# GENE AND INNOVATIVE THERAPIES GLOSSARY

## A

**Allele:** one of two or more versions of a gene located at the same place on the chromosome that is inherited from each parent. Hemophilia is an allele that is passed down from parent to offspring.[21]

Adeno-Associated Virus (AAV): A single-stranded DNA virus that has not been found to cause disease in humans. This virus is most frequently used in gene therapy, including gene therapy for hemophilia A and B.[8]

Adeno-Associated Virus Vector: Viruses used as vehicles for genes, whose core genetic material has been removed and replaced by the (F) VIII- or (F) IX- gene in gene therapy for hemophilia A or B.[8]

Adenovirus: A member of a family of viruses that is also used in other gene therapies, primarily for cancer-related illnesses.[4]

Amino Acids: organic compounds that are the building blocks of all proteins. Twenty-two amino acids make up the genetic code of all life.

Antibody: a protein produced by our immune cells that responds to a foreign molecule. Antibodies act by binding to the molecule to make it inactive or to destroy it. Those that have antibodies against Adeno-Associated Virus (AAV) may not be candidates for gene therapy for hemophilia because AAV is used to get gene therapy in the body.[2]

Antigen: a marker on a molecule or cell in the body that the immune system recognizes as friendly or harmful. Harmful markers initiate an immune response. In gene therapy, it is important that the body's immune system recognizes the antigens as friendly.

Autophagy: the body's means of removing old cells or those that are working by consuming damaged parts. The liver's process of autophagy can impact how effective gene therapy is in the body.[19]

## B

Baculovirus: family of viruses that commonly infect insects and are considered resilient. Baculoviruses can live outside of a host and have been used for gene therapy, similar to AAV.[17]

Blood Brain Barrier: the blood brain barrier is a natural, protective membrane that protects our central nervous system (the brain and spinal cord) from any toxins or foreign materials that could be in our blood.[46]

## C

Capsid: the protein shell of a virus that surrounds the genetic material. In gene therapy for hemophilia, the AAV capsid is what brings the genetic material to the liver.[8]

Chimeric: tissue that contains cells with different genes than the rest of the person, organ, or tissue. This may happen because of a mutation (genetic change) that occurs during development, or as a result of a transplant of cells, organs, or tissues.[35]

Chromosome: a chromosome is a string of DNA wrapped around proteins that contains the genetic material of a person. A chromosome is like a book, carrying a specific group of genes. Hemophilia is passed down from parent to child through the chromosomes that determine sex.[7]

Cell: Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells also contain the body's hereditary material and can make copies of themselves.[45]

Cellular Therapy: Another type of treatment where "donor" cells are collected and transplanted into the body to produce the missing factor. Cell therapy is different from gene therapy in that gene therapy infuses genetic material as the therapy, but cell therapy uses actual cells as the therapy.[12]

Clinical Trials: clinical trials are research studies where researchers test treatments to determine how well the treatment works and how safe the treatment is before it can be used by the general public.

Clinical Trials Phase: The stage of a clinical trial studying a new treatment. The phase is based on the study's plan for the treatment, the number of people that are part of the clinical trial testing, and other characteristics. There are five phases: Early Phase 1 (formerly Phase 0), Phase 1, Phase 2, Phase 3, and Phase 4. "Not Applicable" is a term used to describe trials that do not have FDA-defined phases, an example would be a trialfor behavioral interventions.

- Phase 1: In this phase, a small group of healthy volunteers (people who don't have the condition being treated) is given the new treatment for the first time. The goal is to find out if the treatment is safe and to figure out the right dosage.
- Phase 2: In this phase, a larger group of people with the condition being studied is given the treatment. This phase helps researchers understand if the treatment works for the specific condition and to further study its safety.
- Phase 3: This is the final and largest phase before a new treatment can be approved. It involves a much larger group of people with the condition. Researchers compare the new treatment to the current standard treatment to see if it's better, safer, or equally effective.
- Phase 4: This phase occurs after the treatment is approved and is available to the public. It's sometimes called post-marketing surveillance. In this phase, doctors and scientists continue to monitor the treatment to ensure it remains safe and effective in a larger population.

Codon: a code in our DNA that tells our cells to build specific parts of our body. A codon is made up of three building blocks, called nucleotides.

