

Stopping Type 1 Diabetes: Attempts to Prevent or Cure Type 1 Diabetes in Man

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Type 1 diabetes—or, more accurately, type 1A diabetes—is thought to arise from selective immunologically mediated destruction of the insulin-producing β -cells in the pancreatic islets of Langerhans with consequent insulin deficiency (1). This occurs in individuals in whom genetic susceptibility outweighs genetic protection and is probably initiated by environmental factors not yet clearly defined. The disease arises via a cellular-mediated immune process, presumably a specific reaction to one or more β -cell proteins (autoantigens). There is consequent progressive impairment of β -cell function and apparent decline in β -cell mass. A secondary humoral immune response is characterized by the appearance of autoantibodies that serve as markers of the immune damage to β -cells. This insidious type 1 diabetes disease process generally evolves over a variable period of years (Fig. 1). The decline in β -cell function—and presumably in mass—is evidenced metabolically by loss of first-phase insulin response to an intravenous glucose challenge and later by the appearance of impairment in glycemic regulation, which is manifested as dysglycemia either as impaired glucose tolerance, impaired fasting glucose, or “indeterminate” glucose levels (values >200 mg/dl [11.1 mmol/l] at 30, 60, or 90 min during an oral glucose tolerance test). Ultimately, the clinical syndrome of type 1 diabetes becomes evident when the majority of β -cell function has been lost and presumably most β -cells have been destroyed; at this juncture, frank hyperglycemia supervenes. Although that broad sequence can be articulated, there are still gaps in many of the details. Further understanding of the nature of the disease process will facilitate the design of intervention strategies aimed at abrogating β -cell destruction and ultimately at prophylaxis of type 1 diabetes.

It should be evident from the above sequence of events that if type 1 diabetes is to be conquered, it is necessary 1) to stop immune destruction of β -cells, 2) to replace or regenerate β -cells, and 3) to preserve β -cell function and mass. In regards to all three of these, much has been accomplished in animal models of type 1 diabetes. Yet in human beings, success has been elusive. That is not to say that progress has not been made, for indeed it has. In this *Perspectives in Diabetes* article, written in honor of the 40th anniversary of the Juvenile Diabetes Research Foun-

ation (JDRF), we review the progress that has been made, indicate the challenges that have confronted investigators in these efforts, and propose a vision for how such research efforts might unfold in the future. We also note that several important consortia are addressing various aspects of this sequence, and these are listed in Table 1. These consortia have been supported by several institutes of the National Institutes of Health (NIH), JDRF, and the American Diabetes Association (ADA).

Stopping immune destruction of β -cells. Much investigation has been directed at interrupting the type 1 diabetes disease process both during the stage of evolution of the disease and at the time of disease onset.

The goal of intervention before clinical disease onset is to arrest the immune destruction and thus delay or prevent clinical disease. To effectively accomplish this requires identification of individuals at risk of type 1 diabetes (14). Therefore, a significant amount of attention has been given to identify potential risk markers and to quantify risk projection—with considerable success among relatives of individuals with type 1 diabetes (15,16) and some success based on the screening of newborns for genetic markers (17). Such prediction of the development of type 1 diabetes is based on risk assessment, which is accomplished using genetic, immunologic, and metabolic parameters. Yet, the majority of individuals who present with type 1 diabetes do not have a known relative who had the disease, and newborn screening programs for genetic risk markers are not yet universal. If there were an available clinical prevention strategy with demonstrated effectiveness, the case could be made that such newborn screening be mandatory. At some point, that clearly will be the case. This approach would identify most (over 95%) of those destined to develop type 1 diabetes, but it would also identify a larger number of people who will not develop the disease. This would facilitate the introduction of interventions designed to prevent autoimmunity as opposed to interventions in individuals with autoimmune markers in whom the goal is to prevent clinical type 1 diabetes. Yet, because of the fact that many newborns identified as having genetic risk will not ultimately develop type 1 diabetes, any intervention imposed at such time must be very safe.

