Immunotherapy for the Prevention and Treatment of Type 1 Diabetes

Human trials and a look into the future

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In the past 15 years, multiple clinical trials have attempted to find prevention for type 1 diabetes. The accompanying article by Bresson and von Herrath (1) reviews basic mechanisms underlying immunoprevention and immunotherapy of type 1 diabetes as well as selected human trials in the context of data from animal models. The second part of this minisymposium provides an overview of the recent or ongoing human trials. Immunotherapy for prevention of type 1 diabetes or to ameliorate the course of the disease after clinical diagnosis is currently restricted to research studies. References are provided to the clinical.trials.gov database or other sources where the reader can find additional information.

Type 1 diabetes is an autoimmune disease caused by interplay of genetic and environmental factors. Figure 1 summarizes the main stages in the development of type 1 diabetes and examples of prevention trials at these stages. The initial step—development of islet autoimmunity marked by the presence of autoantibodies to insulin, GAD (GAD_{65}), insulinoma-associated protein 2 (IA-2), and tyrosine phosphatase or zinc transporter (ZnT8)—is believed to be driven by environmental trigger(s) (2). Over the past 40 years, the incidence of childhood type 1 diabetes worldwide has increased by 3–5% annually (3–6). Elimination of the environmental trigger(s) responsible for this epidemic would be the most efficient approach to primary prevention. However, there is lack of consensus regarding which environmental factor(s) initiates islet autoimmunity. The National Institutes of Health have established The Environmental Determinants of type 1 Diabetes in the Young (TEDDY) consortium to evaluate the leading candidates (7,8).

After initiation of islet autoimmunity, most patients have a long preclinical period (9–12) that offers opportunity for secondary prevention—halting progression to clinical diabetes (Fig. 1). Large randomized trials initiated in the 1990s, including the Diabetes Prevention Trial Type 1 (DPT-1), the European Nicotinamide Diabetes Intervention Trial (ENDIT), and the Diabetes Prediction and Prevention (DIPP) project (13–16), have targeted this stage of pre–type 1 diabetes. The trials (17,18) and a cohort study (19) have shown that mild asymptomatic hyperglycemia, detected by oral glucose tolerance test (OGTT) or A1C, may precede by months or years overt insulin dependence among individuals with islet autoantibodies. Intervention at this "dysglycemic" stage of pre–type 1 diabetes may theoretically preserve endogenous insulin secretion and prevent acute and long-term complications of type 1 diabetes (20–22).

For the same reasons, preservation or restoration of insulin secretion after diagnosis of diabetes continues to be an attractive goal. Such tertiary prevention trials have used a number of immunomodulatory agents. These agents are often considered first in patients with established diabetes and, when proven safe, may be applied to patients with dysglycemic pre–type 1 diabetes and eventually those with normoglycemic pre–type 1 diabetes. However, efficacy in preserving C-peptide after diagnosis of type 1 diabetes should not be a precondition to applying an intervention to patients with pre–type 1 diabetes, as there may be a "point of no return" in the autoimmune destruction of the islets, rendering some interventions effective only at the earlier stages of the process.

Current approaches to prevent type 1 diabetes include:

- Avoidance of environmental triggers of islet autoimmunity such as cow's milk or gluten. Celiac disease provides an encouraging example of autoimmune disease that can be prevented in this way. Alternatively, diet is supplemented with nutrients for which deficiency presumably promotes islet autoimmunity, e.g., n-3 fatty acids or vitamin D.
- Antigen-specific "vaccination" using islet autoantigens, e.g., intact insulin, altered insulin or proinsulin peptides, GAD_{65}, or heat shock protein 60 (HSP60) peptide. The goal is to induce autoantigen-specific tolerance by induction of regulatory T-cells that downregulate immunity to a specific autoantigen as well as promote tolerance to additional autoantigens.
- Non–antigen-specific systemic therapies that range from mild modulation with oral nicotinamide or bacille Calmette–Guerin (BCG) vaccination to immunosuppression and cellular therapies.
- Stimulation of β-cell regeneration in conjunction with suppression of apoptosis that is increased in islet autoimmunity to overcome the relapsing-remitting course of pre-diabetes.
- Metabolic modifications, such as weight loss and maintenance, increased physical activity, and β-cell rest.

PRIMARY PREVENTION OF ISLET AUTOIMMUNITY — The target population for primary prevention trials are young children who carry high-risk HLA-DR,DQ genotypes. Finding such children in the general population is hampered by low specificity of these genotypes; the specificity is much higher in

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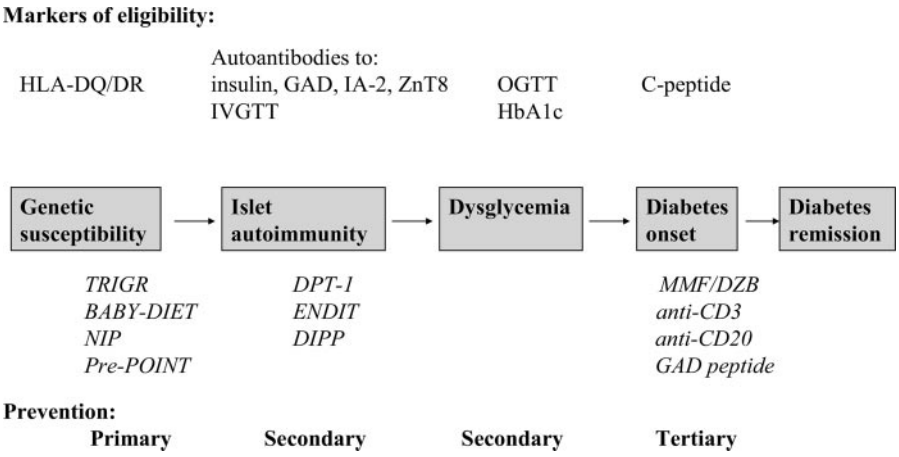

Figure 1—*Natural history of type 1 diabetes and prevention opportunities.*

populations with higher a priori risk of type 1 diabetes, i.e., first-degree relatives. While a number of non-HLA susceptibility gene markers have been reported, they have yet to be included in the design of primary prevention trials. The young age of potential trial participants and that most of them will never develop diabetes sets the safety bar high for prevention trials in this population. Ongoing primary prevention trials, summarized in Table 1, include largely low-risk dietary modifications: elimination of cow's milk (23) or gluten (24) and supplementation of diet with n-3 fatty acids (25) or vitamin D. A pilot trial of antigen-specific immunomodulation is using insulin (26) found previously to be safe in large secondary prevention trials.