Codon Optimization: a process that scientists use to increase production of proteins using codons. This process is used in gene therapy for hemophilia to increase the effectiveness of the treatment.[2]

CRISPR: a newer approach to gene editing, the CRISPR system is a groundbreaking technology that changes the non-working gene in the body. This is done by changing a person's DNA to remove the non-working gene and put in the correct gene. CRISPR is different than gene therapy due to the difference in where the gene is located. Gene therapy inserts a healthy version of the gene but the non-working gene is still in the body. CRISPR corrects, replaces, and removes the mutated gene on the DNA level, by completely removing the incorrect gene from the body. There are currently no treatments for bleeding disorders that use CRISPR, however, scientists are researching CRISPR for bleeding disorders.[10]

Cytokines: proteins that send messages throughout the body. Cytokines are typically associated with regulating the immune system. Cytokines are also associated with inhibitors in bleeding disorders when the body incorrectly attacks the bleeding disorder treatment as an "invader." [3]

## D

Dendritic cell: a type of immune cell that acts as a messenger between the innate immune system and the adaptive immune system. Dendritic cells are created from bone marrow and typically are found in the skin, intestines, and nostril. Dendritic cells play an important role in the development of inhibitors for hemophilia.[42]

Deoxyribonucleic Acid (DNA): the molecules inside cells that carry genetic information and pass it from one generation to the next.

DNA Backbone: a part of DNA that is a repeated pattern of sugar and phosphate molecules that join together the building blocks of DNA, nucleotides, in a sequence which provides the structural framework.

Dominant: a member of a pair of alleles that expresses the specific phenotype (trait) while the other remains silent. For example, Von Willebrand Disease can be a dominant trait, which means that if two parents are having a child and one parent has VWD and one does not, it is more likely that the child will have mild to moderate VWD due to the dominance of the trait.[22]

Dose escalation: the percent increase between dose levels in treatments.

De novo: the first occurrence of something in science research also called new mutation or new variant. A genetic change that is present for the first time in one family member as a result of a variant (or mutation) in a germ cell (egg or sperm) of one of the parents, or a variant that happens in the fertilized egg.[36]

Double helix: the three-dimensional structure of DNA where two strands are wound together in a helix pattern.

## E

Endocytosis: the process by which molecules are brought into a cell. Endocytosis is important in gene therapy because the Adeno-associated virus with the correct genetic information is brought into the target cells through endocytosis.[48]

Endothelial Cells: cells that line the blood vessels and are important in the process of blood clotting and preventing too much bleeding.[1]

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Enzyme: a special type of protein that speeds up reactions in the body. Blood factors are considered enzymes. Enzyme replacement therapy is the more technical term for Factor Replacement Therapy.[13]

Exogenous: introduced from or produced outside the organism or system

Ex vivo: outside of the living body

## F

Functional gene: A portion of the chromosome DNA that provides instructions for a specific function. The functional gene is what is targeted for gene therapy for hemophilia.[2]

Functional protein: A protein that serves a function in the body, for example: Coagulation Factors are functional proteins that help the body clot blood. Gene therapy for hemophilia generates a functional protein to help with blood clotting.[13]

## G

Gene: Genes act as instructions for the body's DNA which tells our body how to make specific things, like proteins. Clotting factors that allow the blood to clot are created by specific genes that get passed down from parent to offspring. Bleeding disorders, like hemophilia, would have a mutation in the genes that create clotting factors.[29]

Gene deletion: a type of genetic mutation that results in the loss of genetic material, such as specific sections of DNA. This is a common type of genetic mutation that causes bleeding disorders, such as hemophilia. There is evidence that large gene deletions in hemophilia patients may have a correlation to inhibitor development.[14]

Gene duplication: a type of genetic mutation that results in genetic material being copied. This type of genetic mutation is typically evidence of genetic evolution. An example would be how dogs can see different color pigments than humans can, which occurred over time.[28]

Gene editing: Gene editing is where the gene of a person gets changed by either adding, deleting, or correcting bits of DNA. Scientists are currently researching ways that gene editing can help hemophilia patients beyond gene therapy or factor replacement therapy.[39]

Genetic mutation: A permanent change or alteration to the order of DNA that makes up a gene. Mutations can be good, bad, or have no impact at all. Certain mutations cause disease. For example, a genetic mutation is what causes hemophilia (Factor VIII(8) or Factor IX(9)) deficiency.[21]

Gene therapy: A type of treatment in which foreign or altered genetic material (DNA or RNA) is inserted into a person's cells to prevent or fight disease. Gene therapy has recently been approved as a treatment for people with hemophilia A or B.[38]

Genome: All the genetic information of a cell or organism. In humans, almost every cell in the body contains a complete copy of the genome. The genome contains all the information needed for a person to develop and grow.

