and a passive (Masliah, E., et al., PLoS One 6 (2011) e19338) immunization paradigm. Binding of extracellular alpha-synuclein by specific antibodies prevents cell-to-cell aggregate transmission was reported by Bae, E-J., et al. (J. Neurosci. 32 (2012) 13454-13469).

The use of mimotopes of alpha-synuclein epitopes for treating Lewy body diseases is reported in WO 2011/020133. In WO 2007/011907 alpha-synuclein antibodies and methods related thereto are reported. Fusion to a highly charged proteasomal retargeting sequence increases soluble cytoplasmic expression and efficacy of diverse anti-synuclein intrabodies is reported by Joshi et al. (MABS 4 (2012) 686-693). Emadi et al. (J. Mol. Biol. 368 (2007) 1132-1144) report the isolation of a human single chain antibody fragment against oligomeric alpha-synuclein that inhibits aggregation and prevents alpha-synuclein-induced toxicity. The detection of morphologically distinct oligomeric forms of alpha-synuclein is reported by Emadi et al. (J. Biol. Chem. 284 (2009) 11048-11058). Zhou et al. (Mol. Ther. 10 (2004) 1023-1031) report that a human single-chain Fv intrabody blocks aberrant cellular effects of overexpressed alpha-synuclein. That antibodies against alpha-synuclein reduce oligomerization in living cells is reported by Nasstrom et al. (PLoS One 6 (2011) e27230). Protofibril-binding antibodies and their use in therapeutic and diagnostic methods for Parkinson's Disease, dementia with Lewy bodies and other alpha-synucleinopathies are reported in WO 2011/104696. Isolating recombinant antibodies against specific protein morphologies using atomic force microscopy and phage display technologies is reported by Barkhordarian et al. (Prot. Eng. Des. Select. 19 (2006) 497-502). Kvam et al. (PLoS One 4 (2009) e5727) report that conformational targeting of fibrillar polyglutamine proteins in live cells escalates aggregation and cytotoxicity.

SUMMARY

The disclosure provides anti-human alpha-synuclein antibodies and methods of using the same.

The disclosure provides an antibody that specifically binds to human alpha-synuclein wherein the human alpha-synuclein has a free N-terminal methionine residue.

The term "free N-terminal methionine residue" denotes a methionine residue in a polypeptide that is located at the N-terminus of the polypeptide and that is not modified except for the amide-bond with which it is conjugated to the remainder of

In one embodiment the antibody is a humanized antibody and comprises in the heavy chain variable domain the HVRs of SEQ ID NO: 21, 22 and 17 and in the light chain variable domain the HVRs of SEQ ID NO: 23 to 25, wherein in each HVR 0 to 3 amino acid residues have been changed.

In one embodiment the antibody is a humanized antibody and the heavy chain variable domain is derived from a heavy chain variable domain of SEQ ID NO: 26 and the light chain variable domain is derived from a light chain variable domain of SEQ ID NO: 27.

The disclosure relates to an antibody that binds to the same epitope or an overlapping epitope as an antibody comprising in the heavy chain the HVRs of SEQ ID NO: 15 to 17 and in the light chain the HVRs of SEQ ID NO: 18 to 20.

The disclosure relates to an antibody that binds to the same or an overlapping epitope as an antibody comprising a heavy chain variable domain of SEQ ID NO: 26 and a light chain variable domain of SEQ ID NO: 27.

One aspect as reported herein is an antibody comprising in the heavy chain the HVRs of SEQ ID NO: 15 to 17 and in the light chain the HVRs of SEQ ID NO: 18 to 20.

One aspect as reported herein is an antibody comprising in the heavy chain the HVRs of SEQ ID NO: 21, 22 and 17 and in the light chain the HVRs of SEQ ID NO: 23 to 25.

The disclosure relates to a variant antibody that has been obtained from an antibody comprising a heavy chain variable domain of SEQ ID NO: 26 and a light chain variable domain of SEQ ID NO: 27.

One aspect as reported herein is a pharmaceutical formulation comprising the antibody as reported herein and a pharmaceutically acceptable carrier.

In one embodiment the pharmaceutical formulation further comprises an additional therapeutic agent.

