

CLAIMS

What is claimed is:

1. A method of treating a myelin associated disease, said method comprising administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that said myelin associated disease in said subject is treated.
2. The method 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), RTN4IP1 and TMEM126A.
3. A method of increasing the amount of myelin in a subject with a myelin associated disease, said method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the amount of myelin in said subject is increased.
4. A method of promoting oligodendrocyte maturation in a subject with a myelin associated disease, said method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that oligodendrocyte maturation in said subject is increased.
5. A method of modulating a protein in a subject affected by a myelin associated disease, said method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound such that said protein in said subject is modulated;
wherein said protein is selected from the group consisting of ABCE1, EIF1A, EGR 1, EGR2 (KROX20), EGR3, SERPINE1, CCN1 (CYR61), THBS1, NR41(Nurr77), RTN4 (NOGO), RTN4IP1 and TMEM126A.
6. The method of any one of claims 1-5, wherein said myelin associated disease is not Friedreich's Ataxia.

7. The method of any one of claims 1-6, wherein said myelin associated disease is not Leigh Syndrome, French Canadian Type (LSFC).
8. The method of any one of claims 1-7, wherein said myelin associated disease is a dysmyelination disease characterized by a malformed and/or defective myelin sheath present
5 in the subject.
9. The method of claim 8, wherein said dysmyelination disease is a leukodystrophy.
10. The method of claim 9, wherein said leukodystrophy is selected from the group consisting of Vanishing White Matter Disease (VWMD) and X-Linked adrenoleukodystrophy (ALD).
- 10 11. The method of any one of claims 1-7, wherein said myelin associated disease is a demyelination disease characterized by the destruction of previously normal myelin in the subject.
12. The method of claim 11, wherein said demyelination disease is a central demyelination disease.
- 15 13. The method of claim 12, wherein said central demyelination disease is an inflammatory or an immune central demyelination disease.
14. The method of claim 13, 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
20 encephalomyelitis (ADEM), acute hemorrhagic leucoencephalitis (AHL), paraneoplastic encephalomyelitis, rheumatoid arthritis, systemic lupus erythematosus, Behçet's disease and Sjörgen disease.
15. The method of claim 12, wherein said central demyelination disease is a toxic or metabolic central demyelination disease.
- 25 16. The method of claim 15, wherein said toxic or metabolic central demyelination disease is selected from the group consisting of: a disorder associated with a vitamin B12 deficiency; central pontine myelinolysis; carbon monoxide poisoning; and exposure to radiation and posterior reversible encephalopathy syndrome (PRES).

17. The method of claim 11, wherein said demyelination disease is a peripheral demyelination disease.
18. The method of claim 17, 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, Charcot Marie Tooth Disease, and a copper deficiency associated disorder.
19. The method of any one of claims 1-18, wherein at least one symptom of the myelin associated disease is alleviated in the subject.
20. The method of claim 19, 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.
21. A method of treating a mitochondria associated disease, said method comprising administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that said mitochondria associated disease in said subject is treated.
22. The method of claim 21, wherein administration of the FXN replacement therapeutic compound causes modulation of at least one a protein in said subject,
- 20 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.
23. A method of modulating a protein in a subject affected by a mitochondria associated disease, said method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound such that said protein in said subject is modulated;
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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.

24. The method of any one of claims 21-23, wherein said mitochondria associated disease
5 is not one or more of Friedreich's Ataxia, human mitochondrial trifunctional protein deficiency, sudden infant death syndrome, Kearns-Sayre syndrome, and Leber's Hereditary Optic Neuropathy.

25. The method of any one of claims 21-23, wherein said mitochondria associated disease is not Leigh Syndrome, French Canadian Type (LSFC).

10 26. The method of any one of claims 21-23, wherein said mitochondria associated disease is associated with a defect in the respiratory chain.

27. The method of any one of claims 21-23, wherein said mitochondria associated disease is associated with a defect in mitochondrial DNA (mtDNA).

28. The method of any one of claims 21-23, wherein said mitochondria associated disease
15 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.

29. The method of any one of claims 21-28, wherein at least one symptom of the mitochondria associated disease is alleviated in the subject.

20 30. The method of claim 29, 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 31. The method of any one of claims 1-30, wherein said disease is a myelin and mitochondria associated disease.

32. A method of treating lactic acidosis in a subject with a mitochondria associated disease, said method comprising administering to the subject an effective amount of a

frataxin (FXN) replacement therapeutic compound, such that said lactic acidosis in said subject is treated.

33. A method of treating lactic acidosis in a subject with a myelin and mitochondria associated disease, said method comprising administering to the subject an effective amount
5 of a frataxin (FXN) replacement therapeutic compound, such that said lactic acidosis in said subject is treated.

34. A method of treating Charcot Marie Tooth Disease (CMT), said method comprising administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that said lactic acidosis in said subject is treated.

