

Prevention of Type 1 Diabetes

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KEYWORDS

- Type 1 diabetes • Autoimmunity • Prevention • Immunology
- Genetics • Clinical trials

Type 1 diabetes (T1D) is an autoimmune disease in which the β cells of the pancreatic islets are destroyed, rendering the individual increasingly incapable of mounting a normal insulin response to ingested nutrients.^{1,2} In the early 1980s, Eisenbarth² enunciated the main phases in the pathogenesis of T1D (**Fig. 1**), a framework which continues to be useful in considering approaches to the prevention or cure of this disorder:

1. Susceptibility to T1D is inherited through a series of genes, the most important of which relate to the HLA class II locus on chromosome 6, with lesser contribution from several others, including the insulin gene, CTLA4 and others (see later discussion). Susceptibility genes are essential, but insufficient in explaining the immune pathogenesis of T1D, that is, most individuals with these susceptibility genes never develop the disorder.
2. Exposure to 1 or more environmental triggers alters the immune system in such a way that susceptibility is converted to pathophysiology and destruction of β cells begins. Despite intensive searches for environmental triggers, the number of candidates being assessed in clinical trials remains small, for example, cow's milk proteins, relative lack of vitamin D, and supplementation with omega-3 fatty acids.³⁻⁷
3. Although attack on the β cells is mediated in large part by T cells, it is the presence of humoral (B-cell) markers that punctuates the next phase: normal glucose homeostasis in the presence of 1 or more T1D-specific autoantibodies; ICA512/IA-2, insulin autoantibody (IAA) and glutamic acid decarboxylase (GAD) are the main ones available for measurement. The progression to clinical T1D is highly predictable based on the number of antibodies present.⁸
4. The earliest metabolic abnormality detected is loss of first phase insulin secretion in response to an intravenous glucose load. Glucose levels remain normal in response to meal challenges at this stage. Later, impaired glucose tolerance develops. This leads inexorably to the next phases of clinical diabetes.

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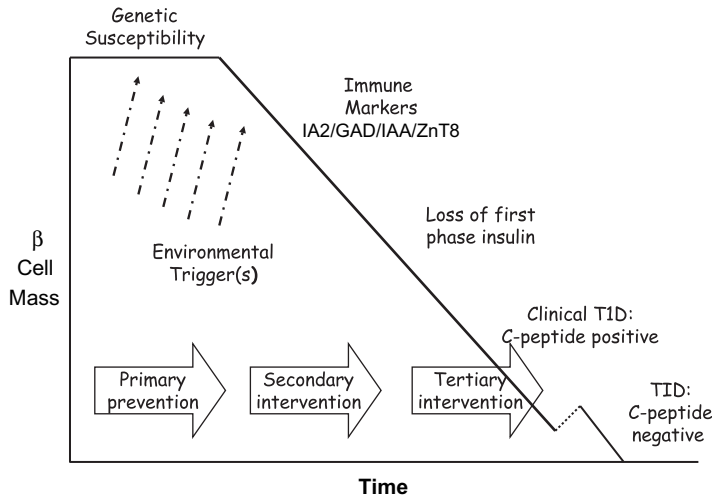


Fig. 1. The natural history of T1D.

5. When β -cell mass is significantly decreased, insulin secretory capacity is damaged to such a degree that it is no longer sufficient to maintain normoglycemia and clinical diabetes supervenes. This phase includes the honeymoon or remission period of T1D when some β -cell function is retained, also called the C-peptide-positive phase of clinical diabetes.
6. Finally, in most, but not all, individuals with T1D, β cell function is eventually completely lost and C-peptide levels become undetectable. There is a relationship between the presence of diabetic ketoacidosis at disease onset and the rapidity of loss of β cells, and between the presence of residual β -cell function and the ability to achieve and maintain better metabolic control.