The ability to predict type 1 diabetes on the basis of immunologic, genetic, and metabolic markers has led to several large studies designed to determine whether type 1 diabetes can be prevented by intervening in individuals with identified autoimmunity (Fig. 2). Unfortunately, to date, such studies have been without clear success (18). In part, this can be attributed to the selection of interventions that impose minimal risk to the subjects participating in the trials. However, it also may be that once autoimmunity is established, the immune process progressively expands, involving more and more components of the immune system and directed at an increasing number of islet

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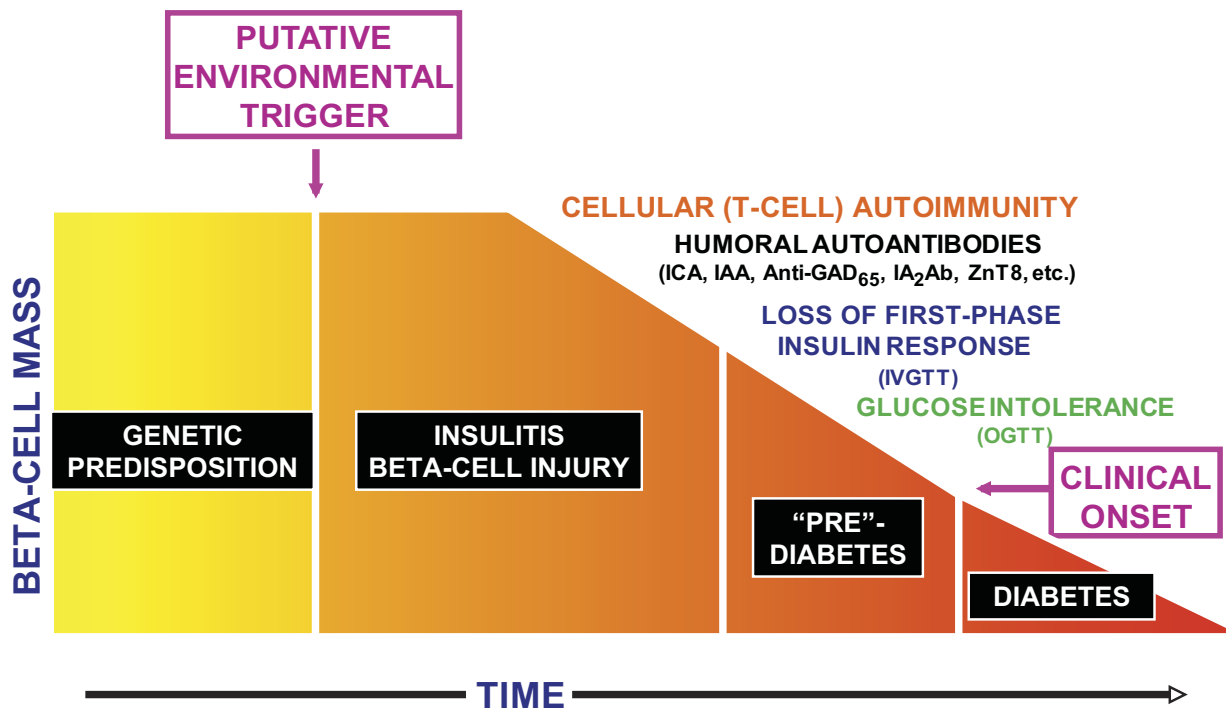


FIG. 1. Progression of the type 1 diabetes disease process. This is a cellular autoimmune process occurring in individuals with a genetic predisposition to the disease, presumably triggered by some environmental factor. Humoral antibodies indicate that the disease process is underway, and there is then progressive impairment of β -cell function manifested by progressive deterioration of glucose metabolism. The time frame is variable, so the x -axis is dimensionless. IAA, insulin autoantibody; ICA, islet cell antibody; IVGTT, intravenous glucose tolerance test; OGTT, oral glucose tolerance test.

autoantigens. The consequence is that therapies targeted at one specific component of the immune system, or at one specific autoantigen, may be inadequate to arrest the type 1 diabetes disease process. Nonetheless, any therapeutic strategy that has proven safe in new-onset type 1 diabetes, even if only with minor or transient efficacy, may be worth considering for prevention. We recognize that safety must be paramount for any study involving individuals who do not yet have disease. On the other hand, one must be cautious to not equate unpleasant but transient side effects, such as those associated with an infusion, as an obstacle for consideration of agents that are devoid of serious sustained adverse effects.

