

CLAIMS

We claim:

1. 1. A modified immunoglobulin, comprising:

an amyloid-reactive peptide; and

an Ig antibody or functional fragment thereof that binds to a human amyloid fibrils, wherein the Ig antibody or functional fragment thereof comprises a heavy chain and a light chain, wherein the peptide and the Ig antibody or functional fragment thereof are joined together at the N-terminal end of the Ig light chain and/or the N- and/or C-terminal end of the Ig heavy chain.

~~2. 2.~~ The modified immunoglobulin of claim 1, ~~wherein the amyloid reactive peptide comprises an amino acid sequence having at least 85% sequence identity to any one of the amino acid sequences set forth as SEQ ID NOS:1-14.~~

~~3. The modified immunoglobulin of claim 1 or claim 2,~~ wherein the amyloid-reactive peptide and the Ig antibody or functional fragment thereof are joined together at the N-terminal end of the Ig light chain or the ~~N~~C-terminal end of the Ig heavy chain.

~~4. 3.~~ The modified immunoglobulin of ~~any one of claims~~claim 1-3, ~~wherein the modified immunoglobulin comprises a spacer sequence between the amyloid-reactive peptide and the Ig antibody or functional fragment thereof.~~

~~5. The modified immunoglobulin any of claims 1-4, wherein the modified immunoglobulin comprises at least two amyloid-reactive peptides and wherein the amyloid-reactive peptides are the same peptide or different peptides.~~

~~6. The modified immunoglobulin of any one of claims 1-5,~~
claim 2, wherein the Ig antibody or functional fragment thereof comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

wherein the VL comprises a ~~CDRL1~~CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:20, a ~~CDRL2~~CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a ~~CDRL3~~CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22; and

wherein the VH comprises a ~~CDRH1~~CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a ~~CDRH2~~CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, a ~~CDRH3~~CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; and

~~7. The modified immunoglobulin of claim 6, wherein the Ig antibody or functional fragment thereof is a chimeric antibody or functional fragment thereof.~~

~~8. The modified immunoglobulin of any one of claims 1-5, wherein the Ig antibody or functional fragment thereof comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein~~

~~ab) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or~~

~~bc) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 20; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or~~

~~d) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NOs: 64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NOs: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.~~

4. The modified immunoglobulin of claim 3, wherein the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

5. The modified immunoglobulin of claim 4, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.
6. The modified immunoglobulin of claim 4, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.
7. The modified immunoglobulin any one of claims 1-6, wherein the modified immunoglobulin is humanized.
8. An antibody-peptide fusion protein that binds human amyloid fibrils comprising an antibody fused to an amyloid-reactive peptide, wherein the antibody comprises a light chain variable region (VL), and a heavy chain variable region (VH); wherein:
- a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19;
- b) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NOs: 64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19;
- c) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 20; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: ~~NO~~NOs: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or

~~ε_d~~) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

~~9. The modified immunoglobulin of any one of claims 1-6 and 8 wherein the Ig antibody or functional fragment thereof comprises human framework sequences.~~

~~10. The modified immunoglobulin of any one of claims 1-9, wherein the Ig antibody comprises a human Fc region.~~

~~11. The modified immunoglobulin any one of claims 1-6, 8 and 10, wherein the modified immunoglobulin is humanized.~~

~~12. The modified immunoglobulin of any one of claims 1-11, wherein the modified immunoglobulin binds to rV λ 6Wil, A β , A β (1-40), IAAP, AL β 4, A β 1, or ATTR fibrils.~~

~~13. — An antibody-peptide fusion protein comprising an antibody that binds human amyloid fibrils fused to an amyloid-reactive peptide, wherein the antibody comprises a light chain variable region (VL), and a heavy chain variable region (VH).~~

~~14. — The antibody-peptide fusion protein of claim 13, wherein the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:20, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.~~

~~15. The antibody-peptide fusion protein of claim 13 or 14, wherein the antibody is a chimeric antibody or humanized antibody.~~

~~16. The antibody-peptide fusion protein of claim 13, wherein~~

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or

b) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 20; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19;

c) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

17. The antibody-peptide fusion protein of claim 14 or 16,

wherein the VL comprises one or more amino acid residues selected from the group consisting of:

