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## New Progress in Type 1 Diabetes: Hopes for the Future

BY MINNA WOO, MD, FRCPC, PhD

Type 1 diabetes is a chronic, polygenic, autoimmune disease that acts selectively against insulin-producing pancreatic  $\beta$  cells. Despite its chronic nature, little is clinically apparent until the disease reaches the end-stage and the  $\beta$  cells are almost entirely eliminated. Milestones in the fields of immunology and clinical research have advanced our understanding of type 1 diabetes. Since the realization that immune tolerance to  $\beta$  cell antigen is "broken," the mission to find the antigen or antigens that the immune system turns against has become a "holy grail."

Historically, autoantigens – most notably glutamic acid decarboxylase (GAD) and insulin<sup>1,2</sup> – were discovered through their respective autoantibodies. Although the autoantibodies serve as predictive markers of disease to some extent, these antigens are not believed to be directly responsible for disease initiation.<sup>3</sup> T cells are now thought to be largely responsible for disease initiation and progression.<sup>4</sup> Programmed cell death or "apoptosis" has been shown to be the mode of cell death during the destructive phase of diabetes. Recent evidence suggests that  $\beta$  cell death is a consequence of an activated immune system and that it also initiates T cell activation. This issue of *Endocrinology Rounds* discusses a new technology for detecting the presence of antigen-specific T cells in peripheral blood and presents new advances in the scientific and clinical literature that have halted the progression of type 1 diabetes.

Type 1 diabetes is a chronic autoimmune disease in which there is selective destruction of insulin-producing  $\beta$  cells in the islets.<sup>5</sup> Both environmental factors and a genetic predisposition contribute to disease onset. About 40% of type 1 diabetes occurs before the age of 20. The disease varies with geographic location, age, sex, ethnicity, and time period. In some areas of the world, particularly the Scandinavian countries, there has been a sharp rise in the incidence of childhood type 1 diabetes (Figure 1).<sup>6</sup> Overall, the risk of developing type 1 diabetes by age 20 is 1/300. There has been a global rise in the incidence of diabetes by 2.5%-3% per year.<sup>7</sup>

Genetic factors play a significant role in disease incidence.<sup>5</sup> A monozygotic twin of a proband has a 33% chance of developing diabetes. Over 20 susceptibility loci have been identified to date. These gene products interact with critical environmental factors that accelerate or decelerate the disease process. Amongst the many susceptibility genes, the single most dominant gene to account for susceptibility to the disease is the major histocompatibility complex (MHC) class II alleles that encode DQ8 and DQ2.

### Natural history

Type 1 diabetes is thought to occur in 2 distinct phases.<sup>8</sup> First,  $\beta$  cell-specific T cells become activated and infiltrate the islets and second, the activated T cells, in conjunction



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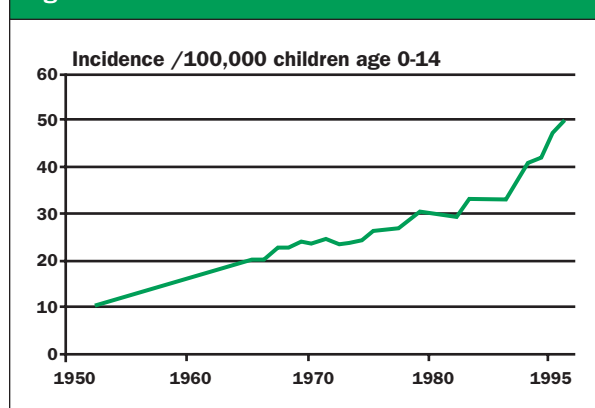
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**Figure 1: Rise in incidence of diabetes in Finland<sup>6</sup>**



with other leukocytes, destroy the islets resulting in clinical diabetes. Experimental models show that type 1 diabetes requires distinct molecular events to progress from one stage to the next.<sup>9</sup> Owing to a prolonged pre-clinical phase and the difficult access to pancreatic tissue in humans, rodent models have been used to study the pathogenesis of diabetes. In particular, non-obese diabetic (NOD) mice have been instrumental in understanding the pathogenesis of type 1 diabetes in humans since they share many susceptibility genes and recapitulate the multigenic and progressive nature of the human disease.<sup>10</sup>

