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Type 1 Diabetes Immunotherapy - Successes, Failures and Promises

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1. Introduction

Type 1 diabetes is an autoimmune disease that usually strikes during adolescence resulting in uncontrolled blood glucose levels. Auto-reactive T-cells target the insulin producing beta cells of the pancreas resulting in their destruction. The only treatment currently available is lifelong administration of insulin to bring blood glucose levels back under control. The identification of insulin and its mass production were the first major success in the treatment of the disease. Building on the work of others, Frederick Banting and Charles Best demonstrated the ability of insulin to maintain normoglycemia in pancreatectomized dogs in 1921 (Banting; Best; Collip, et al., 1922) and with the help of Eli Lilly the mass production of insulin was under way by 1922 for clinical use. Prior to this the disease was fatal by 3 years. No less than 4 Nobel prizes have been rewarded over the years for research on insulin's indentification, sequence, structure, and the production of recombinant human insulin.

Despite the success of insulin therapy, it is now obvious that even rigorous control of blood glucose with insulin injections only delays, but does not prevent the development of diabetic complications (The DCCT Research Group, 1993). Diabetic complications, which include cardiovascular disease, diabetic retinopathy, kidney failure, and neuropathy, account for significant diabetes-related patient morbidity and mortality. Islet transplantation has been attempted to restore the normal release patterns of insulin, but sufficient source donors are limiting, the possibility of lifelong anti-rejection drugs may prove worse than diabetes, and the autoimmune process that destroyed the original beta cells are still active (Huurman; Hilbrands; Pinkse, et al., 2008, Marzorati; Pileggi&Ricordi, 2007, Roelen; Huurman; Hilbrands, et al., 2009, Van Belle&von Herrath, 2008). Therefore therapeutics that modify the immune response and restore normal immune function are necessary to improve the outcomes of patients with type 1 diabetes. Little has changed in the primary treatment of type 1 diabetes over the last 90 years, but immunotherapy techniques hold the promise of finding a true cure.

2. Immunotherapy - small windows of opportunity

Immunotherapy techniques have the potential to restore the proper immune system balance preventing further beta cell death and increasing insulin production with the subsiding of beta cell inflammation (Dib&Gomes, 2009, Mortensen; Hougaard; Swift, et al., 2009, Papoz; Lenegre; Hors, et al., 1990). A favorable window of opportunity must be selected for

immunotherapy techniques to have the greatest impact, especially since patients may have lost as much as 80% of their beta cell mass by the time of clinical diagnosis of type 1 diabetes(Bresson&von Herrath, 2007). Late treatment after further cell loss may not allow for sustainable insulin production levels to maintain euglycemia and therefore would only be a benefit if used in combination with regenerative medicine or beta cell replacement. For this reason, the effective window of opportunity must be explored for each proposed immunotherapy.

2.1 Disease prediction failure

Preservation of beta cell mass sufficient to meet the patients' insulin needs is the target goal of immunotherapy. The chances of successful treatment increase with a greater beta cell preservation and allows a buffer against possible future relapses. Since disease onset rapidly reduces the beta cell population, early detection of the disease or even pre-clinical detection would greatly enhance patient outcomes. Along these lines, efforts have been made to identify predictive biomarkers for type 1 diabetes. These markers include genetic susceptibility loci, autoantibodies, and the population size of regulatory immune cells. With a sufficient understanding of how these factors change at disease onset and over the course of the disease, we could some day even preemptively treat healthy patients that are at significant risk to develop type 1 diabetes.

The human genome has been mined for susceptibility genes that will affect the probability of developing type 1 diabetes. In animal models this is a lengthy process in controlled inter-breeding of two mouse strains. Mice within each strain are genetically identical. By breeding a diabetes-prone mouse strain with a normal mouse strain, the offspring contain one set of chromosomes from each strain. Continued breeding of these offspring over several generations to the normal mouse strain results in a number of new mouse lines that are mostly normal, but contain different fragments of DNA from the diabetes-prone animals. The percentage of animals in each new strain that develop diabetes can then be compared to which DNA fragments they received to identify possible susceptibility genes. For humans, DNA sequence variations are compared in families with a known history of type 1 diabetes. Four genetic regions have been linked to the disease thus far among different populations and they are the HLA locus, Insulin, cytotoxic T lymphocyte antigen-4 (CTLA-4), and phosphatase non-receptor type 22 (PTPN22).

