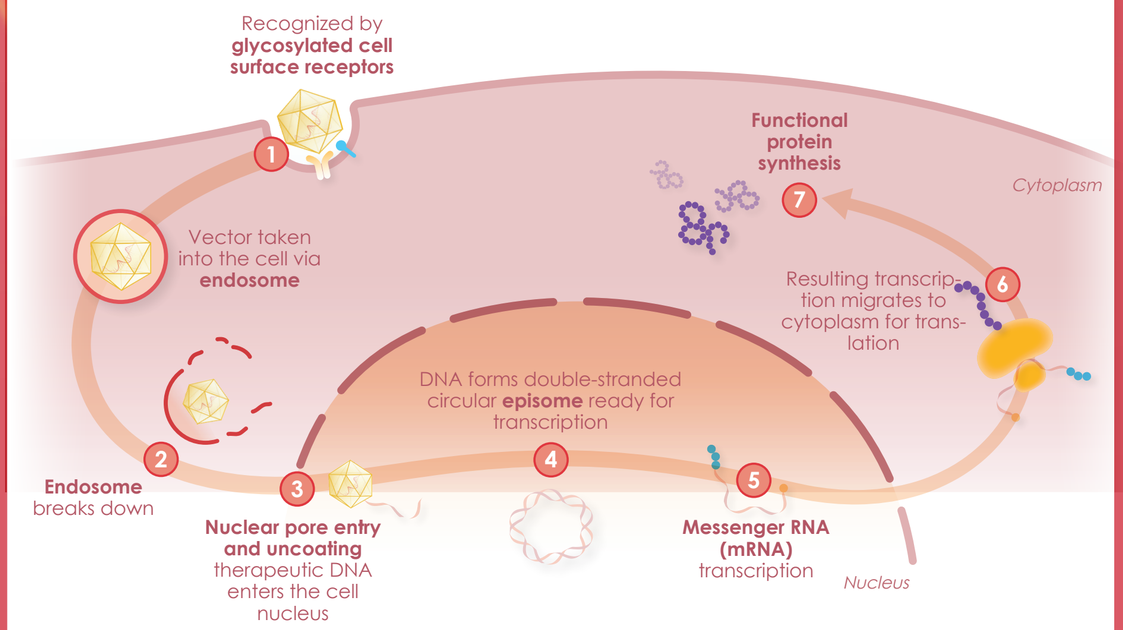
Gene replacement therapy aims to provide sufficient gene expression in enough target cells to ameliorate or correct the disease phenotype[3]



Adapted from Wang D, et al. 2019[1] and Aguti S, et al. 2018[25].

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GENE THERAPIES

Introduction to AAV-mediated Gene Therapy

This Disease Education Brochure is for Healthcare Professionals Only

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GENE THERAPIES

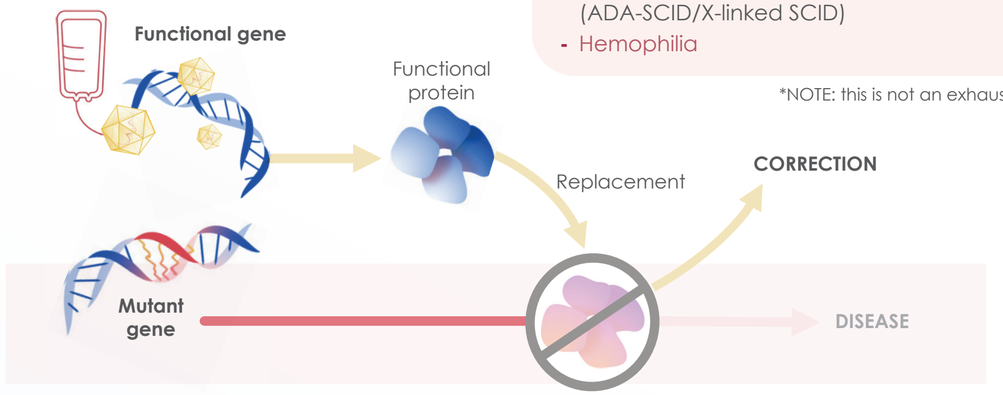
Gene replacement therapy delivers genetic material into the host cell to influence gene expression

