

CLAIMS

1. A human-derived antibody or antigen-binding fragment thereof that binds to a
5 chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat protein (DPR) with
a poly-Glycine-Alanine (GA)₁₅ repeat, wherein the human-derived antibody or
antigen-binding fragment thereof comprises:
 - a heavy chain variable region (VH) comprising VH complementarity
10 determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise
the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:8,
amino acid positions 51-67 of SEQ ID NO:8, and amino acid positions 100-113 of
SEQ ID NO:8, respectively; and
 - a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the
15 VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid
positions 25-35 of SEQ ID NO:10, amino acid positions 51-57 of SEQ ID NO:10, and
amino acid positions 90-98 of SEQ ID NO:10, respectively; and
 - wherein the human-derived antibody or antigen-binding fragment thereof is
detectably labeled, comprises a heterologous sequence that is heterologous to the VH
20 CDRs 1, 2, and 3 and the VL CDRs 1, 2, and 3, or a combination thereof.
2. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein
the VH comprises an amino acid sequence that is at least 95% identical to the amino
acid sequence of SEQ ID NO:8.
- 25 3. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein
the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of
the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion.
4. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein
30 the VL comprises an amino acid sequence that is at least 95% identical to the amino
acid sequence of SEQ ID NO:10.

5. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.
- 5 6. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8, and wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
- 10 7. The human-derived antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion, and wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid
15 deletion.
8. The human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the human-derived antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain
20 comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.
9. The human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 7, wherein the heterologous sequence is an immunoglobulin heavy chain constant
25 region, an immunoglobulin light chain constant region, or a mammalian secretory signal peptide.
10. The human-derived antibody of any one of claims 1 to 9, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and
30 a heavy metal.
11. A pharmaceutical composition comprising the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising a human-derived antibody or antigen-binding fragment thereof that binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat protein (DPR) with a poly-Glycine-Alanine (GA)₁₅ repeat,
5 and a pharmaceutically acceptable carrier;
wherein the human-derived antibody or antigen-binding fragment thereof comprises:
a heavy chain variable region (VH) comprising VH complementarity
determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3
10 comprise the amino acid sequences set forth in amino acid positions 32-36 of
SEQ ID NO:8, amino acid positions 51-67 of SEQ ID NO:8, and amino acid
positions 100-113 of SEQ ID NO:8, respectively; and
a light chain variable region (VL) comprising VL CDRs 1, 2, and 3,
wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth
15 in amino acid positions 25-35 of SEQ ID NO:10, amino acid positions 51-57 of
SEQ ID NO:10, and amino acid positions 90-98 of SEQ ID NO:10,
respectively.
13. The pharmaceutical composition of claim 12, wherein the VH comprises an amino
20 acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID
NO:8.
14. The pharmaceutical composition of claim 12, wherein the VH comprises the amino
acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set
25 forth in SEQ ID NO:8 with one amino acid deletion.
15. The pharmaceutical composition of claim 12, wherein the VL comprises an amino acid
sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
- 30 16. The pharmaceutical composition of claim 12, wherein the VL comprises the amino
acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set
forth in SEQ ID NO:10 with one amino acid deletion.

17. The pharmaceutical composition of claim 12, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8, and wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
18. The pharmaceutical composition of claim 12, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion, and wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.
19. The pharmaceutical composition of any one of claims 12 to 18, wherein the human-derived antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.
20. A combination of polynucleotides for expressing the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9, comprising: (i) a polynucleotide encoding a polypeptide comprising the VH of the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9; and (ii) a polynucleotide encoding a polypeptide comprising the VL of the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9; and wherein the human-derived antibody or antigen-binding fragment thereof comprises the heterologous sequence.
21. The combination of polynucleotides of claim 20, wherein each polynucleotide further comprises a heterologous nucleic acid encoding a secretory signal peptide.
22. A combination of polynucleotides for expressing a human-derived antibody or antigen-binding fragment thereof,
wherein the human-derived antibody or antigen-binding fragment thereof binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat protein (DPR) with a poly-Glycine-Alanine (GA)₁₅ repeat, and a pharmaceutically acceptable carrier;

wherein the human-derived antibody or antigen-binding fragment thereof comprises:

a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:8, amino acid positions 51-67 of SEQ ID NO:8, and amino acid positions 100-113 of SEQ ID NO:8, respectively; and

a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-35 of SEQ ID NO:10, amino acid positions 51-57 of SEQ ID NO:10, and amino acid positions 90-98 of SEQ ID NO:10, respectively;

wherein the combination of polynucleotides comprises (i) a first polynucleotide encoding a polypeptide comprising the VH of the human-derived antibody or antigen-binding fragment thereof; and (ii) a second polynucleotide encoding a polypeptide comprising the VL of the human-derived antibody or antigen-binding fragment thereof; and

wherein each polynucleotide further comprises a heterologous nucleic acid encoding a secretory signal peptide.

