

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 embodiments, the disease or disorder is a neurological disorders.

In one aspect, the disclosure provides use of an SCD inhibitor in the manufacture of a medicament for treating Parkinson's disease or Lewy body dementia in a subject in need thereof.

In another example, the disclosure provides use of an SCD inhibitor in the manufacture of a medicament for suppressing toxicity in a cell related to protein misfolding and/or aggregation in a subject.

In another example, the disclosure provides use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein:

(a) the expression level of α -synuclein, ApoE4, or an undesired form thereof is to be determined in the subject; and

(b) an effective amount of the medicament is to be administered to the subject if the level of α -synuclein, ApoE4, and/or the undesired form thereof is greater than a predetermined level.

In another example, the disclosure provides use of an effective amount of an SCD inhibitor in the manufacture of a medicament for treating a neurological disease in a subject in need thereof, wherein the subject has an elevated level, or is predicted to have an elevated level of α -synuclein, ApoE4, or an undesired form thereof.

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.

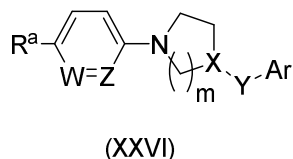
In another example, the disclosure provides a method of suppressing toxicity in a cell (e.g., a neural cell) related to a protein (e.g., toxicity related to misfolding and/or aggregation of a protein such as α -synuclein or ApoE4). This method includes contacting a cell with an SCD inhibitor.

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:

- 5 1. Use of an SCD inhibitor in the manufacture of a medicament for treating Parkinson's disease or Lewy body dementia in a subject in need thereof.
2. The use of claim 1, wherein the SCD inhibitor is an SCD1 inhibitor.
- 10 3. The use of claim 2, wherein the SCD1 inhibitor is selective for SCD1 over SCD5.
4. The use of claim 1, wherein the SCD inhibitor is an SCD5 inhibitor.
5. The use of claim 4, wherein the SCD5 inhibitor is selective for SCD5 over SCD1.
- 15 6. The use of claim 1, wherein the subject carries one or two copies of the ApoE4 allele.
7. The use of claim 1, wherein the SCD inhibitor is a compound of Formula XXVI:



- 20 wherein each n is independently 0, 1 or 2;
- each p is independently 0, 1, or 2;
- m is 1, 2, or 3;
- W and Z are each independently CH or N, with the proviso that at least one of W and Z is N;
- X-Y is N-C(O), N-S(O)₂, N-CR¹R², CH-O, CH-S(O)_p, CH-NR⁵, or CH-CR¹R²;
- 25 Ar is phenyl, benzyl, naphthyl, or heteroaryl each of which is optionally substituted with one to five R³ substituents;
- R^a is phenyl, naphthyl, or a heteroaromatic ring selected from the group consisting of: oxazolyl, thiazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,5-
- 30 thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, indolyl, benzthiazolyl, benzoxazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, and imidazo[1,2-*a*]pyridyl;
- wherein phenyl, naphthyl, and the heteroaromatic ring are optionally substituted with one to three substituents independently selected from R⁶;
- R¹ and R² are each independently hydrogen or C₁₋₃alkyl, wherein alkyl is optionally substituted
- 35 with one to three substituents independently selected from halogen and hydroxy;

each R⁶ is independently selected from the group consisting of: C₁₋₆alkyl, C₂₋₄alkenyl, (CH₂)_nOR⁴, (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nOC(O)R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴,
5 (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nO(CH₂)_nP(=O)(OR⁴)₂, O(CH₂)_nC(O)N(R⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkylsulfonyl, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines;
10 and wherein any methylene (CH₂) carbon atom in R⁶ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R³ is independently selected from the group consisting of: C₁₋₆alkyl, (CH₂)_nOR⁴,
15 (CH₂)_n-phenyl, (CH₂)_n-naphthyl, (CH₂)_n-heteroaryl, (CH₂)_n-heterocyclyl, (CH₂)_nC₃₋₇cycloalkyl, halogen, (CH₂)_nN(R⁴)₂, (CH₂)_nC≡N, (CH₂)_nCO₂R⁴, (CH₂)_nCOR⁴, NO₂, (CH₂)_nNR⁴SO₂R⁴, (CH₂)_nSO₂N(R⁴)₂, (CH₂)_nS(O)_pR⁴, (CH₂)_nNR⁴C(O)N(R⁴)₂, (CH₂)_nC(O)N(R⁴)₂, (CH₂)_nC(O)N(OR⁴)R⁴, (CH₂)_nC(O)N(NH₂)R⁴, (CH₂)_nNR⁴C(O)R⁴, (CH₂)_nNR⁴CO₂R⁴, O(CH₂)_nC(O)N(R⁴)₂, (CH₂)_nP(=O)(OR⁴)₂, (CH₂)_nOP(=O)(OR⁴)₂, (CH₂)_nO(CH₂)_nP(=O)(OR⁴)₂, CF₃, CH₂CF₃, OCF₃, and OCH₂CF₃;

20 in which phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocyclyl are optionally substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄alkoxy, C₃₋₆cycloalkyl, and C₁₋₄alkyl wherein alkyl is optionally substituted with hydroxy or one to three fluorines; and wherein any methylene (CH₂) carbon atom in R³ is optionally substituted with one to two groups independently selected from fluorine, hydroxy, and C₁₋₄alkyl optionally substituted with one to five fluorines; or two
25 substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

each R⁴ is independently selected from the group consisting of: hydrogen, C₁₋₆alkyl, (CH₂)_n-phenyl, (CH₂)_n-heteroaryl, (CH₂)_n-naphthyl, and (CH₂)_nC₃₋₇cycloalkyl;

wherein alkyl, phenyl, heteroaryl, and cycloalkyl are optionally substituted with one to three
30 groups independently selected from halogen, C₁₋₄alkyl, and C₁₋₄alkoxy; or two R⁴ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and NC₁₋₄alkyl; and

R⁵ is hydrogen or C₁₋₆alkyl optionally substituted with one to five fluorines,
or a pharmaceutically acceptable salt thereof.

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8. The use of claim 1, 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.

5 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.