SUMMARY ~~OF THE INVENTION~~

In one aspect, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 aspect, 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 ~~aspect~~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 ~~embodiment~~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 ~~aspect~~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 ~~aspect~~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 ~~aspect~~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 ~~embodiment~~examples, the myelin associated disease is not Friedreich's Ataxia.

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

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

In some ~~embodiment~~examples, the dysmyelination disease is a leukodystrophy.

In some ~~embodiment~~examples, the leukodystrophy is selected from the group consisting of Vanishing White Matter Disease (VWMD) and X-Linked adrenoleukodystrophy (ALD).

In some ~~embodiment~~examples, the myelin associated disease is a demyelination disease characterized by the destruction of previously normal myelin in the subject.

In some ~~embodiment~~examples, the demyelination disease is a central demyelination disease.

In some ~~embodiment~~examples, the central demyelination disease is an inflammatory or an immune central demyelination disease.

In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, the central demyelination disease is a toxic or metabolic central demyelination disease.

In some ~~embodiment~~examples, the 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; exposure to radiation and posterior reversible encephalopathy syndrome (PRES).

In some ~~embodiment~~examples, the demyelination disease is a peripheral demyelination disease. In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, the at least one symptom of the myelin associated disease is alleviated in the subject. In some ~~embodiment~~examples, the 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.

In some ~~aspect~~examples, the present disclosure also provides a method of treating a mitochondria 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 mitochondria associated disease in said subject is treated. In some ~~embodiment~~examples, the 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.

In some ~~aspect~~examples, the present disclosure provides 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; wherein the 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.

In some ~~embodiment~~examples, the mitochondria associated disease 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.

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

In some ~~embodiment~~examples, the mitochondria associated disease is associated with a defect in the respiratory chain.

In some ~~embodiment~~examples, the mitochondria associated disease is associated with a defect in mitochondrial DNA (mtDNA).

In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, at least one symptom of the mitochondria associated disease is alleviated in the subject. In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, the disease is a myelin and mitochondria associated disease.

In some ~~aspect~~examples, the present disclosure provides a method of treating lactic acidosis in a subject with a mitochondria associated disease, the method comprising administering to the subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the lactic acidosis in the subject is treated.

In some ~~aspect~~examples, the present disclosure provides a method of treating lactic acidosis in a subject with a myelin and mitochondria associated disease, the method comprising administering to the subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the lactic acidosis in the subject is treated.

In some ~~aspect~~examples, the present disclosure provides a method of treating Charcot Marie Tooth Disease (CMT), the method comprising administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the lactic acidosis in the subject is treated.

In some ~~embodiment~~examples, the 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 GDAP1 gene or a SURF1 gene.

In some ~~aspect~~examples, the present disclosure provides a method of promoting neuronal survival in a subject in with , the method comprising administering to said subject an effective amount of a frataxin (FXN) replacement therapeutic compound, such that neuronal survival in the subject is promoted.

In some ~~embodiment~~examples, the subject has a myelin associated disease. In some ~~embodiment~~examples, the subject has a myelin and a mitochondria associated disease.

In some ~~embodiment~~examples, 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, EGR1 and NR4A1.

In some ~~embodiment~~examples, the frataxin replacement therapeutic compound comprises a frataxin protein or a nucleic acid sequence encoding a frataxin protein. In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, the frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence of SEQ ID NO: 1, or a fragment, variant or derivative of SEQ ID NO: 1. In some ~~embodiment~~examples, the frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence having at least about 85% sequence identity to SEQ ID NO: 1. In some ~~embodiment~~examples, the 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.

In some ~~embodiment~~examples, the additional amino acid sequence comprises a cell penetrating peptide (CPP). In some ~~embodiment~~examples, the CPP comprises a peptide selected from the group of CPPs listed in the Database of Cell-Penetrating Peptides CPPsite 2.0. In some ~~embodiment~~examples, 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.

In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of the amino acid sequence of SEQ ID NO: 22.

