NOVEL COMPOSITIONS OF ADENO-ASSOCIATED VIRUSES ENGINEERED FOR ENHANCED TISSUE TRANSDUCTION AND SPECIFICITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of Singapore application No. 10202300637W, filed 9 March 2023, the contents of it being hereby incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

[0002] The invention is in the field of biotechnology. In particular, the invention relates to production of engineered adeno-associated viruses. More specifically, the invention provides the use of engineered adeno-associated viruses for enhanced tissue transduction and specificity and compositions thereof.

BACKGROUND OF THE INVENTION

[0003] Adeno-associated virus (AAV) vector-based therapeutics are rapidly advancing to the clinic. Systemic vector infusion represents the ideal delivery route in many gene therapy applications, especially when local administration is not feasible. Currently, most AAV capsids are based on naturally occurring serotypes, which are sequestrated in the liver and have reduced therapeutic efficacy in organs such as in the central nervous system (CNS) or in skeletal muscles. Consequently, higher vector doses are required, resulting in off-target toxicities. Thus, there is a need for AAV capsids with organ-specific tropism at low vector doses.

SUMMARY

[0004] In one aspect, provided herein is a modified adeno-associated virus (AAV), comprising a nucleotide sequence encoding a 7-mer peptide inserted in its capsid, wherein the 7-mer peptide confers reduced tropism towards the liver.

[0004a] In one example, provided herein is a modified adeno-associated virus serotype DJ (AAV-DJ), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1767th and 1768th nucleotides of SEQ ID NO: 399, wherein the modified AAV-DJ has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 399 outside the nucleotide sequence encoding the 7-mer peptide.

[0005] In another example, provided herein is a modified adeno-associated virus serotype 2 (AAV2), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 401, wherein the modified AAV2 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%,

85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 401 outside the nucleotide sequence encoding the 7-mer peptide.

[0006] In another example, provided herein is a modified adeno-associated virus serotype 5 (AAV5), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1722th and 1723th nucleotides of SEQ ID NO: 402, wherein the modified AAV5 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 402 outside the nucleotide sequence encoding 7-mer peptide.

[0007] In another example, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1770th and 1771th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding 7-mer peptide.

[0008] In another example, provided herein is a modified adeno-associated virus serotype 6 (AAV6), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 403, wherein the modified AAV6 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 403 outside the nucleotide sequence encoding the 7-mer peptide.

[0009] In yet another example, provided herein is a modified adeno-associated virus serotype 9 (AAV9), comprising a nucleotide sequence encoding a 7-mer peptide inserted between the 1764th and 1765th nucleotides of SEQ ID NO: 404, wherein the modified AAV9 has a range of at least 50% to 60%, 60% to 65%, 65% to 70%, 70% to 75%, 75% to 80%, 80% to 85%, 85% to 90%, 90% to 95%, or 95% to 99% sequence identity with the sequence of SEQ ID NO: 404 outside the nucleotide sequence encoding the 7-mer peptide.

[0010] In another aspect, provided herein is a composition comprising any modified AAV as described herein, and a pharmaceutically acceptable excipient.

[0011] In another aspect, provided herein is a nucleic acid encoding any modified AAV as described herein.

DEFINITIONS

[0012] As used herein, the term “AAV” or “adeno-associated virus” refers to a non-pathogenic, small viruses of the *Parvovirus* family which infect humans. The term “AAV” includes, but is