THERAPEUTIC AGENTS FOR NEURODEGENERATIVE DISEASES

This application claims priority benefit to UK 1702551.1, filed February 16, 2017, UK 1705766.2, filed April 10, 2017, UK 1706867.7, filed April 28, 2017, International Application No. PCT/IB2017/054929, filed August 11, 2017, and U.S. Provisional Patent Application No. 62/574,137, filed October 18, 2017; all of which are incorporated herein by reference in their entirety.

Neurodegenerative diseases are those that affect neurons. The degenerative process can involve the progressive loss of neuronal structure, the progressive loss of neuronal function, or progressive neuron cell death. Such progressive neurodegeneration often results in physical disability and mental deterioration. Many neurodegenerative diseases are severely progressive and unremitting, and there are few, if any, curative treatments.

Although the process of neurodegeneration is not fully understood, therapeutic agents that are shown to be broadly neuroprotective are thought to be applicable to neurodegenerative diseases generally. In addition, many neurodegenerative diseases are associated with lysosomal dysfunction. This includes both neurodegenerative lysosomal storage disorders (LSDs) and many other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, where links to lysosomal defects have been suggested.

The present disclosure addresses a need to develop improved and widely applicable treatments for neurodegenerative diseases. In particular, the present disclosure describes leucine and acetyl-leucine for treating a neurodegenerative disease or one or more symptoms of a neurodegenerative disease in a subject. The neurodegenerative disease may, but need not, be associated with lysosomal dysfunction.

In one aspect, there is provided a use of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating restless legs syndrome (RLS) in a subject who has a neurodegenerative disease.

In one ~~embodiment~~example, the present disclosure includes leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating restless legs syndrome (RLS) in a subject who has a neurodegenerative disease. In one ~~embodiment~~example, the neurodegenerative disease is parkinsonism. In one ~~embodiment~~example, the neurodegenerative disease is a Motor Neuron Disease. In one ~~embodiment~~example, the neurodegenerative disease is Parkinson's Disease. In one ~~embodiment~~example, the neurodegenerative disease is associated with dopaminergic system dysfunction.

In one ~~embodiment~~example, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof is disclosed for use in a method of treating restless legs syndrome (RLS) in a subject in need thereof, wherein the RLS is a neurodegenerative disease

In one ~~embodiment~~example, there is disclosed leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof. In one ~~embodiment~~example, the neurodegenerative disease is not cerebellar ataxia or Niemann-Pick type C disease.

In one ~~embodiment~~ example of the present disclosure, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of treating a neurodegenerative disease in a subject in need thereof, wherein the subject is asymptomatic.

In another ~~embodiment~~example, there is disclosed leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying onset of a neurodegenerative disease or one or more symptoms of a neurodegenerative disease that would otherwise be expected to manifest according to typical disease progression.

In a further ~~embodiment~~example, the present disclosure includes leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the method comprises administering a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In one ~~embodiment~~example, the present disclosure describes leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying progression of a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease over time as compared to typical disease progression, wherein the method comprises administering a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In a further ~~embodiment~~example, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of reversing progression of a neurodegenerative

disease or one or more symptoms associated with a neurodegenerative disease over time, wherein the method comprises administering a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another ~~embodiment~~example, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of improving in a subject in need thereof a biochemical marker of a neurodegenerative disease over time, wherein the method comprises administering a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another ~~embodiment~~example, the present disclosure includes leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of a neurodegenerative disease or reducing the severity of or eliminating one or more existing symptoms associated with a neurodegenerative disease in a subject in need thereof. In one ~~embodiment~~example, the neurodegenerative disease is not cerebellar ataxia or Niemann-Pick Type C.

In a further ~~embodiment~~example, the present disclosure includes leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of providing neuroprotection in a subject having, suspected of having, or at risk of having a neurodegenerative disease, wherein the method comprises administering a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In one ~~embodiment~~example, the present disclosure includes leucine, or a pharmaceutically acceptable salt thereof, for direct delivery to the central nervous system in a method disclosed herein, wherein the direct delivery is by an administration chosen from intranasal administration, intraventricular administration, intrathecal administration, intracranial administration, and administration via nasal mucosal grafting.

In one ~~embodiment~~example, leucine, or a pharmaceutically acceptable salt thereof, is disclosed for direct delivery to the central nervous system in a method disclosed herein, wherein the direct delivery is by intrathecal administration.

