substitutions in VP1 as provided in the tables set forth herein. In another embodiment, the AAV vector is of the AAV8 serotype and contains an alteration provided in Table 3.

In one embodiment, there is provided an improved adeno-associated virus (AAV) vector comprising a VP1 capsid protein comprising one or more lysine substitutions, said vector further comprising a minigene comprising AAV inverted terminal repeats and a heterologous nucleic acid sequence operably linked to regulatory sequences which direct expression of a product from the heterologous nucleic acid sequence in a host cell, said lysine substitution being effective to inhibit ubiquitination of said capsid protein, thereby increasing transduction of said AAV vector into a target cell.

In a preferred embodiment, the AAV vectors of the invention comprising the variant capsid proteins are useful for expression of therapeutic peptides or therapeutic nucleic acids. Such peptides include, without limitation, an anti-viral RNAi molecule, Factor VIII, Factor IX or a functional fragment thereof. Additional expression products include for example, IgG, IgM, IgA, IgD, IgE, chimeric immunoglobulins, humanized antibodies, or single chain antibodies. In one aspect the expression product is an RNAi that is useful for inhibiting HCV infection and replication. In another embodiment, the expression product is an antisense nucleic acid useful for down modulating a target cell of interest.

In another embodiment of the invention, a pharmaceutical composition comprising the variant AAV vectors of the invention in a biologically compatible carrier is provided. Also encompassed by the present invention are cell cultures comprising the vectors disclosed herein.

In one embodiment, there is provided a cell culture comprising the AAV vector as described herein.

The invention also encompasses a method of delivering a transgene to a cell in a subject, said method comprising the step of contacting the cell with an AAV vector as disclosed herein, wherein said AAV vector comprises the transgene, wherein the presence of lysine substitution in the VP1 capsid sequence in said vector is associated with reduced ubiquitination and increased transduction efficiency.

In one embodiment, a method of delivering a transgene to a cell in a subject, said method comprising the step of contacting the cell with the pharmaceutical composition as described herein wherein said AAV vector comprises the transgene, wherein the presence of said lysine substitution in said VP1 capsid protein is associated a reduction in ubiquitination of said capsid, thereby increasing transduction efficiency of target cells with said vector.

In one embodiment, there is provided a method of delivering a transgene to a cell in a subject, said method comprising the step of contacting the cell with the pharmaceutical composition as described herein wherein said first AAV vector comprises the transgene, wherein the presence of said lysine substitution in said VP1 capsid protein is associated a reduction in ubiquitination of said capsid, thereby increasing transduction efficiency of target cells with said vector and said second vector exhibits reduced transduction efficiency relative to wild type and is effective to neutralize an undesired antibody response to said first AAV vector.

In a final aspect, the invention provides decoy viral variants that are inefficient at infecting cells but are effective to block antibody neutralization of viral variants carrying beneficial transgenes due to the structural similarities of the two viral variants. Exemplary capsid variants for this purpose include for example, K38R, K143R, K510R and K709R.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Lysines on the surface of AAV1, AAV2 and AAV8: PDB numbers of AAV serotypes used here are as follows: AAV1: 3NG9, AAV2: 1LP3, and AAV8: 2QA0. The arrows represent the respective Lysine residues. (A) There are 11 Lysines on the surface of AAV1 VP3. Residue colors are as follows: K258 red, K459 blue, K491 yellow, K493 magenta, K508 cyan, K528 dark salmon, K533 light green, K545 light blue (slate), K567 dark salmon, K666 light cyan, K707 gray. (B) There are 10 Lysines on the surface of AAV2 VP3. Residue colors are as follows: K258 red, K490 yellow, K507 cyan, K527 dark salmon, K532 light green, K544 light blue (slate), K549 light yellow, K556 light magenta,