CLAIMS:

1. A recombinant adeno-associated virus (rAAV) having an AAV capsid and a vector genome comprising a FXN gene having the sequence of SEQ ID NO: 3 or a sequence at least 95% identical thereto that encodes human frataxin, and regulatory sequences which direct expression of the FXN gene in targeted human cells.

2. The rAAV according to claim 1, wherein

(i) the FXN gene encodes a frataxin protein having a sequence of SEQ ID NO: 2 or a sequence at least 95% identical thereto~~.~~;

~~3. The rAAV according to claim 1 or 2, wherein~~ (ii) the vector genome comprises an AAV2 5' inverted terminal repeat (ITR), a CB7 promoter, an intron, the FXN gene, a polyA, and an AAV2 3' ITR, optionally comprising the sequence of nucleotides 198 to 2737 of SEQ ID NO: 8 or nucleotides 198 to 2736 of SEQ ID NO: 12~~.~~; and/or

~~4. The rAAV according to any one of claims 1 to 3, wherein~~ (iii) the vector genome further comprises at least one, at least two, or at least three tandem repeats of dorsal root ganglion (DRG)-specific miRNA targeted sequences.

~~5~~3. The rAAV according to claim ~~4~~2, wherein the at least two or at least three miRNA target sequences are the same.

~~6~~4. The rAAV according to any one of claims 1 to ~~5~~3, wherein the AAV capsid is an AAVrh91 capsid~~.~~, or

~~7. The rAAV according to any one of claims 1 to 5, wherein the AAV capsid is~~ an AAV clade F capsid.

~~8~~5. The rAAV according to claim ~~7~~4, wherein the clade F capsid is an AAVhu68 capsid.

~~9~~6. The rAAV according to claim ~~8~~5, wherein the AAV capsid is an AAVhu68 capsid, the AAVhu68 capsid comprising one or more of:

(1) AAV hu68 capsid proteins comprising:

a heterogenous population of AAVhu68 vp1 proteins selected from: vp1 proteins produced by expression from a nucleic acid sequence which encodes the predicted amino acid sequence of 1 to 736 of SEQ ID NO: 5, vp1 proteins produced from SEQ ID NO: 4, or vp1 proteins produced from a nucleic acid sequence at least 70% identical to SEQ ID NO: 4 which encodes the predicted amino acid sequence of 1 to 736 of SEQ ID NO: 5,

a heterogenous population of AAVhu68 vp2 proteins selected from: vp2 proteins produced by expression from a nucleic acid sequence which encodes the predicted amino acid sequence of at least about amino acids 138 to 736 of SEQ ID NO: 5, vp2 proteins produced from a sequence comprising at least nucleotides 412 to 2211 of SEQ ID NO: 4, or vp2 proteins produced from a nucleic acid sequence at least 70% identical to at least nucleotides 412 to 2211 of SEQ ID NO: 4 which encodes the predicted amino acid sequence of at least about amino acids 138 to 736 of SEQ ID NO: 5,

a heterogenous population of AAVhu68 vp3 proteins selected from: vp3 produced by expression from a nucleic acid sequence which encodes the predicted amino acid sequence of at least about amino acids 203 to 736 of SEQ ID NO: 5, vp3 proteins produced from a sequence comprising at least nucleotides 607 to 2211 of SEQ ID NO: 4, or vp3 proteins produced from a nucleic acid sequence at least 70% identical to at least nucleotides 607 to 2211 of SEQ ID NO: 4 which encodes the predicted amino acid sequence of at least about amino acids 203 to 736 of SEQ ID NO: 5; and/or

(2) AAV capsid proteins comprising a heterogenous population of vp1 proteins, a heterogenous population of vp2 proteins optionally comprising a valine at position 157, and a heterogenous population of vp3 proteins, wherein at least a subpopulation of the vp1 and vp2 proteins comprise a valine at position 157 and optionally further comprising a glutamic acid at position 67 based on the numbering of the vp1 capsid of SEQ ID NO: 5; and/or

(3) a heterogenous population of vp1 proteins which are the product of a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 5, a heterogenous population of vp2 proteins which are the product of a nucleic acid sequence encoding the amino acid sequence of at least about amino acids 138 to 736 of SEQ ID NO: 5, and a heterogenous population of vp3 proteins which are the product of a nucleic acid sequence encoding at least amino acids 203 to 736 of SEQ ID NO: 5, wherein: the vp1, vp2 and vp3

proteins contain subpopulations with amino acid modifications comprising at least two highly deamidated asparagines (N) in asparagine - glycine pairs in SEQ ID NO: 5 and optionally further comprising subpopulations comprising other deamidated amino acids, wherein the deamidation results in an amino acid change

~~10~~7. An aqueous pharmaceutical composition comprising a formulation buffer and a stock of the rAAV according to any one of claims 1 to ~~9~~6.

