

ANTI-TAU ANTIBODIES

The invention relates to specific binding molecules, such as antibodies, directed to key epitopes of tau. The specific binding molecules of the invention find applications in diagnostics and therapeutics of tauopathies including Alzheimer's disease.

Disorders related to tau are collectively referred to as neurodegenerative tauopathies. Alzheimer's disease (AD) is part of this group of neurodegenerative diseases. Conditions of dementia such as Alzheimer's disease (AD) are frequently characterised by a progressive accumulation of intracellular and/or extracellular deposits of proteinaceous structures such as  $\beta$ -amyloid plaques and neurofibrillary tangles (NFTs) composed of tau, in the brains of affected patients. The appearance of tau aggregation lesions largely correlates with pathological neurofibrillary degeneration and brain atrophy, as well as with cognitive impairment. In AD, tau protein self-assembles to form paired helical filaments (PHFs) and straight filaments that constitute the neurofibrillary tangles within neurons and dystrophic neurites in the brain. Protein misfolding to form amyloid fibrils is a hallmark of many different diseases collectively known as the amyloidoses, each of which is characterised by a specific precursor protein.

The long history of research into the causes of AD and other protein conformational disorders has not led to the hoped-for major advances in diagnostics or therapeutics. One reason for the limited progress is thought to be a lack of high-affinity specific binding molecules targeted to key epitopes of tau. The present inventors address this shortcoming by the creation of the specific binding molecules disclosed herein. The disclosed specific binding molecules are derived from antibodies isolated from sheep immunised with full length tau protein and a truncated tau fragment from the core of the PHF. The use of sheep as a source of specific binding molecules is thought to have contributed to the high affinity of the specific binding molecules of the invention.

Summary of the invention

According to a first aspect, the invention provides a specific binding molecule that binds to an epitope within SEQ ID NO: 1 with a binding affinity greater than the binding affinity with which antibody mAb423 binds to an epitope within SEQ ID NO: 1.

According to a second aspect, the invention provides a composition comprising a specific binding molecule according to the first aspect of the invention, wherein at least 90% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM.

According to a third aspect, the invention provides a nucleic acid molecule comprising a nucleic acid sequence encoding a specific binding molecule according to the first aspect of the invention.

According to a fourth aspect, the invention provides a construct comprising a nucleic acid molecule of the third aspect of the invention.

- 5 According to a fifth aspect, the invention provides a vector comprising a nucleic acid molecule of the third aspect of the invention or a construct of the fourth aspect of the invention.

According to a sixth aspect, the invention provides a host cell comprising a nucleic acid molecule of the third aspect of the invention, a construct of the fourth aspect of the invention or a vector of the  
10 fifth aspect of the invention.

According to a seventh aspect, the invention provides a method of preparing a specific binding molecule according to the first aspect of the invention comprising:

- i) introducing into a host cell a nucleic acid molecule of the third aspect of the invention, a construct  
15 of the fourth aspect of the invention or a vector of the fifth aspect of the invention;  
ii) expressing the nucleic acid molecule such that the specific binding molecule is produced; and  
iii) collecting the specific binding molecule, preferably by purification.

- 20 According to an eighth aspect, the invention provides a specific binding molecule obtainable by a method according to the seventh aspect of the invention.

According to a ninth aspect, the invention provides a pharmaceutical composition comprising a specific binding molecule according to the first aspect of the invention or a composition according to  
25 a second aspect of the invention and one or more pharmaceutically acceptable diluents, carriers or excipients.

According to a tenth aspect, the invention provides a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a  
30 pharmaceutical composition according to the ninth aspect of the invention for use in therapy.

According to an eleventh aspect, the invention provides a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention for use in treatment of a  
35 tauopathy.

According to a twelfth aspect, the invention provides a method of treating a tauopathy, comprising administering to a subject in need thereof a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical  
40 composition according to the ninth aspect of the invention.

According to a thirteenth aspect, the invention provides an *in vitro* method of inhibiting aggregation of a tau protein or a fragment thereof comprising contacting the tau protein or a fragment thereof with a specific binding molecule according to the first aspect of the invention.

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According to a fourteenth aspect, the invention provides an *in vitro* method for detecting a tau protein or a fragment thereof in a sample comprising contacting the sample with a specific binding molecule of the first aspect of the invention.

- 10 According to a fifteenth aspect, the invention provides a diagnostic method comprising contacting a sample with a specific binding molecule of the first aspect of the invention.

According to a sixteenth aspect, the invention provides a diagnostic device for use in a method according to the fifteenth aspect of the invention.

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According to a seventeenth aspect, the invention provides a kit comprising a specific binding molecule according to the first aspect of the invention and reagents for detecting a tau protein or a fragment thereof in a sample.

- 20 Reference is made to a number of Figures as follows:

**FIGURE 1.** Alternative CDR definitions for S1D12 according to Kabat, Chothia and Martin.

- 25 **FIGURE 2.** The sequence of the predominant fragment isolated from the proteolytically stable core of the paired helical filament (PHF; Wischik et al., 1988). This fragment (referred to 'dGAE') comprises residues 296 – 391 of full-length tau and encompasses the fragment identified by cryo-electron-microscopy (residues 308 – 378) as constituting the PHF core (Fitzpatrick et al., 2017) and shown in Fig 3. The locations of the epitopes of the selected antibodies/scAbs are also shown

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**FIGURE 3.** The PHF core shown in the context of a PHF.

- FIGURE 4.** The same core sequence and locations of corresponding epitopes in relation to the fundamental C-shaped subunit structure of the core. The 1D12 epitope forms the critical fold or "hairpin" of the C-shaped subunit.

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**FIGURE 5.** Molecular modelling showing how a new dGAE unit progressively unfolds and becomes aligned with the structure of the existing oligomer.

**FIGURE 6.** The attachment sequence shown in terms of 3 stages corresponding to progressive binding of key segments of dGAE and their epitopes into the oligomer. As can be seen, the hinge region recognised by 1D12 is the primary site of attachment, followed by progressive symmetrical binding of the other domains.

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**FIGURE 7.** (A) dGAE antigen specific immune response of sheep polyclonal sera after various rounds of immunisation. (B) hT40 antigen specific immune response of sheep polyclonal sera after various rounds of immunisation. MPBS coated wells included as negative control.

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**FIGURE 8.** ELISA based characterisation of the cross-reactivity of 'E' group scAbs using hT40, dGA and dGAE antigens (A) E1E8 scAb, (B) E2B7 scAb, (C) E2C5 scAb, (D) E2E8 scAb, (E) E1B8 scAb. All these scAbs except E1B8 showing specific dGAE binding and therefore requires C terminally accessible '391E' epitope for immunoreactivity. E1B8 cross-reacts with dGA and a detailed mapping of its binding region is shown in Fig.9

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**FIGURE 9.** Detailed mapping of E1B8 scAb which shows specific binding to the tau peptide representing amino acids from 313-336 on hT40 protein.

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**FIGURE 10.** ELISA based characterisation of the cross-reactivity of 'NS' group scAbs using various short tau fragments with numbers corresponding to hT40 amino acid residues. (A) 337-368, (B) 275-305 (C) 266-359 (R1-3) (D) 360-378 (E) 369-391, (F) 369-390. A summary of specific NS scAb binding to these shorter antigens are shown in Table 16

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**FIGURE 11.** ELISA based characterisation of the cross-reactivity of 'S' group scAbs using various short tau fragments numbered according to their corresponding amino acid residues on hT40 molecule. (A) 186-350, (B) 275-305 (C-D) 266-359 (R1-3), (E-I) 297-391, (J) 360-378 (K-N) 369-391, (O-R) 369-390. A summary of specific 'S' scAb binding to these shorter antigens are shown in Table 16

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**FIGURE 12.** ELISA based characterisation of the cross-reactivity of 'C' group scAbs using various short tau fragments numbered according to their corresponding amino acid residues on hT40 molecule. (A) 1-49, (B) 1-155 (C-D) 1-319, (E) 113-251 (F) 113-319, (G) 186-350 (H) 239-441 (I) 266-359 (R1-3), (J) 297-441, (K) 348-441, (L) 391-441. A summary of specific 'C' scAb binding to these shorter antigens are shown in Table 17

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**FIGURE 13.** Cross-reactivity of '412' group scAbs to hT40. (A) showing binding of scAbs to biotinylated 412-441 peptide which was used as the antigen for the selection of C terminal binders. (B) binding profiles of four scAbs which were shown to be cross-reactive in hT40 binding ELISA.

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**FIGURE 14.** ELISA based characterisation of the cross-reactivity of '3a' & '3b' group scAbs using various short tau fragments numbered according to their corresponding amino acid residues on hT40 molecule. (A) 1-49, (B) 1-111 (C-D) 1-155, (E) 113-251. A summary of specific '3a' & '3b' group scAbs binding to these shorter antigens are shown in Table 18

**FIGURE 15.** (A) Immunoreactivity of CE2 scAb to the parent peptide and a series of alanine substituted residues at positions indicated in table 19. (B) Percentage binding of 500 nM scAb to each of these ASM peptides with respect to the parent peptide.

**FIGURE 16.** (A-B) Immunoreactivity of S1D12 scAb to the parent peptide and a series of alanine substituted residues at positions indicated in table 20. (C) Percentage binding of 500 nM scAb to each of these ASM peptides with respect to the parent peptide.

**FIGURE 17.** (A-B) Immunoreactivity of ME12 scAb to the parent peptide and a series of alanine substituted residues at positions indicated in table 20. (C) Percentage binding of 100 nM scAb to each of these ASM peptides with respect to the parent peptide.

**FIGURE 18.** (A) Immunoreactivity of CA4 scAb to the parent peptide and a series of alanine substituted residues at positions indicated in table 21. (B) Percentage binding of 500 nM scAb to each of these ASM peptides with respect to the parent peptide.

**FIGURE 19.** (A-B) Immunoreactivity of S1G2 scAb to the parent peptide and a series of alanine substituted residues at positions indicated in table 22. (C) Percentage binding of 500 nM scAb to each of these ASM peptides with respect to the parent peptide.

**FIGURE 20.** Percentage binding of various 367-379 region scAbs to ASM peptides with respect to the parent peptide. The scAbs tested included (A) S1B1, (B) CA12, (C) CB2, (D) CB8, (E) S1D9, (F) S1G10, (G) S2C6, (H) S1F4, (I) MC5, (J) MD12. The critical binding residues of these scAbs are similar to the representative clone S1G2, where alanine substitution in positions 370, 373, 374, 377 or 378 resulted in reduction in antibody binding.

**FIGURE 21.** Ranking of the binding affinities of anti-Tau scAbs using hT40. scAbs with known KD values such as NS2A1 and S1D12 were used to rank the relative binding affinities of test scAbs and those with similar binding profiles were shortlisted and selected for Biacore analysis (A) 'S' group clones, (B-C) 'C' clones, (D) '412' clones (E) '3a' clones

**FIGURE 22.** Schematic representation of the sandwich ELISA format for calculating the LoDs of various antibody pairs.

**FIGURE 23.** Schematic representation of the sandwich ELISA format for calculating the LoDs using S1G2 mAb as the capture antibody and HRP conjugated S1D12 mAb for detection

5 **FIGURE 24.** Sandwich ELISA graph showing the LoD achieved using S1G2 mAb as the capture antibody and HRP labelled S1D12 mAb detection. Antibody binding was measured using chemiluminescence and the LOD for hT40 is ~1 ng/ml for this assay set up.

10 **FIGURE 25.** ELISA#1 hT40 standard curve generated using S1D12 mAb capture and CB7 scAb detection. Concentrations of the four spiked samples – Sample A, B, C and D were determined by plotting their respective absorbance values on this standard curve. Sample C did not generate a binding signal and therefore confirmed the absence of any tau species with N terminal region in this mix. Concentrations and types of tau species deduced from this assay is given in table 29.

15 **FIGURE 26.** ELISA#2 dGAE standard curve generated using S1D12 mAb capture and E2E8 scAb detection. Concentrations of the four spiked samples – Sample A, B, C and D were determined by plotting their respective absorbance values on this standard curve. Samples A, C and D did not generate any binding signals and therefore confirmed the absence of dGAE species within these mixes. Concentrations and types of tau species deduced from this assay is given in table 29.

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25 **FIGURE 27.** ELISA#3 Average standard curve generated using S1D12 mAb capture and S1G2 scAb detection. Concentrations of the four spiked samples – Sample A, B, C and D were determined by plotting their respective absorbance values on this standard curve. Concentrations and types of tau species deduced from this assay is given in table 29.

30 **FIGURE 28.** Comparison of the binding profiles of various SDS (+/- Triton X-100) treated dGAE monomer or aggregates in a sandwich ELISA system. S1D12 mAb was used as the capture antibody and S1G2 as the detection scAb. Here the effect of SDS + Triton X-100 in restoring the immunoreactivity of is noticed. This mAb-scAb pairing can detect approximately 2 ng/ml dGAE aggregates in a simple sandwich ELISA.

35 **FIGURE 29.** A) L66 cDNA containing human tau (hT40) and the point mutations P301S and G335D (2N4R Tau, 441 amino acids) B) L1 cDNA codes for human tau amino acid residues 296-390 with a signal sequence and murine Thy1 expression sequences as described in Melis et al., 2015

40 **FIGURE 30.** (A) Detection of tau protein in 50 µg brain homogenate isolated from WT, L1, L66 +/- and L66 +/- mice using S1D12mAb capture and S-1G2 scAb detection. All four

samples have similar tau levels when detected using a core region specific antibody pairing (B) Detection of tau protein in 50 µg brain homogenate isolated from WT, L1, L66 +/- and L66 +/- mice using S1D12mAb capture and CB7 scAb detection. N' terminally directed CB7 scAb can specifically detect human tau in Line66 homozygous and heterozygous samples and able to differentiate levels of expression between the two groups.

