Gene therapy: an overview

This article is designed to explain what gene therapy is and how it may be a potential treatment for monogenic lysosomal disorders, such as Fabry disease, Gaucher disease, Pompe disease, cystinosis, and Hunter syndrome. Look out for other articles, including: "**A closer look at lentiviral gene therapy**", "**Taking part in a gene therapy clinical trial**" and "**Gene therapy and me**".

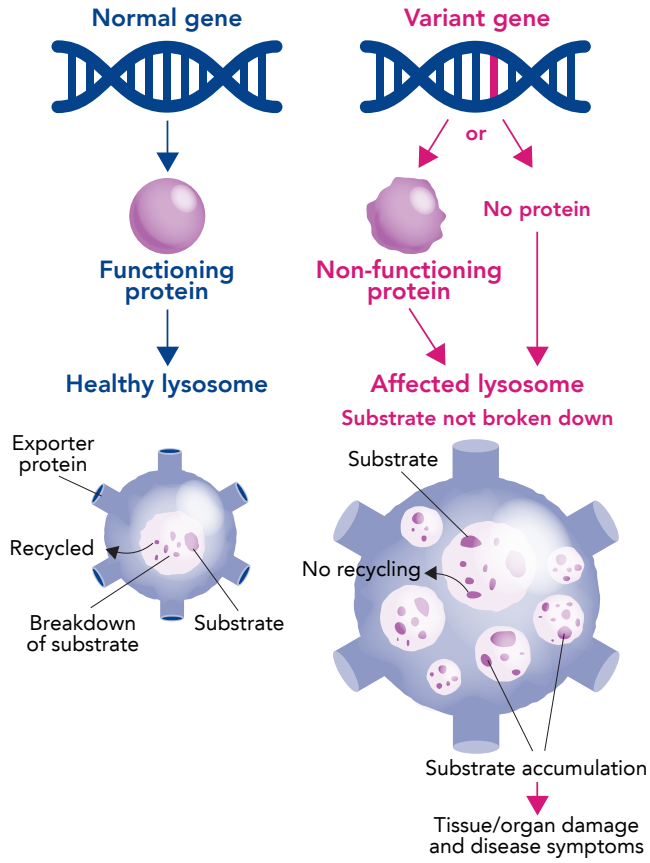
Introduction

Gene therapy is a technique that uses genetic material for the long-term treatment or potential cure of genetic disorders. The concept has been around since the 1960s with early attempts to treat various conditions having had some success.[1] However, in the last decade, considerable advances in technology have been made in the field. To date, seven gene therapies for various monogenic disorders (i.e. those that result from changes in a single gene) have been approved by regulatory authorities around the world.[2,3] More than 330 gene therapy clinical trials for monogenic disorders had been reported globally as of the end of 2019.[4]

What are lysosomal disorders?

Lysosomal disorders are inherited conditions[5] caused by a change in a gene (also known as a gene mutation or variation). Gene variations affect proteins within the lysosome – a structure that recycles cellular components. Proteins are an important class of molecule that have multiple functions in the body. They include enzymes and structural proteins. Both types are affected, e.g. the structural protein cystinosin in cystinosis and enzymes in Fabry, Gaucher and Pompe diseases and Hunter syndrome. Variations in a gene result in a lack of a functioning enzyme meaning that lysosomes are unable to break down substances (in this context, known as substrate) for recycling. Over time, the build-up of substrate is toxic to the cells and leads to tissue damage and debilitating symptoms, affecting many parts of the body (Figure 1).

A normal gene will produce a fully functioning enzyme that is involved in the normal process of successfully breaking down the substrate



In lysosomal disorders, the variant gene results in either a non-functioning protein or no protein made, and prevents the substrate from being broken down (e.g. in Fabry, Gaucher, and Pompe diseases, and Hunter syndrome)

Figure 1

Treatments for lysosomal disorders

Treatment options available for lysosomal disorders include enzyme replacement therapy (ERT), chaperone therapy and substrate replacement/reduction therapy (SRT).[6] Each approach has its benefits and limitations as shown in Table 1.

Table 1. Treatment options for selected lysosomal disorders*

Treatment	Mechanism of action	Benefits	Limitations	Disease
 **Enzyme replacement therapy (ERT)**	Delivers the functional enzyme to break down the substrate	Slows the worsening of disease	Requires regular infusions Cannot reach the brain to address neurological symptoms	Fabry disease Gaucher disease Pompe disease Hunter syndrome
 **Chaperone therapy**	Stabilizes the faulty enzyme allowing the protein to enter the lysosome	Oral medication Slows the worsening of disease	Only works for certain gene variations	Fabry disease
 **Substrate reduction therapy (SRT)**	Stops substrate production	Oral medication Slows the worsening of disease	Adults only Metabolism dependent	Gaucher disease
 **Gene therapy†**	Inserts a therapeutic gene into cells to make the functional enzyme	Potential for one-time treatment	Not approved for use outside of clinical trials – safety and efficacy not fully established in lysosomal disorders	In clinical trials for: • Fabry disease • Gaucher disease • Cystinosis