~~11~~8. The pharmaceutical composition according to claim ~~10~~7, wherein the formulation buffer comprises:

an artificial cerebrospinal fluid comprising buffered saline and one or more of sodium, calcium, magnesium, potassium, or mixtures thereof; and

a surfactant.

~~12~~9. The pharmaceutical composition according to claim ~~11~~8, wherein the surfactant is present at 0.0005 % w/w to about 0.001% w/w of the pharmaceutical composition~~.~~, and/or

~~13. The pharmaceutical composition according to any one of claims 10 to 12,~~ wherein the composition is at a pH in the range of 7.5 to 7.8, or 6.2 to 7.7, or about 7.

10. The rAAV according to any one of claims 1 to 6 or the pharmaceutical composition according to any one of claims 7-9, wherein the rAAV or pharmaceutical composition is suitable for intravenous administration, intrathecal administration, and/or intraparenchymal (dentate nucleus) administration.

~~14~~11. A first rAAV according to any one of claims 1 to 6 and a second rAAV according to any one of claims 1 to 6 for use in a treatment regimen for FRDA comprising dual-route of administration of rAAV, the regimen comprising of intravenous administration of ~~a~~ said first rAAV for intravenous administration ~~according to any one of claims 1 to 9~~ and said second rAAV for intraparenchymal (dentate nucleus) or intrathecal administration ~~of a second rAAV according to any one of claims 1 to 9~~.

12. Use of a first rAAV according to any one of claims 1 to 6 and of a second rAAV according to any one of claims 1 to 6 in the preparation of a medicament for a treatment regimen for FRDA comprising dual-route of administration of rAAV, the regimen comprising said first rAAV for intravenous administration and said second rAAV for intraparenchymal (dentate nucleus) or intrathecal administration.

~~15~~13. The first rAAV and second rAAV ~~regimen~~ according to claim ~~14~~11 or the use according to claims 12, wherein the intraparenchymal (dentate nucleus) administration is to be performed unilaterally~~.~~ or bilaterally.

~~16. The regimen according to claim 14, wherein the intraparenchymal (dentate nucleus) administration is performed bilaterally.~~

~~17~~14. The first rAAV and second rAAV according to claim 11 or the use according to claim 12~~regimen according to any one of claims 14 to 16~~, wherein the intravenous and intraparenchymal (dentate nucleus) administrations of the rAAV are to be performed sequentially and within a 24-hour period.

~~18. A regimen comprising co-administration of a first rAAV according to any one of claims 1 to 9 intravenously and a second rAAV according to any one of claims 1 to 9 intrathecally.~~

~~19~~15. An rAAV according to any one of claims 1 to 6 or a pharmaceutical composition according to any one of claims ~~10~~ 7 to ~~13~~ 9 for use in treatment of FRDA, the treatment comprising a dual-route administration according to any one of claims 11, 13 to 14~~14 to 18~~, wherein an amelioration of FRDA includes reduction of cardiac and/or neurological symptoms.

16. The use according to any one of claims 12 to 14, wherein an amelioration of FRDA includes reduction of cardiac and/or neurological symptoms.

~~20. The rAAV according to any one of claims 1 to 9 for use in the treatment of FRDA, the treatment comprising a dual-route administration according to any one of claims~~

~~14 to 18, wherein an amelioration of FRDA includes reduction of cardiac and neurological symptoms.~~

~~21. The rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 for use in the treatment of FRDA, wherein the rAAV or pharmaceutical composition is suitable for intravenous administration.~~

~~22. The rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 for use in the treatment of FRDA, wherein the rAAV or pharmaceutical composition is suitable for intrathecal administration.~~

~~23. The rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 for use in the treatment of FRDA, wherein the rAAV or pharmaceutical composition is suitable for intraparenchymal (dentate nucleus) administration.~~

~~24. The rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 for use in the treatment of FRDA, wherein the rAAV or the pharmaceutical composition is suitable for administration to a patient in need thereof to ameliorate one or more symptoms of FRDA.~~

~~25. The use according to claim 24, wherein the amelioration of FRDA includes increased average life span, reduction in progression towards neuromuscular decline and/or improvement in neuromuscular development, reduction in progression towards cardiomyopathy and/or improvement in cardiac symptoms.~~

17. The rAAV according to any one of claims 1 to 6 or the pharmaceutical composition according to any one of claims 7 to 9 for use in treating FRDA in a subject.

