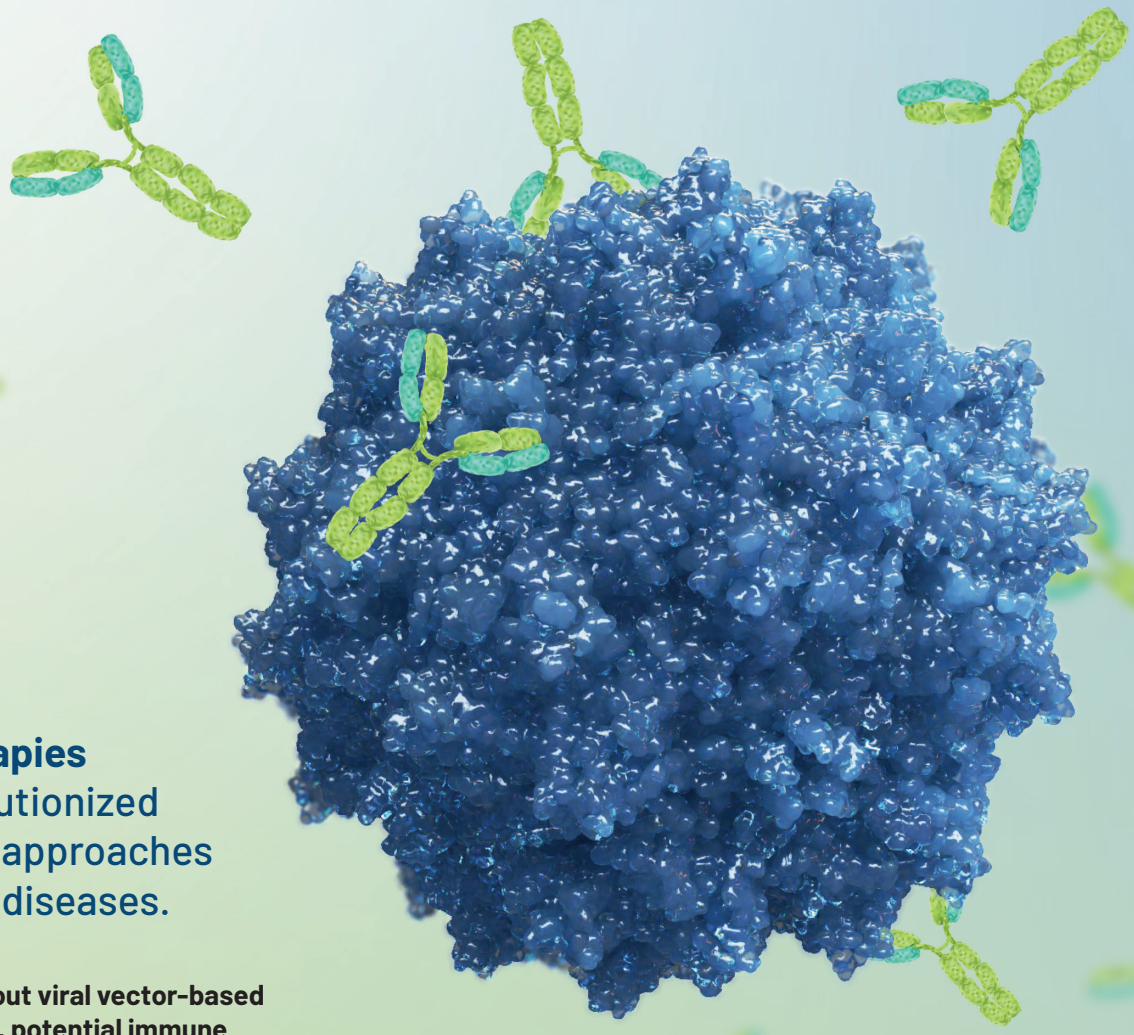
Immunogenicity
in Gene Therapy



Gene therapies have revolutionized treatment approaches to genetic diseases.

Learn more about viral vector-based gene therapies, potential immune response challenges, and optimizing patient outcomes.

Gene therapy for hemophilia A or B is not approved or for sale in Canada. Before prescribing any product, always refer to the local materials such as the Prescribing Information, Product Monograph, and/or the Summary of Product Characteristics in your country.

