Learning to lock down genetic diseases without throwing away the key

Molecular Therapy
Editorial

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Spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by progressive degeneration of α-motor neurons, resulting in muscle weakness and atrophy.[1] The disease is caused by loss-of-function mutations in the survival motor neuron 1 gene (*SMN1*), affects approximately 1 in 11,000 newborns, and remains the leading genetic cause of infantile death.[1–4] Patients with SMA who enrolled into clinical trials for onasemnogene abeparvovec (brand name: Zolgensma), a systemically administered adeno-associated virus (AAV) vector that uses the AAV9 capsid to deliver *SMN1* under the control of a strong and ubiquitously active promoter,[5] will soon enter their 10th year post-treatment. These patients and those who were among the first to receive the commercially approved gene therapy have permitted the evaluation of long-term outcomes in humans.

Since its initial commercial approval in the US in 2019 for patients with severe SMA (type I), onasemnogene abeparvovec has been administered to more than 2,000 patients worldwide. This relatively large population of treatment recipients now enable deep inquiry into the safety and long-term efficacies of Zolgensma. In addition to some serious adverse effects reported for recipients of Zolgensma,[6–9] the lifetime stability of the therapeutic transgene is not a certainty. Vector genomes can become lost overtime due to cell division or natural cell turnover.[10] These outcomes have sparked interest in improving upon current AAV-based gene therapy approaches. One such facet for improvement is the option to redose with vectors to boost transgene therapy during the lifetime of the patient. However, redosing has always been a major limitation because of immunological responses to the AAV capsid protein.

In the important study entitled "Structural and functional characterization of capsid binding by anti-AAV9 monoclonal antibodies from infants after SMA therapy" by Logan et al., anti-AAV9 immunoglobulin Gs (IgGs), which cross-reacted with multiple AAV serotypes, were detected in Zolgensma-treated patients with SMA nearly 3 years following gene therapy. Several monoclonal antibodies (mAbs) were also recovered from switched memory B cells. Many of the characterized mAbs showed specific neutralization of recombinant AAV9 (rAAV9) transduction, but two showed strong cross-reactivity with multiple serotypes. Upon analyses by cryoelectron microscopy (cryo-EM), these two mAbs were found to bind to the 5-fold axis. One key finding was that the binding of the antigenically dominant human mAbs identified in the study were at the 2-fold depression and the side of the 3-fold protrusion of the AAV9 capsid, whereas mouse anti-AAV9 mAbs appear to preferentially bind to the 3-fold regions. These findings suggest that the mechanisms for antibody-mediated neutralization of AAV vectors studied in mice may not reflect those that operate in humans.

The work by Logan et al. opens the door to pursue the development of strategies that can overcome cross-neutralization so that patients can be dosed with gene therapies using complementary capsids. Equally important is the potential to develop similar therapies to treat patients with adult-onset SMA (types 3 and 4), or patients with type 2 (intermediate severity) SMA who survive into adulthood but may not receive gene therapy until beyond infancy. These patients may have been exposed to natural AAV infections throughout the course of life. The information gleaned from human patients after AAV vector gene therapy will guide more effective capsid engineering efforts to escape antibody responses.

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AUTHOR CONTRIBUTIONS

P.W.L.T. and J.X. contributed equally to this editorial and share the opinions stated within.

DECLARATION OF INTERESTS

P.W.L.T. and J.X. are inventors on patents related to AAV-based gene therapies with royalties licensed to biopharmaceutical companies.

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