**FIGURE 31.** Plasma tau levels in WT (5 month: 1.947 ng/ml), (9 month: 2.177 ng/ml); L66 (Both 5 month) (+/-: 0.567 ng/ml), (+/+ : 1.937 ng/ml); and L1 (5 month: 12.355 ng/ml) (9 month 13.661 ng/ml). Data collected using S1D12 mAb capture and S1G2 scAb detection. Tau species concentrations were determined using standard curves of hT40 for WT and L66 and dGA (296-390) for L1.

**FIGURE 32.** Detection of plasma tau levels in Line66+/+ mouse sample no: 23 at 1.5 months and comparison with age matched wild type mouse plasma using two different sandwich ELISA pairing. (A) Shows the chemiluminescent signal readings for Line66+/+ and wildtype mice using S1D12 mAb capture and CB7 scAb detection. (b) the signal readings for the same samples using S1D12 mAb capture and S1G2 scAb detection. Line66+/+ mouse shows at least 1000-fold increase in signal intensity compared to the wild type when using S1D12 mAb - CB7 scAb pairing which specifically detects N terminal hT40 in this sample.

**FIGURE 33.** Plasma tau levels in AD samples vs age matched controls using S1D12-S1G12 (core region) and S1D12-CB7 (N terminal) detection pairs.

**FIGURE 34.** Sandwich ELISA graphs showing the increase in immunoreactivity of core region scAbs to dGAE 'total', 'supernatant' and 'pellet' aggregation inhibition samples prepared in the presence of LMTM. dGAE monomer was included as assay control to indicate the binding profiles of each test scAbs to their corresponding epitopes in non-aggregated samples. (A-C) CA4 scAb, (D-F) CA9, (G-I) CB3 scAb, (J-L) CE2 scAb, (M-O) CE3, (P-R) S1D12 scAb. Lack of antibody binding in some dGAE + LMTM pellet samples corresponds to the absence protein present in this group as confirmed by SDS gel (data not included)

**FIGURE 35.** An example data plot of S1D12 scAb mediated aggregation inhibition of dGAE.

**FIGURE 36.** Ranking of aggregation inhibition properties of anti-tau scAbs by thioflavin T assay. Aggregation inhibition dGAE was quantified by calculating the percentage change from aggregates without the presence of a scAb. scAbs 3bA3, 3aD6 and 3aD3 were used as negative controls and show no cross reactivity to dGAE (data not shown). n = 3, error bars represent SD, N.S. = Not Significant \* = P < 0.05, \*\* = P < 0.01, \*\*\* = P < 0.001 (one-way analysis of variance (ANOVA) and post-hoc Dunnett's test compared to scAb 3aD3).

**FIGURE 37.** Schematic representation of tau-tau immunoassay to rank the inhibitory effects of anti-tau scAbs during the aggregation of truncated tau containing the core repeat domain. (a) Tau-tau aggregation takes place when dGAE is added to the wells precoated with dGA and the presence of dGAE is detected using 391E epitope specific E2E8 scAb. (b) When dGAE was preincubated with core region binding scAbs, this binding event inhibits dGAE-dGA interaction which is measured by a loss in antibody detection by E2E8 scAb.

**FIGURE 38.** Ranking of aggregation inhibition properties of anti-tau scAbs by tau-tau immunoassay (B50). A - An example of B50 quantification of NS2A1 and 3aD6 (negative control). Quantification of aggregation inhibition properties was made by calculating a B50 value (concentration of scAb where 50 % of dGAE binding to dGA is evident). Error bars = SD, n = 4, -ve = negative control. b – Summary of B50 ranking of the scAb panel.

**FIGURE 39.** mAb capture of dGAE aggregates.

**FIGURE 40.** Experimental design to investigate the effect of intraperitoneal administration of S1D12 in line 1, line 66 and WT mice. Animals will be injected intraperitoneally (i.p.) with either vehicle or S1D12 (10- or 50-mg/kg), once per week (Tuesdays) for twelve (Group 1), eight (Group 2) or four (Group 3) consecutive weeks. Age of mice at the end of the experiment will be the same for all three groups (i.e. 6 months).

**FIGURE 41.** Western blot showing tau labelled with a human-specific CB7 antibody. Bands are present in lanes containing 20 ug protein homogenate from 5-month-old L66<sup>+/+</sup> mouse brain but not in either WT or L1<sup>+/+</sup> lanes. The protein ladder superimposed on the left of the blot provides an approximation of the relative size of proteins on the gel, but it is known that the apparent size of tau is considerably greater than the actual molecular mass.

**FIGURE 42.** Western blot showing tau labelled with human specific CC7. Results and ladder are as described in Fig 41.

**FIGURE 43.** Western blot labelled with S1D12 tau core antibody. Bands are present in lanes containing 20 ug protein homogenate from 5-month-old L66<sup>+/+</sup>, L1 and WT mice brains. Mouse tau (indicated by the lower arrow) appears as a band of approximately 55 kDa in each of the samples. Human tau (indicated by the upper arrow) appears as a protein at 68 kDa that is present only in the L66<sup>+/+</sup> samples. Protein ladder as for Fig 41.

**FIGURE 44.** Western blot labelled with S1G2 core antibody. Bands are present in lanes containing 20 ug protein homogenate from 5-month-old L66<sup>+/+</sup>, L1<sup>+/+</sup> and WT mice brains. Mouse tau (indicated by the lower arrow) appears as a band at about 55 kDa in each of the

samples. Human tau (indicated by the upper arrow) appears at about 68 kDa but only in the L66<sup>+/+</sup> samples. Using this antibody, a band at around 10 kDa is visible in the L1<sup>+/+</sup> samples. Protein ladder as for Fig 41.

5 **FIGURE 45.** Sequence comparison of human and mouse tau. The sequences shown consist of SEQ ID No. 1 for human tau (two gaps introduced to allow sequence alignment) and SEQ ID NO: 589 for mouse tau. The protein regions that contain the epitopes of candidate antibodies are superimposed. Both CB7 and CC7 binding regions in human tau are not present in mouse tau. In contrast, protein regions containing the epitopes for the antibodies  
10 S1D12 and S1G2 show 100 % homology between the 2 species.

**FIGURE 46.** A) Paired antibody ELISAs with S1D12 capture and CB7 detection show a progressive decrease in signal with advanced age in L66<sup>+/+</sup> mice. B) When reversing the orientation of the assay, and using CB7 as the capture along with S1G2 as detector, a similar  
15 pattern is observed.

**FIGURE 47.** Paired antibody ELISA with CB7 capture and HT7 detection shows a progressive increase in signal with age in L66<sup>+/+</sup> mice. This suggests an accumulation of small N-terminally intact fragments created by some sort of truncation event between the core region and the N'-terminal region of tau protein or protein fragments.  
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**FIGURE 48.** (A) Plasma tau levels in healthy control (HC) and patients with a confirmed diagnosis of Alzheimer's disease (AD/MCI). The concentration of the core-proline region measured using S1D12 capture beads paired with BT2 as detector is significantly higher in healthy control than in AD samples. A total of 12 healthy control plasma samples and 42 AD/MCI samples were analysed using the Simoa® assay. \*\*\*\* p<0.0001 (B) NT1 assay data (Chen et al 2019) reported detecting slightly increased levels of NT-1 plasma tau in AD-MCI (AD biomarker positive – mild cognitive impairment) and AD (AD biomarker positive – clinical AD) patients compared to NC (normal control) using Tau12-BT2 antibodies.  
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**FIGURE 49.** Plasma tau levels in healthy control (HC) and patients with a confirmed diagnosis of Alzheimer's disease (AD/MCI). The concentration of the core-proline region measured using S1D12 capture beads paired with HT7 detector is significantly higher in healthy control than in AD samples. A total of 4 healthy control plasma samples and 34 AD/MCI samples were analysed using the Simoa® assay. \*\*\*\* p<0.0001  
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**FIGURE 50.** Plasma tau levels are increased by LMTM treatment of L66<sup>+/+</sup> mice. (A) NT1 assay using BT2 and HT7 antibodies detect slightly elevated levels of human specific N terminal tau in the plasma of L66<sup>+/+</sup> mice receiving LMTM (15 mg/kg) (B) Similarly, the core-proline assay using S1D2 and BT2 antibodies also measured higher levels of tau in LMTM-  
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treated mice plasma with concentrations significantly higher than the levels seen using the human-specific NT1 assay. The increased levels in treated mice suggest improved clearance of pathologic tau from the brain into the blood.

5 **FIGURE 51.** Concentration of S1D12 mAb in mouse plasma at various time points. Values plotted are average concentrations in groups of mice analysed at 24, 48, 72-hours and 7-, 14- and 31-days following the administration of a single dose of S1D12 mAb at 30 mg/kg.

10 **FIGURE 52.** Comparison of the concentrations of free S1D12 mAb in the plasma of WT mice 7 days post single or repeat dosing at 30 mg/kg. Values plotted are mean concentrations (+ standard error) in groups of mice, n=6 .

15 **FIGURE 53.** Detection of S1D12 in the brain of wild type, L1 and L66<sup>+/+</sup> mice receiving a weekly dose of S1D12 mAb at 30 mg/kg for 6 weeks. Values are expressed as a percentage of brain vs plasma S1D12 concentrations in groups of mice receiving the treatment (mean + standard error; n=6).

20 **FIGURE 54.** Comparison of the ratio of human tau to mouse tau in the brain homogenates of L66<sup>+/+</sup> vehicle treated and S1D12 mAb-treated groups. A decrease in the levels of human tau was observed in mAb-treated mice brains when using a core region antibody S1G2 for detection in western blots. Values plotted are the ratio of human and mouse tau protein band densities from each group (mean + standard error; n=6). \* p <0.05

25 **FIGURE 55.** Levels of sarkosyl-insoluble tau detected in the brain homogenates of vehicle- and S1D12 mAb-treated L66<sup>+/+</sup> mice using a core-proline region specific antibody pairing (S1G2-BT2). Between five to six-fold reduction in the levels of core-proline fragment was observed in mice receiving mAb treatment compared to the vehicle group. Individual mouse samples were analysed in duplicate and values represent the mean of relative luminescence readings from each group. (mean + standard error; n=6).

30 **FIGURE 56.** Plasma tau levels are increased following S1D12 mAb treatment of mice. Using S1G2 (367-379) and BT2 (194-198) antibodies, human specific core-proline region tau levels were elevated in S1D12 mAb-treated mice compared to the vehicle group. Individual mouse samples were analysed in duplicate and values represent mean concentration of the tau fragment detected by S1G2 -BT2 antibody pairing. In L66, more than a threefold increase was achieved in the treatment group, whereas in L1 and wildtype mice, the differences were not statistically significant. (n= 6, mean values + standard error). Unpaired t-test was performed between vehicle and treatment groups, \*\*P ≤ 0.01, n.s., not significant.

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**FIGURE 57.** Plasma tau levels of N-terminal tau is increased by S1D12 treatment in L66 mice. Using BT2 (194-198) and Tau 12 (6-18) antibodies, human specific N-terminal tau levels were elevated in S1D12 mAb-treated mice compared to the vehicle group. Individual mouse samples were analysed in duplicate and values represent mean concentration of the tau fragment detected by BT2-Tau12 antibody pairing (n= 6, standard error bars); unpaired t-test was performed between vehicle and treatment groups, \*\*\*P ≤ 0.001.

**FIGURE 58.** Plasma tau levels of N-terminal tau is increased by S1D12 treatment in L66 mice. Using BT2 (194-198) and HT7 (159-163) antibodies, human-specific proline tau levels were elevated in S1D12 mAb-treated mice compared to the vehicle group, however the difference was not statistically significant. Individual mouse samples were analysed in duplicate and values represent mean concentration of the tau fragment detected by BT2-HT7 antibody pairing (n= 6; standard error bars).

**FIGURE 59.** Transmission electron microscopy images of dGAE assembled in the presence and absence of antibodies. (A) dGAE (100 μM); (B) dGAE (25 μM); (C) dGAE (10 μM); (D) dGAE (100 μM) + s1D12 (25 μM; 4:1); (E) dGAE (25 μM) + s1D12 (25 μM; 1:1); (F) dGAE (10 μM) + s1D12 (2.5 μM; 4:1); (G) dGAE (10 μM) + anti-ovalbumin (2.5 μM; 4:1); (H) s1D12 (25 μM); (I) anti-ovalbumin (2.5 μM). Fibrils are only observed in preparations in the absence of s1D12 (A-C) or in a control of dGAE prepared in the presence of a non-tau IgG antibody, anti-ovalbumin (G). When s1D12 is added to the assembly mixture at dGAE protein:antibody ratios of either 1:1 or 4:1 (D, E, and F), no fibril formation is observed. Fibrils are also absent from antibody controls in the absence of dGAE (H and I). Scale bar (on I for all panels), 200 nm.

**FIGURE 60.** CD spectra in millidegrees (mdeg) of (A) 100 μM dGAE with (dashed line) and without (solid line) 25 μM s1D12 (ratio 4:1) and antibody alone (dotted line) and (B) with the antibody spectra subtracted. dGAE (solid line) displays a β-sheet conformation (positive ~200 nm, negative ~220 nm) but shows random coil (negative at ~200 nm, positive at ~220 nm) when the s1D12 spectra is subtracted (B; dashed and dotted line), indicating that dGAE has not assembled into fibrils.

**FIGURE 61.** Fluorescence of samples incubated with ThS. An emission peak at 483 nm is clearly observed with 25 (A, 1:1) and 100 μM (B, 4:1) dGAE (solid lines) which is abolished when s1D12 is included in the assembly mixture (dashed lines), showing that only samples that do not include s1D12 contain self-assembled amyloid fibrils. Dotted lines show that s1D12 alone does not contribute to the fluorescence.