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What is Immunogenicity?

Immunogenicity is the ability of an antigen or foreign substance to trigger a coordinated immune response in the body. Treatment-induced immune responses may occur when exposed to a biologic therapy that the body perceives as foreign, such as protein-based or gene therapies. This response, as well as the presence of preexisting immunity to components of biologic therapies, may be an immunological obstacle to effective treatment.[1,2]

The immune system is comprised of a network of cell types that work together to protect the body from further infection and eliminate foreign substances. The cellular networks that drive immunogenicity are divided into two types: innate and adaptive immunity. Innate and adaptive immune mechanisms occur simultaneously to allow a full range of responses of appropriate strength and specificity.[3]

Innate vs Adaptive Immunity

INNATE IMMUNITY

Rapid, nonspecific immune responses that are the first line of defense against foreign antigens[3,4]

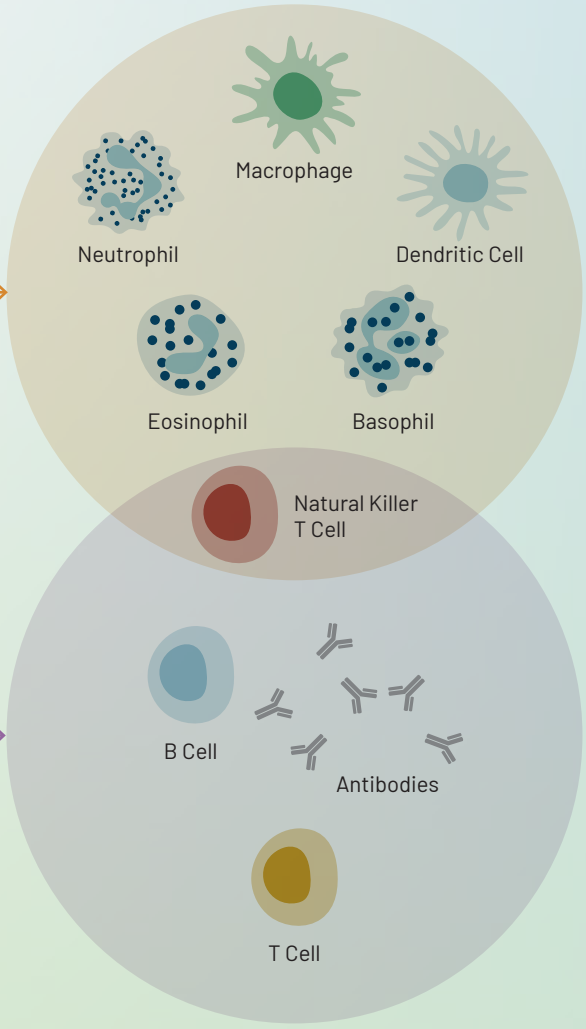
- Broad recognition of antigens
- Nonspecific with no immunological memory such that the same speed and strength of immune response is mounted upon subsequent exposures
- Target cell lysis is carried out primarily by neutrophils, macrophages, and natural killer cells. Dendritic cells interact with pathogen antigens and can activate the adaptive immune response

