has from the N-terminus to the C-terminus the formula I: X_{1A}-X_{1B}-X_2-X_3-X_4-X_5-X_6-X_7 (formula I) wherein X_5 is selected from P (Pro), L (Leu) and V (Val); wherein X_7 is R (Arg); wherein X_{1A} and/or X_{1B} is/are selected from G, S, N, V and P; wherein X_2 is selected from L, S and N; wherein X_3 is selected from S, P, T, Q; wherein X_4 is selected from P, G, S, A and T; wherein X_6 is selected from T, P, N, Q and S; and wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present, or wherein X_5 is selected from S (Ser) and T (Thr); wherein X_7 is S (Ser); wherein X_{1A} and/or X_{1B} is/are selected from G, R, H and S; wherein X_2 is selected from A, S and Q; wherein X_3 is selected from H, N and A; wherein X_4 is selected from R, Q and D; wherein X_6 is selected from R, S and D; and wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present, or wherein X_5 is selected from A (Ala) and Q (Gln); wherein X_7 is A (Ala); wherein X_{1A} and/or X_{1B} is/are selected from N and R; wherein X_2 is selected from S and G; wherein X_3 is selected from R and S; wherein X_4 is selected from P and L; wherein X_6 is selected from A and N; and wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present, wherein viral AAV DNA is present in mouse retinal nuclear extracts after 24 hours, when the AAV is to be administered intravenously into the tail vein of a C57-Bl6J mouse, and wherein viral AAV DNA is present in MAC-sorted rods using anti-CD73-coated magnetic beads and/or FACS-sorted cones, wherein the cones express eGFP and are FACS sorted based on their eGFP expression, 24 hours after administration, when the AAV is to be administered intravenously into the tail vein of a C57-Bl6J mouse for rod sorting and into the tail vein of RG-eGFP mice line R685933 for cone sorting.

[14] In another aspect, the present disclosure relates to an AAV of the present disclosure for use as a medicament, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

[15] In addition, the present disclosure relates to an AAV of the present disclosure for use in treating a photoreceptor cell disease, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide. In yet another aspect, the present disclosure relates to use of the AAV of the present disclosure in the manufacture of a medicament for treating a photoreceptor cell disease, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

[16] In yet another aspect, the present disclosure further concerns pharmaceutical composition comprising an AAV of the present disclosure, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

[17] In yet another aspect, the present disclosure relates to an in vitro use of an AAV of the present

disclosure for transduction of the nucleus of retinal cells.

[18] Furthermore, the present disclosure relates to a method for screening an insertion sequence, the method comprising i) intravenously administering an AAV library, wherein each AAV comprises an insertion sequence, into a subject; ii) isolating viral AAV DNA from retinal nuclear extracts; iii) subcloning the isolated viral AAV DNA into a second AAV library; iv) intravenously administering the second AAV library as obtained in step iii) into a subject; v) isolating viral AAV DNA from rod or cone photoreceptors; vi) determining the sequence of the insertion sequence, thereby obtaining the insertion sequence.

[18a] In yet another aspect, the present disclosure relates to a method for screening an insertion sequence in mice, the method comprising

i) an AAV library to be intravenously administered into a subject, wherein each AAV comprises an insertion sequence of 6-8 amino acids between the positions corresponding to position 578 and 588 of SEQ ID NO: 1;

ii) isolating viral AAV DNA from retinal nuclear extracts;

iii) subcloning the isolated viral AAV DNA into a second AAV library;

iv) the second AAV library as obtained in step iii) to be intravenously administered into a subject;

v) isolating viral DNA from rod or cone photoreceptors;

vi) determining the sequence of the insertion sequence, thereby obtaining the insertion sequence.

[19] In yet another aspect, the present disclosure additionally relates to a peptide (insertion sequence) obtainable by the method of the present disclosure, wherein the peptide has from the N-terminus to the C-terminus the formula I: X_{1A}-X_{1B}-X_2-X_3-X_4-X_5-X_6-X_7 (formula I), wherein X_5 is selected from P (Pro), L (Leu) and V (Val); wherein X_7 is R (Arg); wherein X_{1A}, X_{1B}, X_2, X_3, X_4, X_6 are independently any amino acid; wherein X_{1A} and/or X_{1B} are independently optionally absent or present, or wherein X_5 is selected from S (Ser) and T (Thr); wherein X_7 is S (Ser); wherein X_{1A}, X_{1B}, X_2, X_3, X_4, X_6 are independently any amino acid; wherein X_{1A} and/or X_{1B} are independently optionally absent or present, or wherein X_5 is selected from A (Ala) and Q (Gln); wherein X_7 is A (Ala); wherein X_{1A}, X_{1B}, X_2, X_3, X_4, X_6 are independently any amino acid; wherein X_{1A} and/or X_{1B} are independently optionally absent or present.

[20] In yet another aspect, the present disclosure also relates to a kit comprising an AAV of the present disclosure.

