proteinaceous aggregates that are associated with amyloid senile plaques and neurofibrillary tangles in AD brains. It has been suggested that AD, PD and ALS may share a common pathogenic mechanism (Choi *et al*, 2005).

[0008] ALS is a fatal neuromuscular disease characterized by selective loss of motor neurons causing muscle atrophy. It is the most common motor neuron disease in adults and the third most common neurodegenerative disease after Alzheimer's disease and Parkinson's disease. The number of people worldwide who develop ALS annually is estimated to be 1.9 people per 100,000 per year, while the number of people who have ALS at any given time is estimated to be about 4.5 people per 100,000. ALS often begins with muscle twitching and weakness in a limb, or slurred speech, and eventually the disease affects control of the muscles needed to move, speak, eat and breathe. The average survival from onset to death is two to four years, and about 10% survive longer than 10 years. Death is usually due to respiratory failure.

[0009] Familial (inherited) ALS is usually said to account for 10% of all cases of ALS, though estimates range from 5% to 20%. About 20% of familial ALS is associated with mutations in the gene encoding superoxide dismutase 1 (SOD1), an intracellular free radical defense enzyme (see Table 1 and Mathis, S., *et al*. (2019), herein incorporated by reference). Intracellular aggregations of misfolded SOD1 that inhibit protein degradation have been observed in familial ALS, and also in the more common non-familial (sporadic) ALS, suggesting that SOD1 aggregation may underlie all ALS.

[0010] Misfolded SOD1 is exported from the cell by both secretory and constitutive mechanisms. Extracellular misfolded SOD1 is highly toxic for motor neurons through activation of killing pathways by local immune cells, and may also participate in the cell-to-cell propagation of disease throughout the nervous system by a prion-like templated misfolding process. The implication that extracellular misfolded SOD1 plays a role in ALS pathogenesis provides an opportunity for the antibody treatment of neurodegenerative diseases, as this compartment is accessible to antibody neutralization. Nonetheless, treatment of human subjects with antibodies targeted to accessible extracellular epitopes on ubiquitous proteins may lead to deleterious autoimmune effects such as those seen with Abeta in Alzheimer disease. There remains a need in the art for compositions and methods for treatment of misfolded SOD1-related diseases, such as ALS, AD and PD.

SUMMARY

[0011] Disclosed herein an isolated antibody or binding fragment thereof, a fusion protein, or a nucleic acid, as well as a pharmaceutical composition comprising the same that targets misfolded SOD1 as well as methods of making and using thereof.

[0012] Accordingly, herein provided in an aspect is an isolated antibody or binding fragment thereof that binds to misfolded superoxide dismutase 1 (SOD1) epitope having an amino acid sequence shown in SEQ ID NO: 144, the antibody or binding fragment thereof comprises:

(i) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6;

(ii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12;

(iii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12;

(iv) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13;

(v) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13;

(vi) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58;

(vii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28; or

(viii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

[0013] In some examples, the antibody or binding fragment thereof comprises:

(i) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 65, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 70;

(ii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO:

68, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 70;

(iii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 72, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 76;

(iv) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 74, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 76;

(v) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 78, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 82;

(vi) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 80, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 82;

(vii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 84, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 86; or

(viii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 88, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 91.

[0014] In some examples, the percentage identity is outside of the CDRs described herein and the antibody or antigen-binding fragment thereof maintains specificity in binding to mutant SOD1.

[0015] In some examples, the binding fragment is a Fab, Fab', F(ab')2, scFv, dsFv, ds-scFv, dimer, minibody, diabody, or bispecific antibody binding fragment. In some examples, the binding fragment is a scFv. In some examples, the antibody or binding fragment thereof comprises one or more amino acids selected from the group consisting of D-amino acids, modified amino acids, amino acid analogs or combinations thereof. In some examples, the modified amino acids comprise a modification selected from the group consisting of methylation, amidation, acetylation, and/or substitution with other chemical groups. In some examples, the antibody or binding fragment thereof is modified by pegylation, acetylation, glycosylation, biotinylation, or prenylation.

[0016] Also provided in another aspect is a fusion protein comprising an antibody or binding fragment thereof described herein and an E3 ligase or active fragment thereof. In some examples, the E3 ligase is CHIP, UBE4A, NEDD4L, UBR5, RNF4, UBOX5, BTrCP, or Parkin, or an active fragment thereof.

[0017] Also provided in a further aspect is a nucleic acid encoding an antibody or binding fragment thereof described herein, or the fusion protein described herein.

