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Autoimmunity and Immunotherapy of Type 1 Diabetes

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1. Introduction

Type 1 diabetes, formerly termed insulin-dependent diabetes mellitus (IDDM), is a chronic organ-specific autoimmune disorder thought to be caused by proinflammatory autoreactive CD4+ and CD8+ T cells, which mediate progressive and selective damage of insulin-producing pancreatic beta-cells (Atkinson & Eisenbarth, 2001). The reduction of beta-cell mass leads to a lack of insulin and thereby loss of blood glucose control (Boettler & von Herrath, 2010).

The worldwide prevalence of T1D was estimated to be 171 million cases among the adult population (Wild et al., 2004). Its annual incidence varies widely from one country to another (from less than 1 per 100,000 inhabitants in Asia to approximately up to 25/100,000 population/year in North America, more than 30 per 100,000 in Scandinavia and up to 41/100,000 population/year in Europe). It is in steady increase across the globe, especially among children aged less than five years (Kajander et al., 2000; Vija et al., 2009).

According to the European Diabetes (EURODIAB) study group, the prevalence of T1D in Europe will increase significantly in children younger than 15 years of age to reach 160,000 cases in 2020 (Patterson et al., 2009). These data will result in an increasing number of patients with longstanding diabetes and with a risk of serious complications (Kessler, 2010). These include heart diseases and strokes, high blood pressure, renal failure and ketoacidosis (DKA) (Boettler & von Herrath, 2010).

To date, it has not been possible to prevent the autoimmune response to beta-cells in human, due probably to its unknown aetiology, although it is known that development of T1D is genetically controlled and thought to be initiated in susceptible individuals by environmental factors such as virus infections (Luo et al., 2010; Mukherjee & DiLorenzo, 2010; von Herrath, 2009).

It is now evident that targeted destruction may go undetected for many years, but antibodies to various beta-cell antigens can be easily demonstrable in the sera of patients at risk before clinical onset (Achenbach et al., 2005). Additionally, some endogenous insulin secretion is generally present at the onset of clinical diabetes (Scheen, 2004), during which time, immunotherapeutic intervention may be effective (Staeva-Vieira et al., 2007).

This chapter emphasizes the principal immunological risk markers of T1D and especially the role of cell-mediated immune response leading to pancreatic beta-cells destruction, as well as the most promising immunotherapeutic approaches for prevention and treatment of the disease.

2. Autoimmunity of the type 1 diabetes

The autoimmune nature of T1D is initially affirmed by several arguments that are primarily indirect, including the association with other autoimmune diseases (Barker, 2006), such as the autoimmune thyroid disease (Hashimoto thyroiditis or Graves disease) (Criswell et al., 2005; Levin et al., 2004), Addison disease (Barker et al., 2005), myasthenia or Biermer's anemia, and the detection of various autoantibodies (Seyfert-Margolis et al., 2006) and islet lymphocytes infiltrates (Bach, 1979).

2.1 Humoral markers of type 1 diabetes

Although T1D is primarily mediated by mononuclear cells (Carel et al., 1999), diagnosis means of the preclinical period are primarily markers of humoral immune response that are represented, for instance, by antibodies to beta-cell antigens, including glutamic acid decarboxylase 65, insulin, insulinoma-associated protein 2 islet tyrosine phosphatase, islet cell cytoplasm and more recently zinc transporter 8 (Luo et al., 2010) (Fig. 1). Studies of twins or in subjects with a family history of autoimmune diabetes have shown that these markers, when associated in the same subject, confer very high risk of developing diabetes within 5 years (Verge et al., 1996). The predictive value increases from less than 5% in the absence of antibodies to more than 90% when antibodies to GAD, tyrosine phosphatase IA-2 and insulin are present (Bingley et al., 1999; Verge et al., 1996). Additionally, taken in aggregate, the use of the level of autoantibody can provide additional predictive information for the persistence of autoantibodies and development of T1D (Barker et al., 2004). Moreover, among metabolic risk markers, the loss of first phase insulin response to intravenous glucose has the same prediction value with multiple positive antibodies when it is associated with one of these autoantibodies (Krischer et al., 2003). Furthermore, the predictive value of having multiple autoantibodies can increase significantly by the presence of a high-risk genotype, with a positive predictive value of 67% in multiple antibody-positive DR3/4 individuals, versus 20% in those without DR3/4 (Yamamoto et al., 1998). While, high sensitivity and specificity are required for detection of prediabetes in the general population where the prevalence is of the order of 0.3% even when genetic susceptibility markers are also included (Hermann et al., 2004).

2.1.1 Islet cell autoantibodies

These are markers with best predictive value (Bonifacio & Christie, 1997), because of their high sensitivity to the pancreatic islet (Kulmala et al., 1998) and their high specificity for T1D (Gorsuch et al., 1981).

Islet cell autoantibodies (ICAs) have been the first disease-specific autoantibodies to be described in patients with T1D (Bottazzo et al., 1974). They appear until ten years before the clinical onset of diabetes (Riley et al., 1990). ICA corresponds to a compounding of different specificities antibodies, because they can be fixed on all cellular types of antigenic structures present in the islet cell cytoplasm (Atkinson & Maclaren, 1993).

High ICA levels could be a marker of strong autoimmune reaction and accelerated depletion of beta-cell function (Zamaklar et al., 2002). In prediabetic subjects, a higher ICA titer is associated with a higher risk for T1D development (Mire-Sluis et al., 2000). In newly diagnosed type 1 diabetic patients, ICAs are present in 80%, and ICA reactivity often waned after diagnosis, with no more than 5% to 10% of patients remaining ICA positive after 10

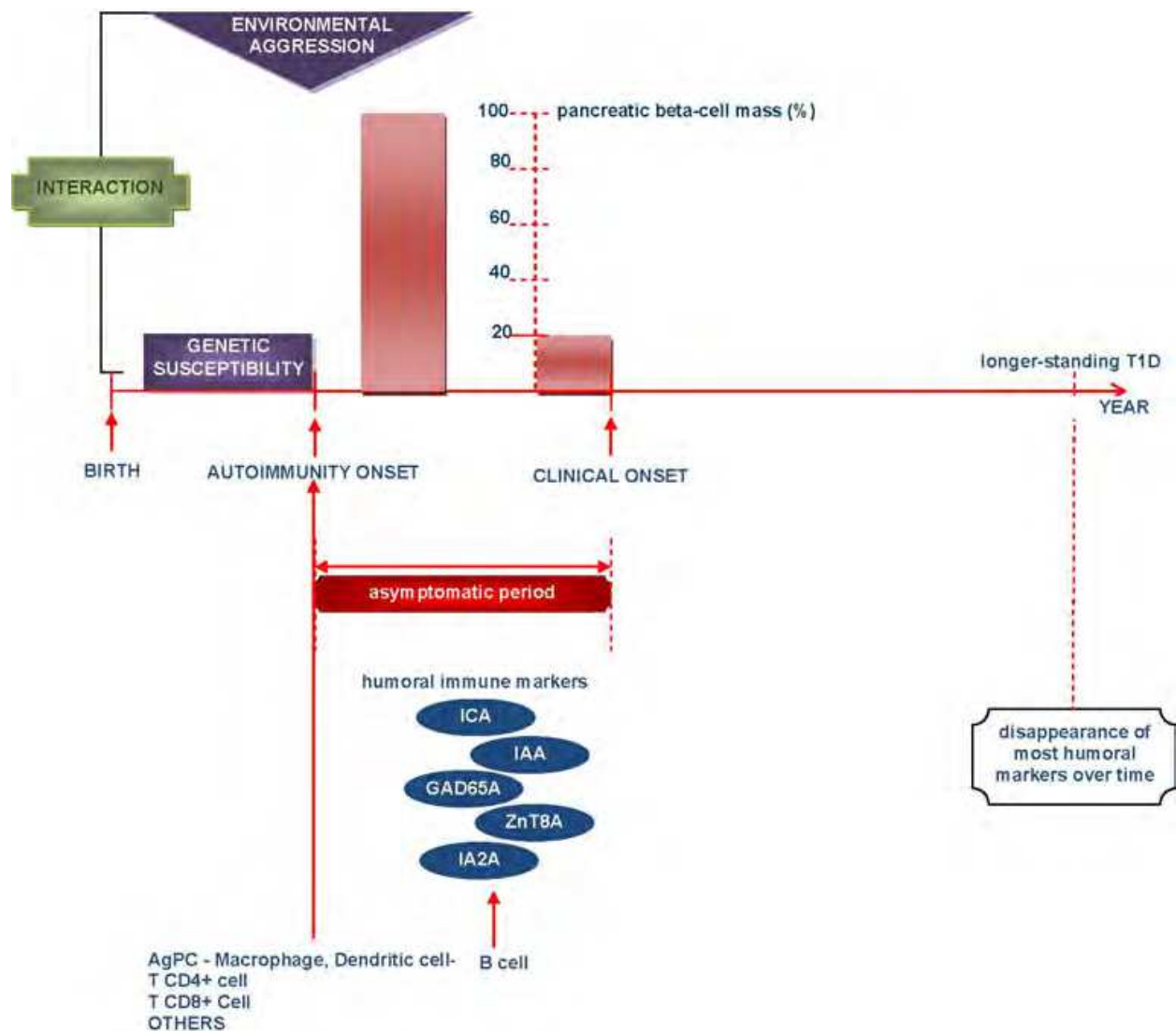


Fig. 1. Natural history of type 1 diabetes. *AgPC*: antigen-presenting cell; *GAD65A*: glutamic acid decarboxylase 65 autoantibody; *IAA*: insulin autoantibody; *ICA*: islet cell autoantibody; *ZnT8A*: zinc transporter 8 autoantibody.

years (Gilliam et al., 2004). The frequency of the positive ICA is 80% to 100% (Schatz et al., 1994) of revelation for a 25 years old T1D or less (Elfvig et al., 2003). It decreases remotely by the primo-decompensation, reaching approximately 3% in related subjects aged of less than 20 years (Schatz et al., 1994).

ICAs are highlighted by indirect immunofluorescence (Borg et al., 2002a; Elfvig et al., 2003; Perez-Bravo et al., 2001) on sera incubated with human blood group O pancreas (Takahashi et al., 1995; Thivolet & Carel, 1996). They can be also detected by complementary-fixing antibody (Knip et al., 1994; Montana et al., 1991), since they mainly belong to the IgG1 subclass antibodies (Bottazzo et al., 1980). The increase in ICAs may indicate the presence of other autoantibodies, corresponding to more IgG1 subclasses (Dozio et al., 1994). Association with other autoantibodies increases the test specificity, with a decrease in sensitivity however (Thivolet & Carel, 1996). ICA levels that exceed 80 JDF (Juvenile Diabetes Foundation) units at the time of diagnosis despite better beta-cell function are associated with short clinical remission (Zamaklar et al., 2002), and include 53% of disease

development risk in five years following their revelation (Dozio et al., 1994). Nevertheless, the high levels of ICA found in the family relatives do not necessarily lead to T1D development (Bingley, 1996). Likewise, the low rates of these antibodies lessen the disease risk (Bonifacio et al., 1990).

2.1.2 Insulin autoantibodies

It would be important to recall that protective alleles of insulin gene *INS VNTR* (variable number of tandem repeats) are associated with higher levels of *INS* messenger RNA expression in the thymus (Aribi, 2008; Pugliese et al., 1997; Vafiadis et al., 1997). Insulin would then be the main antigens engaged in thymic T cell education and immune tolerance induction. Therefore, it has been the first diabetes-related autoantigen to be identified (Gilliam et al., 2004).

Insulin autoantibodies (IAAs) are of weak prevalence at the time of diagnosis (Breidert et al., 1998). Their levels are increased especially in prediabetics (Palmer et al., 1983), but also in newly diagnosed type 1 diabetic subjects. Additionally, IAAs could be confused with insulin antibodies (IAs) produced following injection of exogenous insulin; therefore, we cannot assess the real level of IAAs in treated patients (Gilliam et al., 2004).

On the other hand, various studies have shown that the elevated IAA frequency and levels are observed mainly in young children (Landin-Olsson et al., 1992) and HLA DR4 subjects (Achenbach et al., 2004; Savola et al., 1998; Ziegler et al., 1991). Moreover, IAAs could be detected in all children who develop diabetes when they are associated with multiple autoantibodies. Furthermore, these antibodies confer high risk in T1D relatives (Ziegler et al., 1989), essentially in combination with other autoimmune markers (Bingley et al. 1999; Thivolet et al., 2002; Winnock et al., 2001). However, the actual frequency of positivity varies considerably from one study to another, according to the IAA assay, age at diagnosis, as well as the populations studied (Gilliam et al., 2004).

Interestingly, IAAs do not necessarily reflect beta-cell destruction. Indeed, they have been reported to occur in other autoimmune diseases, such as Hashimoto thyroiditis, Addison disease, chronic hepatitis, pernicious anemia, systemic lupus erythematosus, and rheumatoid arthritis (Di Mario et al., 1990).

IAAs can be detected by two assay methods, a fluid-phase radioimmunoassay (RIA) and a solid-phase enzyme-linked immunosorbent assay (ELISA); however, it has been shown that IAAs measured by RIA were more closely linked to T1D development than those measured by ELISA (Murayama et al., 2006; Schlosser et al., 2004; Schneider et al., 1976; Wilkin et al., 1988).

2.1.3 Glutamic acid decarboxylase autoantibodies

Of note, a 64kDa islet cell protein was initially isolated by precipitation with autoantibodies present in sera of patients with T1D (Baekkeskov et al., 1982). After laborious searches, this protein was identified as glutamic acid decarboxylase (GAD) (Baekkeskov et al., 1990); the enzyme that synthesizes the gamma-aminobutyric acid neurotransmitter in neurons and pancreatic beta-cells (Dirkx et al., 1995). At that time, GAD autoantibodies had been demonstrated to have a common identity in patients with stiff-man syndrome (SMS) and T1D (Baekkeskov et al., 1990; Solimena et al., 1988). During the same period, GAD complementary deoxyribonucleic acid (GAD cDNA) cloning demonstrate that there are two different genes of GAD, designated GAD1 and GAD2 (Bu et al., 1992; Erlander et al., 1991; Karlsen et al., 1991),

located on chromosome 2q31.1 and chromosome 10p11.23, respectively (Bennett et al., 2005). GAD1 mRNA has been reported to be translated into GAD67, which is not detected in human islets (Karlsen et al., 1991), but is predominantly found in mouse islets (Petersen et al., 1993; Velloso et al., 1994). The mRNA for GAD2 gene encodes the GAD65kDa isoform that is expressed in human pancreatic islets and brain (Gilliam et al., 2004).

GAD65 autoantibodies (GAD65A) are revealed in 70% to 80% of cases among prediabetic subjects and newly diagnosed patients (Kulmala et al., 1998). They are considered as a good retrospective marker of the autoimmune progression, because of their persistence in the sera of patients with T1D for many years following diagnosis (Borg et al., 2002b). Whereas, these antibodies have a low positive predictive value for beta-cell failure (47%) compared to ICAs (74%) (Borg et al., 2001) and can be revealed in patients with neurological disorders, including those with gamma-aminobutyric acid (GABA)-ergic alterations (Piquer et al., 2005; Solimena et al., 1990). Similarly, they can be present in patients who have other autoimmune diseases (Davenport et al., 1998; Nemni et al., 1994; Tree et al., 2000) as well as in patients with type 2 diabetes (Hagopian et al., 1993; Tuomi et al., 1993). Consequently, they don't seem to be specific to pancreatic beta-cells destruction (Wie et al., 2004; Costa et al., 2002).

GADAs are usually detected by radioligand-binding assay, which is reported to have higher sensitivity, specificity, and reproducibility than other methods using ELISA, enzymatic immunoprecipitation, and immunofluorescence assays (Damanhoury et al., 2005; Knowles et al., 2002; Kobayashi et al., 2003).

2.1.4 Anti-tyrosin phosphatase autoantibodies

These antibodies are directed against two digestion fragments (Jun & Yoon, 1994; Maugendre et al., 1997) resulting from trypsin hydrolysis of transmembrane protein expressed in islets and the brain, and are present in two related forms with distinct molecular weights, 40kDa and 37kDa (Bonifacio et al., 1995a; Li et al., 1997; Yamada et al., 1997).

Of note, the 40kDa antigen is the receptor tyrosine phosphatase-like protein IA-2 associated with the insulin secretory granules of pancreatic beta-cells (Trajkovski et al., 2004), also called islet cell autoantigen 512 (ICA512)/IA-2 (Bonifacio et al., 1995b; Payton et al., 1995). The 37kDa antigen is a tryptic fragment related protein tyrosine phosphatase, designated IA-2 β /phogrin (Kawasaki & Eisenbarth, 2002), or islet cell autoantigen-related protein tyrosine phosphatase (IAR) (Lu et al., 1996).

It has been shown that antibodies to the two antigens have similar sensitivity; however, epitope mapping studies have suggested that antibodies to IA-2 (IA-2A, insulinoma-associated protein 2 islet tyrosine phosphatase) appear to be more important for the pathogenesis of T1D than those to IA-2 β (Savola, 2000; Schmidli et al., 1998). In fact, the binding of phogrin autoantibodies could be totally blocked if adding ICA512 to sera positive for both ICA512 and phogrin, while the binding of ICA512 antibodies cannot be fully blocked with phogrin (Savola, 2000).

IA-2As can be evaluated by radioligand-binding assay and ELISA (Bonifacio et al., 2001; Chen et al., 2005a; Kotani et al., 2002); whereas, RIAs performed much better than ELISAs, as was found for GAD65A assays (Verge et al., 1998).

2.1.5 Zinc transporter 8 autoantibodies

The human beta-cell-specific zinc transporter Slc30A8 (ZnT8) is a member of the large cation efflux family of which at least seven are expressed in islets (Chimienti et al., 2004). It has

been recently defined as a major target of humoral autoimmunity in human T1D based on a bioinformatics analysis (Dang et al., 2011; Wenzlau et al., 2009). Autoantibodies to ZnT8 (ZnT8A) have been therefore detected in high prevalence in newly diagnosed type 1 diabetic patients (Yang et al., 2010) and obviously overlap with GADA, IA2A, and IAA (Wenzlau et al., 2007).

Of note, ZnT8 autoimmunity could be an independent marker of T1D, given that ZnT8As can be present in antibody-negative individuals and in type 2 diabetes, and in patients with other autoimmune disorders (Wenzlau et al., 2008).

Antibodies to ZnT8 can be measured by radioimmunoprecipitation assay using ^{35}S labelled methionine *in vitro* translation products of different fragments of human ZnT8 (Lampasona et al., 2010).

2.2 Immunological anomalies of type 1 diabetes and cellular autoimmunity

In reality, our understanding of the exact cellular immune mechanisms that lead to the development of T1D is limited, and it is possible that the potential target autoantigens may be less well defined and more diverse, probably because of the epitopes diversification.

The immune reaction against beta-cells is due primarily to a deficit in the establishment of central thymic tolerance and the activation of potentially dangerous autoreactive T cells and B cells that recognize islet antigens. Additionally, aggression of the beta-cells may be initiated by other cells and components of the innate immune system. In fact, it has been observed that the immune cells peripheral infiltration of the Langerhans islets, a process termed perished-insulinitis, begins initially with the monocytes/macrophages and dendritic cells (DCs) (Rothe et al., 2001; Yoon et al., 2005; Yoon et al., 2001). Upon exposure to antigens, islet-resident antigen presenting cells, likely DCs, undergo maturation, leading to the expression of cell surface markers that are subsequently required for T cell activation in the pancreatic lymph nodes (panLN). CD4⁺ T cells and macrophages home to islets and release pro-inflammatory cytokines and other death signals that acutely trigger necrotic and pro-apoptotic pathways (Fig. 2).

2.2.1 T cells and B cells

Although both humoral and cell-mediated immune mechanisms are active during T1D, CD4⁺ and CD8⁺ T cells recognizing islet autoantigens are the main actors of beta-cells death (DiLorenzo et al., 2007; Gianani & Eisenbarth, 2005; Toma et al., 2005). B cells may play a role in inducing inflammation and presentation of self-antigen to diabetogenic CD4⁺ T cells (Silveira et al., 2007).