*Relating to those disorders being studied by AVROBIO; †Investigational for AVROBIO gene therapies

Potential role of gene therapy

Lysosomal disorders may be treatable with gene therapy because the gene variation can be augmented by a therapeutic gene. This could enable cells to make new functional protein in order to potentially treat the underlying cause of the disease.[6] Gene therapy trials for lysosomal disorders are underway to determine the safety and efficacy of the therapy. In addition to studying potential side effects, these trials are studying, among other things, whether gene therapy has the potential to produce long-lasting amounts of functional enzyme, prevent disease progression and address neurological symptoms

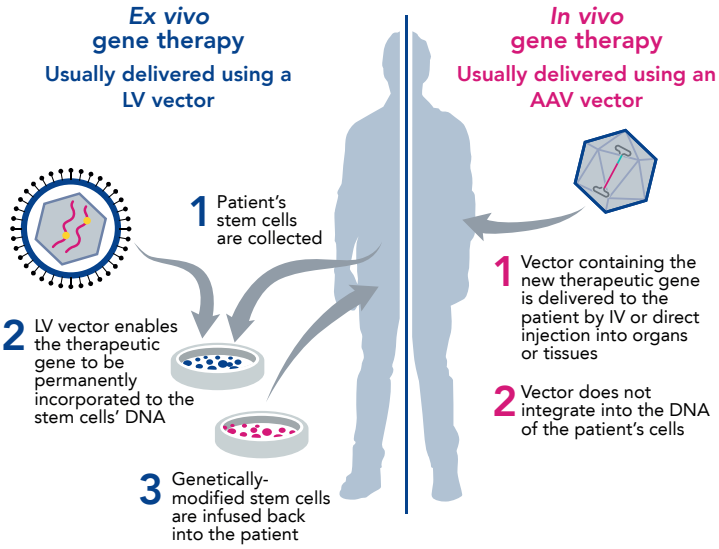
How safe is gene therapy?

Gene therapies for lysosomal disorders remain investigational, which means that they are being studied in the clinical trial setting to determine their safety and efficacy. Gene therapy procedures can cause side effects. It is important to discuss any potential side effects with a doctor.

How does gene therapy work?

For any kind of gene therapy to work, a new therapeutic gene must be introduced into cells so the usual cellular mechanisms can produce proteins such as enzymes.[7,8] A transporter, also called a vector, is manufactured and used to deliver the therapeutic gene into the cell. Commonly used vectors include lentiviral (LV) vectors and adeno-associated viral (AAV) vectors. The main difference between the two vectors is the way they are delivered into the patient's cells, either inside or outside the body (Figure 2).

- LV vectors are delivered to the patient's stem cells outside the body in a process known as *ex vivo* gene therapy. The first step is to collect stem cells from the patient's blood. The vector carrying the therapeutic gene is then introduced to the stem cells in a manufacturing facility. Once the vector has inserted the therapeutic gene, the gene-modified stem cells are given back to the patient intravenously (IV).[7,8] Patients will need to undergo a process called conditioning to prepare the bone marrow to receive the gene-modified stem cells. A proportion of these stem cells are expected to engraft (take hold) or incorporate back in the bone marrow, where they are expected to multiply and differentiate into all the different types of blood cells. In different lysosomal disorders, the new protein can be delivered to all parts of the body, or the cells themselves are corrected by the new enzyme.
- AAV vectors are delivered directly to the patient's body by intravenous or direct injection to organs or tissue being targeted, for example the eye or brain.[7,8] This is known as *in vivo* gene therapy. Once inside the body, the AAV vector is taken up by individual cells and starts making the functional enzyme without integrating into the DNA of the patient's cell.[7] Unlike the *ex vivo* approach, distribution of AAV vector is generally limited to specific organs or tissues.



AAV, adeno-associated viral; IV, intravenously; LV, lentiviral

Figure 2

Gene therapy trials in lysosomal disorders

Gene therapy trials for lysosomal disorders are underway all around the world. AVROBIO's ongoing investigational gene therapy trials for lysosomal disorders are listed in Table 2. Other companies are also conducting gene therapy trials for lysosomal disorders. If you or someone you care for is interested in taking part in a gene therapy trial, it's important to speak with a doctor first to discuss whether it's the right option for you or your loved one. To learn more about AVROBIO's clinical trials, please contact us at patients@avrobio.com

Table 2. AVROBIO gene therapy* clinical trials for lysosomal disorders

Disease	Clinical trial
Fabry disease	Phase II open-label study of efficacy and safety of AVR-RD-01 for treatment-naïve patients with classic Fabry disease (NCT03454893; https://avrobiofabrytrial.com/; www.fabryclinicaltrialau.com/)
Gaucher disease	Phase I/II lentiviral gene therapy – The GuardOne trial of AVR-RD-02 for patients with Type 1 Gaucher disease (NCT04145037; https://www.avrobiogauchertrial.com/)
Cystinosis	Stem cell gene therapy for cystinosis: A Phase I/II study assessing the safety and efficacy of CTNS-RD-04 (NCT03897361)

*Investigational therapies – safety and efficacy have not been established

Frequently asked questions

How quickly does gene therapy have an effect on a patient's body?

