

An Update on Gene Therapy



Celine Al Kazzi, PhD
Candidate¹



Nour Tawk, MSc¹



Dr. Alice Geroges Geagea²



Vanessa Boustani, MSc¹

1) Faculty of Medicine, American University of Beirut, Lebanon

2) The Lebanese Health Society, Lebanon

What is Gene Therapy?

At its core, gene therapy is about addressing disease at the genetic level, altering the DNA or genetic instructions inside our cells to correct what's gone wrong, or to give cells new standard instructions. Because many diseases arise from mutations (errors) in genes, or from missing genes, gene therapy offers the possibility of treating, or sometimes curing, conditions by fixing the root cause rather than just managing symptoms. Over the decades, scientists have developed various strategies to deliver good genes or to edit existing ones. With the rise of powerful molecular tools, especially over the last 15-20 years, gene therapy has moved from theory and early trials to real-world, approved, and efficient treatments. Gene therapy today is

not a single technology but rather a range of approaches. The choice of approach depends on the disease, the target tissue (blood, liver, muscle, brain, etc.), and whether the goal is to change the genome or provide temporary or permanent additional function.

Main Approaches & Techniques

1. Gene addition/gene replacement (via viral or non-viral vectors)

- A healthy copy of a gene is delivered into a patient's cells. It does not necessarily replace the defective gene; instead, the new copy coexists with the defective one and produces the needed protein.
 - Commonly used delivery vehicles or vectors are viruses that have been disabled so they cannot cause disease. Among them, Adeno-Associated Virus (AAV) is currently the most popular: it's relatively safe, not strongly disease-causing, and can infect many different tissues.
 - There are also non-viral delivery methods (e.g., lipid particles, nanoparticles), which reduce certain risks such as immune reactions and allow different kinds of cargo to be inserted within the cells. However, over the years, they have become less efficient than viral methods.
- This approach is often used for diseases caused by missing or nonfunctional genes, also known as monogenic diseases.

2. Gene editing (correct the genome directly)

Instead of simply adding a copy, modern gene therapy aims to edit the patient's own DNA, correcting mutations in situ. This approach has offered many advantages, including:

- It can restore normal regulation in terms of timing and amount of the gene being expressed, and not just provide a new copy of the gene.
 - It avoids the problem of having multiple possibly misregulated copies of the gene.
- The best-known tool for this is CRISPR/Cas9 and other related CRISPR-based systems. In simplest terms, CRISPR uses a guide RNA to locate a precise spot in the genome, and the Cas9 enzyme acts like molecular scissors to cut the DNA there. The cell's own repair mechanisms then fix the cut, and with appropriate design, you can

either deactivate a defective gene, correct a mutated gene, or insert a repaired version.

Because CRISPR editing can, in principle, reach many cell and tissue types and make precise changes from point mutations to insertions and deletions, it has dramatically expanded what gene therapy can aim for.

There are also newer, more refined editing tools derived from CRISPR (e.g., base editors and prime editors), which can change single DNA nucleotides without cutting both strands of DNA, thereby reducing the risk of unintended side effects.

3. Cell-based gene therapy (ex vivo modification)

In some treatments, cells, often from the patient, are removed from the body, genetically modified in the lab, and then returned to the patient. This is particularly useful when targeting blood-forming pluripotent stem cells or immune cells. Because the patient's own cells are used (autologous), the risk of immune rejection is lower. A well-known therapy is editing blood stem cells with CRISPR to produce the correct hemoglobin in blood diseases such as sickle cell disease and thalassemia.

4. Regulatory & control strategies

Beyond editing or adding genes, researchers are also developing ways to control when and how these genes work, for example, to turn them on or off, or to ensure they're active only under certain conditions. This is especially important when the therapeutic approach aims to alter DNA permanently; however, it requires as much precision and safety as possible.

What Gene Therapy Has Already Achieved

Because of these techniques, gene therapy has moved from experimental trials to clinical effectiveness. Several vital diseases, many of them previously untreatable or requiring lifelong therapy, now have approved gene-based treatments. Among the achievements:

- 1. Blood disorders:** For example, a therapy that is a CRISPR-based cell therapy that edits a patient's own blood stem cells. It's approved for diseases like sickle cell disease and transfusion-dependent beta-thalassemia.
- 2. Inherited genetic disorders (various tissues):** Gene addition therapies using AAV or other vectors, for example, to restore missing genes in inherited metabolic, muscular, or neurologic diseases.
- 3. Cancer and immunotherapy:** CAR-T and other

gene-modified cell therapies remain among the major successes, especially for some blood cancers. These involve genetically engineering a patient's immune cells to recognize and kill cancer cells.