[0018] Also provided in another aspect is a vector comprising a nucleic acid described herein.

[0019] Also provided in another aspect is a composition, optionally a pharmaceutical composition comprising an antibody or binding fragment thereof described herein, a fusion protein described herein, a nucleic acid descried herein, or a vector described herein, and optionally at least one carrier such as pharmaceutical carrier.

[0020] In another aspect, is the present disclosure refers to the use of the antibody or antibody thereof as described herein, the fusion protein as described herein, the nucleic acid molecule as described herein, the vector as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a medical condition, disease, or disorder mediated by a misfolded form of SOD1 in a subject in need thereof. In another example, there is described a method for treating a medical condition, disease, or disorder mediated by a misfolded form of SOD1 in a subject in need thereof, the method comprises administering to the subject an antibody or binding fragment thereof described herein, a fusion protein described herein, a nucleic acid described herein, a vector described herein, or a pharmaceutical composition described herein. In some embodiments, the medical condition, disease or disorder is a neurodegenerative condition, disease or disorder. In some embodiments, the neurodegenerative condition, disease or disorder is amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, or frontotemporal dementia. In some embodiments, the ALS is sporadic ALS. In some embodiments, the ALS is familial ALS. In some embodiments, the neurodegenerative condition, disease or disorder is Alzheimer's disease. In some embodiments, the neurodegenerative condition, disease or disorder is Parkinson's disease. In some embodiments, the neurodegenerative condition, disease or disorder is frontotemporal dementia. In some embodiments, the misfolded form of SOD1 comprises SOD1 monomer, a dimer comprising misfolded SOD1 monomers, or an aggregate comprising SOD1 monomers and/or dimers, or toxic trimers. In some embodiments, the SOD1 monomer comprises a mutant SOD1 monomer. In some embodiments, the mutant SOD1 monomer comprise one or more mutations selected from the group consisting of A4V, G93A, G85R, D90A, G127X, V148G, H46R, G37R, C6G, and E100G, and wherein X is truncation mutation.

[0021] Also provided in another aspect is a fusion protein that specifically binds to mutant SOD1, comprising a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223.

[0022] In some embodiments, the fusion protein comprises a heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 68, a first linker, a light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO:

al. (1991); herein incorporated by reference). "Chothia" uses the location of structural loops (Chothia and Lesk, (1987), Chothia *et al*. (1992); herein incorporated by reference). The IMGT numbering scheme is an adaptation of the numbering scheme of Chothia (Lefranc *et al*., (1999); see also http://imgt.cines.fr; herein incorporated by reference). CDRs defined by "AbM" is a compromise between the Kabat and Chothia and is delineated using Oxford Molecular AbM antibody modeling software (see, Martin *et al.* (1989); see also www.bioinf-org.uk/abs; herein incorporated by reference). The antibody numbering scheme developed by the Chemical Computing Group (CCG) combines several antibody numbering schemes and offers a broader definition of CDR boundaries based on Martin and collaborators' CDR definitions (see Maier *et al.* (2014); herein incorporated by reference). The "Contact" CDR delineations are based on analysis of known antibody-antigen crystal structures (see, *e.g*., MacCallum *et al.* (1996)). The "Paratome" approach involves computational programs based on a set of consensus regions derived from a structural alignment of a non-redundant set of known antibody-antigen complexes (Kunik *et al*. (2012); see also www.ofranlab.org/paratome/; herein incorporated by reference). The "Aho" or Honegger scheme numbers the variable domains of the immunoglobulin superfamily in a homogenized format. This system is based on structural alignments of the 3D structures of the immunoglobulin variable regions covering the observed length variation. It allows to define structurally conserved Cα positions and therefore deduces appropriate framework regions and CDR lengths (see Honegger, A. and Pluckthun A. (2001); herein incorporated by reference). The CDRs described herein include those based on CCG, Paratome, Kabat, Chothia, or Aho definition (see Table 7), and it is to be understood that CDRs based on other methods are to be encompassed herein. In some embodiments, the CDRs described herein are based on IMGT, CCG, Paratome, Kabat, Chothia, or Aho.

[0089] In an exemplary embodiment of the present disclosure, the isolated antibody or binding fragment thereof binds to misfolded superoxide dismutase 1 (SOD1) epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises:

(i) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6;

(ii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12;

(iii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12;

(iv) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and

GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13;

(v) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13;

(vi)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58;

(vii)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28; or

(viii)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

[0090] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6.

[0091] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12.

[0092] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12.

[0093] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13.

[0094] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13.

