Gene Therapy for Type 1 Diabetes Moves a Step Closer to Reality

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The prevalence of diabetes mellitus (DM) is assuming pandemic proportions and is currently estimated at 285 million cases (1). Although most cases are due to obesity-associated type 2 DM, there is also an increase in the annual prevalence of type 1 DM (2). It is estimated that 10% of the diabetic population have type 1 DM. Both forms of DM are associated with a long-term risk of microvascular and macrovascular complications (3) and the immediate risk of hypoglycemia.

There is abundant evidence that attainment of near normoglycemia will reduce the risk of complications associated with DM (4). However, attainment of near normoglycemia in patients with type 1 DM is limited by the occurrence of hypoglycemia. Patients with hypoglycemic unawareness are particularly prone to this problem as a limiting factor for achieving the required glycemic control. DM clinics globally have many patients with type 1 DM in whom recurrent hypoglycemia and the phenomenon of hypoglycemic unawareness present major clinical problems. Fortunately, there are many promising and exciting advances on the horizon for patients with this problem, including gene therapy as reported in this issue of *Diabetes* by Bosch and colleagues (5).

In the current study, the authors use an adeno-associated viral (AAV) vector to overexpress the genes for insulin and glucokinase in skeletal muscle in a canine model of DM. The study addresses the question of whether this gene therapy approach will result in long-term benefits in terms of attainment of near normoglycemia and avoidance of hypoglycemia. The approach was successful on both fronts. The authors demonstrate for the first time in a large animal model that this gene therapy approach has a beneficial therapeutic effect for up to 4 years. This is a major advance in the field of gene therapy for DM. Although gene therapy has promised much, progress has been slow largely because of issues with vector-related shortcomings. In this article, the authors use an AAV vector that results in long-lived transgene expression. Indeed, as the authors point out, AAV-mediated transgene expression has been detected 10 years after intramuscular delivery in humans (6). The use of AAV is certainly appropriate given the safety profile and the ability to obtain long-term gene expression (7). This vector has also had successful application in humans in other conditions requiring skeletal muscle expression such as hemophilia (8). In addition, success has been reported with this vector in clinical studies of Leber congenital amaurosis (9). Interestingly, the combination of insulin and glucokinase was necessary to have the beneficial effect while either gene alone was ineffective. The absence of hypoglycemia over 4 years is a particularly gratifying outcome.

The authors' strategy in this article to engineer skeletal muscle is intriguing. Glucokinase was chosen because of its high K_m for glucose and lack of inhibition by glucose-6-phosphate. Of key importance is the fact that glucokinase only stimulates glucose uptake by skeletal muscle when glucose levels are high, thus providing protection against hypoglycemia. However, as the GLUT 4 transporter is reduced in the absence of insulin, low level expression of basal insulin is also necessary. Thus, overexpression of two genes is required, which will certainly increase the complexity of the regulatory process to translate this therapy. This may be a substantial barrier to ultimate clinical application in humans and will need to be considered in the context of competing technologies. In terms of translational progress however, the work by this group progressing from murine to canine models paves the way for a clinical trial for the treatment of type 1 DM in veterinary practice. Another safety issue which will need consideration is the risk of hypoglycemia resulting from basal expression of insulin, which is required for GLUT 4 transporter expression in the cell membrane. While the current study did not demonstrate any hypoglycemic episodes this will need careful monitoring in future studies as the long lived expression of insulin will not be reversible.

Although the results reported in this study are of major significance in progressing the translational research agenda for gene therapy and DM, it should be borne in mind that there are other approaches to develop innovative therapies for type 1 DM (Fig. 1). While limitation of donor organs is a barrier to islet cell transplantation (10), xenotransplantation strategies are under development (11). β-Cell replacement strategies using embryonic stem cells, induced pluripotent stem cells, and adult stem cells hold promise (12,13). There are a number of recent publications suggesting that adult mesenchymal stem cells may have a glucose-lowering effect and therapeutic potential in the treatment of type 1 DM (14). Recent immunotherapy trials have not reported success, but the approach still holds promise (15). Finally, development of medical device technology holds great promise, and the use of continuous glucose monitoring, continuous subcutaneous insulin infusion, sensor-augmented pump therapy, and low glucose suspend technology are already resulting in improvements in clinical care for patients with type 1 DM (16–19). A recent article in this journal on a fully integrated artificial pancreas in type 1 DM demonstrates

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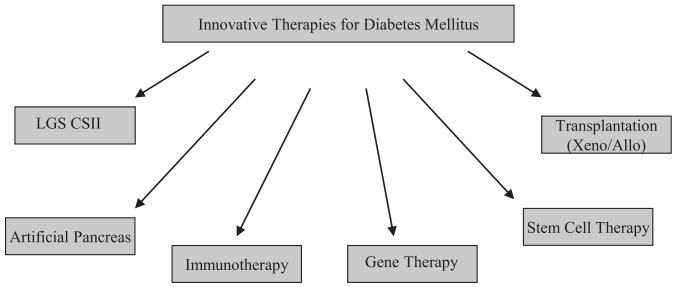

FIG. 1. Innovative therapies for DM. CSII, continuous subcutaneous insulin infusion; LGS, low glucose suspend.

progress toward the development of a closed-loop system for the attainment of near normoglycemia (20). Thus as any new technology, such as gene therapy, is developed competing technologies should be considered, and ultimately the optimal approach to enhance patient care will be discovered.

Overall, the report by Bosch and colleagues is a substantial advance in the attempts to develop clinical gene therapy for type 1 DM. However, though there are substantial challenges on this translational pathway, they are worthy of pursuit given the ultimate prize if the approach is successful. The next step may involve a clinical trial in companion dogs, but ultimately human translation to a phase 1 dose escalation study will require toxicology studies performed under good laboratory practice conditions and further determination of optimal dose of both vectors. If safety is demonstrated, phase 2 and 3 studies will be required, which will demand considerable resources and cost. Although this study paves the way for a veterinary study, the pathway for human translation is still tortuous and over time will be evaluated in the context of competing technologies.

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