Detailed description of the invention

According to a first aspect, the invention provides a specific binding molecule that binds to an epitope within SEQ ID NO: 1 with a binding affinity greater than the binding affinity with which antibody mAb423 binds to an epitope within SEQ ID NO: 1.

All residue numbers of the Tau protein sequence and structure in the present disclosure refer to the residues of SEQ ID NO:1, which is the sequence of the four repeat isoform 2N4R of human Tau protein (Uniprot ID P10636-8), or homologous positions in other species or variants thereof. Human Tau isoform 2N4R (Uniprot ID P10636-8) corresponds to amino acids 1-124, 376-394 and 461-758 of full length Tau, Uniprot ID P10636 or P10636-1, provided as SEQ ID NO:2. SEQ ID NO: 2 relates to a longer form of Tau found in the peripheral nervous system (PNS) but not the central nervous system (CNS). As used herein, references to "full-length" tau refer to SEQ ID NO: 1 (the relevant sequence for the CNS) and not to SEQ ID NO: 2 (which is not relevant in the CNS).

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SEQ ID NO: 1 (Isoform Tau-F, also known as Tau-4, 2N4R, 441 amino acids):

>sp|P10636-8|TAU\_HUMAN Isoform Tau-F of Microtubule-associated protein tau OS=Homo sapiens OX=9606 GN=MAPT

MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG  
 SETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAG  
 HVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQGQANATRIPAKTPPAPK  
 TPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAK  
 SRLQTAPVPMPLKLVKSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHV  
 PGGGSVQIVYKFPVDLSKVTSCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNI  
 THVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVS GDTSPRHLSNVVSSTGSIDMV  
 DSPQLATLADEVSSASLAKQGL

SEQ ID NO: 2 (Full length human Tau, Isoform PNS-Tau, 758 amino acids);

>sp|P10636-1|TAU\_HUMAN Microtubule-associated protein tau OS=Homo sapiens OX=9606  
 GN=MAPT PE=1 SV=5

MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG  
 SETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAG  
 HVTQEPESGKVVQEGFLREPGFPGLSHQLMSGMPGAPLLPEGPREATRQPSGTGPEDTEG  
 GRHAPELLKHQLLGLDLHQEGPPLKGAGGKERPGSKKEEVEDRDVDESSPDSPSPSKASPA  
 QDGRPPQTAAREATSIPGFPAEGAIPLPVDLFLSKVSTEIPASEPDGFSVGRAKGQDAPLE  
 FTFHVEITPNVQKEQAHSEEH LGRAAFPGAPGEGPEARGPSLGEDTKEADLPEPSEKQPA  
 AAPRGKFPVSRVPQLKARMVSKSKDGTGSDDKKAKTSTRSSAKTLKNRPCLSPKHPTPGSS  
 DPLIQPSSPAVCPEPPSPPKYVSSVTSRTGSSGAKEMKLKADGKTKIATPRGAAPPQK  
 GQANATRIPAKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREP  
 KKVAVVRTPPKSPSSAKSRLQTAPVPMPLKLVKSKIGSTENLKHQPGGGKVQIINKKLD  
 LSNVQSKCGSKDNIKHVPGGGSVQIVYKFPVDLSKVTSCGSLGNIHHKPGGGQVEVKSEK  
 LDFKDRVQSKIGSLDNI THVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVS GDT  
 SPRHLSNVVSSTGSIDMVDSPQLATLADEVSSASLAKQGL



As used herein "mouse tau" refers to Isoform Tau-A which has the sequence of Uniprot ID P10637-2, provided as SEQ ID NO: 589:

MADPRQEFDTMEDHAGDYTLQDQEGDMDHGLKESPPQPPADDGAEPPGSETSDAKSTPTAED  
 5 VTAPLVDERAPDKQAAQPHTEIPEGITAEAGIGDTPNQEDQAAGHVTQARVASKDRTGNDEKK  
 AKGADGKTGAKIATPRGAASPAQKGTSNATRIPAKTTSPKTPPGSGEPPKSGERSGYSSPGSPG  
 TPGSRSRTPSLPTPPTREP KKVAVVRTPPKSPSASKSRLQTAPVMPDLKNVRSKIGSTENLKHQ  
 PGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGG  
 QVEVKSEKLDKDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVS  
 10 DTSPRHLSNVSSSTGSDMVDPQLATLADEVSAASLAKQGL

dGAE97 refers to the 97 residues fragment of Tau (2N4R) with N-terminus at residue Asp-295 and C-terminus at residue Glu-391, as described in SEQ ID NO: 3, or at homologous positions in other species (the residues mentioned referring to the human or mouse Tau sequence, which are identical  
 15 in this region). As will be apparent to the skilled person, dGAE97 also corresponds to the fragment of Isoform PNS-Tau (P10636-1) with N-ter at Asp-612 and C-ter at Glu-708.

SEQ ID NO: 3 (dGAE97, human/mouse, 97 amino acids):

DNIKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDFKDRVQSKIGSLDN  
 20 THVPGGGNKKIETHKLTFRENAKAKTDHGAE

dGAE95 refers to the 95 residues fragment of Tau (2N4R) with N-terminus at residue Ile-297 and C-terminus at residue Glu-391, as described in SEQ ID NO: 4, or at homologous positions in other species (the residues mentioned referring to the human or mouse Tau sequence, which are identical  
 25 in this region). As will be apparent to the skilled person, dGAE95 also corresponds to the fragment of Isoform PNS-Tau (P10636-1) with N-ter at Ile-614 and C-ter at Glu-708. This sequence may sometimes be referred to simply as "dGAE". Residues 297 to 391 of Tau (2N4R) are also known as the predominant fragment isolated from proteolytically stable core of the paired helical filament (PHF).

30

SEQ ID NO: 4 (dGAE95 or "dGAE", human/mouse, 95 amino acids):

IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDFKDRVQSKIGSLDNITH  
 VPGGGNKKIETHKLTFRENAKAKTDHGAE

35 "dGA" refers to the 94 residues fragment of Tau (2N4R) with N-terminus at residue Ile-297 and C-terminus at residue Ala-390, as described in SEQ ID NO: 5, or at homologous positions in other species (the residues mentioned referring to the human or mouse Tau sequence, which are identical in this region).

40 SEQ ID NO: 5 (dGA, human/mouse, 94 amino acids):

IKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH  
VPGGGNKKIETHKLTFRENAKAKTDHGA

dGAE73 refers to the fragment of Tau (2N4R) with N-terminus at residue Val-306 and C-terminus at  
5 residue Phe-378, as described in SEQ ID NO: 6, or at homologous positions in other species (the  
residues mentioned referring to the human or mouse Tau sequence, which are identical in this  
region). This fragment corresponds to residues 306-378 of the sequence identified by cryo-EM as  
being the core of PHFs isolated from AD brain tissue (Fitzpatrick et al, 2017; Nature). The core can  
extend beyond these residues but is limited by the resolution of the cryo-EM. As will be apparent to  
10 the skilled person, dGAE73 also corresponds to the fragment of Isoform PNS-Tau (P10636-1) with  
N-ter at Val-623 and C-ter at Phe-695.

SEQ ID NO: 6 (dGAE73, human/mouse, 73 amino acids):

VQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITHVPGGGNKKI  
15 ETHKLTF

The PHF core refers to residues 296 to 391 of Tau (2N4R) as described in SEQ ID NO: 3, or at  
homologous positions in other species (the residues mentioned referring to the human or mouse Tau  
sequence, which are identical in this region).

20

A further fragment of the PHF core is residues 308 to 378 of Tau (2N4R) with N-terminus at residue  
Ile-308 and C-terminus at residue Phe-378, as described in SEQ ID NO: 7, or at homologous  
positions in other species (the residues mentioned referring to the human or mouse Tau sequence,  
which are identical in this region).

25

SEQ ID NO: 7 (dGAE71, residues 308 to 378 of 2N4R, human/mouse, 71 amino acids):

IVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITHVPGGGNKKIET  
HKLTF

30 The epitope of the specific binding molecule may be within SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID  
NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

The epitope of the specific binding molecule may be within residues 297 to 391 of SEQ ID NO: 1.  
Residues 297 to 391 of full-length Tau are also known as the predominant fragment isolated from  
35 proteolytically stable core of the paired helical filament (PHF) or the PHF-core fragment. Therefore,  
the epitope of the specific binding molecule may be within the PHF or within the dGAE fragment.  
Accordingly, the epitope of the specific binding molecule may be within SEQ ID NO 4.

The epitope of the specific binding molecule may be within residues 297 to 390 of SEQ ID NO: 1.

40 Residues 297 to 390 of full-length Tau are also known as the dGA fragment. Therefore, the epitope

of the specific binding molecule may be within the dGA fragment. Accordingly, the epitope of the specific binding molecule may be within SEQ ID NO: 5. The epitope of the specific binding molecule may be within dGAE73 and/or dGAE71. Accordingly, the epitope of the specific binding molecule may be within SEQ ID NO: 6 and/or SEQ ID NO: 7.

5

The epitope of the specific binding molecule may be within residues 308 to 378 of SEQ ID NO: 1. Residues 308 to 378 of full-length Tau are also known as the PHF core. Therefore, the epitope of the specific binding molecule may be within the PHF core. Accordingly, the epitope of the specific binding molecule may be within SEQ ID NO: 7.

10

The epitope of the specific binding molecule may be within residues 297 to 386 of SEQ ID NO: 1. The epitope of the specific binding molecule may be within residues 306 to 391 of SEQ ID NO: 1. The epitope of the specific binding molecule may be within residues 306 to 386 of SEQ ID NO: 1.

15 The epitope of the specific binding molecule may be within an amino acid sequence selected from the group consisting of residues 337 to 355 of SEQ ID NO: 1, residues 367 to 379 of SEQ ID NO: 1, residues 331 to 360 of SEQ ID NO: 1, residues 355 to 367 of SEQ ID NO: 1, residues 379 to 391 of SEQ ID NO: 1, residues 297 to 390 of SEQ ID NO: 1, residues 369 to 390 of SEQ ID NO: 1, residues 337 to 368 of SEQ ID NO: 1, residues 412 to 441 of SEQ ID NO: 1, residues 1 to 49 of SEQ ID NO: 1, residues 49 to 111 of SEQ ID NO: 1, residues 147 to 157 of SEQ ID NO: 1, residues 1 to 155 of SEQ ID NO: 1, residues 1 to 238 of SEQ ID NO: 1, residues 1 to 319 of SEQ ID NO: 1, residues 13 to 25 of SEQ ID NO: 1, residues 49 to 113 of SEQ ID NO: 1, residues 49 to 155 of SEQ ID NO: 1, residues 49 to 238 of SEQ ID NO: 1, residues 113 to 238 of SEQ ID NO: 1, residues 155 to 227 of SEQ ID NO: 1, residues 155 to 238 of SEQ ID NO: 1, residues 186 to 263 of SEQ ID NO: 1, residues 186 to 350 of SEQ ID NO: 1, residues 239 to 348 of SEQ ID NO: 1, residues 266 to 359 of SEQ ID NO: 1, residues 277 to 319 of SEQ ID NO: 1, residues 319 to 331 of SEQ ID NO: 1, residues 348 to 390 of SEQ ID NO: 1, residues 348 to 441 of SEQ ID NO: 1, residues 359 to 391 of SEQ ID NO: 1, and residues 360 to 390 of SEQ ID NO: 1.

30 The epitope of the specific binding molecule may be within an amino acid sequence selected from the group consisting of residues 337 to 355 of SEQ ID NO: 1, residues 367 to 379 of SEQ ID NO: 1, residues 331 to 360 of SEQ ID NO: 1, residues 355 to 367 of SEQ ID NO: 1, residues 379 to 391 of SEQ ID NO: 1, residues 297 to 390 of SEQ ID NO: 1, residues 369 to 390 of SEQ ID NO: 1, residues 337 to 368 of SEQ ID NO: 1, residues 412 to 441 of SEQ ID NO: 1, residues 1 to 49 of SEQ ID NO: 1, residues 49 to 111 of SEQ ID NO: 1, and residues 147 to 157 of SEQ ID NO: 1.

The epitope of the specific binding molecule may be within an amino acid sequence selected from the group consisting of residues 337 to 355 of SEQ ID NO: 1, residues 367 to 379 of SEQ ID NO: 1, residues 331 to 360 of SEQ ID NO: 1 and residues 355 to 367 of SEQ ID NO: 1.

40

The epitope of the specific binding molecule may be within an amino acid sequence selected from the group consisting of residues 341 to 353 of SEQ ID NO: 1.

5 The epitope of specific binding molecules of the invention may be any amino acid sequence of SEQ ID NO: 1 indicated as containing critical binding residues by ELISA or alanine scanning mutagenesis, as described for example in Examples 5 to 12.

Epitopes described herein may be identified as “comprising” a certain amino acid sequence or by the phrase “the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues...”. As will be apparent to the skilled person, when a specific binding molecule binds a polypeptide or protein molecule comprising its epitope, it will also bind a polypeptide or protein molecule consisting of its epitope. As used herein, the phrase “the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues...” may therefore alternatively be substituted wherever it occurs for the phrase “the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence consisting of residues...”; the phrase “the specific binding molecule binds to a polypeptide or protein molecule consisting of an amino acid sequence comprising residues...”; or the phrase “the specific binding molecule binds to a polypeptide or protein molecule consisting of an amino acid sequence consisting of residues...”.

20

The skilled person is aware that not all residues within an epitope are always essential. A specific binding molecule may retain binding to an amino acid sequence with at least 70% identity to an epitope. The specific binding molecule may bind to any of the epitopes disclosed herein or an amino acid sequence having at least 70% identity thereto.

