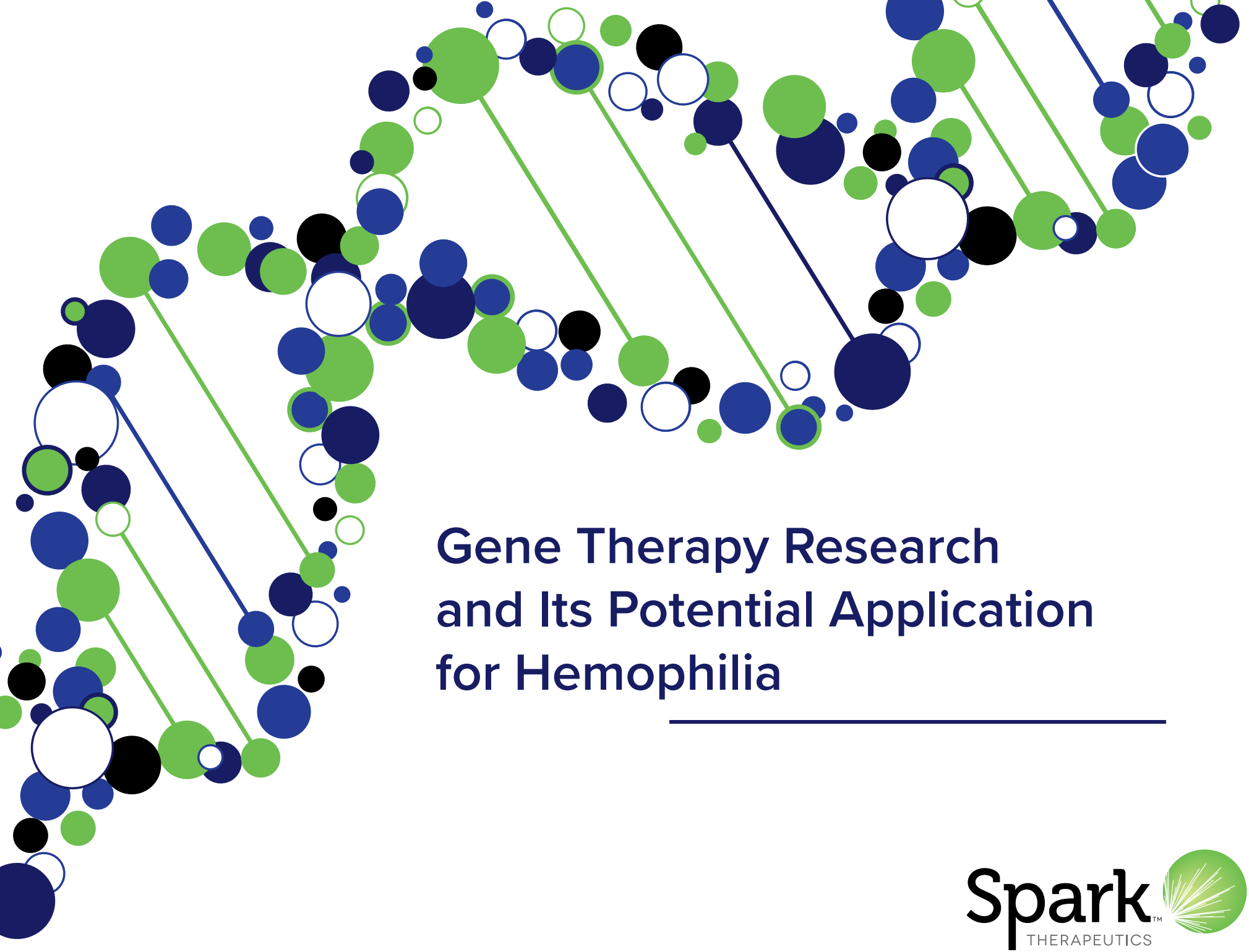


Gene Therapy Research and Its Potential Application for Hemophilia

Spark™ THERAPEUTICS

Table of Contents

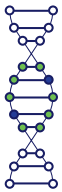
Key Terms Used in This Guide

There's no test. Flip back to these pages as needed.

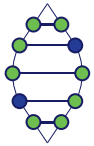
Antibody
Component of the immune system that circulates in the blood, recognizes foreign substances like bacteria and viruses, and destroys them. Antibodies continue to circulate in the blood, providing protection against future exposures from the same substance.

Chromosomes
A structure made of DNA that is found in the nucleus of cells.