ADAPTIVE IMMUNITY

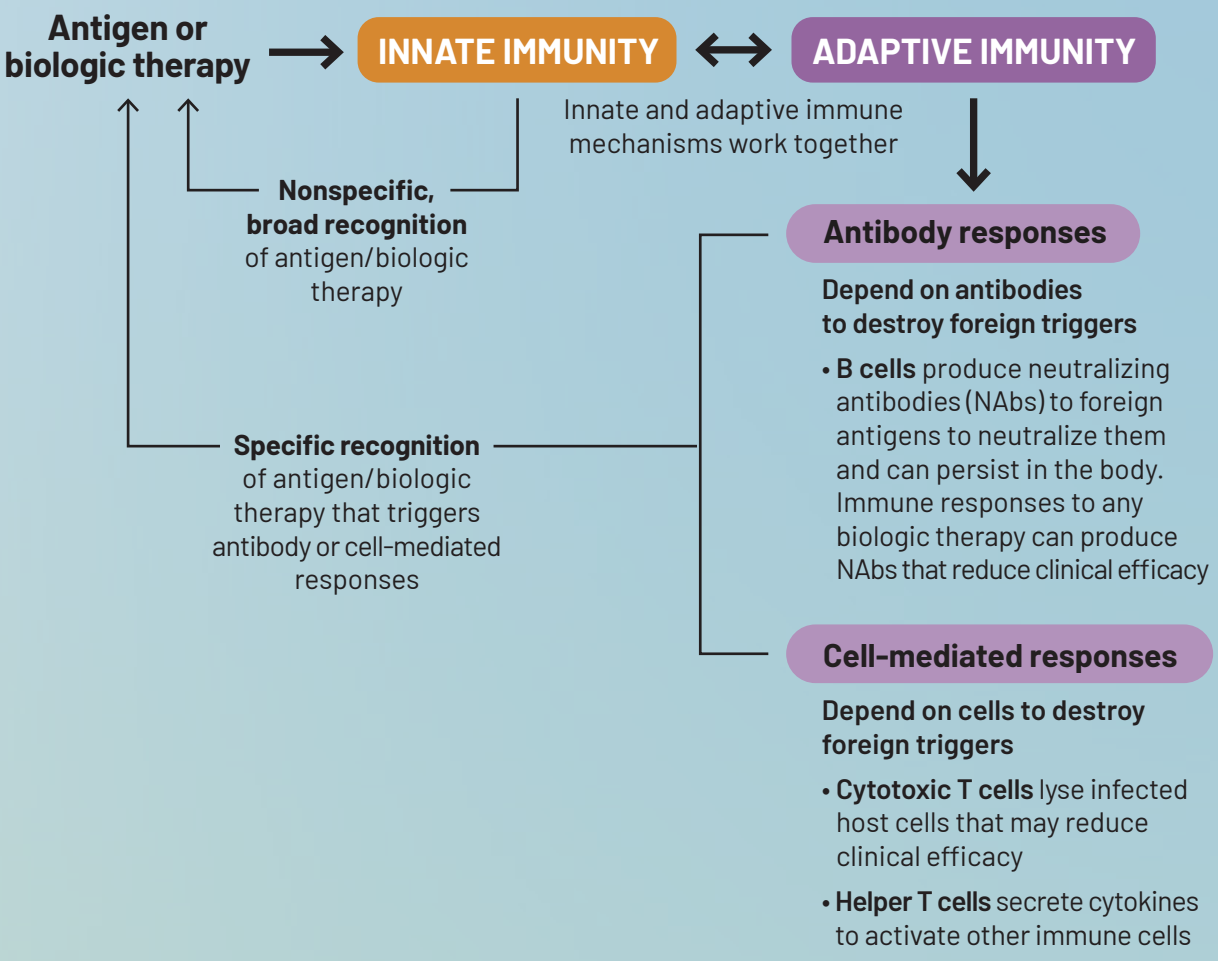
Antigen-specific immune responses that include immune cells designed to recognize and attack foreign antigens[3,4]

- Specific recognition of antigens, or exposure to a foreign substance
- Eliminates antigens while generating an immunological memory so that an enhanced, more potent adaptive response is mounted upon subsequent exposures
- Mechanisms of adaptive immunity include antibody responses mediated by B cells and cell-mediated responses in T cells

Key Cells of the Innate and Adaptive Immune Responses[5]



Immunogenicity: Coordinated Immune Responses[3]



Immunogenicity and the potential for a physiologic response is an important consideration with biologic therapies, such as gene therapy or a protein therapeutic.[2]

The potential for immunogenicity is a factor when using biologic therapies, such as adeno-associated viruses (AAV)-based gene therapies in hemophilia, hereditary retinal dystrophy, and spinal muscular atrophy. Although immune responses and preexisting immunity can be a challenge for patient selection and treatment management, protein-based therapies and gene therapies have been studied for safety and efficacy.[1,6]

Immune Responses to Gene Therapy

The goal of gene therapy strategies based on gene transfer (or gene addition) is to achieve long-term stable transgene expression at therapeutic levels in order to treat genetic diseases. Gene therapies utilize viral vectors to deliver functional genes to patients.[7]