- a. Tyr at position 36;
- b. Leu at position 37;
- c. Leu at position 46;
- d. Leu at position 85; and
- e. Phe at position 87

and/or wherein the VH comprises one or more amino acid residues selected from the group consisting of:

- a. Val at position 37;
- b. Leu at position 48;
- c. Leu at position 67;
- d. Ser at position 68;

- e. Lys at position 71;
- f. Ser at position 76;
- g. Val at position 78;
- h. Leu at position 79;
- ~~i. Phe at position 80;~~
- i. Phe at position 80;
- j. Thr at position 89;
- k. Val at position 93; and
- l. Thr at position 94

wherein the amino acid positions are numbered according to the numbering system of Kabat.

~~1810.~~ The antibody-peptide fusion protein of claim ~~17~~, wherein the VL comprises Tyr at position ~~36~~, Leu at position ~~37~~, Leu at position ~~46~~, Leu at position ~~85~~, and Phe at position ~~87~~, and the VH comprises Val at position ~~37~~, Leu at position ~~48~~, Leu at position ~~67~~, Ser at position ~~68~~, Lys at position ~~71~~, Thr at position ~~89~~, Val at position ~~93~~, and Thr at position ~~94~~.

~~19.~~ The antibody-peptide fusion protein of claim ~~17~~, wherein the VL comprises Leu at position ~~46~~ and Phe at position ~~87~~, and the VH comprises Leu at position ~~48~~, Ser at position ~~96~~, Val at position ~~78~~, Leu at position ~~79~~, Phe at position ~~80~~, and Thr at position ~~94~~.

~~20.~~ The antibody-peptide fusion protein of claim ~~17~~9, wherein the VL comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs: ~~32-42~~

~~21.~~ The antibody-peptide fusion protein of claim ~~17~~ or ~~20~~, wherein; and/or the VH comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs: ~~43-63~~.

~~2211.~~ The antibody-peptide fusion protein of claim ~~17~~9, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:34, and the VH comprises an amino acid sequence set forth in SEQ ID NO:48.

2312. The antibody-peptide fusion protein of claim ~~179~~, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:35, and the VH comprises an amino acid sequence set forth in SEQ ID NO:51.

2413. The antibody-peptide fusion protein of claim 8, wherein the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

14. The antibody-peptide fusion protein of claim 13, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

15. The antibody-peptide fusion protein of claim 13, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.

16. The antibody-peptide fusion protein of any one of claims ~~13-238~~-15, wherein the amyloid-reactive peptide comprises the amino acid sequence set forth in SEQ ID ~~NO: NOs:~~ 1-14.

2517. The antibody-peptide fusion protein of any ~~one of claim 13-24~~claims 8-16, wherein the amyloid reactive peptide~~antibody~~ is fused to the N-terminus of the VL~~a chimeric antibody~~ or the ~~N~~humanized antibody.

18. The modified immunoglobulin of any one of claims 1-7 or the antibody-peptide fusion protein of any one of claims 8-17, wherein the amyloid reactive peptide is fused to the N-terminus of the antibody light chain or the C-terminus of the ~~VH~~antibody heavy chain.

~~26~~19. The modified immunoglobulin or the antibody-peptide fusion protein of claim ~~25~~18, wherein the amyloid reactive peptide is fused to the N-terminus of the ~~VL-antibody light chain~~ by a spacer or the ~~NC~~-terminus of the ~~VH~~.

~~27. The antibody-peptide fusion protein of claim 26, wherein the~~antibody heavy chain by a
spacer is a peptide spacer.

~~28~~20. The modified immunoglobulin or the antibody-peptide fusion protein of claim ~~27~~19, wherein
the spacer is a peptide spacer.

21. The modified immunoglobulin or the antibody-peptide fusion protein of claim 20, wherein
the spacer comprises the amino acid sequence GGGYS.