It has been repeatedly observed that the pancreatic islets of diabetic patients prior to and at diagnosis are infiltrated by T lymphocytes of both CD4 and CD8 subsets (Hanninen et al., 1992; Imagawa et al., 2001; Kent et al., 2005). Additionally, their circulating number among type 1 diabetic patients is higher than those of B cells (Martin et al., 2001). Moreover, the disease can be transferred to NOD-*scid* mice that are genetically deficient in lymphocytes (Christianson et al., 1993; Sainio-Pollanen et al., 1999; Yamada et al., 2003), or to newborn NOD mice exposed to atomic radiation (Miller et al., 1988; Yagui et al., 1992) by injection of T CD4⁺ and CD8⁺ splenocytes from prediabetics. However, injection of anti-islets antibodies does not induce autoimmunity (Timist, 1996) and beta-cell damage may develop in individuals with severe B cells deficiency (Martin et al., 2001).

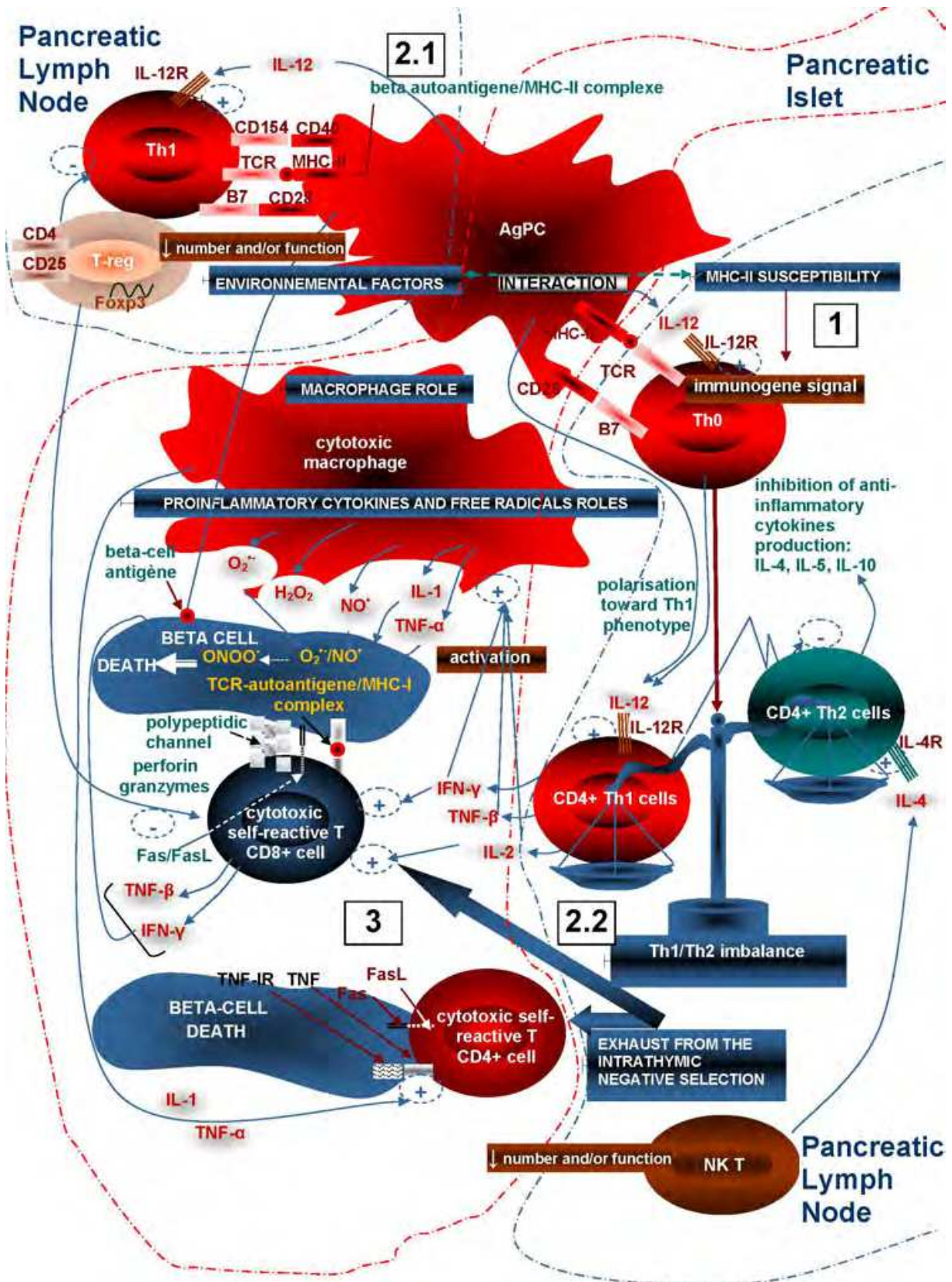


Fig. 2. Hypothetical scheme of the autoimmune response of type 1 diabetes: cellular interaction and molecules that can be involved within the destruction of pancreatic islets beta-cells. (1) Antigen exposure and TCR signalling pathway: AgPC exposes epitopes derived from

beta-cells on its membrane surface by some class II MHC molecules that are involved in the susceptibility of T1D. The autoantigens/class II MHC complex, adhesion molecules, particularly B7, IL-12 derived from AgPC, and possibly other immunogenic signals, could join and cause the activation of CD4⁺ Th0 cells. Many factors (physical, psychological, and chemical stress) are able to guide the Th0 differentiation towards Th1 cell. (2.1 and 2.2) Activation of Th1 cells: immunogenic signals resulting from class II MHC/peptide-TCR, CD40-CD154 and CD28-B7 interactions induce the activation of Th1 cells. (3) Beta-cells destruction: activated Th1 cells produce IL-2, TNF- β and IFN- γ cytokines, increasing the activation of islet-infiltrated macrophage and autoreactive cytotoxic CD8⁺ cells. These cells can destroy pancreatic beta cells by proinflammatory cytokines, granzymes and perforin, FasL-Fas interaction, and oxygen/nitrogen free radicals. Anomalies of autoreactive T cells suppression could be due to the decreased number and/or function of peripheral regulatory cells affecting both NK T cells and natural CD4⁺CD25⁺/CD25^{high}Foxp3⁺ T-reg cells. AgPC: antigen-presenting cell, CD: cluster of differentiation, DC: dendritic cell, Fas/FasL: CD95/CD95 Ligand, Foxp3: transcription factor forkhead box P3, IFN: interferon, IL: interleukin, MHC: major histocompatibility complex, NK T: natural killer T cell, T1D: type 1 diabetes, TCR: T cell receptor, Th: T helper, TNF: tumor necrosis factor. TNF-R1: tumor necrosis factor receptor type I.

2.2.2 CD4⁺ and CD8⁺ T cells and ways of beta-cells destruction

The precise role of each of these cells in pancreatic islets destruction remains unclear and controversial. Therefore, two main pathways may be involved in triggering the disease, both of which are activated following recognition of beta-cell autoantigens.

According to the indirect way, the critical role in T1D development could be attributed to autoreactive CD4 T cells, as exemplified by the observation that the major histocompatibility complex class II (MHC II) genes are the main candidate genes to which a key role can be assigned in the autoimmune process according to their strong association with the disease (Aribi, 2008; Concannon et al., 2009). These cells can initiate beta-cells destruction and lead to tissue cell damage (Peterson & Haskins, 1996), through the secretion of cytokines with toxic effects (Amrani et al., 2000), then recruit T CD8⁺ lymphocytes (McGregor et al., 2004).

According to the direct way, autoreactive T CD8⁺ lymphocytes (Anderson et al., 1999) could initiate beta-cells destruction, as shown in transgenic TCR (NOD/AI4 $\alpha\beta$ Tg) NOD mice, that T1D autoimmunity beginning can be achieved in total absence of CD4⁺ T cells and requires only CD8⁺ T cells (Graser et al., 2000). Additionally, disease development is reduced only when adult NOD mice are injected with anti-class I MHC molecules or anti-CD8 mAb molecules (Wang et al., 1996). Moreover, β 2-microglobulin-deficient (β 2m^{-/-}) and anti-CD8 mAb-treated NOD mice, yet deficient in CD8⁺ T cells develop neither insulinitis nor T1D (Yang et al., 2004).

However, direct evidence for these observations is compelling only in animal models in which adoptive transfer experiments are feasible ethically (Di Lorenzo et al., 2007). Additionally, several differences can be revealed between men and animal models of T1D. For example, in men, immunohistological studies of type 1 diabetic pancreatic-biopsy showed a strong number of islet-infiltrated CD8⁺ cytotoxic T cells compared to that of islet-infiltrated CD4⁺ T helper cells (Itoh et al., 1993). In contrast, in NOD mice, pancreatic islets are infiltrated predominantly by CD4⁺ T cells compared to CD8⁺ T cells (Kida et al., 1998).

2.2.3 Regulatory T cells/effectors T cells imbalance

The primary function of Treg cells is the maintenance of self-tolerance in order to prevent the development of autoimmune diseases (Sakaguchi et al., 1995). They also have the ability

to control a runaway immune response by different feedback mechanisms, involving the production of anti-inflammatory cytokines, direct cell-cell contact or modulating the activation state of antigen-presenting cells (AgPCs) (Corvaisier-Chiron & Beauvillaina, 2010). Normal tolerance to self-antigens is an active process that has a central component and a peripheral component. Central tolerance implies induction of tolerance in developing lymphocyte when they encounter self-antigens that are present in high concentration in the thymus or bone marrow; while peripheral tolerance is maintained by mechanisms of self-reactive T cells elimination by clonal deletion, anergy or ignorance (Wallace et al., 2007). Among these three mechanisms only the deletion is induced by Treg cells (Corvaisier-Chiron & Beauvillaina, 2010).

Different subpopulations of Treg cells have been identified: natural Treg (nTreg) cells that derived from the thymus and migrate to peripheral tissues, and peripherally induced Treg (iTreg) (Corvaisier-Chiron & Beauvillaina, 2010). nTreg cells represent 2-4% of circulating lymphocytes in humans (Wahlberg et al., 2005) and are characterized by the expression of CD4, CD25^{high}, CD127^{low} molecules and high levels of the transcription factor FoxP3 (forkhead box P3) (Corvaisier-Chiron & Beauvillaina, 2010; Wahlberg et al., 2005). They also express surface CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) and GITR (TNF receptor family glucocorticoidinduced-related gene) involved in membrane mechanisms of Treg suppression (Corvaisier-Chiron & Beauvillaina, 2010).

Except pathological conditions, there is a balance between regulatory T cells and effector T cells. Some genetic and environmental factors might cause deregulation of this balance in favor of self-reactive lymphocytes that may induce or predispose to the development of autoimmune diseases, including T1D (Brusko et al., 2008).

In NOD mice and diabetic patients and in several organ-specific animal models of autoimmunity as well as in humans (Furtado et al., 2001; Kriegel et al., 2004; Kukreja et al., 2002), it has been demonstrated that number and/or function of peripheral regulatory cells affecting both nTreg cells (CD4+CD25+Foxp3+) (Fontenot et al., 2003; Hori et al., 2003; Khattri et al., 2003) and natural killer (NK) T cells (Duarte et al., 2004; Hong et al., 2001) are decreased; while self-reactive peripheral T cells number is increased (Berzins et al., 2003). Additionally, decreased contacts between effectors and nT-reg cells seem to belong to additional events leading to autoreactive T cells activation and proliferation (Lindley et al., 2005; Maloy & Powrie, 2001; Piccirillo et al., 2005).

On the other hand, various studies showed that T1D in both humans and NOD mice could be due to the weak secretion of IL-4 resulting from a deficiency in NK T cells (Lehuen et al., 1998; Wilson et al., 1999) and that diabetes can be prevented in mice by transfer of NK T cell-enriched CD4-CD8- double negative cells (Baxter et al., 1997; Falcone et al., 1999; Lehuen et al., 1998) or of thymic-derived nT-reg cells (Chen et al., 2005b; Lindley et al., 2005; Luo et al., 2007).

2.2.4 Regulatory T cells/Th17 cells imbalance

Th17 cells represent a subtype of T cells that can be generated in the presence of IL-23 even from cells deficient in transcription factors required for Th1 (T-bet) or Th2 (GATA-3) cells development (Harrington et al., 2005; Park et al., 2005). However, IL-23 would not be a factor for Th17 cells differentiation but rather intervene in their survival and proliferation. In fact, naive T cells do not express receptors for IL-23 and do not differentiate into Th17 cells only in the presence of IL-23 (Mangan et al., 2006). Additionally, Th17 cells express a specific

transcription factor, RORC2 (retinoic acid receptor-related orphan receptor C2, known as ROR γ t in mice), which is crucial for the generation of Th17 cells, especially *via* the transcriptional induction of the gene encoding IL-17 and the expression of IL-23 receptor (Ivanov et al., 2006). To acquire a full differentiation of such cells, RORC2 acts in cooperation with other transcription factors, including ROR α , STAT3, IRF-4 and Runx1 (Miossec et al., 2009).

The discovery of factors involved in the differentiation of Th17 and Treg cells suggests the existence of Treg/Th17 balance, controlled by IL-6 (Kimura et al., 2011). More recently, increased Th17 immune responses or imbalance of nTreg cells and IL-17 producing Th17 have been found to be associated to the onset of the disease in both humans and NOD mice or Diabetes-prone BioBreeding (DP-BB) rats (Honkanen et al., 2010; Shi et al., 2009; van den Brandt et al., 2010). While, these observations should be confirmed further.

2.2.5 Th1/Th2 imbalance

Different factors, including physical, psychological, and chemical stress (Ernerudh et al., 2004) can produce imbalance in the proportions of CD4+ Th1 cell and CD4+ Th2 cell subsets (Eizirik et al., 2001; Rabinovitch et al., 1994; Thorvaldson et al., 2005). Several studies have shown that the autoimmune aggression leading to T1D involves Th1 cells (Kida et al., 1999; Sharif et al., 2002; Yoon & Jun, 2005). However, Th2 cells seem to be associated with protection against beta-cells destruction (Cameron et al., 1997; Ko et al., 2001; Suarez-Pinzon & Rabinovitch, 2001).

In NOD mouse model, T1D can be transferred among animals through the injection of Th1 cells (Kukreja et al., 2002). T1D-sex relationship has been linked to the type of produced cytokines. Lymphocytes infiltrating female mice pancreatic islets produce high levels of Th1 cytokine mRNA and low levels of Th2 cytokine mRNA. On the other hand, male mice are more resistant to T1D because they produce more Th2 cytokine mRNA and less cytokine Th1 mRNA (Azar et al., 1999; Fox & Danska, 1997). Likewise, young NOD mice spleenocytes expressing CD62L and CD25, *i.e.* CD4+CD45RB^{low} (memory/activated cells) which are involved in dominant protection against T1D development, show an overproduction of Th2 cytokines, yet tend towards an overproduction of Th1 cytokines right before diabetes onset (Shimada et al., 1996). Besides, female NOD mice have more spleenocytes CD45RB^{low} CD4+ and more spleenocytes CD4+CD25+ activated helper cells than do male NOD mice have (Azar et al., 1999). Moreover, it is possible to prevent T1D in NOD mice with a single injection of insulin or GAD peptide (Han et al., 2005), because it causes a reduction in levels of Th1 cytokines and an increase in the ones of Th2 cytokines (Muir et al., 1995; Sai et al., 1996).

2.2.6 Innate immunity

It has been recently observed that innate immunity may play a critical role in the development of T1D. This observation has been supported by works showing that infusions of alpha-1 antitrypsin, a serine protease inhibitor that protects tissues from enzymes produced from inflammatory cells, were found to reverse new-onset diabetes in NOD mice (Koulmanda et al., 2008). Many effects have been described, including reduced insulinitis, enhanced beta-cell regeneration, and improvement in peripheral insulin sensitivity (Luo et al., 2010).

Thanks to many experiments conducted in animal models, it has been shown that toll-like receptors (TLRs), as part of the innate immune system, may have an important role in T1D

development (Filippi & von Herrath, 2010). For example, injection of low dose of TLR-3 stimulus poly I:C has been shown to prevent diabetes in the disease-prone Biobreeding rat model (Sobel et al., 1998). In addition, TLR deficiency has been associated with decreased number of some Treg. Indeed, T cells with a regulatory phenotype can express TLR-2, TLR-4, TLR-5, TLR-7 and TLR-8 (Caramalho et al., 2003; Suttmuller et al., 2006), and the proliferation of Treg cells has been observed especially following the administration of TLR-2 ligands to TLR-2-deficient mice (Suttmuller et al., 2006). Moreover, it has been suggested that protection against T1D in NOD mice through infection with Lymphocytic Choriomeningitis Virus (LCMV) is dependent on the emergence of Tregs and TLR-2 (Boettler & von Herrath, 2011).

2.2.7 Macrophages

Macrophages play a significant role in the oxidative stress (Ishii et al., 1999; Rozenberg et al., 2003), innate immunity (Bedoui et al., 2005; Lawrence et al., 2005) and inflammation (Ishii et al., 1999; Lawrence et al., 2005). Macrophages and other AgPCs in the panLN (Pearl-Yafe et al., 2007) initiate T cell sensitization, and concomitantly activate regulatory mechanisms (Kaminitz et al., 2007). The central role of macrophages in the cellular immune response (Durum et al., 1985) and in the development and activation of beta-cell-cytotoxic T cells during T1D (Yoon & Jun, 2001) has been previously proven in BioBreeding (BB) rats where a macrophage insulinitis preceding lymphocyte insulinitis could be prevented by a silica intraperitoneal injection (Albina et al., 1991). However, macrophages are also able to exert a suppressor effect on lymphocyte proliferation (Albina et al., 1991; Taylor et al., 1998; Zhang & McMurray, 1998). This effect is exerted on T and B cells alike and is mediated by several ways involving especially prostaglandins and nitric oxide as metabolic mediators (Albina et al., 1991; Ding et al., 1988; Jiang et al., 1992).

A mechanism by which macrophages intervene preferentially in Th1 and Th2 clones differentiation has been suggested. Hence, macrophages can interact with Th cells and induce polarization toward the Th1 or Th2 cell subset depending on the oxidation level of their glutathione content. With low levels of oxidized glutathione, they induce a polarization toward Th1 phenotype, whereas high levels of oxidized glutathione lead to Th2 differentiation (Murata et al., 2002). Additionally, some IL-12 antigenic stimulations induce Th1 cells activation (Hsieh et al., 1993). Th2 cells activation goes through the action of IL-4 and IL-10, which can also be produced by activated macrophages in the presence of immune complexes (Fiorentino et al., 1991).

2.2.8 Dendritic cells

DCs play an important role in initiating the immune response and antigen presentation, as well as in maintaining peripheral self-tolerance (Steinman et al., 2003). There are mostly immature DCs (iDCs), which have poor antigen presentation functions (de Vries et al., 2003), may be involved in immunoregulatory functions in autoimmune processes (Dorman et al., 1997). These functions depend largely on co-stimulation during the maturation process. Thus, tolerogenic DCs are iDCs with reduced allostimulatory capacities and low expression levels of costimulatory molecules, like CD40, CD80 and CD86 molecules. However, the transition to the mature state, following exposure to pathogens, leads to increased antigen presentation and expression of T cell co-stimulatory molecules and T cell responses (Steinman & Banchereau, 2007).

Nevertheless, the acquisition of a high degree of maturity and expression of adhesion molecules, especially CD86 molecule, allows the DCs to provoke the activation of CD4⁺CD25⁺ regulatory T cells capable of inhibiting autoimmune disease (Yamazaki et al., 2003). It is therefore quite possible that the DCs involved in triggering the autoimmune process leading to T1D (Clare-Salzler et al., 1992; Feutren et al., 1986; Mathis et al., 2001), are mature cells with a large capacity for antigen presentation, but without effect on regulatory T cells.

Additionally, it has been shown that DCs are the initiators of the islet infiltration in NOD mice (DiLorenzo et al., 2007). Such cells isolated from the panLN could prevent diabetes development when transferred adoptively to young recipients (Bekris et al., 2005), while those from other sites could not, suggesting that the activation of autoreactive T cells occurs at this site and that their suppression would be due to deletion or regulation mechanisms (Belz et al., 2002; Hugues et al., 2002).

