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EDITORIAL

Adeno-associated virus as a powerful tool for gene therapy

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Gene therapy is a revolutionary new approach to treating genetic disorders by fixing errors in DNA, potentially with a single treatment.[1] The U.S. Food and Drug Administration (FDA) and European regulators were expected to approve up to 17 new gene therapies in 2024. These approvals include advances for rare diseases and even therapies that use cells to target illnesses more effectively.[2-4] One of the key tools for delivering these gene therapies is the adeno-associated virus (AAV), a type of virus that can insert corrected genes into specific tissues without causing strong immune responses. This technology has already helped restore vision for people with rare eye disorders and improve movement abilities for young children with severe muscle disease.[5]

AAV is a small, non-harmful virus discovered in the 1960s. It is employed to carry healthy genes into specific body tissues by virtue of several advantages, such as high specificity in cell targeting, long-lasting impact on the body, and minimal immune reactions.[6-8] This makes AAV the top choice for gene delivery in medical treatments. Four AAV therapies have already been approved in the U.S. to treat serious diseases such as certain eye and muscle disorders. AAV vectors present unique advantages, such as specific tissue tropism, high transduction efficiency, low immune responses, long-lasting gene expression, and staying unincorporated into the host chromosome, which make them the most popular viral gene delivery system in clinical trials to achieve long-term correction, addressing the unmet medical needs. Biallelic *RPE65* mutation-associated retinal dystrophy affects approximately 1,000 – 2,000 patients in the U.S. Biallelic mutation carriers are recognized for harboring a mutation in both copies of a particular gene.[9,10] Luxturna, an AAV2 vector for one-time gene therapy treatment of patients with established genetic vision loss due to Leber congenital amaurosis or retinitis pigmentosa, has become the first viral-based drug approved by the FDA in 2017.[11] After receiving treatment with Luxturna, patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy underwent vision restoration within several months. Children with spinal muscular atrophy (SMA) experience difficulty performing essential life functions and surviving past early childhood due to respiratory failure. Zolgensma, also known as AVXS-101, an AAV9 vector for one-time gene therapy treatment of pediatric SMA patients less than 2 years of age with biallelic mutations in the survival motor neuron 1 (*SMN1*) gene, was approved by the FDA in 2019.[12] After receiving treatment with Zolgensma, patients showed improvements in their ability to reach developmental motor milestones, such as head control and the ability to sit without support.

AAV's ability to transfer corrected genes directly into affected tissues without triggering severe immune reactions has opened doors for ground-breaking treatments. AAV vectors are widely applied in clinical delivery system due to their multiple unique advantages, as stated in the above, which allow for the successful delivery

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and transfer of therapeutic genes in gene therapies for cancer, neurodegenerative diseases, retinal diseases, and COVID-19.[13-16] In light of our growing understanding of viral biology and the availability of diverse platforms, it is essential to optimize AAV vector delivery system in terms of capsid properties, production yield, packaging efficiency, immune response, biodistribution potential, and transduction safety, which are critical for the successful application and development of clinically approved therapy. Consequently, future research should focus on creating AI-driven tools for AAV capsid engineering and packaging capacity/immune response prediction methods evolving from the current basic programming to support the learning of more advanced concepts.

Conflict of interest

Ling Yin is the Guest Editor of this special issue. The author declared that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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