### **Insulinitis: Phase 1**

Initiating events that lead  $\beta$  cell-specific T cells to invade the islets are an area of intense research. During T cell development, most of the self-reactive T cells are eliminated in the thymus, a process known as “negative selection.”<sup>11</sup> However, some escape thymic deletion and migrate to the periphery. Under normal circumstances, these self-reactive T cells (in this case,  $\beta$  cell-specific T cells) are not capable of invading the islets. These T cells must first become “activated” to be capable of islet invasion.<sup>12</sup> When and where do the T cells become activated? Cumulative evidence points to events within the islets that instigate T cell activation. Islets must first “shed” the antigen into the local pancreatic draining lymph node. This is a site where T cells can first come in contact with the corresponding antigen.<sup>8</sup>

How do  $\beta$  cell antigens first get shed? Accumulating evidence reveals that islet cells are dynamic and turnover at a slow rate throughout life.<sup>13</sup> Interestingly, during the neonatal period, there is an enhanced turnover of islet cells, with enhanced physiologic islet death or apoptosis. It is thought that during this period of physiologic islet death, some individuals shed  $\beta$  cell antigen that may encounter  $\beta$  cell-specific T cells. Under particular conditions, likely dictated by the genetic make-up and suscep-

tibility of an individual, the  $\beta$  cell-specific T cells may become activated. Once the T cells are activated, they have the capability to invade the islets.<sup>14,15</sup>

### **$\beta$ cell destruction: Phase 2**

Activated T cells differentiate into highly specialized cells equipped with distinct features. The CD8+ cells, also known as cytotoxic T cells, have the ability to kill  $\beta$  cells by direct contact via special receptors (eg, the *Fas* or tumour necrosis factor [TNF] receptors). On the other hand, CD4+ cells have the ability to secrete soluble mediators known as cytokines (eg, interferon [IFN] $\gamma$ , interleukin [IL]1 $\beta$ , or IL6) that either mediate the direct killing of  $\beta$  cells or provide signals for more leukocytes (eg, more T cells,  $\beta$  cells, monocytes, and macrophages) to migrate into the islets, creating massive local inflammation. CD4+ cells also have the ability to secrete other types of cytokines (eg, IL4 and IL10) that predominantly result in immunosuppression. The cumulative effects of these opposing forces ultimately determine the fate of the islets.<sup>8,10</sup>

### **Disease prediction in the preclinical phase**

Autoantibodies to various  $\beta$  cell antigens are helpful in predicting disease in the relatives of people with type 1 diabetes and in the general population. An initial islet cell antibody (ICA) assay, using immunofluorescence and pancreatic tissue, has been notoriously difficult to standardize and has been replaced by a combination of specific  $\beta$  cell antibodies to insulin (IAA), glutamic acid decarboxylase (GAD), and tyrosine phosphatase ICA512 (IA-2). Recent standardized testing shows median sensitivity to GAD to be 84%, IA-2 58%, and IAA 36%.<sup>16</sup>

People with autoantibodies have been shown to have subclinical signs of  $\beta$  cell failure, including:

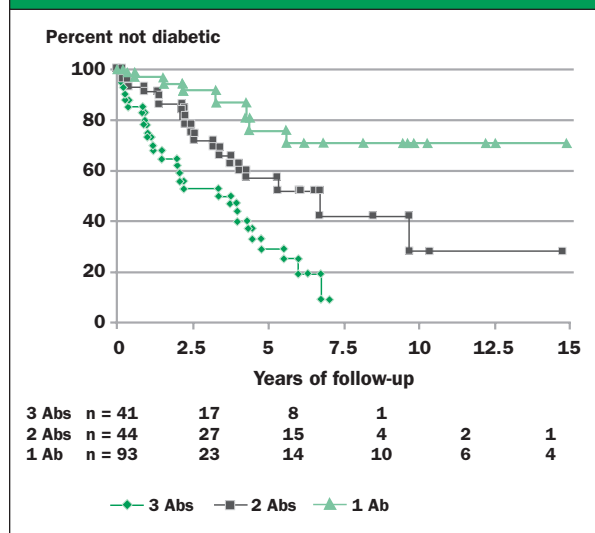
- early loss of pulsatile insulin secretion
- progressive reduction in the acute insulin response to IV glucose load
- decreased response to other  $\beta$  cell secretagogues
- impaired oral glucose tolerance
- fasting hyperglycemia.<sup>17</sup>