One aspect as reported herein is the antibody as reported herein for use as a medicament.

One aspect as reported herein is the antibody as reported herein for use in treating synucleinopathies.

One aspect as reported herein is the antibody as reported herein for use in treating Parkinson's Disease.

The disclosure relates to the antibody as reported herein for use in inhibiting alpha-synuclein induced cytotoxicity in human neurons and glia cells.

The disclosure relates to the antibody as reported herein for use in inhibiting cell-to-cell transmission of oligomeric human alpha-synuclein between neurons and glia cells.

The disclosure relates to the antibody as reported herein for use in reducing alpha-synuclein-induced caspase activity in neuronal cells or glia cells.

The disclosure relates to use of the antibody as reported herein in the manufacture of a medicament. One aspect as reported herein is the use of the antibody as reported herein in the manufacture of a medicament for the treatment of Parkinson's Disease.

In one embodiment the medicament is for treatment of Parkinson's Disease.

In one embodiment the medicament is for inhibiting alpha-synuclein induced cytotoxicity in human neurons and glia cells.

In one embodiment the medicament is for inhibiting cell-to-cell transmission of oligomeric human alpha-synuclein between neurons and glia cells.

In one embodiment the medicament is for reducing alpha-synuclein-induced caspase activity in neuronal cells or glia cells.

Patent Claims

1. An antibody comprising in the heavy chain the HVRs of SEQ ID NO: 15 to 17 and in the light chain the HVRs of SEQ ID NO: 18 to 20.

2. An antibody comprising in the heavy chain the HVRs of SEQ ID NO: 21, 22 and 17 and in the light chain the HVRs of SEQ ID NO: 23 to 25.

3. An antibody that has been obtained from an antibody comprising a heavy chain variable domain of SEQ ID NO: 26 and a light chain variable domain of SEQ ID NO: 27.

4. A humanized antibody comprising in the heavy chain variable domain the HVRs of SEQ ID NO: 15 to 17 and in the light chain variable domain the HVRs of SEQ ID NO: 18 to 20, wherein in each HVR 0 to 3 amino acid residues have been changed.

5. A humanized antibody comprising in the heavy chain variable domain the HVRs of SEQ ID NO: 21, 22 and 17 and in the light chain variable domain the HVRs of SEQ ID NO: 23 to 25, wherein in each HVR 0 to 3 amino acid residues have been changed.

6. A humanized antibody wherein the heavy chain variable domain is derived from a heavy chain variable domain of SEQ ID NO: 26 and the light chain variable domain is derived from a light chain variable domain of SEQ ID NO: 27.

7. The antibody according to any one of claims 1 to 6, wherein the antibody is conjugated to a blood-brain-barrier shuttle module.

8. The antibody according to claim 7, wherein the blood-brain-barrier shuttle module is an antibody or antibody fragment that specifically binds to LRP1, LRP8, human transferrin receptor or human insulin-like growth factor receptor.

9. The antibody according to any one of claims 1 to 8, wherein the antibody is
   a) a full length antibody of the human subclass IgG1, or
   b) a full length antibody of the human subclass IgG4, or
   c) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G,
   d) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G,
   e) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain, or
   f) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain.

10. The antibody according to any one of claims 1 to 9, wherein the antibody
   i) inhibits alpha-synuclein induced cytotoxicity in human neurons and glia cells, and/or
   ii) inhibits cell-to-cell transmission of oligomeric human alpha-synuclein between neurons and glia cells, and/or
   iii) reduces alpha-synuclein-induced caspase activity in human neuronal cells, and/or
   iv) specifically binds to alpha-synuclein that has a free N-terminal methionine residue and does not specifically bind to alpha-synuclein has a modified N-terminal methionine residue.

11. A pharmaceutical formulation comprising the antibody according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. The antibody according to any one of claims 1 to 10 for use as a medicament.

13. The antibody according to any one of claims 1 to 10 for use in treating synucleinopathy.

14. The antibody according to any one of claims 1 to 10 for use in treating Parkinson's disease.

15. Use of the antibody according to any one of claims 1 to 10 in the manufacture of a medicament treatment of Parkinson's disease.

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