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Immunotherapies and immune biomarkers in Type 1 diabetes: A partnership for success

Niels V. Rekers [a,b], Matthias G. von Herrath [a], Johnna D. Wesley [a,*]

[a] Type 1 Diabetes R&D Center, Novo Nordisk Inc., Seattle, WA, USA
[b] Pacific Northwest Diabetes Research Institute, Seattle, WA, USA

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ABSTRACT

The standard of care (SoC) for Type 1 diabetes (T1D) today is much the same as it was in the early 1920s, simply with more insulin options—fast-acting, slow-acting, injectable, and inhalable insulins. However, these well-tolerated treatments only manage the symptoms and complications, but do nothing to halt the underlying immune response. There is an unmet need for better treatment options for T1D that address all aspects of the disease. For decades, we have successfully treated T1D in preclinical animal models with immune-modifying therapies that have not demonstrated comparable efficacy in humans. The path to bringing such options to the clinic will depend on the implementation and standard inclusion of biomarkers of immune and therapeutic efficacy in T1D clinical trials, and dictate if we can create a new SoC that treats the underlying autoimmunity as well as the symptoms it causes.

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1. Introduction

Type 1 diabetes (T1D) is a chronic metabolic disorder that results from autoimmune-mediated infiltration and destruction of the pancreatic islets [1]. This disease is characterized by the gradual emergence of pancreas-specific autoantibodies and severe hyperglycemia, and frequently associated with serious health complications [2,3]. It can be diagnosed at any age, regardless of sex, though it is most associated with children and adolescents [4]. Much of our understanding of the immunopathology of T1D has been gained through extensive studies of the non-obese diabetic (NOD) mouse model. The disease that develops in this model occurs spontaneously and is autoimmune-driven [5].

It was long believed that, at diagnosis, patients had lost the majority, if not all, of their β cell function; this was supported by numerous in vivo studies and by the surrogate measurements used to determine function, i.e., stimulated C-peptide and hemoglobin A1c (HbA1c) [1,6]. However, recent work using more sensitive C-peptide measurements has demonstrated that many patients have detectable β cell function at diagnosis and that individuals with long-standing diabetes retain some insulin production capacity [7]. This suggests that β cells may be recoverable and T1D could be reversible, especially if diagnosed early [8]. Additional studies, in large part from the Network of Pancreatic Organ Donors and associated investigators, have elegantly shown the variability in and rarity of detectable immune infiltration and β cell mass at diagnosis and beyond [9,10].

Current approved treatment options are limited to mostly insulin replacement, which is dependent on estimation of insulin need following meals and activities, and on constant monitoring of blood glucose levels [11]. Other emerging therapies hope to improve glucose uptake via improving insulin sensitivity or increasing insulin secretion and decreasing glucagon [12–14]. These treatments focus on improving and/or maintaining glycemic control but do little to dampen the underlying immune response or address the immune defect orchestrating β cell death and dysfunction. Development of immunotherapeutics to cure or prevent T1D represents one of the greatest medical challenges of our era—and the development of tools to understand their impact remains a hurdle to implementation of such therapies in the clinic. T1D represents a significant financial and emotional burden on society [15], and there is an unmet need for better treatment options that address all aspects of the disease. With this review, we provide an overview of the hurdles in developing immunotherapies and bringing them to market, and the role of immune biomarkers as tools for the prediction, progression, and validation of therapeutic responses in T1D.

2. Immunotherapies for T1D: a complicated road to the clinic

Immune modification holds significant therapeutic promise for cancer [16], allergy [17], and autoimmunity [6,18], as well as challenges. Developing immunotherapies for T1D has been difficult in part to

Abbreviations: ELISpot, enzyme-linked immunosorbent spot assay; FDA, Food and Drug Administration; $HbA1_c$, hemoglobin $A1_c$; NOD, non-obese diabetic; pMHC, peptide-MHC; SoC, standard of care; T1D, Type 1 diabetes.

* Corresponding author at: Type 1 Diabetes R&D Center, Novo Nordisk, Inc., 530 Fairview Avenue North, Seattle, WA 98109, USA.
E-mail address: JoWy@NovoNordisk.com (J.D. Wesley).

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traditional response criteria favored by regulatory agencies and the medical community at-large that fails to account for the heterogeneous nature of T1D and differences in immune status between children and adults [9,19]. Additionally, the discordance of efficacy in preclinical models with the reality in human populations, the lack of validated immune biomarkers that facilitate translation from preclinical to clinical [20–22], and the lack of distinction of safety, immune efficacy, and therapeutic efficacy [11,19] have had a negative impact on T1D immunotherapies. Collectively, these developmental road blocks have slowed progression of new treatments to the clinic and often resulted in disappointing clinical trial results.

2.1. Preclinical challenges

Over the last 30 years, numerous NOD studies have investigated the impact of both systemic, non-antigen-specific immune-modulators as well as antigen-specific therapies on the diabetes-associated immune response [5,22]. This preclinical model has been critical to our understanding of autoimmune diabetes yet there are caveats that have complicated translating efficacy into the clinic including differences in β cell replication; islet structure; severity and composition of the immune infiltrate in the islets; and the main T-cell subset involved [21]. In fact, diabetes can be prevented or cured in the NOD, yet we have not seen such successes in human studies [20–22]. Often, the interpretation of efficacy is complicated by the prevalent low-rate of reproducibility associated with published preclinical results. This is, in part, due to the shortage of GMP-sourced compounds for preclinical testing, variability in methods used for analyses, and what is shared in publications. Further, most preclinical studies fail to resemble, in any way, studies conducted in clinical settings. Many animal studies, usually with small numbers of animals per group (<10/group), start treatment before insulitis begins or the day hyperglycemia is confirmed. This is not possible in the clinic as we have little guidance as to when insulitis begins and treatment immediately at diagnosis is complicated, and for immunotherapies, may be too late. Also, often only one sex of mice are treated and all mice in a given cage are given the same treatment rather than randomizing treatments across multiple cages or involving both sexes when possible. Additionally, the lack of immune biomarkers that can move from mouse to man as the compound moves through development only further hinders this translation—this is discussed further in Section 3.