Studies of immune intervention begun at or shortly after diagnosis of clinical type 1 diabetes have the advantage that research subjects have an unambiguous diagnosis, but they have the disadvantage that such individuals have fewer β -cells to preserve. The goal of such studies is the preservation of residual β -cell function, thus allowing for easier glycemic management while also decreasing the likelihood of both hypoglycemia and long-term complications. β -Cell function is assessed by measuring C-peptide response to a provocative stimulus (19). A whole variety of interventions have been explored at this stage (20). Some interventions have shown potential benefit but were limited by toxicity or by the benefit being of limited magnitude and/or short duration of benefit. A number of agents showed promising preliminary effects but were not studied further. Others have failed to show efficacy. Some have shown mixed results. Others have only been evaluated in pilot studies that were too small to draw firm conclusions. Yet some approaches have shown promise in recent-onset type 1 diabetes, including two different anti-CD3 monoclonal antibodies (teplizumab [21] and oteelixizumab [22]), the

anti-CD20 monoclonal antibody rituximab (23), a GAD vaccine (24), and a somewhat extreme approach involving profound immunoablation with cyclophosphamide and anti-thymocyte globulin followed by rescue with autologous bone marrow transplantation to prevent the theoretical risk of aplastic anemia that could, in theory, develop after the cytoreductive-induction treatment (25). However, this risk should be virtually absent since the induction is not fully cytoablative. Additional strategies continue to be explored including cellular approaches such as the use of immature autologous dendritic cells (26).

Yet careful examination even of the approaches that have shown promise in recent-onset type 1 diabetes reveals that the effects seen are transient in nature (Fig. 3). As noted above, this could be due to progressive expansion of the immune process to involve more of the immune system and/or expansion of the number of islet autoantigens involved. One insight into the complicated and aggressive nature of the autoimmune response in type 1 diabetes is the observation that in individuals who have received combined kidney and pancreas transplants, there is often recurrent autoimmunity in the face of significant immunosuppression and absent the signs of organ rejection (27). This suggests that the immune pathways leading to autoimmunity are different than those leading to allograft rejection, and it implies that different approaches may be needed if both are to be controlled. Yet in organ transplantation, combinations of multiple immunologic modulators or suppressants are routinely used. Moreover, in animal models of type 1 diabetes, some of the best successes are seen with combination therapies. Thus it may very well be that combination therapy is needed if we are to successfully abrogate the immune processes leading to β -cell destruction (28). In Fig. 4, one example of a theoretical

TABLE 1
Consortia studying type 1 diabetes

Consortium	Full name of consortium	Consortium activities	Consortium website
T1DGC	Type 1 Diabetes Genetics Consortium	T1DGC was established with the primary goal of organizing international efforts to identify genes that determine an individual's risk of type 1 diabetes (2).	www.t1dgc.org
TEDDY	The Environmental Determinants of Diabetes in the Young	The primary objective(s) of TEDDY is the identification of infectious agents, dietary factors, or other environmental exposures that are associated with increased risk of autoimmunity and type 1 diabetes (3).	teddy.epi.usf.edu
nPOD	Network for Pancreatic Organ donors with Diabetes	The mission of nPOD is to characterize pancreata and related tissues from organ donors with type 1 diabetes or who are islet autoantibody positive and utilize the tissues to address key immunological, histological, viral, and metabolic questions related to how type 1 diabetes develops (4).	www.jdrfnpod.org
SEARCH	Search for Diabetes in Youth	SEARCH identifies cases of diabetes in children/youth <20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States (5).	www.searchfordiabetes.org
TrialNet	Type 1 Diabetes TrialNet	TrialNet is an international network conducting studies that will improve the understanding of type 1 diabetes disease development and test interventions to interdict the type 1 diabetes disease process, particularly strategies for type 1 diabetes prevention (6).	www.diabetestrialnet.org
ITN	Immune Tolerance Network	ITN is an international consortium dedicated to the clinical evaluation of novel tolerogenic approaches for the treatment of autoimmune diseases (including type 1 diabetes), asthma, and allergic diseases, and the prevention of graft rejection (7).	www.immunetolerance.org
TRIGR	Trial to Reduce IDDM in the Genetically at Risk	TRIGR is testing whether weaning to a casein hydrolysate formula during the first 6–8 months of life—in place of cow's milk-based formula—reduces the incidence of autoimmunity and type 1 diabetes in genetically susceptible newborn infants (8).	trigr.epi.usf.edu/
ICRs	Islet Cell Resource Centers	ICRs' goals are: 1) to provide high-quality islets for use in transplantation; 2) to optimize characterization of quality and effectiveness of islets transplanted into patients; and 3) to provide islets for basic science studies (9).	icr.coh.org/
CITR	Collaborative Islet Transplant Registry	CITR is expediting progress and promoting safety in islet transplantation through the collection, analysis, and communication of comprehensive and current data on all such transplants performed in North America (10).	www.citregistry.org
CIT	Clinical Islet Transplantation Consortium	This consortium is implementing a program of clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes (11).	www.isletstudy.org
DirecNet	Diabetes Research in Children Network	DirecNet is investigating the potential use of glucose monitoring technology and its impact on the management of type 1 diabetes in children (12).	public.direc.net/
EDIC	Epidemiology of Diabetes Interventions and Complications	EDIC is studying the clinical course and risk factors associated with long-term complications of type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) cohort (13).	www.bsc.gwu.edu/bsc/studies/edic.html

