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Information Bulletin

Gene Therapy

What is gene therapy?

Gene therapy involves using genes to cure or prevent disease. Most treatments for genetic diseases can only address the symptoms, but the hope for gene therapy is to cure the disease itself. There are several different approaches to gene therapy, including:

- Replacing a gene that causes disease with a healthy copy of the gene;
- Disrupting, or "knocking out," a gene that is causing disease; and
- Introducing a new gene into the body to help fight a disease.

Is gene therapy effective?

Gene therapy has shown some promising results in treating a variety of diseases, including: Severe Combined Immune Deficiency, several types of hereditary blindness, hemophilia, sickle cell disease and beta-Thalassemia, some forms of cancer, and Parkinson's disease. However, gene therapy is still experimental. Since 1989, over 2400 clinical trials have been approved worldwide, but fewer than 100 have reached the final stages and very few gene therapy treatments have been approved.

- **Gendicine**, approved in 2004, was the first gene therapy approved anywhere in the world. It contains a form of the human p53 gene, which controls cell growth. The gene exists naturally in human cells, but is mutated or deleted in tumour cells. When Gendicine is delivered, it enters tumour cells and exerts its anti-tumour effects.
- The second approved gene therapy, **Glybera**, was licensed in 2015. Glybera is a treatment for lipoprotein lipase deficiency, in which patients have a defect in the gene for an enzyme that is responsible for breaking down fats. Glybera contains the functioning lipoprotein lipase gene which, when injected into the patient's muscles, enables the muscle cells to produce the enzyme. Canadian scientists were involved in the clinical trials that validated the efficacy of Gybera.
- **Strimvelis** was approved in 2016 to treat Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID). Children with ADA-SCID are genetically unable to produce ADA which is required to produce the white blood cells that fight infection. Everyday infections become severe and life-threatening illnesses. During treatment, patients' bone marrow cells are removed from their bodies and treated with Strimvelis, which contains normal copies of the ADA gene. The treated cells are infused back into the patients and the cells that return to the bone marrow are able to produce ADA.

What are the challenges of gene therapy?

When the potential for gene therapy began to emerge in the early 1990's, the possibility of curing hundreds of previously untreatable diseases generated enormous public and scientific interest. Gene therapy proved to be more challenging than anticipated, however, and progress toward effective treatments has been slow.

Gene therapy only becomes possible if the disease of interest is well understood, the associated gene (or genes) has been identified, and a functional copy of the gene is available. But the biggest challenges in gene therapy are gene delivery and activation: how to get genes

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into only the desired tissues and how to activate the gene—and keep it activated—once it has been delivered to the target tissues.

Viruses reproduce by attacking host cells, introducing their genetic material into the cell, and taking over the cell's reproductive mechanisms. Some viruses incorporate their genes into the genome of the host cell. Scientists have harnessed the invasive abilities of viruses in order to use them as vectors to deliver therapeutic genes. The harmful genes carried by viruses are removed and the therapeutic genes are inserted, then the patient is inoculated with the modified virus. In successful cases, the virus infects the target cells and inserts the therapeutic gene into the cell's genome.

Viruses can solve the delivery problem for gene therapy, but they carry their own risks and challenges. Although the viruses are deactivated, they can still provoke an immune response. Viruses can also insert the therapeutic genes into the wrong location in the genome. This occurred during trials of a treatment for SCID: in several of the patients, the treatment cured their SCID but caused leukemia by dysregulating cell growth and division.

Viruses can deliver therapeutic genes to target cells, but then the gene has to be activated. To be effective, the therapeutic gene has to be expressed at the appropriate level for a specific period of time. Cells sometimes interfere with gene therapy by deactivating genes that are showing unusual activity. In other cases, the insertion of a therapeutic gene into the genome can affect the activation of nearby genes—or vice versa. Scientists are discovering strategies to address these challenges, including control systems to manage gene expression, promoter genes that switch other genes on or off, and "insulator" sequences of DNA that protect genes from the signals of other surrounding genes.

How can gene editing contribute to gene therapy?

Gene editing consists of a relatively new set of molecular techniques that are much more precise than earlier forms of genetic engineering. Theoretically, gene editing could push gene therapy dramatically forward. Rather than ferrying therapeutic genes into cells and trying to insert them into harmless locations in the genome, gene editing techniques such as CRISPR/Cas9 could fix disease-causing genes directly by editing out faulty genetic sequences and editing in repaired sequences. The repaired gene would remain in its natural location within the genome and would be controlled by its natural promoter gene, eliminating many of the delivery and activation challenges associated with gene therapy.

Gene editing techniques, however, carry their own challenges and cannot provide immediate solutions to the challenges of gene therapy. The gene editing mechanism has to be delivered to the appropriate cells. In some cases, cells can be removed from the patient, edited in vitro, and then returned. But when large numbers of cells have to be treated, the treatment has to occur in vivo and this generates the same delivery challenges as other forms of gene therapy. As well, gene editing mechanisms make very precise cuts in the DNA to edit out a defective gene, but they can make additional unintended cuts and cause critical damage.

What are the next steps for gene therapy?

After three decades of research and slower than anticipated progress, effective gene therapies are beginning to emerge. At least two new therapies will likely be approved this year and several more are moving through the final stages of clinical trials. Innovations in molecular biology, such as gene editing, can potentially push gene therapy in new directions and open the door to applying gene therapy to a wide range of different diseases. For the moment, though, gene therapy remains largely experimental.

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More information and resources

https://ghr.nlm.nih.gov/primer/therapy/genetherapy

http://learn.genetics.utah.edu/content/genetherapy/

http://www.abedia.com/wiley/index.html

http://angt.austrianova.com/angt/gendicine%20in%20china.pdf

https://globalgenes.org/raredaily/first-gene-therapy-drug-approved-europe-set-launch-priced-u-s-1-4-million/

http://www.gsk.com/en-gb/media/press-releases/2016/strimvelistm-receives-european-marketing-authorisation-to-treat-very-rare-disease-ada-scid/

http://www.genetherapynet.com/viral-vectors.html

https://www.geneticliteracyproject.org/2016/10/06/early-setbacks-gene-therapys-comeback-nearly-complete/

http://www.nature.com/nature/journal/v420/n6912/full/420116a.html

http://www.asgct.org/general-public/educational-resources/faqs#faq2

http://www.sciencemag.org/news/2016/05/gene-editor-crispr-won-t-fully-fix-sick-people-anytime-soon-here-s-why

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