

# Far from replacing insulin in type 1 diabetes

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## Editorial

The incidence of type 1 diabetes in the pediatric population has been increasing steadily over the past three decades and is projected to increase further over the next decade.<sup>1,2</sup> To date, no cure has been identified to prevent or postpone the onset, halt the further progression, or reverse the course of the disease.<sup>3</sup> Since its introduction in 1922, insulin-replacement therapy has become the life-saving first-line therapy for patients diagnosed with type 1 diabetes. The introduction of insulin therapy changed significantly both patient survival rates and life expectancy. In the pre-insulin era, more than 50% of patients died within the first two years of diagnosis and fewer than 10% survived for more than five years. Today, intensive insulin therapy and tight glycemic control have become the standard of care in type 1 diabetes. Despite therapy, however, acute and chronic diabetes complications persist, resulting in premature mortality and reduced life expectancy, especially for those diagnosed in childhood.<sup>4,5</sup> Thus, the development of disease-modifying therapies and cures for patients with recent-onset (newly diagnosed) as well as established type 1 diabetes remains a major unmet medical need.<sup>3</sup>

Type 1 diabetes has been described as an autoimmune disease characterized by T cell-mediated destruction of pancreatic  $\beta$ -cells, resulting in insulin deficiency and hyperglycemia. Immunologic and metabolic changes arise in the patient long before clinical onset and diagnosis of the disease. Thus, most strategies towards finding a cure or developing disease-modifying therapies have evolved around immune-based approaches aimed at halting or reversing the further destruction of  $\beta$ -cells in patients with recent-onset type 1 diabetes. The expectation was that by inducing immune tolerance or by modulating the autoimmune, secondary immune or inflammatory responses the disease course could be altered or even reversed. In contrast, non-immune-based treatment strategies are rare in number. They are mostly aimed at stabilizing or restoring functional  $\beta$ -cell mass by enhancing  $\beta$ -cell proliferation or neogenesis.

Most of our knowledge and basic understanding of type 1 diabetes pathogenesis is based on findings in rodent models. Accordingly, data generated in rodents have provided the primary rationale for most clinical trials of immune-based and non-immune-based treatment strategies. Many of the novel therapies investigated in animal models demonstrated beneficial effects, some halting or even reversing the course of the disease. Most sobering, however, none of the strategies shown to be efficacious in animal models translated into meaningful clinical benefits in patients with recent-onset type 1 diabetes.

To date, all clinical phase IIB and phase III trials aimed at modulating the immune system in recent-onset type 1 diabetes patients have failed to meet their clinical endpoints.<sup>6-10</sup> None of these trials provided evidence that any of the treatment regimens tested were able to preserve functional  $\beta$ -cell mass or halt further progression of the disease course. Similarly, a number of phase II trials involving recent-onset type 1 diabetes patients showed no effect or did not meet their respective primary clinical endpoints.<sup>11,12</sup> While some studies have demonstrated no effect on disease progression in newly diagnosed

patients, a small number of therapies have transiently delayed the decline of functional  $\beta$ -cell mass.

Similarly, investigations into altering the type 1 diabetes disease course by means of non-immune based strategies failed to restore pancreatic  $\beta$ -cell function. A recent multicentre, randomized, placebo-controlled, phase II trial attempted to stabilize or increase functional  $\beta$ -cell mass in newly diagnosed type 1 diabetes patients by enhancing  $\beta$ -cell proliferation and neogenesis.<sup>13</sup> This combination therapy trial did not meet any of its clinical endpoints nor was there any treatment effect noted neither on restoring pancreatic  $\beta$ -cell function nor on altering further progression towards disease.

Based on the recent results of a significant number of failed phase II/III trials in recent-onset type 1 diabetes patients,<sup>6-13</sup> it seems time to pause and reassess the unsuccessful strategies. It must be recognized that in spite of years of preclinical studies unraveling the disease-underlying molecular mechanisms of type 1 diabetes in animals, we still fail to have a good grasp on how, when and where to interfere with the immune system to alter the natural history of the disease in humans. Similarly, we still do not know nearly enough about the molecular mechanisms and factors involved in stimulating meaningful  $\beta$ -cell proliferation and neogenesis in healthy tissues and under disease conditions in humans. Equally important, ample data clearly demonstrates that the preclinical animal models used to test potential, novel therapies in type 1 diabetes, do not appear to be the best predictors of clinical success, benefits and outcomes in humans. Taken together, it thus seems prudent that moving forward human data generation in pilot studies should always precede resource-intensive, well-powered, randomized, double-blind, placebo-controlled, phase II/III trials.<sup>14</sup> Even in a small number of patients, clinically relevant and meaningful benefits of therapies will be recognized. Only once we know that a specific therapy has promise in humans is the design and execution of costly and resource-intensive Phase II/III trials justified.

In conclusion, to date, the two major strategies of immune-based and non-immune-based therapies have not delivered any clinically relevant results towards delivering a cure for type 1 diabetes. Patients and their families are left with the sobering message that in spite of major efforts and investments into basic research and clinical trials, we are still not closer to a cure. Insulin, discovered almost 100 years ago, remains the most significant breakthrough in type 1 diabetes research. While no cure, insulin will hold its place as a life-saving first-line replacement therapy for years to come.

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## Conflicts of interest

The authors declare there is no conflict of interests.

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