approach to combination therapy for interdicting the type 1 diabetes disease process is schematically depicted. This potential approach involves the use of a number of agents, including 1) an anti-inflammatory agent, such as an anti-interleukin-1 β or an anti-tumor necrosis factor, since considerable evidence exists that pancreatic islets are engulfed by an inflammatory response in both type 1 and type 2 diabetes (29); 2) transient use of a potent immunomodulator such as an anti-CD3 (21,22), or an anti-CD20 monoclonal antibody (23), or a co-stimulation blocker; 3)

provision of an antigen-specific therapy such as GAD vaccine (24), and/or oral insulin (30), or another antigen-specific approach, perhaps continued indefinitely; 4) enhancement of the protective immune response, perhaps by stimulation with granulocyte colony stimulation factor (31) or the infusion of regulatory T-lymphocytes (T-regs) (32); and 5) the addition of agents that may enhance β -cell function and potentially stimulate repair, regeneration, or neogenesis of β -cells, such as glucagon-like peptide 1 (33), exenatide (34), islet neogenesis-associated peptide, or

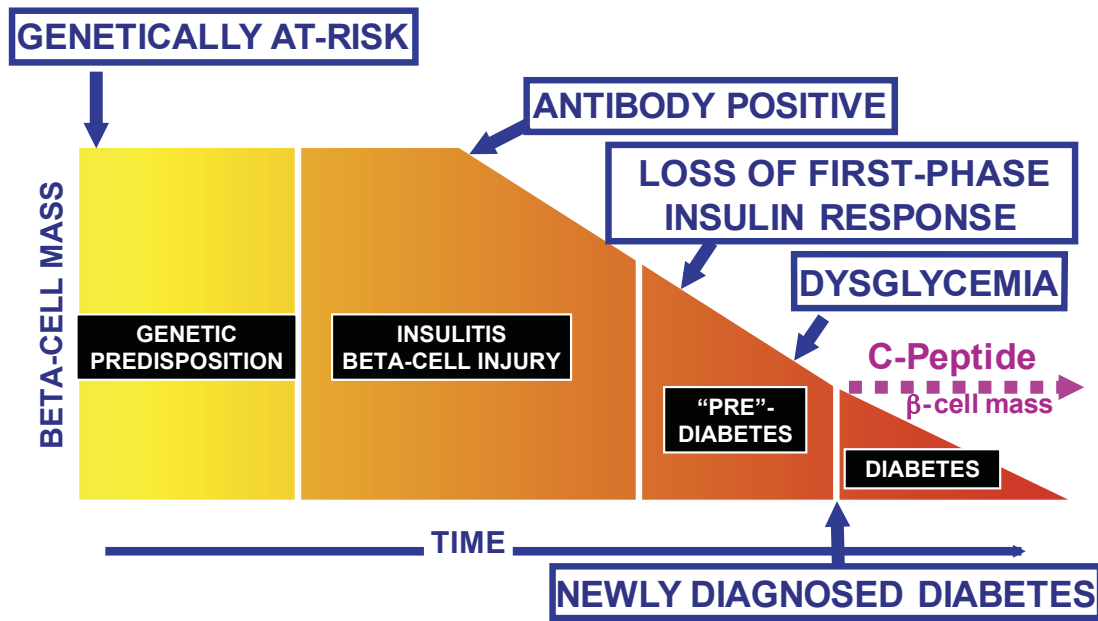


FIG. 2. Potential time points for intervention to alter the type 1 diabetes disease process. Intervention may be attempted in the genetically at-risk to try to abrogate autoimmunity, in those with antibodies signifying that the disease process is underway, or in those with varying degrees of metabolic abnormalities, including at the time of clinical onset of type 1 diabetes.

