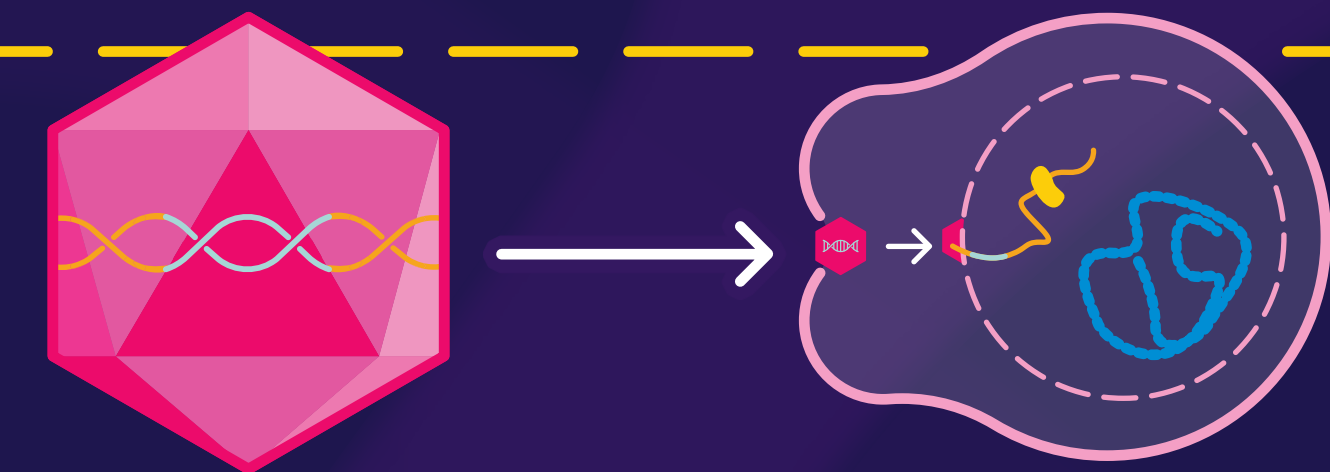


Viral Vector Platforms for Gene Therapy

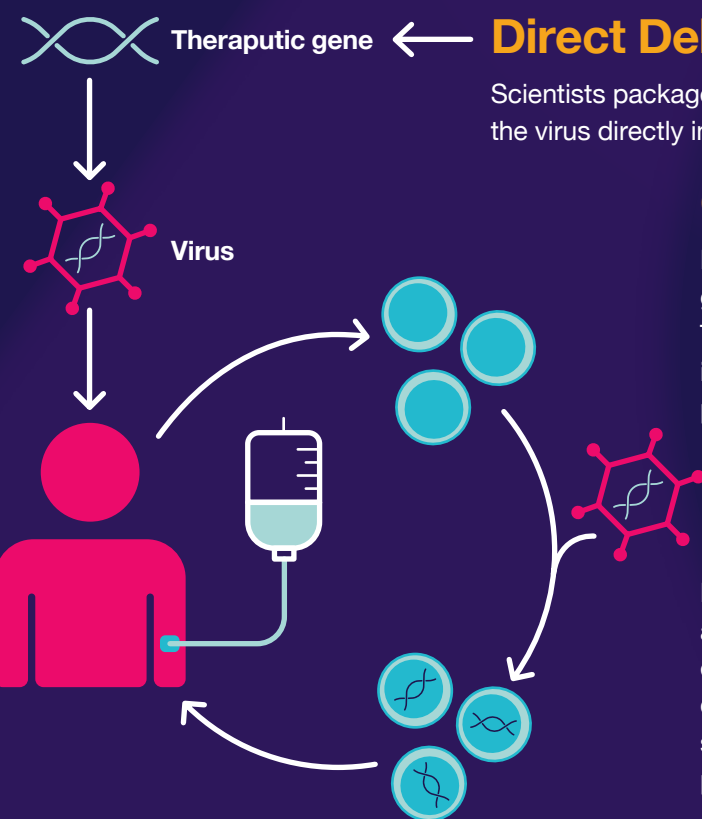
Viruses naturally reproduce by transferring genetic material into cells for transcription and translation. In both the laboratory and clinic, scientists harness this ability to develop gene therapies that modulate cellular function. Although viral delivery of gene therapies comes with safety and efficacy challenges, viral vector-based therapeutics are promising alternatives to conventional therapeutic strategies, in some cases offering better clinical benefit and less toxicity.



