ANTIBODIES RECOGNIZING ALPHA-SYNUCLEIN

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit under 35 U.S.C. § 119(e) of US Application Nos. 61/711,204 filed October 8, 2012, 61/719,281 filed October 26, 2012, 61/840,432 filed June 27, 2013 and 61/872,366 filed August 30, 2013, all of which are incorporated by reference in its entirety for all purposes.

SEQUENCE LISTING

[0002] A Sequence Listing, comprising SEQ ID NOs: 1-41, is attached and incorporated herein by reference in its entirety.

BACKGROUND

[0003] Synucleinopathies, also known as Lewy body diseases (LBDs), are characterized by degeneration of the dopaminergic system, motor alterations, cognitive impairment, and formation of Lewy bodies (LBs) and/or Lewy neurites. (McKeith et al., Neurology (1996) 47:1113-24). Synucleinopathies include Parkinson's disease (including idiopathic Parkinson's disease), Diffuse Lewy Body Disease (DLBD) also known as Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson disease, pure autonomic failure and multiple system atrophy (MSA; *e.g.*, Olivopontocerebellar Atrophy, Striatonigral Degeneration and Shy-Drager Syndrome). Several nonmotor signs and symptoms are thought to be harbingers for synucleinopathies in the prodromal phase of the diseases (i.e., the presymptomatic, subclinical, preclinical, or premotor period). Such early signs include, for example, REM sleep behavior disorder (RBD), loss of smell and constipation (Mahowald et al., Neurology (2010) 75:488-489). Lewy body diseases continue to be a common cause for movement disorders and cognitive deterioration in the aging population (Galasko et al., Arch. Neurol. (1994) 51:888-95).

[0004] α-synuclein is part of a large family of proteins including β- and γ- synuclein and synoretin. α-synuclein is expressed in the normal state associated with synapses and is believed to play a role in neural plasticity, learning and memory. Several studies have implicated α-

Claims

1. An isolated monoclonal antibody that binds to a human alpha synuclein at an epitope consisting of residues 120-124 of SEQ ID NO: 1, wherein alanine mutagenesis of the human alpha synuclein at any of residues 118, 119, 125 and 126 does not change binding of the antibody.

2. The antibody of claim 1 wherein the antibody is at least 95% w/w pure.

3. A pharmaceutical composition comprising an antibody as defined in claim 1 and a pharmaceutically-acceptable carrier.

4. The antibody of claim 1, wherein the antibody is chimeric, veneered or humanized.

5. An isolated monoclonal antibody, comprising three light chain CDRs as defined by Kabat and three heavy chain CDRs as defined by Kabat of monoclonal antibody 5C1, wherein 5C1 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO: 9 and light chain variable region having an amino acid sequence comprising SEQ ID NO: 24.

6. The antibody of claim 5 that is an Fab fragment, or single chain Fv.

7. The antibody of claim 5, wherein the isotype is human IgG1.

8. The antibody of claim 5 having at least one mutation in the constant region, wherein the mutation reduces complement fixation or activation by the constant region.

9. The antibody of claim 8 having a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 322, 329 and 331 by EU numbering.

10. The antibody of claim 5 comprising a mature heavy chain variable region having an amino acid sequence at least 90% identical to SEQ ID NO: 17 and a mature light chain variable region having an amino acid sequence at least 90% identical to SEQ ID NO: 31, wherein the antibody specifically binds to human alpha synuclein.

11. The antibody of claim 10, provided at least one of positions H11, H27, H30, H48, and H73 is occupied by L, Y, T, I, and K, respectively, and at least one of positions L12 and L14 is occupied by S.

12. The antibody of claim 11, provided positions H11, H27, H30, H48, and H73 are occupied by L, Y, T, I, and K, respectively, and positions L12 and L14 are occupied by S.

13. The antibody of claim 11, provided at least one of positions H67, H69, and H94 is occupied by A, L, and S, respectively.

14. The antibody of claim 13, provided positions H67, H69, and H94 are occupied by A, L, and S, respectively.

15. The antibody of claim 13, provided position H94 is occupied by S.

16. The antibody of claim 11, provided at least one of the positions L2, L49, and L87 is occupied by V, N, and F, respectively.

17. The antibody of claim 16, provided positions L2, L49, and L87 are occupied by V, N, and F, respectively.

18. The antibody of claim 11, wherein the mature heavy chain variable region is fused to a heavy chain constant region and the mature light chain variable region is fused to a light chain constant region.

19. The antibody of claim 18, wherein the mature heavy chain variable region is fused to a heavy chain constant region having the sequence of SEQ ID NO: 38 and/or the mature light chain variable region is fused to a light chain constant region having the sequence of SEQ ID NO: 40.

20. The antibody of claim 10, wherein the mature heavy chain variable region has an amino acid sequence designated SEQ ID NO: 17 and the mature light chain variable region has an amino acid sequence designated SEQ ID NO: 31.

21. An isolated monoclonal antibody, wherein the mature heavy chain variable region has an amino acid sequence designated SEQ ID NO: 18 and the mature light chain variable region has an amino acid sequence designated SEQ ID NO: 31.

22. The antibody of claim 10, wherein the antibody is a Fab fragment.