Clinical trial
A research study in which scientists examine a potential intervention (eg, a medical treatment) on people who volunteer to participate.



DNA
Deoxyribonucleic acid, the material in the chromosomes that carries hereditary information in the form of genes.



Gene
A segment of DNA that contains the information, or instructions, for how the body should make proteins.

Immune response
The body's defense reaction in response to the presence of a foreign substance (eg virus) inside the body.

Mutation
A permanent change in the DNA of a specific gene, which in some cases may cause genetic disease, such as hemophilia.

Nucleus
The part of the body's cells containing chromosomes and all of the instructions for how the body operates.

Neutralizing antibodies (NAb)
An antibody that shuts down a virus to block infection.

Protein
Molecules that build, regulate, and maintain the body. Clotting factors are an example of proteins.

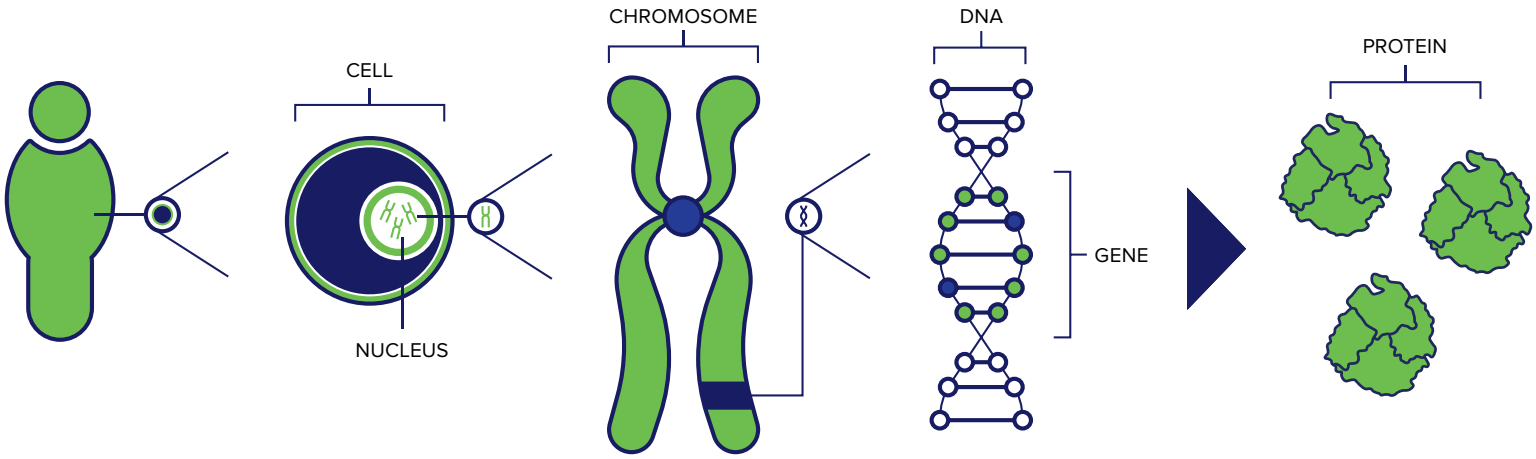
Tropism
A virus or vector's attraction to a specific type of cell or tissue in the body.

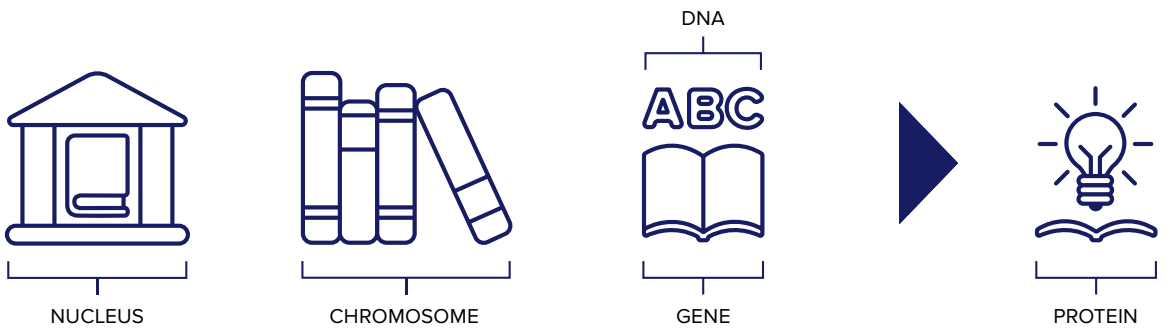
Vector
A transporter or carrier package for delivering new genetic material, such as a gene, to a cell.

