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Immunotherapy for Type 1 Diabetes - Necessity, Challenges and Unconventional Opportunities

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1. Introduction
Type 1 diabetes (T1D) is the leading autoimmune disease of childhood. In this review / prospective, we discuss (1) why there is an urgent need of an immunotherapy for T1D despite success of insulin therapy in improving quality of life of patients and (2) why the limited efficacy of current therapies in phase I/II clinical trials has necessitated a quest for new approaches. In addition, we offer novel views on the potentials of targeting the Fas death pathway as an unconventional therapeutic approach for T1D that is unlikely to cause immune suppression.

2. Why immunotherapy for T1D?
Type 1 diabetes (T1D), also known as insulin dependent diabetes, is a chronic progressively worsening autoimmune disease that occurs early in life and is the leading autoimmune disease of childhood (Bluestone et al.). In genetically susceptible individuals, autoimmune T-cells infiltrate pancreatic islets where they proliferate and destroy insulin-producing beta cells, resulting in insulin deficiency and impaired blood glucose homeostasis manifested as hyperglycemia. Hyperglycemia causes many serious complications including renal failure, proliferative retinopathy/blindness, peripheral neuropathy, and vascular disease. Therefore, all T1D patients need to take exogenous insulin on a daily basis to keep the blood glucose level within a physiologic range. Since insulin is not a cure for the disease, patients must take it throughout life, a routine that requires significant dedication and time from patients and parents in case of children. In addition, patients need to observe a strict diet, check their blood sugar levels on a regular basis, and adjust the insulin dose accordingly. Even with tight glucose control, patients eventually develop a multitude of life threatening vascular and neurologic complications as mentioned above. Thus, although insulin therapy is currently the best available option to manage T1D, it remains a palliative measure and a cure for the disease remains an urgent goal. Consequently, intensive efforts are being directed towards developing an immunotherapy for the disease. These efforts are facilitated by the significant advances made in understanding the disease pathogenesis that resulted in uncovering a multitude of potentially therapeutic targets to control the diabetogenic T cells that drive the disease process.
3. High standard for T1D immunotherapy

The goal of immunotherapy, in general, is to thwart the unwanted immune cells that precipitate and drive the autoimmune response that impairs or destroys the target organ; the pancreas in the case of T1D. Studies in animal models have identified the T cell as the key mediator of the autoimmune responses that destroy insulin-producing beta cells in pancreata of T1D (Anderson and Bluestone, 2005). Therefore, many recent and current T1D immunotherapies are aimed at the T cell. Significant advances have been made in identifying and characterizing molecules and mediators, including cytokines, which regulate T cell activation, trafficking, and effector functions. These advances offer potential targets that can be modulated using recombinant ligands or specific antibodies to suppress or eliminate autoreactive T cells. These molecules and mediators, however, are used primarily by protective T cells to defend individuals from infections. Therefore, while theoretically many approaches can be used to successfully prevent or arrest the autoimmune response by targeting diabetogenic T cells; most of these approaches lack specificity and carry the inherent risk of paralyzing the whole T cell repertoire, resulting in systemic immune suppression. The difficulty is, therefore, lies in finding means to specifically target and safely suppress and/or eliminate autoreactive T cells without damaging protective T cells and causing immunosuppression.

The risk of immune suppression is an accepted trade-off in life threatening autoimmune diseases such as multiple sclerosis, but not for T1D patients. There is an exceptionally high safety standard for immunotherapy for T1D patients. A primary reason for this is the effectiveness of insulin therapy in allowing T1D patients to maintain a significantly good quality of life for a long time. Secondly, most T1D patients are young people with their productive years of life ahead of them. Therefore, the benefits of a successful immunotherapy for T1D must supersede those of the insulin therapy. It must be a cure and not an alternative palliative measure, and must carry minimal risk of causing immunosuppression. The side effects should be tolerable. In summary, although T1D is usually associated with devastating long-term complications, it is currently fairly manageable by the insulin therapy and thus benefits of any appealing immunotherapy should far exceed those of the insulin therapy. In other words, as a gold standard, immunotherapy for T1D must provide a cure for T1D: freedom from insulin usage, and negligible risk of immunosuppression.