22. A humanized antibody that binds to human amyloid fibrils, wherein the humanized antibody
comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:20, a
CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the
amino acid sequence set forth in SEQ ID NO:22, and

the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a
CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the
amino acid sequence set forth in SEQ ID NO:19,

wherein the VL comprises one or more amino acid residues selected from the group
consisting of:

- a. Tyr at position 36;
- b. Leu at position 37;
- c. Leu at position 46;
- d. Leu at position 85; and
- e. Phe at position 87

and/or wherein the VH comprises one or more amino acid residues selected from the group consisting of:

- a. Val at position 37;
- b. Leu at position 48;
- c. Leu at position 67;
- d. Ser at position 68;
- e. Lys at position 71;
- f. Ser at position 76;
- g. Val at position 78;
- h. Leu at position 79;
- i. Phe at position 80;
- j. Thr at position 89;
- k. Val at position 93; and
- l. Thr at position 94;

wherein the amino acid positions are numbered according to the numbering system of Kabat.

23. The humanized antibody of claim 22, wherein the VL comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs: 33-42, and/or the VH comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs: 44-63.

24. The humanized antibody of claim 22, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:34, and the VH comprises an amino acid sequence set forth in SEQ ID NO:48; or wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:35, and the VH comprises an amino acid sequence set forth in SEQ ID NO:51.

25. A humanized antibody that binds to human amyloid fibrils, wherein the humanized antibody comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein:

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the

amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19;

b) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NOs: 64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19;

c) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO: 20; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NOs: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or

d) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NOs: 64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NOs: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

26. The humanized antibody of claim 25, wherein VL comprises one or more amino acid residues selected from the group consisting of:

- a. Tyr at position 36;
- b. Leu at position 37;
- c. Leu at position 46;
- d. Leu at position 85; and
- e. Phe at position 87

and/or wherein the VH comprises one or more amino acid residues selected from the group consisting of:

- a. Val at position 37;
- b. Leu at position 48;

- c. Leu at position 67;
- d. Ser at position 68;
- e. Lys at position 71;
- f. Ser at position 76;
- g. Val at position 78;
- h. Leu at position 79;
- i. Phe at position 80;
- j. Thr at position 89;
- k. Val at position 93; and
- l. Thr at position 94;

wherein the amino acid positions are numbered according to the numbering system of Kabat.

27. The humanized antibody of claim 25, wherein the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

28. The humanized antibody of claim 27, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

29. The ~~humanized antibody-peptide fusion~~ of claim 27, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.

30. The humanized antibody of any one of claims ~~13-28-22-29~~, wherein the antibody is a full-length antibody, a Fab fragment, or a scFv.

31. The modified immunoglobulin of any one of claims 1-7 and 18-21, the antibody-peptide fusion protein of any one of claims 8-21, or the humanized antibody of any one of claims 22-30, wherein the antibody comprises an Fc region.

32. The modified immunoglobulin, the antibody-peptide fusion protein, or the humanized antibody of claim 31, wherein the Fc region is of an IgG1, IgG2, IgG3, or IgG4 isotype.

33. The modified immunoglobulin of any one of claims 1-7, 18-21, and 31-32, the antibody-peptide fusion of any one of claims 8-21 and 31-32, or the humanized antibody of any one of claims 22-32, wherein the modified immunoglobulin, the antibody-peptide fusion, or the humanized antibody binds to rV λ 6Wil-A β , fibrils, Per125 wtATTR extract, KEN hATTR extract, SHI AL λ liver extract, TAL AL κ liver extract, A β , A β (1-40), IAAP, AL β κ 4, AL β λ 1, or ATTR fibrils.

30.

34. A pharmaceutical composition comprising the modified immunoglobulin of any one of claims 1-~~12 or~~7, 18-21, and 31-33, the antibody-peptide fusion protein of any one of claims ~~13-298-~~21 and 31-33, or the humanized antibody of any one of claims 22-33.

~~3135.~~ Nucleic acid(s) encoding the modified immunoglobulin of any one of claims 1-~~12 or~~7, 18-21, and 31-33, the antibody-peptide fusion protein of any one of claims ~~13-298-~~21 and 31-33, or the humanized antibody of any one of claims 22-33.