25

A specific binding molecule may retain binding to an amino acid sequence with at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to an epitope. The specific binding molecule may bind to any of the epitopes disclosed herein or an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity thereto.

30

In embodiments of the invention where specific binding molecule retains binding to an amino acid sequence with less than 100% sequence identity to the amino acid sequence of SEQ ID NO: 1 (or any of SEQ ID NOs: 3 to 7 or any other epitope defined herein), the epitope sequence may be altered by substitution, addition or deletion of an appropriate number of amino acids in the sequences of SEQ ID NO: 1 (or any of SEQ ID NOs: 3 to 7 or any other epitope defined herein). In another embodiment of the invention, the epitope may be modified by the substitution, addition or deletion of up to 2 amino acids relative to SEQ ID NO: 1 (or any of SEQ ID NOs: 3 to 7 or any other epitope defined herein), with the proviso that the resultant epitope sequence has at least 85% or 90% sequence identity to SEQ ID NO: 1 (or any of SEQ ID NOs: 3 to 7 or any other epitope defined

herein), as set out above. By "substitution, addition or deletion" is included combinations of substitutions, additions and deletions.

When an epitope sequence is modified by substitution of a particular amino acid residue, the substitution may be a conservative amino acid substitution. The term "conservative amino acid substitution", as used herein, refers to an amino acid substitution in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Amino acids with similar side chains tend to have similar properties, and thus a conservative substitution of an amino acid important for the structure or function of a polypeptide may be expected to affect polypeptide structure/function less than a non-conservative amino acid substitution at the same position. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g. lysine, arginine, histidine), acidic side chains (e.g. aspartic acid, glutamic acid), uncharged polar side chains (e.g. asparagine, glutamine, serine, threonine, tyrosine), non-polar side chains (e.g. glycine, cysteine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan) and aromatic side chains (e.g. tyrosine, phenylalanine, tryptophan, histidine). Thus a conservative amino acid substitution may be considered to be a substitution in which a particular amino acid residue is substituted for a different amino acid in the same family. However, a substitution of an epitope residue may equally be a non-conservative substitution, in which one amino acid is substituted for another with a side-chain belonging to a different family.

The epitope may be at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19 or at least 20 amino acids in length. The epitope may be five to 20 amino acids in length. The epitope may be five to 15 amino acids in length. The epitope may be five to 12 amino acids in length. The epitope may be six to 12 amino acids in length. The epitope may be seven to 12 amino acids in length.

As used herein, the term "within" means "contained within" or "fully within". No residues thought to be essential for the binding of the specific binding molecule to its target are outside of the epitope. Residues outside the epitope do not significantly contribute to binding. For example, where the epitope of the specific binding molecule is within residues 337 to 355 of SEQ ID NO: 1, residues outside of residues 337 to 355 do not significantly contribute to binding.

The epitope may comprise any residues within SEQ ID NO: 1 bound by the specific binding molecule. The epitope may be a continuous epitope or a discontinuous epitope.

A continuous epitope may be any consecutive residues within SEQ ID NO: 1 bound by the specific binding molecule. Consecutive residues are adjacent to one another in the primary structure of a polypeptide.

A discontinuous epitope may be any non-consecutive residues within SEQ ID NO: 1 bound by the specific binding molecule. Discontinuous epitopes are typically formed by non-consecutive residues adopting nearby positions in three-dimensional space due to the folding of a polypeptide.

- 5 Typically, a specific binding molecule binds to a polypeptide or protein molecule comprising its epitope. Therefore, the specific binding molecule may bind to SEQ ID NO: 1 or a fragment thereof. The specific molecule may bind to SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and/or SEQ ID NO: 7. The specific molecule may bind to the PHF or the dGAE fragment. the specific binding molecule may bind to the dGA fragment. The specific binding molecule may bind to the PHF
- 10 core. The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence selected from the group consisting of residues 337 to 355 of SEQ ID NO: 1, residues 367 to 379 of SEQ ID NO: 1, residues 331 to 360 of SEQ ID NO: 1, residues 355 to 367 of SEQ ID NO: 1, residues 379 to 391 of SEQ ID NO: 1, residues 297 to 390 of SEQ ID NO: 1, residues 369 to 390 of SEQ ID NO: 1, residues 337 to 368 of SEQ ID NO: 1, residues 412 to 441 of SEQ ID
- 15 NO: 1, residues 1 to 49 of SEQ ID NO: 1, residues 49 to 111 of SEQ ID NO: 1, residues 147 to 157 of SEQ ID NO: 1, residues 1 to 155 of SEQ ID NO: 1, residues 1 to 238 of SEQ ID NO: 1, residues 1 to 319 of SEQ ID NO: 1, residues 13 to 25 of SEQ ID NO: 1, residues 49 to 113 of SEQ ID NO: 1, residues 49 to 155 of SEQ ID NO: 1, residues 49 to 238 of SEQ ID NO: 1, residues 113 to 238 of SEQ ID NO: 1, residues 155 to 227 of SEQ ID NO: 1, residues 155 to 238 of SEQ ID NO: 1, residues
- 20 186 to 263 of SEQ ID NO: 1, residues 186 to 350 of SEQ ID NO: 1, residues 239 to 348 of SEQ ID NO: 1, residues 266 to 359 of SEQ ID NO: 1, residues 277 to 319 of SEQ ID NO: 1, residues 319 to 331 of SEQ ID NO: 1, residues 348 to 390 of SEQ ID NO: 1, residues 348 to 441 of SEQ ID NO: 1, residues 359 to 391 of SEQ ID NO: 1, and residues 360 to 390 of SEQ ID NO: 1.
- 25 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence of residues 341 to 353 of SEQ ID NO: 1.

- In the sequences that follow, "/" means "or" and denotes residues that the inventors have shown may vary as specified. In this context, "-" means a gap or no amino acid. X is any amino acid. For example,
- 30 "N/S" means a residue which may be either N or S. Likewise, "G/-" means a residue which may be either G or absent. Likewise, "H/F/Y" means a residue may be H, F or Y. Where sequence identity values are specified, sequence identity may be calculated starting from any one of the residues separated by a "/".

- 35 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. The epitope of the specific binding molecule within an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1 may be within an amino acid sequence comprising residues 341 to 353 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 8 (VEVKSEKLDKDR).

40

The epitope may be within an amino acid sequence comprising residues 337 to 349 of SEQ ID NO: 1, preferably within an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "S1D12" herein. The epitope may comprise the amino acid sequence of SEQ ID NO: 8 (VEVKSEKLDKDR). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 8 (VEVKSEKLDKDR). Critical residues of the epitope may be residues 343 (K), 346 (F) and/or 349 (R) (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 9 (XXXXXXXXKXXFXR, wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO: 8, wherein any one or more residue other than residue number 343 (K), 346 (F) and/or 349 (R) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 8, wherein any one or more residue other than residue number 343 (K), 346 (F) and/or 349 (R) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 8, wherein any one or more residue other than residue number 343 (K), 346 (F) and/or 349 (R) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and any one or more residue other than residue number 343 (K), 346 (F) and/or 349 (R) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1).

20

The epitope may consist of residues 337 to 349 of SEQ ID NO: 1, preferably residues 337 to 355 of SEQ ID NO: 1. The epitope may consist of the amino acid sequence of SEQ ID NO: 8 (VEVKSEKLDKDR). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 8 (VEVKSEKLDKDR).

25

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

30

VHCDR1 comprises the sequence set forth in SEQ ID NO: 10 (N/S N A V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 11 (G C S S D G T/K C Y Y/H N S A L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 12 (G H/F/Y Y S/P I/V Y G Y D Y L/S G T I D Y);

35

VLCDR1 comprises the sequence set forth in SEQ ID NO: 13 (S G S S S N V G/- G G/R N S/D V G/A);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 14 (D/N/G T N/T S R P S);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 15 (V/A T/S G D S T/S T/A H/I D/N D L/I);

40

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto.

- 5 Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.
- 10 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG) or SEQ ID NO: 17 (SNAVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCYNSALKS),  
 15 SEQ ID NO: 19 (GCSSDGKCYHNSALKS) or SEQ ID NO: 20 (GCSSDGKCYNSALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYG DYLG TIDY), SEQ ID NO: 22 (GFYSIYG DYSG TIDY), or SEQ ID NO: 23 (GYYPVYG DYLG TIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG) or SEQ ID NO: 25 (SGSSSNVGRNDVA);  
 20 VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS), SEQ ID NO: 27 (NTNSRPS), or SEQ ID NO: 28 (GTTSRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL), SEQ ID NO: 30 (VTGDSSTHDDL), or SEQ ID NO: 31 (ASGDSSAINDI);  
 or for each CDR sequence, an amino acid sequence with  
 25 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1.
- 30 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCYNSALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYG DYLG TIDY);  
 35 VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 40 (ii) one, two, or three amino acid substitutions relative thereto,



wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "S1D12" (or abbreviated to "1D12") herein.

5

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCCYNSALKS);

10 VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGIDYLGITIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL).

15 Any specific binding molecule disclosed herein may be further defined by reference to one or more framework region (FR). The framework regions (FRs) are non-CDR sequences which together with the CDR sequences form a variable domain.

20 The VH domain may have the formula: VHFR1 - VHCDR1 - VHFR2 - VHCDR2 - VHFR3 - VHCDR3 - VHFR4.

The VL domain may have the formula: VLFR1 - VLCDR1 - VLFR2 - VLCDR2 - VLFR3 - VLCDR3 - VLFR4.

25 The skilled person is able to identify CDR and framework regions within the amino acid sequence of a variable domain using known methods described elsewhere herein. Accordingly, any specific binding molecule disclosed herein may be defined by reference to its CDRs and FRs. In some instances, some of the FR residues may contribute to the affinity with which a specific binding molecule binds its target. However, without being bound by theory, function is more likely to be preserved when replacing an FR residue than when replacing a CDR residue. FR residues may for example be commonly replaced by corresponding residues from human sequences during the process of humanization. FR sequences may therefore be more tolerant of amino acid substitutions than CDR sequences.

35 The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence from any specific binding molecule disclosed herein; or for each FR sequence, an amino acid sequence with

40 (i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence from any specific binding molecule disclosed herein, or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

5 (ii) one, two, or three amino acid substitutions relative thereto.

Said sequence identity in a CDR sequence is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or  
10 at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

Said sequence identity in a FR sequence is at least about 50% sequence identity and may therefore be at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at  
15 least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

Where an FR sequence has at least 50% identity (but less than 100% identity) to an FR sequence disclosed as part of a specific binding molecule disclosed herein, the FR sequence may be a  
20 humanized sequence. In other words, the changes to amino acid sequence may be only those needed to humanize the sequence.

Where an FR sequence has one, two, three, four or five amino acid substitutions relative to an FR sequence disclosed as part of a specific binding molecule disclosed herein, the FR sequence may  
25 be a humanized sequence. In other words, the substitutions may be only those needed to humanize the sequence.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and  
30 VLFR4, wherein each of said FRs comprises an amino acid sequence from any specific binding molecule disclosed herein; and

(b) CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence from any specific binding molecule disclosed herein.

35

Typically, each of the FRs will be from the same specific binding molecule disclosed herein. Typically, each of the CDRs will be from the same specific binding molecule disclosed herein. Typically, there will be no additional amino acid residues intervening between a defined FR and CDR; each of said FRs and each of said CDRs may therefore be said to consist of an amino acid sequence from any  
40 specific binding molecule disclosed herein.

As used herein, the phrase "comprising the CDRs" also encompasses a specific binding molecule comprising the CDRs and FRs of a specific binding molecule disclosed herein, including variants of the FRs including those described above, such as humanized FRs. It also encompasses a specific binding molecule comprising the VH and/or VL domains of a specific binding molecule disclosed herein, including variants of the FRs including those described above, such as humanized FRs. It also encompasses a specific binding molecule comprising the heavy chain and/or light chain of a specific binding molecule disclosed herein, including variants of the FRs and constant regions including those described above, such as humanized FRs and humanized constant regions.

10

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 435  
 15 (QVQLQESGPSLVKPSQTLSTCTVSGFSLN);

VHFR2 comprises the sequence set forth in SEQ ID NO: 436 (WVRQAPGKVPESLV);

VHFR3 comprises the sequence set forth in SEQ ID NO: 437  
 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 438 (WGPGLLVTVSS);

20 VLFR1 comprises the sequence set forth in SEQ ID NO: 439  
 (QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 440 (WYQHLPGSGSLKTIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 441  
 (GVPDRFSGSRSGNTATLTINSLQAEDGDYYC);

25 VLFR4 comprises the sequence set forth in SEQ ID NO: 442(VGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto.

30 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 435  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLN);

35 VHFR2 comprises the sequence set forth in SEQ ID NO: 436 (WVRQAPGKVPESLV);

VHFR3 comprises the sequence set forth in SEQ ID NO: 437  
 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 438 (WGPGLLVTVSS);

40 VLFR1 comprises the sequence set forth in SEQ ID NO:  
 439(QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 440 (WYQHLPGSGGLKTIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 441  
 (GVPDRFSGSRSGNTATLTINSLQAEDEGDYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 442 (VGSGTRLTVLG);  
 5 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. A specific binding  
 10 molecule comprising FRs having 100% identity to those given above is referred to as "S1D12" (or  
 abbreviated to "1D12") herein.