In retrospect, it is not surprising that insulin is one of the identified susceptibility genes for type 1 diabetes. The human insulin 5' promoter region exhibits variability in DNA sequence length depending on the number of a variable number of tandom repeats (VTNR) variation it contains. These variants are named VTNR1, VTNR2, and VTNR3, which are arranged in lengths of increasing order. VTNR1 class alleles are associated with diabetes susceptibility and reduced insulin expression in the thymus (Kantarova&Buc, 2007, Maier&Wicker, 2005). Insulin production in the thymus is closely linked to the expression of the Autoimmune Regulator (AIRE) transcription factor whose role is to participate in the transactivation of a wide range of self-antigens necessary for T-cell negative selection (Anderson; Venanzi; Chen, et al., 2005). The consensus model posits that low levels of thymic insulin facilitates the escape of insulin-reactive thymocytes which enter the periphery and at some point later in life are activated to recognize beta cell insulin (Liston; Lesage; Wilson, et al., 2003). Recent work has demonstrated that AIRE can bind the VTNR1 class allele promoter with a marked reduction in insulin mRNA production(Cai; Zhang; Breslin, et al., 2011). Indeed AIRE disruption leads to a number of other autoimmune diseases.

The strongest genetic linkage to diabetes lies on chromosome 6 (6p21.3) where HLA (MHC in mouse) genes are located (Kantarova&Buc, 2007, Maier&Wicker, 2005). The HLA system encodes a number of highly-polymorphic cell surface proteins that present self and processed antigens to T-cells. HLA class I molecules are expressed on most cells in the body and identify the cell as "self" or part of the body. HLA class II molecules are used to display foreign antigens captured by antigen presenting cells (APC) of the immune system such as dendritic cells (DC). Interactions between DC's HLA class II molecules and T-cell's T-cell Receptor (TCR) activate T-cells to proliferate and to target cells expressing those specific targets. The highest HLA risk is conferred by the DR and DQ alleles. This risk accounts for 40% of the genetic risk for type 1 diabetes (Kantarova&Buc, 2007).

Two additional susceptibility loci are associated with regulation of T-cell activation. CTLA-4 is a protein that is expressed on the surface of activated T-cells. For T-cells to become fully activated, co-stimulatory molecules on DC's interact with the T-cell after initial HLA class II and TCR interaction, and can result in pro-inflammatory cytokine release from the dendritic cells (Bluestone, 1996, Clarkson&Sayegh, 2005, Kishimoto; Dong&Sayegh, 2000, Lenschow; Walunas&Bluestone, 1996, Sayegh&Turka, 1995). CTLA-4 can directly interact with co-stimulatory molecules CD80 and CD86 reducing IL-2 receptor activation and IL-2 production (Kantarova&Buc, 2007). IL-2 is a strong pro-inflammatory cytokine involved in growth and survival for T-cells which undergo apoptosis if IL-2 is removed. T regulatory (Treg) cells characterized as CD4+ CD25+ can also negatively regulate T-cell activation and require CTLA-4 to elicit some of its regulatory actions (Kantarova&Buc, 2007, Maier&Wicker, 2005). Inactive splice variants of CTLA-4 have been detected in mice, but have yet to be identified in human disease (Maier&Wicker, 2005). Disregulated and hypersensitive T-cell populations can develop with genetic modifications to the PTPN22 gene. It's gene product, lymphoid protein tyrosine kinase (LYP), is active at the cell membrane and improper localization results in T-cell defects (Kantarova&Buc, 2007, Maier&Wicker, 2005). Other autoimmune diseases such rheumatoid arthiritis, systemic lupus, and Graves disease have been similarly linked to HLA class II, CTLA-4, and PTPN22 genes and establish a connection between these genes and immune system dysregulation (Jones; Fugger; Strominger, et al., 2006, Kantarova&Buc, 2007, Maier&Wicker, 2005). Further research is still needed to use this information to develop a predictive test that can be used in a wide segment of the population.