In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, 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.

In some ~~embodiment~~examples, the frataxin fusion protein further comprises a target enhancing sequence (TES). In some ~~embodiment~~examples, 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.

In some ~~embodiment~~examples, the frataxin fusion protein comprises or consists of, starting at the N-terminus: CPP; TES; and full-lenth frataxin (SEQ ID NO: 1).

In some ~~embodiment~~examples, the CPP is located at the C-terminus of the fusion protein and wherein the TES is fused at the N-terminus of the CPP. In some ~~embodiment~~examples, the frataxin fusion protein comprises or consists of, starting at the N-terminus: full-length FXN (SEQ ID NO: 1); TES; and CPP.

In some ~~embodiment~~examples, the TES comprises a nuclear export signal peptide. In some ~~embodiment~~examples, the nuclear export signal peptide comprises a sequence having at least 85% sequence identity to any one of SEQ ID NOs. 42-49. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, the nuclear export signal peptide comprises a peptide selected from the group consisting of NES1 and NES2, or a variant or derivative thereof.

In some ~~embodiment~~examples, the TES comprises a protease sensitive peptide. In some ~~embodiment~~examples, the protease sensitive peptide comprises a ubiquitin-like modifier. In some ~~embodiment~~examples, the protease sensitive peptide comprises an amino acid sequence having at least 85% sequence identity to any one of SEQ ID NOs. 23-41. In some ~~embodiment~~examples, the protease sensitive peptide comprises an amino acid sequence having at least 85% sequence identity to human ubiquitin (SEQ ID NO: 23). In some ~~embodiment~~examples, 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). In some ~~embodiment~~examples, 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.

In some ~~embodiment~~examples, 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.

In some ~~embodiment~~examples, the subject is a human.

In some ~~embodiment~~examples, the present disclosure provides methods for treating a myelin associated disease, that comprise 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 ~~embodiment~~examples, the present disclosure also provides methods of modulating a protein in a subject affected by a myelin associated disease, that comprise 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 ~~aspect~~examples, the myelin associated disease is not Friedreich's Ataxia. In some ~~aspect~~examples, the myelin associated disease is not Leigh Syndrome, French Canadian Type (LSFC).

In some ~~aspect~~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~~example, the dysmyelination disease is a leukodystrophy, *e.g.*, selected from the group consisting of Vanishing White Matter Disease (VWMD) and X-Linked adrenoleukodystrophy (ALD).

In some ~~embodiment~~examples, the myelin associated disease is a demyelination disease characterized by the destruction of previously normal myelin in the subject. In a further ~~embodiment~~example, the demyelination disease is a central demyelination disease, *e.g.*, an inflammatory or an immune central demyelination disease. In one ~~aspect~~example, the inflammatory or the 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.

In some ~~embodiment~~examples, the central demyelination disease is a toxic or metabolic central demyelination disease, *e.g.*, selected from the group consisting of a disorder associated with a vitamin B12 deficiency; central pontine myelinolysis, carbon monoxide poisoning; exposure to radiation and posterior reversible encephalopathy syndrome (PRES).

In some ~~embodiment~~examples, the demyelination disease is a peripheral demyelination disease, *e.g.*, 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.

In some ~~aspect~~examples, at least one symptom of the myelin associated disease is alleviated in the subject. In further ~~aspect~~examples, the 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.

In some ~~embodiment~~examples, the present disclosure also provides methods for treating a mitochondria associated disease that comprise administering to a subject in need thereof an effective amount of a frataxin (FXN) replacement therapeutic compound, such that the mitochondria associated disease in the subject is treated.

In some ~~embodiment~~examples, the present disclosure also provides a method of modulating a protein in a subject affected by a mitochondria associated disease that comprises 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 MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-CO2, MT-CO3, MT-ATP6, MT-ATP8, CYCS, SLIRP, RTN4, and TMEM-126A.