The specific binding molecule may comprise:  
 (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
 15 wherein each of said FRs comprises an amino acid sequence as follows:  
 VHFR1 comprises the sequence set forth in SEQ ID NO: 435  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLN);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 436 (WVRQAPGKVPESLV);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 437  
 20 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 438 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 439  
 (QAVLTQPSSVSGSLGQRVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 440 (WYQHLPGSGGLKTIY);  
 25 VLFR3 comprises the sequence set forth in SEQ ID NO: 441  
 (GVPDRFSGSRSGNTATLTINSLQAEDEGDYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 442 (VGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 30 (ii) one, two, three, four or five amino acid substitutions relative thereto; and  
 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
 CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCCYNSALKS);  
 35 VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGIDYLGITIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL);  
 or for each CDR sequence, an amino acid sequence with  
 40 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as  
 5 "S1D12" (or abbreviated to "1D12") herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

10 VHFR1 comprises the sequence set forth in SEQ ID NO: 435  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLN);

VHFR2 comprises the sequence set forth in SEQ ID NO: 436 (WVRQAPGKVPESLV);

VHFR3 comprises the sequence set forth in SEQ ID NO: 437  
 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);

15 VHFR4 comprises the sequence set forth in SEQ ID NO: 438 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 439  
 (QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 440 (WYQHLPGSGGLKTIY);

20 VLFR3 comprises the sequence set forth in SEQ ID NO: 441  
 (GVPDRFSGSRSGNTATLTINSLQAEDEGDYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 442 (VGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

25 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCTCYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGYDYLGITIDY);

30 VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL);

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. The specific binding  
 35 molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "S1D12" (or abbreviated to "1D12") herein.

The specific binding molecule may comprise:

(a) A VH domain comprising the sequence set forth in SEQ ID NO: 443

40 (QVQLQESGPSLVKPSQTLSTCTVSGFSLNNAVGWVRQAPGKVPESLVGCSSDGTCTCY

YNSALKSRLDITRDTSKNQISLSLSSVTTDDAAVYYCTRGHYSIYGYDYLGTIDYWGPGLL  
VTVSS); and/or

- (b) a VL domain comprising the sequence set forth in SEQ ID NO: 444  
(QAVLTQPSSVSGSLGQQRVSITCSGSSSNVGGNSVGWYQHLPGLKTIYDTNSRPSG  
5 VPDRFSGSRSGNTATLTINSLQAEDEGDYYCVTGDSTTHDDLVGSGTRLTVLG);  
or a humanized variant thereof.

The specific binding molecule may comprise:

- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 445  
10 (QVQLQESGPSLVKPSQTLSTCTVSGFSLNNNAVGVWRQAPGKVPESLVGCSSDGTCTY  
YNSALKSRLDITRDTSKNQISLSLSSVTTDDAAVYYCTRGHYSIYGYDYLGTIDYWGPGLL  
VTVSSAKTTAPSVYPLAPVCGDGTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA  
VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPN  
LLGGPSVFIFPPKIKDVLMSLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHRED  
15 YNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPE  
EEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSGYSFMYSKLRVEK  
KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or  
(b) a light chain comprising the sequence set forth in SEQ ID NO: 446  
20 (QAVLTQPSSVSGSLGQQRVSITCSGSSSNVGGNSVGWYQHLPGLKTIYDTNSRPSG  
VPDRFSGSRSGNTATLTINSLQAEDEGDYYCVTGDSTTHDDLVGSGTRLTVLGGQPKSS  
PSVTLFPPSSEELETNKATLVCTITDFYPGVTVDWKVDGTPVTQGMETTQPSKQSNNKY  
MASSYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);  
or a humanized variant thereof.

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 1 below. The epitope may be within residues 337 to 355 of SEQ ID NO: 1.

**Table 1**

| Clone name | VH                                        |                                                                            |                                                                                                             | VL                                                                   |                                                      |                                                                                      | Epitope |
|------------|-------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------|---------|
|            | <u>CDR1</u>                               | <u>CDR2</u>                                                                | <u>CDR3</u>                                                                                                 | <u>CDR1</u>                                                          | <u>CDR2</u>                                          | <u>CDR3</u>                                                                          |         |
| S1D12      | NNAV <del>G</del> (SEQ ID NO: 16)         | GCSSDGT <del>C</del> Y <del>N</del> SALKS (SEQ ID NO: 18)                  | GHYSI <del>G</del> Y <del>D</del> Y <del>L</del> GTIDY (SEQ ID NO: 21)                                      | SGSSSNVGGGNSVG (SEQ ID NO: 24)                                       | DTNSRPS (SEQ ID NO: 26)                              | VTGDS <del>T</del> THDDL (SEQ ID NO: 29)                                             | 337-355 |
| S2C1       | NNAV <del>G</del> (SEQ ID NO: 16)         | GCSSDGT <del>C</del> Y <del>N</del> SALKS (SEQ ID NO: 18)                  | NA                                                                                                          | NA                                                                   | NA                                                   | NA                                                                                   | 337-355 |
| ME12       | <u>S</u> NAV <del>G</del> (SEQ ID NO: 17) | GCSSD <del>G</del> <u>K</u> CY <del>H</del> <u>N</u> SALKS (SEQ ID NO: 19) | <u>G</u> EY <del>S</del> I <del>G</del> Y <del>D</del> Y <del>L</del> <u>S</u> GTIDY (SEQ ID NO: 22)        | SGSSSNVGGGNSVG (SEQ ID NO: 24)                                       | <u>N</u> TNSRPS (SEQ ID NO: 27)                      | VTGDS <del>S</del> THDDL (SEQ ID NO: 30)                                             | 337-355 |
| NS3D9      | <u>S</u> NAV <del>G</del> (SEQ ID NO: 17) | GCSSD <del>G</del> <u>K</u> CY <del>N</del> <u>S</u> ALKS (SEQ ID NO: 20)  | <u>G</u> Y <del>P</del> <u>V</u> Y <del>G</del> Y <del>D</del> Y <del>L</del> <u>G</u> TIDY (SEQ ID NO: 23) | SGSSSNV- <u>G</u> R <del>N</del> <u>D</u> <u>V</u> A (SEQ ID NO: 25) | <u>G</u> T <del>I</del> <u>S</u> RPS (SEQ ID NO: 28) | <u>A</u> S <del>G</del> <u>D</u> <u>S</u> <u>S</u> AIND <del>I</del> (SEQ ID NO: 31) | 337-355 |

The CDRs specified herein are defined according to Kabat. The skilled person is aware that other methods for identifying CDRs are available, such as Chothia and Martin. The use of an alternative method to define CDRs may on occasion alter the residues defined as belonging to one or more CDRs. For example, alternative CDR definitions for S1D12 according to Chothia and Martin are shown in Figure 1. Any alternative CDR definitions for the specific binding molecule sequences disclosed herein fall within the scope of the invention.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 1;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 1;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 1;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 1;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 1; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 1;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1 with a  $K_D$  of less than around 500 pM. The  $K_D$  may be less than around 400 pM, less than around 300 pM, less than around 200 pM or less than around 150 pM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 5. The  $K_D$  for binding to SEQ ID NO: 1 may be around 50 pM to around 150 pM. The  $K_D$  for binding
- 20 to SEQ ID NO: 1 may be around 101 pM or 122 pM, optionally wherein the specific binding molecule comprises the CDRs of S1D12. The  $K_D$  for binding to SEQ ID NO: 5 may be around 300 pM to around 400 pM. The  $K_D$  for binding to SEQ ID NO: 5 may be around 344 pM, optionally wherein the specific binding molecule comprises the CDRs of S1D12.
- 25 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 32 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
- 30 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 30. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 32. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 30 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 32. The specific
- 35 binding molecule may comprise the amino acid sequence of SEQ ID NO: 32.

SEQ ID NO: 32 (S1D12 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLNNAVGWVRQAPGKVPESLVGCSSDGTCCYYNSALK  
SRLDITRDTSKNQISLSLSSVTDDAAVYYCTRGHYSIYGYDYLGTIDYWGPGLLVTVSSEGEKSSGA



SGESKVDDQAVLTQPSSVSGSLGQRVSITCSGSSSNVGGGNSVGWYQHLPGLKTIHYDTNSRP  
SGVPDRFSGSRSGNTATLTINSLQAEDEGDYYCVTGDSTTHDDLVGSGTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising  
5 residues 367 to 379 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
sequence of SEQ ID NO: 33 (GNKKIETHKLTFR).

The epitope may be within an amino acid sequence comprising residues 367 to 379 of SEQ ID NO:  
1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "S1G2"  
10 herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 33 (GNKKIETHKLTFR). The  
epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at  
least 90%, at least 95% or at least 99% identity to SEQ ID NO: 33 (GNKKIETHKLTFR). Critical  
15 residues of the epitope may be residues 370 (K) and/or 374 (H) (numbering according to SEQ ID  
NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 34 (XXXXXXXXXXXXX,  
wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO:  
33, wherein any one or more residue other than residue number 370 (K) and/or 374 (H) is replaced  
by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope  
20 may comprise the amino acid sequence of SEQ ID NO: 33, wherein any one or more residue other  
than residue number 370 (K) and/or 374 (H) is replaced by a conservative amino acid substitution  
(numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of  
SEQ ID NO: 33, wherein any one or more residue other than residue number 370 (K) and/or 374 (H)  
is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and  
25 any one or more residue other than residue number 370 (K) and/or 374 (H) is replaced by a non-  
conservative amino acid substitution (numbering according to SEQ ID NO: 1).

The epitope may consist of the amino acid sequence of SEQ ID NO: 33 (GNKKIETHKLTFR). The  
epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at  
30 least 90%, at least 95% or at least 99% identity to SEQ ID NO: 33 (GNKKIETHKLTFR).

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino  
acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. Said specific binding molecule may  
comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each  
35 of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 35 (S/T N/Y S/A/Y V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 36 (G/S/N I/V D/Y T/S D/T G  
E/Y/D/R E/T/A G/Y/F Y/F N P A/V L N/K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 37 (S/T Y/V/A R/N A/T/G/S D/-  
40 G/- L/Y/F/- A/- Y/H G/P Y/D V Q/Y A/Y I D/E Y/R/K) or SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);

- VLCDR1 comprises the sequence set forth in SEQ ID NO: 38 (S G S/R F/Y/D I/L/V G/S I/S/R S S/R/A/G V G) or in SEQ ID NO: 39 (SGSSSNVGYGNYVG)
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 40 (A/D S/A D/S/T G/S R P/A S);
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 41 (G/S S/I/V S/F/Y/T D/G/A/Q
- 5 R/P/- T/- P/Q/D/G Y/R/H/N T/N G/Y V/I/L);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto.
- 10 Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.
- 15 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG), SEQ ID NO: 17 (SNAVG), SEQ ID NO: 44 (SYYVG), or SEQ ID NO: 45 (TNSVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS),
- 20 SEQ ID NO: 47 (SVDSGDYTYNPALKS), SEQ ID NO: 48 (GIDSDGEEGYNPALNS), SEQ ID NO: 49 (GIDSDGEEGYNPALKS), SEQ ID NO: 50 (SVDSGDYTYNPALKS), SEQ ID NO: 51 (GIDTDGEEGYNPALKS), SEQ ID NO: 52 (NIYSTGRAFYNPALKS), or SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY),
- 25 SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY), SEQ ID NO: 56 (SVNGHPDVYYIDR), SEQ ID NO: 57 (TYRTDGYAYGYVQAIDY), SEQ ID NO: 58 (SYRSDGLAYGYVQAIDY), SEQ ID NO: 59 (SANGHPDVYYIDK), SEQ ID NO: 60 (TYRTDGFAYGYVQAIDY), SEQ ID NO: 61 (SYRTDGLAYGYVQAIEY), or SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG); SEQ ID NO:
- 30 64 (SGSYISSSRVG); SEQ ID NO: 65 (SGSDLGSSRVG); SEQ ID NO: 66 (SGSYIGSSAVG); SEQ ID NO: 67 (SGRFIGISSVG); SEQ ID NO: 68 (SGSYIGSSGVG); or SEQ ID NO: 69 (SGSYVSRSRVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); SEQ ID NO: 71 (DSSSRPS); or SEQ ID NO: 72 (AATSRAS);
- 35 VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGV); SEQ ID NO: 74 (GSSDRTQYTGV); SEQ ID NO: 75 (GVFGDRNYI); SEQ ID NO: 76 (GIFGDRNYI); SEQ ID NO: 77 (GSTAPTPHTGV); SEQ ID NO: 78 (SSYQRGNTGV); SEQ ID NO: 79 (GSSDRTQYTGL); or SEQ ID NO: 80 (GIYGDRNYI);
- or for each CDR sequence, an amino acid sequence with
- 40 (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGTV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "S1G2" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGTV).

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 447 (QVQLQESGSPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 448 (WVRQAPGKAPEWVA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 449 (RLSITRDTSKSQVSLSLSSVTSEDATVYYCGR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 450 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 451 (QAVWTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 452 (WFQQLPGSGLRTIIV);

VLFR3 comprises the sequence set forth in SEQ ID NO: 453  
(GVPDRFMSKSGNTATLTISLQAEDEADYFC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 454 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

- 5 (i) at least 50% identity thereto, and/or  
(ii) one, two, three, four or five amino acid substitutions relative thereto.

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
10 sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 447  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 448 (WVRQAPGKAPEWVA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 449  
15 (RLSITRDTSKSQVSLSLSSVTSEDTAVYYCGR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 450 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 451  
(QAVVTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 452 (WFQQLPGSGLRTIIV);

20 VLFR3 comprises the sequence set forth in SEQ ID NO: 453  
(GVPDRFMSKSGNTATLTISLQAEDEADYFC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 454 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

- 25 (i) at least 50% identity thereto, and/or  
(ii) one, two, three, four or five amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. A specific binding molecule comprising FRs having 100% identity to those given above is referred to as "S1G2" herein.