human proinsulin peptide-2B (35). Such a combination approach involves many challenges, including projecting the timing and duration of use of each of the components,

concerns over additive toxicities, regulatory hurdles, and ethical considerations. Nonetheless, similar combination approaches have been required both for the prevention of

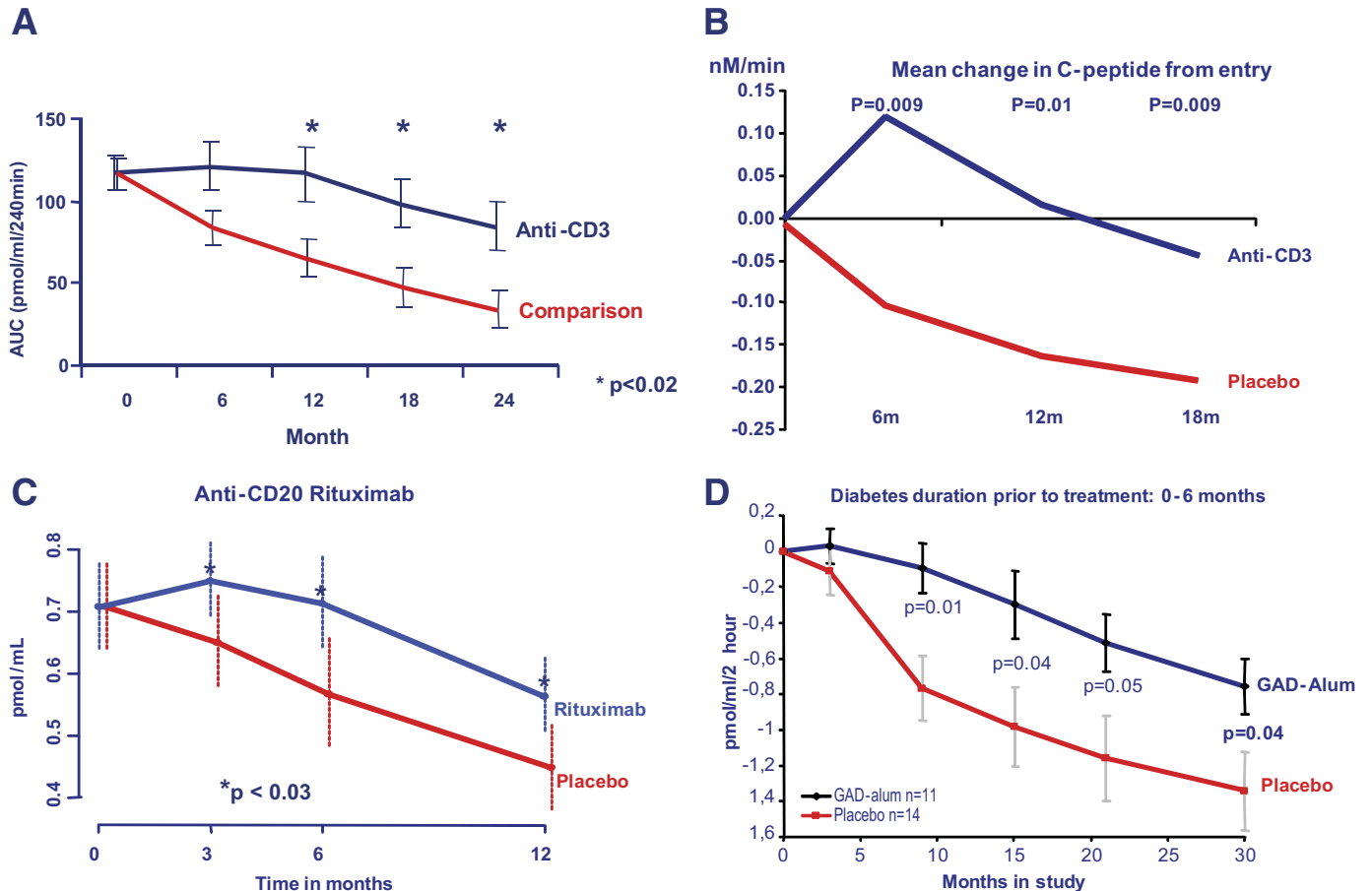


FIG. 3. Progressive decline of β -cell function (measured by C-peptide) is evident even in studies that are successful. These include intervention with the anti-CD3 monoclonal antibodies teplizumab (A) (21) and oteplizumab (B) (22), the anti-CD20 monoclonal antibody rituximab (C) (23), and a GAD vaccine with aluminum (Alum) adjuvant (D) (24). AUC, area under the curve.