2.2.9 Adhesion and costimulation molecules and cell signaling

T-cell-receptor (TCR)-mediated recognition of pancreatic autoantigens is a central step in the diabetes pathogenesis (Bach, 2002). Interaction between TCR and pancreatic peptides aberrantly complexed with class II MHC molecules on pancreatic beta-cells (Foulis, 1996) or expressed on the AgPCs in panLN is required for the activation of Th1 lymphocytes. Similarly, TCR interaction with autoantigen peptides presented by class I MHC molecules on pancreatic beta-cells is essential for the activation of cytotoxic CD8⁺ autoreactive T lymphocytes in pancreatic islet. Activated Th1 cells induce positive signals involving IL-2, TNF- β and IFN- γ cytokines to increase the activation of islet-infiltrated macrophage and cytotoxic CD8⁺ cells.

Beta-cells aggression can be mediated by proinflammatory cytokine-mediated cell killing (IL-1 (Aribi et al., 2007; Sparre et al., 2005), TNF- α (Christen et al., 2001; Lee et al., 2005), TNF- β , IFN- γ , IL-18 (Nakanishi et al., 2001; Szeszko et al., 2006), IL-12 (Giulietti et al., 2004; Holtz et al., 2001), IL-6 (Kristiansen & Mandrup-Poulsen, 2005; Targher et al., 2001), and IL-8 (Erbağci et al., 2001; Lo et al., 2004), etc.), granzymes (GRZ) and perforin (PRF1), FasL-Fas (CD95L-CD95) interactions, hydrogen peroxide and free radicals (Mukherjee & DiLorenzo, 2010).

Numerous adhesion molecules and signalling proteins, can amplify activation of the CD3/TCR complex leading to self-reactive T cells proliferation within panLN. Experimental NOD mice studies highlighted three principal costimulation pathways for such activation: CD28-B7, CD40-CD40L (CD 154) (Bour-Jordan et al., 2004) and NKG2D-RAE-1 (von Boehmer, 2004). Therefore, it has been previously shown that the T1D occurrence is decreased by injection of anti-B7.2 mAb's (Lenschow et al., 1995). Meanwhile, invalidation of B7.2 (CD86) (NOD/B7.2^{-/-}) confers protection against the disease (Salomon et al., 2001). Additionally, ablation of CD40-CD40L pathway with neutralizing antibodies (anti-CD40L mAb's) or with invalidation of CD40L (NOD/B7.2^{-/-}) prevents the early stages of T cell activation in the panLN (Green et al., 2000). Moreover, it has been demonstrated that the activated islet-infiltrated CD8⁺ T cells express NKG2D molecules and that the treatment of NOD mice with anti-NKG2D mAb's can prevent T1D development (Ogasawara et al., 2004).

2.2.10 Vitamin D status

The gradual increase in the frequency of T1D from the Equator to the Poles, especially among children born in spring or early summer and in the winter months has been

interpreted as the consequence of limited exposure to sun and low vitamin D status. Additionally, case-control studies have consistently demonstrated an association between the incidence of T1D and vitamin D status in children and pregnant women, and an inverse relationship between vitamin D intake from diet and supplements and seasonal variations in the incidence of T1D (Pittas & Dawson-Hughes, 2010).

Experimental data could also confront the observation about the relationship between vitamin D and T1D. Indeed, the insulin-producing beta-cells, as well as other cell types of the immune system (Stoffels et al., 2006), express the vitamin D receptor (VDR) and 1-alpha-hydroxylase enzyme (Nikalji & Bargman, 2011). By regulating the extracellular calcium concentration and transmembrane calcium fluxes, vitamin D may extend to preservation of insulin secretion and insulin sensitivity. Besides, vitamin D has immunomodulatory properties and is able to affect the autoimmune process leading to T1D (Bobryshev, 2010).

3. Immunotherapy of type 1 diabetes

Intervention and prevention strategies currently under consideration for T1D aim to reverse immune autoreactivity and restore beta-cell mass (Boettler & von Herrath, 2010; Bougneres et al., 1988). Immunotherapy can be used to induce immunological tolerance to beta-cell antigens using various protocols (Haase et al., 2010), involving both islets antigen-non-specific and antigen-specific approaches, but so far success has been limited.

Immunomodulation strategies have been generally achieved in two stages of the disease: prior to clinical onset but after the appearance of islet autoantibodies (secondary prevention) and immediately after diagnosis (intervention) (Staeva-Vieira et al., 2007) (Fig. 3). Based on the preclinical and clinical outcomes of studies using these therapies, combination with islet

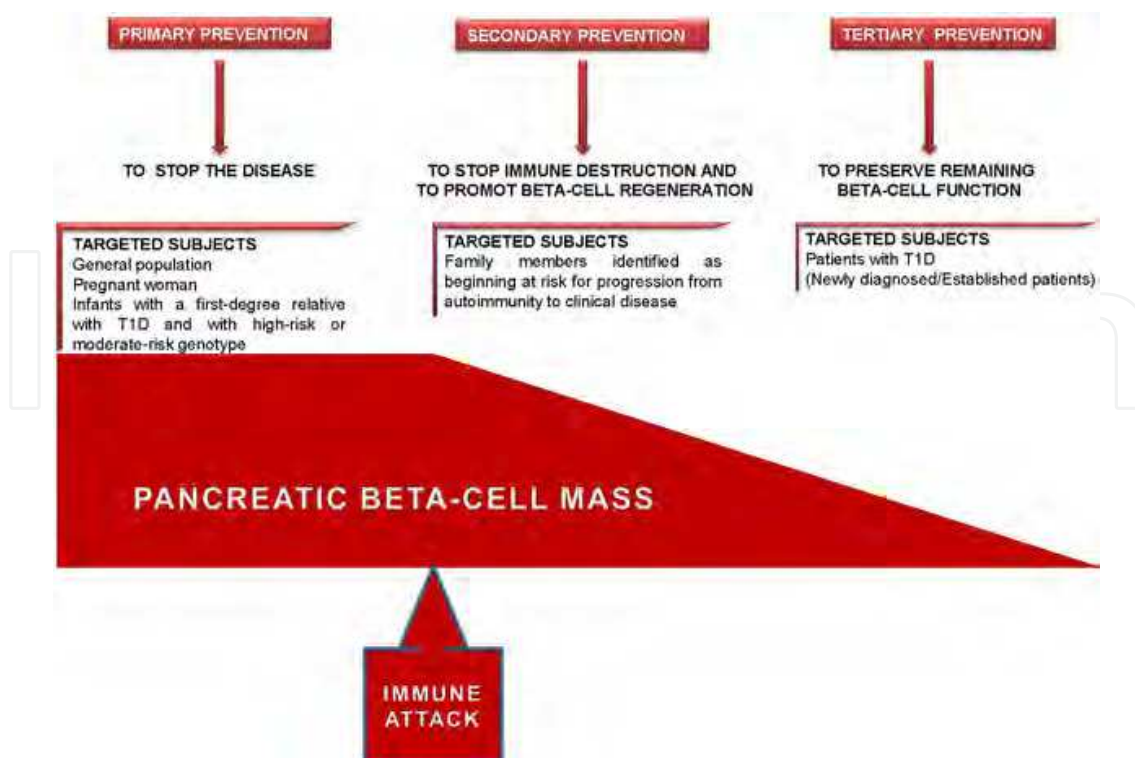


Fig. 3. Stages of type 1 diabetes prevention: objectives and selective targeting.

transplantation or stem cells for beta-cell regeneration are required in order to re-establish peripheral tolerance and to achieve a lasting remission (Marin-Gallen et al., 2010). Nevertheless, it is important to select eligible patients for such therapy, both to avoid toxicity and improve the chances of successful treatment (June & Blazar, 2006).

3.1 Non-antigen-specific immunotherapeutic approach for type 1 diabetes

For non-antigen-specific immunomodulation approach, many protocols using chemical- and antibody-mediated therapies have shown promise to the effects of various immunosuppressive drugs, including cyclosporine A (CsA), corticosteroids, azathioprine, T cell modulators (anti-CD3, anti-thymocyte globulin (ATG)), B cell-depleting agents (Rituximab: anti-CD20), anti-inflammatory molecules (anti-interleukin (IL)-1, anti-tumour necrosis factor (TNF)- α and anti-TNF- γ), cytokine-receptor-directed therapies and small-molecule protease inhibitors (Boettler & von Herrath, 2011; Luo et al., 2010; Sia, 2005; Silverstein et al., 1988) (Table 1). However, we have to acknowledge that these drugs increase the risk of developing infections and malignancies, favor the occurrence of metabolic complications such as dyslipidemia and hypertension and that some of them have been shown to inhibit beta-cell regeneration (Nir et al., 2007; Vantyghem et al., 2009). In addition to the immunosuppressant toxicity, recurrence or persistence of the autoimmune process has been observed after withdrawal of the immunosuppressive agents.

Immunomodulation therapies with nicotinamide and Bacillus Calmette-Guérin (BCG) have been tested in many clinical T1D prevention trials, but they showed no advantageous effects (Huppmann et al., 2005). Despite these negative results, large placebo-controlled clinical trials continue to illustrate the efficacy of these drugs in preventing T1D in newly diagnosed patients or in first-degree relatives of subjects with the disease.

Other immunomodulatory drugs that directly target immune cells have also been tested with success, especially in animal models of T1D, but some of them have run into major difficulties. They include DCs-based therapy, mainly the endocytic receptor involved in antigen processing and presentation DCs (DEC-205 (Ly75/CD205)), drugs targeting T cells (CTLA4-Ig: anti-CD4, anti-CD45) (Staeva-Vieira et al., 2007; Gregori et al., 2005), AgPCs (antibodies to CD40L or CD40) and NK T cells (alpha-galactosyl-ceramide (α -Gal-Cer), etc. (Chen et al., 2005c; Hong et al., 2001; Rewers & Gottlieb, 2009).

Although most of the immunomodulator treatments induce Treg cells activation, the direct infusion of ex vivo-expanded regulatory T cells has been considered to be a potential to prevent T1D (Lundsgaard et al., 2005; Tang et al., 2004; Tarbell et al., 2004) as well as other diseases, such as systemic lupus erythematosus (SLE) (Zheng et al., 2004), multiple sclerosis (MS) (Kohm et al., 2002) and inflammatory bowel disease (IBD) (Mottet et al., 2003). Treg-based cell therapy must meet at least four important therapeutic criteria: to (1) avoid the induction of immunogenicity of the infused cells; (2) prevent or delay cellular immunosenescence; (3) maximize help; and (4) be cognizant of the known differences between mouse and human T-cell biology (June & Blazar, 2006).

Moreover, drugs targeting adhesion molecules, such as Alefacept (antibody to leucocyte function-associated antigen-3 (LFA-3)), Efalizumab (antibody to LFA-1), FTY720 (immunosuppressive drug inhibiting activated T cell extravasation and trafficking to sites of inflammation), show promise in a significant proportion of patients with other diseases and are therefore of high potential interest for testing in T1D (Staeva-Vieira et al., 2007).

Therapeutic agent	Method of delivery	Phase	Population targeted	ClinicalTrials.gov identifier
Otelixizumab	SC	III	ND	NCT00946257 NCT00451321 NCT00678886 NCT01123083
Teplizumab	IV, SC	I/II	ND	NCT01030861 NCT00378508 NCT00870818 NCT00806572
INGAP peptide	SC	II	EP	NCT00995540 NCT00071409
Peptide-MHC class II dimmers	PRT	//	//	No trials on humans
CsA	O	PS	ND	NCT/URL links no longer available
Nicotinamide	O	ES	SR	NCT/URL links no longer available
Atorvastatin	O	I	ND	NCT00974740
BCG	ID	I	ND	NCT00607230
Gluten-free diet	O	OG	NR	NCT01115621 NCT00279318
DHA	O	II	CR	NCT00333554
BP/Hyd. casein	O	II	CR	NCT01055080 NCT00607230
Vitamin D3	O	I	NR	NCT00141986
Diazoxide	O	IV	ND	NCT00131755
hrIFN- α	O	II	ND	NCT00024518
hrIL-1Ra	SC	III	ND	NCT00711503 NCT00645840
Canakinumab	SC	II	ND	NCT00947427
AAT	O	I	ND	NCT01319331
Rituximab	IV	III	ND	NCT00279305
Alemtuzumab	IV	I	ND	NCT00214214
ATG	IV	II	ND	NCT00515099
CTLA4-Ig	IV	II	ND	NCT00505375
Auto UCB	INF	II	EP	NCT00305344
Auto ODN DC	INF	I	EP	NCT00445913
Prochymal	IV	II	ND	NCT00690066

Table 1. Non-antigen-specific tolerance-based clinical trials for type 1 diabetes. AAT: *alpha 1-antitrypsin (Aralast NP)*; Alemtuzumab: *anti-CD52 monoclonal antibody (Campath 1H®)*; ATG: *anti-thymocyte globulin*; Auto ODN DC: *autologous dendritic cells treated ex vivo with the mixture of the antisense oligodeoxynucleotides*; Auto UCB: *autologous umbilical cord blood*; BCG: *Bacillus Calmette-Guérin*; BP/Hyd. casein: *bovine protein (cow's milk) or hydrolyzed casein formula*; Canakinumab: *human anti-interleukin-1 β monoclonal antibody*; CR: *children at risk of T1D*; CTLA4-Ig: *cytotoxic T lymphocyte antigen-4 immunoglobulin (Abatacept)*; DHA: *docosahexaenoic acid (omega-3 fatty acid supplementation diet)*; EP: *established patients*; ES: *efficacy studies*; hrIFN- α : *human recombinant interferon- α (Roferon, Roche)*; hrIL-1Ra: *human recombinant interleukin-1 receptor antagonist (Anakinra [Kineret®])*; ID: *intradermal*; INF: *infusion*; INGAP: *islet neogenesis associated protein (15 amino-acid sequence in INGAP peptide, Exsulin)*; CsA: *cyclosporin A*; IV: *intravenously*; ND: *newly diagnosed*; NR: *newborns at risk of T1D*; O: *oral*; OG: *ongoing*; Otelixizumab: *ChAglyCD3 (aglycosylated human anti-CD3 monoclonal antibody, TRX4)*; Prochymal: *mesenchymal stem cells*; PRT: *parenteral vaccination*; PS: *pilot studies*; Rituximab: *anti-CD20 monoclonal antibody*; SC: *subcutaneously*; SR: *subjects at risk of T1D*; Teplizumab: *hOKT3 γ 1 (ala-ala) (mutated human anti-CD3 monoclonal antibody)*.

3.2 Antigen-specific tolerance strategies for type 1 diabetes

The interest in induction of antigen-specific tolerance to beta-cell antigens for immune prevention of T1D development increased due to the lack of mild non-antigen-specific immunosuppressive agents. This therapeutic approach improves remarkable longevity and long term health in T1D patients and allows most of them to escape the major degenerative complications (Bach, 2003). It can occur as a result of clonal anergy and deletion of antigen-specific autoreactive T cells or induction of regulatory cells and immune deviation (Peakman & Dayan, 2001).

Paradoxically, the induction of tolerance may not be limited to the immune response against the injected antigen, but could be extended to responses against other antigens by a close proximity mechanism involving immunosuppressive cytokines (Bach, 2003). Therefore, the administration of the antigenic epitope specifically recognized by receptors on autoreactive T cells as part of the beta-cells would be more attractive than the whole antigen administration, given the higher levels of its specificity, but also the relatively modest costs of its synthesis (Atassi & Casali, 2008) (Fig. 4).

Different antigen-specific therapeutic approaches have shown efficacy in mouse models of T1D and have been studied most intensively in terms of inducing tolerance in humans (Boettler & von Herrath, 2010). They mainly include administration of immunogenic epitope peptide or whole protein from islet autoantigen, through parenteral, oral and nasal routes. Most of these approaches have been translated into clinic, but none of them have shown convincing promise in recent-onset T1D so far.

The most important clinical trials that have been reported with particular interest have focused on oral administration of parenteral and oral insulin clinical trials, efficacy and safety study on subcutaneous administration of heat-shock protein peptide (hsp60), DiaPep277, in C-peptide positive type 1 diabetes patients and safety experience on subcutaneous injection with the 65kDa isoform of glutamic acid decarboxylase in alum (GAD-alum) and an altered peptide ligand based on putative major autoantigenic sites in the insulin B9-23 chain, which had induced strong Th2 responses in animal models (Alleva et al., 2006; Alleva et al., 2002; Thrower & Bingley, 2009) (Table 2).

It has been observed in the Diabetes Prevention trial – Type1 (DPT-1) that oral administration of insulin in a group of patients with high IAA titers might allow an important delay in T1D onset (Skyler et al., 2005). TrialNet is now testing the efficacy of oral insulin in decreasing the chances of high-risk individuals converting to T1D (Haller et al., 2007). The immunomodulation with hsp60 has shown to provide some preservation of C-peptide in newly diagnosed adult type 1 diabetics and a significant reduction in inflammation of the pancreas with continued insulin production, suggesting that the progression of the disease may be prevented (Elias et al., 2006; Lazar et al., 2007; Raz et al., 2001). Additionally, the safety experience with subcutaneous GAD65 (Diamyd's GAD65) has been demonstrated in latent autoimmune diabetes of adulthood (LADA) patients (Agardh et al., 2005). The results indicate that this treatment increases fasting p-C-peptide concentrations after 24 weeks in subjects treated with a moderate dose (20 µg) but not in subjects treated with higher doses (100 or 500 µg) or lower doses (4 µg) (Stenström et al., 2005).

Other trials using a DNA vaccine-based approaches include BHT-3021 (Bayhill Therapeutics) (Burn, 2010), a plasmid encoding proinsulin, designed to target specific pathogenic immune cells. BHT-3021 has shown considerable effectiveness in the new-onset

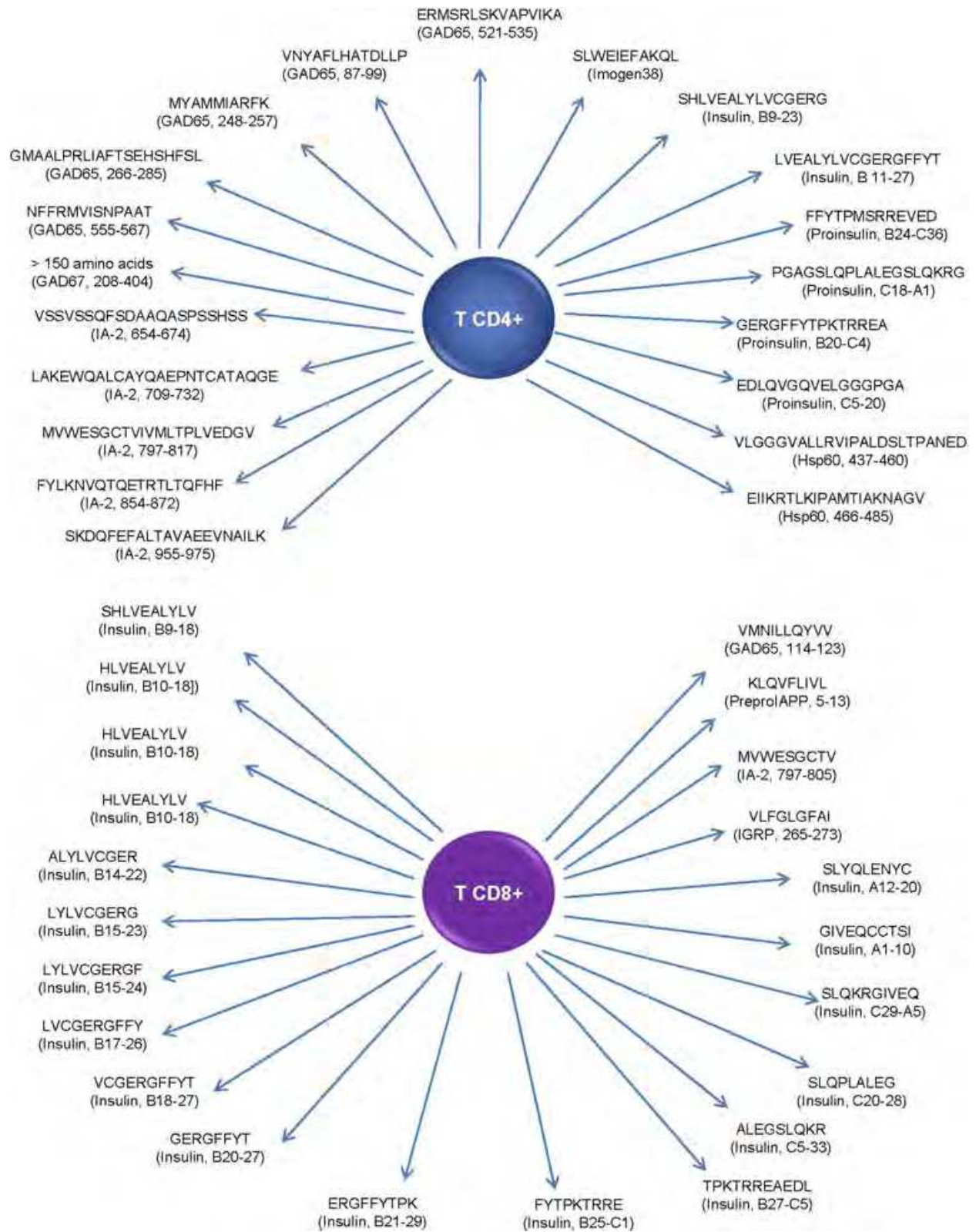


Fig. 4. CD4 and CD8 T cell epitopes for human pancreatic beta-cell antigens. (Amino acid positions are indicated in brackets.)

diabetes in the NOD mice. In the current phase I/II clinical trial, BHT-3021, administered by intra-muscular route, demonstrated preservation of C-peptide and an acceptable safety and tolerance in patients with T1D (Sanjeevi, 2009).