30 The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 447(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

35 VHFR2 comprises the sequence set forth in SEQ ID NO: 448 (WVRQAPGKAPEWVA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 449  
(RLSITRDTSKSQVSLSLSSVTSEDTAVYYCGR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 450 (WGPGLLVTVSS);

40 VLFR1 comprises the sequence set forth in SEQ ID NO: 451  
(QAVVTQPSSVSGSLGQRVSITC);

- VLFR2 comprises the sequence set forth in SEQ ID NO: 452 (WFQQLPGSGLRTIIV);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 453 (GVPDRFSMSKSGNTATLTISLQAEDEADYFC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 454 (FGSGTRLTVLG);
- 5 or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
  - (ii) one, two, three, four or five amino acid substitutions relative thereto; and
- (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- 10 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
- 15 VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGTV).  
 or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising
- 20 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "S1G2" herein.
- The specific binding molecule may comprise:
- 25 (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- VHFR1 comprises the sequence set forth in SEQ ID NO: 447 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 448 (WVRQAPGKAPEWVA);
- 30 VHFR3 comprises the sequence set forth in SEQ ID NO: 449 (RLSITRDTSKSQVSLSLSSVTSED TAVYYCGR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 450 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 451 (QAVVTQPSSVSGSLGQRVSITC);
- 35 VLFR2 comprises the sequence set forth in SEQ ID NO: 452 (WFQQLPGSGLRTIIV);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 453 (GVPDRFSMSKSGNTATLTISLQAEDEADYFC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 454 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with
- 40 (i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and  
 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
- 5 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTG).
- 10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "S1G2" herein.
- 15 The specific binding molecule may comprise:
- (a) A VH domain comprising the sequence set forth in SEQ ID NO: 455  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPEWVAGIDTDGEEG  
 YNPALNSRLSITRDTSKSQVSLSLSSVTSEDTAVYYCGRSYRADGLAYGYVQAIDYWGP  
 LLVTVSS); and/or
- 20 (b) a VL domain comprising the sequence set forth in SEQ ID NO: 456  
 (QAVVTQPSSVSGSLGQRVSITCSGSFIGISSVGWFQQLPGSGLRTIIVASDGRPSGVPDR  
 FMSKSGNTATLTISLQAEDEADYFCGSSDRTPYTG VFGSGTRLTVLG);  
 or a humanized variant thereof.
- 25 The specific binding molecule may comprise:
- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 457  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPEWVAGIDTDGEEG  
 YNPALNSRLSITRDTSKSQVSLSLSSVTSEDTAVYYCGRSYRADGLAYGYVQAIDYWGP  
 LLVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTF  
 30 PAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPA  
 PNLLGGPSVFIFPPKIKDVLMI SLSPIVTCVVDVSEDDPDVQISWVNNVEVHTAQTQTHR  
 EDYNSTLRVVSALPIQHQQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSRAPQVYVLP  
 PEEEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRV  
 EKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or
- 35 (b) a light chain comprising the sequence set forth in SEQ ID NO: 458  
 (QAVVTQPSSVSGSLGQRVSITCSGSFIGISSVGWFQQLPGSGLRTIIVASDGRPSGVPDR  
 FMSKSGNTATLTISLQAEDEADYFCGSSDRTPYTG VFGSGTRLTVLGGQPKSSPSVTL  
 FPPSSEETNKATLVCTITDFYPGVVTDWKVDGTPVTQGMETTQPSKQSNKYMASS  
 YLTLTARAWERHSSYSCQVTHEGHTVEKSLRADCS);
- 40 or a humanized variant thereof.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 5 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 10 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);  
 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
     (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 15 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "S1B1" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 25 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 30 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 48 (GIDSDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 57 (TYRTDGYAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 35 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);  
 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
     (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 40 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding

molecule comprising CDRs having 100% identity to those given above is referred to as "S1D9" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 48 (GIDSDGEEGYNPALNS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 57 (TYRTDGYAYGYVQAIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGTV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGTV);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "S1F4" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGTV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);



VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);  
 5 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
     (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding  
 10 molecule comprising CDRs having 100% identity to those given above is referred to as "S1G10"  
 herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 15 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 20 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 51 (GIDTDGEEGYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 60 (TYRTDGFAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);  
 30 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
     (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding  
 35 molecule comprising CDRs having 100% identity to those given above is referred to as "S2C6"  
 herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 40 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

- VHCDR2 comprises the sequence set forth in SEQ ID NO: 51 (GIDTDGEEGYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 60 (TYRTDGFAYGYVQAIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);  
5 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 2 below. The epitope may be within residues 367 to 379 of SEQ ID NO: 1.

Table 2

| Clone name | VH                       |                                     |                                      | VL                          |                            |                              | Epitope                    |
|------------|--------------------------|-------------------------------------|--------------------------------------|-----------------------------|----------------------------|------------------------------|----------------------------|
|            | CDR1                     | CDR2                                | CDR3                                 | CDR1                        | CDR2                       | CDR3                         |                            |
| S1B1       | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46) | SYRIDGLAYGYVQAIDY<br>(SEQ ID NO: 55) | SGSFIGISSVG (SEQ ID NO: 63) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG V (SEQ ID NO: 74) | 367-379                    |
| S1D2       | SNAVG<br>(SEQ ID NO: 17) | SVDSDGYTYYNPALKS<br>(SEQ ID NO: 47) | SVNG----HPDVYYIDR<br>(SEQ ID NO: 56) | SGSYISSSRVG (SEQ ID NO: 64) | DSSSRPS<br>(SEQ ID NO: 71) | GVFG--DRNYI_ (SEQ ID NO: 75) | 367-379                    |
| S1D9       | SNSVG<br>(SEQ ID NO: 42) | GIDSDGEEGYNPALNS<br>(SEQ ID NO: 48) | TYRIDGYAYGYVQAIDY<br>(SEQ ID NO: 57) | SGSFIGISSVG (SEQ ID NO: 63) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG V (SEQ ID NO: 74) | 367-379                    |
| S1F4       | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46) | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54) | SGSFIGISSVG (SEQ ID NO: 63) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG V (SEQ ID NO: 74) | 367-379                    |
| S1G2       | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46) | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54) | SGSFIGISSVG (SEQ ID NO: 63) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTPYTG V (SEQ ID NO: 73) | PCT/EP2021/069160<br>367-3 |
| S1G10      | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46) | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54) | SGSFIGISSVG (SEQ ID NO: 63) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG V (SEQ ID NO: 74) | 367-3                      |

|      |                          |                                                      |                                                     |                                                  |                            |                                                        |                            |
|------|--------------------------|------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|----------------------------|--------------------------------------------------------|----------------------------|
| S1H6 | SNAVG<br>(SEQ ID NO: 17) | <u>S</u> VDSDGYTYNPALKS<br>(SEQ ID NO: 47)           | <u>S</u> VG---HPD <u>V</u> YIDR<br>(SEQ ID NO: 56)  | SGS <u>D</u> LG <u>S</u> SRVG<br>(SEQ ID NO: 65) | DSSRPS<br>(SEQ ID NO: 71)  | <u>G</u> IFG- <u>D</u> RNYI (SEQ ID NO: 76)            | 367-3                      |
| S1H9 | SNSVG<br>(SEQ ID NO: 42) | GID <u>S</u> DGEEGYNPALKS<br>(SEQ ID NO: 49)         | SYRSDGLAYGYVQAIDY<br>(SEQ ID NO: 58)                | SGSFIGISSVG (SEQ ID NO: 63)                      | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG <u>V</u> (SEQ ID NO: 74)                    | 367-3                      |
| S2C3 | SNAVG<br>(SEQ ID NO: 17) | <u>S</u> VDSDGDTYYPALKS<br>(SEQ ID NO: 50)           | <u>S</u> ANG---HPD <u>V</u> YIDK<br>(SEQ ID NO: 59) | SGSYISSSRVG (SEQ ID NO: 64)                      | DSSRPS<br>(SEQ ID NO: 71)  | <u>G</u> IFG- <u>D</u> RNYI (9)                        | 367-379                    |
| S2C6 | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALKS<br>(SEQ ID NO: 51)                  | TYRIDG <u>F</u> AYGYVQAIDY<br>(SEQ ID NO: 60)       | SGSFIGISSVG (SEQ ID NO: 63)                      | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG <u>V</u> (SEQ ID NO: 74)                    | 367-379                    |
| S2D1 | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46)                  | SYRIDGLAYGYVQAIDY<br>(SEQ ID NO: 55)                | SGSYIG <u>S</u> SAVG<br>(SEQ ID NO: 66)          | ASDGRPS<br>(SEQ ID NO: 70) | Incomplete                                             | 367-379                    |
| S2D4 | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46)                  | SYRIDGLAYGYVQA <u>I</u> EY<br>(SEQ ID NO: 61)       | SGRFIGISSVG (SEQ ID NO: 67)                      | ASDGRPS<br>(SEQ ID NO: 70) | G <u>S</u> TAP <u>T</u> PH <u>T</u> GV (SEQ ID NO: 77) | 367-379                    |
| CA9  | SNSVG<br>(SEQ ID NO: 42) | GIDTDGEEGYNPALNS<br>(SEQ ID NO: 46)                  | SYRSDGLAYGYVQAIDY<br>(SEQ ID NO: 58)                | SGSFIGISSVG (SEQ ID NO: 63)                      | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG <u>V</u> (SEQ ID NO: 74)                    | 367-379                    |
| CA12 | SYVVG<br>(SEQ ID NO: 44) | <u>N</u> IY <u>S</u> TGRAFYNPALKS<br>(SEQ ID NO: 52) | GSY <u>Y</u> HGGGNGMVDFFDY<br>(SEQ ID NO: 265)      | SGSSNVGYGNYVG<br>(14)                            | AATSRAS<br>(SEQ ID NO: 72) | <u>S</u> SYQR-GNTGV (SEQ ID NO: 78)                    | PCT/EP2021/069160<br>367-3 |

|      |                                   |                                                       |                                               |                                         |                            |                                      |         |
|------|-----------------------------------|-------------------------------------------------------|-----------------------------------------------|-----------------------------------------|----------------------------|--------------------------------------|---------|
| CB2  | <u>I</u> NSVG<br>(SEQ ID NO: 45)  | GIDTDGEEG <u>F</u> NPVL <u>K</u> S<br>(SEQ ID NO: 53) | SYR <u>I</u> DGLAYGYVQAIDY<br>(SEQ ID NO: 55) | SGSYIG <u>S</u> SGVG<br>(SEQ ID NO: 68) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYT <u>G</u> L (SEQ ID NO: 79) | 367-3   |
| CC12 | SNSVG<br>(SEQ ID NO: 42)          | GIDSDGEEGYNPALNS<br>(SEQ ID NO: 48)                   | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54)          | SGRFIGISSVG (SEQ ID NO: 67)             | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYT <u>G</u> V (SEQ ID NO: 74) | 367-3   |
| MC5  | SNA <u>V</u> G<br>(SEQ ID NO: 17) | <u>S</u> VDSDGDTYYNPAL <u>K</u> S<br>(SEQ ID NO: 50)  | SVNG----HPDVVYIDR<br>(SEQ ID NO: 56)          | SGSYV <u>S</u> RSRVG<br>(SEQ ID NO: 69) | DSSSRPS<br>(SEQ ID NO: 71) | GI <u>G</u> --DRNYI (SEQ ID NO: 80)  | 367-379 |
| MD12 | SNA <u>V</u> G<br>(SEQ ID NO: 17) | <u>S</u> VDSDGTYTYNPAL <u>K</u> S<br>(SEQ ID NO: 47)  | SVNG----HPDVVYIDR<br>(SEQ ID NO: 56)          | SGSYISSSRVG (SEQ ID NO: 64)             | DSSSRPS<br>(SEQ ID NO: 72) | GVFG--DRNYI (SEQ ID NO: 75)          | 367-379 |

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The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 2;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 2;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 2;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 2;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 2; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 2;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1 with a  $K_D$  of less than around 500 pM. The  $K_D$  may be less than around 400 pM, less than around 300 pM, or less than around 200 pM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 5. The  $K_D$  for binding to SEQ ID NO: 1 may be around 100 pM to around 200 pM. The  $K_D$  for binding to SEQ ID NO: 1 may
- 20 be around 140 pM or 170 pM, optionally wherein the specific binding molecule comprises the CDRs of S1G2. The  $K_D$  for binding to SEQ ID NO: 5 may be around 400 pM to around 500 pM. The  $K_D$  for binding to SEQ ID NO: 5 may be around 447 pM, optionally wherein the specific binding molecule comprises the CDRs of S1G2.
- 25 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 81 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,
- 30 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 81. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 81. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 81 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 81. The specific
- 35 binding molecule may comprise the amino acid sequence of SEQ ID NO: 81.

SEQ ID NO: 81 (S1G2 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPWVAGIDTDGEEGYNPALN  
SRLSITRDTSKSQVSLSLSSVTSEDVAVYYCGRSYRADGLAYGYVQAIDYWGPGLLVTSSEKGS

SGASGESKVDDQAVVTQPSSVSGSLGQQRVSITCSGSFIGISSVGWVFQQLPGSGLRTIIVASDGRPS  
GVPDRFSMSKSGNTATLTISSLQAEDEADYFCGSSDRTPYTGVFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least  
5 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 412 wherein  
the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid  
sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding  
molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,  
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at  
10 least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 412. The CDRs may be 100%  
identical to the CDRs of SEQ ID NO: 412. The specific binding molecule may comprise an amino  
acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least  
99% identity to SEQ ID NO: 412 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 412.  
The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 412.

15

SEQ ID NO: 412 (S1B1 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSSNSVGWVRQAPGKAPEWVAGIDTDGEEGYNPALN  
SRLSITRDTSKSQVLSLSSVTSEDTAVYYCVRSYRTDGLAYGYVQAIDYWGPGLLVTVSSEKSS  
GASGESKVDDQAVLTQPSSVSGSLGQQRVSITCSGSFIGISSVGWVFQQLPGSGLRTVIVASDGRPS  
20 GVPDRFSNSKSGNTATLTISSLQAEDEADYFCGSSDRTQYTGVPFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least  
75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 413 wherein  
the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid  
25 sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding  
molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,  
at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at  
least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 413. The CDRs may be 100%  
identical to the CDRs of SEQ ID NO: 413. The specific binding molecule may comprise an amino  
30 acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least  
99% identity to SEQ ID NO: 413 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 413.  
The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 413.