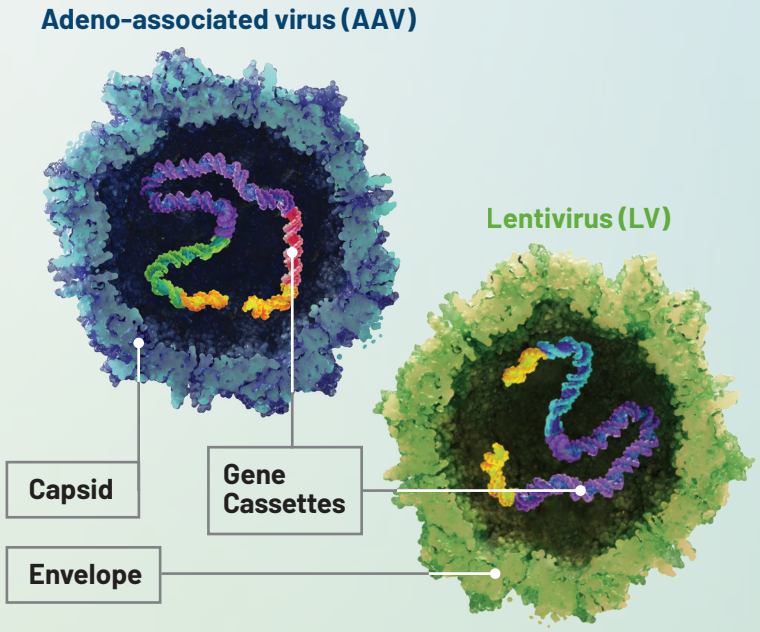
Gene therapy, specifically gene transfer, takes advantage of the ability of viruses to deliver genetic material to host cells. A functional gene is inserted into the viral vector and is transferred to target tissue or cells through either **in vivo (viral vector directly to patients)** or **ex vivo (extraction and viral transduction of patient stem cells that are transplanted back into the body)** gene delivery methods.[7,8]

Viral vectors can be engineered to minimize unwanted replication and deliver modified genes to physiologically relevant target tissues and cells.[7,8]

Most Common Viral Vectors Used in the Development of Gene Therapies

The two most common types of viral vectors are **lentiviruses** and **adeno-associated viruses**. Immune responses may be triggered by various components of viral vectors that the body recognizes as foreign.[1,7]

- The **capsid** and **envelope** are derived from wild type (WT) viruses to deliver genetic material into cells. Virally derived capsid or envelope proteins constitute foreign antigens that can become the target of immune responses. Immune responses can limit the number of target cells that express the functional gene[1]
- **Gene cassettes** include a therapeutic gene, or transgene, and regulatory elements necessary for transgene expression. The transgene product that constitutes foreign antigens may be similarly targeted by immune responses[9,10]



Considerations for Viral Vector Design and Gene Therapy Strategies

Gene therapy techniques utilize a delivery system through a viral vector to aid delivery of the therapeutic gene. Design considerations for gene therapy depend on the primary genetic defect, the size of the modified gene, and the features of the target organ or tissue.[8]

- **Target cell or organ** (dividing, non-dividing cells)[7]
- **Size** of the gene cassette[7]
- **Packaging capacity** of the virus[7]
- **Delivery method** (in vivo, ex vivo)[7]
- Potential to **integrate** into the host genome[7]

Overview of Common Viral Vectors and Immune Responses

During the process of administering gene therapy, either by in vivo or ex vivo administration, the viral vector can be recognized as foreign and can elicit an immune response.[1]

Viral Vector	**AAV** • Capsid, ≤5-kb ssDNA genome • In vivo delivery method	**LV** • Envelope, 10-kb ssRNA genome • Ex vivo delivery method
Preexisting immunity to WT viruses	**Varies** by serotype based on lifelong exposures to WT AAVs	**Low** preexisting immunity due to limited natural exposure to LVs
Innate immunity	**Weak and transient;** immunotoxicities seen in some patients receiving high doses of gene therapy	**Strong;** interferon-α/β response limits transduction and drives adaptive responses
Adaptive immunity to vector	**NAb formation;** T-cell responses to capsid	**NAb formation;** possibly T-cell responses to envelope protein
Adaptive immunity to transgene product	**Low inducer** of T-cell responses	**High inducer** of B- and T-cell responses

