

CLAIMS

1. An antibody or an antigen-binding fragment thereof which specifically recognizes misfolded TDP-43, in which the antibody or an antigen-binding fragment thereof: (a) does not bind to physiologically functional TDP-43; and (b) specifically binds to an epitope within
5 amino acids 215-222 of mature human TDP-43.
2. An antibody or an antigen-binding fragment thereof according to Claim 1, which specifically binds to cytoplasmic misfolded and/or extracellular misfolded TDP-43, optionally in which the misfolded TDP-43 is:
 - (a) monomeric;
 - 10 (b) oligomeric;
 - (c) aggregated; and/or
 - (d) post-translationally modified TDP-43, optionally in which the post-translationally modified TDP-43 is phosphorylated TDP-43.
3. An antibody or an antigen-binding fragment thereof according to Claim 1 or 2, which
15 blocks TDP-43 cell-to-cell spreading, and/or disaggregates TDP-43 aggregates and/or inhibits the aggregation of TDP-43 protein or fragments thereof.
4. An antibody or an antigen-binding fragment thereof according to Claim 1, 2 or 3, in which mature human TDP-43 is represented by SEQ ID NO:1.
5. An antibody or an antigen-binding fragment thereof according to any preceding claim,
20 which specifically binds to cytoplasmic aggregated and/or extracellular aggregated TDP-43.
6. An antibody or an antigen-binding fragment thereof according to any preceding claim, in which the antibody is:
 - (a) a monoclonal antibody; and/or
 - (b) a murine antibody;
 - 25 (c) a murinized antibody;
 - (d) a human antibody;
 - (e) a humanized antibody; or

(f) a chimeric antibody.

7. An antibody or an antigen-binding fragment thereof according to any preceding claim, which comprises:

(a) the variable regions VL and/or VH of the amino acid sequence set forth in SEQ ID NO: 10 and SEQ ID NO: 20; SEQ ID NO: 30 and SEQ ID NO: 40; SEQ ID NO: 50 and SEQ ID NO: 60; SEQ ID NO: 70 and SEQ ID NO: 80; SEQ ID NO: 90 and SEQ ID NO: 100; SEQ ID NO: 110 and SEQ ID NO: 120; SEQ ID NO: 130 and SEQ ID NO: 140; or SEQ ID NO: 150 and SEQ ID NO: 160; SEQ ID NO: 170 and SEQ ID NO: 180; SEQ ID NO: 190 and SEQ ID NO: 200; SEQ ID NO: 210 and SEQ ID NO: 220; SEQ ID NO: 230 and SEQ ID NO: 232; SEQ ID NO: 234 and SEQ ID NO: 236; SEQ ID NO: 238 and SEQ ID NO: 240; SEQ ID NO: 242 and SEQ ID NO: 244; SEQ ID NO: 246 and SEQ ID NO: 248; SEQ ID NO: 250 and SEQ ID NO: 252; SEQ ID NO: 254 and SEQ ID NO: 256 or SEQ ID NO: 258 and SEQ ID NO: 260, respectively; or

(b) amino acid sequences of the variable regions VL and/or VH having at least 70%, 80%, 90% or 95% sequence homology to the amino acid sequence set forth in SEQ ID NO: 10 and SEQ ID NO: 20; SEQ ID NO: 30 and SEQ ID NO: 40; SEQ ID NO: 50 and SEQ ID NO: 60; SEQ ID NO: 70 and SEQ ID NO: 80; SEQ ID NO: 90 and SEQ ID NO: 100; SEQ ID NO: 110 and SEQ ID NO: 120; SEQ ID NO: 130 and SEQ ID NO: 140; or SEQ ID NO: 150 and SEQ ID NO: 160; SEQ ID NO: 170 and SEQ ID NO: 180; SEQ ID NO: 190 and SEQ ID NO: 200; SEQ ID NO: 210 and SEQ ID NO: 220; SEQ ID NO: 230 and SEQ ID NO: 232; SEQ ID NO: 234 and SEQ ID NO: 236; SEQ ID NO: 238 and SEQ ID NO: 240; SEQ ID NO: 242 and SEQ ID NO: 244; SEQ ID NO: 246 and SEQ ID NO: 248; SEQ ID NO: 250 and SEQ ID NO: 252; SEQ ID NO: 254 and SEQ ID NO: 256 or SEQ ID NO: 258 and SEQ ID NO: 260, respectively.

8. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 6, having:

(a) a Light Chain Variable Region (VL) comprising an amino acid sequence selected from the group of SEQ ID NO: 10; SEQ ID NO: 30; SEQ ID NO: 50; SEQ ID NO: 70; SEQ ID NO: 90; SEQ ID NO: 110; SEQ ID NO: 130; SEQ ID NO: 150; SEQ ID NO: 170; SEQ ID NO: 190; SEQ ID NO: 210; SEQ ID NO: 230; SEQ ID NO: 234; SEQ ID

NO: 238; SEQ ID NO: 242; SEQ ID NO: 246; SEQ ID NO: 250; SEQ ID NO: 254; and SEQ ID NO: 258; or

(b) a Heavy Chain Variable Region (VH) comprising an amino acid sequence selected from the group of SEQ ID NO: 20; SEQ ID NO: 40; SEQ ID NO: 60; SEQ ID NO: 80; SEQ ID NO: 100; SEQ ID NO: 120; SEQ ID NO: 140; SEQ ID NO: 160; SEQ ID NO: 180; SEQ ID NO: 200; SEQ ID NO: 220; SEQ ID NO: 232; SEQ ID NO: 236; SEQ ID NO: 240; SEQ ID NO: 244; SEQ ID NO: 248; SEQ ID NO: 252; SEQ ID NO: 256; and SEQ ID NO: 260.

9. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 6, in which the antibody comprises:

(a) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 10 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 10 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 20 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 20;

(b) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 30 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 30 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 40 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 40;

(c) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 50 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 50 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 60 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 60;

- (d) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 70 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 70 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 80 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 80;
- (e) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 90 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 100 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 100;
- (f) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 110 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 110 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 120 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 120;
- (g) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 130 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 130 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 140 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 140;
- (h) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 150 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 150 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 160 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 160;

(i) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 170 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 170 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 180 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 180;

(j) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 190 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 190 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 200 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 200;

(k) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 210 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 210 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 220 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 220;

(l) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 230 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 230 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 232 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 232;

- (m) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 234 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 234 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 236 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 236;
- (n) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 238 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 238 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 240 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 240;
- (o) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 242 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 242 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 244 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 244;
- (p) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 246 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 246 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 248 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 248;
- (q) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 250 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 250 and a Heavy Chain Variable Region (VH)

comprising the sequence of SEQ ID NO: 252 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 252;

(r) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 254 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 254 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 256 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 256; or

(s) a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 258 or a light chain variable region (VL) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 258 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 260 or a heavy chain variable region (VH) having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 260.

10. An antibody or an antigen-binding fragment thereof according to any preceding claim:

(a) comprising CDR sequences selected from the group of:

(i) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 12; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 14; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 16;

(ii) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 32; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 34; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 36;

(iii) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 52; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 54; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 56;

- (iv) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 72; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 74; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 76;
- 5 (v) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 92; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 94; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 96;
- (vi) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 112; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 114; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 116;
- 10 (vii) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 132; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 134; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 136;
- (viii) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 152; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 154; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 156;
- 15 (ix) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 172; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 174; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 176;
- (x) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 192; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 194; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 196; and
- 20 (xi) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 212; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 214; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 216; or
- 25 (b) comprising CDR sequences selected from the group of:
 - (i) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 22; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 24; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 26;

- (ii) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 42; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 44; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 46;
- 5 (iii) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 62; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 64; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 66;
- (iv) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 82; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 84; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 86;
- 10 (v) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 102; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 104; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 106;
- (vi) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 122; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 126;
- 15 (vii) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 142; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 144; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 146;
- (viii) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 162; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 164; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 166;
- 20 (ix) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 182; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 184; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 186;
- 25 (x) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 202; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 204; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 206; and
- (xi) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 222; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 224; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 226.
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11. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 9, comprising CDR sequences selected from the group of:

(a) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 12; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 14; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 16; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 22; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 24; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 26;

(b) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 32; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 34; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 36; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 42; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 44; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 46;

(c) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 52; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 54; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 56; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 62; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 64; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 66;

(d) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 72; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 74; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 76; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 82; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 84; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 86;

(e) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 92; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 94; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 96; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 102; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 104; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 106;

(f) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 112; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 114; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 116; VH-CDR1 comprising the amino acid

sequence of SEQ ID NO: 122; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 124; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 126;

(g) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 132; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 134; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 136; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 142; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 144; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 146;

(h) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 152; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 154; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 156; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 162; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 164; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 166;

(i) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 172; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 174; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 176; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 182; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 184; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 186;

(j) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 192; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 194; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 196; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 202; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 204; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 206; and

(k) VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 212; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 214; VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 216; VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 222; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 224; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 226.