Therapeutic agent	Method of delivery	Phase	Population targeted	ClinicalTrials.gov identifier
Insulin	O	III	RR	NCT00004984
	IN	III	CR	NCT00223613 NCT00336674
	PRT	II	RR	NCT00654121
IBC-VS01	IM	I	ND	NCT00057499
NBI-6024	SC	I	ND	NCT00873561
BHT-3021	IM	I	EP	NCT00453375
rhGAD-alum	SC	II	ND	NCT00529399 NCT01129232
DiaPep277	SC	III	ND	NCT01103284 NCT00615264 NCT00644501

Table 2. Antigen-specific tolerance-based clinical trials for type 1 diabetes. CR: *children at risk of T1D*; EP: *established patients*; DiaPep277: *Hsp60 immunodominant peptide p277*; IBC-VS01: *human insulin B chain in incomplete Freund's adjuvant (IFA) vaccine*; IM: *intramuscular*; IN: *intranasal*; NBI-6024: *altered peptide ligand (APL) insulin B9-23*; ND: *newly diagnosed*; PRT: *parenteral*; rhGAD-alum: *recombinant human glutamic acid decarboxylase (rhGAD65) formulated in alum*; RR: *relatives at risk of T1D*; SC: *subcutaneously*; SR: *subjects at risk of T1D*.

3.3 Combination immunotherapy approaches

Failure to induce a lasting complete remission in patients with T1D using any single agent suggests that combination therapies may be needed for effective prevention of the disease or reversal of new-onset T1D (Luo et al., 2010). Among these approaches that are currently being tried, combinations between immunosuppressive or anti-inflammatory and antigen-specific vaccines are of particular interest, because of their quite promising early preclinical trial results. The most potent and promising ones were schemes based on a combination of anti-CD3 treatment with GAD-alum, intranasal proinsulin peptide (Bresson et al., 2006), proinsulin DNA (BHT-3021), oral insulin or anti-inflammatory drugs (Matthews et al., 2010) (Fig. 5).

4. Conclusions

T1D results from selective autoimmune destruction of insulin-producing pancreatic islet beta-cells.

Although the cause of the disease is still not fully understood, multiple immune abnormalities, involving dysfunctional regulation of the immune system that leads to the activation of self-reactive CD4+ and CD8+ T cells as well as DCs and macrophages, are believed to be a major component behind beta-cells destruction.



Fig. 5. Main combination immunotherapies for type 1 diabetes. A1AT: *alpha 1-antitrypsin*; Anakinra: *IL-1RA (Amgen)*; ATG: *anti-thymocyte globulin*; ATNFA: *anti-tumor necrosis factor alpha*; BHT-3021: *proinsulin deoxyribonucleic acid*; CTB-INS plasmid: *cholera toxin B chain insulin*; DZB: *daclizumab (anti-CD25 monoclonal antibody)*; GAD-ALUM: *glutamic acid decarboxylase formulated in Alum (Diamyd)*; GLP1: *glucagon-like peptide-1*; MMF: *mycophenolate mofetil*; PGCSF: *pegylated granulocyte colony stimulating factor*; PRO-IP: *proinsulin peptide*; Riloncept: *IL-1 Trap*.

Given that there is evidence that the inflammatory phase preceding the destruction of beta-cells may be reversible and that humoral markers of the autoimmunity are usually present many years prior to and at the time of diagnosis, various approaches are being explored in order to slow down the progression of diabetes using antigen-specific and non-antigen-specific immunotherapies. The most promising results could be based on the induction of specific immunotolerance, because of the harmful health effects that could be observed when non-antigen-specific drugs are used.

Finally, it is possible that the etiological factors may be different from one patient to another and humoral immune response would be a relatively late marker for the disease progression. Most clinical trials have therefore been hampered by the lack of cellular markers of the immune processes that cause the disease.

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6. References

- Achenbach, P., Koczwara, K., Knopff, A., Naserke, H., Ziegler, A.G. & Bonifacio, E. (2004). Mature high-affinity immune responses to (pro)insulin anticipate the autoimmune cascade that leads to type 1 diabetes. *The Journal of Clinical Investigation*, Vol.114, No.4, (August 2004), pp. 589-97, ISSN 0021-9738
- Achenbach, P., Bonifacio, E. & Ziegler, A.G. (2005). Predicting type 1 diabetes. *Current Diabetes Reports*, Vol.5, No.2, (April 2005), pp. 98-103, ISSN 1534-4827
- Agardh, C.D., Cilio, C.M., Lethagen, A., Lynch, K., Leslie, R.D.G., Palmer, M., Harris, R.A., Robertson, J.A. & Lernmark, Å. (2005). Clinical evidence for the safety of GAD65 immunomodulation in adult-onset autoimmune diabetes. *Journal of Diabetes and its Complications*, Vol.19, No.4, (July-August 2005), pp. 238-246, ISSN 1056-8727
- Albina, J.E., Abate J.A. & Henry, Jr.W.L. (1991). Nitric oxide production is required for murine resident peritoneal macrophages to suppress mitogen-stimulated T cell proliferation. Role of IFN-g in the induction of the nitric oxide-synthesizing pathway. *Journal of Immunology (Baltimore, Md.: 1950)*, (July 1991), Vol.147, No.1, pp. 144-148, ISSN 0022-1767
- Alleva, D.G., Gaur, A., Jin, L., Wegmann, D., Gottlieb, P.A., Pahuja, A., Johnson, E.B., Motheral, T., Putnam, A., Crowe, P.D., Ling, N., Boehme, S.A. & Conlon, P.J. (2002). Immunological characterization and therapeutic activity of an altered-peptide ligand, NBI-6024, based on the immunodominant type 1 diabetes autoantigen insulin B-chain (9-23) peptide. *Diabetes*, (July 2002), Vol.51, No.7, pp. 2126-2134, ISSN 0012-1797
- Alleva, D.G., Maki, R.A., Putnam, A.L., Robinson, J.M., Kipnes, M.S., Dandona, P., Marks, J.B., Simmons, D.L., Greenbaum, C.J., Jimenez, R.G., Conlon, P.J. & Gottlieb, P.A. (2006). Immunomodulation in type 1 diabetes by NBI-6024, an altered peptide ligand of the insulin B epitope. *Scand Journal of Immunology*, (January 2006), Vol.63, No.1, pp. 59-69, ISSN 0300-9475
- Amrani, A., Verdaguer, J., Thiessen, S., Bou, S. & Santamaria, P. (2000). IL-1alpha, IL-1beta, and IFN-gamma mark beta cells for Fas-dependent destruction by diabetogenic

- CD4(+) T lymphocytes. *The Journal of Clinical Investigation*, (February 2000), Vol.105, No.4, pp. 459-468, ISSN 0021-9738
- Anderson, B., Park, B.J., Verdaguer, J., Amrani, A. & Santamaria, P. (1999). Prevalent CD8(+) T cell response against one peptide/MHC complex in autoimmune diabetes. *Proceedings of the National Academy of Sciences of the United States of America*, (August 1999), Vol.96, No.16, pp. 9311-9316, ISSN 0027-8424
- Aribi, M. (2008). Candidate genes implicated in type 1 diabetes susceptibility. *Current Diabetes Reviews*, (May 2008), Vol.4, No.2, pp. 110-121, ISSN: 1573-3998
- Aribi, M., Moulessehoul, S., Kendouci-Tani, M., Benabadi, A.B., Hichami, A. & Khan, N.A. (2007). Relationship between interleukin-1beta and lipids in type 1 diabetic patients. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, (August 2007), Vol.13, No.8, pp. CR372-378, ISSN 1234-1010
- Atassi, M.Z., Casali, P. (2008). Molecular mechanisms of autoimmunity. *Autoimmunity*, (March 2008), Vol.41, No.2, pp. 123-132, ISSN 0891-6934
- Atkinson, M.A. & Eisenbarth, G.S. (2001). Type 1 diabetes: New perspectives on disease pathogenesis and treatment. *Lancet*, (July 2001), Vol.358, No.9277, pp. 221-229, ISSN 0140-6736
- Atkinson, M.A. & Maclaren, N.K. (1993). Islet cell autoantigens in insulin-dependent diabetes. *The Journal of Clinical Investigation*, (October 1993), Vol.92, No.4, pp. 1608-1616, ISSN 0021-9738
- Azar, S.T., Tamim, H., Beyhum, H.N., Habbal, M.Z. & Almawi, W.Y. (1999). Type I (insulin-dependent) diabetes is a Th1- and Th2-mediated autoimmune disease. *Clinical and Diagnostic Laboratory Immunology*, (May 1999), Vol.6, No.3, pp. 306-310, ISSN 1071-412X
- Bach, J.F. (2002). Immunotherapy of type 1 diabetes: lessons for other autoimmune diseases. *Arthritis Research* (May 2002), Vol.4, No.Suppl 3, pp. S3-S15, ISSN 1465-9905
- Bach, J.F. (2003). Prevent and cure insulin-dependent diabetes. *Pathologie-Biologie*, (April 2003), Vol.51, No.3, pp. 151-155, ISSN 0369-8114
- Baekkeskov, S., Aanstoot, H.J., Christgau, S., Reetz, A., Solimena, M., Cascalho, M., Folli, F., Richter-Olesen, H. & De Camilli, P. (1990). Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. *Nature*, (September 1990), Vol.347, No.6289, pp. 151, ISSN 0028-0836
- Baekkeskov, S., Nielsen, J.H., Marnier, B., Bilde, T., Ludvigsson, J. & Lernmark, A. (1982). Autoantibodies in newly diagnosed diabetic children immunoprecipitate human pancreatic islet cell proteins. *Nature*, (July 1982), Vol.298, No.5870, pp. 167, ISSN 0028-0836
- Barker, J.M. (2006). Clinical review: Type 1 diabetes associated autoimmunity: Natural History, Genetic Associations and Screening. *The Journal of Clinical Endocrinology and Metabolism*, (April 2006), Vol.91, No.4, pp. 1210-1217, ISSN 0021-972X
- Barker, J.M., Barriga, K.J., Yu, L., Miao, D., Erlich, H.A., Norris, J.M., Eisenbarth, G.S. & Rewers, M. (2004). Diabetes Autoimmunity Study in the Young. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). *The Journal of Clinical Endocrinology and Metabolism*, (August 2004), Vol.89, No.8, pp. 3896-3902, ISSN 0021-972X

- Barker, J.M., Ide, A., Hostetler, C., Yu, L., Miao, D., Fain, P.R., Eisenbarth, G.S. & Gottlieb, P.A. (2005). Endocrine and immunogenetic testing in individuals with type 1 diabetes and 21-hydroxylase autoantibodies: Addison's disease in a high-risk population. *The Journal of Clinical Endocrinology and Metabolism*, (January 2005), Vol.90, No.1, pp. 128-134, ISSN 0021-972X
- Baxter, A.G., Kinder, S.J., Hammond, K.J., Scollay, R. & Godfrey, D.I. (1997). Association between alphabetaTCR+CD4-CD8- T-cell deficiency and IDDM in NOD/Lt mice. *Diabetes* (April 1997), Vol.46, No.4, pp. 572-582, ISSN 0012-1797
- Bedoui, S., Velkoska, E., Bozinovski, S., Jones, J.E., Anderson, G.P. & Morris, M.J. (2005). Unaltered TNF-alpha production by macrophages and monocytes in diet-induced obesity in the rat. *Journal of Inflammation (London, England)*, (March 2005), Vol.2, No.1, pp. 2, ISSN 1476-9255
- Bekris, L.M., Shephard, C., Peterson, M., Hoehna, J., Van Yserloo, B., Rutledge, E., Farin, F., Kavanagh, T.J. & Lernmark, A. (2005). Glutathione-s-transferase M1 and T1 polymorphisms and associations with type 1 diabetes age-at-onset. *Autoimmunity*, (December 2005), Vol.38, No.8, pp. 567-575, ISSN 0891-6934
- Belz, G.T., Behrens, G.M., Smith, C.M., Miller, J.F., Jones, C., Lejon, K., Fathman, C.G., Mueller, S.N., Shortman, K., Carbone, F.R. & Heath, W.R. (2002). The CD8alpha(+) dendritic cell is responsible for inducing peripheral self-tolerance to tissue-associated antigens. *The Journal of Experimental Medicine*, (October 2002), Vol.196, No.8, pp. 1099-1104, ISSN 0022-1007
- Bennett, C.L., Huynh, H.M., Chance, P.F., Glass, I.A. & Gospe, S.M.Jr. (2005). Genetic heterogeneity for autosomal recessive pyridoxine-dependent seizures. *Neurogenetics*, (September 2005), Vol.6, No.3, pp. 143-149, ISSN 1364-6745
- Berzins, S.P., Venanzi, E.S., Benoist, C. & Mathis, D. (2003). T-cell compartments of prediabetic NOD mice. *Diabetes*, (February 2003), Vol.52, No.2, pp. 327-334, ISSN 0012-1797
- Bingley, P.J. (1996). Interactions of age, islet cell antibodies, insulin autoantibodies, and first-phase insulin response in predicting risk of progression to IDDM in ICA+ relatives: the ICARUS data set. Islet Cell Antibody Register Users Study. *Diabetes*, (December 1996), Vol.45, No.12, pp. 1720-1728, ISSN 0012-1797
- Bingley, P.J., Williams, A.J. & Gale, E.A. (1999). Optimized autoantibody-based risk assessment in family members. Implications for future intervention trials. *Diabetes Care*, (November 1999), Vol.22, No.11, pp. 1796-1801, ISSN 0149-5992
- Bobryshev, Y.V. (2010). Vitamin D3 suppresses immune reactions in atherosclerosis, affecting regulatory T cells and dendritic cell function. *Arteriosclerosis, Thrombosis, and Vascular Biology*, (December 2010), Vol.30, No.12, pp. 2317-2319, ISSN 1079-5642
- Boettler, T. & von Herrath M. (2010). Immunotherapy of type 1 diabetes--how to rationally prioritize combination therapies in T1D. *International Immunopharmacology*, (December 2010) Vol.10, No.12, pp. 1491-1495, ISSN 1567-5769
- Boettler, T. & von Herrath, M. (2011). Protection against or triggering of Type 1 diabetes? Different roles for viral infections. *Expert Review of Clinical Immunology*, (January 2011), Vol.7, No.1, pp. 45-53, ISSN 1744-666X

- Bonifacio, E. & Christie, M.R. (1997). Islet cell antigens in the prediction and prevention in insulin-dependent diabetes mellitus. *Annals of Medicine*, (October 1997), Vol.29, No.5, pp. 405-412, ISSN 0785-3890
- Bonifacio, E., Atkinson, M., Eisenbarth, G., Serreze, D., Kay, T.W., Lee-Chan, E. & Singh, B. (2001). International Workshop on Lessons From Animal Models for Human Type 1 Diabetes: identification of insulin but not glutamic acid decarboxylase or IA-2 as specific autoantigens of humoral autoimmunity in nonobese diabetic mice. *Diabetes*, (November 2001), Vol.50, No.11, pp. 2451-2458, ISSN 0012-1797
- Bonifacio, E., Bingley, P.J., Shattock, M., Dean, B.M., Dunger, D., Gale, E.A. & Bottazzo, G.F. (1990). Quantification of islet-cell antibodies and prediction of insulin-dependent diabetes. *Lancet*, (January 1990), Vol.335, No.8682, pp. 147-149, ISSN 0140-6736
- Bonifacio, E., Genovese, S., Braghi, S., Bazzigaluppi, E., Lampasona, V., Bingley, P.J., Rogge, L., Pastore, M.R., Bognetti, E. & Bottazzo, G.F., et al. (1995a). Islet autoantibody markers in IDDM: risk assessment strategies yielding high sensitivity. *Diabetologia*, (July 1995), Vol.38, No.7, pp. 816-822, ISSN 0012-186X
- Bonifacio, E., Lampasona, V., Genovese, S., Ferrari, M. & Bosi, E. (1995b). Identification of protein tyrosine phosphatase-like IA-2 (islet cell antigen 512) as the insulin-dependent diabetes-related 37/40K autoantigen and a target of islet-cell antibodies. *Journal of Immunology (Baltimore, Md.: 1950)*, (December 1995), Vol.155, No.11, pp. 5419-5426, ISSN 0022-1767
- Borg, H., Gottsater, A., Fernlund, P. & Sundkvist, G. (2002a). A 12-year prospective study of the relationship between islet antibodies and beta-cell function at and after the diagnosis in patients with adult-onset diabetes. *Diabetes*, (June 2002), Vol.51, No.6, pp. 1754-1762, ISSN 0012-1797
- Borg, H., Gottsater, A., Landin-Olsson, M., Fernlund, P. & Sundkvist G. (2001). High levels of antigen-specific islet antibodies predict future beta-cell failure in patients with onset of diabetes in adult age. *The Journal of Clinical Endocrinology and Metabolism*, (July 2001), Vol.86, No.7, pp. 3032-3038, ISSN 0021-972X
- Borg, H., Marcus, C., Sjoblad, S., Fernlund, P. & Sundkvist, G. (2002b). Insulin autoantibodies are of less value compared with islet antibodies in the clinical diagnosis of autoimmune type 1 diabetes in children older than 3 yr of age. *Pediatric Diabetes*, (September 2002), Vol.3, No.3, pp. 149-154, ISSN 1399-543X
- Bottazzo, G.F., Dean, B.M., Gorsuch, A.N., Cudworth, A.G. & Doniach, D. (1980). Complement-fixing islet-cell antibodies in type-I diabetes: possible monitors of active beta-cell damage. *Lancet*, (March 1980), Vol.1, No.8170, pp. 668-672, ISSN 0140-6736
- Bottazzo, G.F., Florin-Christensen, A. & Doniach, D. (1974). Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet*, (November 1974), Vol.2, No.7892, pp. 1279-1283, ISSN 0140-6736
- Bougneres, P.F., Carel, J.C., Castano, L., Boitard, C., Gardin, J.P., Landais, P., Hors, J., Mihatsch, M.J., Paillard, M. & Chaussain, J.L., et al. (1988). Factors associated with early remission of type I diabetes in children treated with cyclosporine. *The New England Journal of Medicine*, (March 1988), Vol.318, No.11, pp. 663-670, ISSN 0028-4793

