EMERGENCE OF ADENO ASSOCIATED VIRUS VECTOR IN GENE THERAPY:

(Soumya Bandi[1], Medical content writer and Dr. Pranjal Bordoloi[2], SVP Medical and Clinical Affairs Jodas Expoim Pvt. Ltd)

ABSTRACT:

Gene therapies, using viral and non-viral vectors, introduce therapeutic genes into patient cells to treat diseases, particularly genetic disorders. Adeno-associated viral (AAV) vector-based treatments are preferred due to their unique safety and efficacy features.[1] Viral vectors have an excellent delivery system and may provide both short- and long-term virus-based transgene expression, depending on the situation, they are essential in gene therapy.[2] This article aim to provide an overview of introducing the basic AAV biology and vectorology, outlining general vector design principles, and summarizing current therapeutic strategies and clinical progress.

INTRODUCTION:

The identification of genetic inheritance and illness through DNA has led to the development of gene-editing medicines. Quick advances in human genetics and sequencing have made it possible to identify the genes responsible for various disease states by providing a wealth of nucleic acid sequence data. For almost 40 years, the aim of gene therapy has been to achieve this idea, especially for monogenic disorders.[3]

Gene therapy involves injecting particular genetic material into a patient that alters cell activity in order to address hereditary illnesses. It implies the effective delivery of genes using vectors, which may or may not be viral. Adenoviruses or retroviruses are used to deliver therapeutic genes in vivo. Ex vivo delivery involves extracting cells out of the body, cultivating them elsewhere, genetically modifying them with a therapeutic transgene, and then reintroducing them into the patient. Gene silencing, gene addition, gene replacement, and gene editing are the four fundamental gene therapy techniques. In order to affect cellular function, each strategy includes either overexpressing foreign genes to affect cellular function or delivering a functioning gene to replace a non-working gene.[4]

Adeno-associated virus (AAV) is a gene therapy vehicle that was initially discovered as a contaminant of adenovirus preparations. AAV is a protein shell surrounding and protecting a small, single-stranded DNA genome of approximately 4.8 kilobases. It belongs to the parvovirus family and relies on co-infection with other viruses for replication.

STRUCTURE OF AAV:

AAV has hundreds of unique strains in numerous species, with its single-stranded genome containing three genes: Rep (Replication), Cap (Capsid), and aap (Assembly). These genes produce at least nine gene products through promoters, alternative translation start sites, and differential splicing.[3] A viral vector is a complex structure consisting of three main components: the protein capsid or envelope that encapsulates the genetic payload, the transgene of interest that confers a desired effect when expressed in cells, and the "regulatory cassette," which controls the stable or transient somatic expression of the transgene as an episome or a chromosomal integrant. These components work together to define the vector's tissue or cell tropism and antigen recognition, and to control the transgene's expression as an episome or chromosomal integrant.[4]

Adeno-associated viruses (AAVs) are non-enveloped, 25-nm viruses with a 4.7-kb single-stranded DNA genome. The AAV cap gene encodes three capsid subunits, VP1–VP3, which assemble into a T = 1 icosahedral capsid. VP1 contains a unique N-terminal domain with a phospholipase A2 domain responsible for endosomal escape. VP3 establishes tissue tropism through cell receptor recognition and antigenic response. Serotype diversity is defined by amino acid differences within nine variable regions found in VP3.[5]

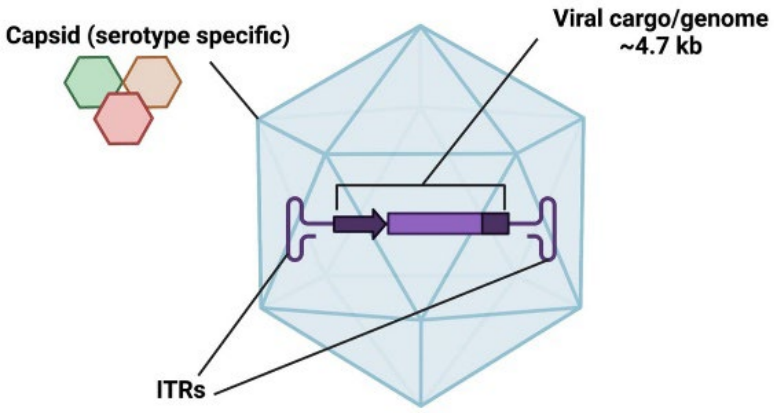

Fig: Structure of Adeno associated viral vector [6]

EVOLUTION AND APPLICATIONS OF AAV:

The first human gene therapy study was conducted in 1970 when American physician Stanfield Rogers tried to cure argininemia with a papillomavirus-containing arginase. However, the trial was unsuccessful.[7]

The primary vector for in vivo gene therapy delivery is recombinant AAVs (rAAVs). Alipogene tiparvovec (Glybera), the first rAAV gene therapy treatment, received approval in 2012 for the treatment of lipoprotein lipase deficiency.

