INCREASING TISSUE SPECIFIC GENE DELIVERY BY CAPSID MODIFICATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119 (e) to U.S. Provisional Application Serial No. 62/644,317, filed March 16, 2018, the contents of which are incorporated by reference herein.

STATEMENT REGARDING GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant No. TR001068 from the National Institutes of Health. The government has certain rights in the invention.

SEQUENCE LISTING

[0002.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on February 26, 2019, is named 106887-7170_SL.txt and is 18,492 bytes in size.

BACKGROUND

[0003] Efforts have been made to modify AAV capsids for improved gene delivery. For example, WO 2017/165859A1 describes a viral capsid modification where Cas9 is fused or conjugated to viral capsid protein to promote customizable gene editing. Further references have describe using DNA family shuffling (Grimm and Kay), lysine substitutions to AAVrh74 (US 2015/006556), mutations at positions 195, 199, 201, or 202 of AAVrh74 (US 9,840,719), and modifications to AAVrh48 (EP 2359866). Still further references detail random peptide libraries being displayed on an AAV surface (e.g., Muller (2003) Nat. Biotechnol., Perabo (2003) Mol. Ther., and 7,588,722 (Grimm and Kay)).

[0004] Gene therapy treatments for Muscular Dystrophies will require systemic delivery of genes to muscle cells throughout the body. The most efficient delivery option is to use the body's circulatory system to distribute the virus to the peripheral muscle cells. An issue for systemic delivery is that most serotypes of AAV have a natural propensity to infect liver cells [1]. There are approximately 20 times more liver cells than muscle cells in the body, which the virus must traverse during systemic delivery [2]. It is estimated that more than 50% of AAV vectors remain trapped in the liver after a systemic intravenous injection.