Dietary modifications

The cow's milk hypothesis is being tested by the Trial to Reduce type 1 diabetes in the Genetically at Risk (TRIGR) (23). This randomized, double-masked trial is evaluating the effect of hydrolyzed infant formula, where protein fragments are too small to stimulate the immune system, compared with cow's milk–based formula. Eligible to participate were newborns who had a first-degree relative with type 1 diabetes and one of the high-risk HLA-DQ genotypes. The recruitment of 2,160 children from 77 centers in 15 countries was completed at the end of 2006. All participant mothers received the recommendation to breast-feed for at least the first 6 months of life. If a mother was unable to exclusively breast-feed before the baby was 8 months of age, her child was randomly assigned to either a formula of extensively hydrolyzed protein (Nutramigen) or a formula based on non-hydrolyzed cow's milk (Enfamil) containing a small amount of Nutramigen (for masking purpose).The main end point of the trial is development of diabetes by the age of 10 years.

The Finnish Intervention Trial for the Prevention of Type I Diabetes (FINDIA) tests an extension of the cow's milk hypothesis, i.e., that bovine insulin present in cow's milk triggers islet autoimmunity. FINDIA includes two arms similar to TRIGR, and, in addition, one-third of high-risk infants receive insulin-free whey-based formula. In contrast to TRIGR, none of the 982 high-risk children participating in FINDIA has a first-degree relative with type 1 diabetes (O.Vaarala, unpublished data). The interim results of the 3-year follow-up of study participants is expected in early 2009.

BABY DIET is another example of an elimination diet trial (24). This randomized, unmasked feasibility study is evaluating the effect of delaying exposure to gluten until the age of 1 year.

The TrialNet Nutritional Intervention to Prevent type 1 diabetes (NIP) (27) is a pilot study that enrolled pregnant women in their 3rd trimester expecting high-risk babies based on family history. In addition, newborn first-degree relatives with high-risk HLA-DR,DQ genotypes were enrolled. The trial was not powered to formally test efficacy of dietary supplementation with docosahexaenoic acid (DHA) before 6 months of age but rather to pilot the feasibility of a definitive trial.

Vitamin D supplementation in early childhood has attracted attention as a possible primary preventive measure (28,29). However, this interest has been mitigated by potential nephrotoxicity of vitamin D (30). At least one phase I clinical trial is testing the feasibility of this approach (31).

Antigen-specific vaccines

The Primary Oral/intranasal INsulin Trial (POINT) investigators (26), encouraged by the excellent safety profile in secondary prevention trials of oral (15) and intranasal insulin (16), have initiated a feasibility trial of primary prevention with oral or intranasal insulin vaccination. The pre-POINT phase I trial will determine the dose and route of insulin administration that is safe and is bioavailable to the immune system. The study will determine whether administration of insulin leads to both B- and T-cell responses that have characteristics consistent with protection. Protective B-cell responses may potentially include production of IgA-insulin antibodies, lower-affinity insulin antibodies, and insulin antibodies that do not react with proinsulin. T-cell responses to insulin will be evaluated by ELISpots, with increased production Th2-type cytokines such as interleukin (IL)-4, IL-10, and transforming growth factor-β suggesting protection. Eligible are children who have multiple first-degree relatives with type 1 diabetes or those who have the HLA-DR3/DR4-DQ8 genotype inherited identical by descent with a sibling proband; such siblings have type 1 diabetes risk as high as 80% (32). Children will be monitored for the development of islet autoantibodies, diabetes, and protective immune responses to insulin. Depending upon the outcome of pre-POINT, the study will continue to the phase II POINT study, which will determine the efficacy of mucosal insulin administration in primary prevention.

SECONDARY PREVENTION OF CLINICAL DIABETES

— Approximately 1 in 20 first-degree relatives and 1 in 300 people without type 1 diabetes in the immediate family has multiple islet autoantibodies. That is, 1 million people in the U.S. alone are currently at an increased risk of developing type 1 diabetes. Most young individuals with multiple islet autoantibody positivity progress to diabetes in 5–10 years; however, the rate of progression decreases with age. Preventing insulin dependency in a significant proportion of this population would be a major public health achievement. However, it is expensive to identify these high-risk subjects, about

Table 1—*Primary or secondary prevention trials prior to clinical diagnosis of diabetes*

Study (ref.)	Drug/phase	Sponsor/contact	Age	Eligibility	Dosing	Placebo	Follow-up duration/primary end point	Status/target size
TRIGR (23)	Cow's milk hydrolyzate/ phase III	NIH, NICHD, et al./www.trigr.org	0–7 days	FDRs, high-risk HLA	Supplementation of breast-feeding up to the age of 8 months	Yes	10 years/type 1 diabetes	Enrollment closed/ $n = 2,160$
BABY DIET (24)	Gluten-free diet/phase II pilot	German Research Foundation/ anziegler@lrz.uni-munchen.de	<3 months	Relatives, high-risk HLA DR, DQ	Gluten-free diet until age 12 months	No	3 years/islet autoantibodies	Enrollment closed/ $n = 50$
TrialNet NIP (27)	DHA/phase II pilot	NIH, NIDDK/www.diabetestrialnet.org	>24 weeks gestation/ newborn	Relatives, HLA-DR3 or DR4	Oral DHA once daily	Yes	2 years/20% higher plasma levels of DHA	Enrollment closed/ $n = 119$
Vitamin D (31,82)	Vitamin D3/ phase I pilot	Canadian Diabetes Association/dcatte@mich.ca	0–4 weeks	High-risk HLA DR, DQ	Oral vitamin D 2,000 IU once daily	No	1 year/25(OH) vitamin D levels, serum/urine Ca, islet autoantibodies	Enrolling/$n = 20$
TrialNet Oral Insulin (33)	Human insulin/ phase III	NIH, NIDDK/www.diabetestrialnet.org	1–45 years	Relatives, 2+ islet antibodies including to insulin	Oral insulin 7.5 mg once daily	Yes	7–8 years/type 1 diabetes	Enrolling/$n \approx 400$
INIT II (34)	Human insulin/ phase II	Melbourne Health/harrison@wehi.edu.au	4–30 years	Relatives, 2+ islet antibodies HLA not DR2, DQ6	Intranasal 1.6 mg and 16 mg/day	Yes	5 years/type 1 diabetes	Enrolling/$n = 262$
Pre-POINT (26)	Human insulin/ phase I/II	JDRF/prevent.diabetes@crt-dresden.de	1.5–7 years	FDRs/>50% risk of type 1 diabetes	Insulin daily for the first 10 days, after that twice a week. Increasing dose: oral 2.5–67.5 mg/day, intranasal 0.28–7.5 mg/day*	Yes	3–18 months/islet autoantibodies	Enrolling/$n = 40$
FINDIA	Insulin-free whey-based formula/ phase I/II	National Public Health Institute, Helsinki, Finland/ outi.vaarala@ktl.fi	Infants	General population, high-risk HLA DQ		Yes	2 years/islet autoantibodies, type 1 diabetes	Enrollment closed/ $n = 982$