~~3236.~~ A vector comprising the nucleic acid(s) of claim ~~3135.~~

~~3337.~~ A host cell comprising the vector of claim ~~3236.~~

~~3438.~~ A method of making a modified immunoglobulin-~~or~~, an antibody-peptide fusion protein, or a humanized antibody comprising culturing the host cell of claim ~~3337~~ under conditions suitable for expression of the vector encoding the modified immunoglobulin-~~or~~, the antibody-peptide fusion

protein, or the humanized antibody and recovering the modified immunoglobulin ~~or, the~~ antibody-peptide fusion protein, or the humanized antibody.

~~35. A method of treating a subject having an amyloid related disorder, comprising administering to the subject an effective amount~~39. Use of the modified immunoglobulin of any one of claims 1-~~12 or~~7, 18-21, and 31-33, the antibody-peptide fusion protein of any one of claims ~~13-29~~8-21 and 31-33, or the humanized antibody of any one of claims 22-33 in the manufacture of a medicament, wherein the medicament is for treating an amyloid related disorder.

~~36~~40. The ~~method~~use of claim ~~35~~39, wherein the amyloid related disorder is amyloidosis.

~~37~~41. The ~~method~~use of claim ~~35~~39, wherein the amyloid related disorder is selected from the group consisting of AL, AH, A β 2M, ATTR, transthyretin, AA, AApoAI, AApoAII, AGel, ALys, ALEct2, AFib, ACys, ACal, AMed, AIAPP, APro, AIns, APrP, α -synuclein, tau, or A β amyloidosis.

~~38~~42. The ~~method~~use of any one of claims ~~35-37~~39-41, wherein the subject is a human.

~~39~~43. Use of the modified immunoglobulin of any one of claims 1-7, 18-21, and 31-33, the antibody-peptide fusion protein of any one of claims 8-21 and 31-33, or the humanized antibody of any one of claims 22-33 in the manufacture of a medicament, wherein the medicament is for treating an amyloid-based disease in a subject, comprising:

determining whether the subject has an amyloid deposit by:

detectably labeling the modified immunoglobulin, the antibody-peptide fusion

protein, or the humanized antibody of the medicament,

administering the medicament to the subject,

determining whether a signal associated with the detectable label can be detected

from the subject; and,

if the signal is detected, administering to the subject an amyloidosis treatment.

44. A method of identifying an amyloid deposit in a subject, comprising detectably labeling the modified immunoglobulin of any one of claims 1-7, 18-21, and 31-33, the antibody-peptide fusion protein of any one of claims 8-21 and 31-33, or the humanized antibody of any one of claims 22-33, administering the modified immunoglobulin, the antibody-peptide fusion protein, or the humanized antibody to the subject, and detecting a signal from the modified immunoglobulin, the antibody-peptide fusion protein, or the humanized antibody.

45. A method of targeting an amyloid deposit for clearance, comprising contacting an amyloid deposit with the modified immunoglobulin of any one of claims 1-~~12~~7, 18-21, and 31-33 or the antibody-peptide fusion protein of any one of claims ~~13-29~~8-21 and 31-33.

~~40. The method of claim 39, wherein the amyloid deposit is removed.~~

~~41. The method of claim 39 or 40, wherein the amyloid deposit is opsonized by the modified immunoglobulin or the antibody-peptide fusion protein.~~

~~42-46. A method of targeting an amyloid deposit for clearance~~detecting a ligand, comprising: contacting ~~an amyloid deposit~~the ligand with the modified immunoglobulin of any one of claims 1-~~12~~7, 18-21, and 31-33 or ~~the~~ antibody-peptide fusion protein of any one of claims ~~13-29~~.

~~43. The method of claim ~~42~~8-21 and 31-33, wherein targeting the amyloid deposit for clearance results in clearance of the amyloid deposit.~~

~~44. The method of claim ~~42~~modified immunoglobulin or ~~43~~antibody-peptide fusion protein comprises a detectable label, wherein clearance results from opsonization of the amyloid deposit.~~

~~45. The method of any of claims 42-44, wherein the half-life of the amyloid reactive the peptide in~~of the modified immunoglobulin or antibody-peptide fusion protein ~~is increased by about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% or more as compared~~has binding affinity to the amyloid-reactive-peptide-alone-~~ligand and~~.

