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

One aspect as reported herein is 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 ~~One aspect as reported herein is~~ 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. One aspect as reported herein is an antibody that binds to the same 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 ~~One aspect as reported herein is~~ 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 that binds to the same epitope as 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.

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 ~~One aspect as reported herein is~~ 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 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.

In one embodiment the variant antibody is a humanized antibody that has been obtained by humanizing 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 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.

One aspect as reported herein is 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.

One aspect as reported herein is 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.

In one embodiment of ~~all previous aspects~~the disclosure the antibody is conjugated to a blood-brain-barrier shuttle module.

In one embodiment 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.

In one embodiment of the disclosure~~all previous aspects~~ the antibody is a monoclonal antibody.

In one embodiment of the disclosure~~all previous aspects~~ the antibody is a humanized antibody or a chimeric antibody.

In one embodiment of the disclosure~~all previous aspects~~ 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 26,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 27,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,
b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 27,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 27,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region.

In one embodiment the antibody fragment, which specifically binds to human transferrin receptor, comprises a heavy chain variable domain that is a humanized form of the heavy chain variable domain of SEQ ID NO: 56 and a light chain variable domain that is a humanized form of the light chain variable domain of SEQ ID NO: 57.

In one embodiment of ~~all previous aspects~~the disclosure 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.

The disclosure relates to ~~One aspect as reported herein is~~ an antibody that specifically binds to human alpha-synuclein, 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.

In one embodiment of ~~all aspects and embodiments~~the disclosure the human neuronal cell is a tetracycline-controlled, v-myc-overexpressing human mesencephalic-derived cell line. In one embodiment of ~~all aspects and embodiments~~ the disclosure the human neuronal cells are Lund human mesencephalic (LUHMES) cells.

In one embodiment the caspase activity is caspase 3 and/or caspase 7 activity.

In one embodiment the antibody is for use in the treatment of synucleinopathies.

In one embodiment the antibody is for use in the treatment of Parkinson's Disease.

In one embodiment the antibody is effector function silent. In one embodiment the antibody has no effector function.

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.

In one embodiment 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 02, SEQ ID NO: 03 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 05, SEQ ID NO: 06 and SEQ ID NO: 07, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 09 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 13,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,
b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 14,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 26,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 27,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 31, SEQ ID NO: 32 and SEQ ID NO: 33, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 34 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 35, SEQ ID NO: 36 and SEQ ID NO: 37, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 38,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain is a humanized form of the non-human (rabbit) variable domain of SEQ ID NO: 39,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 02, SEQ ID NO: 03 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 05, SEQ ID NO: 06 and SEQ ID NO: 07, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 09 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 13,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 14,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 21, SEQ ID NO: 22 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 23, SEQ ID NO: 24 and SEQ ID NO: 25, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 27,
   ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 31, SEQ ID NO: 32 and SEQ ID NO: 33, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 34 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 35, SEQ ID NO: 36 and SEQ ID NO: 37, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises two antibody heavy chains each comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 38,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent, and

iii) the constant region comprises the amino acid changes L234A, L235A and P329G,

b) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 39,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

c) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 02, SEQ ID NO: 03 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain comprises the HVRs of SEQ ID NO: 02, SEQ ID NO: 03 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 05, SEQ ID NO: 06 and SEQ ID NO: 07, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 08, SEQ ID NO: 09 and SEQ ID NO: 04, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) reduces alpha-synuclein-induced caspase activity in human neuronal cells.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 13,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 13,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 14,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 15, SEQ ID NO: 16 and SEQ ID NO: 17, wherein in each HVR

independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 18, SEQ ID NO: 19 and SEQ ID NO: 20, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein
   i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 26,
   ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,
   iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and
   iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V

and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 27,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 28, SEQ ID NO: 29 and SEQ ID NO: 30, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain comprises the HVRs of SEQ ID NO: 31, SEQ ID NO: 32 and SEQ ID NO: 33, wherein in each HVR independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

independently of each other 0, 1, 2 or 3 amino acid residues are changed,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

The disclosure relates to ~~One aspect as reported herein is~~ an anti-human alpha-synuclein antibody, characterized in that

a) the antibody comprises a first antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain, a heavy chain constant region, a peptidic linker and a scFab or scFv antibody fragment, which specifically binds to human transferrin receptor, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 38,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises either the amino acid changes T366W and S354C or the amino acid changes T366S, L368A, Y407V and Y349C,

b) the antibody comprises a second antibody heavy chain comprising in N- to C-terminal direction a heavy chain variable domain and a heavy chain constant region, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 38,

ii) the constant region is a human IgG1 constant region, wherein the C-terminal lysine residue can be present or absent,

iii) the constant region comprises the amino acid changes L234A, L235A and P329G, and

iv) the constant region comprises the amino acid changes T366W and S354C if the first antibody heavy chain comprises the amino acid changes T366S, L368A, Y407V and Y349C or the constant region comprises the amino acid changes T366S, L368A, Y407V and Y349C if the first antibody heavy chain comprises the amino acid changes T366W and S354C,

c) the antibody comprises two antibody light chains each comprising a light chain variable domain and a light chain constant domain, wherein

i) the variable domain is a humanized form of the rabbit variable domain of SEQ ID NO: 39,

ii) the constant region is a human kappa light chain constant region or a human lambda light chain constant region,

and

d) 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.

