The Novartis Gene Therapies AAV9 Platform

What is Gene Therapy?

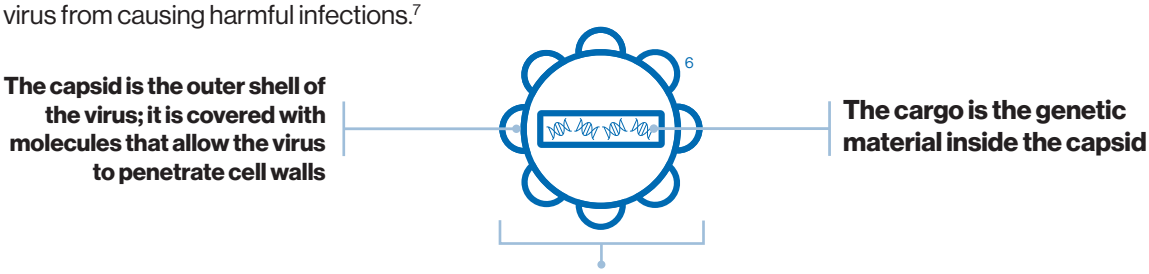
Gene therapy addresses the root cause of a genetic disease by restoring the function of a missing or faulty gene with a new working copy (the transgene) — or by blocking the function of a harmful mutant gene.[1]

Gene therapy is an especially useful approach to treating diseases caused by mutations in a single gene (monogenic diseases).[2]

More than
10,000
human diseases are known to be monogenic[3]

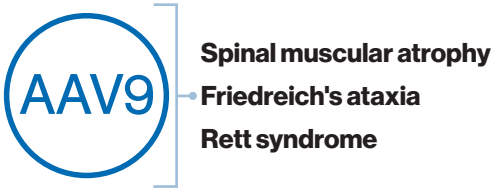
Viral Vectors for Gene Therapy

Modified viruses are an efficient way to transport therapeutic genetic material to affected cells. When modified, viruses (called vectors) act as "delivery trucks," capable of transporting genetic material to where it is needed within the body.[4,5,6] In gene therapy, the virus' normal cargo is removed to prevent the virus from causing harmful infections.[7]



The Novartis Gene Therapies AAV9 Platform

At Novartis Gene Therapies, our current gene therapy platform is built around a specific type of adeno-associated virus (AAV) called AAV9. This vector has unique properties and is versatile enough to yield potential treatments for a variety of rare monogenic diseases using the same underlying science and technology.[7]



Characteristics of the AAV9 Vector

AAV9 has certain qualities that make it especially useful for targeting certain types of monogenic diseases.

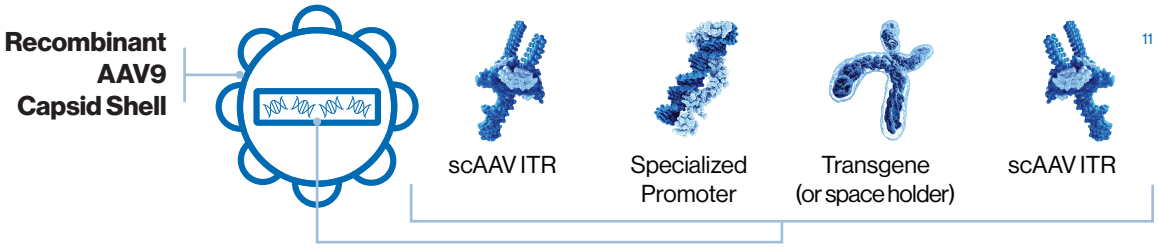
- AAV9 vectors can cross the blood-brain barrier to treat cells of the central nervous system (CNS)[7]
- AAV9 vectors yield high levels of therapeutic genes and protein expression in targeted tissues[8]
- AAV9 vectors can be delivered directly in vivo to the tissue of interest; for diseases of the CNS, transgenes may be administered via intrathecal or systemic administration[5]
- The packaging capacity, or the size of the genetic material that can be packaged inside AAV vectors, is relatively small[5]

NOVARTIS | Reimagining Medicine

Making the Medicine Efficient: Ways We Modify the Cargo Within

The genetic cargo within the capsid can be adjusted to ensure consistent, persistent gene expression, enhance efficiency, and regulate expression levels.

- Once inside the target cell, the genetic cargos within the AAV9 capsid form circular units called episomes that do not integrate into the host DNA and remain in the cells, potentially providing long-lasting benefits in non-dividing cells[9]
- The process of making the protein can be "jump-started" with the use of double stranded, self-complementary recombinant AAV (scAAV) vectors, making the process quick, consistent, and efficient[10]
- The amount of gene product being made by the vector can be controlled by adding certain "promoter" sequences to the DNA sequence[5]



We Have Built an End-to-End Gene Therapy Platform

Gene Therapy Platform

Key Success Factors

Scientific/Clinical

- Flexibility in cargo and vehicles to address multiple disease areas
- Preclinical models and system to rapidly progress therapeutic candidates

Manufacturing

- Analytical methods for product characterization
- Ability to efficiently scale-up and adapt production to match populations and pipeline diversity

Patient Access

- Core commitment to working with patient advocates and regulators
- Long-term commitment to each disease area backed by ongoing innovation

1. What is gene therapy? NIH.gov. https://ghr.nlm.nih.gov/primer/therapy/genetherapy. Last accessed April 29, 2020. **2**. Gonçalves GAR, Paiva RMA. Gene therapy: advances, challenges and perspectives. Einstein (Sao Paulo). 2017;15(3):369-375. **3**. Genes and human disease. WHO.int. https://www.who.int/genomics/public/geneticdiseases/en/index2.html. Last accessed April 29, 2020. **4**. McCarty D, Monahan P, Samulski R. Self-complementary recombinant adeno-associated virus (scAAV) vectors promote ecient transduction independently of DNA synthesis. Gene Ther. 2001;(8): 1248–1254. **5**. Naso MF, Tomkowicz B, Perry WL 3rd, Strohl WR. Adeno-associated virus (AAV) as a vector for gene therapy. BioDrugs. 2017;31(4):317-334. **6**. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov. 2019;18(5):358-378. **7**. DiMattia M, Nam HJ, Vliet KM, et al. Structural insight into the unique properties of adeno-associated virus serotype 9. J Virol. 2012;86(12):6947-6958. **8**. Colella P, Ronzitti G, Mingozzi F. Emerging issues in AAV-mediated in vivo gene therapy. Mol Ther Methods Clin Dev. 2017;(8):87-104. **9**. Goswami R, Subramanian G, Silayeva L, et al. Gene therapy leaves a vicious cycle. Front Oncol. 2019;(9):297. **10**. Sumner C, Crawford T. Two breakthrough gene-targeted treatments for spinal muscular atrophy: challenges remain. J Clin Invest. 2018;128(8):3219–3227. **11**. Data on file.

US-UNB-20-0088 | June 2021

NOVARTIS | Reimagining Medicine