A few additional facts are important in considering targets for prevention or early intervention in the pathogenesis of T1D⁹: Firstly, the incidence of this condition is increasing by 2% to 5% per year worldwide, especially in the youngest age group (<5 years of age).¹⁰ Secondly, there is enormous variability in incidence of T1D around the world, from less than 4 per 100,000 in a population younger than 14 years in much of Africa and Asia to more than 20, in Canada, Australia, and parts of Europe, with the highest incidence being in Finland (>50 per 100,000 in the population reported in 2008).¹¹ Thirdly, migrating populations take on the increased incidence of their new countries fairly rapidly, for example, Asian immigrants to the United Kingdom, immigrants from the Horn of Africa (Somalia, Eritrea, and Ethiopia) to North America.¹² Fourthly, there is evidence that genetically similar populations may have enormously dissimilar incidence rates, for example, Finland and Russian Karelia.¹³ These factors strongly indicate an important role for environmental factors in the cause of T1D, because genetic drift cannot explain the rapidity of these changes. Furthermore, where incidence is increasing most rapidly, the contribution of genetic susceptibility seems to be less.¹⁴

GENETICS OF T1D

T1D is 15 times more common in siblings of those with T1D, with the general population prevalence of approximately 0.4% and the sibling prevalence of approximately 6%.¹⁵ Genes located within the HLA class II region on chromosome 6p21 account

for approximately 50% of genetic risk of T1D.^{16,17} Haplotypes associated with T1D include DQ2 (DQB1*0201–DQA1*0501–DRB1*03) and DQ8 (DQB1*0302–DQA1*0301–DRB1*04).¹⁸ Other HLA alleles, DQA1*0102, DQB1*0602 confer protection from T1D.¹⁹ A region in the regulatory region of the insulin gene (INS) locus has also been shown to provide approximately 10% of the genetic susceptibility to T1D.¹⁸ A polymorphism in the PTPN22 (protein tyrosine phosphatase non-receptor type 22) gene has been found to be associated with several autoimmune diseases, including T1D and autoimmune thyroid disease.¹⁸ The gene product, a lymphoid tyrosine phosphatase, inhibits the T-cell receptor signaling pathway. Polymorphisms in the cytotoxic T-lymphocyte-associated gene (CTLA4) are also associated with T1D and several other autoimmune diseases.²⁰ Signaling through CTLA4 is critical in the down-regulation of T-cell responses. Over 40 genes/regions have been confirmed to be associated with T1D. Identification of these genes provides investigative targets for new understanding of disease pathogenesis.

Although there have been important discoveries in the genetics of T1D and the autoimmune processes involved, little progress has been made in identifying highly specific environmental factors pivotal in triggering this disorder. Two hypotheses remain prominent in this respect: (1) the hygiene hypothesis suggests that in modern society, the lack of exposure to pathogens early in life prevents the genetically predisposed immune system from protecting itself from autoimmune phenomena, (2) the accelerator hypothesis suggests that increasing worldwide obesity stresses the susceptible β -cell, thereby triggering its early demise.^{21–27} The only environmental trigger undergoing active investigation is early exposure to cow's milk proteins, which may be important in T1D pathogenesis; conversely, breast milk may protect against triggering of the autoimmune attack. The effort to better identify environmental factors is currently being led by The Environmental Determinants of Diabetes in the Young study. This study is scheduled to enroll 7800 infants by the end of 2009 with high-risk HLA genotypes for serial assessment of islet autoimmunity and environmental exposures, such as diet, infectious diseases, and immunizations.²⁸

TARGETS FOR PREVENTION OR EARLY INTERVENTION

Prevention of T1D would require interventions aimed at (1) avoiding exposure to environmental triggers early in life—primary prevention; (2) interfering with the autoimmune cascade that occurs during β -cell destruction—secondary prevention or intervention; or (3) halting or reversing β -cell loss after clinical presentation of T1D—tertiary intervention. Once full-blown clinical T1D has developed, the only approach to disease reversal would be physiologic insulin replacement using either an artificial pancreas or β -cell replacement with islet or pancreatic transplantation. T1D is seen as one of the disorders most likely to be amenable to stem cell therapy in the future.