10 35. The method of claim 34, wherein said CMT is selected from the group consisting of CMT type 1A (CMT1A) associated with the duplication the PMP22 gene; CMT type 2A2 (CMT2A2) associated with mutations in the gene *MFN2* gene; X-linked CMT (CMTX) associated with a mutation in the *GJB1* gene; CMT type 1B (CMT1B) associated with a mutation in the *MPZ* gene; and CMT type 4 (CMT4) associated with a mutation in the
15 GDAP1 gene or a SURF1 gene.

36. A method of promoting neuronal survival in a subject in need thereof, said method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that neuronal survival in said subject is promoted.

37. The method of claim 36, wherein said subject has a myelin associated disease.

20 38. The method of claim 36, wherein said subject has a myelin and a mitochondria associated disease.

39. The method of any one of claims 36-38, wherein administering of the FXN replacement therapeutic compound to said subject modulates at least one protein in said subject, wherein said at least one protein is selected from the group consisting of CYR61,
25 EGR1 and NR4A1.

40. The method of any one of claims 1-39, wherein said frataxin replacement therapeutic compound comprises a frataxin protein or a nucleic acid sequence encoding a frataxin protein.

41. The method of claim 40, wherein said frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising a frataxin protein, or a fragment or variant thereof, and an additional amino acid sequence.
42. The method of claim 41, wherein said frataxin fusion protein comprises a frataxin
5 protein comprising an amino acid sequence of SEQ ID NO: 1, or a fragment, variant or derivative of SEQ ID NO: 1.
43. The method of claim 41, wherein said frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence having at least about 85% sequence identity to SEQ ID NO: 1.
- 10 44. The method of claim 43, wherein said frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence having at least about 90%, at least about 95% or at least about 99% sequence identity to SEQ ID NO: 1.
45. The method of any one of claims 41-44, wherein said additional amino acid sequence comprises a cell penetrating peptide (CPP).
- 15 46. The method of claim 45, wherein the CPP comprises a peptide selected from the group of CPPs listed in the Database of Cell-Penetrating Peptides CPPsite 2.0.
47. The method of claim 45, wherein the CPP comprises a peptide selected from the group consisting of a transduction domain of HIV-TAT, galanin, mastoparan, transportan, penetratin, polyarginine, VP22, and a variant or derivative thereof.
- 20 48. The method of claim 45, 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, variant or derivative of SEQ ID NO: 3.
49. The method of any one of claims 1-46, wherein the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of the amino acid
25 sequence of SEQ ID NO: 22.
50. The method of any one of claims 1-48, wherein the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of an amino acid sequence having at least about 85% sequence identity to SEQ ID NO: 22.

51. The method of claim 50, wherein the FXN replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of an amino acid sequence having at least about 90%, at least about 95% or at least about 99% sequence identity to SEQ ID NO: 22.
- 5 52. The method of any one of claims 45-51, wherein said frataxin fusion protein further comprises a target enhancing sequence (TES).
53. The method of claim 52, wherein the CPP is located at the N-terminus of the frataxin fusion protein and wherein the TES is fused at the C-terminus of the CPP.
54. The method of claim 52 or 53, wherein the frataxin fusion protein comprises or
10 consists of, starting at the N-terminus:
- CPP;
- TES; and
- full-length frataxin (SEQ ID NO: 1).
55. The method of claim 52, wherein the CPP is located at the C-terminus of the fusion
15 protein and wherein the TES is fused at the N-terminus of the CPP.
56. The method of claim 52 or 55, wherein the frataxin fusion protein comprises or
consists of, starting at the N-terminus:
- full-length FXN (SEQ ID NO: 1);
- TES; and
- 20 CPP.
57. The method of any one of claims 52-56, wherein the TES comprises a nuclear export signal peptide.
58. The method of claim 57, wherein the nuclear export signal peptide comprises a sequence having at least 85% sequence identity to any one of SEQ ID NOs. 42-49.

59. The method of claim 58, wherein the nuclear export signal peptide comprises a peptide selected from the group consisting of NES1, NES2, NES3, NES4, NES5, NES6, NES7, NES8, and a variant or derivative thereof.
60. The method of claim 59, wherein the nuclear export signal peptide comprises a peptide selected from the group consisting of NES1 and NES2, or a variant or derivative thereof.
61. The method of any one of claims 52-56, wherein the TES comprises a protease sensitive peptide.
62. The method of claim 61, wherein the protease sensitive peptide comprises a ubiquitin-like modifier.
63. The method of claim 61, 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.
64. The method of claim 61, wherein the protease sensitive peptide comprises an amino acid sequence having at least 85% sequence identity to human ubiquitin (SEQ ID NO: 23).
65. The method of claim 61, wherein the protease sensitive peptide comprises an amino acid sequence having at least 85% sequence identity to a calpain cleavage domain EPLFAERK (SEQ ID NO: 25).
66. The method of claim 61, wherein the protease sensitive peptide comprises a peptide selected from the group consisting of ubiquitin, a caspase cleavage domain, a calpain cleavage domain, SUMO1, SUMO2, SUMO3, SUMO4, ISG15, Atg8, Atg12, NEDD8, and a variant or derivative thereof.
67. The method of claim 52 or 53, 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.
68. The method of any one of claims 1-67, wherein said subject is a human.