Duration of the preclinical stage varies and may precede the diagnosis of type 1 diabetes by up to 13 years.<sup>18,19</sup> Relatives with multiple antibodies and/or low first phase insulin secretion have a  $\leq 50\%$  risk of developing the disease over the next 3-5 years.<sup>20</sup>

### **New clinical tools for diabetes prediction: T cell immunology**

T cells are essential for disease initiation and progression; however, their specific antigenic targets are largely unknown. To date, most autoantigens were discovered

**Figure 2: Progression to diabetes with increasing number of autoantibodies<sup>33</sup>**



abs = autoantibodies

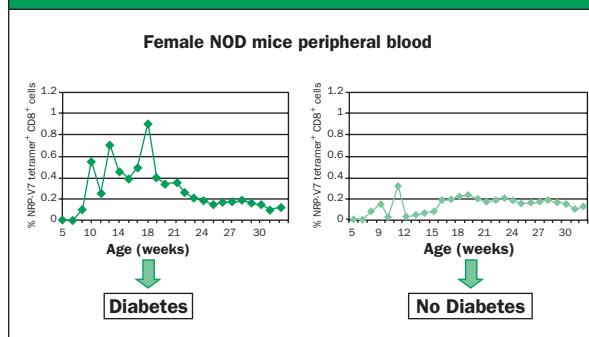
through autoantibodies rather than by T cell recognition. Although islet autoantibodies serve as a marker of disease progression, neither these autoantibodies nor the corresponding islet antigens have been revealed as playing a significant role in disease initiation or progression.

Recently, a naturally-occurring ligand that reacts against a prominent diabetogenic T cell (8.3-like T cells) has been discovered in NOD mice. The ligand is an islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP).<sup>21</sup> Although the physiological role of IGRP is not yet known, finding a naturally-occurring ligand that is specific to  $\beta$  cells is exciting since it enables further insight into the development of clinically useful tools for immunomodulation.

### Potential new tools to predict type 1 diabetes

Despite much evidence supporting the theory that type 1 diabetes is T cell-mediated, prediction of disease has been based primarily on circulating autoantibodies (Figure 2). As expansion of autoreactive T cells relevant for disease progression occurs primarily in the local draining lymph nodes, it is difficult to develop clinical tools to predict disease in a non-invasive manner. Although the peripheral circulation of relevant T cell populations likely occurs, tools for detecting low frequency T cell types have not been widely implemented in a clinical setting. Experimentally, *in vitro* manipulation (eg, artificial expansion of the T cell population) is necessary for detection. Consequently, little is known about the evolution of autoreactive T cell populations during the natural history of type 1 diabetes.

**Figure 3: Measurement of diabetogenic T cells in peripheral blood using tetramers<sup>3</sup>**



### Peptide/MHC tetramers

The advent of peptide/MHC tetramers has revolutionized the ability to detect low quantities of the T cell populations in question. A peptide/MHC tetramer, as the name suggests, is a cluster of 4 molecules consisting of a portion of the MHC molecule and the peptide that is recognized by the T cells. Since T cells bind to a given ligand in a much more efficient manner when the peptide is presented in the context of MHC, the tetramer allows for a much more stable interaction between the T cells and the respective ligand, thereby enhancing the sensitivity of relevant T cell detection. Although this methodology has made detection of T cells against viral antigens feasible, detection of T cells against naturally occurring ligands (eg,  $\beta$  cell autoantigens) that have low avidity to T cell receptors, is still a challenge.

To overcome this limitation, Santamaria's group at University of Calgary has developed a high-avidity peptide/MHC tetramer for a known diabetogenic T cell clone in NOD mice. Using this technology, they were able to determine the temporal relationship between the appearance of autoreactive T cells in the peripheral blood, secondary lymphoid organs, and pancreatic islets, and the development of diabetes (Figure 3).<sup>3</sup> For the first time, this technology has been employed to predict the development of diabetes based on the presence of antigen-specific T cells in the peripheral blood.