PRIMARY PREVENTION

An environmental role in the pathophysiology of T1D is supported by a number of factors: low concordance rate of the disorder in identical twins (20%–50%); different incidence rates in populations of similar genetic makeup but significantly different socioeconomic status (eg, Finland and Russian Karelia); and rapid shifts in incidence in different areas of the world and with population migration. The specific environmental factors involved remain largely unproven, although epidemiologic and animal-model data suggest a potential role for dietary factors, more specifically, early exposure to cow's milk and **low vitamin D concentrations**, with much more data pointing to a role for **cow's milk proteins**.^{3–7,29}

There are good data to indicate that the pathogenetic processes leading to T1D may begin very early in life. This data, with animal-model and epidemiologic data, has provided the impetus to evaluate carefully the role of weaning diets on the evolution of T1D, especially the role of early exposure to cow's milk proteins. A more detailed description of the supporting data is beyond the scope of this article but can be found in references.^{3-7,29}

The Trial to Reduce IDDM (insulin-dependent diabetes mellitus) in the Genetically at Risk (TRIGR) is a double-blind, randomized placebo-controlled trial that is intended for definitively testing the hypothesis that weaning to a hydrolyzed diet, thereby avoiding early cow's milk protein exposure, protects high-risk newborns from initiation of the β -cell-specific autoimmune response, and therefore prevents T1D.³⁰ This international multicenter study is powered to meet these objectives. The recruitment of high-risk neonates allows for concentration of subjects more likely to develop T1D, the criterion being that their mother, father, or sibling has T1D. They are screened for high-risk HLA haplotypes. If results are positive, the neonates are randomly assigned to 1 of 2 groups: feeding up to 6 to 8 months of age with a regular cow's milk-based formula, or an extensively hydrolyzed cow's milk formula. Breast feeding is encouraged and noted as a potential confounder in the study. The study design is shown in **Fig. 2** and inclusion and exclusion criteria are listed below:

Neonates with a first-degree relative (ie, mother/father/sibling) with T1D are eligible.

Inclusion criteria

1. The infant has one of the following genotypes:
 - a. HLA-DQB1*0302/DQA1*05-DQB1*02
 - b. HLA-DQB1*0302/x (ie, excluding DQB1*02, DQB1*0301, DQB1*0602)
 - c. HLA-DQA1*05-DQB1*02/y (ie, excluding DQA1*0201-DQB1*02, DQB1*001, DQB1*0602/3)
 - d. HLA-DQA1*03-DQB1*02/y (ie, excluding the same ones as in [c]. above)
2. Family able to provide written informed consent

Exclusion criteria

1. An older sibling in TRIGR intervention
2. Multiple gestation
3. Parents unwilling or unable to give study formula
4. Newborn has recognizable severe illness
5. Inability of family to participate in the study

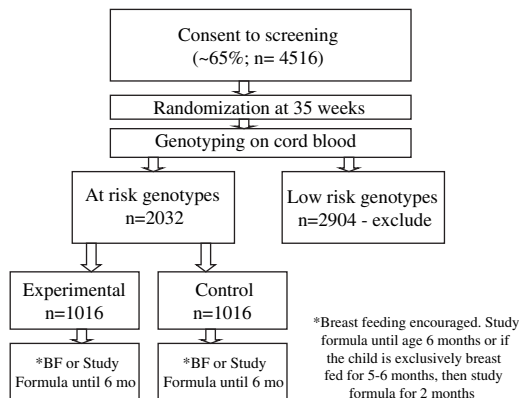


Fig. 2. TRIGR design.

6. Infant received any formula other than Nutramigen before randomization
7. Infant older than 7 days at randomization
8. No HLA sample before 8 days of age.

The major outcome for the first phase of TRIGR is the frequency of T1D-associated autoantibodies and/or development of diabetes by age 6 years. The outcome of the second phase is the manifestation of diabetes by age 10 years according to standard criteria, obviously the more definitive outcome, although the intervention may delay rather than prevent the manifestation of T1D. This latter outcome would be masked by the final outcome being measured at age 10 years.³⁰ Screening for TRIGR began in May 2002, with final enrollment completed by September 2006. The antibody data will be available in 2012 and the T1D outcomes in 2016.

A double-blind placebo-controlled pilot study of omega-3 fatty acid supplementation with docosahexaenoic acid (DHA) to prevent islet autoimmunity is being performed by the Type 1 Diabetes TrialNet study group.³¹ Diets higher in omega-3 fatty acids have been associated with lower risk of islet autoimmunity and diabetes.³² DHA is known to have an anti-inflammatory effect. Entry to the study was during the third trimester for pregnant mothers or during the first 5 months of life for infants with a first-degree relative with T1D. At birth, HLA typing was done on cord blood and those with high risk alleles were eligible. Enrollment of 97 infants is complete with results of compliance, levels of whole blood DHA, and inflammatory markers expected in late 2009.

