

CLAIMS

1. A TDP-43 binding molecule, which is an antibody or an antigen-binding fragment thereof, which binds misfolded aggregated TDP-43 and non-aggregated physiological TDP-43, and which binds to an epitope within amino acid residues 400-405, 183-188, 181-195,
5 199-213, 307-321, 352-366, 389-411, 397-411, 140-200, 203-213, 204-208, 204-211, 205-210, 316-323, 358-361, 400-406 or 400-412 of human TDP-43 (SEQ ID NO: 1) or to an equivalent epitope in non-human TDP-43.
2. A TDP-43 binding molecule according to Claim 1, which binds misfolded aggregated human TDP-43 and non-aggregated physiological human TDP-43.
- 10 3. A TDP-43 binding molecule according to Claim 1 or 2, which exhibits one or more, up to all of the following characteristics:
 - (a) inhibits the aggregation of TDP-43 protein or fragments thereof;
 - (b) blocks TDP-43 cell-to-cell propagation;
 - (c) disaggregates TDP-43 aggregates; and
 - 15 (d) blocks TDP-43 seeding.
4. A TDP-43 binding molecule according to Claim 1, 2 or 3, which reduces:
 - (a) TDP-43 pathology *in vivo*; and/or
 - (b) levels of aggregated TDP-43 and/or phosphorylated TDP-43 *in vivo*.
5. A TDP-43 binding molecule according to any preceding claim, which comprises:
 - 20 (a) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 11; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and VH-CDR3 comprising the amino acid sequence ES (Glu-Ser); VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 15; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 17; or
 - 25 (b) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 21; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 22; and VH-CDR3 comprising the amino acid sequence ES (Glu-Ser); VL-CDR1 comprising the amino acid sequence of

SEQ ID NO: 25; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 27; or

(c) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 31; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 32; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 33; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 35; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 36; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 37; or

(d) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 41; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 42; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 43; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 45; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 46; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 47; or

(e) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 61; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 62; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 63; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 65; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 66; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 67; or

(f) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 71; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 72; and VH-CDR3 comprising the amino acid sequence 73; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 75; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 77; or

(g) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 81; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 82; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 83; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 85; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 86; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(h) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 101; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 102; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 103; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 105; VL-CDR2 comprising the amino acid sequence of SEQ

ID NO: 106; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 107;
or

(i) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 121; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 122; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 123; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 125; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 127; or

(j) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 141; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 142; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 143; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 145; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 146; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 147; or

(k) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 151; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 152; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 153; VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 155; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 156; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 157.

6. A TDP-43 binding molecule according to any preceding claim, which comprises:

(a) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 10 or a Heavy Chain Variable Region (VH) having at least 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 10; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 14 or a Light Chain Variable Region (VL) having at least 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 14; or

(b) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 20 or a Heavy Chain Variable Region (VH) having at least 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 20; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 24 or a Light Chain Variable Region (VL) having at least 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 24; or

(c) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 30 or a Heavy Chain Variable Region (VH) having at least 92%, 93 %, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 30; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 34 or
 5 a Light Chain Variable Region (VL) having at least 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 34; or

(d) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 40 or a Heavy Chain Variable Region (VH) having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID
 10 NO: 40; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 44; or

(e) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 60 or a Heavy Chain Variable Region (VH) having at least 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 60; and a Light
 15 Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 64 or a Light Chain Variable Region (VL) having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 64; or

(f) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 70 or a Heavy Chain Variable Region (VH) having at least 93%, 94%, 95%, 96%, 97%,
 20 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 70; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 74 or a Light Chain Variable Region (VL) having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 74; or

(g) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 80 or a Heavy Chain Variable Region (VH) having at least 90%, 91%, 92%, 93%, 94%,
 25 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 80; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 84 or a Light Chain Variable Region (VL) having at least 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 84; or

(h) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID
 30 NO: 100 or a Heavy Chain Variable Region (VH) having at least 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 100;

and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 104 or a Light Chain Variable Region (VL) having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 104; or

(i) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 120 or a Heavy Chain Variable Region (VH) having at least 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 120; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 124 or a Light Chain Variable Region (VL) having at least 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 124; or

(j) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 140 or a Heavy Chain Variable Region (VH) having at least 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 140; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 144; or

(k) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 150 or a Heavy Chain Variable Region (VH) having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequence of SEQ ID NO: 150; and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 154 or a Light Chain Variable Region (VL) having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 154.