2.2 Auto-antibodies and early disease detection failure

Type 1 diabetes is associated wtih the production of a number of auto-antibodies that bind to a number of self-antigens. Among these are antibodies recognising islet cell antigens of a general nature (ICA), glutamic acid decarboxylase (GAD), islet cell antigen 512 (IA-2) and insulin (IAA) (Isermann; Ritzel; Zorn, et al., 2007). Unfortunately the predictive value of these antibodies cannot reach a level permissive for preemptive clinical intervention. The percentage of diabetic patients that have IA-2 and IAA is reduced as the age of disease onset increases making it challenging to use these criteria as airtight predicitive markers (Isermann; Ritzel; Zorn, et al., 2007) (Bingley; Bonifacio; Williams, et al., 1997, Verge; Howard; Rowley, et al., 1994). Measurement variations between testing labs is still a major concern (Schlosser; Mueller; Torn, et al., 2010), especially in the case of ICA testing where results are dependent on the experience of the operator (Isermann; Ritzel; Zorn, et al., 2007). A single positive auto-antibody titer is also not sufficient to predict the development of

diabetes, only 30% of those patients develop diabetes over the course of 15 years (Verge; Gianani; Kawasaki, et al., 1996).

The current methods cannot accurately predict diabetes development and thus, it is difficult to accept these markers to drive an intervention prior to clinical disease onset. In general, any predictive markers must have a low margin of error and high prediction certainty to justify treating healthy patients for diseases they don't yet have. Additionally it is highly unlikely the entire population will receive the proper diagnostic pre-screening tests to identify all potential type 1 diabetes patients. For these reasons, immunotherapeutics have been focused on diabetes reversal in new onset patients during their "honeymoon" period where blood glucose is elevated but they still have beta cell mass.

3. Immunotherapy treatments - bench and bedside

Immunotherapy defines a broad range of strategies to inhibit autoimmune processes with the intended outcome the long-term restoration of normal immune system function. The most direct approach is to induce the elimination or the silencing of immune cells responsible for the autoimmunity. Other approaches attempt to restore self-antigen tolerance by providing large amounts of self-antigen, or self-antigen decoys to minimize the interaction between HLA and the peptides. Cell based therapies are also underway that introduce modified immune cells to abrogate autoimmune processes. The current clinical status of these methods and others will be covered here in an overview.

3.1 Targeted cell ablation

The beta cells of the pancreas are directly destroyed by activated auto-reactive T-cells making these T-cells an attractive therapeutic target. The two antibodies that have been developed to target T-cells for elimination are specific for CD3 and CD4. These surface proteins are abundant on cytotoxic T-cells, but unfortunately in the case of CD4, can also be found on anti-inflammatory Treg cells characterized as CD4+ CD25+. While treatment with anti-CD4 antibodies did reverse new onset diabetes in the Non-Obese Diabetic (NOD) mouse model, Treg populations were not positively effected and systemic immunosuppression occurred (Makhlouf; Grey; Dong, et al., 2004). The anti-CD3 antibody was also able to reverse new onset diabetes in the NOD mouse model but without these complications (Chatenoud; Primo&Bach, 1997, Chatenoud; Thervet; Primo, et al., 1994). The anti-CD3 antibody treatment elevated Treg cell populations in mouse (Belghith; Bluestone; Barriot, et al., 2003) and then in humans (Bisikirska; Colgan; Luban, et al., 2005, Chatenoud, 2010). These promising data were used to translate the CD3 antibody into expanded phase II and III trials. Cytokine production profiles also were shifted with a reduction in IL-2 and an increase in IL-10 permissive for a more anti-inflammatory state (Herold; Burton; Francois, et al., 2003). Despite the apparent trend towards a more balanced pro-/anti- inflammatory state, non-specific T-cell activation was observed (Chatenoud, 2010). Nevertheless, despite almost a decade of testing, Phase III trials were recently stopped by MacroGenics and Lilly since insulin requirements and Hemogoblin A1C levels remained unaffected after 1 year of drug treatment   http://www.bizjournals.com/washington/quick_news/2010/10/macrogenics-lilly-abandon-diabetes-drug.html;   AND   http://www.inpharm.com/news/150858/gsk-tolerx-otelixizumab-phase-iii-failure