A feasibility study, BABYDIET, of delay of introduction of gluten to prevent islet autoimmunity in infants with a first-degree relative with T1D and high-risk HLA genotypes is under way in Germany.³³ The timing of introduction of cereals to infants has been associated with diabetes.³⁴ Infants were randomized to introduction of gluten at age 6 or 12 months with follow-up every 3 months up to 36 months of age.

Vitamin D is increasingly recognized as an immunomodulator. Its effects on the immune system are multifold:

1. In acquired immunity, Vitamin D induces an inhibitory response through reduction of T-cell proliferation, interleukin-2 and interferon- γ production, and CD8-mediated cytotoxicity. This results in a reduction of T-helper 1 responses and a promotion of T-helper 2 responses. In this way, it improves T-regulatory forces and provides for a more balanced and tolerogenic milieu³⁵;
2. In the innate immune system, Vitamin D inhibits dendritic cell function at multiple levels and mediates antibacterial actions through cathelicidin and the toll-like receptor 4 pathway.³⁵

Animal models show that treatment with 1,25(OH)₂Vitamin D₃ or its analogs can prevent T1D and other immune-modulated disorders.³⁵ Furthermore, there are data on humans that suggest that Vitamin D may also play a role. For example, the incidence of T1D increases with increasing distance from the equator suggesting a role for sun exposure. A published meta-analysis examined the association between vitamin D supplementation and the development of T1D. It found a significantly reduced risk of developing T1D in those supplemented with vitamin D (OR 0.71).³⁶ A definitive prospective study on the effect of vitamin D supplementation on the development of diabetes remains to be performed.

SECONDARY PREVENTION

The goal of secondary prevention studies is to prevent the progression of islet destruction that will lead to overt T1D. To carry out these studies, reliable prediction models

are required. Current prediction models use combinations of autoantibodies and measures of glucose tolerance to stratify risk. It is known that autoantibodies typically develop years before onset of diabetes. These antibodies include ICA, IAA, and antibodies to GAD, tyrosine phosphatase (IA-2/ICA512), and zinc transporter 8 (ZnT8).³⁷ The presence of 2 or more antibodies indicates a significantly increased risk of developing diabetes, with some studies reporting increasing risk with increasing number of antibodies. One study showed that relatives with 1 or more antibodies had a 25% risk of disease development over a 5-year period, 2 or more antibodies had a 39% risk of developing T1D within 3 years, and those with 3 or more antibodies had a 75% risk of disease development over a 5-year period.³⁸ As β -cell destruction progresses, subclinical glucose abnormalities develop. Evidence from the Diabetes Prevention Trial - Type 1 (DPT-1), showed that fasting and 2-hour glucose levels rise gradually, as stimulated C-peptide levels slowly decline in the 30 months before diagnosis.³⁹ Type 1 Diabetes TrialNet, an international study group performing research in the prevention and early treatment of T1D, is running a large longitudinal observational study of relatives of those with T1D to further improve prediction.⁴⁰

Three large multi-center trials of diabetes prevention in autoantibody-positive subjects have been completed. The European Nicotinamide Diabetes Intervention Trial used nicotinamide as a secondary preventative agent. Despite promising animal data and evidence from a previous study, nicotinamide administration in ICA-positive relatives did not delay the onset of T1D when compared with placebo.⁴¹ In DPT-1, insulin was given orally or parenterally to alter the immune response toward insulin.^{42,43} Subjects at high risk (>50% over 5 years with ICA positive and low first-phase insulin response) of developing T1D received parenteral insulin. Those at moderate risk (25%–50% over 5 years with ICA and IAA but normal first-phase insulin secretion) received insulin orally. The primary analysis of both arms of DPT-1 did not show an effect on the development of T1D.⁴² Post hoc analysis of DPT-1 oral insulin arm, however, suggested a beneficial effect in the subgroup with high titers of insulin autoantibodies.⁴³ The results of the T1D Prediction and Prevention Study were recently published.⁴⁴ In this study, newborns from the general population and siblings of those with diabetes had HLA genotyping done at birth. Those with 2 or more islet antibodies and high-risk HLA alleles were treated with nasal insulin or placebo. The study was stopped early as the treatment had no effect. The results of these studies, though disappointing, demonstrate that large scale prevention studies are feasible and provide significant insight into planning for future studies.

