Gene therapy

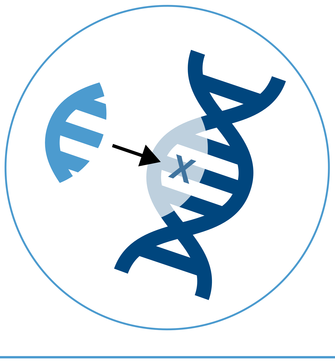
Please take note that gene therapy is not currently approved for the treatment of Gaucher disease

What is gene therapy?

The principle of gene therapy is correcting the genetic basis of a disease through the replacement of a distorted gene with a healthy one (exogenous DNA), in order to express the required protein that is otherwise missing or defective.[1,2]

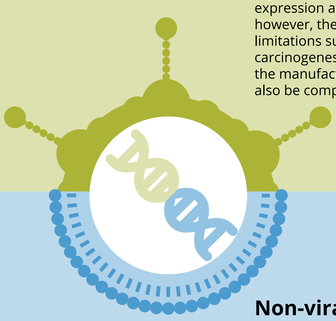
For gene therapy to be successful, it must ensure efficient and safe delivery of exogenous DNA into cells.[3] Ideally, the gene delivery vehicle should avoid immediate uptake by the mononuclear phagocyte system and have prolonged circulation in the blood, in order to increase the probability of reaching the desired target.[3]

During the long journey to the cell nucleus, it is necessary to use a gene delivery system that protects the transgene from extracellular and intracellular degradation, allowing it to pass through the plasma membrane to the nucleus.[4,5]



How is exogenous DNA delivered?

There are two main types of gene delivery vehicle[2]:



Viral vectors

Viral vectors, such as adenovirus and retrovirus, have a reputation of very high efficiency (long-term stable gene expression at therapeutic levels); however, they have significant limitations such as mutagenesis, carcinogenesis and immune response[6]; the manufacturing of viral vectors can also be complex and resource-intensive.[7]

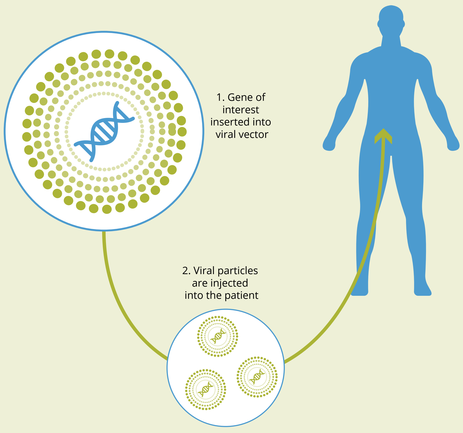
Non-viral vectors

Non-viral vectors are less efficient in delivering genes; however, they are considered to be safe and stable, biocompatible and less immunogenic, and can be custom-synthesised for targeting with a high gene capacity as there is no known limitation in the size of the DNA, making them easily scalable for large-scale production.[1,3]

What is the difference between *in vivo* and *ex vivo* gene therapy?

In vivo gene therapy involves transducing the target cells inside the patient's body, whereas *ex vivo* gene therapy involves transducing the target cells outside the patient's body.[2,8] This means that *in vivo* gene therapy potentially involves a single injection for the patient, while *ex vivo* gene therapy involves taking haematopoietic stem cells from the patient's body, transducing them, and then returning them back to the patient.[2,9]

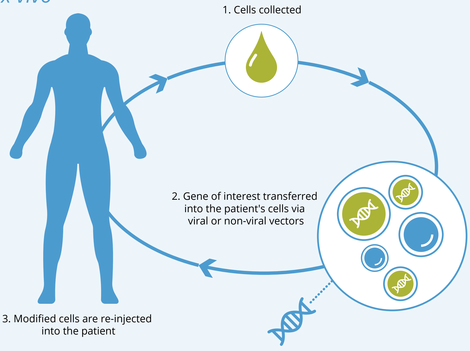
In vivo



The vectors used during *in vivo* gene therapy include:

- Adenovirus vectors[10]
- Adeno-associated viral vectors.[9]

Ex vivo



One of the advantages of *ex vivo* gene therapy is being able to sample the transduced cells before administering them to the patient, which facilitates efficacy and safety checks.[8]

The vectors used during *ex vivo* gene therapy include:

- Retroviral vectors[2,11]
- Lentiviral vectors[2,11]
- Gammaretroviral vectors.[2]

Why is gene therapy being studied in Gaucher disease?

Current treatments do not address all aspects of the disease. Opportunities remain to alleviate neurological problems associated with the disease by overcoming the blood–brain barrier to target the central nervous system.[12]

What are the pros of gene therapy for Gaucher disease and what are the potential challenges?

Pros:

- Monogenic diseases (controlled by a single gene) are the ideal target for gene therapy.[2,13,14]
  - In Gaucher disease, mutations in the *GBA1* gene lead to defective or absent glucocerebrosidase leading to a build-up of the substrate in the lysosome.[15]
  - Gene therapy for Gaucher disease could target the genome to endogenously restore glucocerebrosidase activity.[16]
- Liver-directed gene therapy can produce robust amounts of lysosomal enzymes systemically.[11]
  - The liver serves as a good target for non-neuronopathic Gaucher disease; transduced liver cells might function as a 'metabolic factory' to produce glucocerebrosidase.[12]
- Like most lysosomal storage diseases, Gaucher disease is typically well characterised, with an already identified gene and developed animal models allowing for preclinical testing.[2]

Challenges:

- The delivery of the vector to the cell can be difficult in itself due to the length of the journey and need for avoidance of extracellular and intracellular degradation.[4]
- Furthermore, Gaucher disease affects multiple organs,[17] which makes targeted gene therapy a challenge.
- There may be an unwanted immune system reaction directed against viral vectors administered *in vivo*, due to detection of foreign antigens.[18]
  - A high rate of the population already has antibodies to the vectors in use, meaning it may be ineffective.[18]
- Viral integration into the host genome with the use of viral vectors has been reported in studies of murine models, which raises concerns of mutagenesis leading to possible tumour formation.[19]

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