[0095] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58.

[0096] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28.

[0097] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

[0098] In some embodiments, the CDR described herein has one or two positions mutated. In some embodiments, the CDR comprising one or two mutated positions retain binding activity specific to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144.

[0099] In some embodiments, the isolated antibody or binding fragment thereof binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises:

[00131] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises:

(i) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6;

(ii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12;

(iii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12;

(iv) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13;

(v) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13;

(vi)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58;

(vii)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28; or

(viii)a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

[00132] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6.

[00133] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12.

[00134] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12.

[00135] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13.

[00136] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13.

[00137] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58.

[00138] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28.

[00139] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

[00140] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 97, SEQ ID NO: 99, and SEQ ID NO: 101, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 103, SEQ ID NO: 105, and SEQ ID NO: 107.

[00141] In some embodiments, the CDR described herein has one or two positions mutated. In some embodiments, the CDR comprising one or two mutated positions retain binding activity specific to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144.

[00142] In some embodiments, the fusion protein comprises an E3 ligase or an active fragment thereof, and an antibody or binding fragment thereof that binds to misfolded SOD1 epitope having an amino acid sequence shown in SEQ ID NO: 142 or 144, the antibody or binding fragment thereof comprises:

(i) a heavy chain having a heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 65, and

acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of

SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 186-193, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion

protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence

of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 187. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3

having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 188. In some embodiments,

the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID

NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 189. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a

heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 190. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a

second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 191. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and

CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 192. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and DDL, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a the heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and GSV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, a first linker, a the light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, a second linker, and an active E3 ligase

fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and GAV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the fusion protein comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and GNV, a first linker, a light chain variable region comprising CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 193. In some embodiments, the antibody or antigen-binding fragment thereof, or the fusion protein described herein further comprises a methionine or a signal peptide at the N-terminus. In some embodiments, a polypeptide comprising at least 85% identity to the amino acid sequence of SEQ ID NO: 65, 68, 72, 74, 78, 80, 84, 88, 162, 164, 166, 168, 170, 172, 174, or 176 further comprises a methionine or a signal peptide at the N-terminus. In some embodiments, the signal peptide is not at the N-terminus, for example it may be present in a fusion protein and may not function as a cleavage site. In other embodiments, the antibody or antigen binding fragment thereof or the fusion protein lacks any signal peptide. In some embodiments, the signal peptide comprises the amino acid sequence of SEQ ID NO: 224. In some embodiments, a polypeptide comprising at least 85% identity to the amino acid sequence of SEQ ID NO: 82, 86, 91, 166, 168, 170, 172, 174, or 176 further comprises a methionine or a signal peptide at the N-terminus. In some embodiments, the signal peptide comprises the amino acid sequence of SEQ ID NO: 225. In some embodiments, a polypeptide comprising at least 85% identity to the amino acid sequence of SEQ ID NO: 70, 162, or 164, further comprises a methionine or a signal peptide at the N-terminus. In some embodiments, the signal peptide comprises the amino acid sequence of SEQ ID NO: 226. In some embodiments, any antibody, antigen-binding fragment, fusion protein, or polypeptide described herein can be with or without a signal peptide and/or a methionine at the N-terminus. In some embodiments, any amino acid sequence in Tables 5, 6, or 12 can be with or without a signal peptide and/or a methionine at the N-terminus. In some embodiments, any antibody, antigen-binding fragment, fusion protein, or polypeptide described herein can be with or without a signal peptide, optionally SEQ ID NO: 224, 225, or 226. In some embodiments, the polypeptide comprising at least 85% identity to the amino acid sequence of SEQ ID NO: 166, 168, 170, 172, 174, or 176 can have a deletion of the amino acid sequence comprising SEQ ID NO: 225. In some embodiments, the polypeptide comprising at least 85% identity to the amino acid sequence of SEQ ID NO: 162 or 164 can have a deletion of the amino acid sequence comprising SEQ ID NO: 226. In some embodiments, a signal peptide can be used as a linker. In some embodiments, the first linker comprises an amino acid sequence GSGSG (SEQ ID NO: 222) or SEQ ID NO: 221. In some embodiments, the second linker comprises an amino acid sequence GSGSG (SEQ ID NO: 222) or SEQ ID NO: 221. In some embodiments, the fusion protein comprises a polypeptide having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of any one of SEQ ID NOs: 162, 164, 166, 168, 170, 172, 174, and 176. In some embodiments, the fusion protein comprises a polypeptide having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to