~~26~~18. Use of the rAVV according to any one of claims 1 to 6 or the pharmaceutical composition according to any one of claims 7 to 9 in the preparation of a medicament for~~A method of~~ treating FRDA in a subject~~ with FRDA, the method comprising administering the rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 to the subject~~.

~~27~~19. The rAAV or the pharmaceutical composition according to claim 17 or the use according to claim 18, ~~method of claim 26,~~ wherein the rAAV ~~according to any one of claims 1 to 9~~ or the pharmaceutical composition ~~according to any one of claims 10 to 13~~ is to be administered intravenously, ~~or~~ intrathecally~~.~~, or via intraparenchymal injection.

~~28. The method of claim 26, wherein the rAAV according to any one of claims 1 to 9 or the pharmaceutical composition according to any one of claims 10 to 13 is administered via intraparenchymal injection.~~

~~29~~20. The rAAV or the pharmaceutical composition according to claim 17 and 19, or the use according to claims 18 to 19, ~~method of any one of claims 26-28,~~ wherein ~~the method comprises administering~~ the rAAV is to be administered by a first route of administration and by a second route of administration.

~~30~~21. The rAAV, pharmaceutical composition or use of claim 20~~method of claim 29~~, wherein the first route is intravenous and the second route is intrathecal~~.~~, or

~~31. The method of claim 29,~~ wherein the first route is intravenous and the second route is intraparenchymal.

~~32~~22. The rAAV, pharmaceutical composition or use ~~method~~ according to claim ~~31~~21, wherein the intraparenchymal (dentate nucleus) administration is to be performed unilaterally or bilaterally~~.~~, and/or

~~33. The method according to claim 31, wherein the intraparenchymal (dentate nucleus) administration is performed bilaterally.~~

~~34. The method according to any one of claims 31 to 33,~~ wherein the amount of dose of rAAV to be administered intravenously and the amount of rAAV to be administered IDN is a ratio of about 10 to about 1.

~~35~~23. The rAAV, pharmaceutical composition or use ~~method~~ according to any one of claims ~~39 to 34~~17 to 22, wherein the first route and second route are to be administered simultaneously or sequentially~~.~~ and/or

~~36. The method according to any one of claims 29 to 35,~~ wherein the first route and second route are administered within 24 hours of one another.

~~37~~24. The rAVV, pharmaceutical composition or use according to any one of claims 17 to 23, ~~method according to any one of claims 26 to 36,~~ wherein the method ameliorates one or more symptoms of FRDA in the subject.

~~38~~25. The rAVV, pharmaceutical composition or use~~method~~ of claim ~~37~~24, wherein the amelioration of one or more symptoms of FRDA includes increased average life span, reduction in progression towards neuromuscular decline, improvement in neuromuscular development, reduction in progression towards cardiomyopathy, or improvement in cardiac symptoms, or any combination thereof.

~~39. The method of claim 38, wherein the amelioration of one or more symptoms of FRDA is an increased average life span.~~

~~40. The method of claim 38, wherein the amelioration of one or more symptoms of FRDA is a reduction in progression towards neuromuscular decline.~~

~~41. The method of claim 38, wherein the amelioration of one or more symptoms of FRDA is an improvement in neuromuscular development.~~

~~42. The method of claim 38, wherein the amelioration of one or more symptoms of FRDA is a reduction in progression towards cardiomyopathy.~~

~~43. The method of claim 38, wherein the amelioration of one or more symptoms of FRDA is an improvement in cardiac symptoms.~~

~~44~~26. The rAAV, pharmaceutical composition or use ~~method~~ of claim ~~43~~25, wherein the improvement in cardiac symptoms is a reduction or elimination of an arrhythmia in the subject.

~~46~~27. A plasmid comprising

(i) an expression cassette comprising a FXN gene having the sequence of SEQ ID NO: 3 or a sequence 95% identical thereto that encodes human frataxin~~.~~, or

(ii) the vector genome of SEQ ID NO: 8 or 12, or a sequence at least 95% identical to SEQ ID NO: 8 or 12.

~~47~~28. The plasmid according to claim ~~46~~27, wherein the FXN gene encodes a sequence of SEQ ID NO: 2, or a sequence at least 95% identical thereto.

~~48~~29. The plasmid according to claim ~~47~~28, the expression cassette further comprising a CB7 promoter, an intron, and a polyA~~.~~ and/or

~~49. The plasmid according to claim 48,~~ wherein the expression cassette is flanked by an AAV2 5' ITR and an AAV2 3' ITR.

~~50. A plasmid comprising the vector genome of SEQ ID NO: 8 or 12, or a sequence at least 95% identical to SEQ ID NO: 8 or 12.~~

~~51~~30. A host cell comprising the plasmid according to any one of claims ~~46~~ 27 to ~~50~~29.