Autoantibody production occurs in a number of autoimmune diseases and contributes to ongoing pathogenesis. Under normal conditions, B cells generate antibodies to allow the

body to quickly recognize and clear antigens it has encountered in the past. This system is particularly dangerous when auto-anitbodies are generated because it establishes an ongoing and self-sustaining immune reaction in the host. For this reason the anti-CD20 antibody Rituximab was developed to deplete B cell populations and their ability to produce antibodies. Rituximab was initially approved for the treatment of Non-Hodgkin's Lymphoma (McLaughlin; White; Grillo-Lopez, et al., 1998, Scott, 1998) and later rheumatoid arthritis (Edwards; Szczepanski; Szechinski, et al., 2004). Numerous clinical trials are now underway for the treatment of other autoimmune diseases (Reis; Athanazio; Lima, et al., 2009, Suzuki; Nagasawa; Kameda, et al., 2009) (Hauser; Waubant; Arnold, et al., 2008) including type 1 diabetes due to favorable pre-clinical NOD mouse data (Hu; Rodriguez-Pinto; Du, et al., 2007, Xiu; Wong; Bouaziz, et al., 2008). The Phase II trial results did show a trend towards increased beta cell mass preservation, but the treated group did not have significantly different C-peptide levels and were all still insulin dependent during the course of the trial (Pescovitz; Greenbaum; Krause-Steinrauf, et al., 2009). At this time cell ablation strategies have not been effective in the treatment of type 1 diabetes and confer numerous side effects.

3.2 Competitive and non-competitive tolerance induction

T-cells are educated in the thymus to learn the difference between "self" and foreign antigens and under normal conditions self reactive T-cells are destroyed. This process breaks down with type 1 diabetes and other autoimmune diseases resulting in autoreactive T-cells that attacks the host's body. In some instances this may be due to decreased insulin expression in the thymus, which is believed to be the reason why insulin promoter variations lead to genetic susceptibility(Cai; Zhang; Breslin, et al., 2011). This has lead to the idea that increasing a patient's exposure to self-antigens may allow the T-cells to be properly educated. Clinical trials are currently underway where patients are given insulin through oral (2009, Skyler; Krischer; Wolfsdorf, et al., 2005) or nasal (Harrison; Dempsey-Collier; Kramer, et al., 1996, Harrison; Honeyman; Steele, et al., 2004) routes of delivery. At least one study using oral insulin delivery, ORALE, failed to show any preservation in beta cell function (Chaillous; Lefevre; Thivolet, et al., 2000). Similarly, synthetic peptides are under development that have greater stability and can be delivered by injection. Both heat shock protein 60 (HSP60) (Atkinson&Maclaren, 1994, Delovitch&Singh, 1997, Durinovic-Bello, 1998, Wicker; Todd&Peterson, 1995) and GAD65 (Agardh; Cilio; Lethagen, et al., 2005, Hinke, 2008, Ludvigsson, 2010) are diabetes auto-antigens being considered as treatment. DeveloGen Inc has manufactured DiaPep277 which shares sequence homology with amino acids 437-460 of HSP60. To increase peptide stability, two single amino acid changes were made at the 6th and 11th position changing cysteine to valine (Raz; Avron; Tamir, et al., 2007, Raz; Elias; Avron, et al., 2001). Early trials have showed a trend in preserved C-peptide levels(Schloot; Meierhoff; Lengyel, et al., 2007). Additionally, increases in anti-inflammatory cytokine IL-10 and T-helper 2 cells (Th2) were observed in ongoing phase II clinical trials(Huurman; van der Meide; Duinkerken, et al., 2008). Likewise the GAD65 peptide Diamyd has conferred increased levels of anti-inflammatory cytokines and the Treg transcription factor marker forkhead box protein (FOXP3) in clinical trials (Agardh; Cilio; Lethagen, et al., 2005, Hinke, 2008, Ludvigsson, 2010). Phase III trials are still ongoing for Diamyd (Ludvigsson, 2010). The clinical outcomes of insulin requirements or restoration of euglycemia have yet to be addressed, but at the very least these studies hold promise at delaying disease onset.