There are currently 3 diabetes prevention trials underway. The first is the Type 1 Diabetes TrialNet study, "Oral Insulin For Prevention of Diabetes In Relatives at Risk for Type 1 Diabetes Mellitus." This study is further investigating the suggestion of oral insulin benefit as seen in the DPT-1 subjects with high IAA titers. Subjects have insulin autoantibodies and one of ICA, GAD antibodies, or ICA512 antibodies. The study intervention is oral insulin 7.5 mg/d or placebo for the study's duration with the endpoint, the development of diabetes. Recruitment began in 2007. The Pre-POINT trial is an international multicenter study that is examining intervention with nasal and oral insulin in children aged 18 months to 7 years who have a sibling or 2 or more relatives with T1D.⁴⁵ These children also have high-risk HLA alleles but no islet autoantibodies. The effects of 4 doses of oral and nasal insulin are being studied to determine whether autoimmunity will be affected. If the study is successful, a larger trial is planned.

The Intranasal Insulin Trial is based in Australia and New Zealand and is assessing the effect of intranasal insulin in first- and second-degree relatives aged 4 to 30 years who are at increased risk of diabetes based on data from an earlier pilot study.⁴⁶ Treatment continues for one year with follow-up for the development of diabetes for 4 years.

TERTIARY PREVENTION

It has long been recognized that most individuals presenting with T1D have little residual insulin secretion (as measured by C-peptide secretion) at the time of diagnosis.^{47,48} However, in the weeks to months after diagnosis and initiation of insulin treatment, there can be substantial recovery of β -cell function with falling insulin requirements, increasing C-peptide concentrations, and easily controlled blood glucose levels.^{47,48} This “honeymoon” or remission period of diabetes may last from weeks to months and occasionally years.⁴⁹ The honeymoon period is believed to be the result of the recovery of residual β cells unable to cope with the metabolic demands of the body. With institution of insulin treatment and reestablishment of glycemic control, these cells recover their capacity for insulin secretion only to be finally destroyed by the underlying autoimmune process. In addition, changes in insulin sensitivity probably also play a role in the expression of the honeymoon period, with decreased sensitivity at the time of diagnosis due to the hyperglycemia, with improvement after establishment of metabolic control.⁵⁰

The ability to measure C-peptide concentrations in those receiving insulin therapy allows an accurate assessment of residual β -cell function, and it can be used as a marker of the efficacy of therapeutic intervention.⁵¹ Prolongation of the honeymoon period has the potential to have significant beneficial effects in those with T1D. Metabolic control is much easier to establish in the presence of some residual insulin secretion. As a result, long-term diabetes-related complications are significantly less prevalent in those with residual insulin secretion. This was well demonstrated in the Diabetes Control and Complications Trial in which those subjects with sustained C-peptide production were found to have rates of nephropathy, retinopathy, and hypoglycemia that were half that of those without any residual insulin.⁵² The population of newly diagnosed T1D patients therefore represents an important group for future study of promising new interventions. Therapies that can safely maintain endogenous insulin secretion in the longer term would represent an important clinical advance.

