Therapeutic Agents for Neurodegenerative Diseases

This application claims priority benefit to UK 1613829.9, filed August 11, 2016, UK 1702551.1, filed February 16, 2017, UK 1705766.2, filed April 10, 2017, and UK 1706867.7, filed April 28, 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 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 disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the neurodegenerative disease is chosen from Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple system atrophy Parkinson type (MSA-P), multiple system atrophy cerebellar type (MSA-C), frontotemporal dementia with parkinsonism, progressive supranuclear palsy, corticobasal degeneration, cerebellar downbeat nystagmus, Lewy Body dementia,

and ataxia telangiectasia (Louis Barr disease), and wherein acetyl-leucine, or a pharmaceutically acceptable salt thereof is to be administered at least two times a day to achieve a total daily dose of from about 0.5 g to about 15 g; and wherein the acetyl-leucine is selected from the group consisting of acetyl-DL-leucine, acetyl-leucine having an enantiomeric excess of the L-enantiomer, and acetyl-leucine as a single enantiomeric form of the L-enantiomer.

In one example, there is disclosed 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 neurodegenerative disease is not cerebellar ataxia or Niemann-Pick type C disease.

In one example of the present disclosure, 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 example, there is disclosed 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 example, the present disclosure includes 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 acetyl-leucine 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 example, the present disclosure describes 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 acetyl-leucine 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 example, 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 acetyl-leucine 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 example, 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 acetyl-leucine 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 example, the present disclosure includes 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, wherein the neurodegenerative disease is not cerebellar ataxia or Niemann-Pick Type C.

In a further example, the present disclosure includes 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 acetyl-leucine 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.

Additional examples of the present disclosure include, 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 example, 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 example, the 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 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 example, the methods further comprise administering the acetyl-leucine for a treatment duration of two weeks or more. For example, the methods comprise administering the acetyl-leucine, or a pharmaceutically acceptable salt thereof, before the onset of a symptom of the disease or disorder to be treated. Yet in an additional example, the methods further comprise administering another therapy or agent intended to prevent or treat the disease or disorder to be treated. In an 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 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 acetyl-leucine or a pharmaceutically acceptable salt thereof. In a further example of the present disclosure, it provides for use of 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 example of the methods, the kits, or the uses, the neurodegenerative disease is associated with defects in lysosomal storage. In an 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 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 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 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 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.

Figures 3A - 3G show gait analysis data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning. For example, diagonal support, cadence and step sequence data are shown in Figures 3A - 3C, respectively. Figures 3D and 3E show front paw (FP) data (stand mean and step cycle in panel D; duty cycle in panel E). Figures 3F and 3G show hind paw (HP) data (stand mean and step cycle in panel F; duty cycle in panel G).

Figures 4A - 4H show motor function analysis data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning. Centre rearing, activity, rearing and front to back (FR) count are shown in Figures 4A - 4D, respectively. Active time, mobile time, rearing time and total manual rearing count are shown in Figures 4E - 4H, respectively.

Figure 5 shows that treatment with acetyl-DL-leucine (0.1 g/kg from 3 weeks of age) is associated with a small but statistically significant increase in lifespan in the Npc1-/- mouse.

Figures 6A and 6B shows the reduction of lysosomal volume in non-neuronal NPC cells following treatment with acetyl-DL-leucine. Figures 6C-6H show the effect of treatment with acetyl-DL-Leucine on lysosomal volume in NPA, MLII, MPS IIIB, Aspartylglucosaminuria, MLIIIA, and MPS VII patient fibroblasts, respectively.

Claims:

1. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating a neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease in a subject in need thereof, wherein the neurodegenerative disease is chosen from Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple system atrophy Parkinson type (MSA-P), multiple system atrophy cerebellar type (MSA-C), frontotemporal dementia with parkinsonism, progressive supranuclear palsy, corticobasal degeneration, cerebellar downbeat nystagmus, Lewy Body dementia, and ataxia telangiectasia (Louis Barr disease), and wherein acetyl-leucine, or a pharmaceutically acceptable salt thereof is to be administered at least two times a day to achieve a total daily dose of from 0.5 g to 15 g; and wherein the acetyl-leucine is selected from the group consisting of acetyl-DL-leucine, acetyl-leucine having an enantiomeric excess of the L-enantiomer, and acetyl-leucine as a single enantiomeric form of the L-enantiomer.

2. The use according to claim 1, wherein the subject is asymptomatic.

3. The use according to claim 2, wherein the subject has been found to have a genetic and/or biochemical marker of the neurodegenerative disease.

4. The use according to claim 1, for delaying the onset of the neurodegenerative disease or one or more symptoms of a neurodegenerative disease that would otherwise be expected to manifest according to typical disease progression.

5. The use according to claim 1, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.

6. The use according to claim 1, for delaying the progression of the neurodegenerative disease or one or more symptoms associated with the neurodegenerative disease over time as compared to typical disease progression, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.

7. The use according to claim 1, for reversing the progression of the neurodegenerative disease or one or more symptoms associated with a neurodegenerative disease over time,

wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.

8. The use according to claim 1, for improving in a subject in need thereof a biochemical marker of the neurodegenerative disease over time, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.

9. The use according to claim 8, wherein the biochemical marker is increased lysosomal volume.

10. The use according to any of claims 1-9, wherein a therapeutically effective amount of acetyl-leucine is to be administered to the subject in need thereof when the subject is asymptomatic.

11. The use according to claim 10, wherein the therapeutically effective amount of acetyl-leucine is to be administered after the subject has been found to have a genetic and/or biochemical marker of the neurodegenerative disease.

12. The use according to any of claims 1-4, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.

13. The use according to any of claims 1-4, wherein the acetyl-leucine is to be administered to the subject in need thereof at a therapeutically effective amount of from 0.5 g to 15 g per day, from 1 g to 10 g per day, from 1.5 g to 7 g per day, from 4 g to 6 g per day, or from 4 g to 5 g per day.

14. The use according to any of claims 5-12, wherein the therapeutically effective amount of acetyl-leucine is of from 0.5 g to 15 g per day, from 1 g to 10 g per day, from 1.5 g to 7 g per day, from 4 g to 6 g per day, or from 4 g to 5 g per day.

15. The use according to claim 1, for reducing the severity of the neurodegenerative disease or reducing the severity of or eliminating one or more existing symptoms associated with the neurodegenerative disease in a subject in need thereof.

16. The use according to claim 1, for providing neuroprotection in a subject having, suspected of having, or at risk of having the neurodegenerative disease, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least 3 months, at least 6 months, at least 1 year, at least 2 years, and at least 5 years.