Altered peptide ligands (APL) offer a similar antigen based strategy but their mechanism of action appears to involve competition for the natural antigen at the TCR. The T-cell's TCR have highly variable structures that allow for conformations that can identify all the possible antigens the body has previous been exposed to, in the context of presentation by HLA class I and II. Each individual T-cell has only one TCR confirmation capable of recognizing a single specific antigen. The TCR is targeted to a short amino acid sequence found in the antigen, with important specific primary and secondary sites needed for T-cell activation(Sloan-Lancaster&Allen, 1996). Modification to the amino acid sequence at the primary site allows the TCR to bind the antigen but maintains the specific T-cell subset in an inactive state(Sloan-Lancaster&Allen, 1996). This phenomenon has been exploited for beta cell reactive T-cells, most notably with Neurocrine Biosciences NBI-6024 APL (Nicholson&Kuchroo, 1997, Sloan-Lancaster&Allen, 1996) (Alleva; Gaur; Jin, et al., 2002). NBI-6024 is an insulin APL that covers amino acid region 9-23, the primary TRC recognition site for insulin(Alleva; Crowe; Jin, et al., 2001, Alleva; Gaur; Jin, et al., 2002, Wong; Karttunen; Dumont, et al., 1999). Positions 16 and 19 are modified to alanine. Initial studies in the NOD mouse model demonstrated increased anti-inflammmatory Th2 cells and their production of IL-4 and IL-10(Alleva; Gaur; Jin, et al., 2002, Alleva; Maki; Putnam, et al., 2006). Administration into the NOD mouse strain delayed the onset and reduced the incidence of diabetes development (Alleva; Gaur; Jin, et al., 2002). Unfortunately phase I and II clinical trials were unable to demonstrate preserved beta cell mass resulting in the cessation of testing(Alleva; Maki; Putnam, et al., 2006, Walter; Philotheou; Bonnici, et al., 2009).

A serious hurdle to tolerance induction using peptide antigens may be the sheer number of auto-antigens detected by the immune system. While a single target may exist at disease onset, continued inflammation in the beta cells leads to the development of additional self-antigen targets. Therefore early detection of pre-clinical diabetes might be required for this approach to prevent diabetes. Additionally a single universal disease-initiating auto-antigen would have to be identified, or if this does not exist, a means of screening for which autoantigens are present at clinical onset in order to select an agent that would eliminate those specific T-cells.

3.3 Cell based therapeutics

Cell based therapeutics use natural or modified immune cells transplanted into a host in an attempt to restore the balance of pro- and anti-inflammatory cells. The majority of cell-based research to date has focused on DC's, the regulators of the immune system(Shortman&Naik, 2007). In 2010 the FDA approved the first DC based approach for the treatment of prostate cancer which has been recently accepted for coverage by medicare(Perrone, 2011). That approach is focused on hyperstimulating patient DC *ex vivo* with prostate cancer antigens, while applications for type 1 diabetes have focused on dampening the immune response. Under normal conditions the DC migrate through the body sampling the environment around them. DC then present the self-antigens to naïve T-cells promoting and maintaining self-tolerance(Kurts; Cannarile; Klebba, et al., 2001, Kurts; Carbone; Barnden, et al., 1997, Lutz&Schuler, 2002, Randolph, 2001, Shortman&Naik, 2007, Vlad; Cortesini&Suciu-Foca, 2005). If instead, a foreign antigen is detected, the DC undergo a series of maturation steps that increase surface levels of HLA class II complex and co-stimulatory molecules which in turn facilitate T-cell activation(Mellman&Steinman, 2001). T-cell hypo-responsiveness to self and foreign antigens has been clearly demonstrated in a number of models when co-

stimulatory molecule interaction between DC and T-cells is inhibited (Bluestone, 1996, Clarkson&Sayegh, 2005, Hackstein; Morelli&Thomson, 2001, Kishimoto; Dong&Sayegh, 2000, Lenschow; Herold; Rhee, et al., 1996, Morelli&Thomson, 2003, Sayegh&Turka, 1995, Steinman, 2003, Steinman; Inaba; Turley, et al., 1999). This aspect of DC makes it an ideal target for autoimmune disease therapy in order to maintain auto-reactive T-cell populations silent or hyporesponsive.