Several agents, including cyclosporine, azathioprine, and prednisone, were studied in the 1980s for their efficacy in maintaining insulin production after the diagnosis of diabetes.^{53–56} Some beneficial effects were observed, but toxicity concerns made further use of these agents unfavorable. Several immunomodulatory monoclonal antibodies have been studied. The monoclonal antibody hOKT3 γ 1 (Ala-Ala), interferes with T-cell activation by binding the T-cell receptor, CD3.⁵⁷ Herold and colleagues^{58,59} showed that this modified anti-CD3 monoclonal antibody maintained C-peptide production over 2 years after 1 course administered in newly diagnosed patients within 6 weeks of diagnosis. A reduction in HbA1c and lower insulin doses were found in the treated group when compared with the untreated group. A European multicenter trial showed that a single course of a very similar modified anti-CD3 antibody, ChA-glyCD3, in newly diagnosed patients resulted in higher C-peptide production and reduced insulin doses for 18 months following treatment when compared with placebo.⁶⁰ These results were most pronounced among patients with C-peptide production at, or higher than, the 50th percentile. Another study of this modified CD3 molecule has recently completed enrollment through the Immune Tolerance Network. In this study, new onset subjects between 3 and 30 years of age within 8 weeks of diagnosis will receive 2 doses of hOKT3 γ 1 (Ala-Ala), one at the initiation of the study and a second dose one year later. The study will follow C-peptide production over 2 years from the initiation of treatment. In addition, the manufacturers of these modified CD3 molecules are sponsoring trials of these agents, the DEFEND-1 and Protégé studies, in recent-onset patients.

Table 1 Active studies with ongoing enrollment and their eligibility criteria	
Natural History Study of the Development of Type 1 Diabetes Sponsor: TrialNet Study Group	<ul style="list-style-type: none"> • Does not have diabetes • 1–45 years of age and first-degree relative of a person with T1D • 1–20 years of age and second- or third-degree relative of a person with T1D
Oral Insulin For Prevention of Diabetes In Relatives at Risk for Type 1 Diabetes Mellitus Sponsor: TrialNet Study Group	<ul style="list-style-type: none"> • 3^a–45 years of age with a relative with T1D • Insulin autoantibodies and one other diabetes autoantibody • Normal glucose tolerance
Effects of Recombinant Human Glutamic Acid Decarboxylase Formulated in Alum on the Progression of T1D in New Onset Subjects Sponsor: TrialNet Study Group	<ul style="list-style-type: none"> • 3–45 years of age • Within 3 months of diagnosis of diabetes • GAD antibodies • Stimulated C-peptide levels ≥ 0.2 pmol/mL^a
Study of Thymoglobulin to Arrest Newly Diagnosed Type 1 Diabetes (START) Sponsor: Immune Tolerance Network	<ul style="list-style-type: none"> • 12–35 years of age • Diagnosis of diabetes within the 12 weeks before study entry • Positive for 1 or more autoantibodies (anti-GAD, anti-insulin, or IA-2 autoantibodies) • Stimulated C-peptide level >0.4 pmol/mL
Trial of Intranasal Insulin in Children and Young Adults at Risk of Type 1 Diabetes (INIT II) Sponsor: Melbourne Health/Diabetes Vaccine Development Center	<ul style="list-style-type: none"> • Age 4–30 years if first-degree relative of a person with T1D • Age 4–20 years if second-degree relative of a person with T1D • Two or more diabetes autoantibodies • Normal glucose tolerance • First phase insulin release more than threshold

<p>Primary Intervention with Oral/Nasal Insulin for Prevention of Type 1 Diabetes in Infants at High Genetic Risk to Develop Type 1 Diabetes (Pre-POINT) Sponsor: Juvenile Diabetes Research Foundation</p>	<ul style="list-style-type: none"> • Ages between 18 months and 7 years • High-risk HLA genotype • Sibling or both parents with diabetes • Does not have diabetes or diabetes autoantibodies
<p>Phase 3 Trial of Otelixizumab for Adults With Newly Diagnosed Type 1 Diabetes Mellitus (Autoimmune): DEFEND-1 Sponsor: Tolerx/Juvenile Diabetes Research Foundation</p>	<ul style="list-style-type: none"> • Ages 18–35 years • Diagnosis of diabetes mellitus, no more than 90 days between diagnosis and administration of study drug • Stimulated C-peptide level greater than 0.20 nmol/L and less than or equal to 3.50 nmol/L • Positive for one or both of the following antibodies: ICA (anti-IA2) and/or GAD autoantibodies
<p>The Protégé Study - Clinical Trial of Teplizumab in Children and Adults With Recent-Onset Type 1 Diabetes Mellitus Sponsor: MacroGenics</p>	<ul style="list-style-type: none"> • Ages 8–35 years • Diagnosis of T1D mellitus within 12 weeks • Detectable fasting or stimulated C-peptide level • Positive for ICA512/IA-2, GAD autoantibodies, or IAA (if present during the first 2 weeks, but not beyond 2 weeks, of insulin treatment)

^a Currently 16–45, will be changed to 3–45 after regulatory approval.