*Staggered enrollment. DHA, docosahexaenoic acid; FDR, first-degree relative; JDRF, Juvenile Diabetes Research Foundation; NICHD, National Institute of Child Health and Human Development; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; NIP, Nutritional Intervention to Prevent type 1 diabetes.

$1,200 per subject, according to the DPT-1, and four large prevention trials have found no effect on the rate of progression to clinical type 1 diabetes for insulin administered parenterally (13), orally (15), or intranasally (16), as well as for oral nicotinamide (14). Smaller studies have evaluated other agents, also with little success. We will not review details of these studies, as they have been widely publicized. Two large randomized double-masked secondary prevention trials using oral and intranasal insulin are still underway (33,34) (Table 1). Interestingly, a post hoc analysis of data from the DPT-1 trial of oral insulin suggested that relatives with high levels of insulin autoantibodies appeared to experience a delay in progression to diabetes by ~4 years (15). This observation led to a second oral insulin trial, conducted by the Type 1 Diabetes TrialNet consortium. The study is enrolling first-degree relatives age 1–45 years and second-degree relatives age 1–20 years (the relative with diabetes must have been diagnosed before the age of 40 years and started on insulin within the 1st year of diagnosis). Eligible subjects must be positive for insulin autoantibodies on two samples within a 6-month period and meet additional criteria for other islet autoantibodies. As of February 2009, an initial 121 of the anticipated 400 subjects have been randomized.

The DPT-1 and ENDIT data have provided a wealth of information concerning prediction of type 1 diabetes and trial design. In October 2001, the DPT-1 trial centers and several new centers formed the Type 1 Diabetes TrialNet consortium (www.diabetestrialnet.org) for the prevention of type 1 diabetes. TrialNet systematically evaluates therapies in new-onset patients, as well as in pre-diabetic subjects, and invites proposals from the research community at large. The Immune Tolerance Network (ITN) (www.immunetolerance.org) is also accepting applications to support therapies aimed at tolerance induction and assays of tolerance.

Although the secondary prevention trials have failed to prevent or delay the onset of diabetes thus far, a growing body of evidence suggests that prevention of diabetic ketoacidosis (DKA) and hospitalization in newly diagnosed children is possible and should be a major goal of diabetes care systems. The DPT-1 demonstrated that DKA can be prevented by testing for islet autoantibodies and close biochemical monitoring (13), and the Diabetes Autoimmunity Study in Youth (DAISY) has confirmed this observation in the setting of an observational study (35). Early diagnosis and treatment not only eliminates mortality and greatly reduces the cost of initial treatment but may also help preserve endogenous insulin secretion and prevent acute and long-term complications of the disease (20–22). In the near future, we will likely see a resurgence of secondary prevention trials translating the most successful findings from tertiary prevention trials in patients with established type 1 diabetes.

TERTIARY PREVENTION AFTER DIAGNOSIS OF DIABETES

— In the past several years, trials in patients with newly diagnosed type 1 diabetes became the main focus of the research community. This shift away from secondary to tertiary prevention trials has been partially due to the ease of finding and retaining trial participants as well as the realization of how difficult and expensive trials of the magnitude of TRIGR, DIPP, ENDIT, or DPT-1 are to perform. The goal is preservation of remaining islet β-cells to induce and prolong partial remission. Unfortunately, most islets have already been destroyed by the time diabetes is diagnosed (36). Autoimmune β-cell destruction continues after the diagnosis of diabetes. A spontaneous temporary remission from insulin dependency may occur in up to 27% of patients, soon after diagnosis (37), and may be related to β-cell rest caused by insulin treatment (22). Younger age at onset, male sex, high titer of islet autoantibodies, severe DKA at diagnosis, and a short duration of symptoms prior to diagnosis are associated with a more rapid loss of C-peptide secretion (38). There are conflicting reports concerning the effect of the HLA-DR,DQ genotypes (37–39). Residual β-cell function can be retained for decades after the onset of diabetes in a subset of patients; however, for most patients very little normal function is retained, β-cell apoptosis continues, and there is little spontaneous β-cell regeneration (40). Complete spontaneous remission of type 1 diabetes is rare (41).

A realistic outcome of tertiary prevention trials is prolongation of residual insulin secretion, rather than complete reversal of diabetes. Benefits may include simpler insulin regimen, lower A1C, and reduced risk of hypoglycemia and microvascular complications. Success is usually measured by higher fasting and stimulated C-peptide secretion in the treatment versus placebo arm, with both groups of patients maintaining good glycemic control. Preserved C-peptide is associated with better glycemic control despite use of less insulin. Lower insulin dose, lower A1C, decreased glycemic variability, and decreased incidence of hypoglycemia have been used as secondary end points. On behalf of the Immunology of Diabetes Society, Greenbaum and Harrison (42) have developed useful guidelines for intervention trials in subjects with newly diagnosed type 1 diabetes.

