

MISFOLDED TDP-43 BINDING MOLECULES

FIELD OF THE INVENTION

The present invention is in the field of transactive response DNA binding protein with a molecular weight of 43 kDa (TARDB or also TDP-43). The invention relates to TDP-43 specific binding molecules, in particular to anti-TDP-43 antibodies or an antigen-binding fragment or a derivative thereof and uses thereof. The present invention provides means and methods to diagnose, prevent, alleviate and/or treat a disorder and/or abnormality associated with misfolded TDP-43 including but not limited to frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD, sporadic and familial), and/or Parkinson's disease (PD). The present invention provides modified conformation-specific antigenic peptides and peptide fragments derived from the TDP-43 protein and the antibodies obtainable by said peptides or fragments for use in the diagnosis, prevention, alleviation and/or treatment of TDP-43-related disorders and/or abnormalities.

BACKGROUND

Age-associated brain disorders characterized by pathological aggregation of proteins in the central nervous system (CNS) (proteinopathies) and peripheral organs represent one of the leading causes of disability and mortality in the world. The best characterized protein that forms extracellular aggregates is amyloid beta in Alzheimer's disease and related disorders. Other disease-associated, aggregation-prone proteins leading to neurodegeneration include but are not limited to tau, alpha-synuclein (aSyn), huntingtin, fused in sarcoma (FUS), dipeptide repeat proteins (DPRs) produced by unconventional translation of the C9orf72 repeat expansion, superoxide dismutase 1 (SOD1), and TDP-43. Diseases involving TDP-43 aggregates are generally listed as TDP-43 proteinopathies including, but not limited to, ALS and FTD.

I. TDP-43 introduction

Transactive response (TAR) DNA binding protein 43 kDa (TDP-43) is a 414-amino acid protein encoded by the TARDBP gene on chromosome 1p36.2 (ALS10). TARDBP is comprised of six exons (exon 1 is non-coding; exons 2-6 are protein-coding). TDP-43 belongs to the family of heterogeneous ribonucleoprotein (hnRNP) RNA binding proteins (Wang et al., Trends in Molecular Medicine Vol.14 No.11, 2008, 479-485; Lagier-Tourenne et al., Human Molecular Genetics, 2010, Vol. 19, Review Issue 1 R46-R64). TDP-43 contains five functional domains (Figure 1 in Warraich et al., The International Journal of Biochemistry & Cell Biology 42 (2010) 1606–1609): two RNA recognition motifs (RRM1

and RRM2), which have two highly conserved hexameric ribonucleoprotein 2 (RNP2) and octameric ribonucleoprotein 1 (RNP1) regions, a nuclear export signal (NES) and a nuclear localization signal (NLS) enabling it to shuttle between the nucleus and the cytoplasm transporting bound mRNA, and a glycine rich domain at the C-terminal, which mediates protein-protein interactions. TDP-43 is involved in multiple aspects of RNA processing, including transcription, splicing, transport, and stabilization (Buratti and Baralle, *FEBS Journal* 277 (2010) 2268–2281). It is a highly conserved, ubiquitously expressed protein with a tightly autoregulated expression level that shuttles continuously between the nucleus and cytoplasm, but is predominantly localized to the nucleus. In 2006, TDP-43 was identified as the protein that accumulates in the vast majority of cases of frontotemporal lobar degeneration (FTLD) with tau-negative, ubiquitin-positive inclusions (then referred to as FTLD-TDP), and in most cases of amyotrophic lateral sclerosis (ALS) (Arai et al., *Biochemical and Biophysical Research Communications* 351 (2006) 602–611; Neumann et al., *Science* 314, (2006), 130-133).

Thirty-eight negative-dominant mutations in TDP-43 have been identified in sporadic and familial ALS patients as well as in patients with inherited FTD mainly located in the glycine rich domain (Figure 1; Lagier-Tourenne and Cleveland, *Cell* 136, 2009, 1001-1004). TDP-43 is inherently aggregation-prone, as shown by sedimentation assays, and this propensity is further increased by some of the ALS-associated TARDBP mutations (Ticozzi et al., *CNS Neurol. Disord. Drug Targets*. 2010, 9(3), 285-296.) connecting TDP-43 aggregation with clinical disease manifestation.

II. TDP-43 in neurodegeneration

TDP-43 aggregates have been identified in a growing list of neurodegenerative conditions (Lagier-Tourenne et al., *Human Molecular Genetics*, 2010, Vol. 19, Review Issue 1 R46-R64), including but not limited to: Frontotemporal dementia (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 (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 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)).

Aggregated TDP-43 from patient brains shows a number of abnormal modifications, including hyperphosphorylation, ubiquitination, acetylation and C-terminal fragments through proteolytic cleavage (Arai et al., Biochemical and Biophysical Research Communications 351 (2006) 602–611; Neumann et al., Science 314, (2006), 130-133; Neumann et al., Acta Neuropathol. (2009) 117: 137–149; Hasegawa et al., (2008) Annals of Neurology Vol 64 No 1, 60–70; Cohen et al., Nat Commun. 6: 5845, 2015). Another characteristic feature of TDP-43 pathology is redistribution and accumulation of TDP-43 from nucleus to cytoplasm. The hallmark lesions of FTLN-TDP are neuronal and glial cytoplasmic inclusions (NCI and GCI, respectively) and dystrophic neurites (DN) that are immunoreactive for TDP-43, as well as ubiquitin and p62, but negative for other neurodegenerative disease-related proteins. Differences in inclusion morphology and tissue distribution thereof are associated with specific mutations and/or clinical representations. Four types of TDP-43 pathology are described so far by histological classification (Mackenzie and Neumann, J. Neurochem. (2016) 138 (Suppl. 1), 54-70). FTLN-TDP type A cases are characterized by abundant short DN (dystrophic neuritis) and compact oval or crescentic NCI (neuronal cytoplasmic inclusions), predominantly in layer II of the neocortex (Fig. 2f in Mackenzie et al., 2016 J. Neurochem. 138 (Suppl. 1), 54–70). Cases with this pathology usually present clinically with either behavioral-variant frontotemporal dementia (bvFTD) or nonfluent/agrammatic variants of Primary Progressive Aphasia (nfvPPA) and are associated with progranulin (GRN) mutations. Type B cases show moderate numbers of compact or granular NCI in both superficial and deep cortical layers with relatively few DN and NII (neuronal intranuclear inclusions; Fig. 2g in Mackenzie et al., 2016 J. Neurochem. 138 (Suppl. 1), 54–70). Most cases with co-appearance of FTD and ALS symptoms are found to have FTLN-TDP type B pathology. Type C cases have an abundance of long tortuous neurites, predominantly in the superficial cortical laminae, with few or no NCI (Fig. 2j in Mackenzie et al., 2016 J. Neurochem. 138 (Suppl. 1), 54–70). This pathology is particularly found in cases presenting with semantic variant of primary progressive aphasia (svPPA). FTLN-TDP type D displays with abundant lentiform neuronal intranuclear inclusions (NII) and short DN in the neocortex with only rare NCI (Fig. 2k in Mackenzie et al., 2016 J. Neurochem. 138 (Suppl. 1), 54–70). This pattern of pathology is only found in cases with VCP in association with inclusion body myositis.

III. TDP-43 in FTD

Frontotemporal dementia (FTD) is a clinical term that covers a wide spectrum of disorders based on the degeneration of frontal and temporal lobes – a pathological feature termed frontotemporal lobar degeneration (FTLD). FTD is the second most abundant cause of early degenerative dementias in the age group below 65 years (Le Ber, Revue Neurologique 169 (2013) 811-819). FTD is presented by several syndromes including bvFTD which is characterized by changes in personality and behavior; semantic dementia (SD) and progressive nonfluent aphasia (PNFA) characterized by changes in the language function; corticobasal syndrome (CBS), progressive supranuclear palsy syndrome and motor

neuron disease (FTD-MND) characterized by movement dysfunction. Diagnosis of these syndromes is complicated and final conclusion can only be achieved through postmortem tissue analysis based on immunohistochemistry to detect aggregated protein and description of the affected brain regions. In terms of pathological, proteinaceous inclusions, about 45% of cases show pathological accumulation of misfolded Tau, 45% of cases have pathological TDP-43 and a smaller subgroup has aggregates of FUS and other proteins.

IV. TDP-43 in ALS

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the premature loss of upper and lower motor neurons. The progression of ALS is marked by fatal paralysis and respiratory failure with a disease course from diagnosis to death of 1 to 5 years. In most cases of sporadic ALS, the neuropathology is characterized by abnormal cytoplasmic accumulations of TDP-43 in neurons and glia of the primary motor cortex, brainstem motor nuclei, spinal cord and the associated white matter tracts. ALS with dementia involves accumulation of TDP-43 in extramotor neocortex and hippocampus. The role of phosphorylation of TDP-43 in ALS patients has been explored with the help of antibodies that specifically bind to phosphorylated TDP-43 in nuclear and cytoplasmic inclusions with amino acids S379, S403, S404, S409, S410 as the major sites of phosphorylation of TDP-43 (Hasegawa et al., *Ann Neurol* 2008; 64: 60–70; Neumann et al., *Acta Neuropathol* (2009) 117: 137–149).

V. TDP-43 in AD and other diseases

TDP-43 pathology occurs in up to 57% of brains of patients with Alzheimer's disease (Josephs KA et al., *Acta Neuropathol.* 2014; 127(6): 811–824; Josephs KA et al., *Acta Neuropathol.* 2014; 127(3): 441–450; McAleese et al., *Brain Pathol.* 2017 Jul; 27(4): 472–479). TDP-43 aggregation is associated with patient's age and correlates with cognitive decline, memory loss and medial temporal atrophy in AD. TDP-43 positive patients are 10-fold more likely to be cognitively impaired at death compared to TDP-43 negative subjects. It appears that in AD TDP-43 represents a secondary or independent pathology that shares overlapping brain distribution with amyloid beta and tau pathologies in the medial temporal lobe. Pathologic TDP-43 follows a stereotypical pattern of progressive deposition that has been described by the so-called TDP-43 in AD (TAD) staging scheme: TDP-43 first deposits in the amygdala (stage I) followed by hippocampus, limbic, temporal, and finally the frontostriatum (stage V) (Josephs KA et al., *Acta Neuropathol.* 2014;127(6): 811–824; Josephs KA et al., *Acta Neuropathol.* 2014; 127(3): 441–450).

VI. TDP-43 spreading

Recent evidence supports the notion of protein propagation in neuronal tissue for amyloid-beta, tau, alpha-synuclein and TDP-43 by a prion-like mechanism (Hasegawa et al., 2017), although the starting

points and the topographical spreading patterns are fundamentally different for the four proteins (Brettschneider J et al., *Nature Rev. Neuroscience*, 2015, 109). Although ALS onset and first symptoms vary significantly between patients, the common feature of disease progression is spreading of pathology from an initial focal area to most neurons. The continuous worsening of symptoms might be explained by this progressive spreading of TDP-43 pathology. TDP-43 pathology in an ALS patient's brain appears to be spreading in a four-stage process and it is believed that propagation occurs transynaptically via corticofugal axonal projections using anterograde axonal transport (Brettschneider et al., *Ann Neurol.* 2013 July; 74(1): 20–38.).

Some recent reports address TDP-43 spreading at molecular level in various in vitro models. Insoluble TDP-43 preparations from patient brain are able to induce intracellular aggregate formation in vitro (Nonaka et al., *Cell Reports* 4 (2013), 124–134; Feiler et al., 2015; Porta et al., *Nat. Comm.*, 2018). Also, it has been shown recently that patient-derived, pathological TDP-43 can lead to widespread deposition of endogenous TDP-43 following inoculation into transgenic and wildtype mice (Porta et al., *Nat. Comm.*, 2018). Further it has been shown that intracellular TDP-43 aggregates are released in association with exosome prior to spreading to the next cell (Nonaka et al., *Cell Reports* 4 (2013, 124–134)). Similarly, adenovirus-transduced TDP-43 expression lead to cytoplasmic aggregates which were phosphorylated, ubiquitinated and most importantly acted as seeds initiating cell to cell spreading (Ishii et al., *PLoS ONE* 12(6): e0179375, 2017).

VII. Prevention and Treatment of TDP-43 proteinopathies

TDP-43 aggregation and spreading of pathology are major hallmarks of ALS and FTD – fatal diseases for which currently no cure is available. Mutations in TDP-43 are associated with familial cases of ALS and FTD providing causative link between TDP-43 misfolding and disease progression. Therefore there is a need for a prevention and treatment therapy which aims at preventing and/or slowing down the development and propagation of TDP-43 aggregates, in diseases with clinical symptoms associated with TDP-43 proteinopathies.

Without wishing to be bound by any hypothesis, the present invention was developed based on the assumption that modified conformation-specific antigenic peptides and peptide fragments derived from TDP-43 protein or the whole TDP-43 protein and the antibodies obtainable or obtained by said peptides or fragments or the whole TDP-43 protein block TDP-43 cell-to-cell spreading, and/or disaggregate TDP-43 aggregates and/or inhibit the aggregation of TDP-43 protein or fragments thereof. The binding molecules of the invention, in particular polypeptides, more particularly antibodies or antigen-binding fragments thereof, specifically bind to misfolded TDP-43, particularly to cytoplasmic and extracellular misfolded TDP-43. In one embodiment, the binding molecules of the invention, in particular

polypeptides, more particularly antibodies or antigen-binding fragments thereof, specifically bind to cytoplasmic misfolded TDP-43.

In one embodiment, the binding molecules of the invention, in particular polypeptides, more particularly antibodies or antigen-binding fragments thereof, specifically bind to extracellular misfolded TDP-43.

VIII. Diagnostics of TDP-43 proteinopathies

The diagnosis of FTD based on clinical manifestations is insufficient since the clinical representation can overlap with other diseases in particular in the earlier stages. Therefore, the development of sensitive and specific biomarkers allowing the differentiation between types of pathology within the FTD spectrum is an urgent task. Such tools will allow better detecting and understanding the specific type of pathology causing neurodegeneration. Eventually this will lead to the development of diagnostic biomarkers enabling more efficient and precise patient selection for longitudinal monitoring in clinical studies, supporting the development of novel therapeutics for TDP-43 proteinopathies.

A number of approaches aim at development of biochemical biomarkers to distinguish different types of FTD pathology. Development of antibodies against different conformations of TDP-43 may permit generating more sensitive and specific diagnostic tools. In parallel to biochemical biomarkers the development of imaging biomarkers may enable early and specific detection of the pathology in TDP-43 proteinopathies. The ability to image TDP-43 deposition in the brain may be a substantial achievement for diagnosis and drug development for TDP-43 proteinopathies. Using cell permeable antibody fragments will enable such detection.

The earliest event in neurodegenerative diseases based on misfolding of different proteins is the acquisition of an alternative conformation that renders the protein toxic. Furthermore, this misfolded conformation can self-propagate by recruiting the endogenous, normal protein into the misfolded conformation as mechanistic basis for the observed spread through affected tissue. Therefore, targeting the misfolded over the normal conformation of a protein target offers a very precise therapeutic and diagnostic approach.

To develop antibodies against different conformational states of a given protein supramolecular antigenic constructs were designed in which the conformation of the presented antigen was controlled to raise conformational-specific antibodies against a given target in a specific conformational state (WO2012/055933 and WO2012/020124). Conformational-specific antibodies offer many advantages since they can discriminate between the disease-associated and the benign, endogenous conformation of these proteins. This approach offers many advantages in the therapeutic application since such

antibodies are less likely to be adsorbed by the normal conformation of proteins while targeting the misfolded, disease associated isoform thereof. Similar to this in diagnostic application such antibodies only recognize the structural state of a protein and therefore detect the entity that most likely correlates with disease which is paramount for the development of the most sensitive and specific diagnostics.

IX. Prior art

Patent application WO 2008/151055 discloses methods and materials for using the levels of TDP-43 polypeptides and/or TDP-43 polypeptide cleavage products (e.g. 25 kD and 35 kD TDP-43 polypeptide cleavage products) in a biological fluid to determine whether or not a mammal has a neurodegenerative disease.

Patent application WO 2013/061163 discloses TDP-43 specific binding molecules including polypeptides such as human antibodies as well as fragments, derivatives and variants thereof.

SUMMARY OF THE INVENTION

The invention relates to binding molecules, in particular antibodies or antigen-binding fragments thereof, which specifically recognize misfolded TDP-43. In a preferred embodiment of the invention, the binding molecules, in particular antibodies or antigen-binding fragments thereof, do not bind physiologically functional TDP-43. Within the invention, misfolded TDP-43 includes misfolded monomeric and/or misfolded oligomeric and/or misfolded aggregated and/or post-translationally modified and/or misfolded truncated TDP-43. Thus, the invention provides binding molecules, in particular antibodies or antigen-binding fragments thereof, which specifically recognize misfolded TDP-43, wherein the misfolded TDP-43 is oligomeric and/or aggregated and/or post translationally modified TDP-43, wherein the binding molecules, in particular antibodies or antigen-binding fragments thereof, do not bind physiologically functional TDP-43.

The misfolded TDP-43 specific binding molecules of the invention, in particular antibodies or antigen-binding fragments thereof, block TDP-43 cell-to-cell spreading, and/or disaggregate TDP-43 aggregates and/or inhibit the aggregation of TDP-43 protein or fragments thereof.

In particular, the misfolded TDP-43 specific binding molecules of the invention, in particular antibodies or antigen-binding fragments thereof, block TDP-43 cell-to-cell spreading.

In one embodiment, the misfolded TDP-43 specific binding molecules of the invention, in particular antibodies or antigen-binding fragments thereof disaggregate TDP-43 aggregates.

In one embodiment, the misfolded TDP-43 specific binding molecules of the invention, in particular antibodies or antigen-binding fragments thereof inhibit the aggregation of TDP-43 protein or fragments thereof.

