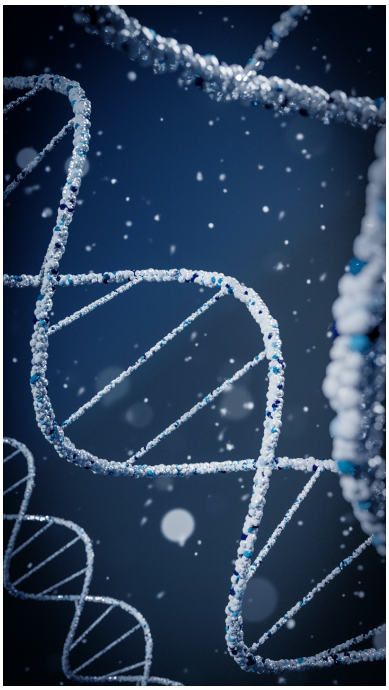
POMPE Connections

Guide to Cell and Gene Therapies



Gene therapy is revolutionising medicine for people with life-threatening, rare conditions, offering the potential for longer, healthier lives. In some cases, a single one-time treatment can provide a lifetime of benefits. These therapies should provide huge benefits for patients, for their families and for broader society.

Gene therapy is the collective name of therapies, in which the genetic material of a patient is repaired or restructured for therapeutic effect.

The concept of gene therapy is to fix a genetic problem at its source. If, for instance, in an (usually recessively) inherited disease a mutation in a certain gene results in the production of a dysfunctional protein, gene therapy could be used to deliver a copy of this gene that does not contain the deleterious mutation, and thereby produces a functional protein. This strategy is referred to as gene replacement therapy.

Gene therapies are still under investigation for Pompe disease, although the development processes are becoming well understood through licenced therapies for other diseases. Research and clinical trials are extremely important, and highly valuable, to ensure the safety and efficacy of these therapies over the long term. It is likely to take several years to develop a successful gene therapy for Pompe disease that may or may not meet the current expectations.

Gene therapy is classified into two types

Somatic Cell Gene Therapy

In somatic cell gene therapy (SCGT), the therapeutic genes affect the individual patient only, and are not inherited by offspring. Somatic gene therapy represents mainstream basic and clinical research, in which therapeutic DNA is used to treat disease.
Such single gene disorders, such as Pompe Disease, are good candidates for somatic cell therapy.

Germline

In germline gene therapy (GGT), germ cells (sperm, egg and fertilised egg cells) are modified by the introduction of functional genes into their genomes. Modifying a germ cell causes all the organism's cells to contain the modified gene. The change is therefore heritable and passed on to later generations. Many countries prohibit GGT for application in human beings for technical and ethical reasons, and because there is insufficient knowledge about possible risks to future generations and higher risks versus SCGT.

Gene therapies for Pompe disease

There are currently three different SCGT strategies being explored for Pompe disease:

1. Adeno-associated Virus (AAV)

To replicate, viruses introduce their genetic material into the host cell, tricking the host's cellular machinery into using it as blueprints for viral proteins. Scientists exploit this by substituting a virus's genetic material with therapeutic genetic material.

In AAV based therapy the envelope of the adeno associated virus (AAV) is used. This is a harmless virus. The AAV vector has had its disease-causing genes removed so that it is no longer effective, and the gene of interest added. There are different AAV subtypes, which are indicated by a number. For example, subtype AAV5 or AAV8 target the liver and subtype AAV1 targets muscle cells.

The vector/gene construct is hardly integrated within the human genome (within the chromosomes which carry the DNA) but persists as an extra chromosomal entity. This has consequences because when a cell divides, the AAV construct is not duplicated like all other DNA. Therefore, the AAV will be diluted over time, as cells divide (e.g. blood stem cells).

For Pompe disease the therapy will usually be designed to target the liver or muscle cells. The brain is protected from infection by a membrane known as the Blood-Brain Barrier (BBB) so these types of AAV gene therapies are not expected to correct diseased cells in the brain or the central Nervous System (CNS). There are other AAV vectors that can target the brain, but these are not currently being considered for Pompe disease.