Immunogenicity to WT AAV and AAV vectors is complex and varies by individual. In clinical trials, AAV vectors are widely studied due to their lack of pathogenicity, low immunogenicity, and low risk of integration into the host genome. Ongoing trials for AAV-based gene therapies continue to gain a better understanding of patient risk factors, safety, efficacy, and durability of treatment. Real-world experience gained by recently approved therapies will also contribute to a better understanding of the impact.[1,7,11,12]

Despite immunogenicity challenges, gene therapies have demonstrated durable clinical benefit from a single administration.[12-15]

Factors That Influence AAV Vector Immunogenicity

AAV vectors are generally considered less immunogenic than other vectors, but immune responses have the potential to impact outcomes (magnitude, predictability, and/or durability of efficacy) in some individuals.[7,16]

Preclinical studies and clinical trials have provided important information about immunogenicity. Numerous factors, including patient- and vector- related factors, may contribute to the extent and the impact of the immune responses to AAV-based gene therapies. Other factors in manufacturing and administration should also be noted.[17]

Patient-related Factors[17]

Targeted tissue

Type and health of targeted tissue can influence the severity of immune responses

Genetic background

Type of genetic mutation and its phenotype may influence the potential for immune response (eg, if the phenotype limits protein expression, transgene protein may be identified as foreign)

Geographic location

Preexisting immunity varies based on AAV exposure, which differs based on the location of the individual

Age

Potential for preexisting immunity based on AAV exposure is less likely at a younger age

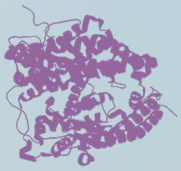
Vector-related Factors[17]

Capsid

Development of adaptive immune response and neutralizing antibodies to the capsid may prevent treatment

Transgene

Ubiquitous expression of a transgene in the body, as opposed to tissue-specific expression, may increase the risk of an immune response



Transgene product

Activation of immune response to the protein encoded by the transgene may be associated with immunotoxicities and loss of efficacy

Additional Factors[17]

- Route of administration (local vs systemic administration)
- Dosing (eg, higher dose levels can mean higher risk)
- Impurities introduced during the manufacturing process

Immunogenicity of AAV gene therapies is complex and variable due to the number of risk factors associated with individual patients and components of viral vectors.[17,18]

Immune Responses to AAV-based Gene Therapy:

The Interplay Between Treatment-induced and Preexisting Immunity

Adaptive immune system mechanisms that include antibody-mediated immune responses and cell-mediated responses can affect patients throughout the treatment journey.[16,17]

Antibody-mediated Immune Response to the AAV Capsid

Individual is exposed to AAVs in their lifetime[9]

Individual develops neutralizing antibodies against AAVs[9]

- About 30%–80% of people have preexisting antibodies to AAV serotypes due to natural exposure to AAVs[12]
- AAV serotypes differ in terms of their capsid properties[18]
- Immune responses can be influenced by the serotype of the particular vector and seropositivity varies based on an individual's past exposures[18]

Gene therapy administration[13]

- If the vector capsid is identical or nearly identical to the capsid proteins from past exposures, it can trigger host immune responses that produce NAbs, limiting the therapeutic effects of gene therapy[18]