4. Limited efficacy of clinically tested T1D immunotherapies generates new challenges

The non-obese diabetic (NOD) mouse is the widely-used animal model to study the pathogenesis of T1D. T1D disease development in these mice shares many properties with T1D disease development in humans (Anderson and Bluestone, 2005) and many key insights into the etiology and pathogenesis of the disease have been initially discovered in NOD mice (Anderson and Bluestone, 2005), resulting in a wide range of potential therapeutic targets, a number of which have been tested in clinical trials. These agents can generally be divided into two categories: nonspecific and antigen specific modulators. Among the promising non-specific modulators are anti-CD3 mAb and more recently, anti-CD20 therapy that modulate and temporally delete T and B cells, respectively. Among antigen specific therapies, attention is focused on GAD65 and insulin therapies. Because
both non-specific and antigen specific therapies can potentially cause serious side effects depending on the dosage and frequency of administration, therapeutic regimens are carefully calculated.

Therapeutic trials of two humanized Fc-engineered monoclonal anti-CD3 antibodies called teplizumab (Herold et al., 2005; Herold et al., 2002) and otelixizumab (Bolt et al., 1993; Keymeulen et al., 2005) showed initial promising results. Short term treatment of recently-diagnosed T1D patients demonstrated a significant reduction in the loss of beta-cell function for at least two years. These subjects showed no evidence of long term immune suppression and experienced improvement in hemoglobin A1c levels and insulin usage. Although anti-CD3 mAb treatment was generally well-tolerated due to the largely-eliminated T cell activation-associated cytokine storm with the development of a non-Fc binding anti-CD3 mAb, some subjects experienced flu-like side effects in the first days and weeks after treatment that were attributed to cytokine release. Symptoms were severe enough to cause 10% of subjects to discontinue treatment. In the European trial, some subjects experienced transient reactivation of Epstein-Barr virus, however, these EBV copies returned to normal pre-treatment levels within 3 weeks in all cases (Keymeulen et al.).

A humanized CD20 mAb called Rituximab, which was initially approved to treat lymphomas, has also advanced to T1D clinical trials. A recent randomized, double-blind trial of Rituximab on newly-diagnosed T1D patients showed promise (Pescovitz et al., 2009). Three months after treatment, Rituximab-treated subjects had significantly lower hemoglobin A1c levels, reduced insulin use, and improved beta-cell function compared to placebo. Rituximab patients, however, experienced a decline in beta-cell function that paralleled those of placebo-treated subjects at months 3-12 of the study. Despite this, Rituximab patients showed overall improvement in the previously described clinical parameters at 1 year compared to placebo-treated subjects.

Antigen specific immunization with beta cell autoantigens (Insulin and GAD65) also made it to clinical trials. Glutamate Decarboxylase 65 (GAD65) is secreted by all endocrine islet cells and is thought to be one of the earliest autoantibody targets during the initiation of T1D (Kaufman et al., 1993; Tisch et al., 1993). The antigenic region of the GAD protein is initially a small region consisting of two adjacent peptides. T cell autoimmunity eventually spreads intermolecularly to additional GAD determinants and then to other beta-cell antigens, resulting in a diverse population of autoreactive T cells. Elimination of the anti-GAD T cell response halts the spread of autoimmunity to other beta-cell antigens and disease progression. Based on success in animal studies (Tian et al., 1996), two clinical trials using alum-formulated human recombinant GAD65 have shown encouraging results. Agardh et al. (2005) conducted a Phase II study to evaluate dosage and safety in adults (Agardh et al., 2005). No adverse effects of treatment were identified and both fasting and stimulated c-peptide levels were increased from baseline in the group receiving 20 µg compared to placebo at 24 weeks. A different trial conducted by Ludvigsson et al., (2011) on recent onset adolescents showed longer preservation of both fasting and stimulated C-peptide levels in GAD-treated subjects as compared to placebo. This study also demonstrated that improvement in clinical parameters after GAD treatment was most pronounced in patients with <6 months disease duration at baseline.