12. An antibody or an antigen-binding fragment thereof according to any preceding claim, in which the antibody or an antigen-binding fragment thereof has a dissociation constant (KD) of $\leq 1\mu\text{M}$, $\leq 100\text{ nM}$, $\leq 10\text{ nM}$, $\leq 1\text{ nM}$, $\leq 0.1\text{ nM}$, $\leq 0.01\text{ nM}$, or $\leq 0.001\text{ nM}$.

13. An antibody or an antigen-binding fragment thereof according to any preceding claim, in which the antibody or an antigen-binding fragment thereof is linked to a detectable label.
14. An immunoconjugate comprising an antibody or an antigen-binding fragment thereof according to any preceding claim, in which the antibody or an antigen-binding fragment thereof is covalently linked to a therapeutic agent.
15. A pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13 and/or an immunoconjugate according to Claim 14 and a pharmaceutically acceptable carrier or diluent or adjuvant.
16. A diagnostic kit comprising an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13 and/or an immunoconjugate according to Claim 14.
17. An immunodiagnostic method for diagnosing a TDP-43 proteinopathy in a subject, in which the immunodiagnostic method comprises the *in vitro* or *ex-vivo* use of an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13 and/or an immunoconjugate according to Claim 14.
18. An immunodiagnostic method according to Claim 17, comprising the use of a sample obtained from the subject, in which the sample is a blood sample, CSF sample, brain tissue sample or urine sample; optionally comprising the use of an ELISA-based or surface adapted assay.
19. Use of an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13 and/or an immunoconjugate according to Claim 14 in the preparation of a medicament for the prevention of a TDP-43 proteinopathy.
20. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13 or an immunoconjugate according to Claim 14 for use in preventing and/or treating a TDP-43 proteinopathy.
21. Use according to Claim 19, or an antibody or an antigen-binding fragment thereof, or an immunoconjugate for use according to Claim 20, which reduces the level of TDP-43 aggregates in the brain.
22. Use according to Claim 19 or 21, or an antibody or an antigen-binding fragment thereof, or immunoconjugate for use according to Claim 20 or 21, or an immunodiagnostic method

- according to Claim 17 or 18, in which the TDP-43 proteinopathy is selected from Frontotemporal dementia (FTD, Sporadic or familial with or without motor-neuron disease (MND), with progranulin (GRN) mutation, with TARDBP mutation, with valosine-containing protein (VCP) mutation, linked to chromosome 9p, corticobasal degeneration, frontotemporal
- 5 lobar degeneration with ubiquitin-positive inclusions, Argyrophilic grain disease, Pick's disease and the like), Amyotrophic lateral sclerosis (ALS, Sporadic ALS, with TARDBP mutation, with angiogenin (ANG) mutation), Alzheimer's disease (AD, sporadic and familial), Down syndrome, Familial British dementia, Polyglutamine diseases (Huntington's disease and spinocerebellar ataxia type 3 (SCA3; also known under Machado Joseph Disease)),
- 10 Hippocampal sclerosis dementia and Myopathies (Sporadic inclusion body myositis, Inclusion body myopathy with a mutation in the valosine-containing protein (VCP; also Paget disease of bone and frontotemporal dementia), Oculo-pharyngeal muscular dystrophy with rimmed vacuoles, Myofibrillar myopathies with mutations in the myotilin (MYOT) gene or mutations in the gene coding for desmin (DES)), or Parkinson's disease (PD).
- 15 23. Use according to Claim 19 or 21, or an antibody or an antigen-binding fragment thereof, or an immunoconjugate for use according to Claim 20 or 21, or an immunodiagnostic method according to Claim 17 or 18, in which the TDP-43 proteinopathy is a disorder or abnormality associated with TDP-43 aggregates including but not limited to frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's
- 20 disease (PD).
24. A nucleic acid encoding an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13, optionally in which the nucleic acid comprises a sequence selected from the group of:
- (a) SEQ ID NO: 19; SEQ ID NO: 29; SEQ ID NO: 39; SEQ ID NO: 49; SEQ ID NO:
- 25 59; SEQ ID NO: 69; SEQ ID NO: 79; SEQ ID NO: 89; SEQ ID NO: 99; SEQ ID NO: 109; SEQ ID NO: 119; SEQ ID NO: 129; SEQ ID NO: 139; SEQ ID NO: 149; SEQ ID NO: 159; SEQ ID NO: 169; SEQ ID NO: 179; SEQ ID NO: 189; SEQ ID NO: 199; SEQ ID NO: 209; SEQ ID NO: 219; SEQ ID NO: 229; SEQ ID NO: 231; SEQ ID NO: 233; SEQ ID NO: 235; SEQ ID NO: 237; SEQ ID NO: 239; SEQ ID NO: 241; SEQ ID
- 30 NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 249; SEQ ID NO: 251; SEQ ID NO: 253; SEQ ID NO: 255; SEQ ID NO: 257; SEQ ID NO: 259; and SEQ ID NO: 261;