A-63 H3	QSVEESGGGLVTPGTPLTLTCTVSGFSLSSYGVSWVRQAPGKGLEYIGFI STRGNPYYASWAKGRFTISKTSTTVDLKITSPTTEDTATYFCAGATVVGD SIWGPGTLVTVSS (SEQ ID NO: 80)	SEQ ID NO: 81
A-63 L1	QVLTQTASSVSAAVGGTVTISCQSSQSVYKGYWQAWYQQKPGQPPKLLIY ETSTLASGVPSRFSGSGSGTQFTLTISGVQCDDAATYYCAGGYSNNIYTF GGGTEVVVK (SEQ ID NO: 82)	SEQ ID NO: 83
A-85 H3-2	QSVEESGGRLVTPGTPLTLTCTVSGIDLSRSVMAWVRQAPGKGLEWIGIV TNRGNRYYANWAKGRFTISKTSTTVGLKIPSPTTADTATYFCGKGAVWGP GTLVTVSS (SEQ ID NO: 84)	SEQ ID NO: 85
A-85 L1-2, L2-2	QVLTQTPSSVSAAVGGTVTINCQSSQSFLDDNDLAWFQQKPGRPPKRLIK SASTLDSGVPSRFKGSGSGTQFTLTISDVQCNDAATYYCLGDYDCSVGDC SAFGGGTEVVVK (SEQ ID NO: 86)	SEQ ID NO: 87
A-93 H1	QSVEESGGRLVTPGTPLTLTCTVSGIDLRRSVMAWVRQAPGKGLEWIGII SDRGNTYYASWAKGRFTISRTSTTVALKMTSPTTADTATYFCGRGNVWGP GTLVTVSS (SEQ ID NO: 88)	SEQ ID NO: 89
A-93 H3	(SEQ ID NO: 88)	SEQ ID NO: 90
A-93 L1, L3	QVLTQTPSSVSAAVGGTVTINCQSSQRLYDDNDCAWYQKKPGQPPKRLIH DASILDSGVSSRFSGSGSGTQFTLTISGVQCEDAATYYCLGDYDCSVADC STFGGGTEVVVK (SEQ ID NO: 91)	SEQ ID NO: 92

Table 7. Amino Acid Sequences of CDRs

SEQ ID NO:	CDR	Sequence
1	A-7-35 / H / CDR1	GSDRRTYVMR
2	A-7-35 / H / CDR2	TIRLDGSRNY
	A-7-35 / H / CDR3	DDL
4	A-7-35 / L / CDR1	QASQSISNLLA
5	A-7-35 / L / CDR2	KASTLES
6	A-7-35 / L / CDR3	QQGFDSTDVDN
7	A-7-58a / H / CDR1	GIDLSSSVMA
8	A-7-58a / H / CDR2	IITNRGNRYY
	A-7-58a / H / CDR3	GSV
10	A-7-58a or b / L1 / CDR1	QSSQSFLDDNDLA
11	A-7-58a or b / L1 / CDR2	SASTLDS
12	A-7-58a or b / L1 / CDR3	LGDYDCSVGDCS
13	A-7-58a or b / L2 / CDR3	LGDYDCSVGDCSA
14	A-7-58b / H / CDR1	GIDLSSSVMV
15	A-7-58b / H / CDR2	IITNRGNRYY
	A-7-58b / H / CDR3	GSV
17	A-7-63 / H / CDR1	GFSLSSYGVS
18	A-7-63 / H / CDR2	FISTRGNPYY
19	A-7-63 / H / CDR3	ATVVGDSI
20	A-7-63 / L / CDR1	QSSQSVYKGY
21	A-7-63 / L / CDR2	ETSTLAS
22	A-7-63 / L / CDR3	AGGYSNNIYT
23	A-7-85 / H / CDR1	GIDLSRSVMA
24	A-7-85 / H / CDR2	IVTNRGNRYY
	A-7-85 / H / CDR3	GAV
26	A-7-85 / L / CDR1	QSSQSFLDDNDLA
27	A-7-85 / L / CDR2	SASTLDS
28	A-7-85 / L / CDR3	LGDYDCSVGDCSA
29	A-7-93 / H / CDR1	GIDLRRSVMA
30	A-7-93 / H / CDR2	IISDRGNTYY