~~46. determining a signal from the detectable label, thereby detecting the ligand.~~

47. A method for generating a modified immunoglobulin, comprising:

providing a first expression vector and a second expression vector,

wherein the first expression vector comprises a first nucleic acid sequence encoding an Ig antibody light chain or functional fragment thereof;

wherein the second expression vector comprises a second nucleic acid sequence encoding an Ig antibody heavy chain or functional fragment thereof; and

wherein the first expression vector and/or the second expression vector comprise a third nucleic acid sequence that encodes a first peptide, the third nucleic acid sequence being located adjacent to the first nucleic acid sequence and/or the second nucleic acid sequence; and

inserting the first and second expression vectors into a cell, wherein expression of the first and second expression vectors in the cell results in an immunoglobulin that is joined to the first peptide.

~~47. The method of claim 46, wherein the first expression vector and/or the second expression vector comprise a fourth nucleic acid sequence that encodes a second peptide, the fourth nucleic acid sequence being located adjacent to the first nucleic acid sequence and/or the second nucleic acid sequence.~~

~~48. The method of claim 46, wherein expression of the first and second expression vectors in the cell results in an immunoglobulin that is joined to the first peptide and the second peptide.~~

~~49. The method of claims 46, wherein a spacer nucleic acid sequence is located between the third nucleic acid sequence and the first nucleic acid sequence and/or the second first nucleic acid sequence.~~

50. A method of treating a subject suffering from, or suspected to be suffering from, an amyloid-based disease, comprising:

a) determining whether the subject has an amyloid deposit by:

i) ~~administering the modified immunoglobulin of any one of claims 1-12 or the antibody-peptide fusion protein of any one of claims 13-29 to the subject, wherein~~

~~the modified immunoglobulin or antibody-peptide fusion protein comprises a detectable label and~~

~~ii) determining whether a signal associated with the detectable label can be detected from the subject; and~~

~~b) if the signal is detected, administering to the subject an amyloidosis treatment.~~

51. ~~The method of claim 50, wherein, if a signal is not detected, monitoring the subject for a later development of an amyloid deposit.~~

52. ~~The method of claim 51, further comprising determining the intensity of the signal and comparing the signal to a threshold value, above which the subject is determined to possess an amyloid deposit.~~

53. ~~The method of any of claims 50–52, wherein the amyloidosis treatment comprises administering the modified immunoglobulin of any of claims 1–12 or the antibody-peptide fusion protein of claims 13–29 to the subject.~~

54. ~~The method of claim 53, wherein administration of the modified immunoglobulin or the antibody-peptide fusion protein results in clearance of the amyloid deposit in the subject.~~

55. ~~A method of identifying an amyloid deposit in a subject, comprising administering the modified immunoglobulin of any one of claims 1–12 or antibody-peptide fusion protein of any one of claims 13–29 to the subject, wherein the modified immunoglobulin or antibody-peptide fusion protein comprises a detectable label and detecting a signal from the modified immunoglobulin or antibody-peptide fusion protein.~~

56. ~~The method of any of claims 50–55, wherein the subject is determined to be amyloid free or suffering from monoclonal gammopathy of unknown significance (MGUS), multiple myeloma (MM), or one or more related plasma cell diseases.~~

57. ~~A method of detecting a ligand, comprising:~~

contacting the ligand with the modified immunoglobulin of any one of claims 1-12 or antibody-peptide fusion protein of any one of claims 1-29, wherein the modified immunoglobulin or antibody-peptide fusion protein comprises a detectable label, wherein the peptide of the modified immunoglobulin or antibody-peptide fusion protein has binding affinity to the ligand and, determining a signal from the detectable label, thereby detecting the ligand.