- Bour-Jordan, H., Salomon, B.L., Thompson, H.L., Szot, G.L., Bernhard, M.R. & Bluestone, J.A. (2004). Costimulation controls diabetes by altering the balance of pathogenic and regulatory T cells. *The Journal of Clinical Investigation*, (October 2004), Vol.114, No.7, pp. 979-987, ISSN 0021-9738
- Breidert, M., Temelkova-Kurktschiev, T., Hanefeld, M., Leonhardt, W., Schmoeckel, A. & Seissler, J. (1998). Prevalence of diabetes-specific autoantibodies in patients at risk for adult onset diabetes mellitus. *Experimental and Clinical Endocrinology & Diabetes: Official Journal, German Society of Endocrinology [and] German Diabetes Association*, (1998), Vol.106, No.2, pp. 113-116, ISSN 0947-7349
- Bresson, D., Togher, L., Rodrigo, E., Chen, Y., Bluestone, J.A., Herold, K.C. & von Herrath, M. (2006). Anti-CD3 and nasal proinsulin combination therapy enhances remission from recent-onset autoimmune diabetes by inducing Tregs. *The Journal of Clinical Investigation*, (May 2006), Vol.116, No.5, pp. 1371-1381, ISSN 0021-9738
- Brusko, T.M., Putnam, A.L. & Bluestone, J.A. (2008). Human regulatory T cells: role in autoimmune disease and therapeutic opportunities. *Immunological Reviews*, (June 2008), Vol.223, No.1, pp. 371-390, ISSN 0105-2896
- Bu, D.F., Erlander, M.G., Hitz, B.C., Tillakaratne, N.J., Kaufman, D.L., Wagner-McPherson, C.B., Evans, G.A. & Tobin, A.J. (1992). Two human glutamate decarboxylases, 65-kDa GAD and 67-kDa GAD, are each encoded by a single gene. *Proceedings of the National Academy of Sciences of the United States of America*, (March 1992), Vol.89, No.6, pp. 2115, ISSN 0027-8424
- Burn, P. (2010). Type 1 diabetes. *Nature Reviews. Drug Discovery*, (March 2010), Vol.9, No.3, pp. 187-188, ISSN 1474-1776
- Cameron MJ, Arreaza GA, Zucker P, Chensue SW, Strieter RM, Chakrabarti S, Delovitch TL. (1997). IL-4 prevents insulinitis and insulin-dependent diabetes mellitus in nonobese diabetic mice by potentiation of regulatory T helper-2 cell function. *Journal of Immunology (Baltimore, Md.: 1950)*, (November 1997), Vol.159, No.10, pp. 4686-4692, ISSN 0022-1767
- Caramalho, I., Lopes-Carvalho, T., Ostler, D., Zelenay, S., Haury, M. & Demengeot, J. (2003). Regulatory T cells selectively express Toll-like receptors and are activated by lipopolysaccharide. *The Journal of Experimental Medicine*, (2003), Vol.197, No.4, pp. 403-411, ISSN 0022-1007
- Carel, J.C., Lotton, C., Timisit, J., Bougnères, P. & Boitard, C. (1999). Auto-anticorps dans le diabète auto-immun. Signification et utilisation pratique. *Médecine thérapeutique Endocrinologie & Reproduction*, (May-June 1999), Vol.1, No.1, pp. 47-54, ISSN 1295-9359
- Chen, S., Willis, J., Maclean, C., Ananieva-Jordanova, R., Amoroso, M.A., Brooking, H., Powell, M., Collins, A., Bennett, S., Mitchell, S., Burne, P., Furmaniak, J. & Smith, B.R. (2005a). Sensitive non-isotopic assays for autoantibodies to IA-2 and to a combination of both IA-2 and GAD65. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, (July 2005), Vol.357, No.1, pp. 74-83, ISSN 0009-8981
- Chen, Y.G., Choisy-Rossi, C.M., Holl, T.M., Chapman, H.D., Besra, G.S., Porcelli, S.A., Shaffer, D.J., Roopenian, D., Wilson, S.B. & Serreze, D.V. (2005b). Activated NKT cells inhibit autoimmune diabetes through tolerogenic recruitment of dendritic

- cells to pancreatic lymph nodes. *Journal of Immunology (Baltimore, Md.: 1950)*, (February 2005), Vol.174, No.3, pp. 1196-1204, ISSN 0022-1767
- Chen, Z., Herman, A.E., Matos, M., Mathis, D. & Benoist, C. (2005c). Where CD4+CD25+ T reg cells impinge on autoimmune diabetes. *The Journal of Experimental Medicine*, (November 2005), Vol.202, No.10, pp. 1387-1397, ISSN 0022-1007
- Chimienti, F., Devergnas, S., Favier, A. & Seve, M. (Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. *Diabetes*, (September 2004), Vol.53, No9, pp. 2330-2337, ISSN 0012-1797
- Christen, U., Wolfe, T., Möhrle, U., Hughes, A.C., Rodrigo, E., Green, E.A., Flavell, R.A. & von Herrath, M.G. (2001). A dual role for TNF-alpha in type 1 diabetes: islet-specific expression abrogates the ongoing autoimmune process when induced late but not early during pathogenesis. *Journal of Immunology (Baltimore, Md.: 1950)*, (June 2001), Vol.166, No.12, pp. 7023-7032, ISSN 0022-1767
- Christianson, S.W., Shultz, L.D. & Leiter, E.H. (1993). Adoptive transfer of diabetes into immunodeficient NOD-scid/scid mice. Relative contributions of CD4+ and CD8+ T-cells from diabetic versus prediabetic NOD. NON-Thy-1a donors. *Diabetes*, (January 1993), Vol.42, No.1, pp. 44-55, ISSN 0012-1797
- Clare-Salzler, M.J., Brooks, J., Chai, A., Van Herle, K. & Anderson, C. (1992). Prevention of diabetes in nonobese diabetic mice by dendritic cell transfer. *The Journal of Clinical Investigation*, (September 1992), Vol.90, No.3, pp. 741-748, ISSN 0021-9738
- Concannon, P., Rich, S.S. & Nepom, G.T. (2009). Genetics of type 1A diabetes. *The New England Journal of Medicine*, (April 2009), Vol.360, No.16, pp. 1646-1654, ISSN 0028-4793
- Corvaisier-Chiron, M. & Beauvillain, C. (2010). T regulator and Th17 lymphocytes: physiological and pathological functions. *Revue Francophone des Laboratoires*, (July-August 2010), Vol.40, No.424, pp. 31-40 ISSN 1773-035X
- Costa, M., Saiz, A., Casamitjana, R., Castañer, M.F., Sanmartí, A., Graus, F. & Jaraquemada, D. (2002). T-cell reactivity to glutamic acid decarboxylase in stiff-man syndrome and cerebellar ataxia associated with polyendocrine autoimmunity. *Clinical and Experimental Immunology*, (September 2002), Vol.129, No.3, pp. 471-478, ISSN 0009-9104
- Criswell, L.A., Pfeiffer, K.A., Lum, R.F., Gonzales, B., Novitzke, J., Kern, M., Moser, K.L., Begovich, A.B., Carlton, V.E., Li, W., Lee, A.T., Ortmann, W., Behrens, T.W. & Gregersen, P.K. (2005). Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. *American Journal of Human Genetics*, (April 2005), Vol.76, No.4, pp. 561-571, ISSN 0002-9297
- Damanhour, L.H., Dromey, J.A., Christie, M.R., Nasrat, H.A., Ardawi, M.S., Robins, R.A. & Todd, I. (2005). Autoantibodies to GAD and IA-2 in Saudi Arabian diabetic patients. *Diabetic Medicine: a Journal of the British Diabetic Association*, (April 2005), Vol.22, No.4, pp. 448-452, ISSN 0742-3071
- Dang, M., Rockell, J., Wagner, R., Wenzlau, J.M., Yu, L., Hutton, J.C., Gottlieb, P.A. & Davidson, H.W. (2011). Human Type 1 Diabetes Is Associated with T Cell Autoimmunity to Zinc Transporter 8. *Journal of Immunology (Baltimore, Md.: 1950)*, (April 2011) [Epub ahead of print], ISSN 0022-1767

- Davenport, C., Radford, P.M., Al-Bukhari, T.A., Lai, M., Bottazzo, G.F. & Todd, I. (1998). Heterogeneity in the occurrence of a subset of autoantibodies to glutamic acid decarboxylase in autoimmune polyendocrine patients with islet cell antibodies. *Clinical and Experimental Immunology*, (March 1998), Vol.111, No.3, pp. 497-505, ISSN 0009-9104
- de Vries, I.J., Lesterhuis, W.J., Scharenborg, N.M., Engelen, L.P., Ruiter, D.J., Gerritsen, M.J., Croockewit, S., Britten, C.M., Torensma, R., Adema, G.J., Figdor, C.G. & Punt, C.J. (2003). Maturation of dendritic cells is a prerequisite for inducing immune responses in advanced melanoma patients. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*, (November 2003), Vol.9, No.14, pp. 5091-5100, ISSN 1078-0432
- Di Mario U, Perfetti R, Anastasi E, Contreas G, Crisà L, Tiberti C, Amendolea MA, Masala C. (1990). Autoantibodies to insulin do appear in non-diabetic patients with autoimmune disorders: comparison with anti-immunoglobulin antibodies and other autoimmune phenomena. *Acta Endocrinologica*, (March 1990), Vol.122, No.3, pp. 303, ISSN 0001-5598
- DiLorenzo, T.P., Peakman, M. & Roep, B.O. (2007). Translational mini-review series on type 1 diabetes: systematic analysis of T cell epitopes in autoimmune diabetes. *Clinical and Experimental Immunology*, (April 2007) Vol.148, No.1, pp. 1-16, ISSN 0009-9104
- Ding, A.H., Nathan, C.F., & Stuehr, D.J. (1988). Release of reactive nitrogen intermediates and reactive oxygen intermediates from mouse peritoneal macrophages. Comparison of activating cytokines and evidence for independent production. *Journal of Immunology (Baltimore, Md.: 1950)*, (October 1988), Vol.141, No.7, pp. 2407-2412, ISSN 0022-1767
- Dirkx, R. Jr., Thomas, A., Li, L., Lernmark, A., Sherwin, R.S., De Camilli, P. & Solimena, M. (1995). Targeting of the 67-kDa isoform of glutamic acid decarboxylase to intracellular organelles is mediated by its interaction with the NH₂-terminal region of the 65-kDa isoform of glutamic acid decarboxylase. *The Journal of Biological Chemistry*, (February 1995), Vol.270, No.5, pp. 2241-2246, ISSN 0021-9258
- Dorman, J. (1997). Molecular epidemiology of insulin-dependent diabetes mellitus: WHO DiaMond Project. WHO DiaMond Molecular Epidemiology Sub-Project Group. *Gaceta Medica de Mexico*, pp. 151-154. Vol.133, No.Suppl 1, ISSN 0016-3813
- Dozio, N., Belloni, C., Girardi, A.M., Genovese, S., Sodoyez, J.C., Bottazzo, G.F., Pozza, G. & Bosi, E. (1994). Heterogeneous IgG subclass distribution of islet cell antibodies. *Journal of Autoimmunity*, (February 1994), Vol.7, No.1, pp. 45-53, ISSN 0896-8411
- Duarte, N., Stenström, M., Campino, S., Bergman, M.L., Lundholm, M., Holmberg, D. & Cardell, S.L. (2004). Prevention of diabetes in nonobese diabetic mice mediated by CD1d-restricted nonclassical NKT cells. *Journal of Immunology (Baltimore, Md.: 1950)*, (September 2004), pp. 3112-3118. Vol.173, No.5, ISSN 0022-1767
- Durum, S.K., Schmidt, J.A. & Oppenheim, J.J. (1985). Interleukin 1: an immunological perspective. *Annual Review of Immunology*, (April 1985), Vol.3, No.1, pp. 263-287, ISSN 0732-0582
- Eizirik, D.L. & Darville, M.I. (2001). Beta-cell apoptosis and defense mechanisms: lessons from type 1 diabetes. *Diabetes*, Vol.50, No. Suppl 1, pp. S64-S69, ISSN 0012-1797

- Elfving, A.M., Lindberg, B.A., Nystrom, L., Sundkvist, G., Lernmark, A., Ivarsson, S.A. & DISS Study Group. (2003). Islet autoantibodies in cord blood from patients who developed type 1 diabetes mellitus at 15-30 years of age. *Autoimmunity*, (June 2003), Vol.36, No.4, pp. 227-231, ISSN 0891-6934
- Elias, D., Avron, A., Tamir, M. & Raz, I. (2006). DiaPep277 preserves endogenous insulin production by immunomodulation in type 1 diabetes. *Annals of the New York Academy of Sciences*, (October 2006), Vol.1079, No.1, pp. 340-344, ISSN 0077-8923
- Erbagci, A.B, Tarakcioğlu, M., Coşkun, Y., Sivasli, E. & Namiduru, E.S. (2001). Mediators of inflammation in children with type 1 diabetes mellitus: cytokines in type 1 diabetic children. *Clinical Biochemistry*, (November 2001), pp. 645-650. Vol.34, No.4, ISSN 0009-9120
- Erlander MG, Tillakaratne NJ, Feldblum S, Patel N, Tobin AJ. (1991). Two genes encode distinct glutamate decarboxylases. *Neuron*, (July 1991), Vol.7, No.1, pp. 91, ISSN 0896-6273
- Ernerudh, J., Ludvigsson, J., Berlin, G. & Samuelsson, U. (2004). Effect of photopheresis on lymphocyte population in children with newly diagnosed type 1 diabetes. *Clinical and Diagnostic Laboratory Immunology*, (September 2004), Vol.11, No.5, pp. 856-861, ISSN 1071-412X
- Falcone, M., Yeung, B., Tucker, L., Rodriguez, E. & Sarvetnick, N. (1999). A defect in interleukin 12-induced activation and interferon gamma secretion of peripheral natural killer T cells in nonobese diabetic mice suggests new pathogenic mechanisms for insulin-dependent diabetes mellitus. *The Journal of Experimental Medicine*, (October 1999), pp. 963-972. Vol.190, No.7, ISSN 0022-1007
- Feutren, G., Papoz, L., Assan, R., Vialettes, B., Karsenty, G., Vexiau, P., Du Rostu, H., Rodier, M., Sirmai, J. & Lallemand A., et al. (1986). Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. Results of a multicentre double-blind trial. *Lancet*, (July 1986), Vol.2, No.8499, pp. 119-124, ISSN 0140-6736
- Filippi, C.M. & von Herrath, M.G. (2010). 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: viruses, autoimmunity and immunoregulation. *Clinical and Experimental Immunology*, (2010), Vol.160, No.1, pp. 113-119, ISSN 0009-9104
- Fiorentino, D.F., Zlotnik, A., Mosmann, T.R., Howard, M. & O'Garra, A. (1991). IL-10 inhibits cytokine production by activated macrophages. *Journal of Immunology (Baltimore, Md.: 1950)*, (December 1991), pp. 3815-3822. Vol.147, No.11, ISSN 0022-1767
- Fontenot, J.D., Gavin, M.A. & Rudensky, A.Y. (2003). Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nature Immunology*, (April 2003), Vol.4, No.4, pp. 330-336, ISSN 1529-2908
- Foulis, A.K. (1996). The pathology of the endocrine pancreas in type 1 (insulin-dependent) diabetes mellitus. *APMIS : Acta Pathologica, Microbiologica, et Immunologica Scandinavica*, (March 1996), Vol.104, No.3, pp. 161-167, ISSN 0903-4641
- Fox, C.J. & Danska, J.S. (1997). IL-4 expression at the onset of islet inflammation predicts nondestructive insulinitis in nonobese diabetic mice. *Journal of Immunology (Baltimore, Md.: 1950)*, (March 1997), Vol.158, No.5, pp. 2414-2424, ISSN 0022-1767

- Furtado, G.C., Olivares-Villagomez, D., Curotto de Lafaille, M.A., Wensky, A.K., Latkowski, J.A. & Lafaille, J.J. (2001). Regulatory T cells in spontaneous autoimmune encephalomyelitis. *Immunological Reviews*, (August 2001), Vol.182, No.1, pp. 122-134, ISSN 0105-2896
- Gianani, R. & Eisenbarth, G.S. (2005). The stages of type 1A diabetes: 2005. *Immunological Reviews*, (April 2005), Vol.204, No.1, pp. 232-249, ISSN 0105-2896
- Gilliam, L.K., Palmer, J.P. & Lernmark, Å. (2004). Autoantibodies and the disease process of type 1 diabetes mellitus, In: *Diabetes Mellitus: A Fundamental and Clinical Text*, D. LeRoith, S.I. Taylor & J.M., Olefsky, (Eds), 499-518, Lippincott, ISBN 0-7817-4097-5 (hc), Philadelphia PA 19106, USA
- Giulietti, A., Stoffels, K., Decallonne, B., Overbergh, L. & Mathieu, C. (2004). Monocytic expression behavior of cytokines in diabetic patients upon inflammatory stimulation. *Annals of the New York Academy of Sciences*, (December 2004), Vol.1037, No.1, pp. 74-78, ISSN 0077-8923
- Gorsuch, A.N., Spencer, K.M., Lister, J., McNally, J.M., Dean, B.M., Bottazzo, G.F. & Cudworth, A.G. (1981). Evidence for a long prediabetic period in type I (insulin-dependent) diabetes mellitus. *Lancet*, (December 1981), Vol.2, No8260-61., pp. 1363-1365, ISSN 0140-6736
- Graser, R.T., DiLorenzo, T.P., Wang, F., Christianson, G.J., Chapman, H.D., Roopenian, D.C., Nathanson, S.G. & Serreze, D.V. (2000). Identification of a CD8 T cell that can independently mediate autoimmune diabetes development in the complete absence of CD4 T cell helper functions. *Journal of Immunology (Baltimore, Md.: 1950)*, (April 2000), Vol.164, No.7, pp. 3913-3918, ISSN 0022-1767
- Green, E.A., Wong, F.S., Eshima, K., Mora, C. & Flavell, R.A. (2000). Neonatal tumor necrosis factor alpha promotes diabetes in nonobese diabetic mice by CD154-independent antigen presentation to CD8(+) T cells. *The Journal of Experimental Medicine*, (January 2000), Vol.191, No.2, pp. 225-238, ISSN 0022-1007
- Gregori, S., Mangia, P., Bacchetta, R., Tresoldi, E., Kolbinger, F., Traversari, C., Carballido, J.M., de Vries, J.E., Korthäuer, U. & Roncarolo, M.G. (2005). An anti-CD45RO/RB monoclonal antibody modulates T cell responses via induction of apoptosis and generation of regulatory T cells. *The Journal of Experimental Medicine*, (April 2005), Vol.201, No.8, pp. 1293-1305, ISSN 0022-1007
- Haase, C., Yu, L., Eisenbarth, G. & Markholst, H. (2010). Antigen-dependent immunotherapy of non-obese diabetic mice with immature dendritic cells. *Clinical and Experimental Immunology*, (June 2010), Vol.160, No.3, pp. 331-339, ISSN 0009-9104
- Hagopian, W.A., Karlsen, A.E., Gottsäter, A., Landin-Olsson, M., Grubin, C.E., Sundkvist, G., Petersen, J.S., Boel, E., Dyrberg, T. & Lernmark, A. (1993). Quantitative assay using recombinant human islet glutamic acid decarboxylase (GAD65) shows that 64k autoantibody positivity at onset predicts diabetes type. *The Journal of Clinical Investigation*, (January 1993), Vol.91, No.1, pp. 368, ISSN 0021-9738
- Haller, M.J., Gottlieb, P.A. & Schatz, D.A. (2007). Type 1 diabetes intervention trials 2007: where are we and where are we going? *Current Opinion in Endocrinology, Diabetes, and Obesity*, (August 2007), Vol.14, No.4, pp. 283-7, ISSN 1752-296X