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

In some ~~embodiment~~examples, the mitochondria associated disease is associated with a defect in the respiratory chain. In some ~~embodiment~~examples, the mitochondria associated disease is associated with a defect in mitochondrial DNA (mtDNA).

In some ~~aspect~~examples, the 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.

In some ~~embodiment~~examples, at least one symptom of the mitochondria associated disease is alleviated in the subject. In some ~~embodiment~~examples, the 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.

In some ~~aspect~~examples, the frataxin replacement therapeutic compound comprises a frataxin protein or a nucleic acid sequence encoding a frataxin protein. In some ~~aspect~~examples, the 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.

In some ~~embodiment~~examples, the frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence of SEQ ID NO: 1, or a fragment, variant or derivative of SEQ ID NO: 1.

In some ~~embodiment~~examples, the frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence having at least about 85% sequence identity to SEQ ID NO: 1.

In some ~~embodiment~~examples, the 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.

In some ~~aspect~~examples, the additional amino acid sequence comprises a cell penetrating peptide (CPP). In further ~~aspect~~examples, the CPP comprises a peptide selected from the group of CPPs listed in the Database of Cell-Penetrating Peptides CPPsite 2.0. In other ~~aspect~~examples, 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.

In one ~~embodiment~~example, 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.

In some ~~embodiment~~examples, the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of the amino acid sequence of SEQ ID NO: 22. In some ~~embodiment~~examples, 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. In some ~~embodiment~~examples, 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.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a series of bar graphs showing 12 FXN-sensitive genomic markers (FSGMs) selected from Table 11. Specifically, **Figure 1, panel A** is a bar graph illustrating the fold change in gene expression in the heart tissue of WT mice treated with Vehicle *vs*. the heart tissue of KO mice treated with Vehicle. **Figure 1, panel B** is a bar graph illustrating the fold change in gene expression in the heart tissue of KO mice treated with Vehicle *vs*. the heart tissue of KO mice treated with an exemplary TAT-hFXN fusion protein.

Figure 2, panel A shows clusters generated by string analysis of predicted interactions of protein products of 42 FSGMs based on Table 11 with additional genes additions. **Figure 2, panel B** shows the list of genes that were used to generate the String Model shown in Figure 2, panel A.

Figure 3 shows the effect of NGF treatment of PC12 cells morphology and the effect of NGF and EGF treatment on the expression of FSGMs. Specifically, **Figure 3, panel A** is a series of photographs showing the appearance of neurite outgrowth in cells treated with NGF for 1.5 hours over 4 days. **Figure 3, panel B** shows the effect of NGF and EGF treatment on the expression of selected FSGMs in PC12 cells.

CLAIMS

What is claimed is:

1. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for ~~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~~ 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 ~~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. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for ~~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), RTN4IP1and TMEM126A.~~

~~6~~5. The ~~method~~ use of any one of claims 1-~~5~~4, 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~~6. The ~~method~~ use of any one of claims 1-~~7~~5, wherein said myelin associated disease is a dysmyelination disease characterized by a malformed and/or defective myelin sheath present in the subject.

~~9~~7. The ~~method~~ use of claim ~~8~~6, wherein said dysmyelination disease is a leukodystrophy.

~~10~~8. The ~~method~~ use of claim ~~9~~7, wherein said leukodystrophy is selected from the group consisting of Vanishing White Matter Disease (VWMD) and X-Linked adrenoleukodystrophy (ALD).

~~11~~9. The ~~method~~ use of any one of claims 1-~~7~~5, wherein said myelin associated disease is a demyelination disease characterized by the destruction of previously normal myelin in the subject.

~~12~~10. The ~~method~~ use of claim ~~11~~9, wherein said demyelination disease is a central demyelination disease.

~~13~~11. The ~~method~~ use of claim ~~12~~10, wherein said central demyelination disease is an inflammatory or an immune central demyelination disease.

~~14~~12. The ~~method~~ use of claim ~~13~~11, 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.

~~15~~13. The ~~method~~ use of claim ~~12~~10, wherein said central demyelination disease is a toxic or metabolic central demyelination disease.