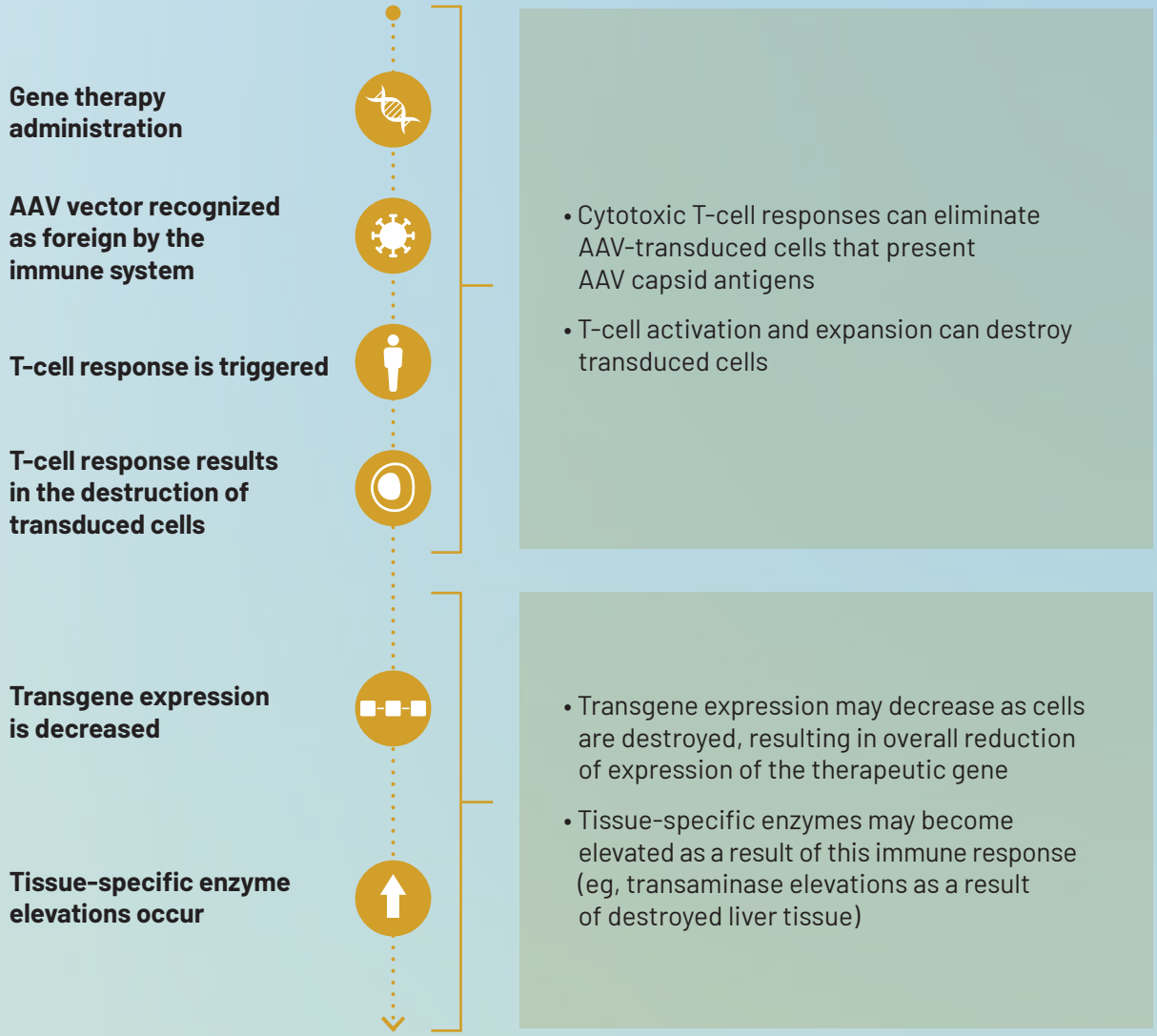
NAbs recognize and bind to the AAV vector[13]

Transgene expression is decreased in this individual[13]

- Preexisting NAbs can bind to AAV capsids and block them from entering target cells, (eg, hepatocytes), preventing transduction; hence, expression of the therapeutic gene is prevented[18]
- Treatment-induced AAV NAbs can also develop following gene therapy administration[18]

Capsid proteins of AAV vectors: Vector capsid proteins can be recognized as foreign antigens by targeted cells, leading to T-cell activation and destruction of the transduced cells.[10]

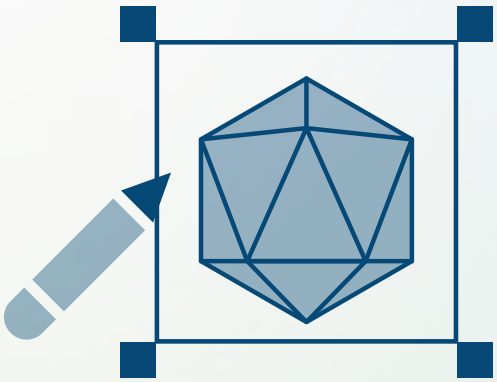
Cell-mediated Immune Response to the Transgene Protein[12,18]



Transgene immunogenicity may be less of a concern in liver-directed gene therapy: Constant exposure to non-self-antigens gives liver immunological properties that prevent uncontrolled immune activation. As muscles are not immune-privileged, administering therapy intramuscularly or targeting muscle tissue may lead to increased transgene immunogenicity.[10]