Spark™ THERAPEUTICS

4

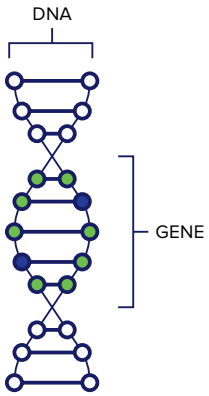
The Role of Genes and the Potential of Gene Therapy Research





Genes: The Body's Instruction Manual

The human body is made up of trillions of **cells**. At the center of each cell is the **nucleus**. You can think of the nucleus as a reference library containing all the instructions the body needs to function.



All of these instructions are stored on **chromosomes**, which act like "how to" books inside the reference library.

Chromosomes are made up of **DNA**, which acts as a genetic alphabet and contains all the hereditary information in our body.

Unique sections of DNA are organized into **genes**. These are small sets of instructions and can be thought of as specific chapters or instructions within those books. These genes provide the instructions the body needs to make **proteins**, including clotting factors.

What is Investigational Gene Therapy?

Gene therapy is a potential approach to treating or preventing genetic diseases. The goal of investigational gene therapy is to address a genetic disease at its source—the gene.

Investigational gene therapy aims to deliver genetic material (like DNA) to cells to potentially treat genetic diseases. Research is underway to determine whether a new, functional gene could restore the function of a nonworking, or mutated, gene.

Investigational gene therapy has the potential to treat many diseases, including some caused in part or in full by gene mutations, such as:

- Blood-clotting diseases, such as hemophilia
- Cardiovascular diseases
- Infectious diseases
- Neurodegenerative diseases
- Vision disorders

Spark™ THERAPEUTICS

6

Explore the Science Behind Gene Therapy Research

Multiple Approaches to Addressing Genetic Disease

Scientists are studying several approaches to potentially treat or prevent a genetic disease at its source–the gene.

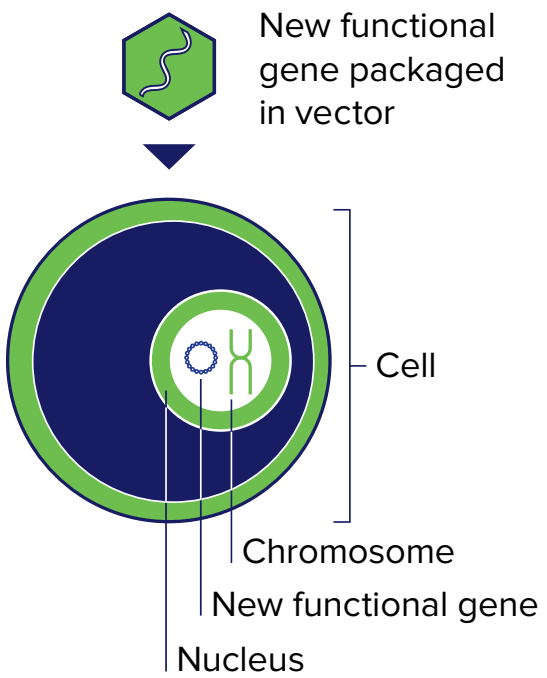
Gene therapy

- This approach creates new functional genes in a laboratory for delivery by a vector to specific cells in the body (eg, liver cells) with an aim to restore or enhance normal function.
- There are a few terms you may have heard of to describe this same process—gene transfer, gene augmentation, or gene replacement.

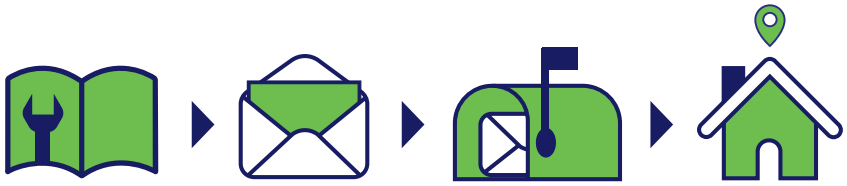
Other approaches

- **Gene editing:** An approach that will modify or change a person's existing genes to correct specific mutations. You may have heard of a couple of these techniques—CRISPR or Zinc Finger Nucleases.
- **Cell therapy:** Involves the transfer of cells into a person that are capable of performing a desired/needed function. The genes in the cells may or may not be modified by gene therapy or gene editing while outside of the body (in a laboratory).