	A-7-93 / H / CDR3	GNV
32	A-7-93 / L / CDR1	QSSQRLYDDNDCA
33	A-7-93 / L / CDR2	DASILDS
34	A-7-93 / L / CDR3	LGDYDCSVADCST
35	A-7-63 / H / CDR1 (CCG)	GFSLSSYGVS
36	A-7-63 / H / CDR2 (CCG)	FISTRGNPYYAS
37	A-7-63 / H / CDR3 (CCG)	AGATVVGDSI
38	A-7-63 / L / CDR1 (CCG)	QSSQSVYKGYWQA
39	A-7-63 / L / CDR2 (CCG)	ETSTLAS
40	A-7-63 / L / CDR3 (CCG)	AGGYSNNIYT
41	A-7-63 / H / CDR1 (PARATOME)	FSLSSYGVS
42	A-7-63 / H / CDR2 (PARATOME)	YIGFISTRGNPYY
43	A-7-63 / H / CDR3 (PARATOME)	GATVVGDSI
44	A-7-63 / L / CDR1 (PARATOME)	QSVYKGYWQA
45	A-7-63 / L / CDR2 (PARATOME)	LLIYETSTLAS
46	A-7-63 / L / CDR3 (PARATOME)	GGYSNNIYT
47	A-7-63 / H / CDR1 (KABAT)	YGVSWVR
48	A-7-63 / H / CDR2 (KABAT)	FISTRGNPYYASWAKGR
49	A-7-63 / H / CDR3 (KABAT)	GATVVGDSIW
50	A-7-63 / L / CDR1 (KABAT)	SSQSVYKGYWQ
51	A-7-63 / L / CDR2 (KABAT)	YETSTLA
52	A-7-63 / L / CDR3 (KABAT)	CAGGYSNNI
53	A-7-63 / H / CDR1 (CHOTHIA)	FSLSSYGV
54	A-7-63 / H / CDR2 (CHOTHIA)	TRGNP
55	A-7-63 / H / CDR3 (CHOTHIA)	GATVVGDSIW
56	A-7-63 / L / CDR1 (CHOTHIA)	SSQSVYKGYWQ
57	A-7-63 / L / CDR2 (CHOTHIA)	YETSTLA
58	A-7-63 / L / CDR3 (CHOTHIA)	CAGGYSNNIY
59	A-7-63 / H / CDR1 (AHO)	SGFSLSSYGVSWVR
60	A-7-63 / H / CDR2 (AHO)	YYASWAKGRFTISKTSTTVDL
61	A-7-63 / H / CDR3 (AHO)	LVTVSSGQPKAPSVFPLAPCCGDTPSSTVT
62	A-7-63 / L / CDR1 (AHO)	SQSVYKGYWQAWYQQK
63	A-7-63 / L / CDR2 (AHO)	GVPSRFSGSGSGTQFTL
64	A-7-63 / L / CDR3 (AHO)	KGDPVAPTVLIFPPAADQVATGTVTIVCV

Example 3B. Generating Rabbit Anti-misfolded SOD1 Antibodies Via Hybridomas

[00240] Three-month-old New Zealand rabbits are immunized with 100 μg of soluble synthetic peptides NEESTKTGN (SEQ ID NO: 142) or ESTKTGN (SEQ ID NO: 144) administered with Freund's adjuvant under a protocol of five subcutaneous injections and two test bleeds per rabbit. Titers are monitored regularly during the immunization period. Positive immunoreactive rabbits are identified by ELISA and Western blot analysis and chosen for rabbit monoclonal preparation. To generate rabbit hybridomas, splenocytes from the immunized rabbits are isolated and fused with a rabbit hybridoma fusion partner. Hybridoma clones secreting the misfold-specific SOD1 antibody are selected through ELISA screens of hybridoma supernatants.

[00241] Clonal cell lines expressing rabbit IgG for the misfold-specific antigen are further screened by Western blot analysis and immunohistochemistry using a panel of cell lines expressing either wild-type SOD1, with or without amplification, or misfolded SOD1 with a linearized alpha-helical sequence from the electrostatic loop.

WE CLAIM:

1. An isolated antibody or binding fragment thereof that binds to misfolded superoxide dismutase 1 (SOD1) epitope having an amino acid sequence shown in SEQ ID NO: 144, the antibody or binding fragment thereof comprises:

(i) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6;

(ii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12;

(iii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12;

(iv) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 13;

(v) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 13;

(vi) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 53, SEQ ID NO: 54, and SEQ ID NO: 55, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58;

(vii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 23, SEQ ID NO: 24, and SEQ ID NO: 25, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28; or

(viii) a heavy chain comprising a heavy chain variable region, wherein the heavy chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 29, SEQ ID NO: 30, and SEQ ID NO: 31, and a light chain comprising a light chain variable region, wherein the light chain variable region comprises CDR1, CDR2 and CDR3 having the amino acid sequence of SEQ ID NO: 32, SEQ ID NO: 33, and SEQ ID NO: 34.