Genotoxicity: the ability of a substance to damage the genetic material in a cell. This is a type of complication that can happen in gene therapy for hemophilia where the gene therapy has a genotoxic effect on the body. Many researchers are looking into what can cause genotoxicity and how to overcome it.[33]

Germline cells: The cells from which eggs or sperm come from, essentially the sex cells that sexually reproducing organisms (such as humans) pass down genomes from one generation to the next. Researchers that focus on gene therapy, study the effect gene therapy can have on the germline of humans.[15]

Glycoprotein: A type of protein that has specific types of sugar molecules. The key molecules in our innate and adaptive immune systems are made up of glycoproteins. These immune systems are vital to understanding how gene therapy affects the body.[41]

## H

Hematopoietic Stem Cells: To understand Hematopoietic stem cells, it is important to understand stem cells. Stem cells are considered the "master" cells in the body, all other cells in the body originally come from stem cells. Hematopoietic stem cells are stem cells that come from bone marrow and make types of blood cells. Researchers are currently looking into how hematopoietic stem cells can be used in gene therapy for hemophilia, specifically the challenges that inhibitors present in gene therapy.[32]

Hepatocytes: Hepatocytes are liver cells; they make up 80% of the liver. The liver is an important organ in gene therapy for hemophilia because the blood clotting factors associated with hemophilia are located in the liver.[13]

Herpes Simplex Virus (HSV): A type of virus that causes herpes infections and has DNA as its genetic material. HSV is a type of virus, similarly to AAV, that can be used for gene therapy.[11]

Human Embryonic Kidney Cells: Human Embryonic Kidney Cells (HEK for short) are specific to a cell line called HEK 239 which are kidney cells from a human embryo back in 1973. What is special about HEK 239 is that when the cell line was exposed to adenovirus, the cells rapidly regenerated, and are very stable.. HEK 239 is important to know for gene therapy because these cells are used to create the gene therapy for hemophilia.[34,37]

# GENE AND INNOVATIVE THERAPIES GLOSSARY

## I

In vivo: In the body. The opposite of in vitro.

In vitro: In the laboratory (outside the body). The opposite of in vivo.

Integration: The process where new genetic information is put into the host genome. Integration describes the process in gene therapy where the genetic information to make the missing blood clotting factor is put into the viral host genome, AAV in the case of hemophilia gene therapy.[40]

Inverted Terminal Repeats: Inverted Terminal Repeats (ITR) are a sequence of nucleotides at the ends of the genome in Adeno-Associated Viruses. ITRs are the foundation of gene replication (the process where a gene is copied for new cells) which is a vital process for gene therapy for hemophilia.[6]

Immune Response: The activity of the immune system against things it does not recognize (antigens). The immune response to gene therapy for hemophilia can determine how long the therapy continues to improve factor levels in the body.[16]

## L

Lentiviral Vectors: A viral vector used in gene therapy that uses lentivirus as its blueprint. Lentivirus (LV) is the type of virus found in HIV. Lentiviral vectors are just as effective in gene therapy as Adeno-associated virus. LV vectors are good for gene therapy because of how much genetic material the vector can hold and bring into the body.[30]

Liposome: A tiny structure in the body that acts as a delivery system. Liposomes are commonly used in drug delivery for certain treatments because the liposome can be modified easily. For example, there have been promising treatments and clinical trials for people with hemophilia with an inhibitor that use liposomes to bring concentrated factor into the body. The outside of the liposome gets changed so that it can stay in the body for longer, extending its half-life.[24,47]

## M

Monogenic: Traits that are caused by one single gene. Hemophilia is a monogenic mutation.[5]

Mutagenesis: how genetic mutations are created.