58. — A humanized antibody that binds to human amyloid fibrils, wherein the humanized antibody comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein — the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:20, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and

the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19,

wherein the VL comprises one or more amino acid residues selected from the group consisting of:

- a. — Tyr at position 36;
- b. — Leu at position 37;
- c. — Leu at position 46;
- d. — Leu at position 85; and
- e. — Phe at position 87

wherein the VH comprises one or more amino acid residues selected from the group consisting of:

- a. — Val at position 37;
- b. — Leu at position 48;
- c. — Leu at position 67;
- d. — Ser at position 68;
- e. — Lys at position 71;
- f. — Ser at position 76;
- g. — Val at position 78;
- h. — Leu at position 79;
- i. — Phe at position 80;
- j. — Thr at position 89;
- k. — Val at position 93; and
- l. — Thr at position 94;

wherein the amino acid positions are numbered according to the numbering system of Kabat.

59. The humanized antibody of claim 58, wherein the VL comprises Tyr at position 36, Leu at position 37, Leu at position 46, Leu at position 85, and Phe at position 87, and the VH comprises Val at position 37, Leu at position 48, Leu at position 67, Ser at position 68, Lys at position 71, Thr at position 89, Val at position 93, and Thr at position 94.

60. The humanized antibody of claim 58, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

61. The humanized antibody of claim 58, wherein the VL comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs:33-42.

62. The humanized antibody of claim 58 or 61, wherein the VH comprises an amino acid sequence set forth in the group consisting of SEQ ID NOs:44-63.

63. The humanized antibody of claim 58, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:34, and the VH comprises an amino acid sequence set forth in SEQ ID NO:48.

64. The humanized antibody of claim 58, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:35, and the VH comprises an amino acid sequence set forth in SEQ ID NO:51.

65. A humanized antibody that binds to human amyloid fibrils, wherein the humanized antibody comprises a light chain variable region (VL) and a heavy chain variable region (VH), wherein

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64-70, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:18, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19; or

b) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:20; a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid

sequence set forth in SEQ ID NO: 71-81; and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

66. ~~The humanized antibody of claim 65, wherein VL comprises one or more amino acid residues selected from the group consisting of:~~

- ~~a. Tyr at position 36;~~
- ~~b. Leu at position 37;~~
- ~~c. Leu at position 46;~~
- ~~d. Leu at position 85; and~~
- ~~e. Phe at position 87~~

~~wherein the VH comprises one or more amino acid residues selected from the group consisting of:~~

- ~~a. Val at position 37;~~
- ~~b. Leu at position 48;~~
- ~~c. Leu at position 67;~~
- ~~d. Ser at position 68;~~
- ~~e. Lys at position 71;~~
- ~~f. Ser at position 76;~~
- ~~g. Val at position 78;~~
- ~~h. Leu at position 79;~~
- ~~i. Phe at position 80;~~
- ~~j. Thr at position 89;~~
- ~~k. Val at position 93; and~~
- ~~l. Thr at position 94;~~

~~wherein the amino acid positions are numbered according to the numbering system of Kabat.~~

67. ~~The humanized antibody of any one of claims 58-66, wherein the antibody is a full-length antibody, a Fab fragment, or a scFv.~~

68. ~~The humanized antibody of any one of claims 58-66, wherein the antibody comprises an Fc region.~~

69. ~~The humanized antibody of claim 68, wherein the Fc region is of an IgG1, IgG2, IgG3, or IgG4 isotype.~~

70. ~~The humanized antibody of any one of claims 58-69, wherein the humanized antibody or is conjugated to a detectable label.~~

71. ~~The humanized antibody of any one of claims 58-70, wherein the humanized antibody binds to rV λ 6Wil fibrils, Per125-wtATTR extract, KEN-hATTR extract, SHI-AL λ liver extract, and/or TAL-AL κ liver extract.~~

72. ~~The humanized antibody of any one of claims 58-71, wherein the humanized antibody binds to rV λ 6Wil, A β , A β (1-40), IAAP, AL β 4, AL β 1, or ATTR fibrils.~~

73. ~~A pharmaceutical composition comprising the humanized antibody of any one of claims 58-72.~~

74. ~~Nucleic acid(s) encoding the humanized antibody of any one of claims 58-73.~~

75. ~~A vector comprising the nucleic acid(s) of claim 74.~~

76. ~~A host cell comprising the vector of claim 75.~~

77. ~~A method of making a humanized antibody comprising culturing the host cell of claim 76 under conditions suitable for expression of the vector encoding the humanized antibody and recovering the humanized antibody.~~

