The next group of articles discusses other intervention approaches.

Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicenter, randomized double-masked, placebo-controlled trials

Moran A[1], Bundy B[2], Becker DJ[3], DiMeglio LA[4], Gitelman SE[5], Goland R[6], Greenbaum CJ[7], Herold KC[8], Marks JB[9], Raskin P[10], Sanda S[7], Schatz D[11], Wherrett D[12], Wilson DM[13], Krischer JP[2], Skyler JS[14] for the Type 1 Diabetes TrialNet Canakinumab Study Group; and Pickersgill L[15], de Koning E[16], Ziegler A-G[17], Böehm B[18], Badenhoop K[19], Schloot N[20], Bak JF[21], Pozzilli P[22], Mauricio D[23], Donath MY[24], Castaño L[25], Wägner A[26], Lervang HH[27], Perrild H[28], Mandrup-Poulsen T[29] for the AIDA Study Group

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*Lancet 2013; **381**: 1905–15*

Background

Innate immunity may contribute to the pathogenesis of type 1 diabetes. This article reports two randomized trials that evaluated two approaches to blockade of the innate immune mediator interleukin-1 (IL-1)—an anti-IL-1 antibody canakinumab and an IL-1 receptor antagonist anakinra.

Methods

In the canakinumab trial, 69 subjects (age 6–45) were randomized, 47 to canakinumab and 22 to placebo, with the dosage being 2 mg/kg subcutaneously monthly for 12 months. In the anakinra trial, 69 subjects (age 18–35) were randomized, 35 to anakinra and 34 to placebo, with the dosage being 100 mg/day for 9 months. The primary outcome measure was C-peptide area under curve (AUC) from a mixed-meal tolerance test, at 12 months for canakinumab and at 9 months for anakinra.

Results

The difference in C peptide AUC between the canakinumab and placebo groups at 12 months was 0.01 nmol/L (95% CI −0.11 to 0.14; $p=0.86$), and between the anakinra and the placebo groups at 9 months was 0.02 nmol/L (−0.09 to 0.15; $p=0.71$).

Conclusion

Canakinumab and anakinra were safe but were not effective as single immunomodulatory drugs in recent-onset type 1 diabetes.

Comment

In these studies, there was no benefit on beta-cell function from blocking the effects of IL-1. Although the innate immune system may be critically important in the evolution of type 1 diabetes, blocking inflammation by itself may be insufficient to alter the course of the disease. On the other hand, decreasing inflammation may prove to be a crucial component of a combination therapy approach to interrupting the type 1 diabetes disease process. That canakinumab was safe and was used successfully in children as young as age 6 supports its use in future studies using a combination approach.

Plasmid-encoded proinsulin preserves C-peptide while specifically reducing proinsulin-specific CD8+ T cells in type 1 diabetes

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*Sci Transl Med 2013; **5**: 191ra82*

Background

Because proinsulin is a major target of adaptive immunity in type 1 diabetes, the authors hypothesized that an engineered DNA plasmid encoding proinsulin would preserve beta-cell function in type 1 diabetes through reduction of insulin-specific T-lymphocytes.

Methods

Sixty-nine subjects over age 18 diagnosed with type 1 diabetes within 5 years were randomized 2:1 to receive intramuscular injections of plasmid or placebo weekly for 12 weeks. Four dose levels of plasmid were evaluated: 0.3, 1.0, 3.0, and 6.0 mg. C-peptide served as an exploratory measure of efficacy and safety. Islet-specific CD8+ T-cell frequencies were assessed with multimers of monomeric HLA class I molecules loaded with peptides containing pancreatic or unrelated antigens.

Results

No serious adverse events related to plasmid occurred. The authors claim that C-peptide levels were improved relative to placebo at all doses, most notably at 1 mg at 15 weeks (+19.5% with plasmid versus −8.8% with placebo, $p < 0.026$). Proinsulin-reactive CD8+ T-cells, but not T-cells against unrelated islet or foreign molecules, declined in the plasmid arm ($p < 0.006$).