Mutation: Any change in the DNA. Mutations may be caused by mistakes during cell division or may be caused by exposure to DNA-damaging agents in the environment. Mutations can be good, bad, or have no impact at all. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases. Hemophilia is a genetic mutation of the X Chromosome, one of two genes that relate to biological sex. This makes hemophilia an inheritable disease.[21]

## N

Neutralizing Antibody: when the immune system determines that there is a foreign invader in the body, it will send immune cells to the invaders. One type of cell that gets sent is called a neutralizing antibody and what it does is to bind to the invader and prevent that invader from doing any harm in the body. What makes neutralizing antibodies different and important is that they can prevent harm from an invader all by itself instead of having to rely on other immune cells. Neutralizing antibodies can be good for the body, however, in the case of gene therapy for hemophilia, some people may develop neutralizing antibodies towards the Adeno-Associated virus, preventing the gene therapy from working.[26]

Nucleus: In biology, the nucleus is the structure in a cell that contains chromosomes – the building blocks to all the body's genes.

Nucleotide: A nucleotide is a chain of molecules called nucleic acids. Nucleic acids store all the body's genes, which makes the nucleotide the main structure of DNA and RNA.

Non-viral vector: A delivery system in the body that does not use a virus to get the gene into the body. Gene therapy for hemophilia uses viral vectors, so there is still a virus being used to get the functioning gene into the body. Researchers are trying to find ways to create gene therapy using non-viral vectors.[44]

Nanoparticle: A particle that is smaller than 100 nanometers (one-billionth of a meter). In medicine, nanoparticles can be used to carry antibodies, drugs, imaging agents, or other substances to certain parts of the body.

Nucleases: A type of enzyme that breaks apart nucleotides into smaller pieces, like scissors.

## P

Placebo: A substance or treatment that looks the same, and is given in the same way, as the real drug or intervention/treatment being studied but does not have any effect on the person taking it. Placebos are important in clinical trials so that researchers can make sure the drug is what is affecting the patient and not the placebo.

Protein: A large molecule in the body that is important to life. Proteins are directly involved with chemical processes in the body, such as DNA copying, responding to a stimulus, and providing structure to our cells.[27]

## R

Replication cycle: In biology, refers to the reproduction cycle of viruses. A replication cycle begins with the infection of a host cell and ends with the release of new virus particles. The replication cycle does not exist in adeno-associated virus, the viral vector for gene therapy for hemophilia.[25]

Ribonucleic Acid (RNA): One of two types of nucleic acids made by cells. RNA contains information that has been copied from DNA (the other type of nucleic acid). Cells make several different forms of RNA, and each form has a specific job in the cell. Many forms of RNA have functions related to making proteins. RNA is also the genetic material of some viruses instead of DNA. RNA can be made in the laboratory and used in research studies.

Retroviruses: type of RNA-based virus that can copy DNA into the intended cell's nucleus. Retroviruses were first looked at for hemophilia gene therapy back in the 1990's.[18]

Recessive: Certain body characteristics (like eye color) will only be present in offspring when both sets of parents have that specific trait. In cases where parents have different traits (like different eye colors) the dominant trait will be present. Hemophilia is a recessive genetic disease.

## S

Somatic Cells: Any cell of the body except for sperm and egg cells. Somatic cells are diploid, meaning they have two sets of chromosomes, one from each parent. Mutations in somatic cells can affect the individual, but they are not passed on to offspring.

Starting dose: The dose chosen to treat the first group of patients in a phase I clinical trial.

Systemic administration: A method to deliver medication into the cardiovascular system so it circulates in the blood and affects the whole body.

## T

TALENs: TALEN (transcription activator-like effector nuclease) is a new nuclease technique in gene editing where sections of DNA can be targeted and edited (changed). This technique is precise and efficient for gene editing and is being studied as part of gene editing to correct hemophilia. TALEN is similar in mechanism to CRISPR, a more popular gene editing technique.[39]

Titer: A measurement of the amount (concentration) of something in a solution. It commonly refers to the number of antibodies found in a person's blood.[23]

Transgene: A gene that has been transferred from the genome of one species into that of another to produce therapeutic results. An example of this would be a genetic hybrid of human and porcine (pig) (F)VIII had higher expression of the clotting factor than standalone human (F)VIII in viral-vector gene therapy in 2009. Essentially, the pig (F)VIII had been genetically engineered (transgene) with the human (F)VIII to create a more efficient therapeutic for gene therapy.[9]

Transcription: For the body to express a gene, our DNA needs to be made into proteins. The first step in this process is called transcription, where DNA is copied (like a copy machine) to create RNA. After transcription is done, RNA is translated to make the proteins – called translation.