~~16~~14. The ~~method~~ use of claim ~~15~~13, 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~~15. The ~~method~~ use of claim ~~11~~9, wherein said demyelination disease is a peripheral demyelination disease.

~~18~~16. The ~~method~~ use of claim ~~17~~15, 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~~17. The ~~method~~ use of any one of claims 1-~~18~~16, wherein at least one symptom of the myelin associated disease is alleviated in the subject.

~~20~~18. The ~~method~~ use of claim ~~19~~17, 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~~19. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for ~~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~~20. The ~~method~~ use of claim ~~21~~19, 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.

~~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;~~

~~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~~21. The ~~method~~ use of claim 19 or 20~~any one of claims 21-23~~, wherein said mitochondria associated disease 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).~~

~~26~~22. The ~~method~~ use of any one of claims ~~21-23~~19- 20, 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).

~~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~~23. The ~~method~~ use of any one of claims ~~21-23~~19-22, 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.

~~29~~24. The ~~method~~ use of any one of claims ~~21-28~~19-23, wherein at least one symptom of the mitochondria associated disease is alleviated in the subject.

~~30~~25. The ~~method~~ use of claim ~~29~~24, 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.

~~31~~26. The ~~method~~ use of any one of claims 1-~~30~~25, wherein said disease is a myelin and mitochondria associated disease.

~~32~~27. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for ~~A method of~~ 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~~, 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 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.~~

~~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 GDAP1 gene or a SURF1 gene.~~

~~36~~28. Use of a frataxin (FXN) replacement therapeutic compound in the manufacture of a medicament for ~~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.~~

~~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, EGR1 and NR4A1.~~

~~40~~29. The ~~method~~ use of any one of claims 1-~~39~~28, wherein said frataxin replacement therapeutic compound comprises a frataxin protein or a nucleic acid sequence encoding a frataxin protein.

~~41~~30. The ~~method~~ use of claim ~~40~~29, 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~~31. The ~~method~~ use of claim ~~41~~30, wherein said frataxin fusion protein comprises a frataxin protein comprising an amino acid sequence of SEQ ID NO: 1, or a fragment, variant or derivative of SEQ ID NO: 1.

~~43~~32. The ~~method~~ use of claim ~~41~~30, 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.

~~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~~33. The ~~method~~ use of any one of claims ~~41-44~~30-32, wherein said additional amino acid sequence comprises a cell penetrating peptide (CPP).

~~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.~~

~~48~~34. The ~~method~~ use of claim ~~45~~33, 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~~35. The ~~method~~ use of any one of claims 1-~~46~~33, wherein the frataxin replacement therapeutic compound comprises a frataxin fusion protein comprising or consisting of the amino acid sequence of SEQ ID NO: 22.

~~50~~36. The ~~method~~ use of any one of claims 1-~~48~~34, 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.~~

~~52~~37. The ~~method~~ use of any one of claims ~~45-51~~33-36, 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~~38. The ~~method~~ use of claim ~~52 or 53~~37, 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.

~~55. The method of claim 52, wherein the CPP is located at the C-terminus of the fusion 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 consiss of, starting at the N-terminus:~~

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

~~TES; and~~

~~CPP.~~

~~57~~39. The ~~method~~ use of ~~any one of claims 52-56~~claim 37 or 38, wherein the TES comprises a nuclear export signal peptide.

~~58~~40. The ~~method~~ use of claim ~~57~~39, 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~~41. The ~~method~~ use of ~~any one of claims 52-56~~claim 37 or 38, wherein the TES comprises a protease sensitive peptide.

~~62~~42. The ~~method~~ use of claim ~~61~~41, wherein the protease sensitive peptide comprises a ubiquitin-like modifier.

~~63~~43. The ~~method~~ use of claim ~~61~~41, 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~~44. The ~~method~~ use of claim ~~52 or 53~~37, 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~~45. The ~~method~~ use of any one of claims 1-~~67~~44, wherein said subject is a human.