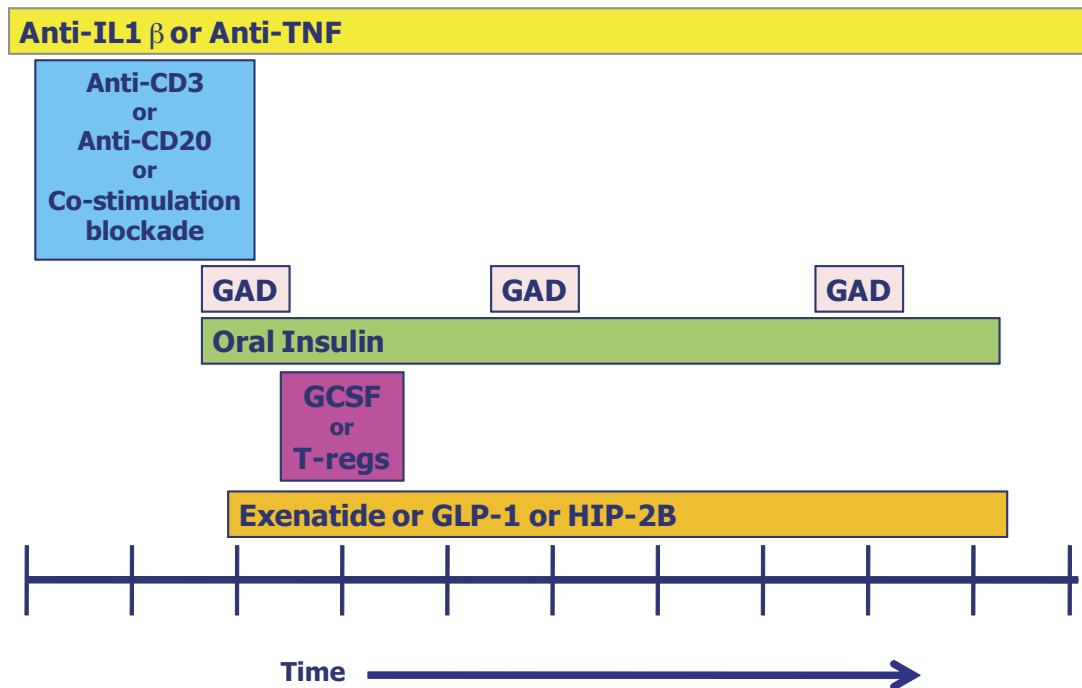


FIG. 4. Potential scheme for combination therapy to interdict the type 1 diabetes disease process. Such a combination might include an anti-inflammatory therapy (e.g., anti-interleukin-1 β [anti-IL1 β] or anti-tumor necrosis factor [anti-TNF]), an immunomodulatory therapy (e.g., anti-CD3, anti-CD20, or co-stimulatory blockade), followed by initiation of antigen-specific therapy (e.g., GAD and/or oral insulin), with stimulation of protective immunity (e.g., with granulocyte colony stimulation factor [GCSF]) or provision of protective immunity by infusion of T-regulatory (T-reg) cells, and with stimulation of β -cells (e.g., with glucagon-like peptide 1 [GLP-1], exenatide, or human proislet peptide-2B [HIP-2B]). The time frame needs to be determined, so the x-axis is dimensionless.

organ rejection and for the treatment of many malignancies. Even in type 1 diabetes, the longest term beneficial effect has been seen with an aggressive combination approach, as noted above (25). Nonetheless, the acceptable cost-to-benefit ratio in type 1 diabetes currently is different from that in organ rejection and malignancy; thus, more caution may be warranted.

It is interesting that intervention studies, particularly those that show beneficial effects, have challenged prevailing views regarding the pathogenesis of type 1 diabetes. An example is the finding that B-lymphocyte depletion with rituximab results in slowing of the decline of β -cell function (23). This suggests that β -cell destruction might also depend on B-lymphocyte antigen capture and presentation, which is associated with determinant spreading. If that is the case, early intervention with a B-lymphocyte-depleting strategy may delay the evolution of type 1 diabetes.