Translation: the second part of gene expression where the RNA that was copied by DNA is then translated to proteins – the building blocks of life.

## V

Virus: In medicine, a very simple microorganism that infects cells and may cause disease. Because viruses can multiply only inside infected cells, they are not considered to be alive.

Vector: In biology, a vector is part of a molecule that carries DNA and is used as a vehicle to carry a specific DNA segment into a host cell. Vectors are used to carry functional genes into the liver cells for gene therapy for hemophilia.[43]

Vector shedding: where the body gets rid of the viral vector gene therapy products after treatment. Typically, the shedding occurs through bodily fluids (blood, semen, saliva).

## X

X-linked dominant inheritance: An inheritance pattern where a genetic condition associated with a disease on the X chromosome is passed down. Males carrying the mutation will always have the trait because there is only one X chromosome. However, in females that have both X chromosomes, the disease will only be present if both X-chromosomes carry the mutation.

X-linked recessive inheritance: An inheritance pattern where a genetic condition is associated with mutations in genes on the X chromosome. A male carrying such a mutation will be affected because he carries only one X chromosome. A female carrying a mutation in one gene, with a normal gene on the other X chromosome, is generally not affected.

## REFERENCES


1. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., & Walter, P. (2002). Blood vessels and endothelial cells. Molecular Biology of the Cell - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK26848/
2. Amit C. Nathwani; Gene therapy for hemophilia. Hematology Am Soc Hematol Educ Program 2019; 2019 (1): 1–8. doi: https://doi.org/10.1182/hematology.2019000007
3. Ananyeva, Natalya Ma; Lacroix-Desmazes, Sebastienb; Hauser, Charlotte AEc; Shima, Midorid; Ovanesov, Mikhail Va; Khrenov, Alexey Va; Saenko, Evgueni La. Inhibitors in hemophilia A: mechanisms of inhibition, management and perspectives. Blood Coagulation & Fibrinolysis 15(2):p 109-124, March 2004.
4. Araújo, N. M., Rubio, I. G. S., Toneto, N. P. A., Morale, M. G., & Tamura, R. E. (2022). The use of adenoviral vectors in gene therapy and vaccine approaches. Genetics and molecular biology, 45(3 Suppl 1), e20220079. https://doi.org/10.1590/1678-4685-GMB-2022-0079
5. Bertamino, M., Riccardi, F., Banov, L., Svahn, J., & Molinari, A. (2017). Hemophilia care in the pediatric age. Journal of Clinical Medicine, 6(5), 54. https://doi.org/10.3390/jcm6050054
6. Blogger, G. (n.d.). Viral Vectors 101: Inverted Terminal repeats. https://blog.addgene.org/viral-vectors-101-inverted-terminal-repeats
7. Chuah, M.K.L., Collen, D. and VandenDriessche, T. (2001), Gene therapy for hemophilia. J. Gene Med., 3: 3-20. https://doi.org/10.1002/1521-2254(200101/02)3:1<3::AID-JGM167>3.0.CO;2-H
8. Daya, S., & Berns, K. I. (2008). Gene therapy using Adeno-Associated virus vectors. Clinical Microbiology Reviews, 21(4), 583–593. https://doi.org/10.1128/cmr.00008-08
9. Doering, C. B., Denning, G., Dooriss, K., Gangadharan, B., Johnston, J. M., Kerstann, K. W., McCarty, D. A., & Spencer, H. T. (2009). Directed engineering of a high-expression chimeric transgene as a strategy for gene therapy of hemophilia A. Molecular Therapy, 17(7), 1145–1154. https://doi.org/10.1038/mt.2009.35
10. Dtvadmin. (2021, June 27). What is the Difference Between Gene Therapy and CRISPR. CRISPR Cas9 - Gene Editing. https://cas9.com/what-is-the-difference-between-gene-therapy-and-crispr/
