

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that binds human transthyretin (TTR), comprising three heavy chain CDRs of SEQ ID NO: 81 and three light chain CDRs of SEQ ID NO: 87.
2. The antibody of claim 1, wherein the three heavy chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 5, 7, and 9) and the three light chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 11, 13, and 15).
3. The antibody of claim 1 that has a human IgG1 isotype, or that has a human IgG2 or IgG4 isotype.
4. The antibody of claim 1 that is an intact antibody.
5. The antibody of claim 1 that is a binding fragment.
6. A pharmaceutical composition comprising a first antibody of claim 1, a second antibody, and a pharmaceutically acceptable carrier, wherein the second antibody is selected from the group consisting of: an antibody comprising three heavy chain CDRs of SEQ ID NOs:75-77 and three light chain CDRs of SEQ ID NOs:78-80; an antibody comprising three heavy chain CDRs of SEQ ID NOs:39-41 and three light chain CDRs of SEQ ID NOs:42-44; an antibody comprising three heavy chain CDRs of SEQ ID NOs:46-48 and three light chain CDRs of SEQ ID NOs:49-51; an antibody comprising three heavy chain CDRs of SEQ ID NOs:52-54 and three light chain CDRs of SEQ ID NOs:55-57; an antibody comprising three heavy chain CDRs of SEQ ID NO:58 and three light chain CDRs of SEQ ID NO:59; an antibody comprising three heavy chain CDRs of SEQ ID NOs:60-62 and three light chain CDRs of SEQ ID NOs:63-65; and an antibody comprising three heavy chain CDRs of SEQ ID NOs:66-68 and three light chain CDRs of SEQ ID NOs:69-71.
7. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically acceptable carrier.
8. A nucleic acid encoding the heavy chain and/or light chain of an antibody as described in claim 1.

9. A recombinant expression vector comprising a nucleic acid of claim 8.

10. A host cell transformed with the recombinant expression vector of claim 9.

11. Use of an effective regime of the antibody of claim 1 in the manufacture of a medicament for treating a transthyretin-mediated amyloidosis in a subject.

12. The use of claim 11, wherein the transthyretin-mediated amyloidosis is associated with a condition selected from any of cardiomyopathy or hypertrophy, familial amyloid polyneuropathy, central nervous system selective amyloidosis (CNSA), senile systemic amyloidosis, senile cardiac amyloidosis, spinal stenosis, osteoarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, age related macular degeneration, and a ligament or tendon disorder.

13. The use of claim 11, wherein the transthyretin-mediated amyloidosis is associated with amyloid accumulation in the heart, peripheral nervous system, autonomic nervous system, kidneys, eyes, abdominal fat, or gastrointestinal tract of the subject.

14. The use of claim 11, wherein the transthyretin-mediated amyloidosis is a familial transthyretin amyloidosis or a sporadic transthyretin amyloidosis.

15. The use of claim 14, wherein the familial transthyretin amyloidosis is familial amyloid cardiomyopathy (FAC), familial amyloid polyneuropathy (FAP), or central nervous system selective amyloidosis (CNSA).

16. The use of claim 15, wherein the sporadic transthyretin amyloidosis is senile systemic amyloidosis (SSA) or senile cardiac amyloidosis (SCA).

17. A method of diagnosing a transthyretin-mediated amyloidosis in a subject, comprising contacting a biological sample from the subject with an effective amount of the antibody of claim 1.

18. A method of detecting the presence or absence of transthyretin deposits in a subject, comprising contacting a biological sample from the subject suspected of comprising the amyloid accumulation with an effective amount of the antibody of claim 1.

19. The antibody of claim 1 that is a chimeric, humanized, or veneered antibody.

20. The antibody of claim 19, wherein the antibody is a humanized antibody.

21. The humanized antibody of claim 20, wherein the mature light chain variable region is fused to a light chain constant region and the mature heavy chain variable region is fused to a heavy chain constant region.

22. The humanized antibody of claim 21, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has reduced binding to a Fcγ receptor relative to the natural human heavy chain constant region.

23. The humanized antibody of claim 21, wherein the mature heavy chain variable region is fused to a heavy chain constant region having the sequence of SEQ ID NO:22 with or without the C-terminal lysine and/or the mature light chain variable region is fused to a light chain constant region having the sequence of SEQ ID NO:24.

24. The humanized antibody of claim 20 comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOs:85-86 and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NOs: 91-92.

25. The humanized antibody of claim 24 wherein the mature heavy chain variable region has an amino acid sequence of any of SEQ ID NO: 85-86 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO: 91-92.

26. The humanized antibody of claim 24 wherein at least one of the following positions is occupied by the amino acid as specified: H37 is occupied by V or A, H45 is occupied by L or Q, H47 is occupied by L or W, H48 is occupied by V or I, H49 is occupied by A or G, and H94 is occupied by S or R.

27. The humanized antibody of claim 26, provided positions H37, H45, H47, H48, H49, and H94 in the VH region are occupied by A, Q, W, I, G, and R, respectively.