The TrialNet study group is performing several trials in individuals newly diagnosed with T1D. The first such TrialNet study assessed the role of mycophenolate mofetil (MMF) and dacluzimab (DZB) in maintaining C-peptide production. MMF and DZB have been shown to be effective in transplantation regimens and are well characterized and tolerated. This study was stopped early when analysis of C-peptide production one year after initiation of treatment revealed no difference between the groups receiving both drugs or placebo.

TrialNet is also investigating the use of the anti-B lymphocyte monoclonal antibody, rituximab, in preserving C-peptide production in 8- to 40-year-olds with new onset diabetes. Rituximab depletes mature B cells thereby reducing antigen presentation to T cells. It has been shown to be effective in other autoimmune diseases including lupus and rheumatoid arthritis.⁶¹ Eighty-seven subjects were randomized to this study with results available in mid-2009.

CTLA4, a costimulatory molecule expressed on T cells is an important negative regulator of T-cell activation. CTLA4-Ig is a monoclonal antibody that binds to the costimulatory molecules CD80 and CD86, blocking the costimulation that is required for full T-cell activation. This antibody is approved for use in rheumatoid arthritis. In the ongoing TrialNet study, CTLA4-Ig (abatacept) is being used in a placebo-controlled study in new-onset subjects. Treatment is being given to 112 subjects with two-thirds receiving active therapy and one-third receiving placebo infusions over 2 years, with recruitment completed in 2009 and results expected in 2011.

GAD is an important antigen in T1D. Animal studies have shown that administration of GAD to induce immune tolerance can prevent diabetes.⁶² A recent study showed that 2 doses of GAD formulated in alum given within 6 months of diagnosis slowed the decrease of C-peptide production over the first 30 months after initiation of therapy.⁶³ This study involved 70 subjects aged between 10 and 18 years with fasting C-peptide greater than 0.1 mmol/L. TrialNet has launched a trial of 2 or 3 injections of GAD in alum versus placebo in 126 new-onset subjects that will include children as young as 3 years. The primary endpoint of this study will be C-peptide production at 1 year after initiation of treatment.

A small randomized placebo-controlled pilot study of the antitumor necrosis factor drug, etanercept, was recently reported.⁶⁴ The drug was given by subcutaneous injection twice weekly for 24 weeks in 18 children within 4 weeks of diagnosis. C-peptide production was significantly greater in the treatment group with lower HbA1c and smaller insulin doses. Other interventions currently under investigation or planned for study in this patient population, are anakinra, thymoglobulin, antithymocyte globulin, GAD/lansoprazole/sitagliptin, efalizumab, intensive metabolic control, and atorvastatin. **Table 1** lists active studies and their eligibility criteria.

"Curing" Established T1D

Once full-blown T1D has developed, immune interventions are unlikely to be effective because the vast majority of β cells have been destroyed. At this stage, effective interventions would include β -cell implantation as part of pancreatic or islet cell transplantation, or of gene therapy using implanted cells capable of producing insulin in response to glycemia, or of stem-cell-derived β cells. Pancreatic transplantation has been successfully applied, particularly in combination with kidney transplantation necessitated by diabetes-related end-stage renal failure. The paucity of donors and the need for lifelong immune suppression to prevent organ rejection have limited the application of these transplants. Islet cell transplantation enjoyed a period of success when investigators in Edmonton were able to show prolonged graft survival and an insulin-free period. However, limited supply of islets, side effects of the

immunosuppression, and eventual return to insulin dependence all challenge the ability of this approach to have a broad impact.

Genetic engineering and stem cell biology hold out the most hope in the long run for a cure for T1D and elimination of the need to inject insulin. With respect to gene therapy, cells have been created in which insulin secretion is possible. However, insulin is produced in small amounts and unregulated by blood sugar concentrations. Stem cells are currently under intensive evaluation; however, successful therapy for diabetes and other immune disorders remains elusive.

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