

cell or the subject in need thereof a therapeutically effective amount of an agent that inhibits TDP-43 mitochondrial localization.

[0005a] In one aspect, there is provided use of a TDP-43 mitochondrial localization inhibitor in the manufacture of a medicament for treating a neurodegenerative disease in a subject.

[0006] In some embodiments, the neurodegenerative disease or disorder can include neurodegenerative diseases or disorders characterized and/or associated with aberrant TDP-43 mitochondrial localization, TDP-43 neuronal toxicity, and/or mutations of TDP-43. The neurodegenerative disease can include, for example, amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's disease, dementias related to Alzheimer's disease, Parkinson's, senile dementia, Huntington's disease, Gilles de la Tourette's syndrome, multiple sclerosis, or hereditary motor and sensory neuropathy.

[0007] Other embodiments relate to methods of treating motor-coordinative and cognitive dysfunction associated with mutant TDP-43 expression. The methods can include administering to a neural cell or the subject in need thereof a therapeutically effective amount of an agent that inhibits TDP-43 mitochondrial localization.

[0008] In some embodiments, the agent or TDP-43 mitochondrial localization inhibitor includes a therapeutic peptide of about 5 to about 10 amino acids having an amino acid sequence that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to about 5 to about 8 consecutive amino acids of a mitochondrial internal targeting signal of TDP-43. For example, the therapeutic peptide can include an amino acid sequence that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to about 5 to about 7 consecutive amino acids of M1 (SEQ ID NO: 1), M3 (SEQ ID NO: 3), or M5 (SEQ ID NO: 5) or TDP-43. In some embodiments, the therapeutic peptide can include, consist essentially of, or consist of a peptide having an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 7.

[0009] In other embodiments, the agent includes a transport moiety that is linked to the therapeutic peptide and facilitates uptake of the therapeutic peptides by the cell. For example, the transport moiety can be an HIV Tat transport moiety.

[0010] In still other embodiments, the cell is in a subject being treated, and the therapeutic agent is administered locally or systemically to the subject being treated.

[0011] In yet other embodiments, the therapeutic peptide is expressed in the neural cell.

Having described the invention, the following is claimed:

1. Use of a TDP-43 mitochondrial localization inhibitor in the manufacture of a medicament for treating a neurodegenerative disease in a subject.
2. The use of claim 1, wherein the TDP-43 localization inhibitor is in an amount required to inhibit TDP-43 induced mitochondrial dysfunction and neuron loss.
3. The use of claim 1, the TDP-43 mitochondrial localization inhibitor includes a synthetic therapeutic peptide of about 5 to about 10 amino acids having an amino acid sequence that is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to about 5 to about 8 consecutive amino acids of at least one mitochondrial internal targeting motif of TDP-43.
4. The use of claim 3, the therapeutic peptide inhibiting TDP-43 mediated disassembly of mitochondrial respiratory complex 1.
5. The use of claim 3, the at least one mitochondrial internal targeting motif of TDP-43 having an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, and SEQ ID NO: 5.
6. The use of claim 3, the therapeutic peptide including an amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 7.
7. The use of claim 3, the therapeutic peptide including an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 8.
8. The use of claim 3, the therapeutic peptide including an amino acid sequence of SEQ ID NO: 5 or SEQ ID NO: 9.

9. The use of claim 6, the TDP-43 localization inhibitor further comprising a transport moiety that is linked to the therapeutic peptide and facilitates uptake of the therapeutic peptides by a cell.

10. The use of claim 9, the transport moiety comprising a TAT peptide.

11. The use of claim 9, the TDP-43 localization inhibitor having an acid sequence selected from the group consisting of SEQ ID NOs: 12-17.

12. The use of claim 1, wherein the neurodegenerative disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Alzheimer's disease, Parkinson's disease, and Huntington's disease.

13. The use of claim 1, wherein the neurodegenerative disease is frontotemporal dementia.

14. The use of claim 1, wherein the neurodegenerative disease is amyotrophic lateral sclerosis.

15. The use of claim 1, the TDP-43 localization inhibitor is to be administered to the subject via continuous subcutaneous infusion.