Of these three different approaches, gene therapy is the most broadly investigated for hemophilia. Information in the rest of this guide is focused on gene therapy.



Transporting a Functional Gene Into Target Cells



Instruction manual (**functional gene**) | Package for delivery (**vector**) | Placed into mailbox for delivery (**body**) | Deliver to correct address (**target cell**)

In gene therapy research, a new functional gene is created in a laboratory. This **functional gene** acts as an instruction manual that tells your body how to make a desired protein.

The new functional gene is then placed into a viral-based shell, creating a delivery package known as a **vector.** A vector is like an envelope, acting as a delivery vehicle for functional genes.

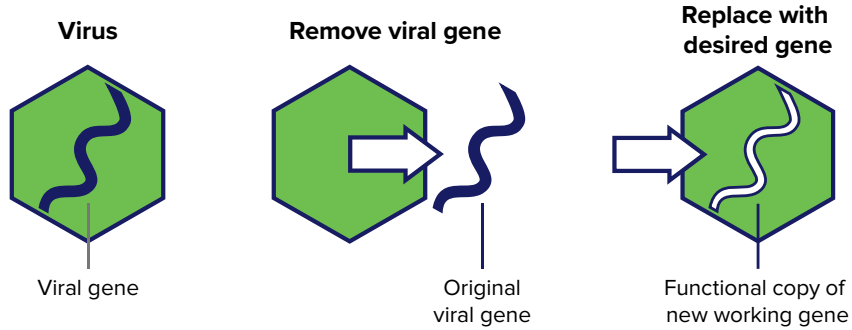
Similar to the way mail is addressed and placed in a mailbox, the vector is placed into the **body** to be sent to the correct address. The correct address, or **target cells**, depends on which cells need the new functional gene.

Choosing a Delivery Vehicle

Over millions of years, viruses have evolved to be very good at placing genetic information into cells. Each virus has an attraction to a specific cell type or types.

This “specific attraction,” referred to as **tropism**, makes viruses a common choice for scientists to modify for use as vectors for delivering genetic material.

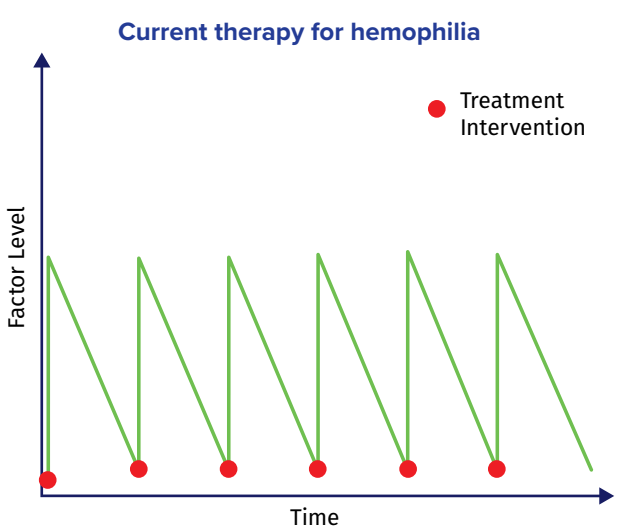
Before being used as a vector, the viral genetic information is removed and replaced with the new functional gene.

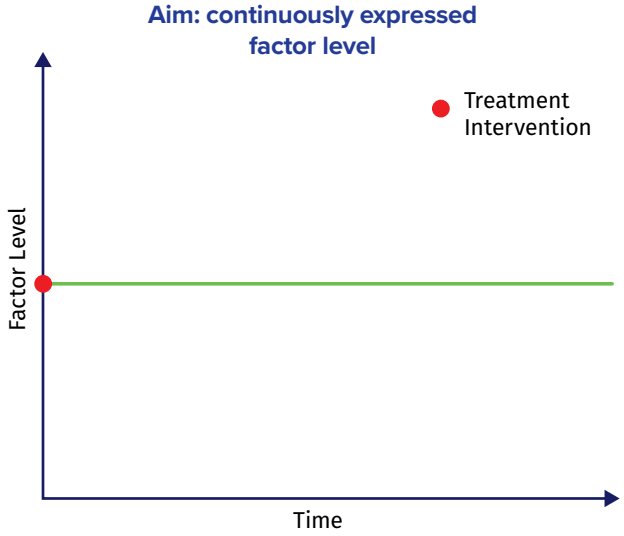


Spark™ THERAPEUTICS

Moving Research Forward in Hemophilia

The Aim of Gene Therapy Research in Hemophilia





Hemophilia has long been the subject of gene therapy research. The goal of this research is to transition treatment from recurrent interventions to a potentially one-time gene therapy infusion (redosing is currently not possible) that could give the liver instructions on how to make its own clotting factor proteins, such as FVIII or FIX.