11. Eisensmith, R. C., & Woo, S. L. C. (1997). Viral Vector-Mediated Gene Therapy for Hemophilia B. Thrombosis and Haemostasis, 78(01), 024–030. https://doi.org/10.1055/s-0038-1657495
12. Fomin, M., Togarrati, P., & Muench, M. (2014). Progress and challenges in the development of a cell-based therapy for hemophilia A. Journal of Thrombosis and Haemostasis, 12(12), 1954–1965. https://doi.org/10.1111/jth.12750
13. George Q. Perrin, Roland W. Herzog, David M. Markusic; Update on clinical gene therapy for hemophilia. Blood 2019; 133 (5): 407–414. doi: https://doi.org/10.1182/blood-2018-07-820720
14. Goodeve, A. C. (2015). Hemophilia B: molecular pathogenesis and mutation analysis. Journal of Thrombosis and Haemostasis, 13(7), 1184–1195. https://doi.org/10.1111/jth.12958
15. Gura, T. (2002). Gene therapy and the germ line. Molecular Therapy, 6(1), 2–4. https://doi.org/10.1006/mthe.2002.0642
16. Herzog, R. W. (2015). Hemophilia gene therapy: caught between a cure and an immune response. Molecular Therapy, 23(9), 1411–1412. https://doi.org/10.1038/mt.2015.135
17. High, K. H., Nathwani, A., Spencer, T., & Lillicrap, D. (2014). Current status of haemophilia gene therapy. Haemophilia, 20(s4), 43–49. https://doi.org/10.1111/hae.12411
18. Hoeben, R. C., Einerhand, M. P. W., Briët, E., Van Ormondt, H., Valerio, D., & Van Der Eb, A. J. (1992). Toward Gene Therapy in Haemophilia A: Retrovirus-Mediated Transfer of a Factor VIII Gene into Murine Haematopoietic Progenitor Cells. Thrombosis and Haemostasis, 67(03), 341–345. https://doi.org/10.1055/s-0038-1648444
19. Hosel, M., Huber, A., Bohlen, S., Lucifora, J., Ronzitti, G., Puzzo, F., Boisgerault, F., Hacker, U. T., Kwanten, W. J., Kloting, N., Bluher, M., Gluschko, A., Schramm, M., Utermohlen, O., Bloch, W., Mingozzi, F., Krut, O., & Buning, H. (2017). Autophagy determines efficiency of liver-directed gene therapy with adeno-associated viral vectors.
20. Hepatology, 66(1), 252–265. https://doi.org/10.1002/hep.29176
21. How hemophilia is inherited. (2024, May 15). Hemophilia. https://www.cdc.gov/hemophilia/testing/how-hemophilia-is-inherited.html?CDC_AAref_Val=https://www.cdc.gov/ncbddd/hemophilia/inheritance-pattern.html
22. How von Willebrand Disease Is Inherited. (2024, May 15). Von Willebrand Disease (VWD). https://www.cdc.gov/von-willebrand/about/how-vwd-is-inherited.html?CDC_AAref_Val=https://www.cdc.gov/ncbddd/vwd/inherited.html
23. Jain, M. et al. (2023). Introduction to Protein Therapeutics. In: Singh, D.B., Tripathi, T. (eds) Protein-based Therapeutics. Springer, Singapore. https://doi.org/10.1007/978-981-19-8249-1_1
24. Jardim, L. L., Chaves, D. G., & Rezende, S. M. (2020). Development of inhibitors in hemophilia A: An illustrated review. Research and Practice in Thrombosis and Haemostasis, 4(5), 752–760. https://doi.org/10.1002/rth2.12335
25. Kimura, T., Ferran, B., Tsukahara, Y. et al. Production of adeno-associated virus vectors for in vitro and in vivo applications. Sci Rep 9, 13601 (2019). https://doi.org/10.1038/s41598-019-49624-w
26. Li, C., Narkbunnam, N., Samulski, R. et al. Neutralizing antibodies against adeno-associated virus examined prospectively in pediatric patients with hemophilia. Gene Ther 19, 288–294 (2012). https://doi.org/10.1038/gt.2011.90
27. Lynn M Knowles, Carolin Wolter, Michael D. Menger, Matthias W. Laschke, Felix Haegele, Hermann Eichler, Jan Pilch; Blood-Induced Inflammation in Hemophilia. Blood 2022; 140 (Supplement 1): 2707. doi: https://doi.org/10.1182/blood-2022-170235

