METHODS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

Background of the Invention

An incomplete understanding of the molecular perturbations that cause disease, as well as a limited arsenal of robust model systems, has contributed to a failure to generate successful disease-modifying therapies against common and progressive neurological disorders, such as Parkinson's Disease (PD) and Alzheimer's Disease (AD). Progress is being made on many fronts to find agents that can arrest the progress of these disorders. However, the present therapies for most, if not all, of these diseases provide very little relief. Accordingly, a need exists to develop therapies that can alter the course of neurological diseases (e.g., neurodegenerative diseases). More generally, a need exists for better methods and compositions for the treatment of neurological disorders in order to improve the quality of the lives of those afflicted by such diseases.

Stearoyl-CoA desaturases (SCDs) introduce a double bond in the C9-C10 position of saturated fatty acids such as palmitoyl-CoA and stearoyl-CoA which are converted to palmitoleoyl-CoA and oleoyl-CoA, respectively. One SCD gene, SCD1, has been characterized in humans for which there are two isoforms, SCD1 and SCD5. In turn, there are two forms of SCD5, SCD5a and SCD5b, which differ at the C-terminus. The present inventors have discovered that inhibition of SCDs is capable of suppressing toxicity in cells related to protein misfolding and/or aggregation. Accordingly, inhibition of SCDs may provide new methods for the treatment of diseases and disorders related to toxicity caused by protein misfolding and/or aggregation.

Summary

This disclosure provides compounds that modulate the activity of SCDs (e.g., SCD1 and/or SCD5), pharmaceutical compositions including such compounds, and methods of utilizing such compounds and compositions for modulating the activity of SCDs for the treatment of diseases and disorders related to toxicity caused by proteins such as toxicity related to misfolding and/or aggregation of proteins. In some examples, the disease or disorder is a neurological disorders.

In one aspect, the disclosure provides use of an SCD5 inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is Parkinson’s disease or dementia with Lewy bodies.

In one example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes administering an effective amount of an SCD inhibitor.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. The method includes administering an SCD inhibitor in an amount sufficient to suppress toxicity in a cell (e.g., in a mammalian neural cell) related to a protein (e.g., toxicity related to misfolding and/or aggregation of a protein such as α-synuclein or ApoE4). In some embodiments, the toxicity is α-synuclein-related toxicity. In some embodiments, the toxicity is ApoE4-related toxicity.

In another example, the disclosure provides a method of suppressing toxicity in a cell (e.g., a neural cell) related to a protein (e.g., toxicity related to misfolding and/or aggregation of a protein such as α-synuclein or ApoE4). This method includes contacting a cell with an SCD inhibitor.

In another example, the disclosure provides a method of treating a neurological disorder in a subject in need thereof. This method includes (a) determining the level (e.g., in a neural cell) of a protein or a particular form of a protein (e.g., a misfolded form of a protein) related to a neurological disorder (e.g., α-synuclein, ApoE4, or an undesired form thereof) in the subject; and (b) administering an effective

CLAIMS

What is claimed is:

1. Use of an SCD5 inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is Parkinson's disease or dementia with Lewy bodies.

2. The use of claim 1, wheren the subject has an elevated level, or is predicted to have an elevated level of α-synuclein, ApoE4, or an undesired form thereof.

3. The use of claim 1 or 2, wherein the SCD5 inhibitor further inhibits SCD1.

4. The use of claim 1 or 2, wherein the SCD5 inhibitor is selective for SCD5 over SCD1.

5. The use of claim 1 or 2, wherein the subject carries one or two copies of the ApoE4 allele.

6. The use of any one of claims 1 to 5, wherein the neurological disorder is Parkinson's disease.

7. The use of any one of claims 1 to 5, wherein the neurological disorder is Lewy body dementia.

8. The use of any one of claims 1 to 7, wherein an additional therapeutic agent is to be administered to the subject.

9. The use of claim 8, wherein the additional therapeutic agent is a small molecule, an antibody or fragment thereof, or a nucleic acid.

10. The use of claim 8 or 9, wherein the additional therapeutic agent is a cognition-enhancing agent, an antidepressant agent, an anxiolytic agent, an antipsychotic agent, a sedative, a dopamine promoter, or an anti-tremor agent.

11. The use of claim 1, wherein the SCD5 inhibitor is to be administered in an amount sufficient to suppress toxicity in a cell related to protein misfolding and/or aggregation.