Antigen-specific vaccines

Antigen-specific therapies are summarized in Table 2. In the past couple of years, perhaps the most exciting development in the area of tolerance induction has been apparent efficacy of Diamyd vaccine based on the whole recombinant human GAD_{65} ($rhGAD_{65}$) molecule suspended in alum. Clinical trials in late-onset autoimmune diabetes in adults (LADA) (43,44) and adolescents with newly diagnosed type 1 diabetes (45) have suggested benefit. In the latter study, patients receiving just two subcutaneous injections of the vaccine experienced a decline in stimulated C-peptide secretion approximately one-half that in the placebo group. Maximum stimulated C-peptide at 15 months also decreased less in the GAD-alum group compared with the placebo group. The protective effect was most pronounced in patients treated within 3 months of diagnosis; these patients preserved their endogenous insulin secretion over 15 months, in contrast to the placebo group. The apparent beneficial effects were not explained by changes in the GAD_{65} epitope pattern. GAD_{65} autoantibody levels increased in some patients; however, no serious side effects were observed, and there has been no evidence of the stiff person syndrome. Treatment with GAD_{65} seemed to induce a deviation of the GAD_{65}-specific T-cell response toward a protective immune profile. Three phase III trials of the $rhGAD_{65}$-alum vaccine are underway in the U.S. and Europe (Table 2), and a secondary prevention trial is under consideration.

Insulin-related molecules continue to attract great interest in vaccine development. An altered peptide ligand of the immunodominant insulin peptide B:9-23 (NBI-6024; Neurocrine Biosciences) completed phase I trials with a suggestion of immunologic efficacy (46) but was not

Table 2—*Tertiary prevention trials of antigen-specific vaccines after diagnosis of diabetes*

Study (ref.)	Drug/phase	Sponsor/contact	Age (years)	Time from diagnosis/ eligibility	Route	Dosing	Treated: placebo	Follow-up duration/primary end point	Status/target size
rhGAD$_{65}$ (45)	rhGAD$_{65}$-alum/ phase II	Diamyd	10–18	≤18 months/C-peptide ≥0.1 pmol/ml, GAD autoantibody positive	s.c.	20 μg twice in 30 days	1:1	15 months/fasting C-peptide, change in fasting and MMTT C-peptide	Published/n = 70
rhGAD$_{65}$ (83)	rhGAD$_{65}$-alum/ phase II/III	NIH, NIDDK, TrialNet/ diabetestrialnet.org	3–45*	≤12 weeks/C-peptide ≥0.2 pmol/ml, GAD autoantibody positive	s.c.	20 μg at 0, 4, and 12 weeks vs. 20 μg at 0 and 4 weeks vs. alum	2:1	2 + 2 years/MMTT C-peptide (4-h AUC)	Enrolling/n = 126
rhGAD$_{65}$ (84)	rhGAD$_{65}$-alum/ phase III	Diamyd Therapeutics/ swolf@tklreserach.com	10–20*	≤12 weeks/C-peptide ≥0.1 pmol/ml, GAD autoantibody positive	s.c.	20 μg at 1, 30, 90, and 270 days vs. 20 μg at 0 and 30 days vs. alum alone	2:1	15 months/MMTT C-peptide	Enrolling/n = 320
rhGAD$_{65}$ (85)	rhGAD$_{65}$-alum/ phase III	Diamyd Therapeutics/ulf.parkhede@trialformsupport.com	10–20	≤12 weeks/C-peptide ≥0.1 pmol/ml, GAD autoantibody positive	s.c.	20 μg at 1, 30, 90, and 270 days vs. 20 μg at 0 and 30 days vs. alum alone	2:1	15 months/MMTT C-peptide	Enrolling/n = 320
Proinsulin peptide (48)	Proinsulin C19-A3/phase I	Diabetes Vaccine Development Centre, JDRF, NHMRC Australia	21–53	>5 years/C-peptide <0.2 pmol/ml	i.d.	Intradermal 30 or 300 μg in 3 monthly doses	3:1	6 months/adverse events	Published/n = 48
IBC-VS01 (86)	Insulin peptide + IFA/phase I	NIAID ITN/Tihamer Orban, MD	18–35	≤30 days		One injection	1:1	2 years/adverse events MMTT C-peptide	Enrollment closed/ n = 12
BHT-3021 (87)	plasmid encoding proinsulin/ phase I	Bayhill Therapeutics/ kwoody@bayhilltx.com	≥18	≤5 years/diagnosed ≤40 years, C-peptide ≥0.066 pmol/ml	i.m.	One of four dose levels (0.3, 1, 3, or 6 mg) weekly for 12 weeks	2:1	25–37 months/crossover optional, adverse events	Enrolling/n = 72
DIA-AID (88)	DiaPep277/phase III	Andromeda Biotech/ merana@andromedabio.com	16–45	≤12 weeks/C-peptide ≥0.22 pmol/ml	s.c.	1 mg nine times in 21 months	1:1	2 years/MMTT C-peptide	Enrolling/n = 500

*Staggered enrollment. AUC, area under the curve; IFA, incomplete Freund's adjuvant; MMTT, mixed-meal tolerance test; NIAID ITN, National Institute of Allergy and Infectious Diseases Immune Tolerance Network; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NHMRC, National Health and Medical Research Council; NIH, National Institutes of Health; JDRF, Juvenile Diabetes Research Foundation.

Table 3—*Tertiary prevention trials of systemic immunomodulation after diagnosis of diabetes*

