

 NONINSULIN THERAPIES FOR T1DM

## A crossroads for diabetes care?

This issue of *Nature Reviews Endocrinology* focuses on novel therapies for type 1 diabetes mellitus (T1DM) that are in development. These therapies are diverse in nature and range from stem-cell transplantation to replenish pancreatic islets to the modulation of key components of the immune system. However, given that a relatively cheap drug with a proven track record is already available to treat individuals with T1DM, why should alternative options be pursued?

Insulin was first used therapeutically in 1922. Considered one of the milestones of twentieth century medicine, daily administration of exogenous insulin has become the mainstay of the clinical management of T1DM. Nonetheless, the therapeutic use of insulin has a number of drawbacks. These limitations include the route of administration; the need to individualize dosage, timing and the type of insulin used to account for daily fluctuations in blood glucose levels in response to food intake or exercise; the potential for overdosing or underdosing; the nonphysiologic nature of bolus administration; and the variability in absorption rates into the blood stream. Furthermore, many patients with T1DM simply find insulin therapy inconvenient or difficult to follow; frustrations with the insulin regimen and fear of needles can lead to poor treatment compliance.

Efforts have been made to address at least some of these problems. For example, the introduction of long-acting insulin analogs and continuous glucose monitoring devices has markedly improved diabetes care. Much of the research has focused on the development of alternative delivery systems: insulin pumps and 'pens' are already widely used by patients with T1DM. Noninvasive delivery systems have also been investigated. Pharmaceutical companies invested considerable resources in developing inhaled preparations of insulin. Unfortunately, however, the efficacy, safety and ease of use of these products failed to live up to the hype during the postmarketing period, and the major pharmaceutical companies have now abandoned their inhaled insulin research and development programs.

Given the chronic nature of T1DM and the problems experienced by patients in managing their disease, it

seems that a major paradigm shift from management of the symptoms to tackling the root causes of this condition could be required. One option is to consider prevention rather than cure. The incidence of autoimmune disease, including T1DM, reported in the developed world is on the rise. One school of thought is that this increase is directly related to improved hygiene: reduced exposure to environmental microbes during the first few years of life might impair development of the immune system. Administration of microbial components or probiotics could, therefore, prevent T1DM by promoting a healthy immune response. Another hypothesis is that T1DM might arise following enteroviral infection. If this is indeed the case, a vaccine could potentially halt the development of T1DM.

An alternative strategy is to work towards a cure. For example, insulin secretory function could be restored by replacing the damaged pancreas with a healthy donor organ. The first successful whole pancreas transplant was performed at the University of Minnesota in 1966. Although this procedure is effective and has since gained wide acceptance, very few whole pancreas transplants are performed each year. Demand quite simply outstrips supply. A similar problem exists for transplants of isolated pancreatic islets. Over the past decade, however, increased understanding of the pathogenesis of T1DM—at both the molecular and cellular level—has fuelled research into cell-based and gene therapy approaches. Furthermore, drugs that modulate the immune response, such as anakinra and rituximab, are now being tested in patients with T1DM.

It is still too early to say whether we are on the cusp of a new era in diabetes care. Clearly, several key issues—efficacy, safety and cost—must be resolved before noninsulin therapies are ready to be incorporated into routine clinical practice. Nevertheless, the sheer volume of research published in this field over the past few years suggests that new therapeutic options for T1DM will be available soon. Patients and clinicians alike should prepare for the ride.

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**Competing interests**  
The author declares no competing interests.