7. A TDP-43 binding molecule according to any preceding claim, which comprises:

(a) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 10 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 14; or

(b) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 20 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 24; or

(c) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 30 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 34; or

(d) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 40 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 44; or

- (e) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 60 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 64; or
 - (f) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 70 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 74; or
 - 5 (g) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 80 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 84; or
 - (h) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 100 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 104; or
 - 10 (i) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 120 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 124; or
 - (j) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 140 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 144; or
 - 15 (k) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 150 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 154.
8. A TDP-43 binding molecule according to any preceding claim, which comprises:
- 20 (a) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 21; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 22; and VH-CDR3 comprising the amino acid sequence ES (Glu-Ser); VL-CDR1 comprising the amino acid sequence of SEQ ID NO: 25; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 16; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 27;
 - 25 (b) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 20 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 24;
 - (c) VH-CDR1 comprising the amino acid sequence of SEQ ID NO: 81; VH-CDR2 comprising the amino acid sequence of SEQ ID NO: 82; and VH-CDR3 comprising the amino acid sequence of SEQ ID NO: 83; VL-CDR1 comprising the amino acid

sequence of SEQ ID NO: 85; VL-CDR2 comprising the amino acid sequence of SEQ ID NO: 86; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 87; and/or

(d) a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 80 and a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 84

5 9. A TDP-43 binding molecule according to any preceding claim, which is:

(a) a monoclonal antibody or an antigen-binding fragment thereof;

(b) a murine, a chimeric, a humanized or a human antibody or an antigen-binding fragment thereof; and/or

10 (c) an IgA, IgD, IgE, IgM, IgG1, IgG2, IgG2a, IgG2b, IgG3 or IgG4 antibody or antigen-binding fragment thereof.

10. A TDP-43 binding molecule according to any preceding claim for use in human or veterinary therapy and/or diagnosis, in which the TDP-43 binding molecule is preferably a diagnostic or a therapeutic tool.

15 11. A TDP-43 binding molecule according to any of Claims 1 to 9 for research use, in particular as an analytical tool or reference molecule.

12. A TDP-43 binding molecule according to any of Claims 1 to 9 for use in the prevention, alleviation, treatment and/or diagnosis of diseases, disorders and/or abnormalities associated with TDP-43, optionally for preventing, alleviating, treating and/or diagnosing a TDP-43 proteinopathy.

20 13. A TDP-43 binding molecule according to Claim 12, in which the disease, disorder and/or abnormality associated with TDP-43, or TDP-43 proteinopathy, is:

25 (a) Frontotemporal dementia (FTD, such as Sporadic or familial with or without motor-neuron disease (MND), with progranulin (GRN) mutation, with C9orf72 mutations, with TARDBP mutation, with valosine-containing protein (VCP) mutation, linked to chromosome 9p, corticobasal degeneration, frontotemporal lobar degeneration (FTLD) with ubiquitin-positive TDP-43 inclusions (FTLD-TDP), Argyrophilic grain disease, Pick's disease, semantic variant primary progressive aphasia (svPPA), behavioural variant FTD (bvFTD), Nonfluent Variant Primary Progressive Aphasia (nfvPPA) and the like), Amyotrophic lateral sclerosis (ALS, such as Sporadic ALS, with

- TARDBP mutation, with angiogenin (ANG) mutation), Alexander disease (AxD), limbic-predominant age-related TDP-43 encephalopathy (LATE), Chronic Traumatic Encephalopathy (CTE), Perry syndrome, Alzheimer's disease (AD, including sporadic and familial forms of AD), 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 Myopathies (Sporadic inclusion body myositis, Inclusion body myopathy with a mutation in the valosin-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), Traumatic Brain Injury (TBI), Dementia with Lewy Bodies (DLB) or Parkinson's disease (PD);
- (b) Frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), Chronic Traumatic Encephalopathy (CTE), or limbic-predominant age-related TDP-43 encephalopathy (LATE);
- (b) amyotrophic lateral sclerosis (ALS).
- (c) Alzheimer's disease (AD); or
- (d) Frontotemporal dementia (FTD).
14. A pharmaceutical composition comprising a TDP-43 binding molecule according to any of Claims 1 to 9 and a pharmaceutically acceptable carrier and/or excipient.
15. A nucleic acid molecule encoding a TDP-43 binding molecule according to any of Claims 1 to 9, optionally in which the nucleic acid molecule comprises a nucleotide sequence set forth as:
- (a) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 18 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 19; or
- (b) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 28 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 29; or
- (c) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 38 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 39; or

- (d) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 48 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 49; or
- (e) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 68 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 69; or
- 5 (f) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 78 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 79; or
- (g) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 88 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 89; or
- 10 (h) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 108 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 109 or
- (i) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 128 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 129; or
- (j) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 148 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 149; or
- 15 (k) a Heavy Chain Variable Region (VH) encoding sequence of SEQ ID NO: 158 and a Light Chain Variable Region (VL) encoding sequence of SEQ ID NO: 159.
- 16. A recombinant vector or expression vector comprising a nucleic acid according to Claim 15.
- 17. A host cell comprising a nucleic acid according to Claim 15 and/or a recombinant vector
20 or expression vector according to Claim 16.
- 18. A host cell that expresses a TDP-43 binding molecule according to any of Claims 1 to 9.
- 19. A cell-free expression system containing an expression vector according to Claim 16.
- 20. A method for producing a TDP-43 binding molecule, in particular an antibody or antigen-binding fragment thereof, comprising the steps of:
 - 25 (a) culturing the host cell according to Claim 17 or 18 or cell-free expression system according to Claim 19 under conditions suitable for producing the binding molecule, in particular the antibody or antigen-binding fragment thereof; and

(b) isolating the binding molecule, in particular the antibody or antigen-binding fragment thereof.

