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Gene therapy and type 1 diabetes

Key points:

- Gene therapy has successfully treated several genetic diseases providing life changing improvements to patients.
- Gene therapy to remove or reduce insulin supplementation in type 1 diabetes has been under investigation for two decades.
- Progress has not advanced beyond pre-clinical (laboratory and mouse) studies in techniques focussing on direct gene or transcription factor insertion.
- Several alternatives including immunotherapy and islet cell transplantation hold promise.

Type 1 diabetes (T1D) is a complex autoimmune disease which destroys beta-cells within the islets of the pancreas and causes insufficient or complete failure of insulin production. This causes high blood sugar – hyperglycaemia – which has a range of acute and chronic side effects including extreme thirst, weight loss, fatigue and, in the long-term, cardiovascular disease, kidney failure and blindness. The beta-cell destruction process is complicated and thought to be an interaction between genetics, lifestyle, and the environment. Almost 100 disease susceptibility genes have been identified along with associations with viral infections, vitamin D intake and climatic conditions as potential causes of T1D.

The discovery of insulin 100 years ago changed the diagnosis of T1D from a death sentence to a treatable condition. Insulin supplementation is the main treatment for T1D. However, insulin is costly, accurate blood sugar management is difficult, and insulin shortages can be life threatening. The current prevalence of T1D is increasing annually even in populations where T1D incidence is low. For example, T1D cases in the Chinese population are expected to increase by more than 1.5-fold over the next 10 years. With the prevalence of T1D expected to reach 13.5-17.4 million globally by 2040, cures are being sought including islet transplantation, stem cell treatments, novel insulin management systems and gene therapy.

Gene therapy describes treatments which alter or manipulate an individual's genetic code including:

- insertion of full, healthy copies of genes to replace pathogenic ones
- silencing of pathogenic genes
- introducing edited genes into cells to aid in treatment and prevention of disease

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Various forms of gene therapy including CRISPR genome editing, whole gene insertion and expression modification using antisense oligonucleotides are being investigated in many diseases including cancer, cystic fibrosis, heart disease and autoimmune disorders such as T1D.

In the case of gene therapy for T1D the goal is to reduce or remove the requirement for insulin supplementation and it has been under investigation for several decades. Progress to date has been slow and the treatment remains in pre-clinical (*in vitro* and mice models) research stages. Current techniques cover a small number of research areas including prevention of the autoimmune attack and correction of hyperglycaemia; however, the most research attention and relative success has been in the conversion of non-beta-cells to beta-like cells. This technique aims to manipulate certain cells to develop glucose responsiveness and management capabilities. This is generally achieved by overexpression of specific transcription factors or genes which can reprogram non-beta-cells, usually pancreatic alpha-cells, into insulin expressing beta-like cells. Delivery of these transcription factors has caused insulin expression in cells in the laboratory and reversal of diabetic symptoms in mouse models[1]. There is currently no unified conversion technique and the volume of studies in this area suggests that more work is required to clarify which techniques are most effective.

Barriers to the progression of gene therapy in T1D

Gene therapy in T1D has not yet progressed beyond pre-clinical animal model stages and there are several barriers that may be contributing to this. There are differences in what people class as a 'cure' for T1D. In some cases this is the complete removal of insulin supplementation. For others a significant reduction in insulin requirements is deemed sufficient. In either context the effect length of gene therapy is particularly important and needs to be a long-term solution. However, in many studies normal sugar levels last from days to months and in mice the autoimmune response often causes reversion to hyperglycaemia.

The use of early interventions in primary preventive initiatives is complicated as the 'at risk' population is heterogenous and pre-diabetes can also present very early in life leaving a small window of detection for preventive interventions.

Due to the success of insulin therapy, there is a high threshold for a novel treatment to be successful. Insulin is convenient, provides rapid blood glucose management and is the main treatment option for almost all T1D patients. Alternative therapies need to achieve comparable clinical utility, safety, and cost-to-benefit ratio.

It is important not to oversimplify this complex disease as successful induction of insulin expression is only part of the puzzle. Target cells require functioning storage and regulatory mechanisms for appropriate insulin release and blood glucose management and T1D has multiple associated risk genes which cannot yet be targeted by standard gene therapy approaches. There is also considerable debate about the reliability of animal models to mimic the complex physiology of T1D.

Universal gene therapy issues

Gene therapy is not a new concept and the advances in genomic technologies have driven progress in many areas however few treatments have reached point of care use. There are extensive considerations which are not limited to T1D:

- **Side effects**

The biggest concern with gene therapies discussed here are life-threatening autoimmune responses to the viral delivery vectors. Certain vectors also prompt neutralising antibody responses, which prevent re-administration of the same type of viral vector.

- **Timelines**

Despite being a rapidly developing field there are gaps in the understanding of long-term safety and efficacy of gene therapies. The follow up for gene therapy associated trials can be up to 15 years for vectors with integrative capabilities, that is, vectors that integrate genetic material into the genomes of target cells.

- **Cost**

The cost to design, develop and market these advanced treatments can be extremely high, which limits their utility and capacity to progress to the patient population. In 2023 the first gene therapy product for use outside a clinical trial in the UK to treat metachromatic leukodystrophy, a lysosomal storage disease, was priced at £2.8 million, making it the most expensive drug in the world at the time.

