SUMMARY

In one example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a myelin associated disease. In another example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for increasing the amount of myelin in a subject with a myelin associated disease.

In one example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting oligodendrocyte maturation in a subject with a myelin associated disease.

In one example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a mitochondria associated disease.

In one example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating lactic acidosis in a subject with a mitochondria associated disease or for treating lactic acidosis in a subject with a myelin and mitochondria associated disease.

In one example, the present disclosure refers to the use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting neuronal survival in a subject in need thereof.

In some examples, the present disclosure provides a method of treating a myelin associated disease, the method comprising administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the myelin associated disease in the subject is treated.

In some examples, administration of the FXN replacement therapeutic compound causes modulation of at least one a protein in said subject, wherein said at least one protein is selected from the group consisting of of ABCE1, EIF1A, EGR 1, EGR2 (KROX20), EGR3, SERPINE1, CCN1 (CYR61), THBS1, NR41(Nurr77), RTN4 (NOGO), RTN4IP1and TMEM126A.

In some examples, the present disclosure provides a method of increasing the amount of myelin in a subject with a myelin associated disease, the method comprising administering to the subject an effective amount of a frataxin replacement therapeutic compound, such that the amount of myelin in the subject is increased.

In some examples, the present disclosure provides a method of promoting oligodendrocyte maturation in a subject with a myelin associated disease, the method comprising administering to the subject an effective amount of a frataxin replacement therapeutic compound, such that oligodendrocyte maturation in the subject is increased.

In some examples, the present disclosure provides a method of modulating a protein in a subject affected by a myelin associated disease, the method comprising administering to the subject an effective amount of a frataxin (FXN) replacement therapeutic compound such that the protein in the subject is modulated; wherein the protein is selected from the group consisting of ABCE1, EIF1A, EGR 1, EGR2 (KROX20), EGR3, SERPINE1, CCN1 (CYR61), THBS1, NR41(Nurr77), RTN4 (NOGO), RTN4IP1and TMEM126A.

In some examples, the myelin associated disease is not Friedreich's Ataxia.

In some examples, the myelin associated disease is not Leigh Syndrome, French Canadian Type (LSFC).

In some examples, the myelin associated disease is a dysmyelination disease characterized by a malformed and/or defective myelin sheath present in the subject.

In one aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

In another aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for increasing the amount of myelin in a subject with a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin

protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

In another aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting oligodendrocyte maturation in a subject with a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

In another aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a mitochondria associated disease, wherein said mitochondria associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

In another aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating lactic acidosis in a subject with a mitochondria associated disease or for treating lactic acidosis in a subject with a myelin and mitochondria associated disease, wherein said mitochondria associated disease or myelin and mitochondria associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

In another aspect, the present disclosure refers to use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting neuronal survival in a subject in need thereof, wherein said subject has a myelin associated disease, and wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising: (i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and (ii) an additional amino acid sequence.

CLAIMS

What is claimed is:

1. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

2. The use of claim 1, wherein administration of the FXN replacement therapeutic compound causes modulation of at least one a protein in said subject,

wherein said at least one protein is selected from the group consisting of of ABCE1, EIF1A, EGR 1, EGR2 (KROX20), EGR3, SERPINE1, CCN1 (CYR61), THBS1, NR41(Nurr77), RTN4 (NOGO), RTN4IP1and TMEM126A.

3. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for increasing the amount of myelin in a subject with a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

4. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting oligodendrocyte maturation in a subject with a myelin associated disease, wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

5. The use of any one of claims 1-4, wherein said myelin associated disease is a dysmyelination disease characterized by a malformed and/or defective myelin sheath present in the subject.

6. The use of claim 5, wherein said dysmyelination disease is a leukodystrophy.

7. The use of claim 6, wherein said leukodystrophy is selected from the group consisting of Vanishing White Matter Disease (VWMD) and X-Linked adrenoleukodystrophy (ALD).

8. The use of any one of claims 1-4, wherein said myelin associated disease is a demyelination disease characterized by the destruction of previously normal myelin in the subject.

9. The use of claim 8, wherein said demyelination disease is a central demyelination disease.

10. The use of claim 9, wherein said central demyelination disease is an inflammatory or an immune central demyelination disease.

11. The use of claim 10, wherein said inflammatory or said immune central demyelination disease is selected from the group consisting of multiple sclerosis (MS), myelinoclastic diffuse sclerosis (Schilder's Disease), optic neuritis, acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leucoencephalitis (AHL), paraneoplastic encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease and Sjörgen disease.

12. The use of claim 9, wherein said central demyelination disease is a toxic or metabolic central demyelination disease.

13. The use of claim 12, wherein said toxic or metabolic central demyelination disease is selected from the group consisting of: central pontine myelinolysis; carbon monoxide

poisoning; and exposure to radiation and posterior reversible encephalopathy syndrome (PRES).