Gene Therapy Delivery Methods

Direct Delivery

Scientists package therapeutic genes into viruses for delivery and inject the virus directly into a patient or animal model.¹



Cell-Based Delivery

Researchers introduce the virus-packaged therapeutic gene into cells, such as patient-derived stem cells or T cells. These genetically modified cells are expanded in the laboratory and scientists administer them to a patient or animal model, or study them in culture.¹

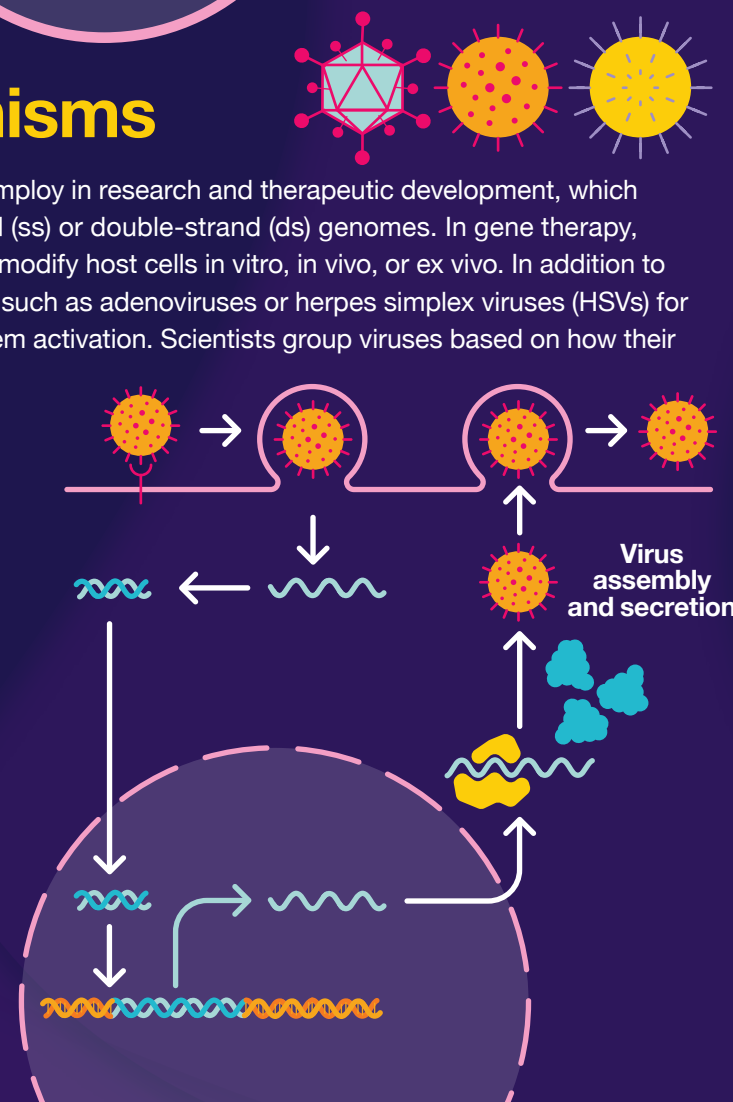
Engineered elements that enhance target specificity and therapeutic gene expression make viral vectors efficient tools for cellular and tissue-specific gene delivery. However, while many are safe and effective, some viral vectors are considered risky due to their potential for oncogenesis or toxic immunogenicity.²

Viral Vector Mechanisms

There are many types of viral vectors that scientists employ in research and therapeutic development, which can be either RNA or DNA viruses, with single-strand (ss) or double-strand (ds) genomes. In gene therapy, scientists deliver genetic material with viral vectors to modify host cells in vitro, in vivo, or ex vivo. In addition to gene delivery, oncolytic therapy relies on viral vectors such as adenoviruses or herpes simplex viruses (HSVs) for cancer cell lysis, tumor eradication, and immune system activation. Scientists group viruses based on how their genetic material modulates the cell.^{2,3}

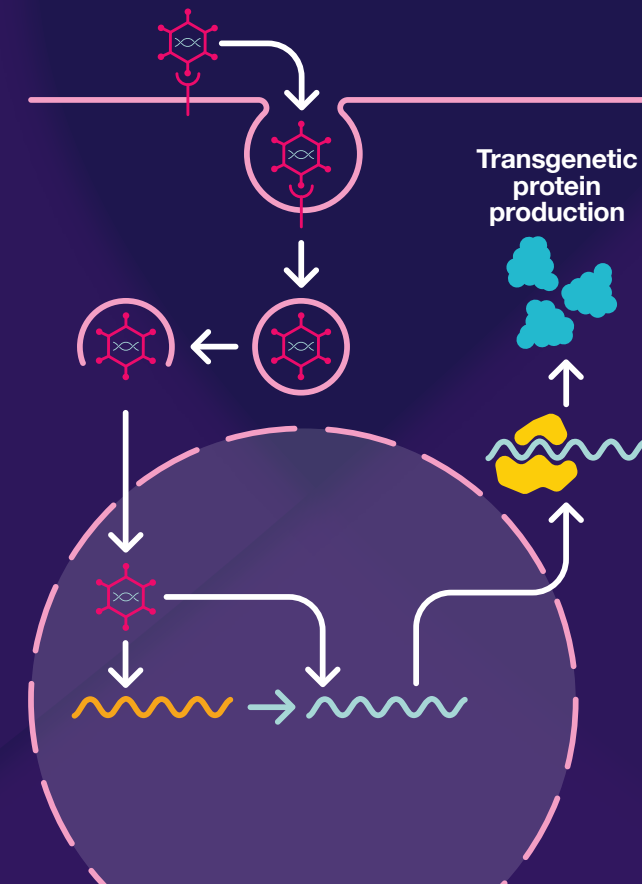
Integrating Viruses

Some viruses integrate their genetic material into the host genome. For instance, retroviruses such as HIV-1 are enveloped RNA viruses that reverse transcribe their genetic material into DNA for host genome integration and long-term replication. Retroviral vectors provide stable and efficient expression of transgenes, modifying the host cell permanently. Unfortunately, this also poses the primary safety risk of integrating viruses, which increase the possibility of insertional mutagenesis and oncogene activation. Current advances in retroviral-mediated gene therapy rely on new vectors derived from lentiviruses, which can infect slow- or non-dividing cells.²



