DISCOVERING THE POTENTIAL OF GENE THERAPY

Spark Therapeutics, a leader in the field of gene therapy research.
The idea of gene therapy is not new—it’s more than 50 years old. Gene therapy research has gone through several decades of development and, to date, more than 2300 gene therapy clinical trials are planned, ongoing, or have been completed across a wide variety of disease targets and approaches. This research continues to show the potential of gene therapy in several disease spaces, including monogenic disorders and chronic conditions, such as:

- Cardiovascular disease
- Neurodegenerative disorders
- Vision disorders
- Diabetes mellitus
- Hemophilia

The potential of gene therapy research brings hope to millions of people living with debilitating and currently untreatable diseases.
Defining gene therapy

Gene therapy is a potential therapeutic approach involving the transfer of genetic material through the administration of nucleic acids, viruses, or genetically engineered microorganisms.\textsuperscript{1,7,8}

The intention of gene therapy is to regulate, repair, replace, add, or delete a genetic sequence for the potential treatment of an inherited or acquired disease.\textsuperscript{1,7,8}

Gene therapy versus cell therapy

It should be noted that gene and cell therapy are overlapping fields of biomedical research with the intent to treat inherited or acquired diseases; however, they are not the same.\textsuperscript{4}

**Cell therapy**

works by infusing or transplanting whole cells\textsuperscript{4}

**Gene therapy**

uses genetic material to manipulate patients’ cells\textsuperscript{4}
There are 2 potential delivery methods for gene therapy:

**IN VIVO**
- The therapeutic transgene is packaged into a vector, such as a virus.
- The therapeutic transgene is delivered into the patient’s body.
- Delivery cells are derived from the patient.
- The target organ (e.g., the liver) is genetically modified by introducing the therapeutic transgene.
- Delivery cells are multiplied and returned to the patient.

**EX VIVO**
- The therapeutic transgene is packaged into a vector, such as a virus.
- Delivery cells are derived from the patient.
- The delivery cells are genetically modified by introducing the therapeutic transgene.
- The therapeutic transgene is delivered into the patient’s body.
- Target organ (e.g., the liver) is used.
- Delivery cells are multiplied and returned to the patient.

Adapted from National Institutes of Health 2001. Use of genetically modified stem cells in experimental gene therapies.\(^{11}\)

An ideal vector should be able to protect a transgene against degradation by nucleases, allow transport of the transgene into the nucleus of target cells, and have minimal inflammatory effects.\(^{11,12}\)

Advances in the development of vector systems and their increasing use in clinical research have increased the potential of gene therapy for the treatment of human disease.\(^{13}\)
The biological evolution and characteristics of viruses make them preferred candidates for most gene therapy applications. Some of the most common viral vectors used for gene therapy research are the lentivirus (LV), adenovirus (Ad), and adeno-associated virus (AAV).

THE VALUE OF THE VIRAL VECTOR

Among the various viral-based vector systems used in research, AAV vectors have demonstrated the greatest success in clinical trials for in vivo gene delivery.
The viral vectors

**AAV** has a broad tropism with the possible exception of hematopoietic cells and is capable of carrying ~5 kb-sized genes. The gene delivered by the AAV vector usually remains within the target tissues as an episomal entity, although integration into the host cell genome can rarely occur.\(^{11,14,16,17}\)

**Ad** has a broad tropism and one of the largest capacities for delivering transgenes (≤36 kb). The gene delivered by the vector is episomal and offers minimal risk of insertional mutagenesis. Ad has a high inflammatory potential.\(^{18}\)

**LV** has a broad tropism and an 8-kb packaging capacity, integrates its genome into the chromosomes of target cells, and can provide long-term expression in dividing cells. LV has a low inflammatory potential.\(^{14,18}\)

Illustrations adapted from Kotterman 2014 and Rastall 2015.\(^{5,19}\)

Episomal vs integrated = a stable DNA molecule that persists in the nucleus without integrating into the cellular genome is considered episomal; those that do integrate into the host genome are considered integrated.\(^{11,12,18}\)

Inflammatory potential = the extent to which a viral vector is capable of triggering inflammatory/immune responses, including cytotoxic T-lymphocyte responses, humoral antibody responses, and cytokine-mediated responses.\(^{14}\)

Kb = kilobase pair, a unit of measurement of DNA or RNA length used in genetics, equal to 1000 base pairs.\(^{21}\)

Tropism = the range of cell types or tissues in which a virus can sustain a productive infection.\(^{17}\)
Few satisfactory therapeutic options currently exist for rare diseases.\textsuperscript{22}

Scientists estimate that more than 10,000 human diseases are monogenic—genetic diseases caused by a mutation in a single gene. Though relatively rare, collectively they affect millions of people worldwide.\textsuperscript{22,23,24}

Gene therapy research raises hope for the development of future treatments that may address rare diseases, which are often easier targets for therapies due to their well defined, heavily researched target genes and accessible clinical indications.\textsuperscript{22,23,25}
We envision a world where no life is limited by genetic disease

Patient organizations, small biotechnology companies, and academic centers have played a crucial role in the advancement of gene therapy research, bringing us into a time filled with potential to address genetic disease.  

Spark Therapeutics, a fully integrated company, strives to challenge the inevitability of genetic disease by seeking to discover, develop, and deliver gene therapies that address inherited retinal diseases (IRDs), neurodegenerative diseases, as well as diseases that can be addressed by targeting the liver.

To learn more about our research in gene therapy, visit us at Sparktx.com.