Study (ref.)	Drug/phase	Sponsor/contact	Age (years)	Time from diagnosis/ eligibility
TTEDD (89)	Anti-CD3 (TRX4)/phase II	TolerX Inc., JDRF/http://www.tolerrx.com and clinicaltrials@tolerx.com	18–45	Any duration/C-peptide detectable
DEFEND (59)	Anti-CD3 (otelixizumab)/phase III	TolerX Inc., JDRF/http://www.tolerrx.com and defend@tolerx.com	18–35	≤12 weeks/C-peptide 0.2–3.5 pmol/ml
AbATE (90)	Anti-CD3 (teplizumab)/phase II	NIH, NIAID ITN/info@abatetrial.org	8–30	<8 weeks
Delay (91)	Anti-CD3 (teplizumab)/phase II	NIH, NIDDK, JDRF/kevan.herold@yale.edu	8–30	4–12 months/C-peptide* ≥0.2 pmol/ml
Protégé (92)	Anti-CD3 (teplizumab)/phase II	MacroGenics, Inc., JDRF/aknesel@mmgct.com	8–35: 12–17†, 8–11†	≤12 weeks/C-peptide detectable
TrialNet Rituximab (93)	Anti-CD20 (rituximab)/phase II	NIH, NIDDK, TrialNet, et al./diabetestrialnet.org	8–45	≤12 weeks/C-peptide* ≥0.2 pmol/ml
START (94)	ATG/phase II	NIH, NIAID ITN/info@type1diabetestrial.org	12–35	≤6 weeks/C-peptide* >0.4 pmol/ml
ATG (95,96)	ATG/phase II	Ministry of Health Czech Republic/frsa@medicon.cz	15–35	≤6 weeks/C-peptide* ≥0.3 pmol/ml
TrialNet Abatacept (97)	Anti–CTLA-4	NIH, NIDDK, TrialNet, et al./diabetestrialnet.org	6–45	≤12 weeks/C-peptide* ≥0.2 pmol/ml
Interferon (62)	hrIFN-α/phase II	NIH, NIDDK/kr58q@nih.gov	3–25	≤6 weeks
Neulasta (98)	Pegylated GCSF (pegfilgrastim)/ phase I/II	JDRF, University of Florida/hallemj@peds.ufl.edu	12–45	≤6 months/C-peptide ≥0.2 pmol/ml
Anakinra (99)	IL-1r antagonist (anakinra)/ phase I/II	University of Texas Southwestern Med Center/Soumya Adhikarti, MD	6–18	≤1 week
AIDA (100)	IL-1r antagonist (anakinra)/ phase II/III	JDRF, Steno Diabetes Center, Oeresund Diabetes Academy/tmpo@steno.dk	18–35	≤12 weeks/C-peptide* ≥0.2 pmol/ml
Etanercept (61)	TNF-α inhibitor (etanercept)/ phase I/II	University of Buffalo, Immunex, Amgen/ tquattrin@upa.chob.edu	7–18	≤4 weeks/positive islet autoantibody
Cord blood (63)	Autologous umbilical cord blood transfusion/phase I/II	JDRF, NIH, University of Florida/hallemj@peds.ufl.edu	>1	Autologous cord blood stored
Prochymal (101)	Adult human mesenchymal stem cells/phase II	Osiris Therapeutics, JDRF/osiris@osiris.com	18–30	2–16 weeks/C-peptide detectable
AdiStem (102)	Autologous adipose-derived stem cells/phase I/II	AdiStem Ltd./lettielucero@yahoo.com	16–60	≤2 years
Dendritic cells (68)	Autologous dendritic cells/phase I	NIH, NIDDK, University of Pittsburgh/ brian.copeman@chp.edu	18–35	>5 years

MMTT C-peptide = area under the curve for C-peptide in response to a 2-h mixed meal tolerance test. *Stimulated. †Pending approval by data monitoring committee. AbATE, Autoimmunity-Blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes; AIDA, Anti–Interleukin-1 in Diabetes Action; ATG, anti–T-cell globulin; AUC, area under the curve; IFN, interferon; GCSF, granulocyte colony–stimulating factor; MMTT, mixed-meal tolerance test; NIAID ITN, National Institute of Allergy and Infectious Diseases Immune Tolerance Network; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; PBMC, peripheral blood mononuclear cell; JDRF, Juvenile Diabetes Research Foundation; START, Study of Thymoglobulin to Arrest Newly Diagnosed Type 1 Diabetes; TNF-α, tumor necrosis factor-α; TTEDD, TRX4 Monoclonal Antibody in Type 1 Diabetes.

shown to be effective in phase II B trials (47). Phase I studies have been completed or are nearing completion for a proinsulin peptide 19-A3 (48), an insulin peptide with incomplete Freund adjuvant and a plasmid encoding proinsulin (Table 2).

The DiaPep277 peptide of HSP60 has been reported to preserve C-peptide in a small trial of LADA patients with relatively short follow-up (49). Phase II trials in children showed no (50) or little (51) effect. A large phase III trial is currently enrolling patients in Europe and South Africa (Table 2).

Systemic immunomodulators

Numerous non–antigen-specific immunomodulators have been tried in newly diagnosed patients. In early 2007, an excellent review by Staeva-Vieira, Peakman, and von Herrath (52) summarized previously completed interventions, now largely of historical value. Some interventions, e.g., cyclosporine A, azatiopirine, and anti-thymocyte globulin (ATG) plus prednisolone, had unattractive side effects, including weakening of immunity to infections, renal and pancreatic toxicity, and potential long-term risk of malignancies. Others, such as nicotinamide, BCG vaccine, vitamin D supplementation, or elimination of dietary gluten, while safer, have shown no efficacy. Cyclosporine A was efficacious in prolonging insulin production (53,54); however, the treatment had to be continued for at

Table 3—*Continued*

Route	Dosing	Treated:placebo	Follow-up duration/primary end point	Status/target size
i.v.	8 daily injections	All:0	4 years/define highest tolerated dose	Enrolling/$n = 100$
i.v.	8 daily injections	2:1	2 years/MMTT C-peptide	Enrolling/$n = 240$
i.v.	14 daily injections/escalation dose; 2nd course after 12 months	2:1/open label	2 years/MMTT C-peptide (4-h AUC)	Enrolling/$n = 81$
i.v.	14 daily injections/escalation dose; 2nd course after 12 months	1:1	1 year/MMTT C-peptide (4-h AUC)	Enrolling/$n = 60$
i.v.	14 daily injections/2nd course after 6 months	3:1	2 years/insulin dose + A1C MMTT C-peptide	Enrolling/$n = 530$
i.v.	4 weekly injections of 375 mg/m^2 each	2:1	2 years/MMTT C-peptide	Enrollment closed/ $n = 87$
i.v.	4 daily injections/escalation dose	2:1	2 years/MMTT C-peptide	Enrolling/$n = 66$
i.v.	4 daily injections	1:1	3 years/C-peptide	Enrollment closed/ $n = 28$
i.v.	10 mg/kg monthly injections for 2 years (27 doses)	2:1	2 + 2 years/MMTT C-peptide	Enrollment closed/ $n = 111$
p.o.	5,000 or 30,000 units once daily for 1 year	2:1	1 year/MMTT C-peptide	Enrollment closed/ $n = 81$
s.c.	6 mg weekly for 12 weeks	1:1	2 years/adverse events, MMTT C-peptide	Enrolling/$n = 21$
s.c	Daily for 28 days	Open label	Change in EGR2 expression by PBMC, C-peptide	Enrolling/$n = 15$
s.c.	100 mg once daily for 2 years	1:1?	2 years/adverse events, MMTT C-peptide	Enrolling/$n = 160$
s.c.	0.4 mg/kg up to 25 mg twice weekly for 24 weeks	1:1	24 weeks/change in A1C, MMTT C-peptide	Enrollment closed/ $n = 18$
i.v.	One infusion	Open label	2 years/MMTT C-peptide, A1C, insulin dose	Enrolling/$n = 23$
i.v.	Infusion once per month for 3 months	1:1?	2 years/MMTT C-peptide	Enrolling/$n = 60$
i.v.	One infusion	Open label	Insulin dependence/insulin dose	Enrolling/$n = 30$
i.d.	Intradermal injection of cells treated ex vivo with antisense oligonucleotides	1:1	Adverse events	Enrolling/$n = 15$