Additional ~~embodiments~~ examples of the present disclosure include, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying progression of a neurodegenerative disease or a lysosomal storage disorder (LSD) in a subject. In another ~~embodiment~~example, leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of providing neuroprotection in a subject having a neurodegenerative disease or a LSD. In an ~~embodiment~~example, the leucine or acetyl-leucine is in racemate form, in an enantiomeric excess of the L-enantiomer or in an enantiomeric excess of the D-enantiomer. In another ~~embodiment~~example, the methods further comprise administering the acetyl-leucine in a dose of between 1.5 g and 10 g per day. Further still, in an ~~embodiment~~example, the methods further comprise administering the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof for a treatment duration of two weeks or more. For example, the methods comprise administering the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof, before the onset of a symptom of the disease or disorder to be treated. Yet in an additional ~~embodiment~~example, the methods further comprise administering another therapy or agent intended to prevent or treat the disease or disorder to be treated. In an ~~embodiment~~ example of the present disclosure provides for a kit for delaying progression of a neurodegenerative disease or a LSD in a subject, the kit comprising a means for diagnosing or prognosing a neurodegenerative disease or a LSD, and leucine, acetyl-leucine or a pharmaceutically acceptable salt thereof. For example, the kit comprises a means for diagnosing or prognosing a neurodegenerative disease or a LSD, and leucine, acetyl-leucine or a pharmaceutically acceptable salt thereof. In a further ~~embodiment~~ example of the present disclosure, it provides for use of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, as a neuroprotective agent in a subject having a neurodegenerative disease or a LSD. In a further ~~embodiment~~ example of the methods, the kits, or the uses, the neurodegenerative disease is associated with defects in lysosomal storage. In an ~~embodiment~~ example of the methods, the kits, or the uses, the neurodegenerative disease is alcoholism, Alexander's disease, Alper's disease, Alzheimer's Disease, amyotrophic lateral sclerosis (ALS), ataxia telangiectasia, neuronal ceroid lipofuscinoses, Batten disease, bovine spongiform encephalopathy (BSE), Canavan disease, cerebral palsy, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, frontotemporal lobar degeneration, Huntington's disease, HIV-associated dementia, Kennedy's disease, Lewy body dementia, neuroborreliosis, Machado-Joseph disease, multiple system atrophy, multiple sclerosis, multiple sulfatase deficiency, mucolipidoses,

narcolepsy, Niemann Pick disease, Parkinson's Disease, Pick's disease, Pompe disease, primary lateral sclerosis, prion diseases, progressive supranuclear palsy, Refsum's disease, Schilder's disease, subacute combined degeneration of spinal cord secondary to pernicious anaemia, Spielmeyer-Vogt-Sjogren-Batten disease, spinocerebellar ataxia, spinal muscular atrophy, Steele-Richardson-Olszewski disease, or Tabes dorsalis. In a further ~~embodiment~~ example of the methods, the kits, or the uses, the LSD is Niemann-Pick Type C (NPC1 and/or NPC2 defect), Smith-Lemli-Opitz Syndrome (SLOS), an inborn error of cholesterol synthesis, Tangier disease, Pelizaeus-Merzbacher disease, a neuronal ceroid lipofuscinosis, a primary glycosphingolipidosis, Farber disease or multiple sulphatase deficiency. For example, in the methods, the kits, or the uses, the primary glycosphingolipidosis is Gaucher disease, Fabry disease, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease or metachromatic leukodystrophy (MLD). Further for example, in the methods, the kits, or the uses, the LSD is NPC, Tay-Sachs disease, Sandhoff disease, GM1 gangliosidosis, Fabry disease, a neurodegenerative mucopolysaccharidosis, MPS I, MPS IH, MPS IS, MPS II, MPS III, MPS IIIA, MPS IIIB, MPS IIIC, MPS HID, MPS, IV, MPS IV A, MPS IV B, MPS VI, MPS VII, MPS IX, a disease with secondary lysosomal involvement, SLOS, or Tangier disease. In an additional ~~embodiment~~ example of the methods, the kits, or the uses, the neurodegenerative disease is cerebellar ataxia, Niemann Pick disease, parkinsonism, neuronopathic Gaucher disease, Sandhoff's disease, Louis-Barr syndrome, Alzheimer's disease, Parkinson's disease, multiple systems atrophy, fronto-temporal dementia or lower body Parkinson's syndrome. In still a further ~~embodiment~~ example of the methods, the kits or the uses, the neurodegenerative disease is Niemann Pick disease, Niemann Pick type C, Niemann Pick type A, Tay-Sachs disease, Sandhoff's disease, amyotrophic lateral sclerosis (ALS), multisystemic atrophy cerebellar type (MSA-C), fronto-temporal dementia with parkinsonism, corticobasal-degeneration-syndrome, progressive supranuclear palsy or cerebellar downbeat nystagmus. In an ~~embodiment~~ example of the methods, the kits, or the uses, the LSD is Niemann Pick disease, Niemann Pick type C, Niemann Pick type A, Tay-Sachs disease, Sandhoff's disease or mucolipidosis type II.

Brief Description of the Figures

Figure 1 shows photographs of treated (Figure 1A) and untreated (Figure 1B) *Npc1*$^{-/-}$ mice at nine weeks of age.

Figures 2A and 2B show weight data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning.

Claims:

1. Use of ~~L~~leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in a method of~~ treating restless legs syndrome (RLS) in a subject who has a neurodegenerative disease.

2. The use ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to claim 1, wherein the neurodegenerative disease is parkinsonism.

3. The use ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to claim 1, wherein the neurodegenerative disease is a Motor Neuron Disease.

4. The use ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to claim 1, wherein the neurodegenerative disease is Parkinson's Disease.

5. The use ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to claim 1, wherein the neurodegenerative disease is associated with dopaminergic system dysfunction.

6. Use of ~~L~~leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in a method of~~ treating restless legs syndrome (RLS) in a subject in need thereof, wherein the RLS is a neurodegenerative disease

7. The use of ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to any of claims 1-6, wherein the leucine is DL-leucine or the acetyl-leucine is acetyl-DL-leucine.

8. The use of ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ according to any of claims 1-6, wherein the leucine or acetyl-leucine has an enantiomeric excess of the L-enantiomer or the D-enantiomer.

9. ~~Leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method~~ The use according to any of claims 1-8, wherein the ~~method~~ use comprises ~~administering~~ the acetyl-leucine to be administered to the subject in need thereof at a therapeutically effect amount of from about 1 g to about 15 g per day, from about 1 g to about 10 g per day, from about 1.5 g to about 7 g per day, from about 4 g to about 6 g per day, or from about 4 g to about 5 g per day.