- Han, G., Li, Y., Wang, J., Wang, R., Chen, G., Song, L., Xu, R., Yu, M., Wu, X., Qian, J. & Shen, B. (2005). Active tolerance induction and prevention of autoimmune diabetes by immunogene therapy using recombinant adenoassociated virus expressing glutamic acid decarboxylase 65 peptide GAD(500-585). *Journal of Immunology (Baltimore, Md.: 1950)*, (April 2005), Vol.174, No.8, pp. 4516-4524, ISSN 0022-1767
- Hanninen, A., Jalkanen, S., Salmi, M., Toikkanen, S., Nikolakaros, G. & Simel, O. (1992). Macrophages, T cell receptor usage, and endothelial cell activation in the pancreas at the onset of insulin-dependent diabetes mellitus. *The Journal of Clinical Investigation*, ISSN 0021-9738 (November 1992), Vol.90, No.5, pp. 1901-1910, ISSN
- Harrington, L.E., Hatton, R.D., Mangan, P.R., Turner, H., Murphy, T.L., Murphy, K.M. & Weaver, C.T. (2005). Interleukin 17-producing CD4⁺ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nature Immunology*, (November 2005), pp. 1123-1132. Vol.6, No.11, ISSN 1529-2908
- Hermann, R., Bartsocas, C.S., Soltész, G., Vazeou, A., Paschou, P., Bozas, E., Malamitsi-Puchner, A., Simell, O., Knip, M. & Ilonen, J. (2004). *Diabetes/Metabolism Research and Reviews*, (July-August 2004), Vol.20, No.4, pp. 322-329, ISSN 1520-7552
- Holz, A., Brett, K. & Oldstone, M.B. (2001). Constitutive beta cell expression of IL-12 does not perturb self-tolerance but intensifies established autoimmune diabetes. *The Journal of Clinical Investigation*, (December 2001), Vol.108, No.12, pp.1749-1758, ISSN 0021-9738
- Hong S, Wilson MT, Serizawa I, Wu L, Singh N, Naidenko OV, Miura T, Haba T, Scherer DC, Wei J, Kronenberg M, Koezuka Y, Van Kaer L. (2001). The natural killer T-cell ligand alpha-galactosylceramide prevents autoimmune diabetes in nonobese diabetic mice. *Nature Medicine*, (September 2001), Vol.7, No.9, pp. 1052-1056, ISSN 1078-8956
- Honkanen, J., Nieminen, J.K., Gao, R., Luopajarvi, K., Salo, H.M., Ilonen, J., Knip, M., Otonkoski, T. & Vaarala, O. (2010). IL-17 immunity in human type 1 diabetes. *Journal of Immunology (Baltimore, Md.: 1950)*, (August 2010), Vol.185, No.3, pp. 1959-1967, ISSN 0022-1767
- Hori, S., Nomura, T. & Sakaguchi, S. (2003). Control of regulatory T cell development by the transcription factor Foxp3. *Science (New York, N.Y.)*, (February 2003), Vol.299, No.5609, pp. 1057-1061, ISSN 0036-8075
- Hsieh, C.S., Macatonia, S.E., Tripp, C.S., Wolf, S.F., O'Garra, A. & Murphy, K.M. (1993). Development of Th1 CD4⁺ T cells through IL-12 produced by listeria-induced macrophages. *Science (New York, N.Y.)*, (1993), pp. 547-549. Vol.260, No., ISSN 0036-8075
- Hugues, S., Mougneau, E., Ferlin, W., Jeske, D., Hofman, P., Homann, D., Beaudoin, L., Schrike, C., Von Herrath, M., Lehuen, A. & Glaichenhaus, N. (2002). Tolerance to islet antigens and prevention from diabetes induced by limited apoptosis of pancreatic β cells. *Immunity*, (February 2002), Vol.16, No.2, pp. 169-181, ISSN 1074-7613
- Huppmann, M., Baumgarten, A., Ziegler, A.G. & Bonifacio, E. (2005). Neonatal Bacille Calmette-Guerin vaccination and type 1 diabetes. *Diabetes Care*, (May 2005), Vol.28, No.5, pp. 1204, ISSN 0149-5992

- Imagawa, A., Hanafusa, T., Tamura, S., Moriwaki, M., Itoh, N., Yamamoto, K., Iwahashi, H., Yamagata, K., Waguri, M., Nanmo, T., Uno, S., Nakajima, H., Namba, M., Kawata, S., Miyagawa, J.I. & Matsuzawa, Y. (2001). Pancreatic biopsy as a procedure for detecting in situ autoimmune phenomena in type 1 diabetes: close correlation between serological markers and histological evidence of cellular autoimmunity. *Diabetes*, (June 2001), pp. 1269-73. Vol.50, No.6, ISSN 0012-1797
- Ishii, T., Itoh, K., Sato, H. & Bannai, S. (1999). Oxidative stress-inducible proteins in macrophages. *Free Radical Research*, (1999), pp. 351-355. Vol.31, No., ISSN 1071-5762
- Itoh, N., Hanafusa, T., Miyazaki, A., Miyagawa, J., Yamagata, K., Yamamoto, K., Waguri, M., Imagawa, A., Tamura, S., Inada, M., Kawata, S., Tarui, S., Kono, N. & Matsuzawa, Y. (1993). Mononuclear cell infiltration and its relation to the expression of major histocompatibility complex antigens and adhesion molecules in pancreas biopsy specimens from newly diagnosed insulin-dependent diabetes mellitus patients. *The Journal of Clinical Investigation*, (November 1993), Vol.92, No.5, pp. 2313-2322, ISSN 0021-9738
- Ivanov, I.I., McKenzie, B.S., Zhou, L., Tadokoro, C.E., Lepelley, A., Lafaille, J.J., Cua, D.J. & Littman, D.R. (2006). The orphan nuclear receptor ROR γ directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*, (September 2006), pp. 1121-1133. Vol.126, No.6, ISSN 0092-8674
- Jiang, H., Stewart, C.A., Fast, D.J. & Leu, R.W. (1992). Tumor target-derived soluble factor synergizes with IFN- γ and IL-2 to activate macrophages for tumor necrosis factor and nitric oxide production to mediate cytotoxicity of the same target. *Journal of Immunology (Baltimore, Md.: 1950)*, (September 1992), pp. 2137-2146. Vol.149, No.6, ISSN 0022-1767
- Jun, H.S. & Yoon, J.W. (1994). Initiation of autoimmune type 1 diabetes and molecular cloning of a gene encoding for islet cell-specific 37kd autoantigen. *Advances in Experimental Medicine and Biology*, (January 1994), Vol.347, No.1, pp. 207-220, ISSN 0065-2598
- June, C.H. & Blazar, B.R. (2006). Clinical application of expanded CD4+25+ cells. *Seminars in Immunology*, (April 2006), pp. 78-88. Vol.18, No.2, ISSN 1044-5323
- Kajander, M., Moltchanova, E., Libman, I., LaPorte, R. & Tuomilehto, J. (2000). Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care*, (October 2000), Vol.23, No.10, pp. 1516-1526, ISSN 0149-5992
- Kaminitz, A., Stein, J., Yaniv, I. & Askenasy, N. (2007). The vicious cycle of apoptotic β -cell death in type 1 Diabetes. *Immunol Cell Biol*, (November-December 2007), Vol.85, No.8, pp. 582-589, ISSN 0818-9641
- Karlsen, A.E., Hagopian, W.A., Grubin, C.E., Dube, S., Disteche, C.M., Adler, D.A., Bärmeier, H., Mathewes, S., Grant, F.J. & Foster, D., et al. (1991). Cloning and primary structure of a human islet isoform of glutamic acid decarboxylase from chromosome 10. *Proceedings of the National Academy of Sciences of the United States of America*, (October 1991), pp. 8337-8341, Vol.88, No.19, ISSN 0027-8424
- Kawasaki, E. & Eisenbarth, G.S. (2000). High-throughput radioassays for autoantibodies to recombinant autoantigens. *Frontiers in Bioscience: a Journal and Virtual Library*, (November 2000), Vol.5, No.1, pp. E181-E190, ISSN 1093-9946

- Kent, S.C., Chen, Y., Bregoli, L., Clemmings, S.M., Kenyon, N.S., Ricordi, C., Hering, B.J. & Hafler, D.A. (2005). Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope. *Nature*, (May 2005), Vol.435, No.7039, pp. 224-228, ISSN 0028-0836
- Kessler, L. (2010). Human pancreatic islet transplantation in type 1 diabetes. State of this art. *Médecine Nucléaire - Imagerie Fonctionnelle et Métabolique*, (October 2010), Vol.34, No.10, pp. 589-596, ISSN 0928-1258
- Khattari, R., Cox, T., Yasayko, S.A. & Ramsdell, F. (2003). An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nature Immunology*, (April 2003), Vol.4, No.4, pp. 337-342, ISSN 1529-2908
- Kida, K., Kaino, Y., Ito, T. & Hirai, H. (1998). Controversies on the prevention of insulin-dependent diabetes mellitus by immunomodulation: lessons from NOD mice treated with beta-1,6;1,3-D-glucan and rhIGF-I. *Journal of Pediatric Endocrinology & Metabolism: JPEM*, (April 1998), Vol.11, No.Suppl2, pp. 327-333, ISSN 0334-018X
- Kida, K., Kaino, Y., Ito, T., Hirai, H. & Nakamura, K. (1999). Immunogenetics of insulin-dependent diabetes mellitus. *Acta Paediatrica*, (January 1999), Vol.82, No.Suppl427, pp. 3-7, ISSN 0001-656X
- Kimura, A. & Kishimoto, T. (2011). Th17 cells in inflammation. *International Immunopharmacology*, (March 2011), pp. 319-322, Vol.11, No.3, ISSN 1567-5769
- Knip, M., Vahasalo, P., Karjalainen, J., Lounamaa, R. & Akerblom, H.K. (1994). Natural history of preclinical IDDM in high risk siblings. Childhood Diabetes in Finland Study Group. *Diabetologia*, (April 1994), Vol.37, No.4, pp. 388-393, ISSN 0012-186X
- Knowles, C.H., Lang, B., Clover, L., Scott, S.M., Gotti, C., Vincent, A. & Martin, J.E. (2002). A role for autoantibodies in some cases of acquired non-paraneoplastic gut dysmotility. *Scandinavian Journal of Gastroenterology*, (February 2002), Vol.37, No.2, pp. 166-170, ISSN 0036-5521
- Ko, K.S., Lee, M., Koh, J.J. & Kim, S.W. (2001). Combined administration of plasmids encoding IL-4 and IL-10 prevents the developments of autoimmune diabetes in nonobese diabetic mice. *Molecular Therapy: the Journal of the American Society of Gene Therapy*, (October 2001), Vol.4, No.4, pp. 313-316, ISSN 1525-0016
- Kobayashi, T., Tanaka, S., Okubo, M., Nakanishi, K., Murase, T. & Lernmark, A. (2003). Unique epitopes of glutamic acid decarboxylase autoantibodies in slowly progressive type 1 diabetes. *The Journal of Clinical Endocrinology and Metabolism*, (October 2003), Vol.88, No.10, pp. 4768-4775, ISSN 0021-972X
- Kohm, A.P., Carpentier, P.A., Anger, H.A. & Miller, S.D. (2002). Cutting edge: CD4+CD25+ regulatory T cells suppress antigen-specific autoreactive immune responses and central nervous system inflammation during active experimental autoimmune encephalomyelitis. *Journal of Immunology (Baltimore, Md.: 1950)* (November 2002), Vol.169, No.9, pp. 4712-4716, ISSN 0022-1767
- Kotani, R., Nagata, M., Moriyama, H., Nakayama, M., Yamada, K., Chowdhury, S.A., Chakrabarty, S., Jin, Z., Yasuda, H. & Yokono, K. (2002). Detection of GAD65-reactive T-Cells in type 1 diabetes by immunoglobulin-free ELISPOT assays. *Diabetes Care*, (August 2002), Vol.25, No.8, pp. 1390-1397, ISSN 0149-5992
- Koulmanda, M., Bhasin, M., Hoffman, L., Fan, Z., Qipo, A., Shi, H., Bonner-Weir, S., Putheti, P., Degauque, N., Libermann, T.A., Auchincloss, H.Jr., Flier, J.S. & Strom, T.B.

- (2008). Curative and beta cell regenerative effects of alpha1-antitrypsin treatment in autoimmune diabetic NOD mice. *Proceedings of the National Academy of Sciences of the United States of America*, (October 2008), Vol.105, No.42, pp. 16242-16247, ISSN 0027-8424
- Kriegel, MA, Lohmann, T, Gabler, C, Blank, N, Kalden, JR, Lorenz, HM. (2004). Defective suppressor function of human CD4+ CD25+ regulatory T cells in autoimmune polyglandular syndrome type II. *The Journal of Experimental Medicine*, (May 2004), Vol.199, No.9, pp. 1285-1291, ISSN 0022-1007
- Krischer, J.P., Cuthbertson, D.D., Yu, L., Orban, T., Maclaren, N., Jackson, R., Winter, W.E., Schatz, D.A., Palmer, J.P. & Eisenbarth, G.S. (2003). Screening strategies for the identification of multiple antibody-positive relatives of individuals with type 1 diabetes. *The Journal of Clinical Endocrinology and Metabolism*, (January 2003), Vol.88, No.1, pp. 103-108, ISSN 0021-972X
- Kristiansen, O.P. & Mandrup-Poulsen, T. (2005). Interleukin-6 and diabetes: the good, the bad, or the indifferent? *Diabetes*, (December 2005), Vol.54, No.Suppl 2, pp. S114-S124, ISSN 0012-1797
- Kukreja, A., Cost, G., Marker, J., Zhang, C., Sun, Z., Lin-Su, K., Ten, S., Sanz, M., Exley, M., Wilson, B., Porcelli, S. & Maclaren, N. (2002). Multiple immuno-regulatory defects in type-1 diabetes. *The Clinical Investigator*, (January 2002), Vol.109, No.1, pp. 131-140, ISSN 0941-0198
- Kulmala, P., Savola, K., Petersen, J.S., Vähäsalo, P., Karjalainen, J., Löppönen, T., Dyrberg, T., Akerblom, H.K. & Knip, M. (1998). Prediction of insulin-dependent diabetes mellitus in siblings of children with diabetes. A population-based study. The Childhood Diabetes in Finland Study Group. *The Journal of Clinical Investigation*, (January 1998), Vol.101, No.2, pp. 327-336, ISSN 0021-9738
- Lampasona, V., Petrone, A., Tiberti, C., Capizzi, M., Spoletini, M., di Pietro, S., Songini, M., Bonicchio, S., Giorgino, F., Bonifacio, E., Bosi E., Buzzetti, R. & Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study Group. (2010). Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: Non Insulin Requiring Autoimmune Diabetes (NIRAD) 4. *Diabetes Care*, (January 2010), Vol.33, No.1, pp. 104-108, ISSN 0149-5992
- Landin-Olsson, M., Palmer, J.P., Lernmark, A., Blom, L., Sundkvist, G., Nyström, L. & Dahlquist, G. (1992). Predictive value of islet cell and insulin autoantibodies for type 1 (insulin-dependent) diabetes mellitus in a population-based study of newly-diagnosed diabetic and matched control children. *Diabetologia*, (November 1992), Vol.35, No.11, pp. 1068-1073, ISSN 0012-186X
- Lawrence, T., Bebien, M., Liu, G.Y., Nizet, V. & Karin, M. (2005). IKKalpha limits macrophage NF-kappaB activation and contributes to the resolution of inflammation. *Nature*, (April 2005), Vol.434, No.7037, pp. 1138-1143, ISSN 0028-0836
- Lazar, L., Ofan, R., Weintrob, N., Avron, A., Tamir, M., Elias, D., Phillip, M. & Josefsberg, Z. (2007). Heat-shock protein peptide DiaPep277 treatment in children with newly diagnosed type 1 diabetes: a randomised, double-blind phase II study. *Diabetes/Metabolism Research and Reviews*, (May 2007), Vol.23, No.4, pp. 286-291, ISSN 1520-7552

- Lee, L.F., Xu, B., Michie, S.A., Beilhack, G.F., Warganich, T., Turley, S. & McDevitt, H.O. (2005). The role of TNF-alpha in the pathogenesis of type 1 diabetes in the nonobese diabetic mouse: analysis of dendritic cell maturation. *Proceedings of the National Academy of Sciences of the United States of America*, (November 2005), Vol.102, No.44, pp. 15995-16000, ISSN 0027-8424
- Lehuen, A., Lantz, O., Beaudoin, L., Laloux, V., Carnaud, C., Bendelac, A., Bach, J.F. & Monteiro, R.C. (1998). Overexpression of natural killer T cells protects Vα14- Jα281 transgenic nonobese diabetic mice against diabetes. *The Journal of Experimental Medicine*, (November 1998), Vol.188, No.10, pp. 1831-1839, ISSN 0022-1007
- Lenschow, D.J., Ho, S.C., Sattar, H., Rhee, L., Gray, G., Nabavi, N., Herold, K.C. & Bluestone, J.A. (1995). Differential effects of anti-B7-1 and anti-B7-2 monoclonal antibody treatment on the development of diabetes in the nonobese diabetic mouse. *The Journal of Experimental Medicine*, (March 1995), Vol.181, No.3, pp. 1145-1155, ISSN 0022-1007
- Levin, L., Ban Y., Concepcion, E., Davies, T.F., Greenberg, D.A. & Tomer, Y. (2004). Analysis of HLA genes in families with autoimmune diabetes and thyroiditis. *Human Immunology*, (June 2004), Vol.65, No.6, pp. 640-647, ISSN 0198-8859
- Li, Q., Borovitskaya, A.E., DeSilva, M.G., Wasserfall, C., Maclaren, N.K., Notkins, A.L. & Lan, M.S. (1997). Autoantigens in insulin-dependent diabetes mellitus: molecular cloning and characterization of human IA-2 beta. *Proceedings of the Association of American Physicians*, (July 1995), Vol.109, No.4, pp. 429-439, ISSN 1081-650X
- Lindley, S., Dayan, C.M., Bishop, A., Roep, B.O., Peakman, M. & Tree, T.I. (2005). Defective suppressor function in CD4(+)CD25(+) T-cells from patients with type 1 diabetes. *Diabetes*, (January 2005), Vol.54, No.1, pp. 92-99, ISSN 0012-1797
- Lo, H.C., Lin, S.C. & Wang, Y.M. (2004). The relationship among serum cytokines, chemokine, nitric oxide, and leptin in children with type 1 diabetes mellitus. *Clinical Biochemistry*, (August 2004), Vol.37, No.8, pp. 666-672, ISSN 0009-9120
- Lu, J., Li, Q., Xie, H., Chen, Z.J., Borovitskaya, A.E., Maclaren, N.K., Notkins, A.L. & Lan, M.S. (1996). Identification of a second transmembrane protein tyrosine phosphatase, IA-2beta, as an autoantigen in insulin-dependent diabetes mellitus: precursor of the 37-kDa tryptic fragment. *Proceedings of the National Academy of Sciences of the United States of America*, (March 1996), Vol.93, No.6, pp. 2307-2311, ISSN 0027-8424
- Lundsgaard, D., Holm, T.L., Hornum, L. & Markholst, H. (2005). In Vivo Control of Diabetogenic T-Cells by Regulatory CD4+CD25+ T-Cells Expressing Foxp3. *Diabetes*, (April 2005), Vol.54, No.4, pp. 1040-1047, ISSN 0012-1797
- Luo, X., Herold, K.C. & Miller, S.D. (2010). Immunotherapy of type 1 diabetes: where are we and where should we be going? *Immunity*, (April 2010), Vol.32, No.4, pp. 488-499, ISSN 1074-7613
- Luo, X., Tarbell, K.V., Yang, H., Pothoven, K., Bailey, S.L., Ding, R., Steinman, R.M. & Suthanthiran, M. (2007). Dendritic cells with TGF-β1 differentiate naïve CD4+CD25- T cells into islet-protective Foxp3+ regulatory T cells. *Proceedings of the National Academy of Sciences of the United States of America*, (February 2007), Vol.104, No.8, pp. 2821-2826, ISSN 0027-8424