Conclusion

The authors concluded that a plasmid encoding proinsulin reduces the frequency of CD8+ T-cells reactive to proinsulin while preserving C-peptide over the course of dosing.

Comment

Although the authors assert that there is benefit to beta-cell function in this study, it is really unclear whether there is such a benefit or not. The effect was seen in but one of four doses tested and at one time point. The number of subjects studied at each dose was small, and there did not appear to be statistical adjustment for multiple comparisons. There were no safety issues. It is now incumbent upon the authors and study sponsor to conduct an adequately powered randomized controlled clinical trial to ascertain whether the effects that they claim to be seeing are confirmed.

Autologous umbilical cord blood infusion followed by oral docosahexaenoic acid and vitamin D supplementation for C-peptide preservation in children with type 1 diabetes

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*Biol Blood Marrow Transplant 2013; **19**: 1126–29*

Background

A previous study demonstrated apparent safety of autologous umbilical cord blood (UCB) infusion accompanied by postinfusion increase in regulatory T-lymphocytes (Treg). In an attempt to provide synergy in altering autoimmunity, the current study was designed to augment UCB by the addition of two agents generally regarded as safe (GRAS) and with immunomodulatory properties—vitamin D (Vit D) and docosoahexaenoic acid (DHA).

Methods

The study was an open-label, 2:1 randomized study in which 15 subjects with type 1 diabetes and stimulated C-peptide >0.2 pmol/mL received either (a) autologous UCB infusion, 1 year of daily oral Vit D (2,000 IU) and DHA (38 mg/kg), and intensive diabetes management, or (b) intensive diabetes management alone. Treated ($n = 10$) and control ($n = 5$) subjects had median ages of 7.2 and 6.6 years, respectively.

Results

While the absolute rate of C-peptide decline was slower in treated versus control subjects, intergroup comparisons failed to reach significance ($p = 0.29$). C-peptide declined and insulin use increased in both groups ($p \leq 0.01$). Not surprisingly, Vit D levels remained stable in treated subjects but declined in controls ($p = 0.01$), and DHA levels rose in treated subjects versus controls ($p = 0.003$). CD4:CD8 ratio remained stable in treated subjects but declined in controls ($p = 0.03$). No changes were seen in regulatory T cell frequency, total CD4 counts, or autoantibody titers. No severe adverse events were observed.

Conclusion

Autologous UCB infusion followed by daily supplementation with Vit D and DHA was safe but failed to preserve C-peptide.

Comment

If one is looking for efficacy, this study once again illustrates the futility of the conduct of pilot studies with a very small sample size. The study did not reveal any severe adverse effects, allowing the authors to claim that the intervention is safe. Yet one should always be cautious with drawing conclusions about safety in small trials. Only 10 subjects were exposed to the intervention. It is easy to miss a serious adverse event. Although I do not suspect that to be an issue with the particular intervention used—autologous UCB and two GRAS substances—the principle should be appreciated that such small trials usually are impossible to interpret.

Antithymocyte globulin treatment for patients with recent-onset type 1 diabetes: 12-month results of a randomised, placebo controlled, phase 2 trial

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Lancet Diabetes Endocrinol 2013 Aug 28; [Epub ahead of print]: DOI: 10.1073/PNAS.1220637110

Background

Type 1 diabetes results from T-lymphocyte-mediated destruction of beta-cells. Antithymocyte globulin (ATG) suppresses T-lymphocytes and has been used in transplantation and in other autoimmune diseases. Therefore, this study evaluated ATG in subjects with recent-onset type 1 diabetes.

Methods

Fifty-eight subjects, age 12–35, with recent-onset type 1 diabetes, were randomized (38 to the ATG arm and 20 to the placebo arm). They received 6.5 mg/kg ATG or placebo over a course of 4 days. The primary endpoint was the baseline-adjusted change in 2-hour area under the curve (AUC) C-peptide response to mixed meal tolerance test from baseline to 12 months.