21. A method of quantifying TDP-43 in a sample obtained from a subject, the method comprising contacting the sample with a TDP-43 binding molecule according to any of

5 Claims 1 to 9 and comparing the TDP-43 levels in the sample to those in a control sample or samples.

22. A method for diagnosing a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy comprising performing a method according to Claim 21 in which higher levels of TDP-43 in the sample compared with a control level based on healthy subjects
10 are indicative of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy.

23. A method for diagnosing a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy comprising performing a method according to Claim 21 or 22 in which similar or higher levels of TDP-43 in the sample compared with a diseased control are
15 indicative of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy.

24. A method for classifying a disease, disorder and/or abnormality associated with TDP-43 or for classifying a TDP-43 proteinopathy comprising:

(a) performing a method according to Claim 22 and/or 23,

20 (b) optionally identifying mutations in the sample including but not limited to progranulin (GRN) mutation, C9orf72 mutations, TARDBP mutation, with valosine-containing protein (VCP) mutation, TARDBP mutation, angiogenin (ANG) mutation), mutation in the valosin-containing protein (VCP), mutation in the myotilin (MYOT) gene or mutations in the gene coding for desmin (DES), and

25 (c) classifying the disease, disorder and/or abnormality associated with TDP-43, or TDP-43 proteinopathy.

25. A method for monitoring a disease, disorder and/or abnormality associated with TDP-43 or for monitoring a TDP-43 proteinopathy at two or more time points using samples from a subject, the method comprising contacting the samples with a TDP-43 binding molecule
30 according to any of Claims 1 to 9 in which:

(a) higher levels of TDP-43 in the later sample compared with one or more earlier samples are indicative of progression of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy; or

5 (b) lower levels of TDP-43 in the later sample compared with one or more earlier samples are indicative of regression of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy.

26. A method for monitoring treatment of a disease, disorder and/or abnormality associated with TDP-43 or for monitoring treatment of a TDP-43 proteinopathy at two or more time points using samples from a subject treated with a therapy for treating a disease, disorder
10 and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy, the method comprising contacting the samples with a TDP-43 binding molecule according to any of Claims 1 to 9 in which lower levels of TDP-43 in the later sample compared with one or more earlier samples are indicative of successful treatment of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy.

15 27. A method according to Claim 25 or 26 in which a first time point is prior to treatment with the therapy and a second time point is following treatment with the therapy.

28. A method for selecting a therapy for treatment of a disease, disorder and/or abnormality associated with TDP-43 or selecting a therapy for treatment of a TDP-43 proteinopathy, the method comprising contacting samples taken before and after treatment with the therapy with
20 a TDP-43 binding molecule according to any of Claims 1 to 9 in which lower levels of TDP-43 in the sample taken after treatment compared with the sample taken before treatment are indicative of successful treatment of a disease, disorder and/or abnormality associated with TDP-43 or a TDP-43 proteinopathy and thus the therapy is selected for treatment.

29. A method according to Claim 28 in which the therapy comprises a TDP-43 binding
25 molecule according to any of Claims 1 to 9 or a pharmaceutical composition according to Claim 14.

30. A method according to any of Claims 21 to 29 in which the sample comprises a blood, CSF, ISF or urine sample.

31. A method according to any of Claims 21 to 30 in which the disease, disorder and/or
30 abnormality associated with TDP-43, or TDP-43 proteinopathy, is:

(a) Frontotemporal dementia (FTD, such as Sporadic or familial with or without motor-neuron disease (MND), with progranulin (GRN) mutation, with C9orf72 mutations, with TARDBP mutation, with valosine-containing protein (VCP) mutation, linked to chromosome 9p, corticobasal degeneration, frontotemporal lobar degeneration (FTLD) with ubiquitin-positive TDP-43 inclusions (FTLD-TDP), Argyrophilic grain disease, Pick's disease, semantic variant primary progressive aphasia (svPPA), behavioural variant FTD (bvFTD), Nonfluent Variant Primary Progressive Aphasia (nfvPPA) and the like), Amyotrophic lateral sclerosis (ALS, such as Sporadic ALS, with TARDBP mutation, with angiogenin (ANG) mutation), Alexander disease (AxD), limbic-predominant age-related TDP-43 encephalopathy (LATE), Chronic Traumatic Encephalopathy (CTE), Perry syndrome, Alzheimer's disease (AD, including sporadic and familial forms of AD), 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 Myopathies (Sporadic inclusion body myositis, Inclusion body myopathy with a mutation in the valosin-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), Traumatic Brain Injury (TBI), Dementia with Lewy Bodies (DLB) or Parkinson's disease (PD);

(b) Frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), Chronic Traumatic Encephalopathy (CTE), or limbic-predominant age-related TDP-43 encephalopathy (LATE);

(c) amyotrophic lateral sclerosis (ALS);

(d) Alzheimer's disease (AD); or

(e) Frontotemporal dementia (FTD).

32. A kit for diagnosis of a disease, disorder and/or abnormality associated with TDP-43, or a TDP-43 proteinopathy, or for use in a method according to any of Claims 21 to 31 comprising a TDP-43 binding molecule according to any of Claims 1 to 9.