

Claims

1. A recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein and a promoter operably linked to a nucleotide sequence encoding a gene product of interest,
 5 wherein the rAAV virion is 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, preferably wherein the product of interest is an immunosuppressant.
- 10 2. An rAAV virion for use 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:

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

 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
 20 120 – 180, more preferably 130 – 170, more preferably 140 – 160 amino acid residues from the C terminus of a wild-type AAV capsid protein.
- 25 3. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an IL-6 inhibitor.
4. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an TNF α inhibitor.
5. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an
 30 IL-1 inhibitor.
6. An rAAV virion for use according to claim 3, wherein the IL-6 inhibitor is selected from the group consisting of an IL-6 receptor antagonist, a humanised anti-IL-6 monoclonal antibody, a chimeric anti-IL-6 monoclonal antibody, a humanized rabbit anti-IL-6 monoclonal antibody and a
 35 soluble IL-6 receptor, preferably wherein at least one of
 - i) the IL-6 receptor antagonist is at least one of tocilizumab and sarilumab;
 - ii) the humanised anti-IL-6 monoclonal antibody is at least one of olokizumab and sirukumab;
 - iii) the chimeric anti-IL-6 monoclonal antibody is siltucimab; and
 - 40 iv) the humanized rabbit anti-IL-6 monoclonal antibody is clazakizumab.

7. An rAAV virion for use according to claim 4, wherein the TNF α inhibitor is selected from the group consisting of etanercept, infliximab, adalimumab, certilizumab pegol and golimumab, preferably wherein the TNF α inhibitor is etanercept

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8. An rAAV virion for use according to claim 5, wherein the IL-1 inhibitor is selected from the group consisting of

i) an IL-1 receptor antagonist, preferably a human IL-1 receptor antagonist, preferably the human IL-1 receptor antagonist anakinra;

10 ii) an anti-IL-1 monoclonal antibody, preferably a human anti-IL-1 monoclonal antibody, preferably the human IL-1 monoclonal antibody canakinumab or gevokizumab

iii) a human dimeric anti-IL-1 fusion protein, preferably the human dimeric anti-IL-1 fusion protein rilonacept; and

15 iv) a human dual variable domain anti-IL-1 immunoglobulin, preferably the human dual variable domain anti-IL-1 immunoglobulin lutikizumab

9. An rAAV virion for use according to any one of the preceding claims, wherein the promoter is a constitutive promoter or an inducible promoter, preferably the promoter is an NF κ B responsive promoter, preferably an NF κ B responsive CMV promoter, preferably an NF κ B responsive minimal
20 CMV promoter .

10. An rAAV virion for use according to any one of the preceding claims, wherein the sequence Z is comprised in the modified capsid protein at a location represented by the formula II:

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$$\text{EEEIxxxPVATExxGxxxxNxQy} - \text{Z} - (\text{x})_n\text{LPGMVWQxRQVYLQGPIWAKIPHTDG}$$

a. wherein Z, x and y are as defined in claim 2; and

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

30 11. 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,

35 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 – 602 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
40 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,

5 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

10 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 – 604 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
15 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.

12. 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, preferably wherein the capsid protein comprises or consists of SEQ ID NO: 4 or SEQ ID NO: 6.

13. An rAAV composition for use in treating or preventing an arthritic disease or for use in treating
25 or preventing symptoms associated with an arthritic disease, wherein the rAAV composition comprises an rAAV virion as defined in any one of claims 1- 12 and a pharmaceutically acceptable carrier.

14. An rAAV composition and an immunosuppressant for use in treating or preventing an
30 arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition is as defined in claim 13 and wherein the treatment or prevention comprises the administration of the rAAV composition and the administration of the immunosuppressant to an individual.

35 15. An rAAV virion for use according to any one of claims 1 – 12, an rAAV composition for use according to claim 13, or an rAAV composition and an immunosuppressant for use according to claim 14, 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
40 trauma, joint replacement and Still's disease.

16. An rAAV virion for use according to any one of claims 1 - 12 or an rAAV composition for use according to claim 13, wherein the rAAV virion and/or the rAAV composition is administered systemically and/or locally.

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

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18. An rAAV virion or an rAAV composition for use according to claim 16 and/or an rAAV composition and an immunosuppressant for use according to claim 17, wherein the local administration is intraarticular administration.