The aim of investigational gene therapy is to potentially replace the peaks and troughs (highs and lows) in factor levels with a steady, continuous level of factor.

Research is underway to explore if keeping factor levels continuously above a certain point could prevent spontaneous bleeding episodes. *The safety and efficacy of investigational gene therapy for hemophilia are still being explored.*

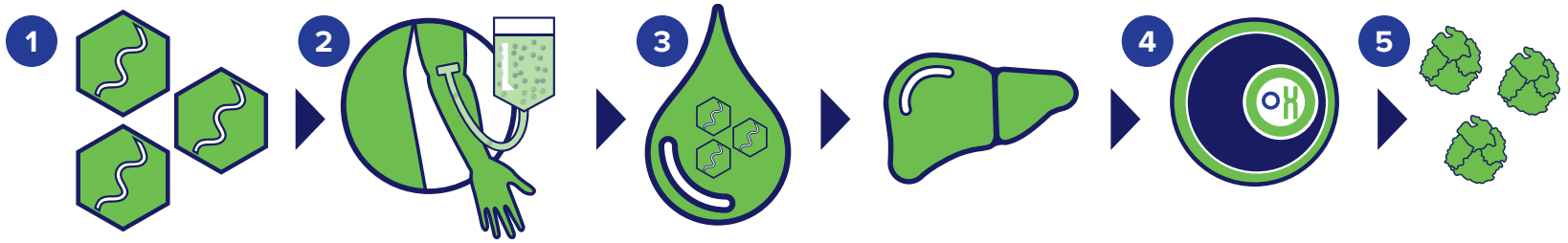
How Gene Therapy Research is Applied to Hemophilia

Investigational gene therapy for hemophilia is designed to add a new functional gene to the nucleus to provide a cell with the correct instructions for making FVIII or FIX.

1. Viral genetic information is removed from the virus. The new functional factor VIII or factor IX gene is placed inside the viral-based shell to create a vector, which can carry the gene into the body.
2. The vector is delivered into the body via intravenous (IV) infusion.
3. The vector travels through the body and aims for, or targets, the liver cells (hepatocytes).
4. Once at the liver cells, the new functional factor VIII or factor IX gene is intended to be placed inside the nucleus.
5. If transferred successfully, the functional gene is intended to provide the cell with instructions for making FVIII or FIX clotting protein.

For more information on the science behind gene therapy research for hemophilia, go to **HemophiliaForward.com.**

Scan here to stay connected.



Spark THERAPEUTICS

10

Evaluating Gene Therapy Research for Hemophilia

Clinical Trials for Investigational Therapies

Clinical trials determine whether potential new drugs or treatments are safe and effective. Clinical trials in human volunteers are carefully conducted and take place after many years of initial (preclinical) research in the laboratory and animal studies. Clinical trials include multiple phases and extensive review of data to—first and foremost—ensure the safety of patients. Regulatory agencies, such as the Food and Drug Administration (FDA) monitor and review the progress of clinical trials.

Clinical trials aim to answer many questions, such as:

- Is the investigational therapy safe?
- What is the ideal dose?
- How long might a potential response last?
- Are the results predictable?
- Do the benefits outweigh the risks?

While much research has been conducted on investigational gene therapy, there are still many questions we don't have complete answers to yet. *All of these questions are being asked and investigated in clinical research through controlled clinical trials and new results and data from clinical trials are being published.*

Clinical trials of investigational gene therapy are ongoing. Participants continue to be monitored for safety and any potential risks.

