CLAIMS

1. A protein analogue comprising:

an N-terminal domain having at least 85% identity to positions 1-60 of SEQ ID NO:1;

a C-terminal domain having at least 85% identity to positions 96-140 of SEQ ID NO:1; and

a modified middle domain corresponding to positions 61-95 of SEQ ID NO:1 and comprising:

deletion of 1 to 35 amino acids; or

one or more substitutions comprising an amino acid, an amino acid analogue, or both.

2. The protein analogue of claim 1, wherein the one or more substitutions comprise a charged amino acid, a polar amino acid, or both.

3. The protein analogue of claim 1, wherein the one or more substitutions comprise an amino acid selected from the group consisting of: proline, glycine, lysine, arginine, histidine, glutamic acid, aspartic acid, serine, threonine, asparagine, glutamine, and cysteine, preferably wherein the protein analogue is selected from SEQ ID NOS:37-438.

4. The protein analogue of claim 1, wherein the modified middle domain comprises a consecutive amino acid deletion that includes at least a valine deletion at position 95, preferably wherein the protein analogue is selected from SEQ ID NOS:2-36.

5. The protein analogue of claim 1, wherein the amino acid analogue is selected from 3-hydroxyproline, 4-hydroxyproline, selenocysteine, pyroglutamic acid, carboxyglutamic acid, octenyl alanine, pyrrolysine, palmitoyl aspartate, D-amino acids including D-proline, β-amino acids, γ-amino acids, homo-amino acids, β-homo-amino acids, α-methyl amino acids, N-methyl amino acids, N-ethyl amino acids, N-alkylated amino acid derivatives (preferably with 1, 2 or 3 carbons in the alkyl moiety), peptoid substituents, pyruvic acid derivatives, branched-chain amino acid derivatives, nitro amino acid derivatives, halogenated amino acid

derivatives, ring-substituted amino acid derivatives, aromatic amino acid derivatives, linear core amino acids, hydroxylated amino acid derivatives, cyclic amino acids, bicyclic amino acids, 3-amino-3-aryl-propionic acids, 3-amino-4-aryl-butyric acids, amino acids with aromatic spacers, alicyclic amino acids and α-phenylglycine derivatives.

6. The protein analogue of claim 1, wherein the C-terminus of the protein analogue includes a modification configured to enhance at least one of circulation time, protease resistance and CSF half-life of the protein analogue as compared to wild type α-syn protein.

7. The protein analogue of claim 1, wherein the C-terminus of the protein analogue is modified with a functional group selected from an amide, an ester, an alcohol, a hydrazide, an aldehyde; and a hydroxamic acid.

8. The protein analogue of claim 7, wherein the C-terminus of the protein analogue is modified to an amide, preferably wherein the protein analogue is SEQ ID NO:439.

9. The protein analogue of claim 8, wherein the modified middle domain comprises at least one consecutive amino acid deletion that includes at least a valine deletion at position 95, preferably wherein the protein analogue is selected from SEQ ID NOS:440-474.

10. The protein analogue of claim 8, wherein the one or more substitutions comprise an amino acid selected from the group consisting of: proline, glycine, lysine, arginine, histidine, glutamic acid, aspartic acid, serine, threonine, asparagine, glutamine, and cysteine, preferably wherein the protein analogue is selected from SEQ ID NOS:475-876.

11. The protein analogue of claim 1, wherein the protein analogue is selected from a group consisting of SEQ ID NOS:2-876.

12. The protein analogue of claim 1, wherein the protein analogue comprises, relative to wild type α-syn protein, at least one of: a decreased beta-sheet-forming propensity, enhanced

solubility, improved stability, improved circulation time, improved brain penetrance, and increased CSF half-life.

13. The protein analogue of claim 12, wherein the half-life is at least about 10 min, at least about 20 min, at least about 30 min, at least about 40 min, at least about 50 min, at least about 1 hours, at least about 5 hours, at least about 10 hours, at least about 1 day, at least about 10 days, at least about 60 days, at least about 10 weeks, or at least about 50 weeks.

14. A nucleic acid encoding a protein analogue comprising:

an N-terminal domain having at least 85% identity to positions 1-60 of SEQ ID NO:1;

a C-terminal domain having at least 85% identity to positions 96-140 of SEQ ID NO:1; and

a modified middle domain corresponding to positions 61-95 of SEQ ID NO:1 and comprising:

deletion of 1 to 35 amino acids; or

one or more substitutions comprising an amino acid, an amino acid analogue, or both.

15. A protein analogue comprising:

an N-terminal domain having at least 85% identity to positions 1-60 of SEQ ID NO:1;

a C-terminal domain having at least 85% identity to positions 96-140 of SEQ ID NO:1; and

a modified middle domain corresponding to positions 61-95 of SEQ ID NO:1 and comprising:

deletion of 1 to 35 amino acids; or

one or more substitutions comprising an amino acid, an amino acid analogue, or both,

for use in therapy.