Ongoing research is helping to determine if and when a difference is noticeable after treatment with gene therapy. Effectiveness of the therapy may vary from person to person as well as by the type of gene therapy being used. Doctors monitor clinical trial patients regularly and perform tests to check on the effect of gene therapy, including measurement of enzyme activity, substrate levels and vector copy number.

How long do the benefits of gene therapy last, and will continued care be needed?

It is currently unknown how long the effects of gene therapy will last, but doctors will continue to monitor a patient's health in similar ways to before treatment. Ongoing research is working to determine how long any treatment effects may last.

Will the new therapeutic gene be passed on to children?

The new therapeutic gene you receive does not get into the reproductive (egg or sperm) cells. Therefore, it will not be passed on to future children. Currently, regulatory agencies do not allow gene therapy involving reproductive cells.

Summary

Gene therapy has come a long way in the last 50 years. Doctors are working to study its effects in hopes of finding a long-lasting effective treatment for lysosomal disorders in the future.

References

1. https://www.whatisbiotechnology.org/index.php/science/summary/gene-therapy. Accessed 28 October 2020.
2. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed 28 October 2020.
3. https://www.pei.de/EN/medicinal-products/atmp/gene-therapy-medicinal-products/gene-therapy-node.htm. Accessed 28 October 2020.
4. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/gene-therapy-coming-of-age-opportunities-and-challenges-to-getting-ahead. Accessed 28 October 2020.
5. https://rarediseases.org/rare-diseases/lysosomal-storage- disorders/. Accessed 28 October 2020.
6. Gonzalez E *et al. J Inborn Errors Metab Screen* 2017;5:1–6.
7. https://ghr.nlm.nih.gov/primer/therapy/procedures. Accessed 28 October 2020.
8. https://www.fda.gov/consumers/consumer-updates/what-gene-therapy-how-does-it-work. Accessed 28 October 2020.
9. Glossary. American Society of Gene & Cell Therapy; 2020. Available at: https://www.asgct.org/education/more-resources/glossary. Accessed 28 October 2020.
10. NCI Dictionary of Cancer Terms. U.S. Department of Health and Human Services. National Institute of Health, National Cancer Institute; 2020. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/. Accessed 28 October 2020.
11. https://www.who.int/genomics/public/geneticdiseases/en/index2.html. Accessed 28 October 2020.
12. https://www.esgct.eu/PublicPatients/Gene-and-cell-therapy-glossary.aspx. Accessed 28 October 2020.
13. https://www.merriam-webster.com/dictionary/transgene. Accessed 28 October 2020.
14. American Society of Gene + Cell Therapy. Patient Education. Vectors 101. http://patienteducation.asgct.org/gene-therapy-101/vectors-101 Accessed 28 October 2020.
15. Charrier S *et al. Gene Therapy* 2011;18:479–87.

Glossary

DNA	Deoxyribonucleic acid, a very long molecule that carries a cell's genetic information. DNA (also called genetic or hereditary material) is made up of four coding elements called: adenine (A), guanine (G), cytosine (C), and thymine (T).[9] DNA encodes instructions for making proteins.
Engraftment	The process of gene-modified stem cells permanently attaching or taking hold in the bone marrow.
Enzyme	A protein that regulates the rate of a reaction or speed of a reaction. An enzyme is a type of protein.[10]
Gene	The basic unit of heredity. Made of DNA, genes act as a blueprint for making specific proteins, including enzymes, in the body. People have tens of thousands of genes.
Lysosome	A compartment in a cell that recycles materials, including large molecules.[10]
Monogenic disorder	A disease caused by mutations or variations in a single gene.[11]
Open-label	A type of clinical trial in which both the physician and patient know what treatment is being given.
Phase	A term used to describe the stage of the clinical trial, each of which is designed to answer certain questions.
Protein	A large molecule made of amino acids that have multiple functions in the body. An example of a protein is an enzyme.[12]
RNA	Ribonucleic acid, a molecule similar to DNA. One of its functions is to convert, or translate, the genetic code of DNA into structural proteins or enzymes.[9,10]
Stem cell	A cell that can self-renew indefinitely and can turn into any other type of cell in the body.[12]
Therapeutic gene	Also known as a transgene, it contains the genetic material intended to treat a genetic condition at the cellular level.[13]
Vector	A delivery system used to introduce genetic material (DNA or RNA) into the nucleus of the cell.[12,14]
Vector copy number (VCN)	The number of copies of the therapeutic gene (also known as transgene) in a cell.[15]