Potential Risks of Gene Therapy

There are 2 broad categories of known potential risks:

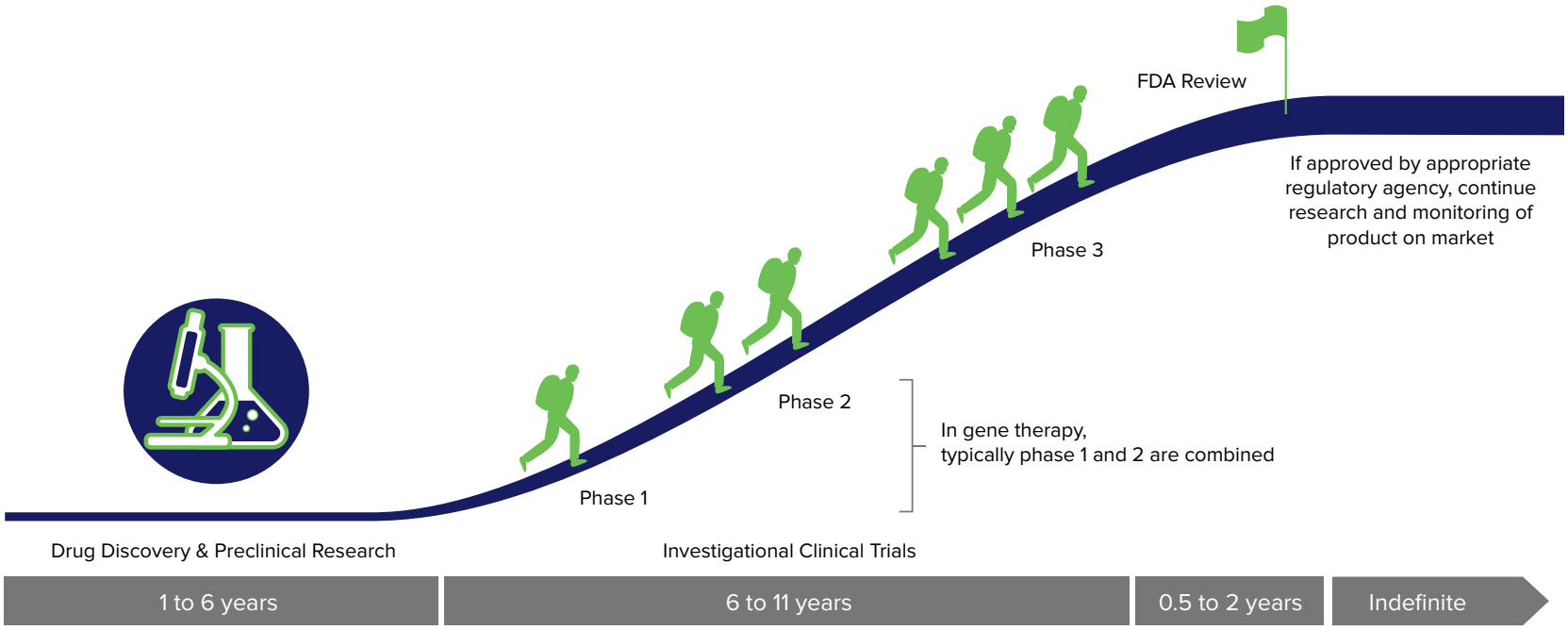
1. The immune system defends against things our body considers harmful, such as viruses. It is possible that the vector could trigger potential immune responses, including:

- Liver inflammation, which, if not controlled, could cause the loss of FVIII or FIX protein production. Treatment, such as a short course of steroids, may be considered to calm the immune system.
- Following the infusion of gene therapy, the body will create antibodies and this could disqualify someone from gene therapy in the future.
- Inhibitor development or allergic reactions.

2. Other risks could occur related to the gene therapy/ transfer itself.

- Vectors tend to be specific in the cells they target, but the risk cannot be ruled out that they could find their way into unintended cells, damaging them or causing inappropriate cell growth, which may lead to tumors or cancer.
- Vector shedding, the natural removal of the vector shell from the body through fluids, could theoretically lead to the development of antibodies to the vector being formed in those who come in contact with these fluids.

This is not a comprehensive list of all risks associated with gene therapy research or investigational gene therapy for hemophilia. Please consult ClinicalTrials.gov or speak with your physician regarding any specific trial.



Phase 1 and 2 are often combined in gene therapy. These trials evaluate safety and efficacy in a small group of individuals living with the disease.

Phase 3 is a larger trial that gathers more information about safety and efficacy in different populations and dosages, and possibly in combination with other drugs.

Upon completion of phase 3, data are collected, analyzed, and reviewed by the FDA for potential approval.

Research doesn't stop just because the drug is approved. Participants continue to be monitored. This is particularly relevant in gene therapy trials.

Spark™ THERAPEUTICS

Gene Therapy Research is Ongoing

Ask Questions. Be Informed.