Much attention has been given to insulin and its immunogenic epitopes as inducers of immune tolerance in pre-T1D and newly diagnosed T1D patients. Insulin and proinsulin are thought to be some of the primary autoantigens targeted by the immune system during T1D.
initiation (Nakayama et al., 2005; Narendran et al., 2003). Mucosal exposure to insulin was shown to impart a $T_{\text{reg}}$-associated delay in disease onset and a reduction in incidence of T1D in NOD mice (Harrison and Hafler, 2000). Due to the largely successful outcomes of laboratory studies, oral and nasal insulin treatment progressed to clinical trials to explore treatment of both prediabetic and recent onset patients. A trial conducted by Harrison et al. (2004) recruited subjects who had antibodies to at least one islet antigen (Harrison et al., 2004). The trial demonstrated that nasally-administered insulin therapy did not result in adverse side effects or accelerated destruction of beta-cells. Subjects also experienced a decrease in T cell response to insulin and increase in antibody which were consistent with mucosal insulin tolerance.

Other trials, however, have indicated that insulin-treated prediabetic subjects were no less likely to develop T1D or experience a delay in T1D onset than their placebo-treated counterparts and that insulin therapy could possibly cause accelerated beta-cell destruction (Skyler et al., 2005; Sosenko et al., 2006).

While assessment of the results of clinical trials has demonstrated feasibility, evaluation of efficacy produced the conclusion that none of the agents currently under clinical investigation hold the key for the cure as a sole therapy. Since escalating dose is not an option because of the serious side effects of these agents, combination therapy strategies are currently being evaluated (Skyler and Ricordi; von Herrath). A prime example combines an antigen-specific therapy with a broad spectrum immunosuppressive drug. Nasally-introduced proinsulin II peptide in combination with anti-CD3 mAb was shown to significantly increase $T_{\text{reg}}$ induction in 2 mouse models (Bresson et al., 2006). In contrast, neither therapy alone could achieve operational antigen-specific $T_{\text{reg}}$ induction late in diabetogenesis. It is suggested by the authors of this study that the induction of proinsulin-specific $T_{\text{reg}}$ cells was made possible by the transient decrease in autoreactive T cells via anti-CD3 mAb, allowing for the modulation of APCs in the PLNs. The hope is to increase the efficacy through synergistic or additive effects of agents that target different pathways. In addition, significant efforts are also being directed towards identifying new, non-suppressive therapeutic agents. In summary, as only few of the diverse immunomodulating agents that have so far been examined in clinical trials show promise, efforts are being directed towards identifying new therapeutic agents and assessing efficacy of combination therapy.

5. The Fas pathway as a counter-intuitive therapeutic target for T1D

For obvious reasons, the focus of immunotherapy for T1D has been on T cells, antigen presenting cells (APC), and molecules that control T cell activation. As noted above, the intimate roles for these cells and molecules in regulating host response to infections has limited the degree to which their activity can be modulated to treat or prevent T1D without causing immune suppression to infections. In this regard, The Fas pathway represents a unique molecule that is not essential for host immune response yet plays a critical role in regulating pathogenesis of autoimmune diabetes in the NOD mouse.

5.1 The Fas pathway regulates T cell homeostasis

The Fas pathway is the prototypical apoptosis pathway that mediates contraction and death of activated T cells (Hamad; Lenardo et al., 1999; Pinkoski and Green, 1999; Takahashi et al., 1994; Watanabe-Fukunaga et al., 1992). It is an extrinsic signaling pathway that initiates
apoptosis, or programmed cell death. The Fas receptor (also known as Apo-1 or CD95) is a transmembrane protein member of the tumor necrosis factor (TNF) receptor superfamily (Strasser et al., 2009). It contains a “death domain” of approximately 80 amino acids in its cytoplasmic region that is essential for apoptotic signal transduction (Lenardo, 1996). Binding of FasL to its receptor results in the formation of a death-inducing signaling complex (DISC) composed of Fas-associated death domain protein (FADD) and caspase 8. The Fas-DISC complex allows for autocatalytic activation of procaspase 8. In type 1 cells, processed caspase-8 directly activates caspase 3 and other caspases which cleave cell substrates and initiate apoptosis. In type 2 cells, less DISC is formed, thus the apoptotic signal must by amplified via a positive feedback loop that involves the release of mitochondrial pro-apoptotic factors.