Results

About 12 months after randomization, the change from baseline in the ATG group did not differ from that in the placebo group for the primary outcome (2-hour AUC of meal-stimulated C-peptide) or for secondary outcomes (HbA1c and insulin dose). Participants in the ATG group had a mean change in C-peptide AUC of −0.195 pmol/mL (95% CI −0.292 to −0.098), and the placebo group had a mean change of −0.239 pmol/mL (−0.361 to −0.118) ($p = 0.591$). All except one subject in the ATG group had both cytokine release syndrome and serum sickness. Acute T-lymphocyte depletion occurred in the ATG group, with slow reconstitution over 12 months; yet, effector memory T-lymphocytes were not depleted, and the ratio of regulatory to effector memory T-lymphocytes declined in the first 6 months and stabilized thereafter. ATG-treated patients had 159 grade-3–4 adverse events, many associated with T-lymphocyte depletion, compared with 13 in the placebo group. However, there were no between-group differences in incidence of infectious diseases.

Conclusion

The authors concluded that a brief course of ATG did not result in preservation of beta-cell function 12 months later in patients with recent-onset type 1 diabetes, and that generalized T-lymphocyte depletion in the absence of specific depletion of effector memory T-lymphocytes and preservation of regulatory T-lymphocytes seems to be an ineffective treatment for type 1 diabetes.

Comment

The full story from this study remains to be told, in my opinion. *Post hoc* analyses showed that there were differences between the 0–6-month change and the 6–12-month change in C-peptide in the antithymocyte globulin (ATG) group, with an apparent early decline in beta-cell function and then stabilization. If the early decline was caused by a cytokine storm—a postulate that would have greater support had there been an assessment of C-peptide at 3 months—then there might be continued stable C-peptide during the ongoing follow-up through 24 months. That might validate the potential benefit of ATG and support further testing at lower doses and/or in combination therapy, such as that being done with low-dose ATG together with granulocyte colony-stimulating factor. The next articles provide insights about potential interventions that could be evaluated in type 1 diabetes.

Acute metabolic effects of exenatide in patients with type 1 diabetes with and without residual insulin to oral and IV glucose challenges

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Diabetes Care 2013 Aug 12: [Epub ahead of print]; DOI: 10.2337/dc13-1169

Background

Treatment with GLP-1 analogs is used for type 2 diabetes. Patients with type 1 diabetes, particularly those with residual beta-cell function, may also respond to treatment. In type 1 diabetes, the acute metabolic effects of GLP-1 analogs on both oral and IV glucose challenges have not been well characterized.

Methods

Seventeen patients with type 1 diabetes, eight of whom had residual insulin production, underwent two mixed meal tolerance tests (MMTT), and two intravenous glucose tolerance tests (IVGTT), with and without pretreatment with exenatide. Glucose excursions, insulin secretion rates (ISR), glucagon, gastric emptying, and incretin levels (endogenous GLP-1 and GIP) were measured following the meal or glucose loads.

Results

During the MMTT, glucose levels were suppressed with exenatide in patients with or without residual insulin production ($p = 0.0003$). Exenatide treatment did not change the absolute ISR, but the ISR to glucose levels were increased ($p = 0.0078$). Gastric emptying was delayed ($p = 0.0017$) and glucagon was suppressed ($p = 0.0015$). None of these hormonal or changes in glucose were detected during the IVGTT with exenatide administration.

Conclusion

Exenatide, given before an oral meal, lowered glycemic excursions in patients with type 1 diabetes, involving glucagon suppression and gastric emptying, while preserving increased insulin secretion. GLP-1 analogs may be useful as an adjunctive treatment in type 1 diabetes.

Comment

GLP-1 analogs have been thought about as potential adjunctive therapy in type 1 diabetes, and several small studies have suggested that they may have potential benefit. The current study evaluated the potential mechanisms by which such therapy may be operating. Using but a single dose of exenatide before a meal, there was sufficient glucagon suppression and delay of gastric emptying to flatten postmeal glycemic excursions even in subjects without residual insulin secretion. This bodes well for the potential use of GLP-1 analogs in type 1 diabetes, for which several larger studies are currently under way. Because GLP-1 analogs may also contribute to beta-cell health, they may be a useful component of a combination therapy approach directed at recent-onset type 1 diabetes.