In the present invention, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically recognize misfolded TDP-43. Binding molecules of the invention include polypeptides and/or antibodies and/or antigen-binding fragments thereof specific to/for the TDP-43 protein. "Specifically recognize misfolded TDP-43" means that the binding molecules of the invention specifically, generally, and collectively, bind to misfolded TDP-43, in particular an epitope within TDP-43, in particular an epitope exposed/accessible in one or more pathological conformation(s) of TDP-43 protein, with greater affinity than for other epitopes, in particular epitopes found in physiologically functional TDP-43. The binding molecules of the invention, in particular polypeptides, more particularly antibodies or antigen-binding fragments thereof, that specifically bind to misfolded TDP-43, specifically bind to misfolded monomeric and/or misfolded oligomeric and/or misfolded aggregated and/or misfolded post translationally modified TDP-43. The binding molecules of the invention, in particular polypeptides, more particularly antibodies or antigen-binding fragments thereof, specifically bind to misfolded TDP-43, particularly to cytoplasmic misfolded TDP-43, particularly to extracellular misfolded TDP-43, particularly to cytoplasmic and extracellular misfolded TDP-43. According to one embodiment of the invention, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded TDP-43, including misfolded monomeric, oligomeric, aggregated and post-translationally modified TDP-43, all of which can comprise full-length and/or truncated TDP-43. In one embodiment, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded monomeric TDP-43. In one embodiment, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded oligomeric TDP-43. In one embodiment, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded aggregated TDP-43. In one embodiment, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded post-translationally modified TDP-43. In a preferred embodiment, full-length human TDP-43 comprises, preferably has, the sequence of SEQ ID NO:1. In another preferred embodiment of the invention, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to an epitope within full-length and/or truncated TDP-43, wherein the epitope consists of residues 215-222 (SEQ ID NO:5) of the full-length human TDP-43 having the sequence of SEQ ID NO:1. Accordingly, the binding molecules, in particular antibodies or antigen-binding fragments thereof, preferably specifically bind to a peptide comprising, preferably consisting of, residues 215-222 (SEQ ID NO:5) of the full-length human TDP-43 having the sequence of SEQ ID NO:1.

Within the present invention, the binding molecules, in particular antibodies or antigen-binding fragments thereof, specifically bind to misfolded extracellular TDP-43. In some embodiments, the binding molecules, in particular antibodies or antigen-binding fragments thereof, of the invention also specifically bind to misfolded cytoplasmic TDP-43.

In some embodiments of the invention, the antibody is a monoclonal antibody. In some embodiments, the antibody is a murine, murinized, human, humanized, or chimeric antibody.

In some embodiments of the invention, the antibody, or antigen-binding fragment or derivative thereof having an immunological binding characteristic of an antibody described herein, is an antibody having the variable regions VL and/or VH of the amino acid sequences 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, 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. In the above sequences, SEQ ID NOs: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 and 160 comprise a tail sequence as part of the VH/VL sequence. The part of these sequences corresponding to the tail sequence is provided in the sequence listing, in particular the tail sequence comprised in SEQ ID NO:10 is provided in SEQ ID NO:18, the tail sequence comprised in SEQ ID NO:20 is provided in SEQ ID NO:28 and so forth. The skilled person is aware that a tail sequence C-terminal of FR4 in the VH/VL sequences is sometimes considered as part of the VH or VL sequence, respectively, whereas it is sometimes not considered to be a part thereof. In the present invention, both versions are provided for some of the antibodies, whereby the VH/VL sequence without tail is preferred. The following Table 1 provides an overview of the provided VH and VL sequences of the antibodies of the invention:

Table 1

Antibody name	Hybridoma clone	VL with tail	VL without tail	VH with tail	VH without tail
ACI-7062-401A2-Ab2	401A2C6	10	230	20	232
ACI-7062-412A7-Ab1	412A7B7	30	234	40	236
ACI-7062-406E3-Ab1	406E3D5	50	238	60	240
ACI-7062-404D6-Ab2	404D6E11	70	242	80	244
ACI-7062-410H3-Ab1	410H3B9	90	246	100	248

ACI-7062-414A5- Ab1	414A5D2	110	250	120	252
ACI-7062-412E12- Ab1	412E12A2	130	254	140	256
ACI-7062-416A11- Ab1	416A11B3	150	258	160	260
ACI-7062-406E3- Ab2	406E3G10		170		180
ACI-7062-415C4- Ab1	415C4C6		190		200
ACI-7062-415H10- Ab2	415H10B7		210		220

In some embodiments, 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;
- 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;
- 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;
- 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;
- 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;
- 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;
 - 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;
 - 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;
 - 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;
 - 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;
 - 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;
 - 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;
 - 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;

- 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;
- 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;
- 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;
- 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;
- 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; 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.

In some embodiments, the antibody comprises:

- a) 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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 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.

In some embodiments, 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.

In some embodiments, the antibody comprises:

- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 16 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 12; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 14; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 16; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 36 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 32; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 34; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 36; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 56 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 52; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 54; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 56; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 76 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 72; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence

identity to SEQ ID NO: 74; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 76; or

- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 96 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 92; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 94; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 96; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 116 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 112; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 114; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 116; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 136 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 132; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 134; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 136;
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 156 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 152; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 154; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 156;
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 176 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 172; a

VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 174; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 176;

- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 196 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 192; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 194; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 196; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 216 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 212; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 214; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 216.

In some embodiments, the antibody comprises:

- a) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 22; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 24; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 26; or
- b) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 42; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 44; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 46; or
- c) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 62; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 64; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 66; or

- d) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 82; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 84; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 86; or
- e) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 102; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 104; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 106; or
- f) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 122; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 124; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 126; or
- g) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 142; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 144; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 146;

- h) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 162; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 164; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 166;
- i) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 182; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 184; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 186;
- j) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 202; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 204; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 206; or
- k) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 222; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 224; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 226.

In some embodiments, the antibody comprises:

- 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; or

- 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; or
- 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; or
- 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; or
- 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; or
- 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; or
- 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;
or
- 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.

In some embodiments, the antibody comprises:

- a) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 12; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 14; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 16; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 22; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 24; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 26; or

- [illegible]

- sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 182; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 184; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 186;
- j) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 192; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 194; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 196; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 202; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 204; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 206; or
- k) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 212; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 214; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 216; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 222; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 224; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 226.

In some particular embodiments, 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;
- 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;
- 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;

- d) 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;
- e) 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;
- f) 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;
- g) 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;
- h) 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;
- i) 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;
- j) 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;
- k) 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;

- l) 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;
- m) 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;
- n) 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;
- o) 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; or
- p) 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.

In some particular embodiments, the antibody comprises:

- a) 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 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 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 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;
- e) 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;
- f) 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;
- g) 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;
- h) 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;
- i) 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;
- j) 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;

- k) 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;
- l) 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;
- m) 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;
- n) 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;
- o) 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
- p) 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.

In some particular embodiments, 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: 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;
- e) 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;
- f) 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;
- g) 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;
 - h) 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;
 - i) 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;
 - j) 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;
 - k) 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;

- l) 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;
- m) 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;
- n) 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;
- o) 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
- p) 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.

In some particular embodiments, the antibody comprises:

- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 16 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 12; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 14; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 16; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 36 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 32; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 34; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 36; or
- 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; and VL-CDR3 comprising the amino acid sequence of SEQ ID NO: 56 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 52; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 54; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 56; or
- d) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 92; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 94; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 96; or

- e) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 112; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 114; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 116; or
- f) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 132; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 134; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 136;
- g) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 152; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 154; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 156;
- h) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 172; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 174; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 176; or
- i) 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 or a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 192; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95%

sequence identity to SEQ ID NO: 194; and a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 196.

In some particular embodiments, the antibody comprises:

- a) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 22; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 24; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 26; or
- b) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 42; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 44; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 46; or
- c) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 62; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 64; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 66; or
- d) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 102; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 104; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 106; or
- e) 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 or a VH-CDR1 comprising an amino acid

sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 122; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 124; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 126; or

- f) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 142; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 144; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 146;
- g) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 162; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 164; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 166;
- h) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 182; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 184; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 186; or
- i) 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 or a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 202; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 204; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 206.

In some particular embodiments, the antibody comprises:

- 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; or
- 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; or
- 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; or
- d) 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; or
- e) 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; or
- f) 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;

- g) 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;
- h) 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;
or
- i) 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.

In some particular embodiments, the antibody comprises:

- a) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 12; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 14; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 16; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 22; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 24; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 26; or
- b) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 32; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 34; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 36; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 42; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 44; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 46.

NO: 44; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 46; or

- c) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 52; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 54; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 56; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 62; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 64; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 66; or
- d) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 92; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 94; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 96; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 102; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 104; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 106; or
- e) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 112; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 114; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 116; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 122; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 124; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 126; or
- f) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 132; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 134; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 136; a VH-CDR1 comprising an amino acid

sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 142; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 144; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 146;

- g) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 152; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 154; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 156; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 162; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 164; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 166;
- h) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 172; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 174; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 176; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 182; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 184; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 186; or
- i) a VL-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 192; a VL-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 194; a VL-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 196; a VH-CDR1 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 202; a VH-CDR2 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 204; and a VH-CDR3 comprising an amino acid sequence having at least 80%, 90% or 95% sequence identity to SEQ ID NO: 206.

In certain embodiments, a binding molecule or an antibody provided herein 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 $\leq 0.001\text{ nM}$ (e.g. 10^{-8} M or less, e.g. from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M), in particular with respect to binding

misfolded TDP-43, in particular misfolded monomeric TDP-43, misfolded aggregated TDP-43 and/or misfolded oligomeric TDP-43.

In one embodiment, K_d is measured using surface plasmon resonance assays using a BIACORE®-2000 or a BIACORE®-3000 (BIAcore, Inc., Piscataway, NJ) at 25°C with immobilized antigen CM5 chips at ~10 response units (RU). Briefly, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 µg/ml (0.2 µM) before injection at a flow rate of 5 µl/minute to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of antibody (0.58 nM to 200 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PEST) at 25°C at a flow rate of approximately 25 µl/min. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one Langmuir binding model (BIACORE® T100 Evaluation Software) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (K_d) is calculated as the ratio k_{off}/k_{on} . See, e.g., Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds $10^6 \text{ M}^{-1} \text{ s}^{-1}$ by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25°C of a 20 nM anti-antigen antibody in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophotometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

In some embodiments, an antibody, particularly an isolated antibody of the invention as described herein that binds human TDP-43 is provided, wherein the antibody binds each of misfolded monomeric TDP-43, misfolded aggregated TDP-43 and misfolded oligomeric TDP-43 with a K_D of less than 100 nM, less than 10 nM, less than 1 nM, less than 200 pM, less than 100 pM, or less than 10 pM. Preferably, the antibody of the invention binds each of misfolded monomeric TDP-43, misfolded aggregated TDP-43, misfolded oligomeric TDP-43, wherein the TDP-43 is post-translationally modified, e.g. phosphorylated TDP-43, with a K_D of less than 100 nM, less than 10 nM, less than 1 nM, less than 200 pM, less than 100 pM, or less than 10 pM.

The invention also relates to compositions comprising a binding molecule, particularly an antibody of the invention (including TDP-43-binding antibody fragments and derivatives) as described herein or TDP-43 agonists and cognate molecules, or alternately, antagonists of the same and to immunotherapeutic and immunodiagnostic methods using such compositions in the prevention,

diagnosis or treatment of a TDP-43 proteinopathy, wherein an effective amount of the composition is administered to a patient in need thereof.

In some embodiments, the invention encompasses molecules, particularly antibodies of the invention as described herein that specifically bind TDP-43 and the use of these molecules to diagnose, prevent, alleviate or treat 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). The methods and compositions disclosed herein have applications in diagnosing, preventing, alleviating or treating a disorder or abnormality associated with TDP-43 aggregates including but not limited to frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS).

In another embodiment, a binding molecule, particularly an antibody of the invention as described herein specific for TDP-43 is contacted with a sample to detect, diagnose or monitor a disorder or abnormality associated with TDP-43 aggregates selected from Frontotemporal dementia (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 (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 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)).

In one embodiment, the invention encompasses molecules, particularly antibodies of the invention as described herein that specifically bind TDP-43 and the use of these molecules, particularly of these antibodies to detect the presence of TDP-43 in a sample. Accordingly, TDP-43 binding molecules of the invention, such as, anti-TDP43 antibodies as described herein, can be used to screen human blood, CSF, and urine for the presence of TDP-43 in samples, for example, by using ELISA-based or surface adapted assay. The methods and compositions of the invention also have applications in diagnosing presymptomatic disease and in monitoring disease progression and therapeutic efficacy. According to some embodiments, an antibody specific for TDP-43 (e.g., a full-length antibody or a TDP-43 binding fragment or derivative of an antibody) is contacted with a sample (e.g., blood, cerebrospinal fluid, or brain tissue) to detect, diagnose or monitor Frontotemporal dementia (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 (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 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)).

In additional embodiments, the invention provides methods for preventing, alleviating or treating a disorder or abnormality associated with TDP-43 aggregates. According to one embodiment, the methods of the invention comprise administering an effective concentration of a binding molecule, particularly an antibody of the invention specific for TDP-43 (e.g., a full-length antibody or a TDP-43 binding fragment or derivative of an antibody) as described herein to a subject. In an additional embodiment, the invention provides a method for preventing, alleviating or treating a TDP-43 proteinopathies. According to some embodiments, a binding molecule, particularly an antibody of the invention as described herein specific for TDP-43 is administered to treat, alleviate or prevent frontotemporal degeneration (FTD) or amyotrophic lateral sclerosis (ALS). In another embodiment, a binding molecule, particularly an antibody of the invention as described herein specific for TDP-43 is administered to prevent, alleviate or treat a neurodegenerative disease selected from frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD, sporadic and familial), and Parkinson's disease (PD).

In another embodiment, a binding molecule, particularly an antibody of the invention as described herein specific for TDP-43 is administered to prevent, alleviate or treat a disease selected from: Frontotemporal dementia (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 (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 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)).

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

X. DEFINITIONS

An “antigen binding molecule,” as used herein, is any molecule that can specifically or selectively bind to an antigen. A binding molecule may include or be an antibody or a fragment thereof. An anti-misfolded TDP-43 binding molecule is a molecule that binds to the misfolded TDP-43 protein, such as an anti-TDP-43 antibody or fragment thereof, at a specific recognition site, epitope. That is, antigen-binding molecules of the invention bind to an epitope within the amino acid sequence of SEQ ID NO: 1, preferably within amino acids 215-222 thereof. Other anti-misfolded TDP-43 binding molecules may also include multivalent molecules, multi-specific molecules (e.g., diabodies), fusion molecules, aptamers, avimers, or other naturally occurring or recombinantly created molecules. Illustrative antigen-binding molecules useful in the present invention include antibody-like molecules. An antibody-like molecule is a molecule that can exhibit functions by binding to a target molecule (See, e.g., Current Opinion in Biotechnology 2006, 17:653-658; Current Opinion in Biotechnology 2007, 18:1-10; Current Opinion in Structural Biology 1997, 7:463-469; Protein Science 2006, 15:14-27), and includes, for example, DARPs (WO 2002/020565), Affibody (WO 1995/001937), Avimer (WO 2004/044011; WO 2005/040229), Adnectin (WO 2002/032925) and fynomers (WO 2013/135588).

The terms "anti misfolded TDP-43 antibody" and "an antibody that binds to misfolded TDP-43" or simply “antibody” as used herein refer to an antibody that is capable of binding misfolded TDP-43 with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting TDP-43. In one embodiment, the extent of binding of an anti-TDP-43 antibody of the invention to an unrelated, non-TDP-43 protein or physiologically functional TDP-43 is less than about 10% of the binding of the antibody to misfolded TDP-43 as measured, e.g., by a radioimmunoassay (RIA). In certain embodiments, an anti-misfolded TDP-43 antibody binds to an epitope of TDP-43 that is not accessible in physiologically functional TDP-43. That is, upon misfolding, the epitope becomes accessible and is bound by the binding molecule, in particular antibody, of the invention. Such an epitope can be within amino acids 215-222 (SEQ ID NO:5) of human TDP-43. In this context, the term “physiologically functional” relates to a TDP-43 protein being in a status able to exhibit its desired function in an *in vivo* cellular environment. In contrast, upon misfolding, the TDP-43 protein will lose its ability to exhibit the same function, at least to an extent defined by more than 50% of the previous, physiologically relevant, function. In general, the term "antibody" is used herein in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), fully-human antibodies and antibody fragments so long as they exhibit the desired antigen-binding activity. Antibodies within the present invention may also be chimeric antibodies, recombinant antibodies, antigen-binding fragments of recombinant antibodies, humanized antibodies or antibodies displayed upon the surface of a phage or displayed upon the surface of a chimeric antigen receptor (CAR) T cell.

An "antigen-binding fragment" of an antibody refers to a molecule other than an intact antibody that comprises a portion of an intact antibody and that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab' -SH, F(ab')₂; diabodies; linear antibodies; single-chain antibody molecules (*e.g.* scFv); and multispecific antibodies formed from antibody fragments.

An "antibody that binds to an epitope" within a defined region of a protein is an antibody that requires the presence of one or more of the amino acids within that region for binding to the protein.

In certain embodiments, an "antibody that binds to an epitope" within a defined region of a protein is identified by mutation analysis, in which amino acids of the protein are mutated, and binding of the antibody to the resulting altered protein (*e.g.*, an altered protein comprising the epitope) is determined to be at least 20% of the binding to unaltered protein. In some embodiments, an "antibody that binds to an epitope" within a defined region of a protein is identified by mutation analysis, in which amino acids of the protein are mutated, and binding of the antibody to the resulting altered protein (*e.g.*, an altered protein comprising the epitope) is determined to be at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the binding to unaltered protein. In certain embodiments, binding of the antibody is determined by FACS, WB or by a suitable binding assay such as ELISA. In some embodiments, the antibodies of the invention bind to an epitope which is not accessible in physiologically functional TDP-43 and which becomes accessible if TDP-43 is misfolded, *i.e.* in a different three dimensional conformation that does not allow the protein to exhibit its physiological function, preferably the epitope lies within amino acids 215-222 (SEQ ID NO:5) of SEQ ID NO:1.

The term "binding to" as used in the context of the present invention defines a binding (interaction) of at least two "antigen-interaction-sites" with each other. The term "antigen-interaction-site" defines, in accordance with the present invention, a motif of a polypeptide, *i.e.*, a part of the antibody or antigen-binding fragment of the present invention, which shows the capacity of specific interaction with a specific antigen or a specific group of antigens of TDP-43. Said binding/interaction is also understood to define a "specific recognition". The term "specifically recognizing" means in accordance with this invention that the antibody is capable of specifically interacting with and/or binding to at least two amino acids of TDP-43 as defined herein, in particular interacting with/binding to at least two amino acids within residues 215-222 (SEQ ID NO:5) of SEQ ID NO:1.

The term "specific interaction" as used in accordance with the present invention means that the antibody or antigen-binding fragment thereof of the invention does not or does not essentially cross-react with (poly)peptides of similar structures. Accordingly, the antibody or antigen-binding fragment

thereof of the invention specifically binds to/interacts with structures of TDP-43 formed by particular amino acid sequences within amino acids 215-222 (SEQ ID NO:5) of SEQ ID NO:1.