23. The combination of polynucleotides of claim 22, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8.
24. The combination of polynucleotides of claim 22, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion.
25. The combination of polynucleotides of claim 22, wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
26. The combination of polynucleotides of claim 22, wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.

27. The combination of polynucleotides of claim 22, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8, and wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.
28. The combination of polynucleotides of claim 22, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion, and wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.
29. The combination of polynucleotides of any one of claims 22 to 28, wherein the human-derived antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.
30. An expression vector for expressing the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9 comprising (i) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VH of the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9; and (ii) a promoter operably linked to a polynucleotide encoding a polypeptide comprising the VL of the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9; and wherein the human-derived antibody or antigen-binding fragment thereof comprises the heterologous sequence.
31. An expression vector for expressing a human-derived antibody or antigen-binding fragment thereof, wherein the expression vector comprises the combination of polynucleotides of any one of claims 22 to 29, wherein the first polynucleotide is operably linked to a promoter, and wherein the second polynucleotide is operably linked to a promoter.

32. An expression vector for expressing the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 9 comprising:

a first polynucleotide encoding a first polypeptide comprising a VH of the human-derived antibody or antigen binding fragment thereof of any one of claims 1 to 9; and

a second polynucleotide encoding a second polypeptide comprising a VL of the human-derived antibody or antigen binding fragment thereof of any one of claims 1 to 9; and wherein the human-derived antibody or antigen-binding fragment thereof comprises the heterologous sequence.

33. A host cell comprising the combination of polynucleotides of any one of claims 20 to 29 or the expression vector of any one of claims 30 to 32.

34. A method for preparing a human-derived antibody or antigen-binding fragment thereof, the method comprising:

- (a) culturing the host cell of claim 33; and
- (b) isolating the human-derived antibody or antigen-binding fragment thereof from the culture.

35. Use of a human-derived antibody or antigen-binding fragment thereof in the manufacture of a diagnostic agent for use in detecting the presence of poly-GA DPR protein species, or fragments thereof, in a sample obtained from a subject, wherein the presence of the poly-GA DPR protein species, or fragments thereof, is indicative for amyotrophic lateral sclerosis (ALS) and/or frontotemporal lobar degeneration (FTLD); and

wherein the human-derived antibody or antigen-binding fragment thereof binds to a chromosome 9 open reading frame 72 (C9orf72) dipeptide repeat protein (DPR) with a poly-Glycine-Alanine (GA)₁₅ repeat and comprises:

a heavy chain variable region (VH) comprising VH complementarity determining regions (CDRs) 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 32-36 of SEQ ID NO:8, amino acid positions 51-67 of SEQ ID NO:8, and amino acid positions 100-113 of SEQ ID NO:8, respectively; and

a light chain variable region (VL) comprising VL CDRs 1, 2, and 3, wherein the VL CDRs 1, 2, and 3 comprise the amino acid sequences set forth in amino acid positions 25-35 of SEQ ID NO:10, amino acid positions 51-57 of SEQ ID NO:10, and amino acid positions 90-98 of SEQ ID NO:10, respectively.

5

36. The use of claim 35, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8.

10

37. The use of claim 35, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion.

15

38. The use of claim 35, wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.

39. The use of claim 35, wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.

20

40. The use of claim 35, wherein the VH comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:8, and wherein the VL comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO:10.

25

41. The use of claim 35, wherein the VH comprises the amino acid sequence set forth in SEQ ID NO:8 or a variant of the amino acid sequence set forth in SEQ ID NO:8 with one amino acid deletion, and wherein the VL comprises the amino acid sequence set forth in SEQ ID NO:10 or a variant of the amino acid sequence set forth in SEQ ID NO:10 with one amino acid deletion.

30

42. The use of claim 35, wherein the human-derived antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein the immunoglobulin heavy chain comprises a human IgG1 constant region, and wherein the immunoglobulin light chain comprises a human kappa constant region.

43. The use of any one of claims 35 to 42, wherein the human-derived antibody or antigen-binding fragment thereof is detectably labeled.
- 5 44. The use of claim 43, wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore, and a heavy metal.
- 10 45. Use of the human-derived antibody or antigen-binding fragment thereof of any one of claims 1 to 10 in the manufacture of a diagnostic agent for *in vivo* detection of a poly-GA DPR protein in a human subject, wherein the human-derived antibody or antigen-binding fragment thereof is detectably labeled.
- 15 46. Use of the pharmaceutical composition of any one of claims 11 to 19 in the manufacture of a medicament for prophylactic and/or therapeutic treatment of a disease associated with poly-GA DPR protein or aggregated forms thereof in a human subject, wherein the disease is selected from the group consisting of amyotrophic lateral sclerosis (ALS), Frontotemporal lobar degeneration (FTLD), and FTLD-ALS.
- 20 47. The use of claim 46, wherein the human-derived antibody or antigen-binding fragment thereof is formulated for intrathecal, intravenous, or subcutaneous delivery.