(b) a nucleic acid sequence having at least 60%, 70%, 80%, 90% or 95% sequence homology to any one of SEQ ID NO: 19; SEQ ID NO: 29; SEQ ID NO: 39; SEQ ID NO: 49; SEQ ID NO: 59; SEQ ID NO: 69; SEQ ID NO: 79; SEQ ID NO: 89; SEQ ID NO: 99; SEQ ID NO: 109; SEQ ID NO: 119; SEQ ID NO: 129; SEQ ID NO: 139; SEQ ID NO: 149; SEQ ID NO: 159; or SEQ ID NO: 169; SEQ ID NO: 179; SEQ ID NO: 189; SEQ ID NO: 199; SEQ ID NO: 209; SEQ ID NO: 219; SEQ ID NO: 229; SEQ ID NO: 231; SEQ ID NO: 233; SEQ ID NO: 235; SEQ ID NO: 237; SEQ ID NO: 239; SEQ ID NO: 241; SEQ ID NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 249; SEQ ID NO: 251; SEQ ID NO: 253; SEQ ID NO: 255; SEQ ID NO: 257; SEQ ID NO: 259; and SEQ ID NO: 261; or

(c) a nucleic acid sequence which hybridizes under stringent conditions to any one of SEQ ID NO: 19; SEQ ID NO: 29; SEQ ID NO: 39; SEQ ID NO: 49; SEQ ID NO: 59; SEQ ID NO: 69; SEQ ID NO: 79; SEQ ID NO: 89; SEQ ID NO: 99; SEQ ID NO: 109; SEQ ID NO: 119; SEQ ID NO: 129; SEQ ID NO: 139; SEQ ID NO: 149; SEQ ID NO: 159; SEQ ID NO: 169; SEQ ID NO: 179; SEQ ID NO: 189; SEQ ID NO: 199; SEQ ID NO: 209; SEQ ID NO: 219; SEQ ID NO: 229; SEQ ID NO: 231; SEQ ID NO: 233; SEQ ID NO: 235; SEQ ID NO: 237; SEQ ID NO: 239; SEQ ID NO: 241; SEQ ID NO: 243; SEQ ID NO: 245; SEQ ID NO: 247; SEQ ID NO: 249; SEQ ID NO: 251; SEQ ID NO: 253; SEQ ID NO: 255; SEQ ID NO: 257; SEQ ID NO: 259; or SEQ ID NO: 261.

25. A host cell comprising a nucleic acid according to Claim 24.

26. A method for producing an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13, in which the method comprises culturing a host cell according to Claim 25 under conditions suitable for producing the TDP-43 binding antibody or antigen-binding fragment thereof.

27. Use of an antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13, an immunoconjugate according to Claim 14 or a pharmaceutical composition according to Claim 15 in the manufacture of a medicament for treating a TDP-43 proteinopathy in a subject.

28. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13, an immunoconjugate according to Claim 14, or a pharmaceutical composition according to Claim 15 for use in reducing the level of misfolded TDP-43 in a subject.

29. An antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13,
an immunoconjugate according to Claim 14, or a pharmaceutical composition according to
Claim 15 for use in retaining or increasing cognitive memory capacity, movement and
language function or preventing and/or slowing decline of cognitive memory capacity,
5 movement and language function in a subject.
31. A method of detecting misfolded TDP-43, comprising contacting a sample with an
antibody or an antigen-binding fragment thereof according to any of Claims 1 to 13,
optionally in which the sample is a brain sample, a cerebrospinal fluid sample, urine sample or
a blood sample.