Betatrophin: a hormone that controls pancreatic β cell proliferation

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*Cell 2013; **153**: 747–58*

Background

Replenishing insulin-producing pancreatic beta-cell mass will benefit both type 1 and type 2 diabetes. In adults, pancreatic beta-cells are generated primarily by self-duplication.

Methods

The authors used a mouse model of insulin resistance that induces dramatic pancreatic beta-cell proliferation and beta-cell mass expansion.

Results

The authors were able to identify a hormone, betatrophin, which is primarily expressed in liver and fat, that correlates with beta-cell proliferation. Transient expression of betatrophin in mouse liver significantly and specifically promoted pancreatic beta-cell proliferation, expanded beta-cell mass, and improved glucose tolerance.

Conclusion

Betatrophin treatment could be used to increase the number of endogenous insulin-producing cells in diabetes.

Comment

This article describes a new hormone, betatrophin, that stimulates beta-cell proliferation and expands islet beta-cell mass. Although to date only studied in rodents, the analogous human sequence has been identified. If betatrophin can be produced, such as by recombinant DNA technology, it could undergo animal toxicology testing to clear the way for initiation of human clinical trials. This represents a most exciting possibility that potentially could be combined with immune intervention for alteration of the course of type 1 diabetes.

Brief demethylation step allows the conversion of adult human skin fibroblasts into insulin-secreting cells

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*Proc Natl Acad Sci USA 2013; **110**: 8948–53*

Background

The advent of induced pluripotent stem cell technology enabled the conversion of adult cells into any other cell type passing through a stable pluripotency state. Unfortunately, indefinite pluripotency is unphysiological, is inherently labile, and makes cells prone to culture-induced alterations. The direct conversion of one cell type to another without an intermediate pluripotent stage is also possible but requires viral transfection of appropriate transcription factors, limiting its therapeutic potential. The aim of this study was to investigate possible direct conversion of skin fibroblasts by exposing them to a demethylating agent immediately followed by culture conditions aimed at differentiating the cells to insulin-secreting cells.

Methods

Adult human skin fibroblasts were exposed for 18 hours to the DNA methyltransferase inhibitor 5-azacytidine, followed

by a three-step protocol for the induction of endocrine pancreatic differentiation that lasted 36 days.

Results

With this treatment, 35 ± 8.9% of fibroblasts became pancreatic converted cells that acquired an epithelial morphology, produced insulin, and then released the hormone in response to a physiological glucose challenge *in vitro*. These pancreatic converted cells were able to protect recipient mice against streptozotocin-induced diabetes, restoring physiological responses to glucose tolerance tests.

Conclusion

It is possible to convert adult fibroblasts into insulin-secreting cells.

Comment

This article represents a remarkable achievement that has the potential to provide insulin-secreting cells from a person's own skin fibroblasts. To use these for beta-cell replacement would obviate the need to deal with alloimmunity responsible for rejection, although the potential for recurrent autoimmunity would still exist. Nonetheless, if further studies demonstrate the clinical feasibility of this approach, it could be quite remarkable.

Overall Commentary

This year has produced some very exciting articles, although many describe preliminary studies and need further development. As noted in previous years, this author believes many of these potential interventions hold promise, particularly if they are used as components of combination therapy. Even by itself, anti-CD3 deserves testing in a well-designed phase 3 trial in recent-onset type 1 diabetes. It also is being explored as a preventative measure in individuals with very high risk of progression to type 1 diabetes. ATG is being explored further at lower doses and in combination with granulocyte colony-stimulating factor. Plasmid containing proinsulin has been demonstrated to be safe and is worthy of further study, perhaps as the antigen-specific component of a combination approach. Another component of combination therapy could be a GLP-1 analog to improve beta-cell health. One could envision adding in betatrophin to expand beta-cell mass, and if beta-cells have already been depleted, one could even imagine using an individual's skin fibroblasts to make new pancreatic islets. This is all science fiction today. Yet, development of the component parts has been proceeding with vigor. I predict that we are embarking on a decade that will see enormous progress in eradicating type 1 diabetes.

Author Disclosure Statement

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