2. The antibody or binding fragment thereof according to claim 1, wherein

(i) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 65, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 70;

(ii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 68, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 70;

(iii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 72, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 76;

(iv) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 74, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 76;

(v) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 78, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 82;

(vi) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 80, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 82;

(vii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 84, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 86; or

(viii) the heavy chain comprises the heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 88, and the light chain comprises the light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 91.

3. The antibody or binding fragment thereof according to claim 1 or 2, wherein the binding fragment is a Fab, Fab', F(ab')2, scFv, dsFv, ds-scFv, dimer, minibody, diabody, or bispecific antibody binding fragment.

4. The antibody or binding fragment thereof according to any one of claims 1 to 3, wherein the binding fragment is a scFv.

5. The antibody or binding fragment thereof according to any one of claims 1 to 4, wherein the antibody or binding fragment thereof comprises one or more amino acids selected from the group consisting of D-amino acids, modified amino acids, amino acid analogs or combinations thereof; and/or

wherein the antibody or binding fragment thereof comprise one or more modified amino acids and the modified amino acids comprise a modification selected from the group consisting of methylation, amidation, acetylation, and/or substitution with other chemical groups; and/or

wherein the antibody or binding fragment thereof is modified by pegylation, acetylation, glycosylation, biotinylation, or prenylation.

6. A fusion protein comprising the antibody or binding fragment thereof according to any one of claims 1 to 5 and an E3 ligase or active fragment thereof.

7. The fusion protein according to claim 6, wherein the E3 ligase is CHIP, UBE4A, NEDD4L, UBR5, RNF4, UBOX5, BTrCP, or Parkin, or an active fragment thereof; and/or

wherein the heavy chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, and SEQ ID NO: 3, a first linker, a light chain variable region comprising CDR1, CDR2, and CDR3 having the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 5, and SEQ ID NO: 6, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223.

8. The fusion protein of claim 6, comprising a heavy chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 68, a first linker, a light chain variable region comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 70, a second linker, and an active E3 ligase fragment comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 186, or a truncated E3 ligase comprising an amino acid sequence having at least 85%, 90%, 95%, 97%, 98%, 99%, 99.5%, 99.5% or 100% identity to the amino acid sequence of SEQ ID NO: 223.

9. The fusion protein of claim 7 or 8, formulated for viral delivery into a subject, or wherein the fusion protein is expressed and delivered by AAV.

10. A nucleic acid molecule encoding the antibody or binding fragment thereof according to any one of claims 1 to 5, or the fusion protein according to any one of claims 6 to 9.

11. A vector comprising the nucleic acid molecule of claim 10.

12. A pharmaceutical composition comprising the antibody or binding fragment thereof according to any one of claims 1 to 5, the fusion protein according to any one of claims 6 to 9, the nucleic acid molecule according to claim 10, or the vector according to claim 11, and at least one pharmaceutical carrier.

13. Use of the antibody or antibody thereof according to any one of claims 1 to 5, the fusion protein according to any one of claims 6 to 9, the nucleic acid molecule according to claim 10, the vector according to claim 11 or the pharmaceutical composition according to claim 12 in the manufacture of a medicament for treating a medical condition, disease, or disorder mediated by a misfolded form of SOD1 in a subject in need thereof.

14. The use according to claim 13, wherein the medical condition, disease or disorder is a neurodegenerative condition, disease or disorder.

15. The use according to claim 13 or 14, wherein the neurodegenerative condition, disease or disorder is amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, or frontotemporal dementia.

16. The use according to claim 15, wherein the ALS is sporadic ALS or wherein the ALS is familial ALS.

17. The use according to any one of claims 13 to 15, wherein the misfolded form of SOD1 comprises SOD1 monomer, a dimer comprising mutant SOD1 monomers, or an aggregate comprising SOD1 monomers and/or dimers, or toxic trimers; or

wherein the misfolded form of SOD1 comprises SOD1 monomer comprises a mutant SOD1 monomer; or

wherein the misfolded form of SOD1 comprises SOD1 monomer comprises a mutant SOD1 monomer, wherein the mutant SOD1 monomer comprises one or more mutations selected from the group consisting of A4V, G93A, G85R, D90A, G127X, V148G, H46R, G37R, C6G, and E100G, and wherein X is truncation mutation.