28. The humanized antibody of claim 24 wherein at least one of the following positions is occupied by the amino acid as specified: L2 is occupied by I or V and L45 is occupied by Q or R.

29. The humanized antibody of claim 28, provided positions L2 and L45 in the VL region are occupied by V and R, respectively.

30. The humanized antibody of claim 20, wherein the CDRs are of a definition selected from the group consisting of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact definitions.

31. The humanized antibody of claim 30, wherein the humanized mature heavy chain variable region comprises three Kabat/Chothia Composite heavy chain CDRs of SEQ ID NOs: 5, 7, and 9 and the humanized mature light chain variable region comprises the three Kabat/Chothia Composite light chain CDRs of SEQ ID NOs: 11, 13, and 15.

32. The humanized antibody of claim 30 wherein the humanized mature heavy chain variable region comprises three Kabat heavy chain CDRs of SEQ ID NO:93, SEQ ID NO:7, and SEQ ID NO:9 and the humanized mature light chain variable region comprises three Kabat light chain CDRs of SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15.

33. The humanized antibody of claim 30 wherein the humanized mature heavy chain variable region comprises three Chothia heavy chain CDRs of SEQ ID NO:94, SEQ ID NO:96, and SEQ ID NO:9 and the humanized mature light chain variable region comprises three Chothia light chain CDRs of SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15.

34. The humanized antibody of claim 30 wherein the humanized mature heavy chain variable region comprises three AbM heavy chain CDRs of SEQ ID NO:5, SEQ ID NO:97, and SEQ ID NO:9 and the humanized mature light chain variable region comprises three AbM light chain CDRs of SEQ ID NO:11, SEQ ID NO:13, and SEQ ID NO:15.

35. The humanized antibody of claim 30 wherein the humanized mature heavy chain variable region comprises three Contact heavy chain CDRs of SEQ ID NOs 100-102 and

the humanized mature light chain variable region comprises three Contact light chain CDRs of SEQ ID NO:95, SEQ ID NO:98, and SEQ ID NO:99.

36. A bispecific antibody comprising two antigen-binding regions, a first antigen-binding domain that comprises three heavy chain CDRs of SEQ ID NO: 81 and three light chain CDRs of SEQ ID NO: 87 and a second antigen-binding domain, wherein the second-antigen-binding domain is selected from the group consisting of: an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:75-77 and three light chain CDRs of SEQ ID NOs:78-80; an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:39-41 and three light chain CDRs of SEQ ID NOs:42-44; an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:46-48 and three light chain CDRs of SEQ ID NOs:49-51; an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:52-54 and three light chain CDRs of SEQ ID NOs:55-57; an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NO:58 and three light chain CDRs of SEQ ID NO:59; an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:60-62 and three light chain CDRs of SEQ ID NOs:63-65; and an antigen-binding domain comprising three heavy chain CDRs of SEQ ID NOs:66-68 and three light chain CDRs of SEQ ID NOs:69-71.

37. A method of humanizing a mouse antibody, the method comprising: (a) selecting one or more human acceptor antibody sequences; (b) identifying amino acid residues of the mouse antibody to be retained; (c) synthesizing a nucleic acid encoding a humanized heavy chain comprising CDRs of the mouse antibody heavy chain and a nucleic acid encoding a humanized light chain comprising CDRs of the mouse antibody light chain; and (d) expressing the nucleic acids in a host cell to produce a humanized antibody; wherein the mouse antibody comprises a mature heavy chain variable region having an amino acid sequence of SEQ ID NO:81 and a mature light chain variable region having an amino acid sequence of SEQ ID NO:87.

38. A method of producing a humanized, chimeric, or veneered antibody, the method comprising: (a) culturing cells transformed with nucleic acids encoding the heavy and light chains of the antibody, so that the cells secrete the antibody; and (b) purifying the antibody from cell culture media; wherein the antibody is a humanized, chimeric, or veneered form of a

mouse antibody characterized by a mature heavy chain variable region having an amino acid sequence comprising SEQ ID NO: 81 and a mature light chain variable region having an amino acid sequence comprising SEQ ID NO: 87.

39. A method of producing a cell line producing a humanized, chimeric, or veneered antibody, the method comprising: (a) introducing a vector encoding heavy and light chains of the antibody and a selectable marker into cells; (b) propagating the cells under conditions to select for cells having increased copy number of the vector; (c) isolating single cells from the selected cells; and (d) banking cells cloned from a single cell selected based on yield of antibody; wherein the antibody is a humanized, chimeric, or veneered form of a mouse antibody characterized by a mature heavy chain variable region having an amino acid sequence comprising SEQ ID NO: 81 and a mature light chain variable region having an amino acid sequence comprising SEQ ID NO: 87.

40. The method of claim 39, further comprising propagating the cells under selective conditions and screening for cell lines naturally expressing and secreting at least 100 mg/L/10⁶ cells/24h.