78. ~~A method of treating a subject having an amyloid related disorder, comprising administering to the subject an effective amount of the humanized antibody of any one of claims 58-73.~~

79. ~~The method of claim 78, wherein the amyloid related disorder is amyloidosis.~~

80. ~~The method of claim 78, wherein the amyloid related disorder is selected from the group consisting of AL, AH, A β 2M, ATTR, transthyretin, AA, AApoAI, AApoAII, AGel, ALys, ALect2, AFib, ACys, ACal, AMed, AIAPP, APro, AIns, APrP, or A β amyloidosis.~~

81. ~~The method of any one of claims 78-80, wherein the subject is a human.~~

82. A method of treating a subject suffering from, or suspected to be suffering from, an amyloid-based disease, comprising:

determining whether the subject has an amyloid deposit by:

detectably labeling the humanized antibody of any one of claims 58-73,

administering the humanized antibody to the subject,

determining whether a signal associated with the detectable label can be detected from the subject; and,

if the signal is detected, administering to the subject an amyloidosis treatment.

83. — The method of claim 82, wherein, if a signal is not detected, monitoring the subject for a later development of an amyloid deposit.

84. — The method of claim 83, further comprising determining the intensity of the signal and comparing the signal to a threshold value, above which the subject is determined to possess an amyloid deposit.

85. — The method of any of claims 82-84, wherein the amyloidosis treatment comprises administering the humanized antibody of any one of claims 58-73 to the subject.

86. — A method of identifying an amyloid deposit in a subject, comprising detectably labeling the humanized antibody of any one of claims 58-73, administering the humanized antibody to the subject, and detecting a signal from the humanized antibody.

87. — The method of any of claims 82-86, wherein the subject is determined to be amyloid free or suffering from monoclonal gammopathy of unknown significance (MGUS), multiple myeloma (MM), or one or more related plasma cell diseases.

88. — The modified immunoglobulin of any one of claims 1-12 or the antibody-peptide fusion protein of any one of claims 13-29, wherein the modified immunoglobulin or antibody-peptide fusion protein is conjugated to a detectable label.

89. The modified immunoglobulin of any one of claims 1-12 or the antibody-peptide fusion protein of any one of claims 13-29, wherein the modified immunoglobulin or antibody-peptide fusion protein comprises a spacer that is N-terminal to the amyloid-reactive peptide.

90. The antibody-peptide fusion protein of claim 16, wherein

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

91. The antibody-peptide fusion protein of claim 90, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

92. The antibody-peptide fusion protein of claim 90, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.

93. The antibody-peptide fusion protein of any one of claims 90-92, wherein the amyloid-reactive peptide comprises an amino acid sequence set forth in the group consisting of SEQ ID NO:1-14.

94. The humanized antibody of claim 65, wherein

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

95. The humanized antibody of claim 94, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

96. The humanized antibody of any claim 94, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.

97. The modified immunoglobulin of claim 8, wherein

a) the VL comprises a CDR-L1 comprising the amino acid sequence set forth in SEQ ID NO:64, a CDR-L2 comprising the amino acid sequence set forth in SEQ ID NO:21, and a CDR-L3 comprising the amino acid sequence set forth in SEQ ID NO:22, and the VH comprises a CDR-H1 comprising the amino acid sequence set forth in SEQ ID NO:17, a CDR-H2 comprising the amino acid sequence set forth in SEQ ID NO:73, and a CDR-H3 comprising the amino acid sequence set forth in SEQ ID NO:19.

98. The modified immunoglobulin of claim 97, wherein the VL comprises Leu at position 46 and Phe at position 87, and the VH comprises Leu at position 48, Ser at position 96, Val at position 78, Leu at position 79, Phe at position 80, and Thr at position 94.

99. The modified immunoglobulin of claim 97, wherein the VL comprises an amino acid sequence set forth in SEQ ID NO:36, and the VH comprises an amino acid sequence set forth in SEQ ID NO:55.

100. The modified immunoglobulin of any one of claims 97-99, wherein the amyloid reactive peptide comprises an amino acid sequence set forth in the group consisting of SEQ ID NO:1-14.