Diabetogenic T cells were detected in a sequential manner, first in the islets starting at ~3 weeks, followed by detection in the peripheral blood starting at ~9 weeks of age. Since insulinitis begins at approximately 3 weeks of age,<sup>22</sup> this timeframe suggests that ~6 weeks is required for the activated or primed T cells in the pancreatic lymph nodes to sufficiently expand and become visible in peripheral blood. Importantly, mice destined to become diabetic had a significantly larger population of tetramer reactive T cells in the peripheral blood before diabetes

onset. As well, the population of T cells appeared in distinct cycles before the onset of hyperglycemia, followed by a decline, presumably due to a lack of antigen as a result of  $\beta$  cell destruction.

### Clinical trials for the prevention of type 1 diabetes

The recognition of type 1 diabetes as an immunological disease led to the first controlled trials of interventions using immunosuppressive treatments in subjects already diagnosed with diabetes. To date, most of the immune suppressive agents prevent T cell responses by depletion or inactivation of T cells. For example, glucocorticoids and calcineurin inhibitors (eg, cyclosporine A and FK-506) block cytokine gene transcription, preventing the production of T cell growth factors, whereas other agents (eg, Campath 1H) cause prolonged depletion of T cells.<sup>23,24</sup>

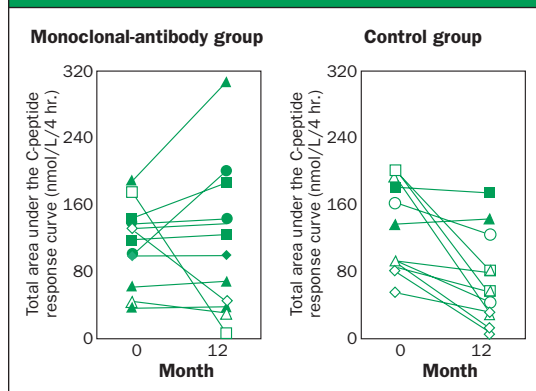
While these approaches were very effective in the short-term, the effects were not antigen-specific and did not persist after the drugs were discontinued. These non-specific drugs delayed disease progression, but were not deemed to be safe. Withdrawal of therapy led to a resumption in disease progression. Nevertheless, these early trials highlighted the importance of immune modulation for changing the course of disease.

Another methodology using nicotinamide has been shown to be potentially protective against  $\beta$  cell toxicities through mechanisms that are not entirely clear. By inhibiting poly (adenosine diphosphate [ADP]-ribose) synthase, it was proposed that nicotinamide acts as a radical scavenger.<sup>25</sup> In addition, it was shown to modulate immunotoxicity by inhibiting macrophage activation.<sup>26</sup> A number of studies have evaluated nicotinamide in new-onset patients.<sup>27</sup> In well-controlled studies, however, there was no effect.<sup>28</sup>

### Monoclonal antibody against CD3 $\epsilon$ : $\beta$ cell preservation post-diabetes onset

Studies in NOD mice initially showed that a modified monoclonal antibody directed at the T cell receptor CD3 molecule was able to halt disease progression when administered at disease onset. This modified monoclonal antibody against CD3 had been altered to prevent binding to the Fc receptor (non-Fc-binding anti CD3 monoclonal antibody). This antibody can be used without the toxic effects (eg, high fevers and hypotension) that are typically associated with T cell activation in vivo.<sup>29</sup>

**Figure 4: Changes in C peptide response in 12 patients to mixed meal tolerance test at 0 and 12 months post hOKT3 monoclonal antibody therapy<sup>30</sup>**



Herold et al reported a first-phase 1/2 trial using the non-activating humanized monoclonal antibody against CD3, called hOKT3 $\gamma$ 1 (Ala-Ala).<sup>30</sup> In this report, the treatment group received a single 14-day course of the monoclonal antibody within 6 weeks of diabetes onset, while controls received no antibody; the groups were followed for one year. Nine of 12 patients in the treatment group maintained or improved insulin production after one year, whereas only 2 of 12 controls had a sustained response (Figure 4). A1C levels and insulin doses were reduced in the monoclonal antibody group. The most common side effects were fever, rash, and anemia; however, there were no severe side effects. The ratio of CD4<sup>+</sup> to CD8<sup>+</sup> cells was changed in the treatment group and this may account for the clinical protection from diabetes progression; however, the mechanisms were not entirely clear.