Potential Approaches for Optimizing Outcomes and Managing AAV Immunogenicity

To optimize therapeutic efficacy of gene therapy, immunogenicity management strategies must consider both antibody and cellular immune responses.[17]



Vector design and development[19]

- Selection of appropriate AAV serotype
- Optimal dosing of viral vectors and vector purity to decrease vector immunogenicity
- Engineering of the capsid and envelope to reduce immunogenicity

Patient selection and monitoring

- Diagnostic test to measure and predict immune response in order to help inform treatment decision (eg, NAb titers)[9,17]
- Monitor for elevated enzymes depending on target tissue[9,20]

Patient management and immunosuppressive regimens[17,18]

- Prophylaxis, prior to gene therapy administration (eg, corticosteroids, mycophenolate mofetil, etc.)
- On demand, in response to a detected immune reaction (eg, corticosteroids)

Immune Response to AAV-based Gene Therapy in Hemophilia

Hemophilia is an X-linked, hereditary, monogenic bleeding disorder that results in the absence or deficiency of coagulation FVIII (hemophilia A) or FIX (hemophilia B). Currently, there is no cure for hemophilia and the standard of care for moderate or severe disease is lifelong prophylaxis with factor replacement therapies. Episodic treatment is also recommended as needed. Recently, gene therapies have been approved to treat hemophilia A and hemophilia B in some countries. The goal of gene therapy in hemophilia is to significantly reduce bleeding episodes and factor replacement usage. Liver-directed gene therapy for hemophilia with AAV vectors has the potential to maintain endogenous factor levels after a single intervention.[13,20]

Both factor replacement therapies and AAV-based gene therapies have the potential for immunogenicity. For factor replacement therapies, the main complication of prolonged use is the development of factor inhibitors due to immune responses to the exogenous factor.[12,21]

Inhibitors are more common in individuals with hemophilia A than B, and factor inhibitors can eventually diminish the effect of these therapies. A history of factor inhibitors is a common exclusion criterion in gene therapy clinical trials. **Preexisting NAbs** are another consideration for AAV-vector based gene therapies, including those for hemophilia. Preexisting NAbs may limit liver transduction and desired therapeutic levels of transgene expression. As mentioned, AAV NAbs can develop following natural exposure with WT AAV or due to previous exposure to an AAV-based gene therapy, which provides humoral immunity to AAV. About 30%–80% of people have preexisting antibodies to AAVs that are acquired through natural infections. Preexisting AAV NAbs have the potential to neutralize the AAV vector, thus interfering with transduction of the therapeutic response to therapy. Presence of AAV NAbs is an exclusion criterion for enrollment in most clinical trials assessing gene therapy in hemophilia, with the exception of valoctocogene roxaparvovec and etranacogene dezaparvovec.[12,21,22]

Difference Between Inhibitors and Neutralizing Antibodies (NAbs)

Factor Inhibitors		NAbs
Antibodies develop through an immune response to exogenous FVIII and FIX replacement therapy and can potentially diminish the effect of the infused factors to prevent bleeding.[20]	VS	Preexisting anti-AAV neutralizing antibodies may develop against components of the AAV vector that can block cell transduction and therapeutic transgene expression levels.[12]

In addition to the humoral immune response to gene therapy, a cellular T-cell response may also be activated to the vector components within or outside of liver cells. Cell-mediated immune responses can lead to the destruction of transduced liver cells resulting in a transient increase in liver enzymes, or transaminitis, after administration of AAV liver-directed gene therapy. Elevations can return back to normal levels through the immune suppression. Transaminitis is a common adverse event in liver-directed gene therapy.[12]

Immune Response to AAV-based Gene Therapy in Hemophilia (continued)