DC based therapies have been successful in the treatment of type 1 diabetes in the NOD mouse model. NFkappaB decoys have been employed to prevent DC maturation preventing co-stimulatory molecule expression and reducing the incidence of diabetes development(Ma; Qian; Liang, et al., 2003). Administration of DC treated ex vivo with antisense oligonucleotides (AS-ODN) targeting the co-stimulatory molecules CD40, CD80, and CD86 similarly prevent diabetes development and could reverse new-onset diabetes in NOD mice(Harnaha; Machen; Wright, et al., 2006, Machen; Harnaha; Lakomy, et al., 2004, Phillips, B.; Nylander; Harnaha, et al., 2008). The effects of the treatment extended beyond cyto-toxic T-cell hyporesponsiveness and include the augmentation of anti-inflammatory Treg (Harnaha; Machen; Wright, et al., 2006, Machen; Harnaha; Lakomy, et al., 2004, Phillips, B.; Nylander; Harnaha, et al., 2008). Both methods are based on harvesting DC's from the mouse and then modifying *ex vivo* before being reintroduced back into the mouse. In essence, co-stimulation deficient DC are phenotypically idnetical to immature DC which promote T-cell hyporesponsiveness and an overall state of tolerance. Stabilization of DC in an immature state has been a popular method of promoting auto- and allo-antigen tolerance in a variety of models (Beissert; Schwarz&Schwarz, 2006, Chen, 2006, Enk, 2006, Harnaha; Machen; Wright, et al., 2006, Huber&Schramm, 2006, Hugues; Boissonnas; Amigorena, et al., 2006, Lohr; Knoechel&Abbas, 2006, Ma; Qian; Liang, et al., 2003, Machen; Harnaha; Lakomy, et al., 2004, Marguti; Yamamoto; da Costa, et al., 2009, Nouri-Shirazi&Thomson, 2006, Phillips, B.; Nylander; Harnaha, et al., 2008, Roncarolo; Gregori; Battaglia, et al., 2006, Shevach; DiPaolo; Andersson, et al., 2006, Tang&Bluestone, 2006, Tarbell; Yamazaki; Olson, et al., 2004, Verhagen; Blaser; Akdis, et al., 2006, Yamazaki; Iyoda; Tarbell, et al., 2003, Zhang; Yi; Xia, et al., 2006). Recently, a phase I trial of AS-ODN treated DC's was completed in our center in established type 1 diabetic patients.

Immunotherapeutic treatments often track Treg frequency as an indicator of increased regulation of the immune system and overall tolerance. Methods have been developed to induce Treg differentiation and expand existing Treg populations so sufficient Treg cells could be generated to directly use as a therapeutic (Apetoh; Quintana; Pot, et al., 2010, Gandhi; Kumar; Burns, et al., 2010). Initial studies in the NOD mouse model have also demonstrated the importance of Treg functions in controlling the autoimmune process and role in new onset diabetes reversal(Godebu; Summers-Torres; Lin, et al., 2008, Luo; Tarbell; Yang, et al., 2007, Tang; Henriksen; Bi, et al., 2004, Weber; Harbertson; Godebu, et al., 2006). Regulation afforded by Treg extends beyond single auto-antigens making it an attractive choice in light of antigen spreading effects seen with type 1 diabetes (Luo; Tarbell; Yang, et al., 2007, Tarbell; Yamazaki; Olson, et al., 2004). Given these factors it seems likely that at Treg cell-based therapeutic will be developed.