AAV gene therapies will generally be administered as a single, one-off, intravenous (IV) infusion although it is likely that health systems will insist on regular monitoring for many years after the infusion.

The two types of AAV gene therapies include:

Liver Targeted

These therapies provide therapeutic DNA to the liver to continuously produce a healthy copy of the enzyme deficient in Pompe disease (Alpha Glucosidase or GAA). This healthy enzyme is then delivered to cells in the body (except the nervous system), especially muscle cells, similar to a continuous infusion of Enzyme Replacement Therapy (ERT).

Muscle Targeted

These therapies provide therapeutic DNA directly to the muscle cells (fibres) to override the genetic fault in the muscle DNA. The treated muscle cells should then be able to produce the enzyme GAA to restore normal muscle function and halt disease progression.

Advantages of AAV gene therapies

- Deliver gene in relatively easy way
- Hardly integrated into host DNA
- Chances of tumorigenesis are small
- Independent of patient's GAA mutation

Disadvantages of AAV gene therapies

- Immune response to AAV vector will be developed such that it is not possible to repeat the treatment
- Not all patients will be eligible due to preexisting antibodies
- Therapy will lose efficacy over time.
- Liver toxicity can occur at high viral doses
- In children AAV will be diluted by child's growth over time.
- Cannot treat classic infantile patients via the liver before age of ~4 years due to growth and dilution of the therapy
- Difficult to reach the brain.

2. Lentiviral gene therapy

Lentiviral gene therapy is a technique that takes the patient's own stem cells from their bone marrow, modifies them outside of the body (ex-vivo) in a sterile environment, and then replaces the modified cells back into the body. As the technique involves the permanent modification of stem cells, it has the potential to provide a life-long therapy following a single intervention. It also provides therapeutic effect in the CNS. A recent example is provided by the EMA approval of lentiviral gene therapy to treat the CNS in MLD, a disorder that is related to Pompe disease.

The treatment process has several steps that may take a few weeks to complete:

1. Prepare the body so that bone-marrow stem cells are released into the blood stream.
2. Remove blood from the patient to collect sufficient bone marrow stem cells.
3. Modify the collected stem cells in a sterile facility by inserting a lentiviral vector containing the therapeutic gene.
4. Prepare the bone marrow using a preconditioning agent such as busulfan.
5. Give an intravenous (IV) infusion of the modified bone marrow stem cells
6. Bone marrow becomes a living factory for the therapeutic protein by supplying a continous source of ERT in the blood.
7. Bone marrow derived cells pass the blood brain barrier and secrete the therapeutic protein in the CNS.

Advantages of Lentiviral gene therapies

- Single intervention for lifelong treatment
- Can also treat the CNS
- Independent of GAA mutation
- Has demonstrated safety in multiple clinical trials for other diseases and has recently been approved for MLD

- Should be suitable for classic infantile patients irrespective of age
- No exclusion of patients based on anti-viral antibodies

Disadvantages of Lentiviral gene therapies

- Integrates into the DNA of bone marrow stem cells: low dosage used to minimize risk of DNA damage.
- Preconditioning agents are invasive and require careful dosing to avoid side-effects. The procedure is part of standard bone marrow transplantation regimes which, to date, are clinical procedures applied world-wide, and which are very safe.

3. AntiSense OligoNucleotide (ASO or AON)

Antisense oligonucleotides are able to influence RNA processing and modulate protein expression. This type of therapy can be applied for example for GAA mutations that affect RNA processsing. In late onset patients from European descent, ~90% of all patients carry the same c.-32-13T>G (IVS1) GAA mutation that affects RNA processing. AONs have been generated that can correct RNA processing in cells from IVS1 patients, as well as for patients with other, more rare mutations.