Increasing evidence indicates that the Fas pathway is critical for elimination of chronically-activated T cells, especially an abnormal subset of double negative (DN) alpha/beta T cells from secondary lymphoid organs (Hamad; Stranges et al., 2007). Spontaneous loss-of-function mutation in either Fas (lpr mutation) or FasL (gld mutation) impairs Fas-mediated apoptosis and animals bearing these mutations develop an age-dependent lymphoproliferation in which DN T cells predominate (Takahashi et al., 1994; Watanabe-Fukunaga et al., 1992). In humans, defects in the Fas pathway cause an autoimmune lymphoproliferative syndrome (ALPS) that is similar to the disease in mutant mice (Fischer et al., 1995).

5.2 Fas/FasL interaction controls a main pathogenic mechanism in insulitis development

Despite the lymphoproliferation, NOD mice (the widely used model for T1D) bearing homozygous gld or lpr mutations become completely resistant to autoimmune diabetes and several other organ-specific autoimmune diseases (Chervonsky et al., 1997; Hamad; Kim et al., 2000; Mohamood et al., 2007; Thomas et al., 1999; Waldner et al., 1997) (Nakayama et al., 2002). The diabetogenic process is arrested at a pre-insulitis stage by the lpr or gld mutation (Chervonsky et al., 1997; Mohamood et al., 2007; Su et al., 2000). This finding established the Fas/FasL interaction as a pivotal pathogenic mechanism that regulates insulitis development. FasL is not required for the normal immune response. Therefore, it has been puzzling that NOD mice bearing homozygous lpr or gld mutations become resistant to autoimmune diabetes. The disease process is arrested at a pre-insulitis stage in mutant NOD mice and the mice never develop overt disease. Initially, it was thought that the protection is due to an essential role of Fas/FasL interactions in mediating death of the insulin-producing beta cells; a mechanism which, if true, would be extremely useful for engineering disease-resistant islets (Chervonsky et al., 1997). Specific deletion of the Fas molecule on pancreatic islets, however, did not spare beta cells from autoimmune attack and destruction or mice from developing overt disease (Allison and Strasser, 1998; Apostolou et al., 2003; Kim et al., 1999; Savinov et al., 2003). In the absence of a plausible alternative explanation of how inhibition of the Fas pathway prevents autoimmune diabetes and the tight association of the protection with lymphoaccumulation of DN T cells, interest in the therapeutic value of targeting the Fas pathway simply faded away.

5.3 Separation of lymphoproliferation from the protective effect of the gld mutation revitalizes interest in therapeutic potential of FasL

Unlike most effector molecules and cytokines that inhibit autoimmune processes, the Fas pathway is not needed for generation of adaptive immune responses and mice bearing spontaneous lpr or gld mutation remain immune competent. The main side effects of
inactivating the Fas pathway are the age-dependent benign lymphoproliferation that occurs in some strains of mice together with lupus-like syndrome (Hamad; Mohamood et al., 2008; Nagata and Suda, 1995). It was believed that the lymphoproliferation and protection from autoimmune diabetes are tightly associated, leading to loss of interest in the therapeutic potential of targeting FasL. We therefore predicted that modulation of FasL to prevent autoimmune diabetes without causing lymphoproliferation will revitalize interest in assessing the therapeutic potential of targeting the Fas pathway: an approach that is unlikely to cause immune suppression. In support of this concept, studies by Su et al and our group showed that protection from autoimmune diabetes as a function of targeting FasL is indeed separable from the lymphoproliferation. NOD mice bearing heterozygote gld mutation (NOD-gld/+), develop no lymphoproliferation (Figure 1), show mild or no insulitis (Figure 2), completely protected from autoimmune diabetes (Figure 3A), and show no sign of producing autoantibodies (Figure 3B). We have not detected a single incidence of diabetes in NOD-gld/+ mice of various ages in our colony whereas NOD-wt littermates developed diabetes with a predicted incidence rate. Insulitis was also curtailed; the majority of NOD-gld/+ mice remained free of insulitis and fewer animals developed peri- or mild insulitis that did not progress to full destruction of islets and diabetes (Fig. 2). NOD-gld/+ mice did not develop significant levels of anti-nuclear antibodies, whereas modest and infrequent anti-nuclear antibodies (ANA) were observed in NOD-gld/gld mice (Fig. 3B). We concluded that complete inactivation of FasL was not essential for prevention of spontaneous diabetes in NOD mice and that partial blockade could be used to induce protection from autoimmune diabetes in wt mice without impairing T cell homeostasis.
Fig. 2. NOD-gld/+ mice develop mild or no insulitis. Pancreata from 12-week-old NOD-wt, NOD-gld/+ or NOD-gld/gld mice were formalin-fixed, sectioned, H&E-stained, and compared with age-matched NOD-wt mice for insulitis. Three mice per group were examined. Top photo: NOD-gld/+ ; Middle photo: NOD-gld/gld , Bottom photo: NOD-WT

