# 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 or delaying the onset of 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,

Claims:

1. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating or delaying the onset of 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, 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.

5. 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.

6. 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.

7. 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.

8. The use according to claim 7, wherein the biochemical marker is increased lysosomal volume.

9. The use according to any of claims 1-8, wherein a therapeutically effective amount of acetyl-leucine is to be administered to the subject in need thereof when the subject is asymptomatic.

10. The use according to claim 9, 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.

11. The use according to any of claims 1-3, 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.

12. The use according to any of claims 1-3, 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.

13. The use according to any of claims 4-11, 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.

14. 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.

15. 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.