As mentioned earlier, T1D can occur at any age, which further complicates the bench-to-bedside translation of immune-modifying compounds [23,24]. It is entirely reasonable to assume that the disease in the young is immunopathologically distinct from diabetes in adults—these may very well be two distinct diseases. This may significantly change how T1D should be treated and underlie the high failure rate in phase II and III trials.

Although advances in diabetes standard of care (SoC) have dramatically increased glycemic control and improved quality of life, it does not match the precision of β cell-mediate glucose regulation nor completely prevent diabetes-associated complications [25]. However, to replace or even supplement current SoC, which is safe and generally well-tolerated, with an immunotherapy, it must be effective, long-lasting, and have minimal side effects. Currently, there are over 1000 open clinical trials being conducted involving T1D patients listed on Clinicaltrials.gov, many investigating new types of insulin or glucose monitoring technology. A review of the first 150 listed showed that 10% involved an immune-modifier tested in children as young as 4 and adults up to 45 years of age. The promise of immunotherapies for the treatment of T1D has been demonstrated in trials investigating T-cell-targeted or -selective compounds, such as teplizumab, alefacept, and abatacept, though they have failed to meet their trial endpoints or provide sustained benefit that outweighs the potential risk [26–29]. These near-misses support the need for better indicators of response, patient identification, and combination options, and highlight the challenges for moving such therapies to market. This section was not meant to be a comprehensive discussion of the challenges of developing immune-modifying therapies for T1D but to promote on-going discussion among researchers and regulatory bodies.

3. Biomarkers: measures of risk, progression, and response

3.1. Primary disease-specific biomarkers

The standard biomarkers favored by regulatory agencies like the Food and Drug Administration (FDA) and most familiar to investigators are disease-associated, e.g., insulin usage, $HbA1_c$, and C-peptide, and provide little insight to the diabetes-associated immune response [2,30,31]. In the 2008 draft guidance on diabetes trials, the FDA recommended that such trials have a primary endpoint of reduction in $HbA1_c$ or maintenance of C-peptide from baseline [31]. $HbA1_c$ is formed in a non-enzymatic glycation pathway when hemoglobin is exposed to glucose, and serves as a marker for the average blood glucose levels over a 3–4 month period [30]. When the average blood glucose level increases, $HbA1_c$ increases in a predictable way and is a fairly stable clinical marker of metabolic control, with little intra-individual variability. C-peptide is excised from proinsulin to generate biologically active insulin; it is used to assess endogenous insulin secretion either in a fasting or non-fasting sample or in a stimulation test using either intravenous glucagon or a standardized mixed meal tolerance test, with latter being the most accurate [32]. A decline in stimulated C-peptide is indicative of reduced insulin production and progression of diabetes [33]. Notably, C-peptide levels are variable among patients and will be impacted by renal complications. Also, the rate of decline in T1D is heterogeneous, and dependent on age, level at diagnosis, gender, and season [34]. Subsets of people have been shown to have residual C-peptide for years after diagnosis. The rate of decline may be a valuable predictor of therapeutic response, perhaps even aid in identifying patients with recoverable β cell function, and be a valuable stratification measure in a trial setting [35]. While these measures provide clear information regarding clinical outcome, they offer no guidance to the effectiveness of a given immunotherapy, especially when it fails to impact these clinical markers—was it because the compound did not affect the intended pathway or because the pathway does not affect disease? Clinical and disease markers are important tools for measuring and comparing treatment effects in T1D trials; however, their usefulness is limited to assessing improvement of glycemic control. They do not reflect disease onset or changes in the underlying immunopathology, or even, truly, the complexity and heterogeneity of T1D. By the time of diagnosis, the autoimmune process is well-established, perhaps even beginning to wane as antigen availability decreases, and months, or even years, may have passed since the smoldering immune attack began.

3.2. Genetic markers

More than 40 genetic loci have been associated with T1D onset [11,36,37], both protective and predisposing. The most striking associations with T1D, accounting for about 50% of the genetic susceptibility/risk alleles, are located in the human leukocyte antigen (HLA) region [11,38]. HLA-DR and HLA-DQ class II loci regions have the strongest association with T1D onset; the DR3/4-DQ2/8 heterozygous haplotype confers the greatest susceptibility [39,40]. This high-risk haplotype is present in 30–50% of patients with T1D but only in ~2% of the general population. Combined with islet-specific antibodies, the DR3/4-DQ2/8 genotype may identify to subgroups with >75% disease risk [41–43]. Association studies have also uncovered HLA class II genotypes (DRB1*1501 and DQA1*01012-DQB1*0602) that confer dominant protection against T1D [38,43]. In addition to class II, HLA class I loci also influence risk for T1D. Most of the residual association can be attributed to HLA-A (e.g., HLA-A*02, -A*24) and HLA-B (e.g., HLA-B*18,

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