A follow-up study characterized the immune effects of the monoclonal antibody. It was observed that in the treatment group, T cells secreted more IL10 compared to IFN $\gamma$ .<sup>31</sup> Since some cytokines (eg, IFN $\gamma$  and IL1) produce cytotoxic effects against the target  $\beta$  cells, while other cytokines (eg, IL10 and IL5) give cytoprotection, it was thought that the monoclonal antibody somehow promoted the survival and actions of T cells that secrete the cytoprotective cytokines, rather than the cytotoxic cytokines.

### Conclusions

The discovery of insulin was a lifesaving breakthrough for all patients with type 1 diabetes. Since then, efforts have been made to mimic the physio-

logical mode of delivery, the ultimate being islet replacement with successful islet transplantation. Multicentre trials are ongoing using the Edmonton protocol.<sup>32</sup> We are now seeing early trials in preservation of islets by immunomodulation following onset of disease. A clearer understanding of the mechanisms of disease initiation and progression will one day lead to prevention of disease onset, long before the clinical appearance of diabetes.

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## Abstracts of Interest

### Prediction of spontaneous autoimmune diabetes in NOD mice by quantification of autoreactive T cells in peripheral blood

TRUDEAU JD, KELLY-SMITH C, VERCHERE CB, ET AL.  
VANCOUVER, BRITISH COLUMBIA

Autoimmune (type 1) diabetes mellitus results from the destruction of insulin-producing pancreatic beta cells by T lymphocytes. Prediction of cell-mediated autoimmune diseases by direct detection of autoreactive T cells in peripheral blood has proved elusive, in part because of their low frequency and reduced avidity for peptide MHC ligands. This article was published online in advance of the print edition.

*J Clin Invest* 2003;111(2):217-23

### Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus.

HEROLD KC, HAGOPIAN W, AUGER JA, ET AL.  
NEW YORK, NY

**BACKGROUND:** Type 1 diabetes mellitus is a chronic autoimmune disease caused by the pathogenic action of T lymphocytes on insulin-producing beta cells. Previous clinical studies have shown that continuous immune suppression temporarily slows the loss of insulin production. Preclinical studies suggested that a monoclonal antibody against CD3 could reverse hyperglycemia at presentation and induce tolerance to recurrent disease.

**METHODS:** We studied the effects of a nonactivating humanized monoclonal antibody against CD3--hOKT3 gamma1(Ala-Ala)--on the loss of insulin production in patients with type 1 diabetes mellitus. Within 6 weeks after diagnosis, 24 patients were randomly assigned to receive either a single 14-day course of treatment with the monoclonal antibody or no antibody and were studied during the first year of disease.

**RESULTS:** Treatment with the monoclonal antibody maintained or improved insulin production after one year in 9 of the 12 patients in the treatment group, whereas only 2 of the 12 controls had a sustained response (P=0.01). The treatment effect on insulin responses lasted for at least 12 months after diagnosis. Glycosylated hemoglobin levels and insulin doses were also reduced in the monoclonal-antibody group. No severe side effects occurred, and the most common side effects were fever, rash, and anemia. Clinical responses were associated with a change in the ratio of CD4<sup>+</sup> T cells to CD8<sup>+</sup> T cells 30 and 90 days after treatment.

**CONCLUSIONS:** Treatment with hOKT3gamma1 (Ala-Ala) mitigates the deterioration in insulin production

and improves metabolic control during the first year of type 1 diabetes mellitus in the majority of patients. The mechanism of action of the anti-CD3 monoclonal antibody may involve direct effects on pathogenic T cells, the induction of populations of regulatory cells, or both.

*N Engl J Med* 2002;346(22):1692-8.

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