28. Libretexts. (2023, October 31). 18.4D: Gene Duplications and Divergence. Biology LibreTexts. https://bio.libretexts.org/Bookshelves/Introductory_and_General_Biology/General_Biology_(Boundless)/18%3A_Evolution_and_the_Origin_of_Species/18.04%3A_Evolution_of_Genomes/18.4D%3A_Gene_Duplications_and_Divergence
29. Mehta, P., & Reddivari, A. K. R. (2023, June 5). Hemophilia. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK551607/
30. Milani, M., Annoni, A., Moalli, F., Liu, T., Cesana, D., Calabria, A., Bartolaccini, S., Biffi, M., Russo, F., Visigalli, I., Raimondi, A., Patarroyo-White, S., Drager, D., Cristofori, P., Ayuso, E.,
31. Montini, E., Peters, R., Iannacone, M., Cantore, A., & Naldini, L. (2019). Phagocytosis-shielded lentiviral vectors improve liver gene therapy in nonhuman primates. Science Translational Medicine, 11(493). Secondary Typography
32. Moayeri, M., Hawley, T. S., & Hawley, R. G. (2005). Correction of murine hemophilia a by hematopoietic stem cell gene therapy. Molecular Therapy, 12(6), 1034–1042. https://doi.org/10.1016/j.ymthe.2005.09.007
33. Monahan, P. E., Négrier, C., Tarantino, M., Valentino, L. A., & Mingozzi, F. (2021). Emerging immunogenicity and genotoxicity Considerations of Adeno-Associated Virus vector gene therapy for hemophilia. Journal of Clinical Medicine, 10(11), 2471. https://doi.org/10.3390/jcm10112471
34. Nathwani A. C. (2019). Gene therapy for hemophilia. Hematology. American Society of Hematology. Education Program, 2019(1), 1–8. Secondary Typography
35. NCI Dictionary of Cancer Terms. (n.d.). Cancer.gov. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chimeric
36. NCI Dictionary of Genetics Terms. (n.d.). Cancer.gov. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/de-novo-mutation
37. News-Medical. (2019, January 8). HEK293 cells: Applications and Advantages. https://www.news-medical.net/life-sciences/HEK293-Cells-Applications-and-Advantages.aspx
38. Nienhuis, A. W., Nathwani, A. C., & Davidoff, A. M. (2017). Gene Therapy for Hemophilia. Molecular Therapy, 25(5), 1163–1167. https://doi.org/10.1016/j.ymthe.2017.03.033
39. Park, CY., Lee, D.R., Sung, J.J. et al. Genome-editing technologies for gene correction of hemophilia. Hum Genet 135, 977–981 (2016). https://doi.org/10.1007/s00439-016-1699-x
40. Rogers, G. L., & Herzog, R. W. (2015). Gene therapy for hemophilia. Frontiers in bioscience (Landmark edition), 20(3), 556–603. https://doi.org/10.2741/4324
41. Rudd, P. M., Elliott, T., Cresswell, P., Wilson, I. A., & Dwek, R. A. (2001). Glycosylation and the immune system. Science, 291(5512), 2370–2376. https://doi.org/10.1126/science.291.5512.2370
42. Tieu, P., Chan, A., & Matino, D. (2020). Molecular Mechanisms of Inhibitor Development in Hemophilia. Mediterranean journal of hematology and infectious diseases, 12(1), e2020001. https://doi.org/10.4084/MJHID.2020.000
43. Vector. (n.d.). Genome.gov. https://www.genome.gov/genetics-glossary/Vector
44. Viral and non-viral vectors | lentiviral, adenoviral & AAV. (n.d.). Gene Therapy. https://www.thegenehome.com/how-does-gene-therapy-work/vectors
45. What is a cell?: MedlinePlus Genetics. (n.d.). https://medlineplus.gov/genetics/understanding/basics/cell/
46. Wu, D., Chen, Q., Chen, X., Han, F., Chen, Z., & Wang, Y. (2023). The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy, 8(1). https://doi.org/10.1038/s41392-023-01481-w
47. Yatuv, R., Robinson, M., Dayan-Tarshish, I., & Baru, M. (2010). The use of PEGylated liposomes in the development of drug delivery applications for the treatment of hemophilia. International Journal of Nanomedicine, 581.
48. Ziello, J. E., Huang, Y., & Jovin, I. S. (2010). Cellular endocytosis and gene delivery. Molecular Medicine, 16(5–6), 222–229. https://doi.org/10.2119/molmed.2009.00101


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