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Fig. 3. *Top:* Cumulative diabetes incidence in NOD-gld/gld \((n = 14)\), NOD-gld/+ \((n = 35)\), and NOD-wt \((n = 29)\) mice that were up to 65 weeks of age.

*Bottom:* Heterozygote gld mutation does not cause production of antinuclear antibodies (ANAs). ANAs in the sera from NOD-gld/gld, NOD-gld/+, and NOD-wt mice between the ages of 15 to 30 weeks \((n = 6\) per group). The concentration of ANAs in each sample is calculated as ANA index \((AI)\), which is defined as the ratio of absorbance of the test sample and net absorbance of the negative (endpoint-cutoff) control. \(AI > 22\) is considered positive.

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FasL molecules randomly preassociate to form functional homotrimers that interact with corresponding Fas homotrimers (Orlinick et al., 1999; Schneider et al., 1997). In NOD mice bearing heterozygote gld mutation, about 85% of FasL homotrimers are inactive due to their incorporation of one or more gld molecules. Mechanistic analyses show that the remaining functional FasL homotrimers (~15%) suffice to maintain T cell homeostasis. Thus, it appears that more or less fully-functional FasL is required to drive the pathogenesis of autoimmune diabetes in NOD mice whereas partially functional FasL is sufficient to maintain immune homeostasis. The results offer the NOD-gld/+ mouse as a model to study the role of FasL in T cell tolerance without the complication caused by the massive DN T cell accumulation.

5.4 FasL-neutralizing antibody prevents diabetes in NOD-wt mice

Indeed, we found that brief antibody blockade of FasL using MFL4 neutralizing mAb (Kayagaki et al., 1997) prevents T1D in NOD mice without causing lymphoproliferation, thereby demonstrating the therapeutic potential of targeting FasL (Figure 4). We treated prediabetic NOD female mice with MFL4 FasL-neutralizing antibody (Kayagaki et al., 1997) as described in Figure legend and monitored them for development of diabetes. Control NOD mice that were treated in parallel with hamster IgG developed diabetes with the normal incidence rate. In contrast, none of the mice in the treated group developed diabetes (Fig. 4, top). Analysis of pancreata from treated mice showed that blockade of FasL also prevented insulitis in the majority of the mice in the group although a few mice developed perinsulitis, whereas severe insulitis was observed in the control group (ref. (Mohamood et al., 2007) and data not shown). Furthermore, anti-FasL treatment was associated with only a small and transient increase in the frequency of DN T cells, which did not exceed 6% of T cells in any of the treated mice (Fig. 4, bottom). As in NOD-gld/+ mice, protection from diabetes was not associated with systemic increase in the level of antinuclear antibodies [(ref. (Mohamood et al., 2007)]. Thus, it appears that there is a wide window for maneuvering to block most FasL activity to inhibit its pathogenic effect without interfering with T cell homeostasis. Together, these studies show the feasibility and suggest that FasL-based intervention may prove beneficial in the future to protect high-risk individuals from T1D. These findings revitalize interest in the therapeutic potentials of targeting FasL by showing that major side effects are avoidable by calibrating the dose.

