Claims

1. A recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the modified capsid protein comprises in the C-terminal part of the protein an amino acid sequence Z, residues of which are exposed on the surface of the capsid protein.

2. An rAAV virion according to claim 1, wherein the amino acid sequence Z:

a. comprises or consists of a sequence of amino acid residues of the formula I:

$$y - G - Q - x - G - (x)_3 - R - (x)_3 - y - A - Q - A - A$$

wherein x represents a single amino acid residue and wherein y represents 0, 1 or 2 amino acid residues; and

b. is present at a location corresponding to a position 100 – 200, preferably 120 – 180, more preferably 130 – 170, more preferably 140 – 160 amino acid residues from the C terminus of a wild-type AAV capsid protein.

3. An rAAV virion for use according to claim 1 or claim 2, wherein the sequence Z is comprised in the modified capsid protein at a location represented by the formula II:

$$EEEIxxxxPVATExxGxxxxNxQy - Z - (x)_n LPGMVWQxRDVYLQGPIWAKIPHTDG$$

a. wherein Z, x and y are as defined in claim 1; and

b. wherein n is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

4. An rAAV virion for use according to any one of the preceding claims, wherein the capsid protein comprises an amino acid sequence selected from the group consisting of:

i) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 1 and wherein amino acids at positions 588 – 602 of SEQ ID NO: 1 have at least 80% sequence identity with SEQ ID NO: 11,

ii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 2 and wherein amino acids at positions 585 – 599 of SEQ ID NO: 2 have at least 80% sequence identity with SEQ ID NO: 10,

iii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 3 and wherein amino acids at positions 587 – 601 of SEQ ID NO: 3 have at least 80% sequence identity with SEQ ID NO: 9,

iv) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 4 and wherein amino acids at positions 586 – 600 of SEQ ID NO: 4 have at least 80% sequence identity with SEQ ID NO: 8,

v) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 5 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 5 have at least 80% sequence identity with SEQ ID NO: 9,

vi) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 6 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 6 have at least 80% sequence identity with SEQ ID NO: 8, and

vii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 7 and wherein amino acids at positions 587 – 601 of SEQ ID NO: 7 have at least 80% sequence identity with SEQ ID NO: 12,

wherein the modified capsid protein provides for an at least two-fold increase in expression, preferably in human FLS cells, in comparison to an unmodified capsid protein with an amino acid sequence selected from the group consisting of SEQ ID NO: 13 – 19, when tested under the same conditions, wherein preferably the unmodified capsid protein has the amino acid sequence SEQ ID NO: 19 or has the same serotype as the modified capsid protein.

5. An rAAV virion for use according to any one of the preceding claims, wherein the capsid protein comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NO:1 – 7.

6. An rAAV virion for use according to any one of the preceding claims, wherein the rAAV virion comprises:

i) a nucleotide sequence comprising at least one AAV inverted terminal repeat (ITR) sequence and

ii) a nucleotide sequence encoding a gene product of interest, wherein preferably the nucleotide sequence encoding a gene product of interest is located between two AAV ITR sequences.

7. An rAAV virion for use according to claim 6, wherein the gene product of interest treats, prevents or suppresses symptoms associated with an arthritic disease, wherein preferably the gene product of interest is selected from the group consisting of interleukins, immune-modulators, antibodies, shRNA, miRNA, guide RNA, growth factors, proteases, nucleotidases/nucleosidases, peptides, protease inhibitors, inhibitors, enzymes and combinations thereof, and wherein more preferably the gene product of interest is at least one of CD39, CD73 and IFN-β.

8. An rAAV virion for use according to any one of claims 1 – 7, wherein the rAAV virion comprises at least one of:

(i) a polynucleotide comprising a sequence encoding at least one guide RNA; wherein the or each guide RNA is substantially complementary to a target polynucleotide sequence(s) in a genome; and

(ii) a polynucleotide comprising a sequence encoding a nuclease; wherein the nuclease forms a ribonuclease complex with the guide RNA, and wherein the ribonuclease complex makes site-specific double-stranded DNA breaks (DSDB) in the genome.

9. An rAAV composition for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition comprises an rAAV virion as defined in any one of claims 1 – 8 and a pharmaceutically acceptable carrier.

10. An rAAV composition for use according to claim 9, wherein the rAAV composition further comprises an empty capsid in a ratio of empty capsid to rAAV virion of at least 1:1.

11. An rAAV composition and an immunosuppressant for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition is as defined in any one of claims 9 or 10 and wherein the treatment or prevention comprises the administration of the rAAV composition and the administration of the immunosuppressant to an individual.

12. An rAAV virion for use according to any one of claims 1 – 8, an rAAV composition for use according to claim 9 or 10, or an rAAV composition and an immunosuppressant for use according to claim 11, wherein the arthritic disease is selected from the group consisting of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, osteoarthritis (OA), gout, pseudogout, spondyloarthritis (SpA), psoriatic arthritis, ankylosing spondylitis, septic arthritis, arthritis, juvenile idiopathic arthritis, blunt trauma, joint replacement and Still's disease.

13. An rAAV virion for use according to any one of claims 1 – 8 and 12 or an rAAV composition for use according to any one of claims 9, 10 and 12, wherein the rAAV virion or the rAAV composition is administered systemically and/or locally.

14. An rAAV composition and an immunosuppressant for use according to claim 11, wherein at least one of the rAAV composition and the immunosuppressant is administered locally.

15. An rAAV virion or an rAAV composition for use according to claim 13 or an rAAV composition and an immunosuppressant for use according to claim 14, wherein the local administration is intraarticular administration.