BRIEF DESCRIPTION OF FIGURES

[21] The figures show:

[22] **Figure 1: Peptide insertions from whole retina**

Claims

1. An adeno-associated virus (AAV), the AAV comprising

an insertion of at least 7 amino acids between the positions corresponding to position 587 and 588 of SEQ ID NO: 1, wherein the insertion sequence has from the N-terminus to the C-terminus the formula I:

X_{1A}-X_{1B}-X_2-X_3-X_4-X_5-X_6-X_7 (formula I)

wherein X_5 is selected from P (Pro), L (Leu) and V (Val);

wherein X_7 is R (Arg);

wherein X_{1A} and/or X_{1B} is/are selected from G, S, N, V and P;
wherein X_2 is selected from L, S and N;
wherein X_3 is selected from S, P, T, Q;
wherein X_4 is selected from P, G, S, A and T;
wherein X_6 is selected from T, P, N, Q and S; and
wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present,

or

wherein X_5 is selected from S (Ser) and T (Thr);

wherein X_7 is S (Ser);

wherein X_{1A} and/or X_{1B} is/are selected from G, R, H and S;
wherein X_2 is selected from A, S and Q;
wherein X_3 is selected from H, N and A;
wherein X_4 is selected from R, Q and D;
wherein X_6 is selected from R, S and D; and
wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present,

or

wherein X_5 is selected from A (Ala) and Q (Gln);

wherein X_7 is A (Ala);

wherein X_{1A} and/or X_{1B} is/are selected from N and R;
wherein X_2 is selected from S and G;
wherein X_3 is selected from R and S;
wherein X_4 is selected from P and L;
wherein X_6 is selected from A and N; and
wherein X_{1A} and X_{1B} are present or wherein X_{1A} is absent and X_{1B} is present or wherein X_{1B} is absent and X_{1A} is present,

wherein viral AAV DNA is present in mouse retinal nuclear extracts after 24 hours, when the AAV is to be administered intravenously into the tail vein of a C57-Bl6J mouse, and

wherein viral AAV DNA is present in MAC-sorted rods using anti-CD73-coated magnetic beads and/or FACS-sorted cones, wherein the cones express eGFP and are FACS sorted based on their eGFP expression, 24 hours after administration, when the AAV is to be administered intravenously into the tail vein of a C57-Bl6J mouse for rod sorting and into the tail vein of RG-eGFP mice line R685933 for cone sorting.

2. The AAV of claim 1, wherein the insertion sequence has from the N-terminus to the C-terminus the formula II:

$$L_3\text{-}L_2\text{-}L_1\text{-}X_{1A}\text{-}X_{1B}\text{-}X_2\text{-}X_3\text{-}X_4\text{-}X_5\text{-}X_6\text{-}X_7\text{-}L_4\text{-}L_5\text{-}L_6 \text{ (formula II)}$$

wherein L is a flexible amino acid; and

wherein L_1, L_2, L_3, L_4, L_5 and L_6 are independently selected from Ala, Leu, Gly, Ser and Thr; and

wherein L_1, L_2, L_3, L_4, L_5 and L_6 are independently optionally absent or present.

3. The AAV of claim 2, wherein X_5 is selected from P (Pro), L (Leu) and V (Val);

wherein X_7 is R (Arg);
wherein X_{1A} and/or X_{1B} is/are selected from G, S, N, V and P;
wherein X_2 is selected from L, S and N;
wherein X_3 is selected from S, P, T, Q;
wherein X_4 is selected from P, G, S, A and T;
wherein X_6 is selected from T, P, N, Q and S and wherein L_1, L_2, L_3, L_4, L_5 and L_6 are present; and
wherein the AAV is preferably AAV2.

4. The AAV of claim 2, wherein one of X_{1A} or X_{1B} is present and the other one of X_{1A} or X_{1B} is absent, and

wherein all of L_1 , L_2, L_3, L_4 and L_5 are present, and wherein L_6 is absent.

5. The AAV of any one of claims 1 to 4, wherein the AAV comprises the insertion sequence GLSPPTR (SEQ ID NO: 10), SSPGLPR (SEQ ID NO: 11), NSTSVNR (SEQ ID NO: 12), VSSSLQR (SEQ ID NO: 13), PNQAPPR (SEQ ID NO: 14) or NNPTPSR (SEQ ID NO: 15).

6. The AAV of claim 5, wherein the AAV comprises the insertion sequence GLSPPTR (SEQ ID NO: 10) or NNPTPSR (SEQ ID NO: 15).

7. The AAV of claim 1 or 2, wherein the AAV comprises the insertion sequence GAHRSDS (SEQ ID NO: 16), RANQTSS (SEQ ID NO: 17), HSARTDS (SEQ ID NO: 18) or SQNDSRS (SEQ ID NO: 19).

8. The AAV of claim 1 or 2, wherein the AAV comprises the insertion sequence NSRPAAA (SEQ ID NO: 20) or RGSLQNA (SEQ ID NO: 21).

9. The AAV of any one of the preceding claims for use as a medicament, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

10. Use of the AAV of any one of the preceding claims in the manufacture of a medicament for treating a photoreceptor cell disease, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

11. Pharmaceutical composition comprising an AAV of any one of claims 1-8, wherein the AAV comprises a heterologous nucleic acid encoding a therapeutic nucleic acid or a therapeutic protein/polypeptide.

12. In vitro use of an AAV of any one of claims 1-8 for transduction of the nucleus of retinal cells.

13. A method for screening an insertion sequence in mice, the method comprising

i) an AAV library to be intravenously administered into a subject, wherein each AAV comprises an insertion sequence of 6 to 8 amino acids between the positions corresponding to position 578 and 588 of SEQ ID NO: 1;

ii) isolating viral AAV DNA from retinal nuclear extracts;

iii) subcloning the isolated viral AAV DNA into a second AAV library;

iv) the second AAV library as obtained in step iii) to be intravenously administered into a subject;

v) isolating viral DNA from rod or cone photoreceptors;

vi) determining the sequence of the insertion sequence,

thereby obtaining the insertion sequence.

14. Kit comprising an AAV of any one of claims 1-8.