Box 1: RNA is the transcript that is made from DNA and from which protein is produced. RNA, like protein, is short lived and needs to be made on demand to produce protein. RNA does not alter the DNA, it is merely a copy of it. After use, it is degraded. AONs that modulate (correct) RNA therefore also need to be given on a regular basis. AONs are chemically modified to enhance their stability; once taken up by cells, they are much more stable compared to proteins. It is therefore expected that when applied in the clinic, AONs need regular infusions that are less frequent compared to ERT.

Advantages of therapeutic Antisense Oligonucleotides for Pompe disease

- Restore normal GAA protein production
- Different mechanism from ERT and so could be beneficial for patients that do not respond well to ERT
- Combination with ERT may be possible
- Relevant for most patients with late onset Pompe disease from european descent as these carry the IVS1 mutation that can be corrected with AONs

Disadvantages of therapeutic Antisense Oligonucleotides for Pompe disease

- Lifelong administration – *not* a one-off treatment
- Side effects unknown at this time
- Not suitable for classical infantile-onset Pompe patients
- Mutation specific: only patients with a particular mutation

Immune Response to Gene Therapies

As with other therapies, such as Enzyme Replacement Therapy (ERT), an antibody response to gene therapies may be experienced. With mild cases these may be managed with common drugs until the symptoms subside, but some people may develop neutralising antibodies to the therapy which prevents the active ingredient working as it should.

Research is underway to understand the antibody response for new therapies and measures are likely to be developed to prevent or remove antibodies during the treatment. These will add to the complexity of the gene therapy protocols, but should only be required during the treatment, so for most people, only once in their lifetime.

One example of a treatment to manage antibodies is plasmapheresis, or Therapeutic Plasma Exchange (TPE). That is a blood transfusion process where the patient's blood is drawn from a vein, the plasma containing the antibodies is replaced with filtered or unaffected plasma, and then the blood replaced. An example of this process is available here:
https://www.verywellhealth.com/plasma-exchange-ms-treatment-2440905

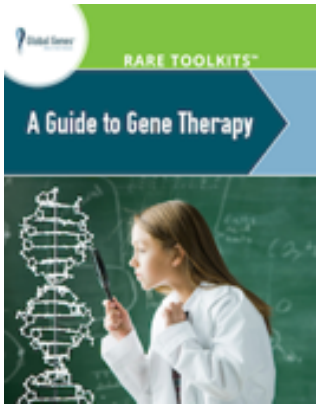
Further reading on cell and gene therapies

There are a growing number of resources online to learn more about cell and gene therapies. The national Pompe organization, your specialist can provide you with information and you can find more info on websites such as:

1. Science of gene therapy brochure – you can download this brochure from https://sparktx.com/scientific-platform-programs/about-gene-therapy/

2. This video from ASGCT:
www.asgct.org/education/pompe-disease

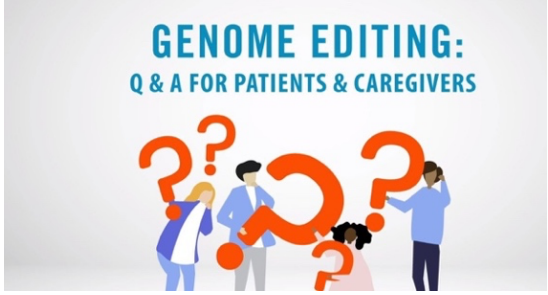
3. The Global Genes toolkit focused on gene therapy
https://globalgenes.org/wp-content/uploads/2018/11/Guide-to-Gene-Therapy_Toolkit_spread_DIGITAL-1.pdf



Gene Therapy: Your Questions Answered

Video presented in a Q&A format, presented by National Organization for Rare Disorders (NORD).

The newest addition to the NORD Rare Disease Video Library is a set of four videos on genome editing.



Information about clinical trials

There are several research groups investigating gene therapy for Pompe disease, each at different stages. Some of these potential therapies have already been tested in clinical trials while others are in the preclinical stage and are being tested in animals.

Information about research studies recruiting pompe patients can be found on international and national websites, for example:

- www.ClinicalTrials.gov
- www.clinicaltrialsregister.eu

and on the IPA website www.worldpompe.org.

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