

CLAIMS

1. A binding molecule which specifically recognizes misfolded TDP-43, in which the binding molecule specifically binds to an epitope within amino acids 215-222 of mature human TDP-43.
- 5 2. A binding molecule according to Claim 1, which specifically binds to cytoplasmic misfolded and/or extracellular misfolded TDP-43, optionally in which the binding molecule does not bind to physiologically functional 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.
- 15 3. A binding molecule according to Claim 1 or 2, which 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. A binding molecule according to Claim 1, 2 or 3, which is an antibody or an antigen-binding fragment thereof.
- 20 5. A binding molecule according to any preceding claim, in which mature human TDP-43 is represented by SEQ ID NO:1.
6. A binding molecule according to any preceding claim, which specifically binds to cytoplasmic aggregated and/or extracellular aggregated TDP-43.
7. A binding molecule according to Claim 4, in which the antibody is:
 - (a) a monoclonal antibody; and/or
 - 25 (b) a murine antibody;
 - (c) a murinized antibody;
 - (d) a human antibody;

- (e) a humanized antibody; or
- (f) a chimeric antibody.

8. A binding molecule 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.

9. A binding molecule according to any of Claims 1 to 7, 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.

10. A binding molecule according to any of Claims 1 to 7, 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)

5 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)

10 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.

11. A binding molecule according to any preceding claim:

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

20 (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;

25 (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;

- (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;
- 5 (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;
- (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;
- 10 (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;
- (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;
- 15 (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
- (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
- 20 (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;
- 25 (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;

- (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;
- 5 (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;
- (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;
- 10 (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;
- (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;
- 15 (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;
- (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;
- 20 (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
- 25 (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.
12. A binding molecule according to any of Claims 1 to 10, comprising CDR sequences selected from the group of:

- 5 (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;
- 10 (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;
- 15 (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;
- 20 (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;
- 25 (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;
- 30 (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.

13. A binding molecule according to any preceding claim, in which the binding molecule 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 $\leq 0.001\text{ nM}$.

14. A binding molecule according to any preceding claim, in which the binding molecule is linked to a detectable label.

15. An immunoconjugate comprising a binding molecule according to any preceding claim, in which the binding molecule is covalently linked to a therapeutic agent.
16. A pharmaceutical composition comprising a binding molecule according to any of Claims 1 to 14 and/or an immunoconjugate according to Claim 15 and a pharmaceutically acceptable carrier or diluent or adjuvant.
17. A diagnostic kit comprising a binding molecule according to any of Claims 1 to 14 and/or an immunoconjugate according to Claim 15.
18. An immunodiagnostic method for diagnosing a TDP-43 proteinopathy in a subject, in which the immunodiagnostic method comprises the use of a binding molecule according to any of Claims 1 to 14 and/or an immunoconjugate according to Claim 15.
19. An immunodiagnostic method according to Claim 18, 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.
20. Use of a binding molecule according to any of Claims 1 to 14 and/or an immunoconjugate according to Claim 15 in the preparation of a medicament for the treatment or prevention of a TDP-43 proteinopathy, in which an effective amount of the binding molecule, and/or the immunoconjugate is to be administered to a subject in need thereof.
21. A binding molecule according to any of Claims 1 to 14 or an immunoconjugate according to Claim 15 for use in preventing and/or treating a TDP-43 proteinopathy.
22. Use according to Claim 20, or a binding molecule, or an immunoconjugate for use according to Claim 21, which reduces the level of TDP-43 aggregates in the brain.
23. Use according to Claim 20 or 22, or a binding molecule, or immunoconjugate for use according to Claim 21 or 22, or an immunodiagnostic method according to Claim 18 or 19, 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 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)), Hippocampal sclerosis dementia and

5 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).

10 24. Use according to Claim 20 or 22, or a binding molecule, or an immunoconjugate for use according to Claim 21 or 22, or an immunodiagnostic method according to Claim 18 or 19, 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 disease (PD).

15 25. A nucleic acid encoding a binding molecule according to any of Claims 1 to 14, 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: 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

20 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; and SEQ ID

25 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

30 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

- 5 (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
 10 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.

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

- 15 27. A method for producing a binding molecule according to any of Claims 1 to 14, in
 which the method comprises culturing a host cell according to Claim 26 under conditions
 suitable for producing the TDP-43 binding molecule.

28. A binding molecule according to any of Claims 1 to 14, an immunoconjugate according
 to Claim 15, or a pharmaceutical composition according to Claim 16 for use in a method of
 20 retaining or increasing cognitive memory capacity, movement and language function or
 preventing and/or slowing decline of cognitive memory capacity, movement and language
 function in a subject.

29. A binding molecule according to any of Claims 1 to 14, an immunoconjugate according
 to Claim 15, or a pharmaceutical composition according to Claim 16 for use in a method of
 25 reducing the level of misfolded TDP-43, in which the binding molecule, immunoconjugate or
 pharmaceutical composition is to be administered to a subject.

30. A binding molecule, immunoconjugate or pharmaceutical composition according to
 Claim 28 or 29, in which at least one additional therapy is to be administered to the subject,
 optionally in which the additional therapy is selected from, but not limited to, neurological
 30 drugs, anti- β antibodies, anti-Tau antibodies, Tau aggregation inhibitors, β -amyloid
 aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

31. Use of a binding molecule according to any of Claims 1 to 14 for manufacture of a medicament for treating a TDP-43 proteinopathy in a subject.
32. A binding molecule according to any of Claims 1 to 14, an immunoconjugate according to Claim 15, or a pharmaceutical composition according to Claim 16 for use in reducing the
5 level of misfolded TDP-43 in a subject.
33. A binding molecule according to any of Claims 1 to 14, an immunoconjugate according to Claim 15, or a pharmaceutical composition according to Claim 16 for use in retaining or increasing cognitive memory capacity, movement and language function or preventing and/or slowing decline of cognitive memory capacity, movement and language function in a subject.
- 10 34. A method of detecting misfolded TDP-43, comprising contacting a sample with the binding molecule according to any of Claims 1 to 14, optionally in which the sample is a brain sample, a cerebrospinal fluid sample, urine sample or a blood sample.