- Maloy, K.J. & Powrie, F. (2001). Regulatory T cells in the control of immune pathology. *Nature Immunology*, (September 2001), Vol.2, No.9, pp. 816-822, ISSN 1529-2908
- Mangan, P.R., Harrington, L.E., O'Quinn, D.B., Helms, W.S., Bullard, D.C., Elson, C.O., Hatton, R.D., Wahl, S.M., Schoeb, T.R. & Weaver, C.T. (2006). Transforming growth factor-beta induces development of the T(H)17 lineage. *Nature*, (2006), Vol.441, No.7090, pp. 231-234, ISSN 0028-0836
- Marin-Gallen, S., Clemente-Casares, X., Planas, R., Pujol-Autonell, I., Carrascal, J., Carrillo, J., Ampudia, R., Verdaguer, J., Pujol-Borrell, R., Borràs, F.E. & Vives-Pi, M. (2010). Dendritic cells pulsed with antigen-specific apoptotic bodies prevent experimental type 1 diabetes. *Clinical and Experimental Immunology*, (May 2010), Vol.160, No.2, pp. 207-214, ISSN 0009-9104
- Martin, S., Wolf-Eichbaum, D., Duinkerken, G., Scherbaum, W.A., Kolb, H., Noordzij, J.G. & Roep, B.O. (2001). Development of type 1 diabetes despite severe hereditary B-lymphocyte deficiency. *The New England Journal of Medicine*, (October 2001), Vol.345, No.14, pp. 1036-1040, ISSN 0028-4793
- Mathis, D., Vence, L. & Benoist, C. (2001). Beta-Cell death during progression to diabetes. *Nature*, (December 2001), Vol.414, No.6865, pp. 792-798, ISSN 0028-0836
- Matthews, J.B., Staeva, T.P., Bernstein, P.L., Peakman, M. & von Herrath, M. (2010). ITN-JDRF Type 1 Diabetes Combination Therapy Assessment Group. Developing combination immunotherapies for type 1 diabetes: recommendations from the ITN-JDRF Type 1 Diabetes Combination Therapy Assessment Group. *Clinical and Experimental Immunology*, (May 2010), pp. 176-84. Vol.160, No.2, ISSN 0009-9104
- Maugendre, D., Chaillous, L., Rohmer, V., Lecomte, P., Marechaud, R., Sai, P., Marre, M., Charbonnel, B., Allannic, H. & Delamaire, M. (1997). Multiple antibody status in type 1 diabetic patients and subjects at various risk with islet-cell antibodies. *Diabetes & Metabolism*, (September 1997), Vol.23, No.4, pp. 320-326, ISSN 1262-3636
- McGregor, C.M., Schoenberger, S.P. & Green, EA. (2004). CD154 is a negative regulator of autoaggressive CD8+ T cells in type 1 diabetes. *Proceedings of the National Academy of Sciences of the United States of America*, (June 2004), Vol.101, No.25, pp. 9345-9350, ISSN 0027-8424
- Miller, B.J., Appel, M.C., O'Neil, J. & Wicker, L.S. (1988). Both the Lyt-2+ and L3T4+ T cell subsets are required for the transfer of diabetes in nonobese diabetic mice. *Journal of Immunology (Baltimore, Md.: 1950)*, (January 1988), Vol.140, No.1, pp. 52-58, ISSN 0022-1767
- Miossec, P., Korn, T. & Kuchroo, V.K. (2009). Interleukin-17 and type 17 helper T cells. *The New England Journal of Medicine*, (August 2009), Vol.361, No.9, pp. 888-898, ISSN 0028-4793
- Mire-Sluis, A.R., Das, R.G. & Lernmark, Å. (2000). The World Health Organization International Collaborative Study for Islet Cell Antibodies. *Diabetologia*, (October 2000), Vol.43, No.10, pp. 1282, ISSN 0012-186X
- Montana, E., Fernandez-Castaner, M., Rosel, P., Gomez, J. & Soler, J. (1991). Age, sex and ICA influence on beta-cell secretion during the first year after the diagnosis of type 1 diabetes mellitus. *Diabetes & Metabolism*, (September-October 1991), pp. 460-468. Vol.17, No.5, ISSN 0338-1684

- Mottet, C., Uhlig, H.H. & Powrie, F. (2003). Cutting edge: cure of colitis by CD4+CD25+ regulatory T cells. *Journal of Immunology (Baltimore, Md.: 1950)*, (April 2003), Vol.170, No.8, pp. 3939-3943, ISSN 0022-1767
- Muir, A., Peck, A. & Clare-Salzler, M. (1995). Insulin immunization of nonobese diabetic mice induces a protective insulinitis characterized by diminished intraislet interferon- γ transcription. *The Journal of Clinical Investigation*, (February 1995), Vol.95, No.2, pp. 628-634, ISSN 0021-9738
- Mukherjee, G. & D'Irenzo, T.P. (2010). The immunotherapeutic potential of dendritic cells in type 1 diabetes. *Clinical and Experimental Immunology*, (August 2010), Vol.161, No.2, pp. 197-207, ISSN 0009-9104
- Murata, Y., Shimamura, T. & Hamuro, J. (2002). The polarization of T(h)1/T(h)2 balance is dependent on the intracellular thiol redox status of macrophages due to the distinctive cytokine production. *International Immunology*, (February 2002), Vol.14, No.2, pp. 201-212, ISSN 0953-8178
- Murayama, H., Matsuura, N., Kawamura, T., Maruyama, T., Kikuchi, N., Kobayashi, T., Nishibe, F. & Nagata, A. (2006). A sensitive radioimmunoassay of insulin autoantibody: Reduction of non-specific binding of [(125)I]insulin. *Journal of Autoimmunity*, (March 2006), Vol.26, No.2, pp. 127-132, ISSN 0896-8411
- Nakanishi, K., Yoshimoto, T., Tsutsui, H. & Okamura, H. (2001). Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. *Cytokine & Growth Factor Reviews*, (March 2001), Vol. 12, No.1, pp. 53-72, ISSN 1359-6101
- Nemni, R., Braghi, S., Natali-Sora, M.G., Lampasona, V., Bonifacio, E., Comi, G. & Canal, N. (1994). Autoantibodies to glutamic acid decarboxylase in palatal myoclonus and epilepsy. *Annals of Neurology*, (October 1994), Vol.36, No.4, pp. 665-667, ISSN 0364-5134
- Nikalji, R. & Bargman, J.M. (2011). Severe hypoglycemia with endogenous hyperinsulinemia in a nondiabetic hemodialysis patient following parathyroidectomy. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association*, (June 2011), Vol. 26, No.6, pp. 2050-2053 ISSN 0931-0509
- Nir, T., Melton, D.A. & Dor, Y. (2007). Recovery from diabetes in mice by beta cell regeneration. *The Journal of Clinical Investigation*, (September 2007), pp. 2553-2556. Vol.117, No.9, ISSN 0021-9738
- Ogasawara, K., Hamerman, J.A., Ehrlich, L.R., Bour-Jordan, H., Santamaria, P., Bluestone, J.A. & Lanier, L.L. (2004). NKG2D blockade prevents autoimmune diabetes in NOD mice. NKG2D blockade prevents autoimmune diabetes in NOD mice. *Immunity*, (June 2004), Vol.20, No.6, pp. 757-767, ISSN 1074-7613
- Palmer, J.P., Asplin, C.M., Clemons, P., Lyen, K., Tatpati, O., Raghu, P.K. & Paquette, T.L. (1983). Insulin antibodies in insulin-dependent diabetics before insulin treatment. *Science (New York, N.Y.)*, (December 1983), Vol.222, No.4630, pp. 1337-1339, ISSN 0036-8075
- Park, H., Li Z., Yang, X.O., Chang, S.H., Nurieva, R., Wang, Y.H., Wang, Y., Hood, L., Zhu, Z., Tian, Q. & Dong, C. (2005). A distinct lineage of CD4 T cells regulates tissue

- inflammation by producing interleukin 17. *Nature Immunology*, (November 2005), Vol.6, No.11, pp. 1133-1141, ISSN 1529-2908
- Patterson, C.C., Dahlquist, G.G., Gyürüs, E., Green, A., Soltész, G. & EURODIAB Study Group. (2009). Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet*, (June 2009), Vol.373, No.9680, pp. 2027-2033, ISSN 0140-6736
- Payton, M.A., Hawkes, C.J. & Christie, M.R. (1995). Relationship of the 37,000- and 40,000-Mr tryptic fragments of islet antigens in insulin-dependent diabetes to the protein tyrosine phosphatase-like molecule IA-2 (ICA512). *The Journal of Clinical Investigation*, (September 1995), Vol.96, No.3, pp. 1506-1511, ISSN 0021-9738
- Peakman, M. & Dayan, C.M. (2001). Antigen-specific immunotherapy for autoimmune disease: fighting fire with fire? *Immunology*, (December 2001), Vol.104, No.4, pp. 361-366, ISSN 0019-2805
- Pearl-Yafe, M., Kaminitz, A., Yolcu, E.S., Yaniv, I., Stein, J. & Askenasy, N. (2007). Pancreatic islets under attack: cellular and molecular effectors. *Current Pharmaceutical Design*, (December 2007), pp. 749-760. Vol.13, No.7, ISSN 1381-6128
- Perez-Bravo, F., Santos, J.L., Carrasco, E., Calvillan, M., Albala, C., Puig-Domingo, M., Piquer, S. & De Leiva, A. (2001). Transmission of high-risk HLA-DQB1 alleles in Chilean type 1 diabetic patients and their parents: stratification by the presence of ICA or GAD65 autoantibodies. *Autoimmunity*, (April 2001), pp. 285-291. Vol.33, No.4, ISSN 0891-6934
- Petersen, J.S., Russel, S., Marshall, M.O., Kofod, H., Buschard, K., Cambon, N., Karlsen, A.E., Boel, E., Hagopian, W.A. & Hejnaes, K.R., et al. (1993). Differential expression of glutamic acid decarboxylase in rat and human islets. *Diabetes*, (March 1993), Vol.42, No.3, pp. 484-495, ISSN 0012-1797
- Peterson, J. & Haskins, K. (1996). Transfer of diabetes in the NOD-scid mouse by CD4 T cell clones. Differential requirement for CD8 T cells. *Diabetes*, (March 1996), Vol.45, No.3, pp. 328-336, ISSN 0012-1797
- Piccirillo, C.A., Tritt, M., Sgouroudis, E., Albanese, A., Pyzik, M. & Hay, V. (2005). Control of type 1 autoimmune diabetes by naturally occurring cd4+cd25+ regulatory T lymphocytes in neonatal NOD mice. *Annals of the New York Academy of Science*, (June 2005), Vol.1051, No.1, pp. 72-87, ISSN 0077-8923
- Piquer, S., Belloni, C., Lampasona, V., Bazzigaluppi, E., Vianello, M., Giometto, B., Bosi, E., Bottazzo, G.F. & Bonifacio, E. (2005). Humoral autoimmune responses to glutamic acid decarboxylase have similar target epitopes and subclass that show titer-dependent disease association. *Clinical Immunology (Orlando, Fla.)*, (October 2005), Vol.117, No.1, pp. 31-35, ISSN 1521-6616
- Pittas, A.G. & Dawson-Hughes, B. (2010). Vitamin D and diabetes. *The Journal of Steroid Biochemistry and Molecular Biology*, (July 2010), Vol.121, No.1-2, pp. 425-429, ISSN 0960-0760
- Pugliese, A., Zeller, M., Fernandez, A.Jr., Zalcberg, L.J., Bartlett, R.J., Ricordi, C., Pietropaolo, M., Eisenbarth, G.S., Bennett, S.T. & Patel, D.D. (1997). The insulin gene transcribed in the human thymus and transcription level correlate with allelic variation at the INS VNTR-IDD3 susceptibility locus for type 1 diabetes. *Nature Genetics*, (March 1997), Vol.15, No.3, pp. 293-297, ISSN 1061-4036

- Rabinovitch, A. (1994). Immunoregulatory and cytokine imbalance in the pathogenesis of IDDM. *Diabetes*, (May 1994), Vol.43, No.5, pp. 613-621, ISSN 0012-1797
- Raz, I., Elias, D., Avron, A., Tamir, M., Metzger, M. & Cohen, I.R. (2001). Beta-cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277): a randomised, double-blind, phase II trial. *Lancet*, (November 2001), Vol.358, No.9295, pp. 1749-1753, ISSN 0140-6736
- Rewers, M. & Gottlieb, P. (2009). Immunotherapy for the prevention and treatment of type 1 diabetes: human trials and a look into the future. *Diabetes Care*, (October 2009), Vol.32, No.10, pp. 1769-1782, ISSN 0149-5992
- Riley, W.J., Maclaren, N.K., Krischer, J., Spillar, R.P., Silverstein, J.H., Schatz, D.A., Schwartz, S., Malone, J., Shah, S. & Vadheim, C., et al. (1990). A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. *The New England Journal of Medicine*, (October 1990), Vol.323, No.17, pp. 1167-1172, ISSN 0028-4793
- Rothe, H., Ito, Y. & Kolb, H. (2001). Disease resistant, NOD related strains reveal checkpoints of immunoregulation in the pancreas. *Journal of Molecular Medicine*, (May 2001), Vol.79, No.4, pp. 190-197, ISSN 0377-046X
- Rozenberg, O., Rosenblat, M., Coleman, R., Shih, D.M. & Aviram, M. (2003). Paraoxonase (PON1) deficiency is associated with increased macrophage oxidative stress: studies in PON1-knockout mice. *Free Radical Biology & Medicine*, (March 2003), Vol.34, No.6, pp. 774-784, ISSN 0891-5849
- Sai, P., Rivereau, A.S., Granier, C., Haertle, T.H. & Martignat, L. (1996). Immunization of non-obese diabetic (NOD) mice with glutamic acid decarboxylase-derived peptide 524-543 reduces cyclophosphamide-accelerated diabetes. *Clinical and Experimental Immunology*, (August 1996), Vol.105, No.2, pp. 330-337, ISSN 0009-9104
- Sainio-Pollanen, S., Liukas, A., Pollanen, P. & Simell, O. (1999). The role of CD8+ cells, cell degeneration, and Fas ligand in insulinitis after intraperitoneal transfer of NOD splenocytes. *Pancreas*, (April 1999), pp. 282-293. Vol.18, No.3, ISSN 0885-3177
- Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M. & Toda, M. (1995). Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *Journal of Immunology (Baltimore, Md.: 1950)*, (August 1995), Vol.155, No.3, pp. 1151-1164, ISSN 0022-1767
- Salomon, B., Rhee, L., Bour-Jordan, H., Hsin, H., Montag, A., Soliven, B., Arcella, J., Girvin, A.M., Padilla, J., Miller, S.D. & Bluestone, J.A. (2001). Development of spontaneous autoimmune peripheral polyneuropathy in B7-2-deficient NOD mice. *The Journal of Experimental Medicine*, (September 2001), Vol.194, No.5, pp. 677-84, ISSN 0022-1007
- Sanjeevi, C.B. (2009). Type 1 diabetes research: Newer approaches and exciting developments. *International Journal of Diabetes in Developing Countries*, (April 2009), pp. 49-51. Vol.29, No.2, ISSN 0973-3930
- Savola, K., Bonifacio, E., Sabbah, E., Kulmala, P., Vahasalo, P., Karjalainen, J., Tuomilehto-Wolf, E., Merilainen, J., Akerblom, H.K. & Knip, M. (1998). IA-2 antibodies--a sensitive marker of IDDM with clinical onset in childhood and adolescence.

- Childhood Diabetes in Finland Study Group. *Diabetologia*, (April 1998), Vol.41, No.4, pp. 424-429, ISSN 0012-186X
- Savola, K. (2000). *Role of IA-2 antibodies in clinical and preclinical type 1 diabetes. Academic Dissertation to be presented with the assent of the Faculty of Medicine, University of Oulu, for public discussion in Auditorium 12 of the University Hospital of Oulu, on June 16th, 2000, at 12 noon. Oulu University Library, ISBN 951-42-5677-8, Oulu: Finland*
- Schatz, D., Krischer, J., Horne, G., Riley, W., Spillar, R., Silverstein, J., Winter, W., Muir, A., Derovanesian, D. & Shah, S., et al. (1994). Islet cell antibodies predict insulin-dependent diabetes in United States school age children as powerfully as in unaffected relatives. *The Journal of Clinical Investigation*, (June 1994), Vol.93, No.6, pp. 2403-2407, ISSN 0021-9738
- Scheen, J. (2004). Pathophysiology of insulin secretion. *Annales d'Endocrinologie*, (February 2004), pp. 29-36 Vol.65, No.1, ISSN 0003-4266
- Schlosser, M., Strebellow, M., Rjasanowski, I., Kerner, W., Wassmuth, R. & Ziegler, M. (2004). Prevalence of diabetes-associated autoantibodies in schoolchildren: the Karlsburg Type 1 Diabetes Risk Study. *Annals of the New York Academy of Science*, (December 2004), Vol.1037, No.1, pp. 114-117, ISSN 0077-8923
- Schmidli, R.S., Colman, P.G., Cui, L., Yu, W.P., Kewming, K., Jankulovski, C., Harrison, L.C., Pallen, C.J. & DeAizpurua, H.J. (1998). Antibodies to the protein tyrosine phosphatases IAR and IA-2 are associated with progression to insulin-dependent diabetes (IDDM) in first-degree relatives at-risk for IDDM. *Autoimmunity*, (January 1998), Vol.28, No.1, pp. 15-23, ISSN 0891-6934
- Schneider, B., Staras, E. & Yalow, R.S. (1976). Some considerations in the preparation of radioiodoinsulin for radioimmunoassay and receptor assay. *Diabetes*, (April 1976), Vol.25, No.4, pp. 260-267, ISSN 0012-1797
- Seyfert-Margolis V, Gisler TD, Asare AL, Wang RS, Dosch HM, Brooks-Worrell B, Eisenbarth GS, Palmer JP, Greenbaum CJ, Gitelman SE, Nepom GT, Bluestone JA, Herold KC. (2006). Analysis of T-cell assays to measure autoimmune responses in subjects with type 1 diabetes: results of a blinded controlled study. *Diabetes*, (September 2006), Vol.55, No.9, pp. 2588-2594, ISSN 0012-1797
- Sharif, S., Arreaza, G.A., Zucker, P. & Delovitch, T.L. (2002). Regulatory natural killer T cells protect against spontaneous and recurrent type 1 diabetes. *Annals of the New York Academy of Sciences*, (April 2002), Vol.958, No.1, pp. 77-88, ISSN 0077-8923
- Shi, B., Wang, Z., Jin, H., Chen, Y.W., Wang, Q. & Qian, Y. (2009). Immunoregulatory *Cordyceps sinensis* increases regulatory T cells to Th17 cell ratio and delays diabetes in NOD mice. *International Immunopharmacology*, (May 2009), pp. 582-586. Vol.9, No.5, ISSN 1567-5769
- Shimada, A., Charlton, B., Taylor-Edwards, C. & Fathman, G. (1996). B-cell destruction may be a late consequence of the autoimmune process in nonobese diabetic mice. *Diabetes*, (August 1996), Vol.45, No.8, pp. 1063-1067, ISSN 0012-1797
- Sia, C. (2005). Imbalance in Th cell polarization and its relevance in type 1 diabetes mellitus. *The Review of Diabetic Studies: RDS*, (Winter 2005), Vol.2, No.4, pp. 182-186, ISSN 1613-6071