Replacement or regeneration of β -cells. Pancreatic transplantation, usually in the context of renal transplantation with the obligatory immunosuppression needed for the latter, has been applied successfully in patients with type 1 diabetes for over two decades. Indeed, when patients with type 1 diabetes develop end-stage renal disease, the most effective intervention strategy is combined kidney and pancreas or islet transplantation. Isolated islet cell transplantation has proven to be an effective treatment modality for patients with type 1 diabetes who suffer from hypoglycemia unawareness resulting in frequent emergency room visits (10). Both approaches to β -cell replacement result in dramatic improvements in prevailing glycemia, yet both are limited by the need for immune system alteration to prevent both allorejection and recurrent autoimmunity, as well as the limited availability of tissue.

The immunologic problems partly may be addressed in an identical manner to that discussed above. In addition, it may be possible to protect cells used for β -cell replacement by immunoisolation (Fig. 5) (36,37). To that end, various encapsulation methods have been attempted for many years. More recently, progress has been made with nanoencapsulation using conformal approaches to fabricate polymer capsules. Biomaterial scaffolds have also been used to provide mechanical stability and three-dimensional distribution of β -cells to reduce stress and improve nutrient distribution (38). Implantable biohybrid devices can be used both to protect cells and to provide localized delivery of immunomodulatory drugs, thereby limiting systemic toxicity (39).

The availability of an adequate source of cells for β -cell replacement has been a vexing problem, but one for which there are a host of potentially innovative solutions (40). Clearly, cadaveric organ donation cannot meet the potential needs, especially since in the U.S. in 2009 there were but 8,021 organ donors with only 1,739 pancreata collected. Although distal pancreatectomy for either pancreas or islet transplantation has been done, this is not likely a robust source of tissue. Xenotransplantation with porcine islets has been successful in nonhuman primates (41,42) and has been attempted in human beings. A variety of stem cells—embryonic, mesenchymal, bone marrow, cord blood, adipocyte-derived, and others—have been explored. There has been progressive improvement in this field, first with insulin-expressing cells being created, then with insulin-producing cells being developed, and finally with the generation of glucose-responsive insulin-secreting cells (43). Another approach to modifying cells is by protein transduction domain strategies, whereby several proteins can be delivered simultaneously to targeted intracellular compartments with their presence in the medium

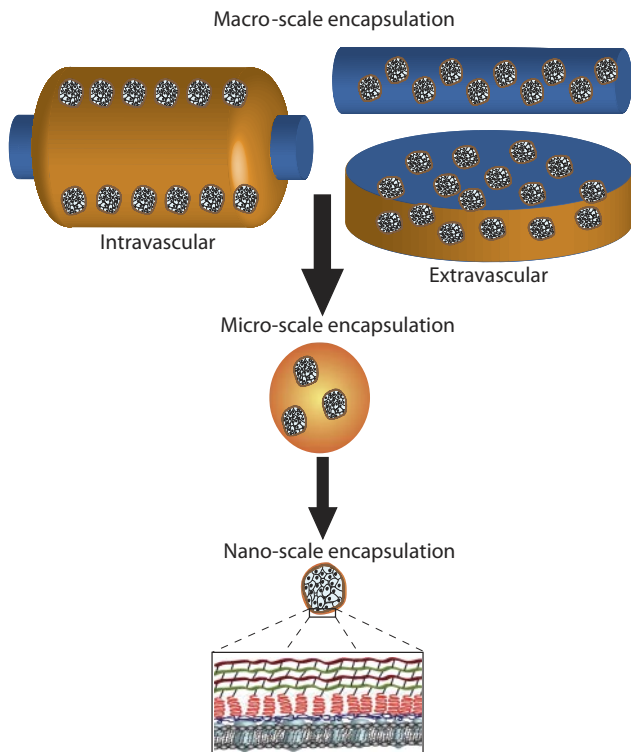


FIG. 5. The scale of various approaches to immunoisolation (37). Macro-scale encapsulation devices include intravascular, which are perfused with blood, or extravascular devices. Micro-scale devices are typically microcapsules (as illustrated). Nano-scale encapsulation commonly employs the coating of the islet spheroid with polymeric layers, such as conformal coating.

only as long as required and with maximum transfection efficiency (44). Although much work still remains, there has been substantial progress in the generation of “ β -cells” from stem cells, such that these cells demonstrate insulin gene expression, insulin synthesis and processing, insulin packaging and storage in granules, glucose sensing, and appropriate release of insulin and C-peptide.