Cross-reactivity of antigen-binding molecules, in particular a panel of antibodies or antigen-binding fragments thereof under investigation may be tested, for example, by assessing binding of said panel of antibodies or antigen-binding fragments thereof under conventional conditions (see, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, (1988) and Using *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, (1999)) to the (poly)peptide of interest as well as to a number of more or less (structurally and/or functionally) closely related (poly)peptides. Only those constructs (i.e. antibodies, antigen-binding fragments thereof and the like) that bind to the certain structure of TDP-43 as defined herein, e.g., a specific epitope or (poly)peptide/protein of TDP-43 as defined herein but do not or do not essentially bind to any of the other epitope or (poly)peptides of the same TDP-43, are considered specific for the epitope or (poly)peptide/protein of interest and selected for further studies in accordance with the method provided herein. These methods may comprise, *inter alia*, binding studies, blocking and competition studies with structurally and/or functionally closely related molecules. These binding studies also comprise FACS analysis, surface plasmon resonance (SPR, e.g. with BIACORE™), analytical ultracentrifugation, isothermal titration calorimetry, fluorescence anisotropy, fluorescence spectroscopy or by radiolabeled ligand binding assays.

Accordingly, specificity can be determined experimentally by methods known in the art and methods as described herein. Such methods comprise, but are not limited to Western Blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans.

The term “monoclonal antibody” as used herein, refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Monoclonal antibodies are advantageous in that they may be synthesized by a hybridoma culture, essentially uncontaminated by other immunoglobulins. The modified “monoclonal” indicates the character of the antibody as being amongst a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. As mentioned above, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method described by Kohler, *Nature* 256 (1975), 495.

The term “polyclonal antibody” as used herein, refers to an antibody which was produced among or in the presence of one or more other, non-identical antibodies. In general, polyclonal antibodies are

produced from a B-lymphocyte in the presence of several other B-lymphocytes which produced non-identical antibodies. Usually, polyclonal antibodies are obtained directly from an immunized animal.

The term “fully-human antibody” as used herein refers to an antibody which comprises human immunoglobulin protein sequences only. A fully human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell or in a hybridoma derived from a mouse cell. Similarly, “mouse antibody” or “murine antibody” refers to an antibody which comprises mouse/murine immunoglobulin protein sequences only. Alternatively, a “fully-human antibody” may contain rat carbohydrate chains if produced in a rat, in a rat cell, in a hybridoma derived from a rat cell. Similarly, the term “rat antibody” refers to an antibody that comprises rat immunoglobulin sequences only. Fully-human antibodies may also be produced, for example, by phage display which is a widely used screening technology which enables production and screening of fully human antibodies. Also phage antibodies can be used in context of this invention. Phage display methods are described, for example, in US 5,403,484, US 5,969,108 and US 5,885,793. Another technology which enables development of fully-human antibodies involves a modification of mouse hybridoma technology. Mice are made transgenic to contain the human immunoglobulin locus in exchange for their own mouse genes (see, for example, US 5,877,397).

The term “chimeric antibodies”, refers to an antibody which comprises a variable region of the present invention fused or chimerized with an antibody region (*e.g.*, constant region) from another, human or non-human species (*e.g.*, mouse, horse, rabbit, dog, cow, chicken).

The term antibody also relates to recombinant human antibodies, heterologous antibodies and heterohybrid antibodies. The term "recombinant (human) antibody" includes all human sequence antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes; antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions (if present) derived from human germline immunoglobulin sequences. Such antibodies can, however, be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

A "heterologous antibody" is defined in relation to the transgenic non-human organism producing such an antibody. This term refers to an antibody having an amino acid sequence or an encoding nucleic acid

sequence corresponding to that found in an organism not consisting of the transgenic non-human animal, and generally from a species other than that of the transgenic non-human animal.

The term "heterohybrid antibody" refers to an antibody having light and heavy chains of different organismal origins. For example, an antibody having a human heavy chain associated with a murine light chain is a heterohybrid antibody. Examples of heterohybrid antibodies include chimeric and humanized antibodies.

The term antibody also relates to humanized antibodies. "Humanized" forms of non-human (e.g. murine or rabbit) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Often, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibody may comprise residues, which are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see: Jones et al., *Nature* 321 (1986), 522-525; Reichmann *Nature* 332 (1998), 323-327 and Presta *Curr Op Struct Biol* 2 (1992), 593-596.

A popular method for humanization of antibodies involves CDR grafting, where a functional antigen-binding site from a non-human 'donor' antibody is grafted onto a human 'acceptor' antibody. CDR grafting methods are known in the art and described, for example, in US 5,225,539, US 5,693,761 and US 6,407,213. Another related method is the production of humanized antibodies from transgenic animals that are genetically engineered to contain one or more humanized immunoglobulin loci which are capable of undergoing gene rearrangement and gene conversion (see, for example, US 7,129,084).

Accordingly, in context of the present invention, the term "antibody" relates to full immunoglobulin molecules as well as to parts of such immunoglobulin molecules (i.e., "antigen-binding fragment thereof"). Furthermore, the term relates, as discussed above, to modified and/or altered antibody molecules. The term also relates to recombinantly or synthetically generated/synthesized antibodies. The term also relates to intact antibodies as well as to antibody fragments thereof, like, separated light

and heavy chains, Fab, Fv, Fab', Fab'-SH, F(ab')₂. The term antibody also comprises but is not limited to fully-human antibodies, chimeric antibodies, humanized antibodies, CDR-grafted antibodies and antibody constructs, like single chain Fvs (scFv) or antibody-fusion proteins.

"Single-chain Fv" or "scFv" antibody fragments have, in the context of the invention, the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Generally, the scFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. Techniques described for the production of single chain antibodies are described, e.g., in Plückthun in *The Pharmacology of Monoclonal Antibodies*, Rosenberg and Moore eds. Springer-Verlag, N.Y. (1994), 269-315.

A "Fab fragment" as used herein is comprised of one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule.

An "Fc" region contains two heavy chain fragments comprising the C_H2 and C_H3 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

A "Fab' fragment" contains one light chain and a portion of one heavy chain that contains the V_H domain and the C_H1 domain and also the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form a F(ab')₂ molecule.

A "F(ab')₂ fragment" contains two light chains and two heavy chains containing a portion of the constant region between the C_H1 and C_H2 domains, such that an interchain disulfide bond is formed between the two heavy chains. A F(ab')₂ fragment thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains.

The "Fv region" comprises the variable regions from both the heavy and light chains, but lacks the constant regions.

Antibodies, antibody constructs, antibody fragments, antibody derivatives (all being Ig-derived) to be employed in accordance with the invention or their corresponding immunoglobulin chain(s) can be further modified using conventional techniques known in the art, for example, by using amino acid deletion(s), insertion(s), substitution(s), addition(s), and/or recombination(s) and/or any other modification(s) known in the art either alone or in combination. Methods for introducing such modifications in the DNA sequence underlying the amino acid sequence of an immunoglobulin chain

are well known to the person skilled in the art; see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory Press, 2nd edition (1989) and 3rd edition (2001). The term “Ig-derived domain” particularly relates to (poly) peptide constructs comprising at least one CDR. Fragments or derivatives of the recited Ig-derived domains define (poly) peptides which are parts of the above antibody molecules and/or which are modified by chemical/biochemical or molecular biological methods. Corresponding methods are known in the art and described *inter alia* in laboratory manuals (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory Press, 2nd edition (1989) and 3rd edition (2001); Gerhardt et al., *Methods for General and Molecular Bacteriology* ASM Press (1994); Lefkovits, *Immunology Methods Manual: The Comprehensive Sourcebook of Techniques*; Academic Press (1997); Golemis, *Protein-Protein Interactions: A Molecular Cloning Manual* Cold Spring Harbor Laboratory Press (2002)).

The term “CDR” as employed herein relates to “complementary determining region”, which is well known in the art. The CDRs are parts of immunoglobulins that determine the specificity of said molecules and make contact with a specific ligand. The CDRs are the most variable part of the molecule and contribute to the diversity of these molecules. There are three CDR regions CDR1, CDR2 and CDR3 in each V domain. CDR-H depicts a CDR region of a variable heavy chain and CDR-L relates to a CDR region of a variable light chain. VH means the variable heavy chain and VL means the variable light chain. The CDR regions of an Ig-derived region may be determined as described in Kabat “Sequences of Proteins of Immunological Interest”, 5th edit. NIH Publication no. 91-3242 U.S. Department of Health and Human Services (1991); Chothia J., *Mol. Biol.* 196 (1987), 901-917 or Chothia, *Nature* 342 (1989), 877-883.

Accordingly, in the context of the present invention, the antibody molecule described herein above is selected from the group consisting of a full antibody (immunoglobulin, like an IgG1, an IgG2, an IgG2a, an IgG2b, an IgA1, an IgGA2, an IgG3, an IgG4, an IgA, an IgM, an IgD or an IgE), F(ab)-, Fab'-SH-, Fv-, Fab'-, F(ab')2- fragment, a chimeric antibody, a CDR-grafted antibody, a fully human antibody, a bivalent antibody-construct, an antibody-fusion protein, a synthetic antibody, bivalent single chain antibody, a trivalent single chain antibody and a multivalent single chain antibody.

“Humanization approaches” are well known in the art and in particular described for antibody molecules, e.g. Ig-derived molecules. The term “humanized” refers to humanized forms of non-human (e.g., murine) antibodies or fragments thereof (such as Fv, Fab, Fab', F(ab')), scFvs, or other antigen-binding partial sequences of antibodies) which contain some portion of the sequence derived from non-human antibody. Humanized antibodies include human immunoglobulins in which residues from a complementary determining region (CDR) of the human immunoglobulin are replaced by residues from a CDR of a non-human species such as mouse, rat or rabbit having the desired binding specificity, affinity and capacity. In general, the humanized antibody will comprise substantially all of at least one,

and generally two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin ; see, *inter alia*, Jones et al., Nature 321 (1986),522-525, Presta, Curr. Op. Struct. Biol. 2 (1992),593-596. Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acids introduced into it from a source which is non-human still retain the original binding activity of the antibody. Methods for humanization of antibodies/antibody molecules are further detailed in Jones et al., Nature 321 (1986),522-525; Reichmann et al., Nature 332 (1988),323-327; and Verhoeyen et al., Science 239 (1988),1534-1536. Specific examples of humanized antibodies, e.g. antibodies directed against EpCAM, are known in the art (see e.g. LoBuglio, Proceedings of the American Society of Clinical Oncology Abstract (1997), 1562 and Khor, Proceedings of the American Society of Clinical Oncology Abstract (1997), 847).

Accordingly, in the context of this invention, antibody molecules or antigen-binding fragments thereof are provided, which are humanized and can successfully be employed in pharmaceutical compositions.

The specificity of the antibody or antigen-binding fragment of the present invention may not only be expressed by the nature of the amino acid sequence of the antibody or the antigen-binding fragment as defined above but also by the epitope to which the antibody is capable of binding to. Thus, the present invention relates, in one embodiment, to an anti-misfolded TDP-43 antibody or an antigen-binding fragment thereof which recognizes the same epitope as an antibody of the invention.

It may be understood by a person skilled in the art that the epitopes may be comprised in the TDP-43 protein, but may also be comprised in a degradation product thereof or may be a chemically synthesized peptide. The amino acid positions are only indicated to demonstrate the position of the corresponding amino acid sequence in the sequence of the TDP-43 protein. The invention encompasses all peptides comprising the epitope. The peptide may be a part of a polypeptide of more than 100 amino acids in length or may be a small peptide of less than 100, preferably less than 50, more preferably less than 25 amino acids, even more preferably less than 16 amino acids. The amino acids of such peptide may be natural amino acids or nonnatural amino acids (e.g., beta-amino acids, gamma-amino acids, D-amino acids) or a combination thereof. Further, the present invention may encompass the respective retro-inverso peptides of the epitopes. The peptide may be unbound or bound. It may be bound, e.g., to a small molecule (e.g., a drug or a fluorophor), to a high-molecular weight polymer (e.g., polyethylene glycol (PEG), polyethylene imine (PEI), hydroxypropylmethacrylate (HPMA), etc.) or to a protein, a fatty acid, a sugar moiety or may be inserted in a membrane.

In order to test whether an antibody in question and the antibody of the present invention recognize the same epitope, the following competition study may be carried out: Vero cells infected with 3 MOI (multiplicity of infection) are incubated after 20 h with varying concentrations of the antibody in question as the competitor for 1 hour. In a second incubation step, the antibody of the present invention is applied in a constant concentration of 100 nM and its binding is flow-cytometrically detected using a fluorescence-labelled antibody directed against the constant domains of the antibody of the invention. Binding that conducts anti-proportional to the concentration of the antibody in question is indicative for that both antibodies recognize the same epitope. However, many other assays are known in the art which may be used.

The present invention also relates to the production of specific antibodies against native polypeptides and recombinant polypeptides of TDP-43 as long as these polypeptides represent the misfolded state of TDP-43. This production is based, for example, on the immunization of animals, like mice. However, also other animals for the production of antibody/antisera are envisaged within the present invention. For example, monoclonal and polyclonal antibodies can be produced by rabbit, mice, goats, donkeys and the like. The polynucleotide encoding a correspondingly chosen polypeptide of TDP-43 can be subcloned into an appropriated vector, wherein the recombinant polypeptide is to be expressed in an organism being able for an expression, for example in bacteria. Thus, the expressed recombinant protein can be intra-peritoneally injected into a mice and the resulting specific antibody can be, for example, obtained from the mice serum being provided by intra-cardiac blood puncture. The present invention also envisages the production of specific antibodies against native polypeptides and recombinant polypeptides by using a DNA vaccine strategy as exemplified in the appended examples. DNA vaccine strategies are well-known in the art and encompass liposome-mediated delivery, by gene gun or jet injection and intramuscular or intradermal injection. Thus, antibodies directed against a polypeptide or a protein or an epitope of TDP-43, in particular the epitope of the antibodies provided herein, can be obtained by directly immunizing the animal by directly injecting intramuscularly the vector expressing the desired polypeptide or a protein or an epitope of TDP-43, in particular the epitope of the antibodies of the invention, which lies within amino acid residues 215-222 of SEQ ID NO.1. The amount of obtained specific antibody can be quantified using an ELISA, which is also described herein below. Further methods for the production of antibodies are well known in the art, see, e.g. Harlow and Lane, "Antibodies, A Laboratory Manual", CSH Press, Cold Spring Harbor, 1988.

Thus, under designated assay conditions, the specified antibodies and the corresponding epitope of TDP-43 bind to one another and do not bind in a significant amount to other components present in a sample. Specific binding to a target analyte under such conditions may require a binding moiety that is selected for its specificity for a particular target analyte. A variety of immunoassay formats may be used to select antibodies specifically reactive with a particular antigen. For example, solid-phase ELISA immunoassays are routinely used to select monoclonal antibodies specifically immunoreactive with an

analyte. See Shepherd and Dean (2000), *Monoclonal Antibodies: A Practical Approach*, Oxford University Press and/ or Howard and Bethell, (2000) *Basic Methods in Antibody Production and Characterization*, Crc. Pr. Inc. for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity. Typically a specific or selective reaction will be at least twice background signal to noise and more typically more than 10 to 100 times greater than background. The person skilled in the art is in a position to provide for and generate specific binding molecules directed against the novel polypeptides. For specific binding-assays it can be readily employed to avoid undesired cross-reactivity, for example polyclonal antibodies can easily be purified and selected by known methods (see Shepherd and Dean, loc. cit.).

The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively.

In certain embodiments, amino acid sequence variants of the antibodies provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, antigen-binding.

In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the CDRs and FRs. Conservative substitutions are shown in Table 2 under the heading of "preferred substitutions." More substantial changes are provided in Table 2 under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, *e.g.*, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 2

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Original Residue	Exemplary Substitutions	Preferred Substitutions
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

Amino acids may be grouped according to common side-chain properties:

- (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
- (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

- (3) acidic: Asp, Glu;
- (4) basic: His, Lys, Arg;
- (5) residues that influence chain orientation: Gly, Pro;
- (6) aromatic: Trp, Tyr, Phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (*e.g.*, improvements) in certain biological properties (*e.g.*, increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, *e.g.*, using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more CDR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (*e.g.* binding affinity).

Alterations (*e.g.*, substitutions) may be made in CDRs, *e.g.*, to improve antibody affinity. Such alterations may be made in CDR "hotspots," *i.e.*, residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (*see, e.g.*, Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or SDRs (a-CDRs), with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, *e.g.*, in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (*e.g.*, error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves CDR-directed approaches, in which several CDR residues (*e.g.*, 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, *e.g.*, using alanine scanning mutagenesis or modeling. CDR H3 and CDR-L3 in particular are often targeted.

In certain embodiments, substitutions, insertions, or deletions may occur within one or more CDRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (*e.g.*, conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in CDRs. Such alterations may be outside of CDR "hotspots" or SDRs. In certain embodiments of the variant VH and VL sequences provided above, each CDR either is unaltered, or contains no more than one, two or three amino acid substitutions.

A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) *Science*, 244: 1081-1085. In this method, a residue or group of target residues (*e.g.*, charged residues such as Arg, Asp, His, Lys, and Glu) are identified and replaced by a neutral or negatively charged amino acid (*e.g.*, alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex is used to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.* for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. *See, e.g.*, Wright et al., *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, *e.g.*, mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

In one embodiment, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (*e. g.* complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of

position 297, *i.e.*, between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. *See, e.g.*, US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; W02005/053742; W02002/031140; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams *et al.*, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, *FUT8*, knockout CHO cells (*see, e.g.*, Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.*, 94(4):680-688 (2006); and W02003/085 107).

Antibodies variants are further provided with bisected oligosaccharides, *e.g.*, in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, *e.g.*, in WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana *et al.*). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, *e.g.*, in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (*e.g.*, a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (*e.g.* a substitution) at one or more amino acid positions.

In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody *in vivo* is important yet certain effector functions (such as complement activation and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes and microglia express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is

described in U.S. Patent No. 5,500,362 (*see, e.g.* Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499- 1502 (1985); 5,821,337 (*see* Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)).

Alternatively, non-radioactive assays methods may be employed (*see, for example*, ACTITM non radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells.

Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo, e.g.*, in a animal model such as that disclosed in Clynes et al., *Proc. Nat'l Acad. sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. *See, e.g.*, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (*see, for example*, Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996); Cragg, M.S. et al., *Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (*see, e.g.*, Petkova, S.B. et al., *Int'l. Immunol.* 18(12):1759-1769 (2006)).

Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581). Alternatively, antibodies with reduced effector function include those with substitution of one or more of Fc region residues 234, 235 and 329, so-called "PG-LALA" Fc mutant with substitution of residues 234 and 235 to alanine and 329 to glycine (Lo, M. et al., *Journal of Biochemistry*, 292, 3900-3908).

Certain antibody variants with improved or diminished binding to FcRs are described. (*See, e.g.*, U.S. Patent No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001)).

In certain embodiments, an antibody variant comprises a Fc region with one or more amino acid substitutions which improve ADCC, *e.g.*, substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or

diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), *e.g.*, as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie et al., *J. Immunol.* 164: 4178-4184 (2000).

Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kirn et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, *e.g.*, substitution of Fc region residue 434 (US Patent No. 7,371,826).

See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

In certain embodiments, it may be desirable to create cysteine engineered antibodies, *e.g.*, "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, *e.g.*, in U.S. Patent No. 7,521,541.

In certain embodiments, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Nonlimiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n vinyl pyrrolidone)polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of

the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., *Proc. Natl. Acad. Sci. USA* 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

Antibodies may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In one embodiment, isolated nucleic acid encoding an anti-misfolded TDP-43 antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (*e.g.*, the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (*e.g.*, expression vectors) comprising such nucleic acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (*e.g.*, has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, *e.g.* a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, YO, NSO, Sp20). In one embodiment, a method of making an anti-misfolded TDP-43 antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

For recombinant production of an anti-misfolded TDP-43 antibody, nucleic acid encoding an antibody, *e.g.*, as described above, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, *see, e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (See also

Charlton, *Methods in Molecular Biology*, Val. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

Plant cell cultures can also be utilized as hosts. See, e.g., US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are macaque kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen. Viral.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); macaque kidney cells (CV 1); African green macaque kidney cells (VER0-76); human cervical carcinoma cells (HeLa); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N. Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as YO, NSO and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Val. 248 (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

Anti-misfolded TDP-43 antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

In one aspect, an antibody of the invention is tested for its antigen binding activity, *e.g.*, by known methods such as ELISA, BIACore®, FACS, immunofluorescence or immunohistochemistry.

In another aspect, competition assays may be used to identify an antibody that competes with any of the antibodies described herein for binding to misfolded TDP-43. In certain embodiments, such a competing antibody binds to the same epitope (*e.g.*, a linear or a conformational epitope) that is bound by an antibody described herein. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

In an exemplary competition assay, immobilized misfolded TDP-43 is incubated in a solution comprising a first labeled antibody that binds to misfolded TDP-43 (*e.g.*, any of the antibodies described herein) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to misfolded TDP-43. As a control, immobilized misfolded TDP-43 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to misfolded TDP-43, excess unbound antibody is removed, and the amount of label associated with immobilized misfolded TDP-43 is measured. If the amount of label associated with immobilized misfolded TDP-43 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to misfolded TDP-43. See Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

The invention also provides immunoconjugates comprising an anti-misfolded TDP-43 antibody provided herein conjugated to one or more therapeutic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (*e.g.*, protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), radioactive isotopes (*i.e.*, a radioconjugate), blood brain barrier penetration moieties or detectable labels.

In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, intravenous (IV) solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At

least one active agent in the composition is an antibody of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

It is understood that any of the above articles of manufacture may include an immunoconjugate of the invention in place of or in addition to an anti-TDP-43 antibody.

XI. EXEMPLARY TDP-43 SPECIFIC BINDING MOLECULES OR ANTIBODIES

In some embodiments, the antibody comprises 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.

In some embodiments, the antibody comprises 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.

In some embodiments, the antibody comprises 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.

In some embodiments, the antibody comprises 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.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 10 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 20.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 30 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 40.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 50 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 60.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 70 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 80.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 90 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 100.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 110 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 120.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 130 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 140.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 150 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 160.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 170 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 180.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 190 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 200.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 210 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 220.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 230 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 232.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 234 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 236.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 238 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 240.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 242 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 244.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 246 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 248.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 250 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 252.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 254 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 256.

In some embodiments, the antibody comprises a Light Chain Variable Region (VL) comprising the sequence of SEQ ID NO: 258 and a Heavy Chain Variable Region (VH) comprising the sequence of SEQ ID NO: 260.

In some embodiments, an antibody is provided which binds to human TDP-43 within an epitope comprised in SEQ ID NO:4. In some particular embodiments, an isolated antibody that binds to human TDP-43 is provided, wherein the antibody binds an epitope within amino acids 215-222 (SEQ ID NO:5) of human TDP-43. In some embodiments an isolated antibody is provided that binds to misfolded TDP-43. In some embodiments, an isolated antibody that binds to human TDP-43 is provided, wherein the antibody binds extracellular or cytoplasmic TDP-43. In some embodiments an isolated antibody that binds to monomeric, oligomeric, or aggregated TDP-43. In some embodiments of the invention, the monomeric, oligomeric or aggregated TDP-43 is post-translationally modified, e.g. phosphorylated.

In some embodiments, the invention relates to an antibody selected from ACI-7062-401A2-Ab2, ACI-7062-404D6-Ab2, ACI-7062-406E3-Ab1, ACI-7062-406E3-Ab2, ACI-7062-

410H3-Ab1, ACI-7062-412A7-Ab1, ACI-7062-412E12-Ab1, ACI-7062-414A5-Ab1, ACI-7062-415C4-Ab1, ACI-7062-415H10-Ab2, and ACI-7062-416A11-Ab1. In a preferred embodiment, the invention relates to an antibody selected from ACI-7062-401A2-Ab2, ACI-7062-406E3-Ab1, ACI-7062-406E3-Ab2, ACI-7062-410H3-Ab1, ACI-7062-412A7-Ab1, ACI-7062-412E12-Ab1, ACI-7062-414A5-Ab1, ACI-7062-415C4-Ab1 and ACI-7062-416A11-Ab1.

In some embodiments, an antibody generated by peptide sequence binds to the same epitope as an antibody selected from ACI-7062-401A2-Ab2, ACI-7062-404D6-Ab2, ACI-7062-406E3-Ab1, ACI-7062-406E3-Ab2, ACI-7062-410H3-Ab1, ACI-7062-412A7-Ab1, ACI-7062-412E12-Ab1, ACI-7062-414A5-Ab1, ACI-7062-415C4-Ab1, ACI-7062-415H10-Ab2, and ACI-7062-416A11-Ab1, preferably from ACI-7062-401A2-Ab2, ACI-7062-406E3-Ab1, ACI-7062-406E3-Ab2, ACI-7062-410H3-Ab1, ACI-7062-412A7-Ab1, ACI-7062-412E12-Ab1, ACI-7062-414A5-Ab1, ACI-7062-415C4-Ab1 and ACI-7062-416A11-Ab1. Antibodies binding the same epitope as any of the antibodies provided herein are also part of the invention.

In some embodiments, an isolated antibody is provided, wherein the isolated antibody has been generated with a peptide comprising SEQ ID NO: 2 and binds to the same epitope comprising the sequence SEQ ID NO: 4.

In some embodiments, an isolated antibody is provided, wherein the isolated antibody has been generated with a peptide comprising SEQ ID NO: 2 binds to the same epitope comprising the sequence SEQ ID NO: 5.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid encodes an antibody described herein.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:19 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:29 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:39 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:49 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:59 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:69 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:235 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:237 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:239 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:241 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:243 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:245 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:247 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:249 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:251 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:253 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:255 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:257 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:259 encoding an anti-TPD-43 antibody.

In some embodiments, an isolated nucleic acid is provided, wherein the isolated nucleic acid comprises SEQ ID NO:261 encoding an anti-TPD-43 antibody.

In some embodiments, a host cell is provided, wherein the host cell comprises an isolated nucleic acid that encodes an antibody described herein. In some embodiments, a method of producing an antibody is provided, comprising culturing the host cell under conditions suitable for producing the antibody.

In some embodiments the misfolded TDP-43 specific antibody comprises an amino acid sequence having a sequence homology of 70%, 80% 90%, 95%, 96%, 97% 98% or 99% with any of the antibodies provided herein.

In some embodiments the TDP-43 specific binding molecule has a sequence homology of 86% or more compared with the Light Chain Variable Region sequences (VL) comprising the 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.

In some embodiments the TDP-43 specific binding molecule has a sequence homology of 86% or more compared with the Heavy Chain Variable Region (VH) comprising the 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.

In some embodiments the TDP-43 specific 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 $\leq 0.001\text{ nM}$ (e.g. 10^{-8} M or less, e.g. from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M).

In some embodiments the TDP-43 specific binding molecule or the anti-TDP-43 antibody binds each of monomeric TDP-43, phosphorylated TDP-43, non-phosphorylated TDP-43, aggregated TDP-43, and oligomeric TDP-43 with a KD of less than 100 nM , less than 10 nM , less than 1 nM , less than 200 pM , less than 100 pM , or less than 10 pM .

XII. COMPOSITIONS AND METHODS

In some embodiments, an immunoconjugate is provided, wherein the immunoconjugate comprises an isolated antibody described herein and a therapeutic agent. In some embodiments, a labeled antibody is provided, comprising an antibody described herein and a detectable label.

In some embodiments, a pharmaceutical composition is provided, comprising an isolated antibody described herein and a pharmaceutically acceptable carrier.

In some embodiments the TDP-43 specific binding molecule of the present invention is linked to a detectable label.

In some embodiments the TDP-43 specific binding molecule is part of an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent.

In some embodiments the TDP-43 specific binding molecule or the immunoconjugate comprising it is present as a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same.

In some embodiments the TDP-43 specific binding molecule is part of pharmaceutical composition comprising a TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same combined with a pharmaceutically acceptable carrier.

In some embodiments the TDP-43 specific binding molecule is part of a diagnostic kit comprising a TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same.

In some embodiments the TDP-43 specific binding molecule is used in an immunodiagnostic method for use in the prevention, diagnosis or treatment of a TDP-43 proteinopathy.

In some embodiments the TDP-43 specific binding molecule is part of an immunotherapeutic method for the prevention, or treatment of a TDP-43 proteinopathy, wherein an effective amount of the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof.

In some embodiments the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof is used to diagnose, prevent, alleviate or treat 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).

In some embodiments the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof is used in a method for diagnosing or monitoring a disorder or abnormality associated with TDP-43 aggregates selected from Frontotemporal dementia (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 (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 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)).

In some embodiments the TDP-43 specific binding molecule is used in a method for diagnosing presymptomatic disease or for monitoring disease progression and therapeutic efficacy, or for predicting responsiveness, or for selecting patients which are likely to respond to the treatment with a TDP-43 specific binding molecule. Said method is preferably performed using a sample of human blood or urine. Most preferably the method involves an ELISA-based or surface adapted assay.

In some embodiments the TDP-43 specific binding molecule is used in a method wherein a TDP-43 specific binding molecule of the present invention is contacted with a sample (e.g., blood, cerebrospinal fluid, or brain tissue) to detect, diagnose or monitor frontotemporal degeneration (FTD) or amyotrophic lateral sclerosis (ALS) Alzheimer's disease (AD) and Parkinson's disease (PD).

In some embodiments the TDP-43 specific binding molecule is used in a method wherein a TDP-43 specific binding molecule of the present invention is contacted with a sample (e.g., blood, cerebrospinal fluid, or brain tissue) to detect, diagnose or a disease selected from Frontotemporal dementia (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 (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 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)).

In some embodiments the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof is used for preventing, alleviating or treating a disorder or abnormality associated with TDP-43 aggregates or TDP-43 proteinopathies or frontotemporal degeneration (FTD) or amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD, sporadic and familial), and Parkinson's disease (PD).

In some embodiments the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof is used for treating a disease selected from: Frontotemporal dementia (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 (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 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), Oculopharyngeal muscular dystrophy with rimmed vacuoles, Myofibrillar myopathies with mutations in the myotilin (MYOT) gene or mutations in the gene coding for desmin (DES)). Preferably said disease treatment helps to retain or increase mental recognition and or reduces the level of TDP-43 aggregates in the brain.

In some embodiments the TDP-43 specific binding molecule, or an immunoconjugate wherein the TDP-43 specific binding molecule is covalently linked to another suitable therapeutic agent, or a composition comprising a TDP-43 specific binding molecule and a TDP-43 agonists and cognate molecules, or alternately, antagonists of the same is administered to a patient in need thereof is used for manufacturing a medicament for treating a disorder or abnormality associated with TDP-43 aggregates or TDP-43 proteinopathies or frontotemporal degeneration (FTD) or amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD, sporadic and familial), and Parkinson's disease (PD).

Pharmaceutical formulations of an anti-misfolded TDP-43 antibody or immunoconjugate as described herein are prepared by mixing such antibody or immunoconjugate having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.* Zn protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary

pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

Exemplary lyophilized antibody or immunoconjugate formulations are described in US Patent No. 6,267,958. Aqueous antibody or immunoconjugate formulations include those described in US Patent No. 6,171,586 and W02006/044908, the latter formulations including a histidine-acetate buffer.

The formulation herein may also contain more than one active ingredient as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other.

Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody or immunoconjugate, which matrices are in the form of shaped articles, e.g. films, or microcapsules. The formulations to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

Any of the antigen-binding molecules, anti-misfolded TDP-43 antibodies or immunoconjugates provided herein may be used in methods, e.g., therapeutic methods.

In another aspect, an anti-misfolded TDP-43 antibody or immunoconjugate for use as a medicament is provided. In further aspects, an anti-misfolded TDP-43 antibody or immunoconjugate for use in a method of treatment is provided. In certain embodiments, an anti-misfolded TDP-43 antibody or immunoconjugate for use in the prevention, diagnosis and/or treatment of a TDP-43 proteinopathy is provided. In a preferred embodiment of the invention, an anti-misfolded TDP-43 antibody or immunoconjugate is provided for use in the prevention, diagnosis and/or treatment of a TDP-43

associated 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/or Parkinson's disease (PD).

In a further aspect, the invention provides for the use of an anti-misfolded TDP-43 antibody or immunoconjugate in the manufacture or preparation of a medicament. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below.

A "subject" or an "individual" or a "patient" according to any of the above embodiments may be an animal, a mammal, preferably a human.

In a further aspect, the invention provides pharmaceutical formulations comprising any of the anti-misfolded TDP-43 antibodies or immunoconjugate provided herein, e.g., for use in any of the above therapeutic methods. In one embodiment, a pharmaceutical formulation comprises any of the anti-misfolded TDP-43 antibodies or immunoconjugates provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises any of the anti-misfolded TDP-43 antibodies or immunoconjugates provided herein and at least one additional therapeutic agent, e.g., as described below.

Antibodies or immunoconjugates of the invention can be used either alone or in combination with other agents in a therapy. For instance, an antibody or immunoconjugate of the invention may be co-administered with at least one additional therapeutic agent.

Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the antibody or immunoconjugate of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent and/or adjuvant. Antibodies or immunoconjugates of the invention can also be used in combination with radiation therapy.

An antibody or immunoconjugate of the invention (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional, intrauterine or intravesical administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g. by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not

limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

Antibodies or immunoconjugates of the invention would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The antibody or immunoconjugate need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody or immunoconjugate present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

For the prevention or treatment of disease, the appropriate dosage of an antibody or immunoconjugate of the invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of antibody or immunoconjugate, the severity and course of the disease, whether the antibody or immunoconjugate is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody or immunoconjugate, and the discretion of the attending physician. The antibody or immunoconjugate is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 $\mu\text{g/kg}$ to 15 mg/kg (e.g. 0.1 mg/kg -10 mg/kg) of antibody or immunoconjugate can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 $\mu\text{g/kg}$ to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody or immunoconjugate would be in the range from about 0.05 mg/kg to about 10 mg/kg . Thus, one or more doses of about 0.5 mg/kg , 2.0 mg/kg , 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, or e.g. about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

It is understood that any of the above formulations or therapeutic methods may be carried out using both an immunoconjugate of the invention and an anti-misfolded TDP-43 antibody.

In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the disorder and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibody or immunoconjugate of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody or immunoconjugate of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution or dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In a further embodiment, the invention relates to a method of 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, comprising administering the binding molecule of the invention, the immunoconjugate of the invention, the composition of the invention or the pharmaceutical composition of the invention.

In a further embodiment, the invention relates to a method of reducing the level of misfolded TDP-43, comprising administering the binding-molecule of the invention, the immunoconjugate of the invention, the composition of the invention or the pharmaceutical composition of the invention.

The methods of the invention may comprise administering at least one additional therapy, preferably wherein the additional therapy is selected from, but not limited to, neurological drugs, anti-abeta

antibodies, anti-Tau antibodies, Tau aggregation inhibitors, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

The invention furthermore relates to a method of detecting misfolded TDP-43, comprising contacting a sample with the binding molecule of the invention, preferably wherein the sample is a brain sample, a cerebrospinal fluid sample, urine sample or a blood sample.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Vaccine response measured in plasma. Binding to recombinant FL TDP-43 for the antibodies present in plasma from immunized mice at day 81 after first immunization was determined using an indirect ELISA. Serial dilution of plasma was used. Results are expressed in optical densities (O.D.). Each curve represents results from an individual mouse.

Figure 2. Screening of hybridomas. Binding of antibodies from hybridomas from fusions of a BALB/c mouse was evaluated in Luminex multiplex assay on FL TDP-43 and on TDP-1 peptide. Data are presented as a correlation of binding of antibodies to two targets using a Luminex multiplex assay and shown as mean fluorescence intensity (MFI).

Figure 3. Determination of binding affinity (EC50) for human FL TDP-43. Binding affinity (EC50) for human FL TDP-43, TDP-1 peptide and irrelevant TDP-3 peptide was determined in Luminex assay. Data are presented as mean fluorescence intensity (MFI).

Figure 4. Antibody binding to human FL TDP-43. Binding to recombinant FL TDP-43 for the antibodies derived from stable hybridoma clones was determined using an indirect ELISA. Results are expressed in optical densities (O.D.). Commercial antibody 2E2-D3 was used as a positive control (+); no sample was used as negative control (-). Same naming as in Table 5 is used.

Figure 5. Epitope mapping for the antibodies derived from stable hybridoma clones was determined using an indirect ELISA on a library of 15-mer peptides covering the sequence of human TDP-43 from 199 to 285 (A), and a library of 8-mer peptides covering the sequence of human TDP-43 from 210 to 231 (B). Results are expressed as optical density (O.D.). Each bar represents data for individual antibody. Same naming as in Table 5 is used. The 2E2-D3 antibody was used as a control.