- Silveira, P.A., Serreze, D.V. & Grey, S.T. (2007). Invasion of the killer B's in type 1 diabetes. *Frontiers in Bioscience: a Journal and Virtual Library*, (January 2007), pp. 2183-2193. Vol.12, No.1, ISSN 1093-9946
- Silverstein, J., Maclaren, N., Riley, W., Spillar, R., Radjenovic, D. & Johnson, S. (1988). Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. *The New England Journal of Medicine*, (September 1988), Vol.319, No.10, pp. 599-604, ISSN 0028-4793
- Skyler, J.S., Krischer, J.P., Wolfsdorf, J., Cowie, C., Palmer, J.P., Greenbaum, C., Cuthbertson, D., Rafkin-Mervis, L.E., Chase, H.P. & Leschek, E. (2005). Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial--Type 1. *Diabetes Care*, (May 2005), Vol.28, No.5, pp. 1068-76, ISSN 0149-5992
- Sobel, D.O., Goyal, D., Ahvazi, B., Yoon, J.W., Chung, Y.H., Bagg, A. & Harlan, D.M. (1998). Low dose poly I:C prevents diabetes in the diabetes prone BB rat. *Journal of Autoimmunity*, (August 1998), Vol.11, No.4, pp. 343-352, ISSN 0896-8411
- Solimena, M., Folli, F., Aparisi, R., Pozza, G. & De Camilli, P. (1990). Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. *The New England Journal of Medicine*, (May 1990), pp. 1555-1560. Vol.322, No.22, ISSN 0028-4793
- Solimena, M., Folli, F., Denis-Donini, S., Comi, G.C., Pozza, G., De Camilli, P. & Vicari, A.M. (1988). Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. *The New England Journal of Medicine*, (April 1988), Vol.318, No.16, pp. 1012-1020, ISSN 0028-4793
- Sparre, T., Larsen, M.R., Heding, P.E., Karlsen, A.E., Jensen, O.N. & Pociot, F. (2005). Unraveling the pathogenesis of type 1 diabetes with proteomics: present and future directions. *Molecular & Cellular Proteomics: MCP*, (April 2005), Vol.4, No.4, pp. 441-457, ISSN 1535-9476
- Staeva-Vieira T, Peakman M, von Herrath M. (2007). Translational mini-review series on type 1 diabetes: Immune-based therapeutic approaches for type 1 diabetes. *Clinical and Experimental Immunology*, (April 2007), Vol.148, No.1, pp. 17-31, ISSN 0009-9104
- Steinman, R.M. & Banchereau, J. (2007). Taking dendritic cells into medicine. *Nature*, (September 2007), Vol.449, No.7171, pp. 419-426, ISSN 0028-0836
- Steinman, R.M., Hawiger, D. & Nussenzweig, M.C. (2003). Tolerogenic dendritic cells. *Annual Review of Immunology*, (December 2003), pp. 685-711. Vol.21, No., ISSN 0732-0582
- Stenström, G., Gottsäter, A., Bakhtadze, E., Berger, B. & Sundkvist, G. (2005). Latent Autoimmune Diabetes in Adults Definition, Prevalence, β -Cell Function, and Treatment. *Diabetes*, (December 2005), Vol.54, No.Suppl2, pp. S68-S72, ISSN 0012-1797
- Stoffels, K., Overbergh, L., Giulietti, A., Verlinden, L., Bouillon, R. & Mathieu, C. (2006). Immune regulation of 25-hydroxyvitamin-D3-1 α -hydroxylase in human monocytes. *Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research*, (January 2006), pp. 37-47. Vol.21, No.1, ISSN 0884-0431

- Suarez-Pinzon, W.L. & Rabinovitch, A. (2001). Approaches to type 1 diabetes prevention by intervention in cytokine immunoregulatory circuits. *International Journal of Experimental Diabetes Research*, (January 2001), Vol.2, No.1, pp. 3-17, ISSN 1560-4284
- Sutmuller, R.P., den Brok, M.H., Kramer, M., Bennink, E.J., Toonen, L.W., Kullberg, B.J., Joosten, L.A., Akira, S., Netea, M.G. & Adema, G.J. (2006). Toll-like receptor 2 controls expansion and function of regulatory T cells. *The Journal of Clinical Investigation*, (February 2006), Vol.116, No.2, pp. 485-494, ISSN 0021-9738
- Szeszko, J.S., Howson, J.M., Cooper, J.D., Walker, N.M., Twells, R.C., Stevens, H.E., Nutland, S.L. & Todd, J.A. (2006). Analysis of polymorphisms of the interleukin-18 gene in type 1 diabetes and Hardy-Weinberg equilibrium testing. *Diabetes*, (February 2006), Vol.55, No.2, pp. 559-562, ISSN 0012-1797
- Takahashi, K., Tasaka, H. & Hasegawa, Y. (1995). Sensitivity and specificity for detection of islet cell cytoplasmic antibodies using rat pancreatic sections. *Japanese Journal of Clinical Immunology*, (April 1995), Vol.18, No.2, pp. 188-196, ISSN 0911-4300
- Tang, Q., Henriksen, K.J., Bi, M., Finger, E.B., Szot, G., Ye, J., Masteller, E.L., McDevitt, H., Bonyhadi, M. & Bluestone, J.A. (2004). In vitro-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. *The Journal of Experimental Medicine*, (June 2004), Vol.199, No.11, pp. 1455-1465, ISSN 0022-1007
- Tarbell, K.V., Yamazaki, S., Olson, K., Toy, P. & Steinman, R.M. (2004). CD25+ CD4+ T cells, expanded with dendritic cells presenting a single autoantigenic peptide, suppress autoimmune diabetes. *The Journal of Experimental Medicine*, (June 2004), pp. 1467-1477. Vol.199, No.11, ISSN 0022-1007
- Targher, G., Zenari, L., Bertolini, L., Muggeo, M. & Zoppini, G. (2001). Elevated levels of interleukin-6 in young adults with type 1 diabetes without clinical evidence of microvascular and macrovascular complications. *Diabetes Care*, (May 2001), Vol.24, No.5, pp. 956-957, ISSN 0149-5992
- Taylor, A.W., Yee, D.G. & Streilein, J.W. (1998). Suppression of nitric oxide generated by inflammatory macrophages by calcitonin gene-related peptide in aqueous humor. *Investigative Ophthalmology & Visual Science*, (July 1998), pp. Vol.39, No.8, 1372-1378, ISSN 0146-0404
- Thivolet, C. & Carel, J.C. (1996). Screening and prediction of diabetes mellitus in children. *La Revue du Praticien*, (March 1996), Vol.46, No.5, pp. 565-569, ISSN 0035-2640
- Thivolet, C., Nicolino, M., Monbeig, S., Estour, B., Halimi, S., Robert, M., Orgiazzi, J., Chatelain, P. & GRADI study. (2002). Combination of autoantibody markers and risk for development of type 1 diabetes: results from a large french cohort of family members. *Diabetes & metabolism*, (September 2002), Vol.28, No. 4 Pt 1, pp. 279-285, ISSN 1262-3636
- Thorvaldson, L., Johansson, S.E., Hoglund, P. & Sandler, S. (2005). Impact of plastic adhesion in vitro on analysis of Th1 and Th2 cytokines and immune cell distribution from mice with multiple low-dose streptozotocin-induced diabetes. *Journal of Immunological Methods*, (December 2005), pp. 73-81. Vol.307, No.1-2, ISSN 0022-1759
- Thrower, S.L. & Bingley, P.J. (2009). Strategies to prevent type 1 diabetes. *Diabetes, obesity & metabolism*, (October 2009), pp. 931-938. Vol.11, No.10, ISSN 1462-8902

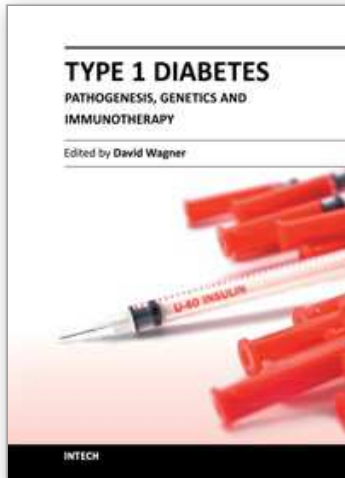
- Timist, J. (1996). Etiopathogenesis of type 1 diabetes mellitus. *La Revue du Praticien*, (March 1996), pp. 560-564. Vol.46, No.5, ISSN 0035-2640
- Toma, A., Haddouk, S., Briand, J.P., Camoin, L., Gahery, H., Connan, F., Dubois-Laforgue, D., Caillat-Zucman, S., Guillet, J.G., Carel, J.C., Muller, S., Choppin, J. & Boitard, C. (2005). Recognition of a subregion of human proinsulin by class I-restricted T cells in type 1 diabetic patients. *Proceedings of the National Academy of Sciences of the United States of America*, (July 2005), Vol.102, No.30, pp. 10581-10586, ISSN 0027-8424
- Trajkovski, M., Mziaut, H., Altkruger, A., Ouwendijk, J., Knoch, K.P., Muller, S. & Solimena, M. (2004). Nuclear translocation of an ICA512 cytosolic fragment couples granule exocytosis and insulin expression in β -cells. *The Journal of Cell Biology*, (December 2004), pp. 1063-1074. Vol.167, No.6, ISSN 0021-9525
- Tree, T.I., Morgenthaler, N.G., Duhindan, N., Hicks, K.E., Madec, A.M., Scherbaum, W.A. & Banga, J.P. (2000). Two amino acids in glutamic acid decarboxylase act in concert for maintenance of conformational determinants recognised by Type I diabetic autoantibodies. *Diabetologia*, (July 2000), pp. 881-889. Vol.43, No.7, ISSN 0012-186X
- Tuomi, T., Groop, L.C., Zimmet, P.Z., Rowley, M.J., Knowles, W. & Mackay, I.R. (1993). Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. *Diabetes*, (February 1993), Vol.42, No.2, pp. 359-362, ISSN 0012-1797
- Vafiadis, P., Bennett, S.T., Todd, J.A., Nadeau, J., Grabs, R., Goodyer, C.G., Wickramasinghe, S., Colle, E. & Polychronakos, C. (1997). Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. *Nature Genetics*, (March 1997), pp. 289-292, Vol.15, No.3, ISSN 1061-4036
- van den Brandt, J., Fischery, H.J., Waltery, L., Hünig, T., Klöting, I. & Reichardt, H.M. (2010). Type 1 diabetes in BioBreeding rats is critically linked to an imbalance between Th17 and regulatory T cells and an altered TCR repertoire. *Journal of Immunology (Baltimore, Md.: 1950)*, (August 2010), Vol.185, No.4, pp. 2285-2294, ISSN 0022-1767
- Vantyghem, M.C., Balavoiney, A.S, Kerr-Contey, J., Pattouy, F. & Noely C. (2009). Who should benefit from diabetes cell therapy? *Annales d'Endocrinologie*, (December 2009), Vol.70, No.6, pp. 443-448, ISSN 0003-4266
- Velloso, L.A., Eizirik, D.L., Karlsson, F.A., Kämpe, O. (1994). Absence of autoantibodies against glutamate decarboxylase (GAD) in the non-obese diabetic (NOD) mouse and low expression of the enzyme in mouse islets. *Clinical and Experimental Immunology*, (April 1994), Vol.96, No.1, pp. 129-137, ISSN 0009-9104
- Verge, C.F, Stenger, D., Bonifacio, E., Colman, P.G., Pilcher, C., Bingley, P.J. & Eisenbarth, G.S. (1998). Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: combinatorial islet autoantibody workshop. *Diabetes*, (December 1998), Vol.47, No.12, pp. 1857-1866, ISSN 0012-1797
- Verge, C.F., Gianani, R., Kawasaki, E., Yu, L., Pietropaolo, M., Jackson, R.A., Chase, H.P. & Eisenbarth, G.S. (1996). Prediction of type I diabetes in first-degree relatives using a

- combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes*, (July 1996), Vol.45, No.7, pp. 926-933, ISSN 0012-1797
- Vija, L., Farge, D., Gautier, J.F., Vexiau, P., Dumitrache, C., Bourgarit, A., Verrecchia, F. & Larghero, J. (2009). Mesenchymal stem cells: Stem cell therapy perspectives for type 1 diabetes. *Diabetes & Metabolism*, (April 2009), Vol.35, No.2, pp. 85-93, ISSN 1262-3636
- von Boehmer, H. (2004). Type 1 diabetes: focus on prevention. *Nature Medicine*, (August 2004), Vol.10, No.8, pp. 783-784, ISSN 1078-8956
- von Herrath, M. (2009). Diabetes: A virus-gene collaboration. *Nature*, (May 2009), Vol.459, No.7246, pp. 518-519, ISSN 0028-0836
- Wahlberg, J., Fredriksson, J., Nikolic, E., Vaarala, O. & Ludvigsson, J. (2005). The ABIS-Study Group. Environmental factors related to the induction of beta-cell autoantibodies in 1-yr-old healthy children. *Pediatric Diabetes*, (December 2005), Vol.6, No.4, pp. 199-205, ISSN 1399-543X
- Wallace, D.J., Hahn, B. & Dubois, E.L. (2007). *Dubois' lupus erythematosus*, Lippincott Williams & Wilkins, ISBN(13) 978-0-7817-9394-0, Philadelphia PA 19106, USA
- Wang, B., Gonzalez, A., Benoist, C. & Mathis, D. (1996). The role of CD8+ T cells in the initiation of insulin-dependent diabetes mellitus. *European Journal of Immunology*, (August 1996), Vol.26, No.8, pp. 1762-1769, ISSN 0014-2980
- Wenzlau, J.M., Frisch, L.M., Gardner, T.J., Sarkar, S., Hutton, J.C. & Davidson, H.W. (2009). Novel antigens in type 1 diabetes: the importance of ZnT8. *Current Diabetes Reports*, (April 2009), Vol.9, No.2, pp.105-112, ISSN 1534-4827
- Wenzlau, J.M., Juhl, K., Yu, L., Moua, O., Sarkar, S.A., Gottlieb, P., Rewers, M., Eisenbarth, G.S., Jensen, J., Davidson, H.W. & Hutton, J.C. (2007). The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. *Proceedings of the National Academy of Sciences of the United States of America*, (October 2007), Vol.104, No.43, pp.17040-17045, ISSN 0027-8424
- Wenzlau, J.M., Moua, O., Sarkar, S.A., Yu, L., Rewers, M., Eisenbarth, G.S., Davidson, H.W. & Hutton, J.C. (2008). Slc30A8 is a major target of humoral autoimmunity in type 1 diabetes and a predictive marker in prediabetes. *Annals of the New York Academy of Sciences*, (December 2008), Vol.1150, No.12, pp. 256-259, ISSN 0077-8923
- Wie, J., Davis, K.M., Wu, H. & Wu, J.Y. (2004). Protein phosphorylation of human brain glutamic acid decarboxylase (GAD)65 and GAD67 and its physiological implications. *Biochemistry*, (May 2004), Vol.43, No.20, pp. 6182-6189, ISSN 0006-2960
- Wild, S., Roglic, G., Green, A., Sicree, R. & King, H. (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, (May 2004), Vol.27, No.5, pp. 1047-1053, ISSN 0149-5992
- Wilkin, T., Palmer J., Kurtz, A., Bonifacio E. & Diaz JL. (1988). The second international workshop on the standardization of insulin autoantibody (IAA) measurement. *Diabetologia*, (July 1988), Vol.31, No.7, pp. 449-450, ISSN 0012-186X
- Wilson, S.B., Kent, S.C., Patton, K.T., Orban, T., Jackson, R.A., Exley, M., Porcelli, S., Schatz, D.A., Atkinson, M.A., Balk, S.P., Strominger, J.L. & Hafler, D.A. (1998). Extreme Th1 bias of invariant Valpha24JalphaQ T cells in type 1 diabetes. *Nature*, (January 1998), Vol.391, No.6663, pp. 177-181, ISSN 0028-0836

- Winnock, F., Christie, M.R., Batstra, M.R., Aanstoot, H.J., Weets, I., Decochez, K., Jopart, P., Nicolaij, D., Gorus, F.K. & Belgian Diabetes Registry. (2001). Autoantibodies to a 38-kDa glycosylated islet cell membrane-associated antigen in (pre)type 1 diabetes: association with IA-2 and islet cell autoantibodies. *Diabetes Care*, (July 2001), Vol.24, No.7, pp. 1181-1186, ISSN 0149-5992
- Yagui, H., Matsumoto, M., Kunimoto, K., Kawaguchi, J., Makino, S. & Harada, M. (1992). Analysis of the roles of CD4+ and CD8+ T cells in autoimmune diabetes of NOD mice using transfer to NOD athymic nude mice. *European Journal of Immunology*, (September 1992), Vol.22, No.9, pp. 2387-2393, ISSN 0014-2980
- Yamada, K., Yuan, X., Inada, C., Hayashi, H., Koyama, K., Ichikawa, F., Eisenbarth, G.S. & Nonaka, K. (1997). Combined measurements of GAD65 and ICA512 antibodies in acute onset and slowly progressive IDDM. *Diabetes Research and Clinical Practice*, (March 1997), Vol.35, No.2-3, pp. 91-98, ISSN 0168-8227
- Yamada, S., Irie, J., Shimada, A., Kodama, K., Morimoto, J., Suzuki, R., Oikawa, Y. & Saruta, T. (2003). Assessment of beta cell mass and oxidative peritoneal exudate cells in murine type 1 diabetes using adoptive transfer system. *Autoimmunity*, (March 2003), Vol.36, No.2, pp. 63-70, ISSN 0891-6934
- Yamamoto, A.M., Deschamps, I., Garchon, H.J., Roussely, H., Moreau, N., Beaurain, G., Robert, J.J. & Bach, J.F. (1998). Young age and HLA markers enhance the risk of progression to type 1 diabetes in antibody-positive siblings of diabetic children. *Journal of Autoimmunity*, (December 1998), Vol.11, No.6, pp. 643-650, ISSN 0896-8411
- Yamazaki, S., Iyoda, T., Tarbell, K., Olson, K., Velinzon, K., Inaba, K. & Steinman, R.M. (2003). Direct expansion of functional CD25+CD4+ regulatory T cells by antigen-processing dendritic cells. *The Journal of Experimental Medicine*, (July 2003), Vol.198, No.2, pp. 235-247, ISSN 0022-1007
- Yang, L., Luo, S., Huang, G., Peng, J., Li, X., Yan, X., Lin, J., Wenzlau, J.M., Davidson, H.W., Hutton, J.C. & Zhou, Z. (2010). The diagnostic value of zinc transporter 8 autoantibody (ZnT8A) for type 1 diabetes in Chinese. *Diabetes/Metabolism Research and Reviews*, (October 2010), Vol.26, No.7, pp.579-584, ISSN 1520-7552
- Yang, W., Hussain, S., Mi, Q.S., Santamaria, P. & Delovitch, T.L. (2004). Perturbed homeostasis of peripheral T cells elicits decreased susceptibility to anti-CD3-induced apoptosis in prediabetic nonobese diabetic mice. *Journal of Immunology (Baltimore, Md.: 1950)*, (October 2004), Vol.173, No.7, pp. 4407-4416, ISSN 0022-1767
- Yoon, J.W. & Jun, H.S. (2005). Autoimmune destruction of pancreatic beta cells. *American Journal of Therapeutics*, (November-December 2005), Vol.12, No.6, pp. 580-591, ISSN 1075-2765
- Yoon, J.W. & Jun, H.S. (2001). Cellular and molecular pathogenic mechanisms of insulin-dependent diabetes mellitus. *Annals of the New York Academy of Sciences*, (April 2001), Vol.928, No.1, pp. 200-211, ISSN 0077-8923
- Zamaklar, M., Jotic, A., Lalic, N., Lalic, K., Rajkovic, N. & Milicic, T. (2002). Relation between course of disease in type 1 diabetes and islet cell antibodies. *Annals of the New York Academy of Sciences*, (April 2002), Vol.958, No.1, pp. 251-253, ISSN 0077-8923

- Zhang, X. & McMurray, D.N. (1998). Suppression of lymphoproliferation by alveolar macrophages in the guinea pig. *Tubercle and Lung Disease: the Official Journal of the International Union against Tuberculosis and Lung Disease*, (January 1998), pp. 119-126. Vol.79, No.2, ISSN 0962-8479
- Zheng, S.G., Wang, J.H., Koss, M.N., Quismorio, Jr.F., Gray, J.D. & Horwitz, D.A. (2004). CD4+ and CD8+ regulatory T cells generated ex vivo with IL-2 and TGF-beta suppress a stimulatory graft-versus-host disease with a lupus-like syndrome. *Journal of Immunology (Baltimore, Md.: 1950)*, (February 2004), Vol.172, No.3, pp. 1531-1539, ISSN 0022-1767
- Ziegler, A.G., Standl, E., Albert, E. & Mehnert, H. (1991). HLA-associated insulin autoantibody formation in newly diagnosed type I diabetic patients. *Diabetes*, (September 1991), Vol.40, No.9, pp. 1146-1149, ISSN 0012-1797
- Ziegler, A.G., Ziegler, R., Vardi, P., Jackson, R.A., Soeldner, J.S., & Eisenbarth, G.S. (1989). Life-table analysis of progression to diabetes of anti-insulin autoantibody-positive relatives of individuals with type I diabetes. *Diabetes*, (October 1989), Vol.38, No.10, pp. 1320-1325, ISSN 0012-1797

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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 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.

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