SEQ ID NO: 413 (S1D9 amino acid sequence)

35 QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPEWVAGIDSDGEEGYNPALN  
SRLSITRDTSKNQVLSLSRVTSSEDTAVYYCGRTYRTDGYAYGYVQAIDYWGPGLLVTVSSEKKS  
SGASGESKVDDRVMILTQPPSVSGSPGQTVSITCSGSFIGISSVGWVFQQLPGSGLRTVIFASDGRP  
SGVPDRFSNSKSGNTATLTISSLQAEDEADYFCGSSDRTQYTGVPFGSGTRTLTVLS

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 414 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 414. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 414. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 414 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 414. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 414.

SEQ ID NO: 414 (S1F4 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSSNSVGWVRQAPGKAPWVAGIDTDGEEGYNPALN  
SRLSITRDTSKSQVLSLSSVTSEDVAVYYCVRSYRADGLAYGYVQAIDYWGPGLLLTISSEGKSS  
GASGESKVDDQAVVTQPSSVSGSLGQQRVSITCSGSFIGISSVGWFQQLPGSGLRTVIVASDGRPS  
GVPDRFSNSKSGNTATLTISLQAEDEADYFCGSSDRTQYTGVFSGSGLRTLVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 415 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 415. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 415. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 415 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 415. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 415.

SEQ ID NO: 415 (S1G10 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPWVAGIDTDGEEGYNPALN  
SRLSITRDTSKSQVLSLSSVTSEDVAVYYCGRSYRADGLAYGYVQAIDYWGPGLLVTSSEGKS  
SGASGESKVDDQAVLTQPSSMSGSLGQQRVSITCSGSFIGISSVGWFQQLPGSGLRTIIVASDGRPS  
GVPDRFSMSKSGNTATLTISLQAEDEADYFCGSSDRTQYTGVFSGSGLRTLVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 416 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding



molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 416. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 416. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 416 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 416. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 416.

SEQ ID NO: 416 (S2C6 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLISNSVGWVRQAPGKAPEWVAGIDTDGEEGYNPALKS  
QYAASDPDTSKSQVSLSLSSVTSEDVAVYYCGRTYRTDGFAYGYVQAIDYWGPGLLLTISSEGKS  
SGASGESKVVDDQAVLTQPSSVSGSLGQRVSITCSGSFIGISSVGWFQQLPGSGLRTIIVASDGRPS  
GVPDRFMSKSGNTATLTISSLQAEDEADYFCGSSDRTQYTGVFSGGTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 82 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

The epitope may be within an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "NS2A3" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 82 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 82 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

The epitope may consist of the amino acid sequence of SEQ ID NO: 82 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 82 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (S Y S V Y)

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (I M Y A S G R V D Y N P A L K S)

VHCDR3 comprises the sequence set forth in SEQ ID NO: 85 (G I E N/D)

VLCDR1 comprises the sequence set forth in SEQ ID NO: 86 (R T S/N Q/E S/N V/I N/G/D N/S Y/G L S/A)

VLCDR2 comprises the sequence set forth in SEQ ID NO: 87 (Y A T Y L Y/H T)

VLCDR3 comprises the sequence set forth in SEQ ID NO: 88 (L Q Y D/G/E S/T T P L A/T)

5 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%,  
10 at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at  
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%  
identity. Preferably said sequence identity is at least 90% or at least 95%.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
15 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN) or SEQ ID NO: 90  
(GIED);

20 VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS), SEQ ID  
NO: 92 (RTNESVGNLYS), SEQ ID NO: 93 (RTSQNIDNGLA), or SEQ ID NO 94 (RTSQSVGSYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT) or SEQ ID NO:  
96 (YATRLHT);

25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA), SEQ ID NO:  
98 (LQYDSTPLT), SEQ ID NO: 99 (LQYESTPLA), or SEQ ID NO: 100 (LQYGTTPLA);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

30 wherein the specific binding molecule binds to a polypeptide or protein molecule  
comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

35 VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);

40 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1. The specific binding  
5 molecule comprising CDRs having 100% identity to those given above is referred to as "NS2A3" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 10 VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and  
15 VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 3 below. The epitope may be within residues 337 to 368 of SEQ ID NO: 1.

Table 3

| Clone name | VH                       |                                  |                      | VL                          |                            |                               | Epitope |
|------------|--------------------------|----------------------------------|----------------------|-----------------------------|----------------------------|-------------------------------|---------|
|            | <u>CDR1</u>              | <u>CDR2</u>                      | <u>CDR3</u>          | <u>CDR1</u>                 | <u>CDR2</u>                | <u>CDR3</u>                   |         |
| NS2A3      | SYSVY<br>(SEQ ID NO: 83) | IMYASGRVDYNPALKS (SEQ ID NO: 84) | GIEN (SEQ ID NO: 89) | RTSQSVNNYLS (SEQ ID NO: 91) | YATRLYT<br>(SEQ ID NO: 95) | LQYDSTPLA<br>(SEQ ID NO: 97)  | 337-368 |
| NS2A8      | SYSVY<br>(SEQ ID NO: 83) | IMYASGRVDYNPALKS (SEQ ID NO: 84) | GIEN (SEQ ID NO: 89) | RTNESVGNYLS (SEQ ID NO: 92) | YATRLHT<br>(SEQ ID NO: 96) | LQYGTTPLA<br>(SEQ ID NO: 100) | 337-368 |
| NS2C5      | SYSVY<br>(SEQ ID NO: 83) | IMYASGRVDYNPALKS (SEQ ID NO: 84) | GIED (SEQ ID NO: 90) | RTSQNDNGLA (SEQ ID NO: 93)  | YATRLHT<br>(SEQ ID NO: 96) | LQYESTPLA<br>(SEQ ID NO: 99)  | 337-368 |
| NS2C8      | SYSVY<br>(SEQ ID NO: 83) | IMYASGRVDYNPALKS (SEQ ID NO: 84) | GIEN (SEQ ID NO: 89) | RTSQSVNNYLS (SEQ ID NO: 91) | YATRLYT<br>(SEQ ID NO: 95) | LQYDSTPLA<br>(SEQ ID NO: 97)  | 337-368 |
| NS2D3      | SYSVY<br>(SEQ ID NO: 83) | IMYASGRVDYNPALKS (SEQ ID NO: 84) | GIED (SEQ ID NO: 89) | RTSQSVGSYLS (SEQ ID NO: 94) | YATRLHT<br>(SEQ ID NO: 96) | LQYDSTPLT<br>(SEQ ID NO: 98)  | 337-368 |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 3;
- VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 3;
- 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 3;
- VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 3;
- VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 3; and
- VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 3;

or for each CDR sequence, an amino acid sequence with

- 10 (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1 with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 5.

- 20 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 101 (KKIETHKLTFRENAKAKTDHGA).

The epitope may be within an amino acid sequence comprising residues 369 to 390 of SEQ ID NO:

- 25 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "NS4E3" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 101 (KKIETHKLTFRENAKAKTDHGA). The epitope may comprise an amino acid sequence having at

30 least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 101 (KKIETHKLTFRENAKAKTDHGA).

- 35 The epitope may consist of the amino acid sequence of SEQ ID NO: 101 (KKIETHKLTFRENAKAKTDHGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 101 (KKIETHKLTFRENAKAKTDHGA).

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1. Said specific binding molecule may

comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (R E S I A);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (G V G I D G T S Y Y S P A  
5 L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (N Y I D F E Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 105 (S G S S/N/Y S/N/- N/- V/-  
G/I Y/S/A/G E/G/S D/N/T Y/G/D V N/S/G)

VLCDR2 comprises the sequence set forth in SEQ ID NO: 106 (G/R T/N/S T/S N/T/R R P/A  
10 S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 107 (L/A/G S Y D R/T/G/S S/T  
G/N S/R/- N/G/S/I F/I/V);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- 15 (ii) one, two, or three amino acid substitutions relative thereto.

Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%,  
at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at  
least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%  
20 identity. Preferably said sequence identity is at least 90% or at least 95%.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);

25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYSPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 108 (SGSSSNVGYEDYVN), SEQ  
ID NO: 109 (SGSNIAGNGVG), SEQ ID NO: 110 (SGSSNNGSGDYVS), or SEQ ID NO: 111  
(SGSYIGSTDVG);

30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 112 (GTTNRPS), SEQ ID NO:  
113 (GSTRRPS), SEQ ID NO: 114 (RNSNRPS), or SEQ ID NO: 115 (RTTTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 116 (LSYDRSGSNF), SEQ ID  
NO: 117 (ASYDTSNRGI), SEQ ID NO: 118 (GSYDGTNSF), or SEQ ID NO: 119 (ASYDSNNSIV);

or for each CDR sequence, an amino acid sequence with

- 35 (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule  
comprising an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1.

40 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYYSPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 108 (SGSSSNVGYEDYVN);  
5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 112 (GTTNRPS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 116 (LSYDRSGSNF);  
or for each CDR sequence, an amino acid sequence with  
(i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1. The specific binding  
molecule comprising CDRs having 100% identity to those given above is referred to as "NS4E4"  
herein.
- 15 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYYSPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);  
20 VLCDR1 comprises the sequence set forth in SEQ ID NO: 108 (SGSSSNVGYEDYVN);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 112 (GTTNRPS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 116 (LSYDRSGSNF).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 4 below. The epitope may be within residues 369 to 390 of SEQ ID NO: 1.

Table 4

| Clone name | VH                     |                                   |                          | VL                              |                           |                                                                     | Epitope |
|------------|------------------------|-----------------------------------|--------------------------|---------------------------------|---------------------------|---------------------------------------------------------------------|---------|
|            | <u>VHCDR1</u>          | <u>VHCDR2</u>                     | <u>VHCDR3</u>            | <u>VLCDR1</u>                   | <u>VLCDR2</u>             | <u>VLCDR3</u>                                                       |         |
| NS3E5      | RESIA (SEQ ID NO: 102) | GVGIDGTSYYSPALKS (SEQ ID NO: 103) | NYIDFEY (SEQ ID NO: 104) | SGSY---IGSID (SEQ ID NO: 111)   | GSTRRP S (SEQ ID NO: 113) | ASYD <u>SN</u> <u>N</u> <u>S</u> <u>I</u> <u>V</u> (SEQ ID NO: 119) | 369-390 |
| NS3H4      | RESIA (SEQ ID NO: 102) | GVGIDGTSYYSPALKS (SEQ ID NO: 103) | NYIDFEY (SEQ ID NO: 104) | SGSN---IAGNGVG (SEQ ID NO: 109) | RNSNRPS (SEQ ID NO: 114)  | GSYDGTN-SF (SEQ ID NO: 118)                                         | 369-390 |
| NS4F2      | RESIA (SEQ ID NO: 102) | GVGIDGTSYYSPALKS (SEQ ID NO: 103) | NYIDFEY (SEQ ID NO: 104) | SGSSNNVSGGDYVS (SEQ ID NO: 110) | RTTTRAS (SEQ ID NO: 115)  | ASYDTSNRGI (SEQ ID NO: 117)                                         | 369-390 |
| NS4E3      | RESIA (SEQ ID NO: 102) | GVGIDGTSYYSPALKS (SEQ ID NO: 103) | NYIDFEY (SEQ ID NO: 104) | SGSSSNVGYEDYVN (SEQ ID NO: 108) | GTTNRPS (SEQ ID NO: 112)  | LSYDRSGSNE (SEQ ID NO: 116)                                         | 369-390 |



The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 4;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 4;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 4;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 4;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 4; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 4;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1 with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 5.

- 20 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 120 (SSTGSIDMVDSPQLATLADEVASLAKQGL).

- The epitope may be within an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "412E10" herein.

- The epitope may comprise the amino acid sequence of SEQ ID NO: 120 (SSTGSIDMVDSPQLATLADEVASLAKQGL). The epitope may comprise an amino acid sequence
- 30 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 120 (SSTGSIDMVDSPQLATLADEVASLAKQGL).

- The epitope may consist of the amino acid sequence of SEQ ID NO: 120 (SSTGSIDMVDSPQLATLADEVASLAKQGL). The epitope may consist of an amino acid sequence
- 35 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 120 (SSTGSIDMVDSPQLATLADEVASLAKQGL).

- The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. Said specific binding molecule may
- 40 comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 121 (S/N D/Y S/G/A V/L A/G);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 122 (A/N S/I G/Y/W S/R S/G G  
 N/S/R K/T/I Y/E Y N P A L K S);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 123 (G I/G I/V A/G G/S V D V),  
 5 or SEQ ID NO: 124 (SGGD);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 125 (S G S/G S/N N V/I G Y/R G  
 N/D/T Y/F V G/D);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 126 (G T/A A/D/T I/S/R R A/P  
 S/P); and  
 10 VLCDR3 comprises the sequence set forth in SEQ ID NO: 127 (A S/T Y Q/D S/Y/R N/S  
 Y/D/N/E A/G/D/S -/G/M/V -/I F/V/I);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto.  
 15  
 Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%,  
 at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at  
 least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%  
 identity. Preferably said sequence identity is at least 90% or at least 95%.  
 20  
 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA), SEQ ID NO: 129  
 (NYGVG), or SEQ ID NO: 130 (SYALG);  
 25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS),  
 SEQ ID NO: 132 (NIWRGGRIEYNPALKS), or SEQ ID NO: 133 (NIYSGGSTYYPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV), SEQ ID NO:  
 135 (GGVGSVDV), or SEQ ID NO: 124 (SGGD);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG), SEQ  
 30 ID NO: 137 (SGGRNNIGRGTFVD), and SEQ ID NO: 138 (SGSSSNVGYGDYVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS), SEQ ID NO: 140  
 (GAASRAS), SEQ ID NO: 141 (GATSRAS), or SEQ ID NO: 142 (GTDRRPP); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF), SEQ ID NO:  
 144 (ASYDRSESVV), SEQ ID NO: 145 (ASYDSSDGGV), or SEQ ID NO 146 (ATYDYSNDMII);  
 35 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule  
 comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1.