Figure 6. Detection of TDP-43 in tissues from FTD type A/C patient. Immunohistochemistry was performed on 10 µm thick frozen sections from frontal cortex of an FTD patient with type A/C pathology (A) and on brain sections from an age-matched control donor (B) using fluorescent secondary antibody detection. Antibodies of the present invention specifically bind to misfolded, aggregated TDP-43 in the cytoplasm in Type A pathology and do not bind to physiological nuclear TDP-43 in patient nor in control brains. The following antibodies were used as controls: rabbit

polyclonal pan TDP-43 antibody (Proteintech, 10782-2-AP) to detect pathological inclusions and physiological nuclear TDP-43; rabbit monoclonal phospho TDP-43 p409/410 antibody (Cosmobio, TIP-TD-P02) to detect pathological aggregated and phosphorylated TDP-43.

Figure 7. Detection of TDP-43 in tissues from FTD type B patient. Immunohistochemistry was performed on 6 μ m thick paraffin-embedded sections from hippocampus (A) and frontal cortex (B) of an FTD patient with type B pathology using DAB detection. Antibodies of the present invention specifically bind to aggregated TDP-43 in the cytoplasm in Type B pathology and do not bind to physiological nuclear TDP-43.

Figure 8. Avidity evaluation by SPR. Sensorgram showing binding of clones 401A2A7 (Fig.8A) and 401A2C6 (Fig. 8B) to human FL TDP-43 monomer covalently coupled to a Biacore sensor chip. Antibody 2E2-D3 was used as control. A 1:1 binding model was applied and is shown as an overlay. The x-axis indicates time (units=seconds). The y-axis indicated Resonance Units (RU).

EXAMPLES

I. Example 1: Preparation of a TDP-43 vaccine composition

The liposome-based antigenic constructs were prepared according to the protocols published in WO2012/055933. The liposomal vaccine with TDP-1 peptide as antigen was used for antibody generation. Briefly, DMPC, DMPG lipids (both by Lipoid AG, Switzerland), cholesterol and monophosphoryl hexa-acyl Lipid A 3-deacyl synthetic (3D-(6-acyl) PHAD®) (Avanti Polar Lipids, AL, USA) at a molar ratio 9:1:7:0.05, respectively, were solubilized in EtOH at 60°C for 30 min. An identical batch was additionally manufactured but without adjuvant for boost vaccinations. Multilamellar liposomes were extruded (EmulsiFlex-C5, Avestin, Germany) through polycarbonate Whatman filters with a pore size of 0.08 µm. TDP-1 peptide used as the antigen was conjugated to liposomes using cysteine-maleimide coupling. The TDP-1 peptide was reduced with TCEP (Sigma-Aldrich, Switzerland) at a TCEP/peptide molar ratio of 100:1 for 30 min at room temperature. The TDP-1 was further coupled to DSPEPEG(2000)maleimide lipid (Avanti Polar Lipids) at a lipid/protein molar ratio of 30:1 at ambient temperature for 4 hours. The coupled product was incubated with preformed liposomes for 15 hours at 37°C. Liposomes were further subjected to ultrafiltration and diafiltration in PBS pH 7.4, sterile filtered by passing through 0.2 µm polyethersulfone (PES) membrane syringe filters, and stored at 5°C until administration.

Table 3: TDP-43 protein and peptide antigen description

SEQ ID NO	Definition	Amino acid sequence (1-letter code)
SEQ ID NO: 1	Q13148 TADBP_HUMAN TAR DNA-binding protein 43 aa 1-414	MSEYIRVTEDENDIEPIEIPSEDDGTVLLSTVTAQFPGAC GLRYRNPVSQCMRGVRLVEGILHAPDAGWGNLVYVV NYPKDNKRKMDETDASSAVKVKRAVQKTSDLIVLGL PWKTTEQDLKEYFSTFGEVLMVQVKKDLKTGHSKGF GFVRFTEYETQVKVMSQRHMDGRWCDCCLPNSKQS QDEPLRSRKVFVGRCTEDMTEDELREFFSQYGDVMDV FIPKPFRAFAFVTFADDQIAQSLCGEDLIKGISVHISNA EPKHNSNRQLERSGRFGGNPGGFGNQGGFGNSRGGG AGLGNNQGSNMGGGMNFGAFSINPAMMAAAQAALQ SSWGMMGMLASQQNQSGPSGNNQNQGNMQREPNQA FGSGNNSYSGSNSGAAIGWGSASNAGSGSGFNNGGFGS SMDKSSGWGM
SEQ ID NO: 2	TDP-1 aa 212-272 (61aa)	SQYGDVMDVFIPKPFRAFAFVTFADDQIAQSLCGEDLII KGISVHISNAEPKHNSNRQLER
SEQ ID NO: 3	TDP-3 aa 310-370 (61aa)	CGMNFGAFSINPAMMAAAQAALQSSWGMMGMLASQ QNQSGPSGNNQNQGNMQREPNQAFGSG

II. Example 2: Generation of anti-TDP-43 Antibodies

A. Mouse immunization

Female C57BL/6JOlaHsd (C57BL/6) and BALB/c OlaHsd (BALB/c) wild-type mice (Harlan, USA) were received at 9 weeks of age. Vaccinations started at 10 weeks. Mice were vaccinated with TDP-1 peptide (198 µg/ml) presented on the surface of liposomes in the presence of MPLA as adjuvant (97 µg/ml).

Mice were vaccinated by subcutaneous injection (s.c.) on days 0, 4, 8, 22, 36, and 62. Mice were bled and heparinized plasma prepared 7 days before immunization (pre-immune plasma) and on days 15, 29, 43 and 81 after first immunization. Mice used for myeloma fusion were additionally vaccinated with three daily booster injections of TDP-1 per i.p. injection without adjuvant.

Table 4: Mice and vaccination protocols

Study group	Mouse strain	TDP-1 µg / injection	Adjuvant	Vaccination route
C	C57BL/6	39.6	MPLA	s.c.
D	BALB/C	39.6	MPLA	s.c.

B. Quantification of antigen-specific antibodies after immunization

Antigen-specific IgG responses were determined by ELISA. Briefly, plates were coated with 1 µg/mL of recombinant human full-length TDP-43 (recFL TDP-43) in carbonate buffer overnight at 4°C. After washing with PBS-0.05% Tween 20 and blocking with 1% BSA, serial dilutions of plasma were added to the plates and incubated at 37°C for two hours. As a positive control a commercial mouse monoclonal antibody 2E2-D3 (Abcam) was used. After washing, plates were incubated with alkaline phosphatase (AP) conjugated anti-mouse IgG antibody (Jackson ImmunoResearch, Lot 123565, diluted at 1/1000) for 1 hour at 37°C. After a final wash, plates were incubated for 30 min, 1 hour or 2 hours with AP substrate (p-nitrophenyl phosphate disodium hexahydrate; pNPP) and read at 405 nm using an ELISA plate reader. Results (Fig.1) are expressed as optical density (O.D).

C. Generation of hybridomas and selection for subcloning

Mice were euthanized and fusion with myeloma cells was performed using splenocytes from two individual mice. For screening fusion products, a 1:32 supernatant dilution was analysed using Luminex bead-based multiplex assay (Luminex, The Netherlands). Luminex beads were conjugated to FL TDP-43, TDP-1 peptide, or TDP-3 peptide (irrelevant target), and with capturing IgGs with anti-mouse IgG-Fc antibodies specific for the IgG1, IgG2a, IgG2b, IgG2c, and IgG3 subclasses (Jackson ImmunoResearch, USA). Binding to beads conjugated to FL TDP-43 and to TDP-1 peptide identified 153 hits derived from mouse from group D (BALB/C) (Fig. 2).

Viable hybridomas were grown using serum-containing selection media, and the best hybridomas binding to both targets were then selected for subcloning. Following limiting dilution, the clonal

hybridomas were grown in low immunoglobulin containing medium and stable colonies were selected for antibody screening and selection. Antibodies shown in table 4 were identified from this screen.

III. Example 3: Determination of binding affinity (EC50)

Luminex assays with serial dilution of antibodies were performed as described before to determine half maximal effective concentration (EC50) of binding of antibodies to FL TDP-43, TDP-1 peptide or TDP-3 peptide (irrelevant target). Results for a subset of antibodies are shown in Fig. 3. EC50 values are shown in Table 5. All tested antibodies bind to full length TDP-43 and to TDP-1 peptide with high affinity (no binding was observed to unrelated TDP-3 peptide).

Table 5: EC50 values by Luminex Assay

Clone numbers used in Figures 5 and 6	Hybridoma Clone	Antibody name	Isotype	EC50 (pM) TDP-43 protein	EC50 (pM) TDP-1 peptide	EC50 (pM) TDP-3 peptide
1	401A2A7	ACI-7062-401A2-Ab1	IgG1, kappa	20	<10	no binding
2	401A2C6	ACI-7062-401A2-Ab2	IgG1, kappa	15	<10	no binding
3	404D6A9	ACI-7062-404D6-Ab1	IgG3, kappa	<10	<10	no binding
4	404D6E11	ACI-7062-404D6-Ab2	IgG3, kappa	<10	<10	no binding
5	406E3D5	ACI-7062-406E3-Ab1	IgG2a, kappa	<10	<10	no binding
6	406E3G10	ACI-7062-406E3-Ab2	IgG2a, kappa	10	<10	no binding
7	410H3B9	ACI-7062-410H3-Ab1	IgG1, kappa	30	<10	no binding
8	410H3G7	ACI-7062-410H3-Ab2	IgG1, kappa	25	<10	no binding
9	412A7B7	ACI-7062-412A7-Ab1	IgG2b, kappa	30	<10	no binding
10	412E12A2	ACI-7062-412E12-Ab1	IgG1, kappa	20	<10	no binding
11	412E12F8	ACI-7062-412E12-Ab2	IgG1, kappa	25	<10	no binding
12	414A5D2	ACI-7062-414A5-Ab1	IgG2a, kappa	100	<10	no binding
13	414A5H4	ACI-7062-414A5-Ab2	IgG2a, kappa	115	<10	no binding
14	415C4C6	ACI-7062-415C4-Ab1	IgG1, kappa	<10	<10	no binding
15	415C4F11	ACI-7062-415C4-Ab2	IgG1, kappa	<10	<10	no binding
16	415H10A1	ACI-7062-415H10-Ab1	IgG3, kappa	180	<10	no binding

17	415H10B7	ACI-7062-415H10-Ab2	IgG3, kappa	160	<10	no binding
18	416A11B3	ACI-7062-416A11-Ab1	IgG2a, kappa	15	<10	no binding
19	416A11G11	ACI-7062-416A11-Ab2	IgG2a, kappa	15	<10	no binding

IV. Example 4: Antibody binding to human FL TDP-43

Antibody binding to human FL TDP-43 was determined using an indirect ELISA. Coating was done overnight in carbonate buffer at 4°C. Plates were washed thoroughly with 0.05% Tween-20/PBS and then blocked with 1% bovine serum albumin (BSA) in 0.05% Tween-20/PBS for 1 hours at 37°C. The antibody contained in the hybridoma supernatant was then added at 1 µg/ml, and incubated for 2 hours at 37°C after which the plates were washed as described previously. An AP-conjugated anti-mouse IgG secondary antibody (Jackson ImmunoResearch Laboratories, United Kingdom) was added at 1/1000 dilution in 0.05% Tween-20/PBS for 1 hour at 37°C. After the final wash, plates were incubated with pNPP (Sigma-Aldrich, Switzerland) phosphatase substrate solution, and read at 405 nm using an ELISA plate reader (Tecan, Switzerland; Fig. 4). All tested clones bind to full length TDP-43 with different affinities.

V. Example 5: Epitope mapping

Serum-free supernatants were harvested from stable hybridomas. The supernatants containing antibodies of interest were then screened by an indirect ELISA assay to determine epitopes. Epitopes were mapped using a library of TDP-43 15-mer peptides. Briefly, 96-well streptavidin-coated 96-well ELISA plates were incubated with 5 µg/mL of biotinylated 15-mer peptides spanning the amino acids (aa) 199-285 of human TDP-43 with 9 aa offset and 6 aa overlap. Peptide sequences are provided in Table 5. Plates were washed thoroughly with 0.05% Tween-20/PBS and then blocked with 1% bovine serum albumin (BSA) in 0.05% Tween-20/PBS for 1 hour at 37°C. The antibody contained in the hybridoma supernatant was then added at the indicated dilutions, and incubated for 2 hours at 37°C after which the plates were washed as described previously. An AP-conjugated anti-mouse IgG secondary antibody (Jackson ImmunoResearch Laboratories, United Kingdom) was added at 1/1000 dilution in 0.05% Tween-20/PBS for 1 hour at 37°C. After the final wash, plates were incubated with pNPP (Sigma-Aldrich, Switzerland) an AP substrate solution, and read at 405 nm using an ELISA plate reader (Tecan). Results are shown in Fig. 5A and OD values for binding to TP-24 and TP-25 peptides are provided in Table 7. All 19 antibodies bind within the sequence SEQ ID NO: 4 REFFSQYGDVMDVFIKPFRAFAF (TP-24 and TP-25 peptides as provided in Table 6).

Table 6: Sequences of 15-mer peptides for epitope mapping

Peptide name	Sequence
TP-23	TEDMTEDELREFFSQ
TP-24	REFFSQYGDVMDVFI
TP-25	VMDVFIPKPFRAFAF
TP-26	FRAFAFVTFADDQIA
TP-27	ADDQIAQSLCGEDLI
TP-28	CGEDLIKGISVHIS
TP-29	ISVHISNAEPKHNSN
TP-30	PKHNSNRQLERSGRF
TP-31	ERSGRFGGNPGGFGN

Table 7: OD values for binding to TP-24 and TP-25 peptides (defined in Table 6)

Hybridoma Clone	TP-24	TP-25
401A2A7	2.2	1.2
401A2C6	2.5	1.0
404D6A9	3.9	0.9
404D6E11	4.0	0.9
406E3D5	3.0	1.0
406E3G10	3.4	0.9
410H3B9	3.8	0.8
410H3G7	3.8	0.9
412A7B7	4.0	1.4
412E12A2	3.2	1.2
412E12F8	3.4	1.1
414A5D2	3.9	1.2
414A5H4	3.2	1.2
415C4C6	3.8	1.2
415C4F11	3.4	1.2
415H10A1	3.9	1.3
415H10B7	3.9	1.2
416A11B3	2.9	0.9
416A11G11	1.5	0.9

Furthermore, antibodies were tested using an indirect ELISA on a peptide library of 8-mer peptides with 7 aa overlap covering the sequence of human TDP-43 from aa 210 to aa 231, using the same ELISA method as describe previously in this section. Peptide sequences are shown in Table 8 and the results of the ELISA are shown in Figure 5B. The antibody 2E2-D3 (Abcam) with a reported epitope of 205-222 was used as control and did not bind to residues 215-222 of TDP-43 (Zhang et al. (2008) Neuroscience Letters 434, Issue 2, pp. 170-4). All antibodies tested bind within the sequence of the peptide GDVMDVFI (SEQ ID NO: 5, TDP-43 residues 215-222). The results also show that the control

antibody does not bind any of the peptides indicating that it has a different epitope from the antibodies presented here.

Table 8: Sequences of 8-mer peptides for epitope mapping

Peptide name	Sequence
TDP-208	REFFSQYG
TDP-209	EFFSQYGD
TDP-210	FFSQYGDV
TDP-211	FSQYGDVM
TDP-212	SQYGDVMD
TDP-213	QYGDVMDV
TDP-214	YGDVMDVF
TDP-215	GDVMDVFI
TDP-216	DVMDVFIP
TDP-217	VMDVFIPK
TDP-218	MDVFIPKP
TDP-219	DVFIPKPF
TDP-220	VFIPKPFR
TDP-221	FIPKPFRA
TDP-222	IPKPFRAF
TDP-223	PKPFRAFA
TDP-224	KPFRAFAF
TDP-220	VFIPKPFR

VI. Example 6: Detection of TDP-43 in brain tissues from FTD/ALS patients

Target engagement was evaluated in immunohistochemistry experiments on tissues from FTD patient brains. The brain samples, human FTD tissues were obtained from The Netherlands Brain Bank (frontal cortex), Netherlands Institute for Neuroscience, Amsterdam (open access: www.brainbank.nl). All Material has been collected from donors from whom a written informed consent for brain autopsy and the use of the material and clinical information for research purposes has been obtained by the NBB. Also, human FTD tissues were obtained from the Department of Neuropathology, University Hospital Tübingen (frontal cortex and hippocampus). Immunohistochemistry was performed on 10 µm thick frozen sections using fluorescent secondary antibody detection or on 6 µm thick paraffin embedded sections using DAB detection. The following antibodies were used as controls: rabbit polyclonal pan TDP-43 antibody (Proteintech, 10782-2-AP) to detect pathological inclusions and physiological nuclear

TDP-43; rabbit monoclonal phospho TDP-43 p409/410 antibody (Cosmobio, TIP-TD-P02) and rat monoclonal phospho TDP-43 p409/410 antibody (Millipore, MAB N14) to detect pathological aggregated and phosphorylated TDP-43.

Antibodies in the present invention specifically bind to misfolded, aggregated TDP-43 in the cytoplasm in Type A/C pathology (Fig. 6) and in Type B pathology (Fig. 7) and do not bind to physiological nuclear TDP-43 in patient nor in control brains. Evaluation of binding and signal to background ration is summarized in Table 9.