- Gene replacement therapy aims to deliver a gene product into specific cells in the body to compensate for **genetic variants**, replacing the defective or missing gene **to address the underlying cause of disease**[1,2]
- The therapeutic gene (or transgene), delivered via **adeno-associated virus (AAV)** shows **low rates of integration** into the host genome, persists predominantly as an extrachromosomal episome, and does not get passed on to children[1,2]

Suitable candidate genetic diseases for gene replacement therapy include* **autosomal or X-linked recessive single-gene disorders**[2–4], e.g.

- Leber congenital amaurosis (retinal dystrophy)
- Spinal muscular atrophy (SMA)
- X-linked myotubular myopathy (XLMTM)
- Duchenne muscular dystrophy (DMD)
- Pompe disease
- Cystic fibrosis
- Severe combined immunodeficiency (ADA-SCID/X-linked SCID)
- Hemophilia

*NOTE: this is not an exhaustive list.



Transgenes delivered via AAV can potentially achieve durable effects

Preclinical and clinical studies have shown evidence of transgene persistence[5]

DISEASE	PRIMARY TARGET	TRANSGENE PERSISTENCE IN TISSUES AND/OR TREATMENT EFFECT	
XLMTM	Muscle	• Mice: • Dogs:	6 months[6,a,b] >4 years[7,a]
Parkinson disease	Neurons	• Non-human primates: • Humans:	15 years[8,a,b] 4 years[9,b]
Hemophilia B	Liver	• Non-human primates: • Dogs: • Humans:	5.5 years[10,a,b] 8 years[11,a,b] At least 8[12,13,a] and 10 years[14,b]
Eye disease	Retinal pigment epithelial cells	• Dogs: • Humans:	11 years[15,a] At least 3 years[16,a]
Spinal muscular atrophy	Motor neurons	• Mice: • Humans:	>250 days[17,a] At least 5 years[18,19,a]

[a]Persistence of treatment effect. [b]Transgene persistence determined by presence in tissues.

Unlike “naked” DNA, AAVs are efficient vehicles to deliver DNA to target cells

- AAVs deliver genes **with low risk of genomic integration**, are **incapable of replicating** on their own, and are **not known to cause disease** in humans[1,20]
- The genome of an AAV can be easily removed and **replaced with the desired therapeutic transgene**[1,20]
- AAVs have **high transduction efficiency**[21]
- There is **potential for long-term, persistent episomal expression** in non-dividing cells[21]
- A **vector genome** is the basic measurement unit of gene therapy[22]

AAV serotypes have tissue tropisms, which can help drive tissue specificity[23]

Specific host tissues can be targeted by the AAV based on the capsid serotype and the presence of a specific receptor on the host cells

SEROTYPE[a]	TISSUE TROPISM
AAV1	Skeletal muscle, lung, central nervous system, retina, pancreas
AAV2	Smooth muscle, skeletal muscle, central nervous system, liver, kidney
AAV3	Hepatocarcinoma, skeletal muscle, inner ear
AAV4	Central nervous system, retina
AAV5	Skeletal muscle, central nervous system, lung, retina, liver
AAV6	Skeletal muscle, heart, lung, bone marrow
AAV7	Skeletal muscle, retina, central nervous system
AAV8	Liver, skeletal muscle, central nervous system, retina, pancreas, heart
AAV9	Liver, heart, brain, skeletal muscle, lungs, pancreas, kidney
AAVrh10	Liver, skeletal muscle, heart, central nervous system

[a]Naturally occurring serotypes investigated for potential therapeutic applications.

Tissue-specific promoters drive expression of human functional protein in target cells[1,22,24]