Review



# Emerging Gene Therapy Strategies for Type 1 Diabetes: A Review of Potential Treatments

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# Emerging Gene Therapy Strategies for Type 1 Diabetes: A Review of Potential Treatments

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**Abstract:** Several studies have shown promising treatments for type 1 diabetes mellitus (T1DM) using developing gene therapy methods. This review article focuses on summarizing possible new treatment options and outlining their pros and cons, since there is no cure for T1DM as of yet. New treatments involve islet and stem cell transplantation, genetic vaccination, and immunological precursor cell-mediated therapy. Since most of these methods are still in their early stages, efficacy in human trials of this type of treatment is still largely unknown, however, researchers are hopeful after numerous successes in trials with non-obese diabetic (NOD) mice.

**Keywords:**

## Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by the immune-regulated destruction of the insulin-producing beta cells in the pancreas (Chellappan et al., 2018). The body's immune system, specifically helper T-cells, perceives the pancreatic beta cells as harmful foreign bodies and therefore mistakenly attacks and destroys them. The lessening number of beta cells result in a lower amount of insulin production, thus negatively affecting the breakdown and absorption of blood sugar, leading to hyperglycemia, or high glucose levels in the bloodstream. This can lead to symptoms such as extreme thirst and urination, feeling hungry and having an increased appetite but still losing weight, chronic tiredness, blurry vision, or tingling sensations in feet (Dhaliwal et al., *Type 1 diabetes* 2024). If left unmanaged, diabetic ketoacidosis can occur, where the body starts rapidly breaking down fat for energy, which can be life-threatening (Dhaliwal et al., *Diabetic Ketoacidosis* 2024). From 2002 to 2018, the number of new T1DM cases in the youth have increased by over 2%, signifying a concerning trend (Centers for Disease Control and Prevention, 2024).

## Possible Solutions

There is no cure for T1DM at present. Therefore, patients with this condition must manage their insulin levels through insulin therapy, the administration of insulin injections and/or use of insulin pumps, in order to minimize symptoms and prevent fatal complications of hyperglycemia (Subramanian et al., 2021). However, there are new technologies being developed that aim to provide a more permanent treatment for T1DM, including pancreatic islet cell transplantation, artificial pancreas systems that automatically adjust and deliver insulin based on blood sugar levels, and gene therapy solutions; the latter of which is the primary focus of this review.

## Gene Therapy

Gene therapy is a groundbreaking therapeutic approach to treat disease and hinder its progression or prevent its onset in the first place. Recent developments in gene therapy mechanics

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and procedures have shown promising signs for breakthrough treatments of previously untreatable conditions (Chellappan et al., 2018). Gene therapy involves introducing a new gene into the body which replaces faulty genes with functional ones or inactivate defective genes that are responsible for causing disease. There are two broad categorizations of gene therapy, somatic cell therapy, which targets genes in diseased cells; and gametic cell therapy, where disease- causing genes are prevented from being passed onto offspring (Chellappan et al., 2018).

While there are some environmental factors that may increase risk for developing T1DM, several genes have been identified that are believed to be responsible for the onset of the disease, manipulating which could help slow or even stop the progression of the disease and/or prevent its initial onset before symptoms arise (Chellappan et al., 2018). Since genes cannot be altered by surgical means, several gene therapy methods are in the development process. However, the studies that are being conducted at the moment rely on animal models to test the impact of a selection of genes, and their possible mutations, on the progression of T1DM. Furthermore, this new method involves the challenges of using viral vectors, which can cause an unwanted negative immune response and worsen the condition of the disease. Therefore, there is not yet concrete evidence of effectiveness and safety of this new development when used in humans.

**Gene Therapy Using Stem Cells**

Gene therapy and genetic engineering have also been experimented with as a method of differentiating stem cells into pancreatic cells. Lentivirus, a viral vector, was used to deliver PDX-1, a gene involved in pancreatic development and beta cell function, into stem cells. These cells began to cluster and aggregate, showing signs of pancreatic differentiation, and can be further developed into insulin-producing beta-cells. Genes inserted into stem cells or other tissues is a new developing way to treat T1DM. The transplantation of bone marrow-derived cells carrying a specific gene has inhibited the progression of autoimmune diseases through the use of regulatory T-cells. This process also decreased insulin antibody levels and blood glucose levels, indicating less autoimmune response. The transplantation of stem cells with genes capable of synthesizing insulin could be more effective in treating T1DM than transplanting islet cells directly, since the stem cell method prevents the likely negative autoimmune response caused by organ transplantation.

**Gene and Protein Overexpression**

While not a gene therapy method, islet transplantation was an initial T1DM treatment proposal. However, this process presents several issues. Immunosuppressive agents need to be constantly used, and even then, there's a chance of the transplanted tissue being rejected. There is also only a limited supply of pancreatic islets from donors.