Subsequently, rAAV gene therapy product, voretigene neparvovec-rzyl (Luxturna), was licensed in the US five years later.[8] In 2017, the US FDA approved Luxturna (Voretigene Neparvovec) as the first retinal gene therapy for human use, specifically for patients with LCA type 2, an inherited retinal degeneration caused by mutations in the RPE65 gene. These mutations disrupt the normal recycling of retinal chromophore, preventing phototransduction and causing retinal degeneration.[9]

In May 2019, the first gene therapy approved for SMA is Onasemnogene abeparvovec (Zolgensma®) is a gene therapy developed by AveXis for spinal muscular atrophy (SMA). It delivers a functional copy of the human survival motor neuron gene to motor neuron cells in SMA patients.[10]

In July 2022, PTC Therapeutics has developed Eladocagene exuparvovec (Upstaza™), a gene therapy for human aromatic L-amino acid decarboxylase (AADC) deficiency. The therapy uses an adeno-associated virus vector to deliver the dopa decarboxylase gene. It is approved in July 2022, and targets patients aged 18 months and older with severe AADC deficiency symptoms.[11]

Eventually, In August 2022, the Valoctocogene roxaparvovec (Roctavian™) product of BioMarin Pharmaceutical Inc. is a gene therapy treatment option for adults with severe haemophilia A. EU granted conditional marketing permission to adults who had no history of FVIII inhibitors or detectable AAV5 antibodies.[12]

Thereafter, in November 2022, marked a significant milestone in hematology and gene therapy. Etranacogene dezaparvovec (Hemgenix) an adeno-associated virus vector-based gene therapy developed by uniQure and CSL Behring, was approved in the USA for treating

haemophilia B in adults with FIX (Factor IX) deficiency, life-threatening haemorrhage, or severe spontaneous bleeding episodes.[13] This was the first FDA approval of a gene therapy for hemophilia, liver-directed AAV vector-mediated gene therapy, and an AAV vector manufactured in insect cells.[14]

In June 2023, Delandistrogene moxeparvovec (ELEVIDYS®) is a gene therapy developed by Sarepta Therapeutics to treat Duchenne muscular dystrophy (DMD). It delivers a micro-dystrophin protein gene to affected muscles, and was approved in the USA for pediatric patients aged 4-5 with confirmed DMD mutations.[15]

Recently, in December 2023 , Spark Therapeutics and Pfizer's Fidanacogene elaparvovec, an AAV vector-based gene therapy, was approved for treating adults with moderately severe to severe haemophilia B who are negative for neutralizing antibodies to variant AAV serotype Rh74.[16]

CONCLUSION:

Gene therapy is an effective technique for personalised medicine that can lessen the adverse effects of prescription medications while increasing the effectiveness of therapy. Its potential encompasses not just the therapy of cancer but also immunological disorders, inflammatory processes, and neurological diseases, in addition to inherited problems. Viral vectors are successful, but they can also trigger immunological reactions, which emphasises the need for more study in this field.

The gene therapy has made significant progress and has the potential to transform various diseases. The range of approved products, including LUXTURNA, ZOLGENSMA, HEMGENIX, UPSTAZA, ROCTAVIAN and ELEVIDYS demonstrates its applicability across various diseases such as melanoma, pancreatic cancer, retinal dystrophy, spinal muscular atrophy, Duchenne muscular dystrophy, hemophilia and more.

Giroctocogene fitelparvove, fordadistrogene movaparvovec and DTX 401 are the AAV gene therapy drugs that are under Phase III clinical trials.

REFERENCES:

1. Nicole Stivers. Introduction to AAV Gene Therapies. *The Scientist*. https://www.the-scientist.com/introduction-to-aav-gene-therapies-71193. Published June 29, 2023.

2. Lundstrom K. Viral Vectors in Gene Therapy: Where Do We Stand in 2023? *Viruses*. 2023;15(3):698. doi:10.3390/v15030698

3. Naso MF, Tomkowicz B, Perry WL, Strohl WR. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. *BioDrugs Clin Immunother Biopharm Gene Ther*. 2017;31(4):317-334. doi:10.1007/s40259-017-0234-5

4. Bulcha JT, Wang Y, Ma H, Tai PWL, Gao G. Viral vector platforms within the gene therapy landscape. *Signal Transduct Target Ther*. 2021;6(1):53. doi:10.1038/s41392-021-00487-6

5. Hsu HL, Brown A, Loveland AB, et al. Structural characterization of a novel human adeno-associated virus capsid with neurotropic properties. *Nat Commun*. 2020;11(1):3279. doi:10.1038/s41467-020-17047-1

6. Multiple authors. An Introduction to AAV. Published online May 30, 2023. https://blog.addgene.org/an-introduction-to-aav

7. Friedmann T. Stanfield Rogers: insights into virus vectors and failure of an early gene therapy model. *Mol Ther J Am Soc Gene Ther*. 2001;4(4):285-288. doi:10.1006/mthe.2001.0454

8. 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. doi:10.1038/s41573-019-0012-9

9. Matthew P. Simunovic a b, Heather G. Mack c, Lauren N. Ayton c, Mark M. Hassall c d. Gene Therapy, Diet and Drug Approaches to Treating Inherited Retinal Disease. *Compr Pharmacol*. Published online June 9, 2022:662-692.

10. Hoy SM. Onasemnogene Abeparvovec: First Global Approval. *Drugs*. 2019;79(11):1255-1262. doi:10.1007/s40265-019-01162-5

11. Keam SJ. Eladocagene Exuparvovec: First Approval. *Drugs*. 2022;82(13):1427-1432. doi:10.1007/s40265-022-01775-3

12. Blair HA. Valoctocogene Roxaparvovec: First Approval. *Drugs*. 2022;82(14):1505-1510. doi:10.1007/s40265-022-01788-y

13. Heo YA. Etranacogene Dezaparvovec: First Approval. *Drugs*. 2023;83(4):347-352. doi:10.1007/s40265-023-01845-0

14. Anguela XM, High KA. Hemophilia B and gene therapy: a new chapter with etranacogene dezaparvovec. *Blood Adv*. 2024;8(7):1796-1803. doi:10.1182/bloodadvances.2023010511

15. Hoy SM. Delandistrogene Moxeparvovec: First Approval. *Drugs*. 2023;83(14):1323-1329. doi:10.1007/s40265-023-01929-x

16. Dhillon S. Fidanacogene Elaparvovec: First Approval. *Drugs*. 2024;84(4):479-486. doi:10.1007/s40265-024-02017-4