In one embodiment the antibody fragment comprises a heavy chain variable domain that is a humanized form of the heavy chain variable domain of SEQ ID NO: 56 and a light chain variable domain that is a humanized form of the light chain variable domain of SEQ ID NO: 57.

The disclosure relates to ~~One aspect as reported herein is~~ an isolated nucleic acid encoding the antibody as reported herein.

The disclosure relates to ~~One aspect as reported herein is~~ a host cell comprising the nucleic acid as reported herein.

The disclosure relates to ~~One aspect as reported herein is~~ a method of producing an antibody comprising the steps of culturing the host cell as reported herein so that the antibody is produced.

In one embodiment the method further comprises the step of recovering the antibody from the cell or the cultivation medium.

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 ~~One aspect as reported herein is~~ the antibody as reported herein for use in inhibiting alpha-synuclein induced cytotoxicity in human neurons and glia cells.

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

One aspect as reported herein is the use of the antibody as reported herein in the manufacture of a medicament.

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.

The disclosure relates to ~~One aspect as reported herein is~~ a method of treating an individual having Parkinson's Disease comprising administering to the individual an effective amount of the antibody as reported herein.

The disclosure relates to~~One aspect as reported herein is~~ a method of inhibiting alpha-synuclein induced cytotoxicity in human neurons and glia cells in an individual comprising administering to the individual an effective amount of the antibody as reported herein to inhibit alpha-synuclein induced cytotoxicity in human neurons and glia cells.

The disclosure relates to ~~One aspect as reported herein is~~ a method of inhibiting cell-to-cell transmission of oligomeric human alpha-synuclein between neurons and glia cells in an individual comprising administering to the individual an effective amount of the antibody as reported herein to inhibit alpha-synuclein induced cytotoxicity in human neurons and glia cells.

The disclosure relates to ~~One aspect as reported herein is~~ the use of an anti-human alpha synuclein antibody as reported herein in the inhibition of alpha-synuclein induced cytotoxicity in human neurons and glia cells.

The disclosure relates to ~~One aspect as reported herein is~~ the use of an anti-human alpha synuclein antibody as reported herein in the inhibition of cell-to-cell transmission of oligomeric human alpha-synuclein between neurons and glia cells.

The disclosure relates to ~~One aspect as reported herein is~~ the use of an anti-human alpha synuclein antibody as reported herein in the reduction of alpha-synuclein-induced caspase activity in neuronal cells or glia cells.

The antibodies as reported herein can be used in the treatment of Parkinson disease. Without being bound by this theory the antibodies inhibit the spreading of toxic oligomeric alpha-synuclein, or inhibit the uptake of toxic oligomeric alpha-synuclein by neurons and glia cells, or reduce neuroinflammation.

With the antibodies as reported herein inhibition/reduction of progression of synucleinopathy and neuropathology can be affected.

The antibodies as reported herein can be used to protect from development of Parkinson's Disease or even be used to stop the progression of Parkinson's Disease.

In one embodiment the antibody as reported herein i) binds to alpha-synuclein on brain sections of alpha-synuclein transgenic mice and Parkinson's Disease patients; and/or labels alpha-synuclein in LUHMES cells.

The antibodies as reported herein can be used for the treatment of a synucleinopathy. Some synucleinopathies are neurodegeneration with brain iron accumulation type 1 (NBIA1), pure autonomic failure, Down's syndrome, complex of Guam, and several Lewy body disorders, such as diffuse Lewy body disease (DLBD), the Lewy body variant of Alzheimer's disease (LBVAD), certain forms of Gaucher's Disease and Parkinson's Disease dementia (PDD).

The disclosure relates to ~~One aspect as reported herein is~~ an antibody that specifically binds to the amino acid sequence of SEQ ID NO: 01 in human alpha-synuclein.

The disclosure relates to ~~One aspect as reported herein is~~ an antibody that binds to the same epitope as an antibody comprising the heavy chain variable domain of SEQ ID NO: 13 and the light chain variable domain of SEQ ID NO: 14.

The disclosure relates to ~~One aspect as reported herein is~~ an antibody that binds to the same epitope as an antibody comprising the heavy chain variable domain of SEQ ID NO: 26 and the light chain variable domain of SEQ ID NO: 27.

The disclosure relates to ~~One aspect as reported herein is~~ an antibody that binds to the same epitope as an antibody comprising the heavy chain variable domain of SEQ ID NO: 38 and the light chain variable domain of SEQ ID NO: 39.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Concentration dependent binding specificity of anti-alpha-synuclein-antibody 0017; Lane: 1) fibrillar alpha-synuclein preparation, 2) triple-proline mutant alpha-synuclein oligomers, 3) type A alpha-synuclein oligomers, 4) type C alpha-synuclein oligomers.

Figure 2: Concentration dependent binding specificity of anti-alpha-synuclein-antibody 0018; Lane: 1) fibrillar alpha-synuclein preparation, 2) triple-proline mutant alpha-synuclein oligomers, 3) type A alpha-synuclein oligomers, 4) type C alpha-synuclein oligomers.