

LONG-TERM EXPRESSION IN GENETIC DISEASE: IN VIVO GENE TRANSFER WITH RECOMBINANT ADENO-ASSOCIATED VIRAL VECTORS

Recombinant adeno-associated viral (AAV) vectors have emerged as attractive gene delivery vehicles for genetic disease. Engineered from a small replication-defective DNA virus, they are devoid of viral coding sequences and trigger very little immune response in experimental animals. They are capable of transducing nondividing target cells, and the donated DNA is stabilized primarily in an episomal form, thus minimizing risks arising from insertional mutagenesis. Because the vector has a tropism for certain long-lived cell types, such as skeletal muscle, the CNS, and hepatocytes, long-term expression can be achieved even in the absence of integration. Of note, because the donated DNA is predominantly nonintegrated, long-term expression requires targeting of nondividing or slowly dividing cells; otherwise, expression is lost as cells divide.

■ FIRST LICENSED PRODUCT

These features of AAV were used to develop the first approved gene therapy product in the Western world, an AAV vector conditionally approved in Europe in 2012 for treatment of the autosomal recessive disorder lipoprotein lipase (LPL) deficiency. This rare disorder (1–2 cases/million) is due to loss-of-function mutations in the gene encoding LPL, an enzyme normally produced in skeletal muscle and required for the catabolism of triglyceride-rich lipoproteins and chylomicrons. Affected individuals have lipemic serum and may have eruptive xanthomas, hepatosplenomegaly, and in some cases, recurrent bouts of acute pancreatitis, and do not respond to treatment with statins. Clinical trials demonstrated the safety of intramuscular injection of AAV-LPL and provided preliminary evidence supporting a reduction in frequency of episodes of pancreatitis. The sponsor allowed the approval to expire in 2017, without completing the postmarketing requirements, but the initial approval, demonstrating a regulatory pathway for this class of therapeutics, was a crucial catalyst for the current robust activity in