Alternatively, other types of existing adult cells may be reprogrammed or transdifferentiated into β -cells. In animal systems, functional insulin-producing cells have been generated from pancreatic α -cells (45), pancreatic ductal cells (46), pancreatic acinar cells (47), and from human liver cells (48). A recent study generated pluripotent stem cells from fibroblasts of patients with type 1 diabetes (49). In theory, one could envision obtaining such tissue (such as liver) by biopsy, manipulating that tissue in the laboratory to convert it to insulin-producing cells, and then reinfusing them as an autotransplant back into the individual from whom the tissue was obtained.

An alternative to external differentiation *in vitro* is to stimulate neogenesis or regeneration of insulin-secreting tissue *in vivo*. As noted above, agents that may enhance β -cell function and potentially stimulate repair, regeneration, or neogenesis of β -cells include glucagon-like peptide 1 (33), exenatide (34), islet neogenesis-associated peptide, and human proislet peptide-2B (35). They clearly have demonstrated the ability to do so in rodents and/or *in vitro*, although the potential for regeneration or neogenesis of β -cells in human beings is still unclear. It should also be noted that, in conjunction with adequate immunomodulation, exenatide has been used in individuals receiving a second islet transplant (50) with remarkable success in

preserving posttransplant islet function and maintaining insulin independence, especially if the drug is administered also in the peritransplant period and not just when islet function is beginning to decline at variable times following transplantation. Yet some investigators have raised concern that the improved β -cell function seen with exenatide in type 2 diabetes is not sustained after discontinuation of exenatide, and they have assumed that this is indicative of the lack of an effect on islet mass. Although islet function serves as a surrogate of islet mass in the absence of an independent measure of islet mass, it may be that continued exposure to the drug is required for improved islet function even after mass has been expanded. Thus the interpretation of such experiments is complex, and they cannot be used to conclude that these agents do not expand islet cell mass in human beings. In addition, the benefit of exenatide could go well beyond an insulinotrophic, β -cell-enhancing effect. This is because an antiapoptotic, anti-inflammatory, and immunomodulatory effect has been associated with exenatide treatment (51).

Preserving β -cell function and mass. A successful approach to the prevention or cure of type 1 diabetes requires that β -cell function and mass be preserved. This is true both for native β -cells, regenerated β -cells, and for any cells used to replace β -cells. From the discussion above, there are at least three components to preserving β -cell function and mass. These include: 1) abrogating or controlling the immune response, both in terms of autoimmunity and allojection (if a nonidentical source of β -cells is used); 2) protecting cells used for β -cell replacement by immunoisolation; and 3) using pharmacologic agents to enhance β -cell function and potentially stimulate repair, regeneration, or neogenesis of β -cells. The appropriate manner of use of such strategies remains to be determined. For example, it may be that it is necessary to arrest autoimmunity and induce immune regulation or immune tolerance prior to replacing or regenerating β -cells. Alternatively, it may be possible to apply such strategies simultaneously, such as combined islet cell and hematopoietic stem cell transplantation to induce chimerism and graft tolerance (52).

Conclusions. Although considerable work remains to be accomplished, the potential to prevent and to cure type 1 diabetes is clearly within reach. The clinical trials necessary to demonstrate this must be well designed, adequately powered, carefully controlled, and vigilantly conducted. Depending on the modality being tested and the population being used for such trials, sample sizes likely will require a collaborative, cooperative, multicenter approach. The diabetes community of scientists, clinical trialists, patients, families, funding agencies, and regulatory agencies must work together in a cooperative and collegial manner if we are to be successful in our efforts to prevent and cure type 1 diabetes. Approaches that are more aggressive than those used in the past, including combination approaches and novel interventions, will likely be needed. Despite current impediments, the progress in recent years has been greater than in preceding decades, and together, we are uniquely poised to address existing challenges and conquer type 1 diabetes.

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J.S.S. notes potential conflicts of interest as a member of the board of directors of Anylin Pharmaceuticals, the manufacturer of exenatide, and as chairman of the Type 1 Diabetes Advisory Board of sanofi-aventis, who have licensed human proislet peptide-2B. No other potential conflicts of interest relevant to this article were reported.

This *Perspectives in Diabetes* article is written in honor of the 40th anniversary of the Juvenile Diabetes Research Foundation (JDRF). An interesting side note is that at 15 years of age, J.S.S. was a newspaper delivery carrier for the Philadelphia *Bulletin* and among the customers on his delivery route was Lee Ducat, the founder of JDRF.

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