Table 9: Detection of TDP-43 in brain tissues from FTD/ALS patients

Hybridoma clone	IHC detection of misfolded aggregates – FTD Type A pathology	IHC detection of nuclear physiological TDP-43 – FTD type A pathology	IHC detection of misfolded aggregates - FTD Type B pathology
401A2A7	++	+/-	NA
401A2C6	+++	+/-	+++
404D6A9	++	-	NA
404D6E11	+	-	NA
406E3D5	+	-	+
406E3G10	++	-	NA
410H3B9	++	-	+++
410H3G7	+++	-	NA
412A7B7	+++	-	+++
412E12A2	+++	-	++
412E12F8	+++	-	NA
414A5D2	++	-	++
414A5H4	++	-	NA
415C4C6	++	-	++
415C4F11	++	-	NA
415H10A1	++	-	NA
415H10B7	+++	-	NA
416A11B3	++	-	+
416A11G11	++	-	NA

NA data not available; - absent; +/- not clear; + weak; ++ medium; +++ abundant

VII. Example 7: Affinity/avidity measurements using SPR

Binding affinity to FL TDP-43 was evaluated by determining the dissociation constant (KD) using surface plasmon resonance (SPR; Biacore 8K, GE Healthcare Life Sciences). Anti-mouse IgG was immobilized on a CM5 Series S sensor chip (GE Healthcare Life Sciences) by amine coupling. Immobilization of anti-IgG was done at a concentration of 30 µg/ml in 10 mM sodium acetate (pH 5.5) with a flow rate of 10 µl/min for 500 s. The purified antibodies being tested, and the control antibody

(2E2-D3), were injected at a concentration of 1 µg/ml at a flow rate of 10 µl/min for 500 s in 10 mM Na-acetate (pH 5.5). To evaluate KDs, recombinant human FL TDP-43 monomer analyte was injected at 2-fold dilutions starting from 400 nM and diluting down to 1.6 nM using single cycle kinetics. The protein analyte was injected at a flow rate of 20 µl/min for 600 s contact time and a 1200 s dissociation phase, without intermediate regeneration steps. Result obtained from kinetics was evaluated using a 1:1 binding model analysis. The affinities for 16 antibodies are shown in Table 10.

Avidity measurements were performed on an SPR instrument (Biacore T200, GE Healthcare Life Sciences) using CM5 Series S sensor chips. Recombinant human FL TDP-43 monomers or aggregated recombinant human FL TDP-43 was immobilized on a CM5 chip using amine coupling, injecting at a flow rate of 5 µl/min for 420 seconds. Conditions were optimized so that less than 200 RU protein was immobilized. Binding of the antibodies and the control antibody (2E2-D3) were obtained by injecting at: 1.37, 4.11, 12.33, 37, 111, and 333 nM in 1x PBS P+ at a flow rate of 50 µl/min for 90 s contact time and 600 s dissociation phase, with three regeneration cycles of the ligand surface by 10 mM Glycine-HCl (pH 1.7). Kinetics were analyzed using a 1:1 fitting model (see Figure 8).

Table 10: Affinity and avidity data

Antibody	SPR affinity (single cycle kinetics): KD [nM] on TDP-43 monomer	SPR avidity: KD [nM] on TDP-43 monomer	SPR avidity: KD [nM] on TDP-43 aggregates
ACI-7062-401A2-Ab1	193	1.4	1.6
ACI-7062-401A2-Ab2	149	2.1	0.3
ACI-7062-404D6-Ab1	NA	NA	NA
ACI-7062-404D6-Ab2	NA	NA	NA
ACI-7062-406E3-Ab1	193	0.8	0.2
ACI-7062-406E3-Ab2	101	0.3	0.4
ACI-7062-410H3-Ab1	242	6.0	19.2
ACI-7062-410H3-Ab2	NA	2.5	31.0
ACI-7062-412A7-Ab1	66.1	1.0	0.3
ACI-7062-412E12-Ab1	327	1.0	0.9
ACI-7062-412E12-Ab2	184	1.3	0.4
ACI-7062-414A5-Ab1	145	3.0	NA
ACI-7062-414A5-Ab2	205	1.1	4.6

ACI-7062-415C4-Ab1	379	2.7	0.7
ACI-7062-415C4-Ab2	NA	1.1	1.2
ACI-7062-415H10-Ab1	NA	NA	NA
ACI-7062-415H10-Ab2	NA	1.1	NA
ACI-7062-416A11-Ab1	307	2.4	1.2
ACI-7062-416A11-Ab2	292	1.2	1.0

VIII. Example 8: Antibody sequencing

Clonal hybridoma cell lysates were used for variable region gene sequencing. Mouse hybridomas were harvested and lysed using a lysis buffer containing guanidinium salts that deactivates RNases. Genomic DNA was then eliminated by RNase-free DNase, and RNA was purified with a silica-based affinity column using multiple washes and eluted from the column using RNase-free water. Once the RNA was extracted, its purity and concentration was measured spectrophotometrically. The integrity of the RNA was assessed on a denaturing agarose gel and RNA was reverse transcribed into cDNA using reverse transcriptase (RT). Before adding the reaction mixture, the RNA was heated to 70°C for 10 min in order to disrupt RNA secondary structures. The RT products were directly used for PCR amplification. For high-fidelity PCR amplification of the cDNA, each of the variable region primers corresponding to the different gene families encoding for antibodies were individually mixed with the constant primer, for VH and VL separately in a total reaction volume of 50 µl. In first intention, a degenerate primer pool was used (12 for VH and 12 for VL) and, depending on the results, a second pool was used to obtain PCR products. After the PCR reaction, the products were analyzed by gel electrophoresis on 2% agarose gels stained with ethidium bromide. The PCR products for VL and VH were individually purified on an agarose gel using tris-acetate-EDTA (TAE). The purified fragments excised from the gel were then sequenced using the dye-terminator sequencing method. The same primers as those used for PCR were used for the sequencing reaction. Sequencing was carried out in both directions to provide overlap at both ends. The sequences were analyzed using multiple sequence alignment (Clustal tool). Sequences were annotated following the algorithm of IMGT Colliers de Perles as described in Pommié C et al., *Journal of Molecular Recognition*, 17, 17-32 (2004). Protein sequences for selected heavy (VH) and light (VL) chain variable domains, and their complementarity-determining regions (CDRs) are shown in Table 11.

Table 11: Antibody variable regions sequences

SEQ ID NO:	Description including antibody name and the sequence information	Hybridoma clone	Sequence
10	ACI-7062-401A2-Ab2-VL Peptide sequence of the light chain variable domain with tail	401A2C6	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGDQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFSLTISSVQAEDLADYFCQQHYSI PLTFGAGTKLELKRADAAPTVSIFP T
11	ACI-7062-401A2-Ab2-VL FR1		DIVMTQSPSSLAMSVGQKVTMSC
12	ACI-7062-401A2-Ab2-VL CDR1		KSSQSLLNSGDQKNYLA
13	ACI-7062-401A2-Ab2-VL FR2		WYQQKPGQSPELLLY
14	ACI-7062-401A2-Ab2-VL CDR2		FASTRAS
15	ACI-7062-401A2-Ab2-VL FR3		GVPDRFIGSGSGTDFSLTISSVQAED LADYFC
16	ACI-7062-401A2-Ab2-VL CDR3		QQHYSIPLT
17	ACI-7062-401A2-Ab2-VL FR4		FGAGTKLELKRA
18	ACI-7062-401A2-Ab2-VL Tail		DAAPTVSIFPT
19	ACI-7062-401A2-Ab2-VL Nucleotide sequence of the light chain variable domain with tail	92	GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCACATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCGATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTGTTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCTCTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC

			GTTTCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCTGATGCTGCA CCAACTGTATCCATCTTCCCTACC
20	ACI-7062-401A2-Ab2-VH Peptide sequence of the heavy chain variable domain with tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSRFGMHVWRQAPEKGLEWV AYIRSGSDIIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYYCAR SGTTVPFDYWGGQTSLTVSSAKTTP PSVYPLAPGSAAQTNSMVTLGCLV KGYFP
21	ACI-7062-401A2-Ab2-VH FR1		DVQLVESGGGLVQPGGSRRLSCAA SGFTFS
22	ACI-7062-401A2-Ab2-VH CDR1		RFGMH
23	ACI-7062-401A2-Ab2-VH FR2		WVRQAPEKGLEWVA
24	ACI-7062-401A2-Ab2-VH CDR2		YIRSGSDIIYYADSVKG
25	ACI-7062-401A2-Ab2-VH FR3		RFTISRDNPENTLFLQMTSLRSEDAMYYCAR
26	ACI-7062-401A2-Ab2-VH CDR3		SGTTVPFDY
27	ACI-7062-401A2-Ab2-VH FR4		WGQGTSLTVSS
28	ACI-7062-401A2-Ab2-VH Tail		AKTTPPSVYPLAPGSAAQTNSMVTL GCLVKGYFP
29	ACI-7062-401A2-Ab2-VH Nucleotide sequence of the heavy chain variable domain with tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGGT TTGGAATGCACTGGGTTCGCCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCCGATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTCACCATCTC CAGAGACAATCCCGAGAACACCC TGTTCTGCAAATGACCAGTCTAA

			GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA GCCAAAACGACACCCCCATCTGTC TATCCACTGGCCCCTGGATCTGCT GCCCAAATAACTCCATGGTGACC CTGGGATGCCTGGTCAAGGGCTAT TTCCCT
30	ACI-7062-412A7-Ab1-VL Peptide sequence of the light chain variable domain with tail	412A7B7	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGNQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFTLTISVVQAEDLADYFCQQHYS IPLTFGAGTKLELKRADAAPTVSIFP
31	ACI-7062-412A7-Ab1-VL FR1		DIVMTQSPSSLAMSVGQKVTMSC
32	ACI-7062-412A7-Ab1-VL CDR1		KSSQSLLNSGNQKNYLA
33	ACI-7062-412A7-Ab1-VL FR2		WYQQKPGQSPPELLLY
34	ACI-7062-412A7-Ab1-VL CDR2		FASTRAS
35	ACI-7062-412A7-Ab1-VL FR3		GVPDRFIGSGSGTDFTLTISVVQAED LADYFC
36	ACI-7062-412A7-Ab1-VL CDR3		QQHYSIPLT
37	ACI-7062-412A7-Ab1-VL FR4		FGAGTKLELKRA
38	ACI-7062-412A7-Ab1-VL Tail		DAAPTVSIFP
39	ACI-7062-412A7-Ab1-VL Nucleotide sequence of the light chain variable domain with tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCAATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTATTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCACTCTT

			ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCTGATGCTGCA CCAACTGTATCCATCTTCCCA
40	ACI-7062-412A7-Ab1-VH Peptide sequence of the heavy chain variable domain with tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSSFGMHWVRQAPEKGLEWV AYIRSGSDIIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYYCAR SGTTVPFDYWGGQGTSLTVSSAKTTP PSVYPLAPGCGDITGSSVTLC
41	ACI-7062-412A7-Ab1-VH FR1		DVQLVESGGGLVQPGGSRRLSCAA SGFTFS
42	ACI-7062-412A7-Ab1-VH CDR1		SFGMH
43	ACI-7062-412A7-Ab1-VH FR2		WVRQAPEKGLEWVA
44	ACI-7062-412A7-Ab1-VH CDR2		YIRSGSDIIYYADSVKG
45	ACI-7062-412A7-Ab1-VH FR3		RFTISRDNPENTLFLQMTSLRSEDTA MYTCAR
46	ACI-7062-412A7-Ab1-VH CDR3		SGTTVPFDY
47	ACI-7062-412A7-Ab1-VH FR4		WGQGTSLTVSS
48	ACI-7062-412A7-Ab1-VH Tail		AKTTPPSVYPLAPGCGDITGSSVTLC GC
49	ACI-7062-412A7-Ab1-VH Nucleotide sequence of the heavy chain variable domain with tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCCGATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTCAACATCTC CAGAGACAATCCCGAGAACACCC

			TG TTCCTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA GCCAAAACAACACCCCCATCAGT CTATCCACTGGCCCCTGGGTGTGG AGATACAACTGGTTCCTCCGTGAC TCTGGGATGC
50	ACI-7062-406E3-Ab1-VL Peptide sequence of the light chain variable domain with tail	406E3D5	DVLMTQTPLSLPVSLGDRASISCRSS QSIVHRSGNTYLEWYLQKPGQSPK LLIYKVS NRFSGVPDRFSGSGSGTD FTLKISRVEAEDLGVYYCFQGSHVP TFGAGTKLELKRADAAPTVSIFPPSS E
51	ACI-7062-406E3-Ab1-VL FR1		DVLMTQTPLSLPVSLGDRASISC
52	ACI-7062-406E3-Ab1-VL CDR1		RSSQSIVHRSGNTYLE
53	ACI-7062-406E3-Ab1-VL FR2		WYLQKPGQSPKLLIY
54	ACI-7062-406E3-Ab1-VL CDR2		KVSNRFS
55	ACI-7062-406E3-Ab1-VL FR3		GVPDRFSGSGSGTDFTLKISRVEAE DLGVYYC
56	ACI-7062-406E3-Ab1-VL CDR3		FQGSHVPT
57	ACI-7062-406E3-Ab1-VL FR4		FGAGTKLELKRA
58	ACI-7062-406E3-Ab1-VL Tail		DAAPTVSIFPPSSE
59	ACI-7062-406E3-Ab1-VL Nucleotide sequence of the light chain variable domain with tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCGAGCCTCCATCTCTTG CAGA TCTAGTCAGAGCATTGTACATCGT AGTGGAACACCTATTTAGAGTG GTACCTGCAGAAACCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG TTTCCAACCGATTTTCTGGGGTCC CAGACAGGTT CAGTGGCAGTGGA

		TCAGGGACAGATTTTCACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTTACATGTTCCACGTTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCTGATGCTGCACCAAC TGTATCCATCTTCCCACCATCCAG TGAG
60	ACI-7062-406E3-Ab1-VH Peptide sequence of the heavy chain variable domain with tail	QVTLKESGPAILQPSQTLTCSFSG FSLTTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYNTALKSRLTVSKD TSNNQVFLKIASVDTADTATYYCA RVYGNLYYFAYWGQGTTLTVSSA KTTAPSVYPLAPVCGDTTGSSVTLG CLVKGY
61	ACI-7062-406E3-Ab1-VH FR1	QVTLKESGPAILQPSQTLTCSFSG FSLT
62	ACI-7062-406E3-Ab1-VH CDR1	TYGIGVG
63	ACI-7062-406E3-Ab1-VH FR2	WIRQPSGKGLEWLA
64	ACI-7062-406E3-Ab1-VH CDR2	HIWWNDNKYYNTALKS
65	ACI-7062-406E3-Ab1-VH FR3	RLTVSKDTSNNQVFLKIASVDTADT ATYYCAR
66	ACI-7062-406E3-Ab1-VH CDR3	VYGNLYYFAY
67	ACI-7062-406E3-Ab1-VH FR4	WGQGTTLTVSS
68	ACI-7062-406E3-Ab1-VH Tail	AKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGY
69	ACI-7062-406E3-Ab1-VH Nucleotide sequence of the heavy chain variable domain with tail	CAGGTTACTCTGAAAGAGTCTGGC CCTGCGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTTCTTTCT CTGGGTTTTCACTGACCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGAAT

			GATAATAAGTACTATAACACAGC CCTGAAGAGCCGGCTCACTGTCTC CAAGGATACCTCCAACAACCAGG TATTCCTCAAGATCGCCAGTGTAG ACACTGCAGATACTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TGTACTACTTTGCCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CAGCCAAAACAACAGCCCCATCG GTCTATCCACTGGCCCCTGTGTGT GGAGATACAACTGGCTCCTCGGT GACTCTAGGATGCCTGGTCAAGG GTTAT
70	ACI-7062-404D6-Ab2-VL Peptide sequence of the light chain variable domain with tail	404D6E11	DVLMTQTPLSLPVSLGDQASISCRS SQSIVHGSGNTYLEWYLQKPGQSP KLLIYKVSNRFSGVPDRFSGSGSGT DFTLRISRVEAEDLGVYYCFQGSHV PTFGAGTKLELKRADAAPTVSIFPPS S
71	ACI-7062-404D6-Ab2-VL FR1		DVLMTQTPLSLPVSLGDQASISC
72	ACI-7062-404D6-Ab2-VL CDR1		RSSQSIVHGSGNTYLE
73	ACI-7062-404D6-Ab2-VL FR2		WYLQKPGQSPKLLIY
74	ACI-7062-404D6-Ab2-VL CDR2		KVSNRFS
75	ACI-7062-404D6-Ab2-VL FR3		GVPDRFSGSGSGTDFTLRISRVEAE DLGVYYC
76	ACI-7062-404D6-Ab2-VL CDR3		FQGSHVPT
77	ACI-7062-404D6-Ab2-VL FR4		FGAGTKLELKRA
78	ACI-7062-404D6-Ab2-VL Tail		DAAPTVSIFPPSS
79	ACI-7062-404D6-Ab2-VL Nucleotide sequence of the light chain variable domain with tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCAAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATGGT TCTGGAAACACCTATTTAGAATGG

		TACCTGCAGAAACCAGGCCAGTC TCCAAAGCTCCTGATCTACAAAGT TTCCAACCGATTTTCTGGGGTCCC AGACAGGTTTCAGTGGCAGTGGAT CAGGGACAGATTTACACTCAGG ATCAGCAGAGTGGAGGCTGAGGA TCTGGGAGTTTATTACTGCTTTCA AGGTTACATGTTCCCACGTTCTGG TGCTGGGACCAAGCTGGAGCTGA AACGGGCTGATGCTGCACCAACT GTATCCATCTTCCCACCATCCAGT
80	ACI-7062-404D6-Ab2-VH Peptide sequence of the heavy chain variable domain with tail	QVTLKESGPGILQPSQTLSTCSFSG FSLSTYGIGVGWIRQPSGKGLEWLA HIWWNDYKYNTALKSRLTISKDT SNNRVFLKIASVDTADTATYYCAR VYGNLYYFDYWGQGTTTLTVSSATT TAPSW
81	ACI-7062-404D6-Ab2-VH FR1	QVTLKESGPGILQPSQTLSTCSFSG FSL
82	ACI-7062-404D6-Ab2-VH CDR1	TYGIGVG
83	ACI-7062-404D6-Ab2-VH FR2	WIRQPSGKGLEWLA
84	ACI-7062-404D6-Ab2-VH CDR2	HIWWNDYKYNTALKS
85	ACI-7062-404D6-Ab2-VH FR3	RLTISKDTSNNRVFLKIASVDTADT ATYYCAR
86	ACI-7062-404D6-Ab2-VH CDR3	VYGNLYYFDY
87	ACI-7062-404D6-Ab2-VH FR4	WGQGTTTLTVSS
88	ACI-7062-404D6-Ab2-VH Tail	ATTTAPSW
89	ACI-7062-404D6-Ab2-VH Nucleotide sequence of the heavy chain variable domain with tail	CAGGTTACTCTGAAAGAGTCTGGC CCTGGGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTTCTTTCT CTGGGTTTTCACTGAGCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG

			TGGCTGGCACACATTTGGTGGGAAT GATTATAAGTACTATAACACAGCC CTGAAGAGCCGGCTCACAATCTCC AAGGATACCTCCAACAACCGGGT ATTCCTCAAGATCGCCAGTGTGGA CACTGCAGATACTGCCACATACTA CTGTGCTCGAGTCTATGGTAACCT GTACTACTTTGACTACTGGGGCCA AGGCACCACTCTCACAGTCTCCTC AGCTACAACAACAGCCCCATCTTG GTCC
90	ACI-7062-410H3-Ab1-VL Peptide sequence of the light chain variable domain with tail	410H3B9	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGNQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFTLTISSVQAEDLADYFCQQHYS IPLTFGAGTKLELKRADAAPTVSIFP T
91	ACI-7062-410H3-Ab1-VL FR1		DIVMTQSPSSLAMSVGQKVTMSC
92	ACI-7062-410H3-Ab1-VL CDR1		KSSQSLLNSGNQKNYLA
93	ACI-7062-410H3-Ab1-VL FR2		WYQQKPGQSPPELLLY
94	ACI-7062-410H3-Ab1-VL CDR2		FASTRAS
95	ACI-7062-410H3-Ab1-VL FR3		GVPDRFIGSGSGTDFTLTISSVQAED LADYFC
96	ACI-7062-410H3-Ab1-VL CDR3		QQHYSIPLT
97	ACI-7062-410H3-Ab1-VL FR4		FGAGTKLELKRA
98	ACI-7062-410H3-Ab1-VL Tail		DAAPTVSIFPT
99	ACI-7062-410H3-Ab1-VL Nucleotide sequence of the light chain variable domain with tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCAGTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCAATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTGTTATAC

		TTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCCTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCTGATGCTGCA CCAACTGTATCCATCTTCCCTACC
100	ACI-7062-410H3-Ab1-VH Peptide sequence of the heavy chain variable domain with tail	DVQLVESGGGLVQPGGSRRLSCAA SGFTFSSFGMHVWRQAPEKGLEWV AYIRSGSDIIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYCAR SGTTVPFDYWGQGTSLTVSSAKTTP PSVYPLAPGSAAQTNSMVTLGCLV KGYFP
101	ACI-7062-410H3-Ab1-VH FR1	DVQLVESGGGLVQPGGSRRLSCAA SGFTFS
102	ACI-7062-410H3-Ab1-VH CDR1	SFGMH
103	ACI-7062-410H3-Ab1-VH FR2	WVRQAPEKGLEWVA
104	ACI-7062-410H3-Ab1-VH CDR2	YIRSGSDIIYYADSVKG
105	ACI-7062-410H3-Ab1-VH FR3	RFTISRDNPENTLFLQMTSLRSEDTA MYCAR
106	ACI-7062-410H3-Ab1-VH CDR3	SGTTVPFDY
107	ACI-7062-410H3-Ab1-VH FR4	WGQGTSLTVSS
108	ACI-7062-410H3-Ab1-VH Tail	AKTTPPSVYPLAPGSAAQTNSMVTL GCLVKGYFP
109	ACI-7062-410H3-Ab1-VH Nucleotide sequence of the heavy chain variable domain with tail	GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG

			GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTACCATCTC CAGAGACAATCCCGAGAACACCC TG TTCCTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA GCCAAAACGACACCCCCATCTGTC TATCCACTGGCCCCTGGATCTGCT GCCCAAATAACTCCATGGTGACC CTGGGATGCCTGGTCAAGGGCTAT TTCCCT
110	ACI-7062-414A5-Ab1-VL Peptide sequence of the light chain variable domain with tail	414A5D2	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSSNQKNYLAWYQQKPGQ SPKLLVYFASTRESGVPDRFIGSGSG TDFTLTINSVQAEDLADYFCQQHYS IPLTFGAGTKLELKRADAAPTVSIFP T
111	ACI-7062-414A5-Ab1-VL FR1		DIVMTQSPSSLAMSVGQKVTMSC
112	ACI-7062-414A5-Ab1-VL CDR1		KSSQSLLNSSNQKNYLA
113	ACI-7062-414A5-Ab1-VL FR2		WYQQKPGQSPKLLVY
114	ACI-7062-414A5-Ab1-VL CDR2		FASTRES
115	ACI-7062-414A5-Ab1-VL FR3		GVPDRFIGSGSGTDFTLTINSVQAED LADYFC
116	ACI-7062-414A5-Ab1-VL CDR3		QQHYSIPLT
117	ACI-7062-414A5-Ab1-VL FR4		FGAGTKLELKRA
118	ACI-7062-414A5-Ab1-VL Tail		DAAPTVSIFPT
119	ACI-7062-414A5-Ab1-VL Nucleotide sequence of the light chain variable domain with tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTAGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG

		TAGCAATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTAAACTTCTGGTATAC TTTGCATCCACTAGGGAATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTCTCACTCTT ACCATCAACAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCTGATGCTGCA CCAACTGTATCCATCTTCCCTACC
120	ACI-7062-414A5-Ab1-VH Peptide sequence of the heavy chain variable domain with tail	DVQLVESGGGLVQPGGSRRLSCAA SGFTFSSFGMHVWRQAPEKGLEWV AYIRSGSDIIYYADTVKGRFTISRDN PENTLFLEMTRLRSEDAMYYCAR SGTTVPFDYWQGTSITVSSAKTT APSVYPLAPVCGDTTGSSVTLGCLV KGYFP
121	ACI-7062-414A5-Ab1-VH FR1	DVQLVESGGGLVQPGGSRRLSCAA SGFTFS
122	ACI-7062-414A5-Ab1-VH CDR1	SFGMH
123	ACI-7062-414A5-Ab1-VH FR2	WVRQAPEKGLEWVA
124	ACI-7062-414A5-Ab1-VH CDR2	YIRSGSDIIYYADTVKG
125	ACI-7062-414A5-Ab1-VH FR3	RFTISRDNPENTLFLEMTRLRSEDTA MYTCAR
126	ACI-7062-414A5-Ab1-VH CDR3	SGTTVPFDY
127	ACI-7062-414A5-Ab1-VH FR4	WGQGTSLTVSS
128	ACI-7062-414A5-Ab1-VH Tail	AKTTAPSVYPLAPVCGDTTGSSVTL GCLVKGYFP
129	ACI-7062-414A5-Ab1-VH Nucleotide sequence of the heavy chain variable domain	GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG

	with tail		CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACAC AGTGAAGGGCCGATTACCATCTC CAGAGACAATCCCGAGAACACCC TGTTTTTGGAAATGACCAGACTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA GCCAAAACAACAGCCCCATCGGT CTATCCACTGGCCCCTGTGTGTGG AGATACAACCTGGCTCCTCGGTGAC TCTAGGATGCCTGGTCAAGGGTTA TTCCCTGA
130	ACI-7062-412E12-Ab1-VL Peptide sequence of the light chain variable domain with tail	412E12A2	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGDQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFSLTISSVQAEDLADYFCQQHYSI PLTFGAGTKLELKRADAAPTVSIFP
131	ACI-7062-412E12-Ab1-VL FR1		DIVMTQSPSSLAMSVGQKVTMSC
132	ACI-7062-412E12-Ab1-VL CDR1		KSSQSLLNSGDQKNYLA
133	ACI-7062-412E12-Ab1-VL FR2		WYQQKPGQSPELLLY
134	ACI-7062-412E12-Ab1-VL CDR2		FASTRAS
135	ACI-7062-412E12-Ab1-VL FR3		GVPDRFIGSGSGTDFSLTISSVQAED LADYFC
136	ACI-7062-412E12-Ab1-VL CDR3		QQHYSIPLT
137	ACI-7062-412E12-Ab1-VL FR4		FGAGTKLELKRA

138	ACI-7062-412E12-Ab1-VL Tail	DAAPTVSIFP
139	ACI-7062-412E12-Ab1-VL Nucleotide sequence of the light chain variable domain with tail	GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCGATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTGTTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCTCTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCTGATGCTGCA CCAACTGTATCCATCTTCCCA
140	ACI-7062-412E12-Ab1-VH Peptide sequence of the heavy chain variable domain with tail	DVQLVESGGGLVQPGGSRRLSCAA SGFTFSRFGMHVWRQAPEKGLEWV AYIRSGSDIIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYYCAR SGTTVPFDYWQGTSITVSSAKTTP PSVYP
141	ACI-7062-412E12-Ab1-VH FR1	DVQLVESGGGLVQPGGSRRLSCAA SGFTFS
142	ACI-7062-412E12-Ab1-VH CDR1	RFGMH
143	ACI-7062-412E12-Ab1-VH FR2	WVRQAPEKGLEWVA
144	ACI-7062-412E12-Ab1-VH CDR2	YIRSGSDIIYYADSVKG
145	ACI-7062-412E12-Ab1-VH FR3	RFTISRDNPENTLFLQMTSLRSEDTA MYTCAR
146	ACI-7062-412E12-Ab1-VH CDR3	SGTTVPFDY
147	ACI-7062-412E12-Ab1 -VH	WGQGTSLTVSS

	FR4		
148	ACI-7062-412E12-Ab1-VH Tail		AKTTPPSVYP
149	ACI-7062-412E12-Ab1-VH Nucleotide sequence of the heavy chain variable domain with tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGGT TTGGAATGCACTGGGTTCGCCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTCACCATCTC CAGAGACAATCCCGAGAACACCC TGTTCTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTCA GCCAAAACGACACCCCCATCTGTC TATCCA
150	ACI-7062-416A11-Ab1-VL Peptide sequence of the light chain variable domain with tail	416A11B3	DVLMTQTPLSLPVSLGDRASISCRSS QSIVHSSGNTYLEWYLQKPGQSPKL LIYKVSNRFSGVPDRFSGSGGTDF TLKISRVEAEDLGVYYCFQGSRVPT FGAGTKLELKRADAAPT VSI
151	ACI-7062-416A11-Ab1-VL FR1		DVLMTQTPLSLPVSLGDRASISC
152	ACI-7062-416A11-Ab1-VL CDR1		RSSQSIVHSSGNTYLE
153	ACI-7062-416A11-Ab1-VL FR2		WYLQKPGQSPKLLIY
154	ACI-7062-416A11-Ab1-VL CDR2		KVSNRFS
155	ACI-7062-416A11-Ab1-VL FR3		GVPDRFSGSGGTDFTLKISRVEAE DLGVYYC
156	ACI-7062-416A11-Ab1-VL		FQGSRVPT

	CDR3		
157	ACI-7062-416A11-Ab1-VL FR4		FGAGTKLELKRA
158	ACI-7062-416A11-Ab1-VH Tail		DAAPT VSI
159	ACI-7062-416A11-Ab1-VL Nucleotide Sequence of the light chain variable domain with tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCGAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATAGT AGTGGAAACACCTATTTAGAATG GTACCTGCAGAAGCCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG TTTCCAACCGATTTTCTGGGGTCC CAGACAGGTT CAGTGGCAGTGGA TCAGGGACAGATTT CACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTT CACGTGTTCCACGTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCTGATGCTGCACCAAC TGTATCCATCT
160	ACI-7062-416A11-Ab1-VH Peptide sequence of the heavy chain variable domain with tail		QVTLKESGPGILQSSQTL SLTCSFSG FSLSTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYNTALKSRLTISKDT SNNQVFLKIASVDTADAATYYCAR VYGNLYYFGYWGQGTTLTVSSAKT TAPSVYPLAPVCGDTTGSSVT
161	ACI-7062-416A11-Ab1-VH FR1		QVTLKESGPGILQSSQTL SLTCSFSG FSL S
162	ACI-7062-416A11-Ab1-VH CDR1		TYGIGVG
163	ACI-7062-416A11-Ab1-VH FR2		WIRQPSGKGLEWLA
164	ACI-7062-416A11-Ab1-VH CDR2		HIWWNDNKYYNTALKS
165	ACI-7062-416A11-Ab1-VH		RLTISKDT SNNQVFLKIASVDTADA

	FR3		ATYYCAR
166	ACI-7062-416A11-Ab1-VH CDR3		VYGNLYYFGY
167	ACI-7062-416A11-Ab1-VH FR4		WGQGTTLTVSS
168	ACI-7062-416A11-Ab1-VH Tail		AKTTAPSVYPLAPVCGDTTGSSVT
169	ACI-7062-416A11-Ab1-VH Nucleotide sequence of the heavy chain variable domain with tail		CAGGTTACTCTGAAAGAGTCTGGC CCTGGGATATTGCAGTCCTCCCAG ACCCTCAGTCTGACTTGTTCTTTCT CTGGATTTTCACTGAGCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGGAAT GATAATAAGTACTATAACACAGC CCTGAAGAGCCGACTCACAATCTC CAAGGATACCTCCAACAACCAGG TATTCCTCAAGATCGCCAGTGTGG ACACTGCAGATGCTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TATACTACTTTGGCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CAGCCAAAACAACAGCCCCATCG GTCTATCCACTGGCCCCTGTGTGT GGAGATACAACTGGCTCCTCGGT GACTC
170	ACI-7062-406E3-Ab2-VL Peptide sequence of the light chain variable domain without tail	406E3G10	DVLMTQTPLSLPVSLGDRASISCRSS QSIVHRSGNTYLEWYLQKPGQSPK LLIYKVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDLGVYYCFQGSHVP TFGAGTKLELKRA
171	ACI-7062-406E3-Ab2-VL-FR1		DVLMTQTPLSLPVSLGDRASISC
172	ACI-7062-406E3-Ab2-VL- CDR1		RSSQSIVHRSGNTYLE
173	ACI-7062-406E3-Ab2-VL-FR2		WYLQKPGQSPKLLIY
174	ACI-7062-406E3-Ab2-VL-		KVSNRFS

	CDR2		
175	ACI-7062-406E3-Ab2-VL-FR3		GVPDRFSGSGSGTDFTLKISRVEAE DLGVYYC
176	ACI-7062-406E3-Ab2-VL- CDR3		FQGSHVPT
177	ACI-7062-406E3-Ab2-VL-FR4		FGAGTKLELKRA
178	ACI-7062-406E3-Ab2-VL-Tail		DAAPTVSIFPPSSEQ
179	ACI-7062-406E3-Ab2-VL Nucleotide sequence of the light chain variable domain without tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCGAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATCGT AGTGGAACACCTATTTAGAGTG GTACCTGCAGAAACCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG TTTCCAACCGATTTTCTGGGGTCC CAGACAGGTTTCAGTGGCAGTGGA TCAGGGACAGATTTCACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTTACATGTTCCACGTTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCT
180	ACI-7062-406E3-Ab2-VH Peptide sequence of the heavy chain variable domain without tail		QVTLKESGPAILQPSQTLSTCSFSG FSLTTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYNTALKSRLTVSKD TSNNQVFLKIASVDTADTATYYCA RVYGNLYYFAYWGQGTTTLTVSS
181	ACI-7062-406E3-Ab2-VH-FR1		QVTLKESGPAILQPSQTLSTCSFSG FSLT
182	ACI-7062-406E3-Ab2-VH- CDR1		TYGIGVG
183	ACI-7062-406E3-Ab2-VH-FR2		WIRQPSGKGLEWLA
184	ACI-7062-406E3-Ab2-VH- CDR2		HIWWNDNKYYNTALKS
185	ACI-7062-406E3-Ab2-VH-FR3		RLTVSKDTSNNQVFLKIASVDTADT ATYYCAR

186	ACI-7062-406E3-Ab2-VH-CDR3		VYGNLYYFAY
187	ACI-7062-406E3-Ab2-VH-FR4		WGQGTTLTVSS
188	ACI-7062-406E3-Ab2-VH-Tail		AKTTAPSVYPLAPVCGDTTGSSVTL
189	ACI-7062-406E3-Ab2-VH Nucleotide sequence of the heavy chain variable domain without tail		CAGGTTACTCTGAAAGAGTCTGGC CCTGCGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTTCTTTCT CTGGGTTTTCACTGACCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGGAAT GATAATAAGTACTATAACACAGC CCTGAAGAGCCGGCTCACTGTCTC CAAGGATACCTCCAACAACCAGG TATTCCTCAAGATCGCCAGTGTAG ACACTGCAGATACTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TGTAATACTTTGCCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CA
190	ACI-7062-415C4-Ab1-VL Peptide sequence of the light chain variable domain without tail	415C4C6	DVLMTQTPLSLPVSLGDQASISCRS SQSIVHSTGNTYLEWYLQKPGQSPK LLIYKVSNRFSGVPDRFSGSGSGTD FTLKISRVEAEDLGVYYCFQGSRVP TFGAGTKLELKRA
191	ACI-7062-415C4-Ab1-VL-FR1		DVLMTQTPLSLPVSLGDQASISC
192	ACI-7062-415C4-Ab1-VL-CDR1		RSSQSIVHSTGNTYLE
193	ACI-7062-415C4-Ab1-VL-FR2		WYLQKPGQSPKLLIY
194	ACI-7062-415C4-Ab1-VL-CDR2		KVSNRFS
195	ACI-7062-415C4-Ab1-VL-FR3		GVPDRFSGSGSGTDFTLKISRVEAE DLGVYYC
196	ACI-7062-415C4-Ab1-VL-CDR3		FQGSRVPT
197	ACI-7062-415C4-Ab1-VL-FR4		FGAGTKLELKRA

198	ACI-7062-415C4-Ab1-VL-Tail	DAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGV
199	ACI-7062-415C4-Ab1-VL Nucleotide sequence of the light chain variable domain without tail	L GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCAAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATAGT ACTGGAAACACCTATTTGGAATG GTACCTGCAGAAACCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG TTCCAACCGATTTTCTGGGGTCC CAGACAGGTTTCAGTGGCAGTGGA TCAGGGACAGATTTCACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTTACGTGTTCCACGTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCT
200	ACI-7062-415C4-Ab1-VH Peptide sequence of the heavy chain variable domain without tail	QVTLKESGPGILQPSQTLSTCSFSG FSLSTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYKTALKSRLTISKDT SNNQVFLKIASVDTADSATYYCAR VYGNLYYFGYWQGTTTLTVSS
201	ACI-7062-415C4-Ab1-VH-FR1	QVTLKESGPGILQPSQTLSTCSFSG FSLS
202	ACI-7062-415C4-Ab1-VH- CDR1	TYGIGVG
203	ACI-7062-415C4-Ab1-VH-FR2	WIRQPSGKGLEWLA
204	ACI-7062-415C4-Ab1-VH- CDR2	HIWWNDNKYYKTALKS
205	ACI-7062-415C4-Ab1-VH-FR3	RLTISKDTSNNQVFLKIASVDTADS ATYYCAR
206	ACI-7062-415C4-Ab1-VH- CDR3	VYGNLYYFGY
207	ACI-7062-415C4-Ab1-VH-FR4	WQGTTTLTVSS
208	ACI-7062-415C4-Ab1-VH-Tail	AKTTPPSVYPLAPGSAAQTNSMVTL