Nonintegrating Viruses

Scientists engineer viral vectors that do not integrate into the host genome, including adeno-associated viruses (AAVs) and nonintegrating lentiviral vectors. These viruses cooperate with host cell machinery for replication of their genetic material (ssDNA for AAVs or ssRNA for lentiviruses), transcription, and protein expression. AAVs are among the most common vectors for gene therapy, as they provide long-term transgene expression with minimal host genome integration and transduce both dividing and nondividing cells. Limitations of AAV efficacy and safety include host immune system neutralization from preexisting immunity to AAV vectors, random host genome integration that activates or inhibits endogenous genes, small packaging capacity (<5 kb), and variable expression patterns in different cell types.^{1,2,4}



Viral Vector Applications

Viruses as Research Tools

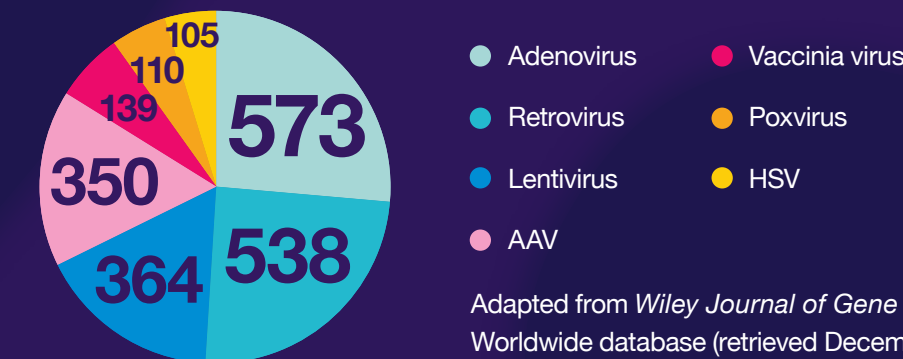
As effective horizontal gene transfer agents, viral vectors are suited for tailored applications in both basic and translational research.⁵ For instance, lentivirus-based technologies are widely adopted for stable transgene overexpression, gene silencing, transgenic animal model production, and site-directed gene editing. Additionally, commercially available viral vectors facilitate and accelerate the rapid expansion of this technology in gene therapeutic research.⁶

Viruses as Clinical Solutions

Viral vectors account for roughly half of gene therapies in clinical trials, and scientists currently employ them for gene therapy, oncolytic treatments, and vaccine development. Researchers and clinicians choose viral vectors based on transgene expression efficiency, ease of production, safety, toxicity, and stability. Novel viral vectors that are nonimmunogenic, nonpathogenic, and can transport large genes for stable and long-term expression are ideal.

The main classes of clinical viral vectors include retroviruses, adenoviruses, AAVs, lentiviruses, and HSVs.^{2,5} As disease therapeutics, several viral vectors are approved to treat specific types of cancer, blood disorders, immune deficiency syndromes, and inherited disorders such as spinal muscular atrophy.^{7,8}

Number of Viral Vectors Used for Gene Transfer in Gene Therapy Clinical Trials



Indication	Vector Type
- Head and neck cancer - Nasopharyngeal cancer	Oncolytic adenovirus
Melanoma	Oncolytic HSV-1
- Severe combined immunodeficiency - Precursor B-cell lymphoblastic leukemia-lymphoma - Beta-thalassemia	Lentivirus
- Adjunctive treatment in haploidentical HSC transplant - Lymphoma	Retrovirus
- Hyperlipoproteinemia type I - Optic atrophy - Spinal muscular atrophy	AAV

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Viral Vector Platforms for Gene Therapy



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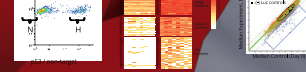


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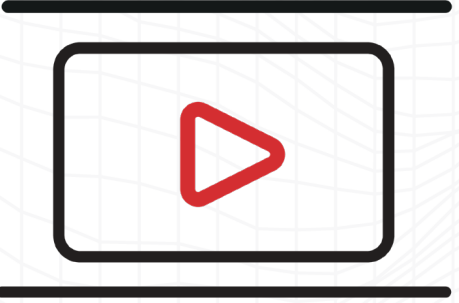


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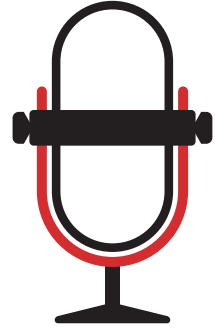
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