14. The use of claim 8, wherein said demyelination disease is a peripheral demyelination disease.

15. The use of claim 14, wherein said peripheral demyelinating disease is selected from the group consisting of: Guillain-Barré Syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), paraproteinemic demyelinating neuropathy, progressive inflammatory neuropathy (PIN), Anti-Myelin Associated Glycoprotein (MAG) neuropathy, POEMS Syndrome, and Charcot Marie Tooth Disease.

16. The use of any one of claims 1-15, wherein at least one symptom of the myelin associated disease is alleviated in the subject.

17. The use of claim 16, wherein said at least one symptom is selected from the group consisting of ataxia, blurred vision, muscle weakness, muscle stiffness, muscle spasms, heart palpitations, dizziness, uncoordinated movements, and fatigue.

18. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating a mitochondria associated disease, wherein said mitochondria associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

19. The use of claim 18, wherein administration of the FXN replacement therapeutic compound causes modulation of at least one a protein in said subject,

wherein said protein is selected from the group consisting of MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO2, MT-CO3, MT-ATP6, MT-ATP8, CYCS, SLIRP, RTN4, and TMEM-126A.

20. The use of claim 18 or 19, wherein said mitochondria associated disease is not one or more of human mitochondrial trifunctional protein deficiency, sudden infant death syndrome, Kearns-Sayre syndrome, and Leber's Hereditary Optic Neuropathy.

21. The use of any one of claims 18- 19, wherein said mitochondria associated disease is associated with a defect in the respiratory chain or wherein said mitochondria associated disease is associated with a defect in mitochondrial DNA (mtDNA).

22. The use of any one of claims 18-21, wherein said mitochondria associated disease is selected from the group consisting of Complex I Deficiency, Complex II Deficiency, Complex III Deficiency, Complex IV Deficiency, Complex V Deficiency, MELAS and Leigh Disease.

23. The use of any one of claims 18-22, wherein at least one symptom of the mitochondria associated disease is alleviated in the subject.

24. The use of claim 23, wherein said at least one symptom is selected from the group consisting of: fatigue, weakness, metabolic strokes, seizure, cardiomyopathy, arrhythmia, developmental disability, cognitive disability, diabetes mellitus, impaired hearing, impaired vision, impaired growth, impaired liver function, impaired gastrointestinal function, and impaired kidney function.

25. The use of any one of claims 1-24, wherein said disease is a myelin and mitochondria associated disease.

26. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for treating lactic acidosis in a subject with a mitochondria associated disease or for treating lactic acidosis in a subject with a myelin and mitochondria associated disease, wherein said mitochondria associated disease or myelin and mitochondria associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

27. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for promoting neuronal survival in a subject in need thereof, wherein said subject has a myelin associated disease, and wherein said myelin associated disease is not Friedreich's Ataxia or Leigh Syndrome, French Canadian Type (LSFC), and wherein said FXN replacement therapeutic compound comprises an FXN fusion protein comprising:

(i) a frataxin protein comprising an amino acid sequence having at least about 90% sequence identity to SEQ ID NO: 1, and

(ii) an additional amino acid sequence.

28. The use of any one of claims 1-27, wherein said frataxin fusion protein comprises a frataxin protein comprising the amino acid sequence of SEQ ID NO: 1.

29. The use of any one of claims 1-27, wherein said frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1.

30. The use of any one of claims 1-29, wherein said additional amino acid sequence comprises a cell penetrating peptide (CPP).

31. The use of claim 30, wherein the CPP comprises the transduction domain of HIV-TAT comprising or consisting of the amino acid sequence of SEQ ID NO: 3, or a fragment of SEQ ID NO: 3.

32. The use of any one of claims 1-30, wherein the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of the amino acid sequence of SEQ ID NO: 22.

33. The use of any one of claims 1-31, wherein the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of an amino acid sequence having at least 85% sequence identity to SEQ ID NO: 22.

34. The use of any one of claims 30-33, wherein said frataxin fusion protein further comprises a target enhancing sequence (TES).

35. The use of claim 34, wherein the frataxin fusion protein comprises or consists of, starting at the N-terminus:

CPP;

TES; and

full-lenth frataxin (SEQ ID NO: 1); or

wherein the frataxin fusion protein comprises or consists of, starting at the N-terminus:

full-length FXN (SEQ ID NO: 1);

TES; and

CPP.

36. The use of claim 34 or 35, wherein the TES comprises a nuclear export signal peptide.

37. The use of claim 36, wherein the nuclear export signal peptide comprises a sequence having at least 85% sequence identity to any one of SEQ ID NOs. 42-49.

38. The use of claim 34 or 35, wherein the TES comprises a protease sensitive peptide.

39. The use of claim 38, wherein the protease sensitive peptide comprises a ubiquitin-like modifier.

40. The use of claim 38, wherein the protease sensitive peptide comprises an amino acid sequence having at least 85% sequence identity to any one of SEQ ID NOs. 23-41.

41. The use of claim 34, wherein the frataxin fusion protein comprises an amino acid sequence having at least 85%, 90%, or 95% sequence identity to any of SEQ ID NOs. 50-57.

42. The use of any one of claims 1-41, wherein said subject is a human.