Alternative treatments

Despite intensive research interest for the past two to three decades, gene therapy for T1D has encountered significant barriers that have prevented progress, and many commercial companies have moved on to other diseases or approaches. There have been notable successes in alternative treatments that centre around replacing the destroyed islets and then protecting replacement islets with *in vitro* developed cells rather than trying to induce change in vivo.

Islet cell transplantation

Islet cell transplantation is subject to considerable research and commercial activity. Healthy islet cells are transplanted to a T1D patient, although the islets are very fragile therefore a high cell volume from 2-3 donors is required. Islet transplantation for T1D has been available in the United Kingdom through the NHS since 2008. However, due to the scarcity of donor pancreata and the required cell volume it is only available for individuals with extreme difficulties in managing blood glucose using insulin. The FDA has recently approved Lantidra (donislecel, CellTrans) the first donor-derived pancreatic islet cell therapy for US patients in this demographic. This therapy does not provide freedom from insulin injections and immunosuppression is required to protect the foreign islet cells. The scarcity of donor organs is a major limitation of this technique, although advances in stem cell therapies are close to resolving this problem.

Stem cell treatments

Stem cell treatments using embryonic (ESC), induced pluripotent (iPSC) and adult stem cells which can differentiate into pancreatic beta-cells are being investigated. This is because they can continually produce the required cell type *in vitro*, circumventing the issue of limited supplies of allogenic pancreata for islet cell transplants.

In conjunction with King's College Hospital, UK, Vertex Pharmaceuticals is currently performing a Phase I/II clinical trial for VX-880, an allogenic, stem cell derived, fully

differentiated, insulin producing islet cell therapy. The trial is showing positive early results[2]. In 2024 islet tissue differentiated from human endoderm stem cells removed the requirement for insulin therapy in a patient with chronically uncontrolled type 2 diabetes. The researchers, based in Shanghai, China, are looking ahead to expand trials to include T1D patients[3]. Autologous transplant of chemically induced pluripotent stem-cell-derived islets (CiPSC) beneath the abdominal anterior rectus has recently resulted in a 25-year-old female producing her own insulin less than three months after the operation. Researchers chemically induced iPSCs to generate 3D clusters of isolates which after 75 days post transplantation enabled the patient to achieve sustained insulin independence[4].

Genome editing

Genome editing approaches are now being used as an important adjunct in cell-based treatments for T1D rather than in efforts to modify the patient's cells in situ. While stem cell therapy holds great promise in T1D treatments, a major drawback is the requirement for immunosuppressants to prevent the body from attacking and destroying the transplanted cells. Genome editing techniques are now being developed to 'disguise' the cells from the immune system to increase their survival and remove the need for a cocktail of immunosuppressive drugs.

In 2021 ViaCyte and CRISPR Technologies developed and began clinical trials of VCTX210 stem cell product with genetic edits designed to reduce its immunogenicity and essentially hide the cells from the immune system[5]. Only specific details regarding the edits have been released so the full suite of modifications is not clear. ViaCyte and CRISPR Technologies have since parted ways on this project, however, ViaCyte claims that VCTX210, now known as VCTX211, will continue to be developed. Similarly, Sana Biotechnology have made three edits to iPSCs that they plan to differentiate into beta-like cells[6]. The focus is on disrupting expression of molecules that identify a cell as foreign. They are also working to overexpress CD47, which is seen as the 'do not eat me' signal molecule that protects cells from the immune response.

As an alternative to cloaking cells from the immune system researchers are also investigating ways to control the immune system's response to foreign cells[7]. Overexpression of a key protein, A20, which is involved in inflammation and autoimmune disorders, was found to display 'thermostat' like behaviour in that it could be used to 'turn up or turn down' the immune response. A viral delivery system was developed to transport the gene that makes A20 into donor islet cells. Pre-clinical testing has been successful and 80-100% survival of donor islet cells grafted into mouse models was seen. Patient recruitment for clinical trials began for this technique in mid-2024.

Immunotherapy

Immunotherapy is being used to try to prevent the initial autoimmune attack. In 2022 the FDA approved the first disease modifying treatment for T1D, Tzield (teplizumab, Sanofi). It has been in development for nearly three decades, targets the pre-symptomatic stage to inhibit beta-cell destruction. Tzield is currently available only to high-risk individuals with stage 2 T1D. In clinical trials it delayed the onset of symptomatic stage 3 T1D by an average of three years. Despite delaying rather than preventing T1D the additional time free of disease reduces the healthcare burden for the person and the impact of long-term side effects.

Conclusion

Gene therapy to remove or reduce daily insulin therapy for T1D has been an attractive prospect for several decades. Despite continued pre-clinical research progress has stalled due to several barriers and the complex pathophysiology of T1D may turn out to be refractory to direct gene therapy approaches. At this stage the cost of developing and providing gene therapy compared to the significant potential demand is prohibitive. Various other therapies are now progressing further including immunotherapy, islet cell transplantation and genome editing.

As genomic medicine advances, future insights might make gene therapy for T1D a more realistic prospect, especially in cases of the rarer monogenic forms of diabetes. But for now, cell-based therapies, particularly genome edited iPSCs, appear to offer significant potential and this area of research is advancing steadily in commercial, academic and clinical practice.

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