3.4 Polymer drug delivery

Polymers are typically immunologically and biologically inert molecules that can be used for drug delievery. DNA oligonuceotides, proteins, or antibodies are examples of

biologically active compounds that can be conjugated to or carried by polymers(Phillips, B.E.&Giannoukakis, 2010). AS-ODN targeting the co-stimulatory molecules CD40, CD80, and CD86 have been used to treat DC *ex vivo* for administration to diabetic animals(Harnaha; Machen; Wright, et al., 2006, Machen; Harnaha; Lakomy, et al., 2004, Phillips, B.; Nylander; Harnaha, et al., 2008). These same AS-ODN molecules have been formulated into polymer microsphere particles consisting of polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), and poly-L-lysine-hydrobromide. Administration of these drug carrying microspheres results in similar reversal of new onset diabetes in the NOD mouse model(Phillips, B.; Nylander; Harnaha, et al., 2008). This technique is able to function because DC constantly sample their surrounding environment picking up these AS-ODN containing microspheres. Microsphere administration is promising in that it is far less invasive and costly than harvesting, treating, and re-introducing cells back into a patient. Also given the limited window of treatment for immunotherapeutics, they can be an off the shelf drug that can be immediately administered to newly diagnosed patients.

4. Conclusion

Immunotherapies are immerging for the treatment of type 1 diabetes. For the first time treatments are focusing on preserving beta cell mass and restoring proper function of the immune system instead of just maintaining blood glucose levels. Independence from insulin treatment could remove concerns of patient compliance in blood glucose monitoring and diabetic complications that occur even with intensive insulin therapy. The technology promises much in improvements in patient health, but has a number of hurdles it must first overcome. The current window of treatment is still very small using these techniques. Treatment must begin within months of diabetes onset to preserve the largest number of beta cells as possible. Unfortunately at this time an effective means of identifying individuals prone to develop diabetes has not been fully developed. Concerns also exist about the ethics of treating patients for a disease they may never develop even if at high genetic risk. The predictive value of any such method would need a high level of confidence and be inexpensive enough to adopt for universal screening. Falling short in either category will result in continued disease detection after disease onset. For these reasons, it seems likely that therapeutics will continue to be designed for new onset treatment unless paired with a cell replacement strategy.

Extensive basic and clinical testing is still required to determine patient outcome. Tolerance induction treatments have reached phase III clinical testing, but they have not examined the restoration of euglycemia and insulin independence. The general trend for these studies is they may delay disease onset. While this is not a cure, it can still be important considering the early age onset of the disease. Patient compliance in blood glucose monitoring is not ideal even in adults so delaying onset in children may help them to reach a more mature age to improve self-monitoring. Diabetic complications are also a function of disease maintenance and length. Even rigorous insulin therapy does not prevent complications, so in well-maintained patients a delay in onset could facilitate a delay in complications onset. Antibody based approaches of cell depletion have had mixed results. Anti-CD3 drugs for T-cell ablation confer extensive side effects and recently failed phase III clinical trials. Other antobody appraoches like Rituximab still have not shown unequivocal effectiveness in preserving residual beta cell function. Last, are the cell-based treatments which are the most and least advanced of the techniques. DC based treatments have already been approved for

use in cancer patients with minimal side effects, but are just completing phase I clinical trials for the treatment of diabetes. *In vivo* cell modification may prove even less invasive and costly, but have yet to reach trials. The future of any treatment will require additional observation as relapse is possible over the lifetime of the patient, but there is promise in the fact that the field is finally moving beyond simple blood glucose control and trying to cure the underlying autoimmune pathology of type 1 diabetes.

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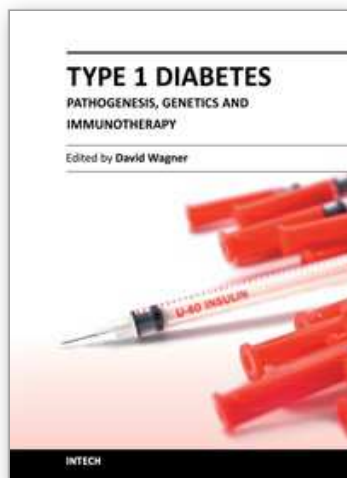
Type 1 Diabetes - Pathogenesis, Genetics and Immunotherapy

Edited by Prof. David Wagner

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 expanse 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.

How to reference

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