least 6–12 months to show benefit, and the effect was lost when the drug was discontinued. In addition, the patients would progress to insulin dependency within 3 years, even if treatment was continued and C-peptide secretion was maintained (55). Renal and pancreatic β-cell toxicity as well as the costs of the drug and the monitoring of its levels in the blood led to a consensus that the risks outweigh the benefits. Nevertheless, cyclosporine trials provided a proof of principle that immunosupression can slow the destruction of the β-cells, even if it cannot stop it. The trials also showed that the effect of immunosupression was greatest if the intervention was started within 6 weeks of diabetes diagnosis, suggesting that β-cell mass at the initiation of immunotherapy may by a key predictor of success. Table 3 summarizes currently registered trials.

Monoclonal anti-CD3 antibody. Monoclonal anti-CD3 antibody treatment has received a lot of attention. The antibody transiently activates the CD3 receptor, causes cytokine release, and ultimately blocks T-cell proliferation and differentiation; the longer-term benefits may be due to the induction of regulatory T-cells. Humanized Ortho-Kung T-cell antibody hOKT3γ1(Ala-Ala) or CHAglyCD3 anti-CD3 monoclonals, engineered to abrogate complement Fc binding, do not induce severe cytokine release syndromes, in contrast to the standard OKT3, but have been associated with fever, rash, and in some patients adenopathy, depending upon the dose (56). Reactivation of Epstein-Barr virus infection observed in some patients appears to be self-limiting with a single course of therapy (57). Two randomized, placebo-controlled phase I/II trials with hOKT3 have suggested slower decline in stimulated C-peptide, lower A1C levels, and lower insulin requirements in patients receiving hOKT3 compared with placebo (56,57). The C-peptide levels held for at least 12 months, especially in patients with higher baseline C-peptide levels, followed by a recurrence of progressive loss of C-peptide. Significant but smaller benefits in C-peptide levels persist up to 4 years after treatment with a single course

of the antibody (58). To achieve better effects, this therapy will likely require repeated administration of the drug, which is being tested in several trials (Table 3) or in combination with another therapeutic agent. While the short-term follow-up results are encouraging, anti-CD3 therapy represents one of the more aggressive approaches to tertiary prevention of type 1 diabetes today, with a significant burden on patients. The typical protocol includes 2–3 screening visits, 8–12 outpatient visits on consecutive days, where patients may spend 4 h each day undergoing treatment and observation, and about 10 additional visits during the 2-year follow-up (59). With two dosing cycles 6–12 months apart, the number of visits increases to 30–40 during the initial 2 years postdiagnosis, clearly more than the 8–10 visits for insulin therapy required by current clinical standards of care.

Rituximab. Rituximab is a monoclonal antibody that targets the CD20 receptor unique to B-cells. Rituximab inhibits the B-cell function, thus reducing presentation of autoantigen to T-cells and theoretically secondarily preventing B-cell expansion and islet autoantibody production. This medication is approved for the treatment of non-Hodgkin's lymphoma and has shown success in treatment of patients with rheumatoid arthritis. TrialNet has completed a phase II trial including 4 weekly injections of rituximab (Table 3), and the results were presented at the American Diabetes Association's Scientific Sessions in June 2009. Newly diagnosed patients with type 1 diabetes (age 8–40 years) treated with rituximab had higher C-peptide 2-h area under the curve after a mixed meal and lower A1C and insulin doses compared with the placebo group. The full results of this trial should be available shortly.

Anti–CTLA-4 Ig. A trial of monthly infusions of anti–CTLA-4 Ig (abatacept) over a 2-year period has finished recruitment, and the results from TrialNet should be available in 2011. A high-affinity variant of CTLA-4 Ig (LEA29Y, belatacept) has been tested in islet transplantation studies and may be next in line.

Antithymocyte globulin. Antithymocyte globulin (ATG) has been used in organ transplantation but has not yet been shown to be effective in inducing immune tolerance. ATG is produced by taking human thymus cells and injecting them into an animal such as a rabbit or horse. The animal makes multiple anti-

Table 4—*Tertiary prevention trials after diagnosis of diabetes: islet regeneration and β-cell rest*

Study (ref.)	Drug/phase	Sponsor/contact	Age (years)	Time from diagnosis/ eligibility	Route	Dosing	Treated: placebo	Follow-up duration/primary end point	Status/target size
Islet regeneration (103)	Exenatide/phase IV	NIH, Baylor College of Medicine/Rubina Heptulla, MD	12–21	≥1 year	s.c.	Each patient to receive 3 different doses	1:1	AUC glucose	Enrollment closed/n = 17
SPIRIT1 (104)	INGAP peptide/phase II	Procter & Gamble/ kathleen.dungan@osumc.edu	18–65	Age of diagnosis <20 years/fasting C-peptide ≤0.1 pmol/ml	s.c.	300 or 600 mg/day for 90 days	1:1	6 months/Arg-stimulated C-peptide	Enrollment closed/n = 63
Islet regeneration and metabolic control (105)	Pioglitazone/phase I	Stony Brook University/ thomas.a.wilson@sunysb.edu	6–18	≤12 week	p.o.		1:1?	4 months/adverse events, MMTT C-peptide	Enrolling/n = ?
TrialNet metabolic control (74)	Near normoglycemia/ phase II	NIH, NIDDK, TrialNet/ diabetestrialnet.org	3–20	1–7 days	NA	Insulin pump therapy and CGM	Open label	2 years/MMTT C-peptide	Not yet enrolling/ n = 108
β-Cell rest (106)	Diazoxide/phase IV	University of Trondheim, Norway/valdemar.grill@ntnu.no	18–40	≤12 weeks/C-peptide* >0.2 pmol/ml	p.o.	Daily at bedtime for 6 months	1:1	At least 1 year/C-peptide, A1C	Enrollment closed/n = 35

*Stimulated. AUC, area under the curve; CGM, continuous glucose monitoring; INGAP, islet neogenesis-associated protein; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; NIH, National Institutes of Health; SPIRIT1, Stimulation of Pancreatic Islet Regeneration In Type 1 and Type 2 diabetes.