See the right side of page for places to get more information.

Always speak with your doctor or healthcare team if you are considering participating in gene therapy research. This research is ongoing, and new or different information may become available.

Additional Resources

Hemophilia Forward
hemophiliaforward.com

American Society of Gene and Cell Therapy
asgct.org

Genetic Alliance
geneticalliance.org

Genetics Home Reference
ghr.nlm.nih.gov

Genes in Life
genesinlife.org

Global Genes
globalgenes.org

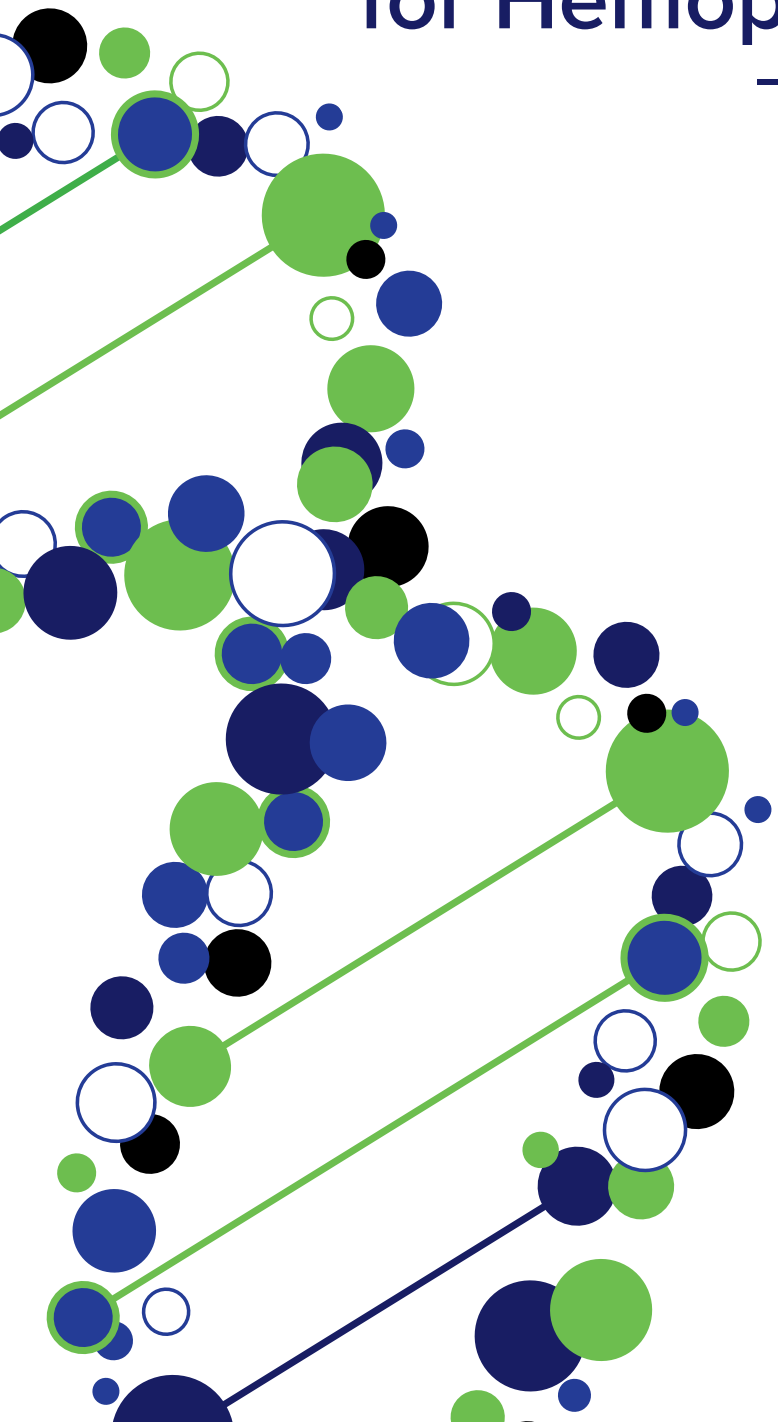
Hemophilia Federation of America
hemophiliafed.org

National Hemophilia Foundation
hemophilia.org

National Organization for Rare Disorders
rarediseases.org

Your Genome
yourgenome.org

Gene Therapy Research and Its Potential Application for Hemophilia



Spark THERAPEUTICS

1-855-SPARKTX