The underexpression of several genes have been shown to lead to T1DM occurrence. Insulin-like growth factor 1 (IGF1) is a mitogenic agent that regulates immunity and factors that are needed for insulin-producing beta-cell growth and development. An underexpression of IGF1 creates an unsuitable environment for insulin production, thus leading to T1DM. In gene therapy trials on non-obese diabetic (NOD) mice, the genetic sequence coding for IGF1 was transferred into the pancreas, in order to overexpress the hormone. After 28 weeks, 80% of the mice displayed normal blood glucose levels, showing a positive sign that IGF1 gene expression can decrease the progression of T1DM. Similarly, the overexpression of other genes, such as Reg3g, G6Pase, and HGF, and proteins, such as Ngn3, AAT, and betacellulin, through gene therapy methods have been shown to help return inhibited or malfunctioning beta-cells to their normal, insulin-producing state in NOD mice (Xia et al., 2015).

**Genetic Vaccination**

Genetic vaccination is another potential therapeutic and preventive approach against T1DM, where plasmid DNA, viral vector-based vaccines, or antisense oligonucleotides are introduced into a host to suppress or induce a host immune response. This allows for flexibility in controlling a T-cell

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response. New proteins can form when a gene of interest is bioengineered into a diseased host system, which may allow for the disease-causing gene to be deleted. Plasmid DNA is the most well-studied method and has shown the most promising results in the prevention and reversal of T1DM in NOD mice. Of the two methods of pDNA administration, the gene gun method has proven to be more successful than the intramuscular method, significantly delaying the onset of T1DM in the mice (Chellappan et al., 2018). Researchers are now also looking to improve the efficacy of this method, by exploring combination therapies that incorporate the use of genetic vaccination. Overall, this method shows promising signs for its potential as a future treatment or prevention method for T1DM in humans, after showing success in mice models.

**Immunological Precursor Cell-Mediated Gene Therapy**

Since T1DM is an autoimmune disorder primarily caused by some T-lymphocytes attacking pancreatic islet cells, there are multiple possible immunological interventions that could be used to develop immunotherapy treatments for T1DM. The ultimate goal of this type of treatment for T1DM is to prevent or stop the breakdown of insulin-producing beta-cells, through the methods of immunoregulatory, anti-inflammatory, and gene modification therapy. While generally a promising field of treatment development, insulin immunotherapy may not be useful in treating T1DM since the insulin antigens are released before the insulin reaches the target site of action.

**Conclusion**

Since T1DM is a global health issue without no cure as of yet, developing gene therapy based treatments provide a hopeful future for the large number of patients who suffer from it. The primary target for any current T1DM management strategy and future treatment possibilities is to reduce elevated blood glucose levels to a value near the normal level, in a safe, efficient, and relatively simple way. This review summarized the ways in which gene therapy can be used to overexpress certain genes and proteins that impact the development and progression of T1DM.

Transplanting stem cells and other cells expressing different genes have slowly shown signs of becoming a potential approach to treating T1DM. Furthermore, genetic vaccination techniques, such as pDNA vaccination and viral-vector based vaccination, also have shown positive outcomes in the prevention or reversal of T1DM, especially since it provides a flexible way to control the strength of a T-cell response. In terms of research that could provide valuable information in the future, the development, efficacy, and safety of non-viral vectors is something that should be studied. Genetic engineering is a promising field, and has the possibility of leading to many more future therapies for T1DM

| Therapy Method | Advantages | Disadvantages |
|---|---|---|
| Gene and Protein Overexpression | - Overexpressing the genes (and encoded proteins) that when underexpressed lead to T1DM can help stop the progression of or even fully prevent | - Not a method in itself; rather a strategy that can be used in conjunction with other methods that deal with inserting the target gene into the correct location efficiently |
| Islet Cell Transplantation | - One of the first treatments for T1DM<br>- humans have access to this treatment | - Requires prolonged dependency on immunosuppressive agents<br>- Chance of grafted cells/tissue being rejected<br>- Short supply of, yet high demand for islet cells |

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|---|---|---|
| Stem Cell Based Gene Therapy | - Led to decreased levels of glucose in blood and lowered count of insulin antibodies<br>- dendritic cells from bone marrow can express various antigens and have the ability to delay disease progression | - Sensitivity of transplanted stem cells have to be regulated to prevent surplus of insulin, which would lead to hypoglycemia |
| Genetic Vaccination | - Plasmid DNA vaccinations are the best studied method, and indicate signs of being able to prevent T1DM in mice<br>- shows promise when used in combination with other treatments, such as antibody therapy | - Intramuscular administration of pDNA didn't work to prevent the progression of T1DM<br>- No tests in humans yet, although it shows potential as both a prevention mechanism and a treatment in the future |
| Immunological Precursor Cell Based Therapy | - Indicates signs of preventing the autoimmune destruction of islets that express antigens by stopping memory T-cells from activating antigen-specific responses<br>- Could reduce dependency on insulin for many patients | - still a relatively new study<br>- Method has not been extensively tested<br>- No tests in humans yet, although it shows potential as both a prevention mechanism and a treatment in the future |

**Figure 1.** Summary of Developing T1DM Treatments Involving Gene Therapy.

**Author Note:** We have no known conflict of interest to disclose.

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