Table 5—*Tertiary prevention trials of combination immunotherapy after diagnosis of diabetes*

Study (ref.)	Drug/phase	Sponsor/contact	Age (years)	Time from diagnosis/ eligibility
TrialNet MMF/DZB (107)	Mycophenolate mofetil & daclizumab/phase III	NIH, NIDDK, TrialNet/diabetestrialnet.org	8–45	≤12 weeks/C-peptide* ≥0.2 pmol/ml
03-DK-0245 (108)	exenatide & daclizumab/phase II	NIH, NIDDK, Amylin Pharmaceuticals/ 1-800-411-1222 (Amylin), prpl@mail.cc.nih.gov	18–60	>5 years/C-peptide* 0.3–1.2 ng/ml
Proleukin + rapamune (109)	hrIL-2 (aldesleukin) & sirolimus/ phase I	NIH, NIAID ITN/diabetes@benaroyaresearch.org	18–45	3–48 months
09-DK-0056 (75)	Sitagliptin/lansoprazole rhGAD$_{65}$ (Diamyd)/phase II	NIH, NIDDK, Diamyd Therapeutics/ 1-800-411-1222 (Diamyd), prpl@mail.cc.nih.gov, davidmh@intra.niddk.nih.gov	16–30	≤4 months/C-peptide ≥0.2 pmol/ml
E1-INT (110)	EGF and gastrin/phase II	Transition therapeutics/Aleksandra Pastrak, MD	18–40	>1 year
Sao Paulo (64,65)	Autologous stem cell transplantation and cyclophosphamide + rabbit ATG/phase II	University of Sao Paulo, Northwestern University, Genzyme/jvoltar@fmrp.usp.br	14–31	≤6 weeks
Shanghai (67)	Autologous stem cell transplantation and cyclophosphamide + rabbit ATG/phase II	Shanghai JiaoTong University/guangning@medmail.com.cn	14–35	≤6 months

*Stimulated. ATG, anti–T-cell globulin; DZB, daclizumab; EGF, epidermal growth factor; MMF, mycophenolate mofetil; NIAID ITN, National Institute of Allergy and Infectious Diseases Immune Tolerance Network.

bodies to the thymic antigens that are primarily but not only T-cell in origin, and then they are purified to ATG. Injected back into the subject, ATG binds to T-cells and other immune cells, causing the host to see these as foreign because of the attached antibodies and eliminate them. A small clinical trial previously showed a reduction of A1C levels and lower insulin requirements (60). However, two patients developed severe thrombocytopenia. A European trial has recently been completed using a newer form of ATG, and a phase II trial of ATG through the ITN is enrolling type 1 diabetic patients (Table 3).

Tumor necrosis factor-α, IL-1 receptor antagonist, pegylated granulocyte colony–stimulating factor, and human recombinant interferon-α. A number of agents previously proven effective in other autoimmune diseases are being evaluated in phase I/II tertiary prevention trails of type 1 diabetes (Table 3). Tumor necrosis factor-α (TNF-α) inhibitor (etanercept) has been previously used in treatment of arthritis and Crohn's disease. A small pilot study has found increased C-peptide area under the curve and lower A1C and insulin doses in type 1 diabetic patients after 24 weeks of etanercept therapy started not more than 4 weeks after diagnosis (61). Trials of IL-1 receptor antagonist (IL-1ra) (anakinra) approved for rheumatoid arthritis and pegylated granulocyte colony–stimulating factor (GCSF) (pegfilgrasim) used for neutropenia are enrolling participants. These agents are administered subcutaneously. Oral human recombinant interferon-α (hrINF-α) has been found safe in doses of 5,000 and 30,000 units/day but slowed C-peptide loss only in the 5,000 units/day arm, a finding that requires replication (62).

Regulatory T-cells. Cell therapy targeting regulatory T-cells (Tregs) in vivo using certain drugs can be potentially hazardous, resulting in significant side effects and "off-target" effects. Therefore, novel approaches to isolate and expand polyclonal and antigen-specific Tregs in vitro have been developed for immunotherapy. While the efficacy of Treg transfer is well established in animal models, clinical trials in new-onset type 1 diabetic patients have just begun (Table 3). Umbilical cord blood may contain higher numbers of functional populations of Tregs. An open-label trial of autologous cord blood transfusion in children with newly diagnosed type 1 diabetes is underway (63). In the future, cord blood may turn out to be a reliable source of pluripotent hematopoetic stem cells applicable to trials of islet regeneration. Two trials of adult stem cell infusions are registered in the clinicaltrials.gov database (Table 3), and more are likely to be added in the near future. Autologous stem cell transplantation, particularly from bone marrow, has been successfully used in cancer patients and is intensively discussed as a treatment option for autoimmune disorders. Autologous nonmyeloablative hematopoietic stem cell transplantation, with concomitant high-dose immunosuppression, has been reported in new-onset type 1 diabetes (64,65). During a mean follow-up of 19 months, 14 of 15 patients became insulin free, their β-cell function increased significantly, their anti-GAD antibody levels decreased, and their A1C levels were maintained at <7%. A longer follow-up (30 months) has suggested increased C-peptide levels in some of these patients (66). Nevertheless, nearly all patients suffered from transplantation-related complications, which may compromise the application of this approach to type 1 diabetes. Trials to replicate this report have been registered in several countries (67).

