

gene therapy

GENE THERAPY FOR GD TYPE I

Massaro G, Waddington SN,
Rahim AA
University College London

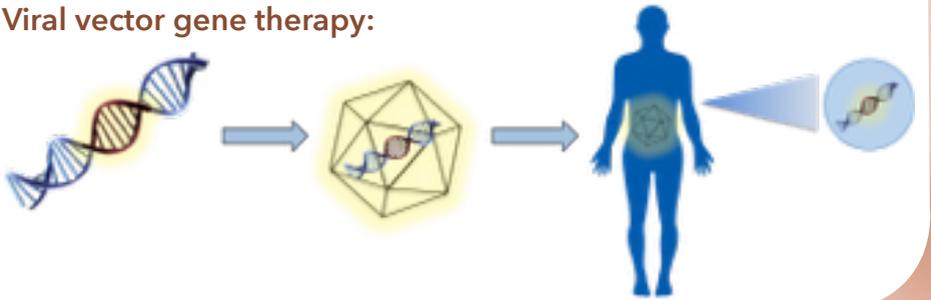


What is gene therapy?

Gene therapy can be defined as the introduction of genetic material to cells of patients for therapeutic benefit. In simple terms, it involves providing a healthy functional copy of a gene to the patient's cells to compensate for a defective copy that causes the disease. Ideally this treatment would only need to be administered once in the lifetime of the patient. Even though the concept underlying gene therapy is straightforward, delivering genes into cells of a living organism is a very challenging process.

Therefore, an essential component of gene therapy studies is the development of vectors that can efficiently deliver genetic material into cells.

Viral vector gene therapy:



How does it work?

The most recent and successful gene therapy clinical trials are based on viral vectors. This is because over millions of years, viruses have evolved clever and intricate mechanisms by which to efficiently enter our cells. For the purpose of gene therapy, these viruses have been heavily modified, eliminating the elements that cause illness and creating a gene delivery tool that is safe to use in animal studies and human clinical trials. Adeno-associated virus (AAV) is an excellent candidate as a gene delivery vector.

In recent years, significant advances in AAV engineering have been achieved, resulting in the production of efficient and safe vectors. Genetically modified AAVs are non-pathogenic, can reach a whole range of different cell types and can be easily administered throughout the body.

Gene therapy for GD type 1

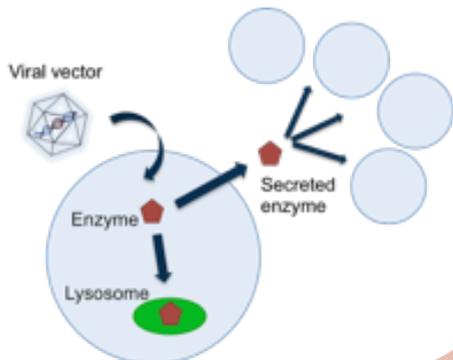
GD type I is caused by a defective copy of a gene called GBA1 and patients present a wide range of symptoms with severe complications in different organs. Developing a unified therapy for several distinctive body systems can be challenging, since each organ and tissue has unique structure and function. Although enzyme replacement therapy has revolutionized the treatment of type I GD, it has a number of drawbacks. This includes the need for repeated and regular infusions for the duration of the patient's life, which is both difficult and expensive and may fail to treat tissues such as the bones.

Gene therapy has the potential to offer an alternative treatment strategy that could overcome these issues through a single administration. We are testing this in a mouse model of Gaucher disease using an AAV that carries a therapeutic copy of the GBA1 gene which is injected directly into the bloodstream. The vector is spread via the blood circulation throughout the body reaching most affected organs - a systemic approach for a systemic disease.

Furthermore, according to the so-called 'cross correction' mechanism, once the virus has penetrated the cells, therapeutic glucosylceramidase protein is produced by the therapeutic GBA1 gene and secreted, so that surrounding cells can benefit from the uptake of this enzyme. This process could increase the efficiency of the treatment, targeting the lysosomes of many defective cells.

Further research is needed to identify the optimal viral vector for the successful treatment of GD type I and safety. The ideal vector should be able to enter different cell types to deliver the gene, efficiently, to organs of the body.

Cross correction mechanism:



Future challenges in gene therapy clinical research

Gene therapy is a relatively new technology, and long-term data from clinical trials in human patients are not available yet. Even though studies have reported life-saving or life-changing benefits of the treatment a few years after the administration of the vector, scientists are not able to predict if the therapy persists for the entire life of the patient.

Most people have been exposed to the natural occurring virus from which the vector is engineered and therefore have developed antibodies against it. Researchers have found different strategies to overcome this problem, but the immune response might still remain an obstacle.

Today the initial cost of gene therapy is one of the principal limitations, as the manufacturing costs are high. However, from an economic perspective, gene therapy is less costly than a lifetime of enzyme replacement therapy. Besides, as with all new technologies, further developments in research will ultimately decrease the cost of developing novel treatments.