What's New - Recent Advances & Frontiers (2023–2025)

1. More precise and safer editing tools

- Recent years have seen improvements in CRISPR technology: newer CRISPR/Cas variants, better guide RNAs, and improved control of when the editing happens. These refinements increase specificity, reduce the risk of editing the wrong part of the DNA, and minimize side effects.
- There is growing use of non-viral delivery methods, such as lipid nanoparticles, which can deliver gene-editing components without using viral vectors. This reduces certain risks, such as immune response, and creates opportunities for repeated dosing and safer delivery.
- Scientists are improving vector design itself. For example, recent research has produced novel versions of AAV capsids (the outer shell of the virus) that are more efficient, more selective for specific tissues, and potentially less prone to immune detection. A recent preclinical study used artificial intelligence (AI) machine-learning techniques to design thousands of candidates AAV capsid sequences and identified many that outperformed older designs, thus, a promising advance toward more efficient and safer delivery using AI.

2. Expansion beyond rare diseases — toward common & chronic conditions

Traditionally, gene therapy has focused on rare monogenic disorders, which are diseases caused by a single-gene defect, because they have a clear genetic cause and can often be corrected or replaced by correcting or replacing a single gene. But researchers are now aiming beyond that.

- There are emerging therapies and trials aimed at common metabolic or chronic diseases, such as certain forms of heart disease, high cholesterol, possibly even diabetes or liver disease, using gene editing to correct genes that contribute to disease risk.
- Because of improved delivery, editing precision, and safety, the idea of a one-time therapy for common diseases every day is more approachable and possible, though many challenges remain.

If successful, this would substantially expand the impact

of gene therapy, from rare inherited diseases to conditions affecting millions worldwide.

3. Better cell-based therapies

Gene therapy is no longer only about static gene addition or editing. New developments are exploring living cell therapies, in which cells are genetically engineered to act as therapeutic agents, and this includes:

- Engineered immune cells, including CAR-T cells, with greater specificity and the ability to target multiple markers at once, aiming to treat more types of cancer (including solid tumors, which have been historically harder to treat).
- Using therapies that target the patient's own cells more frequently, thus reducing the risk of rejection, and allowing personalized therapies. This is made more feasible by improved manufacturing and editing technologies.
- Work toward regulatable therapies: cells or genes whose activity can be turned on/off or adjusted over time depending on needs, potentially improving safety and flexibility.

These living medicines represent a significant shift, meaning not just fixing what's defective but giving patients new, enhanced capabilities or rewiring their bodies to fight disease more efficiently.

Challenges Still Ahead

- **Delivery to the right cells/tissues:** Getting the therapy where it needs to go, especially in humans, remains difficult. Some tissues (e.g., brain, muscle, lungs) are more complex to reach than the blood or liver. Even when using improved vectors, ensuring safe, efficient, and targeted delivery is a significant hurdle.
- **Immune response and safety:** Viral vectors (or repeated dosing) can trigger immune reactions. Editing tools can accidentally modify the wrong part of the genome (off-target effects). Even advanced editing tools need rigorous testing to ensure long-term safety.
- **Manufacturing, cost, and scalability:** Producing gene therapies, especially viral-vector-based ones, is complex and expensive. Purification, quality control, and scaling up to treat many patients are nontrivial challenges. The recent improvements help, but cost and capacity remain key issues.
- **Durability & control:** For permanent editing, researchers want the change to last, but they also want safety and the ability to control expression when needed. For gene addition therapies, long-term expression, regulation, and potential side effects need to be monitored. For editing



therapies, long-term stability and monitoring of off-target effects remain critical. Because of these challenges, each new therapy must be carefully tested in clinical trials, with long-term follow-up, before being widely used. The field, while promising, remains cautious and rigorous.

Conclusion

Gene therapy stands today at a crossroads between revolutionary potential and practical caution. Thanks to breakthroughs, especially in gene editing (CRISPR and its newer variants), delivery technologies, and manufacturing, what was once science fiction is now being translated into real treatments and cures. However, to fulfill its full potential (wide availability, affordability, safety), the field must navigate complex scientific, medical, regulatory, and ethical challenges. For the first time in human history, science is not merely treating symptoms; it is rewriting the instructions that govern life. That is powerful. And while we must remain humble before the complexity of biology, the progress to date gives reason for optimism.

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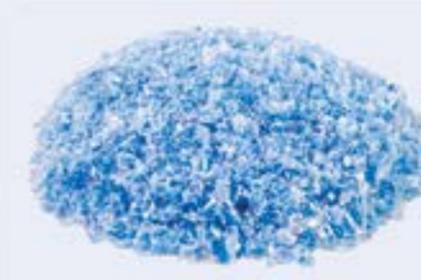
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