Dendritic cells. Cell therapy using-dendritic cells is based on the hypothe-

Table 5—*Continued*

Route	Dosing	Treated: placebo	Follow-up duration/primary end point	Status/target size
MMF p.o., DZB i.v.	MMF twice daily 600 mg/m^2 for 2 years, DZB twice in 2 weeks 1 mg/kg up to 100 mg	2:1	4 years/MMTT C-peptide	Enrollment closed/ $n = 126$
Exendin-4 s.c., DZB i.v.		2 × 2 factorial	20 weeks	Enrollment closed/ $n = 16$
hrIL-2 s.c., sirolimus p.o.	hrIL-2 4.5 × 10^6 IU/day three times weekly for 4 weeks, sirolimus escalating dose for 12 weeks	Open label	2 years/adverse events MMTT C-peptide	Enrolling/$n = 10$
Sitagliptin p.o., rhGAD$_{65}$ s.c.			MMTT C-peptide	Enrolling/$n = 164$
s.c.	Daily for 4 weeks	3:1	6 months/Arg-stimulated C-peptide	Enrollment closed/ $n = 20$
i.v.	Cyclophosphamide 200 mg/kg, rabbit ATG 4.5 mg/kg	Open label	3 years/adverse events, insulin dose	Published/$n = 20$
i.v.	Cyclophosphamide 200 mg/kg, rabbit ATG 4.5 mg/kg	Open label	3 years/insulin dose	Enrolling/$n = 30$

sis that these antigen-presenting cells can be modified to favor a protective phenotype rather than one favoring disease development. These strategies use-"immature" dendritic cells that are in vitro derived from monocyte precursors isolated from diabetic subjects and then either modified with siRNA or an insulin peptide and then reinjected into the same individuals with the hope of resetting the immune response to islet antigens. One protocol is completing phase I safety studies (68), and the other is about to begin this year.

Islet regeneration

This topic has been recently covered by excellent reviews (e.g., 69) and is beyond the focus of the current article. However, we list current clinical trials of monotheraphy (Table 4) or combination therapy (Table 5) that include exenatide, sitaglipin, islet neogenesis–associated protein (INGAP) peptide, and pioglitazone. The promising E1-I.N.T. trial, a combination therapy containing gastrin and epidermal growth factor, will be followed by a trial of proton pump inhibitor to elevated gastrin levels combined with a glucagon-like peptide analog in one arm and further combined with GAD in another arm and will be starting soon.

Metabolic control and β-cell rest

Weight loss and increased physical activity (70) can neutralize the powerful effect of insulin resistance on progression to type 1 diabetes (71,72). Meticulous blood glucose control after diabetes onset resulting in β-cell rest is also believed to help preserve residual insulin secretion (73), and the TrialNet Metabolic Control Trial (74) is about to test this hypothesis.

Combination treatments

Many in the field of immunotherapy today feel that combination therapies may enhance efficacy while lowering risk and predict that one day multidrug immunotherapy will become the standard of care for newly diagnosed type 1 diabetes. Although combination treatments may be more likely to increase the risk of adverse events if chosen within the same therapeutic family, using therapies from different treatment pathways may reduce these risks. Current trials of combination immunotherapy are summarized in Table 5. Initial systemic immunosuppression followed by antigen-specific induction of tolerance or islet regeneration seems to be a logical approach and is about to be tested by a recently opened National Institute of Diabetes and Digestive and Kidney Diseases trial (108).

CONCLUSIONS AND A LOOK INTO THE FUTURE

— Development of safe and effective prevention of type 1 diabetes is a major public health goal in industrialized countries today, as evidenced by strong legislative support in the U.S. in the form of the Special Statutory Funding Program (http://www.t1diabetes.nih.gov). While hundreds of preventive modalities have succeeded in animal models of type 1 diabetes (76,77), prevention of human type 1 diabetes remains elusive as of early 2009. Genetic and environmental factors that determine the relapsing-remitting course of β-cell destruction, culminating in full insulin dependence, are being discovered. In the long run, primary prevention of islet autoimmunity will likely be the optimal approach to the prevention of type 1 diabetes, especially in high-risk groups, such as first-degree relatives. However, environmental triggers of islet autoimmunity need to be better defined. Poor predictive value of the existing genetic screening tools also means that the number of children needing intervention will remain high in relation to the number of type 1 diabetes cases prevented. If a primary prevention is not feasible in the general population, mass screening for islet autoantibodies and secondary prevention may be the next option.

Once more than one islet autoantibody is present, most individuals progress to diabetes in 5–10 years. The presence of more than one islet autoantibody, combined with susceptibility HLA-DR,DQ and protein tyrosine phosphatase N22 (PTPN22) genotypes (78), helps to identify individuals with sufficiently high risk of disease to attempt prevention. However, these screening tools need further improvement to exclude individuals, particularly adults, with loss of β-cells so slow that overt diabetes will not occur during the person's lifetime. Furthermore, prediction algorithms need to be sharpened before being applied to the general population, where the majority of type 1 diabetes cases occur, yet the predictive value of genetic markers is lower than among relatives.

As patients develop autoimmunity, β-cell function declines and so does the potential therapeutic benefit of intervention. Additionally, once the autoimmune process has begun it might become progressively more difficult to alter, as suggested by animal models where antigen-specific therapies used prior to the onset of disease can be far more effective than the same treatments given at the time of disease onset. In retrospect, the DPT-1 and ENDIT trials seem somewhat speculative when viewed in the more complete context of the complexity of immunoregulation and autoimmunity we have now defined. It is something to keep in mind while extrapolating to pre-diabetes, the promising findings from prevention trials in patients with established type 1 diabetes.

Technological advantages of insulin pumps and continuous glucose monitoring influence perceived benefits of immunotherapy after diagnosis of diabetes. Multiple logistic issues remain, e.g., the anticipated duration, toxicity, and complexity of immunotherapy. Unless tolerance can be established or restored permanently in a limited time period, intervention may need to be life-long akin to gluten-free diet for celiac disease. It is currently impossible to compare the cost-to-benefit ratio of such efforts with those of the established and emerging insulin treatment regimens. It is, however, important to keep in mind that insulin therapy, while not easy or complication free, has led to a dramatic improvement of the mortality and morbidity associated with type 1 diabetes over the past 20–30 years (79–81).

Although more targeted antibody therapies are being used, these agents are still relatively nonspecific and potentially toxic to some trial participants. Currently used systemic immunomodulators may carry a risk of long-term complications that is unacceptable for type 1 diabetes prevention. However, this work is important because even with successful primary or secondary prevention programs there will always be patients who develop clinical type 1 diabetes.

Diabetes prevention research is expanding at an unprecedented rate. The history of diabetes is filled with many groundbreaking discoveries. If the past performance does predict future returns, the prevention of type 1 diabetes has a bright future.

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