5.5 Significance of targeting FasL

Developing an immunotherapy that would promote immune tolerance to beta cell autoantigens without generally weakening the immune system is the ultimate goal of researchers involved in studying T1D. Autoreactive T cells that cause T1D utilize more or less the same pathways for their activation, expansion, and differentiation as T cells that protect hosts from infections. Therefore, attempts to inactivate autoreactive T cells by targeting any of the large arrays of molecules along these pathways is inherently fraught with inactivating normal T cells required for fighting legitimate foreign pathogens. This fact imposes heavy restraints on therapeutic strategies targeting these pathways. To circumvent these restraints, scientists resort to using short courses and carefully calibrated doses of neutralizing reagents that undermine efficacy (Greenbaum and Atkinson; Skyler and Ricordi). Using combination therapy is another strategy that is being pursued to maximize additive effects of targeting more than one molecule (von Herrath). Another promising approach aims at expanding regulatory T cells specific for islet antigens that can be used to suppress autoreactive T cells.
Fig. 4. Top: Diabetes incidence and blood glucose levels in mice treated with FasL-neutralizing antibody or hamster IgG control antibody. Bottom: Blockade of FasL leads to mild and transient increase in the frequency of DN T cells in peripheral blood. Blood samples were collected and stained with TCR-, CD4-, and CD8-specific antibodies and analyzed by fluorescence-activated cell sorting. After gating on TCR<sup>+</sup> cells, the frequency of DN T cells was determined. Adopted from ref. Mohamood et al. 2007 with copyright permission from Copyright © 201X, AMERICAN SOCIETY FOR INVESTIGATIVE PATHOLOGY. Published by ELSEVIER INC.
The Fas pathway is unique in this regard and stands in a separate class: FasL is not essential for promoting normal immune response and hence immunosuppression is not a major concern in calibrated targeting of FasL (Hamad; Mohamood et al., 2008). In fact, there is a wide window for modulating FasL activity to suppress autoimmunity without disturbing immune homeostasis (Mohamood et al., 2008; Mohamood et al., 2007). Mechanistically, the long lasting tolerance to beta cell antigens mediated by FasL blockade is due to local immune modulation at the site of inflammation (Xiao et al., In press). It appears that regulatory cells play an important role in controlling diabetogenic T cells as transfer of splenocytes from NOD-gld/+ mice into NOD-scid mice results in diabetes development [ref. (Mohamood et al., 2007) and (Fig. 5)]. We envision that targeting Fas pathway could result in tissue specific tolerance without weakening the immune system.

Fig. 5. Disease-free NOD-gld/+ mice harbor diabetogenic lymphocytes that transfer diabetes to NOD-scid mice. Diabetogenicity of $2 \times 10^7$ splenocytes from diabetes-free NOD-gld/+ mice was tested in adoptive NOD-scid hosts after i.v. transfer and compared to that of equal number of splenocytes from age-matched NOD-wt mice ($n = 7$ per group). Blood glucose levels were monitored weekly to determine diabetes induction. Mice with two consecutive blood glucose levels of $\geq 250$ mg/dL were considered diabetic. Results are from one of two similar experiments. Adopted from ref. Mohamood et al. 2007 with copyright permission from Copyright © 201X, AMERICAN SOCIETY FOR INVESTIGATIVE PATHOLOGY. Published by ELSEVIER INC.
5.6 What should be done to realize the therapeutic potentials of FasL?
Efforts will be directed towards mechanistic understanding of how inactivating FasL prevents T1D and assessing its preclinical ability to reverse new-onset disease in NOD mice. Also, attempts should be made to assess whether blockade of FasL synergizes with anti-CD3 or antigen specific therapy to produce a more effective and safer therapy. Thus, successful testing of the proposed idea is expected to provide convincing rationale for considering FasL as an immunotherapeutic target for T1D.

6. Conclusion
Type 1 diabetes (T1D) is the leading autoimmune disease of childhood. Long term complications association with the disease despite careful use of insulin therapy and restrict diet show the need of an immunotherapy for T1D. Assessment of the results of clinical trials has demonstrated feasibility, but evaluation of efficacy produced the conclusion that none of the agents currently under clinical investigation hold the key for the cure as a sole therapy. Our data and those published by others in the roles of FasL in pathogenesis of T1D offer novel views on the potentials of targeting the Fas death pathway as an unconventional therapeutic approach for T1D that is unlikely to cause immune suppression.

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This book is a compilation of reviews about the pathogenesis of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expansion of this disease. Understanding etiology and pathogenesis of this disease is essential. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes. Areas including T cell development, innate immune responses, imaging of pancreata, potential viral initiators, etc. are considered.

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