SEE HOW FAR WE'VE COME

1989
First approved clinical trial protocol to use gene transfer into humans[1]

1990
Therapeutic gene transfer in patients with ADA-SCID[2]

1999
Death of gene therapy clinical trial patient[3]

2003
China approved a gene therapy-based product for clinical use[4]

2009
Successful Phase 3 gene therapy clinical trial in the EU[5]

2012
EMA approved first gene therapy product for LPL[6]

2016
EMA approved gene therapy to treat patients with ADA-SCID[7]

2017
FDA approved first gene therapies (CAR-T) for ALL[8] and B-cell lymphomas,[9] and the first directly administered gene therapy for retinal dystrophy[10]

2018
FDA approved CAR T-cell therapy for DLBCL[11] and the EMA approved CAR T-cell therapies for B-cell ALL, DLBCL and PMBCL[12]

2019
FDA approved first systemic gene therapy for SMA[13]

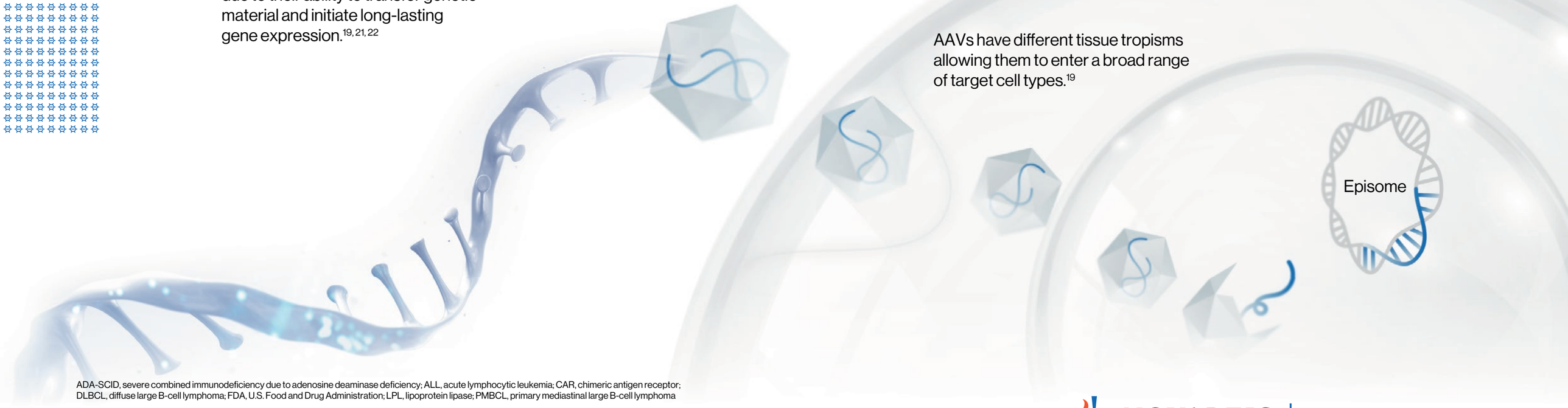
2020
Systemic gene therapy for SMA approved for use in Japan, EU, Israel, Brazil and Canada[14-18]

Gene Therapies

Gene Therapy (GT) and Adeno-Associated Virus (AAV) Transduction

- GT introduces a synthesized transgene that can act as a functional copy of a malfunctioning or missing gene, addressing the root cause of a monogenic disease.[19-21]
- Virus-based vectors are commonly used to deliver transgenes for GT, due to their ability to transfer genetic material and initiate long-lasting gene expression.[19, 21, 22]
- All or some of the coding regions from the viral genome are deleted to avoid replication and toxicity; the inclusion of a promoter can help ensure rapid transcription of the transgene and protein production over time.[22, 23]
- Adeno-associated viruses (AAVs) are non-pathogenic, have a low risk of insertional mutagenesis, and have relatively low immunogenicity.[19]
- The AAV vector enters the target cell, travels to the nucleus, and releases the transgene.[19, 24-26]
- The transgene becomes an episome, a stable unit of DNA that functions separately from the chromosome and is able to employ the cell's innate machinery to activate gene expression.[22, 26]

AAVs have different tissue tropisms allowing them to enter a broad range of target cell types.[19]



ADA-SCID, severe combined immunodeficiency due to adenosine deaminase deficiency; ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FDA, U.S. Food and Drug Administration; LPL, lipoprotein lipase; PMBCL, primary mediastinal large B-cell lymphoma

Please note that this is a diagrammatic representation of gene therapy in general and is not designed to depict specific gene therapies
Adapted from Akst, J. Targeting DNA. Available at https://www.the-scientist.com/features/targeting-dna-40937. Last accessed: February 2021

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