Immunogenicity Considerations From Gene Therapy Clinical Trials in Hemophilia

	Hemophilia A			Hemophilia B	
	Valoctocogene roxaparvovec[20,22-25]	SPK-8011[20,26]	Giroctocogene fitelparvovec[27-29]	Etranacogene dezaparvovec[21,30]	Fidanacogene elaparvovec[18,31-33]
Clinical trials	NCT03370913 NCT03392974 NCT04323098 (Phase 3) NCT03520712 (Phase 1/2)	NCT03003533 (Phase 2)	NCT04370054 (Phase 3)	NCT03569891 (Phase 3)	NCT03861273 (Phase 3)
AAV serotype	AAV5	AAV-Spark200	AAV6	AAV5	AAV-Spark100
Studied in individuals with preexisting NAb titers*	✓†	—	—	✓	—
Studied in individuals with factor inhibitors	—	—	—	—	—
Included use of prophylactic immunosuppression	✓	✓	—	—	—
Use of on-demand immunosuppression after gene therapy administration (as needed)	✓	✓	✓	✓	✓
Post-treatment monitoring for immune response	✓	✓	✓	✓	✓

*Preexisting AAV NAbs (titer >1:5).[22]
†Study ongoing in people with severe hemophilia A and AAV5 NAbs.[22]

While AAV vectors are considered less immunogenic than other vectors, an immune response may pose a challenge for effective gene therapy. Nonetheless, significant progress has been made in vector design strategies of AAV-based gene therapies as well as management strategies to help mitigate the risks of the immunogenicity for individuals receiving therapy. More research is ongoing to thoroughly understand the immune response to gene therapies. Several therapies for hemophilia A and B are now approved for use around the world.[16,17,34-36]

Key Terminology

Antibody: A protein that circulates in the blood and binds to a foreign substance. Antibodies may be neutralizing (ie, inhibiting function) or non-neutralizing.

Antibody titer: A measure of how much antibody has been produced.

Antigen: Any substance, such as bacteria or viruses, that causes the body's immune system to generate antibodies against that substance.

Capsid: The outside protein shell that protects a virus and helps it penetrate a cell membrane. A capsid protects the contents and helps the virus attach to a targeted cell to penetrate the cell membrane. In gene therapy, the special characteristics of a capsid can enable gene delivery to specific cells.

Ex vivo gene therapy: A therapeutic technique in which some of the patient's cells are collected, genetically modified outside the body, and then delivered back into the patient for the treatment of disease.

Gene cassette: The genetic material the gene therapy vector delivers to the target cells. It typically contains the functional gene and other regulatory elements to help direct expression.

In vivo gene therapy: Gene therapy that delivers a new or corrected gene directly to cells inside the patient's body.

Neutralizing antibody (NAb): An antibody that defends hosts from a pathogen or infectious particle by neutralizing any effect it has biologically. In gene therapy, these antibodies may preexist in the host from prior exposure to naturally occurring AAVs and/or develop after exposure to the viral vector, inhibiting transduction and reducing clinical efficacy.

Seroprevalence: The number of people in a population that test positive for the antibody to an antigen, based on exceeding a titer threshold.

Serotype: Different subtypes of AAV are called serotypes. The different serotypes have distinct protein shells that influence delivery of the functional gene, activation of the human immune system, and their ability to enter different types of cells (tropism).

Transduction: The process of introducing genetic material into another cell by an infectious agent, such as a virus.

Transgene (or functional gene): Describes the working gene/genetic material that has been inserted in the gene delivery vehicle (vector).

Tropism: The natural attraction of a virus or vector to receptors present only on certain cells or tissues. Gene therapy researchers exploit tropisms to help different viruses, lipid particles, or other therapeutic carriers reach their target cells.

Vector: Delivery vehicles, or carriers, that encapsulate therapeutic genes for delivery to cells. These include both disabled viruses and non-viral vectors, such as lipid particles. Vectors do not replicate; they carry the functional gene to the cells.

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Immunogenicity in Gene Therapy: Key Takeaways

All biologic therapies, including gene therapy, have the potential to induce innate and adaptive immune responses that can influence safety and efficacy of the products. Gene therapies have been studied for safety and efficacy and some have been approved for use despite these challenges.[1,16]

Immunogenicity of AAV gene therapies can occur due to preexisting immunity to AAVs naturally acquired throughout an individual's lifetime.[12,18]

Strategies have been developed to minimize immunogenicity of AAV vector-based gene therapies, but research is continuing to optimize outcomes.[17-19]

Despite immunogenicity challenges, gene therapies have the potential to significantly improve therapeutic outcomes for many patients with genetic diseases.[16-18]

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