			GCLVKGY
209	ACI-7062-415C4-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail		CAGGTTACTCTGAAAGAGTCTGGC CCTGGGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTCTTTCT CTGGGTTTTCACTGAGCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCCTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGGAAT GATAATAAGTACTATAAGACAGC CCTGAAGAGCCGGCTCACAATCTC CAAGGACACCTCCAACAACCAGG TTTCCTCAAGATCGCCAGTGTGG ACACTGCAGATTCTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TGTAATACTTTGGCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CA
210	ACI-7062-415H10-Ab2-VL Peptide sequence of the light chain variable domain without tail	415H10B7	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSSNQKNYLAWYQQKPGQ SPKLLIYFASTRESGVPDRFIGSGSG TDFTLTISSVQAEDLADYFCQQHYG IPLTFGAGTKLELKRA
211	ACI-7062-415H10-Ab2-VL-FR1		DIVMTQSPSSLAMSVGQKVTMSC
212	ACI-7062-415H10-Ab2-VL-CDR1		KSSQSLLNSSNQKNYLA
213	ACI-7062-415H10-Ab2-VL-FR2		WYQQKPGQSPKLLIY
214	ACI-7062-415H10-Ab2-VL-CDR2		FASTRES
215	ACI-7062-415H10-Ab2-VL-FR3		GVPDRFIGSGSGTDFTLTISSVQAED LADYFC
216	ACI-7062-415H10-Ab2-VL-CDR3		QQHYGIPLT
217	ACI-7062-415H10-Ab2-VL-FR4		FGAGTKLELKRA

218	ACI-7062-415H10-Ab2-VL-Tail	DAAPTVSIFP
219	ACI-7062-415H10-Ab2-VL Nucleotide sequence of the light chain variable domain without tail	GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTAGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TAGCAATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTAAACTTCTAATATAC TTTGCATCCACTAGGGAATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTCTACTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATGGCATTCCGCTCAC GTTTCGGTGCTGGGACCAAGCTGG AACTGAAACGGGCT
220	ACI-7062-415H10-Ab2-VH Peptide sequence of the heavy chain variable domain without tail	DVQLVESGGGLVQPGGSRKLSCAA SGFTFSSFGMHVWRQAPEKGLEWV AYISSGSSNIYYTDTVKGRFTISRDN PKNTLFLQMTSLRSEDTAIYYCARS GTTVPFDYWGQGTTTLTVSS
221	ACI-7062-415H10-Ab2-VH- FR1	DVQLVESGGGLVQPGGSRKLSCAA SGFTFS
222	ACI-7062-415H10-Ab2-VH- CDR1	SFGMH
223	ACI-7062-415H10-Ab2-VH- FR2	WVRQAPEKGLEWVA
224	ACI-7062-415H10-Ab2-VH- CDR2	YISSGSSNIYYTDTVKG
225	ACI-7062-415H10-Ab2-VH- FR3	RFTISRDNPKNTLFLQMTSLRSEDT AIYYCAR
226	ACI-7062-415H10-Ab2-VH- CDR3	SGTTVPFDY
227	ACI-7062-415H10-Ab2-VH- FR4	WGQGTTTLTVSS
228	ACI-7062-415H10-Ab2-VH-	ATTTAPSVYPLVPGCSDTSGSSVTL

	Tail		G
229	ACI-7062-415H10-Ab2-VH Nucleotide sequence of the heavy chain variable domain without tail		GATGTGCAGCTGGTGGAGTCGGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAAACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGTAGTGGCAGT AGTAACATCTACTATACAGACAC AGTGAAGGGCCGATTCACCATCTC TAGAGACAATCCCAAGAACACCC TGTTCTTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATATATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCACTCTCACAGTCTCCTCA
230	ACI-7062-401A2-Ab2-VL Peptide sequence of the light chain variable domain without tail	401A2C6	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGDQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFSLTISSVQAEDLADYFCQQHYSI PLTFGAGTKLELKRA
231	ACI-7062-401A2-Ab2-VL Nucleotide sequence of the light chain variable domain without tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCGATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTGTTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCTCTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCT

232	ACI-7062-401A2-Ab2-VH Peptide sequence of the heavy chain variable domain without tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSRFGMHWVRQAPEKGLEWV AYIRSGSDIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYYCAR SGTTVPFDYWGGQGTSLTVSS
233	ACI-7062-401A2-Ab2-VH Nucleotide sequence of the heavy chain variable domain without tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGGT TTGGAATGCACTGGGTTCGCCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTCACCATCTC CAGAGACAATCCCGAGAACACCC TGTTCTTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA
234	ACI-7062-412A7-Ab1-VL Peptide sequence of the light chain variable domain without tail	412A7B7	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLNLSGNQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGS G TDFTLTISVQAEDLADYFCQQHYS IPLTFGAGTKLELKRA
235	ACI-7062-412A7-Ab1-VL Nucleotide sequence of the light chain variable domain without tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCATATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCAATCAAAGAAGTATTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAAGTCTATTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCACTCTT ACCATCAGCAGTGTGCAGGCTGA

			AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCT
236	ACI-7062-412A7-Ab1-VH Peptide sequence of the heavy chain variable domain without tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSSFGMHWVRQAPEKGLEWV AYIRSGSDIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYCAR SGTTVPFDYWGGQTSLTVSS
237	ACI-7062-412A7-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTCACCATCTC CAGAGACAATCCCGAGAACACCC TGTTCTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA
238	ACI-7062-406E3-Ab1-VL Peptide sequence of the light chain variable domain without tail	406E3D5	DVLMTQTPLSLPVSLGDRASISCRSS QSIVHRSGNTYLEWYLQKPGQSPK LLIYKVSNRFSGVPRFSGSGSGTD FTLKISRVEAEDLGVYYCFQGSHVP TFGAGTKLELKRA
239	ACI-7062-406E3-Ab1-VL Nucleotide sequence of the light chain variable domain without tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCGAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATCGT AGTGGAAACACCTATTTAGAGTG GTACCTGCAGAAACCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG

			TTCCAACCGATTTTCTGGGGTCC CAGACAGGTTTCAGTGGCAGTGGA TCAGGGACAGATTTACACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTTACATGTTCCACGTTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCT
240	ACI-7062-406E3-Ab1-VH Peptide sequence of the heavy chain variable domain without tail		QVTLKESGPAILQPSQTLSTCSFSG FSLTTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYNTALKSRLTVSKD TSNNQVFLKIASVDTADTATYYCA RVYGNLYYFAYWGQGTTTLTVSS
241	ACI-7062-406E3-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail		CAGGTTACTCTGAAAGAGTCTGGC CCTGCGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTTCTTCT CTGGGTTTTCACTGACCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGGAAT GATAATAAGTACTATAACACAGC CCTGAAGAGCCGGCTCACTGTCTC CAAGGATACCTCCAACAACCAGG TATTCCTCAAGATCGCCAGTGTAG ACACTGCAGATACTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TGTACTACTTTGCCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CA
242	ACI-7062-404D6-Ab2-VL Peptide sequence of the light chain variable domain without tail	404D6E11	DVLMTQTPLSLPVSLGDQASISCRS SQSIVHSGNNTYLEWYLQKPGQSP KLLIYKVSNRFSGVDPDRFSGSGSGT DFTLRISRVEAEDLGVYYCFQGS HV PTFGAGTKLELKRA
243	ACI-7062-404D6-Ab2-VL Nucleotide sequence of the light		GATGTTTTGATGACCCAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA

	chain variable domain without tail		GATCAAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATGGT TCTGGAAACACCTATTTAGAATGG TACCTGCAGAAACCAGGCCAGTC TCCAAAGCTCCTGATCTACAAAGT TTCCAACCGATTTTCTGGGGTCCC AGACAGGTTTCAGTGGCAGTGGAT CAGGGACAGATTTTCACTCAGG ATCAGCAGAGTGGAGGCTGAGGA TCTGGGAGTTTATTACTGCTTTCA AGGTTACATGTTCCACGTTCCG TGCTGGGACCAAGCTGGAGCTGA AACGGGCT
244	ACI-7062-404D6-Ab2-VH Peptide sequence of the heavy chain variable domain without tail		QVTLKESGPILQPSQTLSTCSFSG FSLSTYGIGVGWIRQPSGKLEWLA HIWWNDYKYNTALKSRLTISKDT SNNRVFLKIASVDTADTATYYCAR VYGNLYYFDYWQGTTTLTVSS
245	ACI-7062-404D6-Ab2-VH Nucleotide sequence of the heavy chain variable domain without tail		CAGGTTACTCTGAAAGAGTCTGGC CCTGGGATATTGCAGCCCTCCCAG ACCCTCAGTCTGACTTGTCTTTCT CTGGGTTTTCACTGAGCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGAAT GATTATAAGTACTATAACACAGCC CTGAAGAGCCGGCTCACAATCTCC AAGGATACCTCCAACAACCGGGT ATTCCTCAAGATCGCCAGTGTGGA CACTGCAGATACTGCCACATACTA CTGTGCTCGAGTCTATGGTAACCT GTACTACTTTGACTACTGGGGCCA AGGCACCACTCTCACAGTCTCCTC A
246	ACI-7062-410H3-Ab1-VL Peptide sequence of the light	410H3B9	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGNQKNYLAWYQQKPGQ

	chain variable domain without tail		<p>SPELLLYFASTRASGVDPDRFIGSGSG</p> <p>TDFTLTISSVQAEDLADYFCQQHYS</p> <p>IPLTFGAGTKLELKRA</p>
247	<p>ACI-7062-410H3-Ab1-VL</p> <p>Nucleotide sequence of the light chain variable domain without tail</p>		<p>GACATTGTGATGACACAGTCTCCA</p> <p>TCCTCCCTGGCTATGTCAGTTGGA</p> <p>CAGAAGGTCACTATGAGCTGCAA</p> <p>GTCCAGTCAGAGCCTTTTAAATAG</p> <p>TGGCAATCAAAAGAACTATTTGG</p> <p>CCTGGTACCAGCAGAAACCAGGA</p> <p>CAGTCTCCTGAACTTCTGTTATAC</p> <p>TTTGCATCCACTAGGGCATCTGGG</p> <p>GTCCCTGATCGCTTCATAGGCAGT</p> <p>GGATCTGGGACAGATTCTACTCTT</p> <p>ACCATCAGCAGTGTGCAGGCTGA</p> <p>AGACCTGGCAGATTACTTCTGTCA</p> <p>GCAACATTATAGTATTCCGCTCAC</p> <p>GTTCGGTGCTGGGACCAAGCTGG</p> <p>AGCTGAAACGGGCT</p>
248	<p>ACI-7062-410H3-Ab1-VH</p> <p>Peptide sequence of the heavy chain variable domain without tail</p>		<p>DVQLVESGGGLVQPGGSRRLSCAA</p> <p>SGFTFSSFGMHWVRQAPEKGLEWV</p> <p>AYIRSGSDIYYADSVKGRFTISRDN</p> <p>PENTLFLQMTSLRSEDAMYYCAR</p> <p>SGTTVPFDYWGGQGTSLTVSS</p>
249	<p>ACI-7062-410H3-Ab1-VH</p> <p>Nucleotide sequence of the heavy chain variable domain without tail</p>		<p>GATGTGCAGCTGGTGGAGTCTGG</p> <p>GGGAGGCTTAGTGCAGCCTGGAG</p> <p>GGTCCCGGAGACTCTCCTGTGCAG</p> <p>CCTCTGGATTCACTTTCAGTAGCT</p> <p>TTGGAATGCACTGGGTTCGTCAGG</p> <p>CTCCAGAGAAGGGGCTGGAGTGG</p> <p>GTCGCATACATTAGGAGTGGCAG</p> <p>TGATATAATCTACTATGCAGACTC</p> <p>AGTGAAGGGCCGATTACCATCTC</p> <p>CAGAGACAATCCCGAGAACACCC</p> <p>TGTTCTTGCAAATGACCAGTCTAA</p> <p>GGTCTGAGGACACGGCCATGTATT</p> <p>ACTGTGCAAGATCAGGGACTACG</p>

			GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA
250	ACI-7062-414A5-Ab1-VL Peptide sequence of the light chain variable domain without tail	414A5D2	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSSNQKNYLAWYQQKPGQ SPKLLVYFASTRESGVPDRFIGSGSG TDFTLTINSVQAEDLADYFCQQHYS IPLTFGAGTKLELKRA
251	ACI-7062-414A5-Ab1-VL Nucleotide sequence of the light chain variable domain without tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTAGGA CAGAAGGTCACTATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TAGCAATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTAACTTCTGGTATAC TTTGCATCCACTAGGGAATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCACTCTT ACCATCAACAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCT
252	ACI-7062-414A5-Ab1-VH Peptide sequence of the heavy chain variable domain without tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSSFGMHVWRQAPEKGLEWV AYIRSGSDIYYADTVKGRFTISRDN PENTLFLEMTRLRSEDAMYYCAR SGTTVPFDYWGGQTSITVSS
253	ACI-7062-414A5-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGCT TTGGAATGCACTGGGTTCGTCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACAC

			AGTGAAGGGCCGATTCACCATCTC CAGAGACAATCCCGAGAACACCC TGTTTTTGGAAATGACCAGACTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA
254	ACI-7062-412E12-Ab1-VL Peptide sequence of the light chain variable domain without tail	412E12A2	DIVMTQSPSSLAMSVGQKVTMSCK SSQSLLNSGDQKNYLAWYQQKPGQ SPELLLYFASTRASGVDPDRFIGSGSG TDFSLTISSVQAEDLADYFCQQHYSI PLTFGAGTKLELKRA
255	ACI-7062-412E12-Ab1-VL Nucleotide sequence of the light chain variable domain without tail		GACATTGTGATGACACAGTCTCCA TCCTCCCTGGCTATGTCAGTTGGA CAGAAGGTCATATGAGCTGCAA GTCCAGTCAGAGCCTTTTAAATAG TGGCGATCAAAAGAACTATTTGG CCTGGTACCAGCAGAAACCAGGA CAGTCTCCTGAACTTCTGTTATAC TTTGCATCCACTAGGGCATCTGGG GTCCCTGATCGCTTCATAGGCAGT GGATCTGGGACAGATTTCTCTCTT ACCATCAGCAGTGTGCAGGCTGA AGACCTGGCAGATTACTTCTGTCA GCAACATTATAGTATTCCGCTCAC GTTCCGGTGCTGGGACCAAGCTGG AGCTGAAACGGGCT
256	ACI-7062-412E12-Ab1-VH Peptide sequence of the heavy chain variable domain without tail		DVQLVESGGGLVQPGGSRRLSCAA SGFTFSRFGMHVVRQAPEKGLEWV AYIRSGSDIIYYADSVKGRFTISRDN PENTLFLQMTSLRSEDAMYCAR SGTTVPFDYWGGTSLTVSS
257	ACI-7062-412E12-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail		GATGTGCAGCTGGTGGAGTCTGG GGGAGGCTTAGTGCAGCCTGGAG GGTCCCGGAGACTCTCCTGTGCAG CCTCTGGATTCACTTTCAGTAGGT

			TTGGAATGCACTGGGTTCGCCAGG CTCCAGAGAAGGGGCTGGAGTGG GTCGCATACATTAGGAGTGGCAG TGATATAATCTACTATGCAGACTC AGTGAAGGGCCGATTACCATCTC CAGAGACAATCCCGAGAACACCC TGTTCTGCAAATGACCAGTCTAA GGTCTGAGGACACGGCCATGTATT ACTGTGCAAGATCAGGGACTACG GTCCCCTTTGACTACTGGGGCCAA GGCACCAGTCTCACAGTCTCTTCA
258	ACI-7062-416A11-Ab1-VL Peptide sequence of the light chain variable domain without tail	416A11B3	DVLMTQTPLSLPVSLGDRASISCRSS QSIVHSSGNTYLEWYLQKPGQSPKL LIYKVSNRFSGVPDRFSGSGSGTDF TLKISRVEAEDLGVIYCFQGSRVPT FGAGTKLELKRA
259	ACI-7062-416A11-Ab1-VL Nucleotide Sequence of the light chain variable domain without tail		GATGTTTTGATGACCCAAACTCCA CTCTCCCTGCCTGTCAGTCTTGGA GATCGAGCCTCCATCTCTTGCAGA TCTAGTCAGAGCATTGTACATAGT AGTGGAACACCTATTTAGAATG GTACCTGCAGAAGCCAGGCCAGT CTCCAAAGCTCCTGATCTACAAAG TTTCCAACCGATTTTCTGGGGTCC CAGACAGGTTTCAGTGGCAGTGGA TCAGGGACAGATTTCACTCAA GATCAGCAGAGTGGAGGCTGAGG ATCTGGGAGTTTATTACTGCTTTC AAGGTTACGTGTTCCACGTTCG GTGCTGGGACCAAGCTGGAGCTG AAACGGGCT
260	ACI-7062-416A11-Ab1-VH Peptide sequence of the heavy chain variable domain without tail		QVTLKESGPGILQSSQTLSTCSFSG FSLSTYGIGVGWIRQPSGKGLEWLA HIWWNDNKYYNTALKSRLTISKDT SNNQVFLKIASVDTADAATYYCAR VYGNLYYFGYWQGTTTLTVSS

261	ACI-7062-416A11-Ab1-VH Nucleotide sequence of the heavy chain variable domain without tail	CAGGTTACTCTGAAAGAGTCTGGC CCTGGGATATTGCAGTCCTCCCAG ACCCTCAGTCTGACTTGTTCTTTCT CTGGATTTTCACTGAGCACTTATG GTATAGGAGTAGGCTGGATTCGTC AGCCTTCAGGGAAGGGTCTGGAG TGGCTGGCACACATTTGGTGAAT GATAATAAGTACTATAACACAGC CCTGAAGAGCCGACTCACAATCTC CAAGGATACCTCCAACAACCAGG TATTCCTCAAGATCGCCAGTGTGG ACACTGCAGATGCTGCCACATACT ACTGTGCTCGAGTCTATGGTAACC TATACTACTTTGGCTACTGGGGCC AAGGCACCACTCTCACAGTCTCCT CA
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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;

5 (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;

10 (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;

15 (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;

20 (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;

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- (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:

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.

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: 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; and SEQ ID NO: 261;
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(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.

30. 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.