40

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);

5 VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF);

or for each CDR sequence, an amino acid sequence with

10 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "412E10"

15 herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);

20 VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF).

25

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

30 VHFR1 comprises the sequence set forth in SEQ ID NO: 459 (QVQLQESGPSLVKPSQTLSTCTVSGFSVI);

VHFR2 comprises the sequence set forth in SEQ ID NO: 460 (WVRQAPGKVPEWLG);

VHFR3 comprises the sequence set forth in SEQ ID NO: 461 (RLSITRDTSKSQVSLSLSSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 462 (WGRGLLVTVSS);

35 VLFR1 comprises the sequence set forth in SEQ ID NO: 463 (QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 464 (WYQQVPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 465 (GVPDRFSGSRSGDTATLTITSLQAEDEADYYC);

40 VLFR4 comprises the sequence set forth in SEQ ID NO: 466 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

- (i) at least 50% identity thereto, and/or
- (ii) one, two, three, four or five amino acid substitutions relative thereto.

- 5 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 459(QVQLQESGPSLVKPSQTLSTCTVSGFSVI);

- 10 VHFR2 comprises the sequence set forth in SEQ ID NO: 460 (WVRQAPGKVPEWLG);

VHFR3 comprises the sequence set forth in SEQ ID NO: 461 (RLSITRDTSKSQVSLSLSSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 462 (WGRGLLVTVSS);

- 15 VLFR1 comprises the sequence set forth in SEQ ID NO: 463 (QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 464 (WYQQVPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 465 (GVPDRFSGSRSGDTATLTITSLQAEDEADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 466 (FGSGTRLTVLG);

- 20 or for each FR sequence, an amino acid sequence with

- (i) at least 50% identity thereto, and/or
- (ii) one, two, three, four or five amino acid substitutions relative thereto,

- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. A specific binding molecule comprising FRs having 100% identity to those given above is referred to as "412E10" herein.
- 25

The specific binding molecule may comprise:

- (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- 30

VHFR1 comprises the sequence set forth in SEQ ID NO: 459 (QVQLQESGPSLVKPSQTLSTCTVSGFSVI);

VHFR2 comprises the sequence set forth in SEQ ID NO: 460 (WVRQAPGKVPEWLG);

- 35 VHFR3 comprises the sequence set forth in SEQ ID NO: 461 (RLSITRDTSKSQVSLSLSSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 462 (WGRGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 463 (QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 464 (WYQQVPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 465  
(GVPDRFSGSRSGDTATLTITSLQAEDEADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 466 (FGSGTRTLTVLG);

or for each FR sequence, an amino acid sequence with

- 5 (i) at least 50% identity thereto, and/or  
(ii) one, two, three, four or five amino acid substitutions relative thereto; and  
(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);

10 VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF);

15 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding  
20 molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "412E10" herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
25 wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 459  
(QVQLQESGSPSLVKPSQTLSTCTVSGFSVI);

VHFR2 comprises the sequence set forth in SEQ ID NO: 460 (WVRQAPGKVPEWLG);

30 VHFR3 comprises the sequence set forth in SEQ ID NO: 461  
(RLSITRDTSKSQVSLSLSSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 462 (WGRGLLTVTSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 463  
(QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 464 (WYQQVPGSAPKLLIY);

35 VLFR3 comprises the sequence set forth in SEQ ID NO: 465  
(GVPDRFSGSRSGDTATLTITSLQAEDEADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 466 (FGSGTRTLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

40 (ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYNPALKS);  
 5 VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF);  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 10 an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "412E10" herein.

The specific binding molecule may comprise:

- 15 (a) A VH domain comprising the sequence set forth in SEQ ID NO: 467  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSVISDSVAWVRQAPGKVPEWLGASGSSGNKY  
 YNPALKSRLSITRDTSKSQVSLSLSSVTTEDTAVYYCARGIAGVDVWGRGLLVTVSS);  
 and/or  
 (b) a VL domain comprising the sequence set forth in SEQ ID NO: 468  
 20 (QAVLTQPSSVSGSLGQRVSTCSGSSSNVGYGNYVGWYQQVPGSAPKLLIYGTAIRASG  
 VPDRFSGSRSGDTATLTITSLQAEDEADYYCASYQSNYAFFGSGTRLTVLG);  
 or a humanized variant thereof.

The specific binding molecule may comprise:

- 25 (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 469  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSVISDSVAWVRQAPGKVPEWLGASGSSGNKY  
 YNPALKSRLSITRDTSKSQVSLSLSSVTTEDTAVYYCARGIAGVDVWGRGLLVTVSSAKT  
 TAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYT  
 LSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFI  
 30 FPPKIKDVLMISSLPIVTCVVVDVSEDDPDVQISWVNNVEVHTAQTQTHREDYNSTLRVW  
 SALPIQHQQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEEEMTKKQV  
 TLTCMVTDMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNS  
 YSCSVVHEGLHNHHTTKSFSRTPGK); and/or  
 (b) a light chain comprising the sequence set forth in SEQ ID NO: 470  
 35 (QAVLTQPSSVSGSLGQRVSTCSGSSSNVGYGNYVGWYQQVPGSAPKLLIYGTAIRASG  
 VPDRFSGSRSGDTATLTITSLQAEDEADYYCASYQSNYAFFGSGTRLTVLGGQPKSSPSV  
 TLFPPSSEETNKATLVCTITDFYPGVVTVDWKVDGTPVTQGMETTQPSKQSNNKYMAS  
 SYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);  
 or a humanized variant thereof.

40

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);
- 5 VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 140 (GAASRAS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 145 (ASYDSSDGGV);

10 or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding  
15 molecule comprising CDRs having 100% identity to those given above is referred to as "412B9" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 140 (GAASRAS); and
- 25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 145 (ASYDSSDGGV).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 129 (NYGVG);
- 30 VHCDR2 comprises the sequence set forth in SEQ ID NO: 133 (NIYSGGSTYYNPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 135 (GGVGSVDV);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 137 (SGGRNNIGRGTFVD);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 142 (GTDRRPP); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 146 (ATYDYSNDMII);

35 or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding

molecule comprising CDRs having 100% identity to those given above is referred to as "412E6" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 129 (NYGVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 133 (NIYSGGSTYYNPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 135 (GGVGSVDV);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 137 (SGGRNNIGRGTFVD);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 142 (GTDRRPP); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 146 (ATYDYSNDMII).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 130 (SYALG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 132 (NIWRGGRIEYNPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 124 (SGGD);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 144 (ASYDRSESVV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "412G11" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 130 (SYALG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 132 (NIWRGGRIEYNPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 124 (SGGD);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 144 (ASYDRSESVV).



The specific binding molecule may comprise the CDR sequences of a clone set out in Table 5 below. The epitope may be within residues 412 to 441 of SEQ ID NO: 1.

Table 5

| Clone name | VH                     |                                    |                           | VL                               |                                       |                                            | Epitope |
|------------|------------------------|------------------------------------|---------------------------|----------------------------------|---------------------------------------|--------------------------------------------|---------|
|            | CDR1                   | CDR2                               | CDR3                      | CDR1                             | CDR2                                  | CDR3                                       |         |
| 412E10     | SDSVA (SEQ ID NO: 128) | ASGSSGNKYYPAL KS (SEQ ID NO: 131)  | GIIAGVDV (SEQ ID NO: 134) | SGSSSNVGYGNYVG (SEQ ID NO: 39)   | GTAIRAS (SEQ ID NO: 139)              | ASYQSNYAF (SEQ ID NO: 143)                 | 412-441 |
| 412B9      | SDSVA (SEQ ID NO: 128) | ASGSSGNKYYPAL KS (SEQ ID NO: 131)  | GIIAGVDV (SEQ ID NO: 134) | SGSSSNVGYGDIYVG (SEQ ID NO: 138) | GAASRAS (SEQ ID NO: 140)              | ASYDSSDGGV (SEQ ID NO: 145)                | 412-441 |
| 412E6      | NYGVG (SEQ ID NO: 129) | NIYSGGSIYYNPALK S (SEQ ID NO: 133) | GGVGSVDV (SEQ ID NO: 135) | SGGRNNIGRGTFVD (SEQ ID NO: 137)  | GTD <del>RR</del> PP (SEQ ID NO: 142) | ATYDYSND <del>MI</del> II (SEQ ID NO: 146) | 412-441 |
| 412G11     | SYALG (SEQ ID NO: 130) | NWRRGGRIEYNPALK S (SEQ ID NO: 132) | SGGD (SEQ ID NO: 124)     | SGSSSNVGYGNYVG (SEQ ID NO: 39)   | GATSRAS (SEQ ID NO: 141)              | ASYDRSES <del>V</del> V (SEQ ID NO: 144)   | 412-441 |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 5;  
 VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 5;  
 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 5;  
 VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 5;  
 VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 5; and  
 VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 5;  
 or for each CDR sequence, an amino acid sequence with  
 10 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM. The  $K_D$  may be less than around 20 nM, less than around 15 nM, or less than around 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 120. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1 nM to around 10 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be  
 20 around 3.16 nM or 9.0 nM, optionally wherein the specific binding molecule comprises the CDRs of 412E10.

- The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 147 wherein  
 25 the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 147. The CDRs may be 100%  
 30 identical to the CDRs of SEQ ID NO: 147. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 147 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 147. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 147.

- 35 SEQ ID NO: 147 (412E10 amino acid sequence)  
 QVQLQESGPSLVKPSQTLSTCTVSGFVSIDSVAVWRQAPGKVPWLGASGSSGNKYYPALK  
 SRLSITRDTSKSQVSLSLSSVTTEDTAVYYCARGIAGVDVWGRGLLVTSSEGKSSGASGESKVD  
 DQAVLTQPSSVSGSLGQRVSITCSGSSSNVGYGNYVGWYQQVPGSAPKLLIYGTAIRASGVPDRF  
 SGRSGDTATLTITSLQAEDEADYYCASYQSNYAFFGSGTRLTVLG

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The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 417 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 417. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 417. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 417 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 417. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 417.

SEQ ID NO: 417 (412B9 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSVISDSVAWVRQAPGKVPEWLGASGSSGNKYYPALK  
SRLSITRDTSKSQVLSLSSVTEDTAVYYCARGIAGVDWGRGLLVSVSSEGKSSGASGESKVD  
DQAVLTQPSSVSGALGQRVSITCSGSSNVGYGDYVGWYQQVPGSAPKLLIYGAAASRASGVPDR  
FSGSRSGNTATLTISLQAEDEADYCYASYDSSDGGVFGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 418 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 418. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 418. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 418 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 418. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 418.

SEQ ID NO: 418 (412E6 amino acid sequence)

QVQLQESGPSLVKPSETLSLTCTVSGFSLTNYGVGWVRQAPGKALEWLGNIYSGGSTYYNPALKS  
RLSITRDTSKSQVLSLNSVTLEDTAVYYCGRGGVGSVDWGPGLLVTVSSEGKSSGASGESKVD  
DQAVLTQPPSVSGSPGQRVSITCSGGRNNIGRGTTFVDWYQQLPGSGLKTVIYGTDRRPPGVPDR  
FSGSKTGNAATLTITSLQAEDEADYWCATYDYSNDMILGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 434 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1. The CDRs of the specific binding

molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 434. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 434. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 434 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 434. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 434.

SEQ ID NO: 434 (412G11 amino acid sequence)

QVRLQESGPSLVKPSQTLSTCTVSGFSLTSYALGWVRQAPGRAPEWIGNIWRGGRIEYNPALKS  
RLSITRDTSKSQVSLSLSSVTEDTAVYYCSRSGDWGPGLLTVSSEGKSSGASGESKVDDQAV  
LTQPSSVSGSLGQRVSITCSGSSSNVGYGNYVGWYQQVPGSAPKLLIYGATSRASGVPDRFSGS  
RSENTATLTISLQAEDEADYYCASYDRSESVVFGSGTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ). Preferably, the epitope of the specific binding molecule within an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1, may be within an amino acid sequence comprising residues 1 to 15 of SEQ ID NO: 1.

The epitope may be within an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "3aG3" herein.

The epitope may be within an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1, preferably within an amino acid sequence comprising residues 1 to 15 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "3bG4" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ).

The epitope may consist of the amino acid sequence of SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ).

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 5 VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (S N G V G);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 150 (D I S/A S S/V/G G K A/K/V Y A/S/G N/H P A L K S);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 151 (C R D G G V S/T Y G Y D I/S D Y);
- 10 VLCDR1 comprises the sequence set forth in SEQ ID NO: 152 (S G S S/T S/G N I/V G G/S/Y G N/D Y/D L/V S/G);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 153 (G A/V T S/N/E R/L A S);  
 and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 154 (A/G S F/Y D T/S/D S/N S G
- 15 G I/V);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto.
- 20 Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.
- 25 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 155 (DISSSGKAYANPALKS),  
 SEQ ID NO: 156 (DISSGKVGYPALPS), SEQ ID NO: 157 (DISSVGKKYANPALKS), or SEQ ID
- 30 NO: 158 (DIASSGKAYSNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 159 (CRDGGVSYGYDIDY), SEQ ID NO: 160 (CRDGGVSYGYDSY), or SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 163 (SGSSSNIGGGNYLS), SEQ ID NO: 138 (SGSSSNVGYGDYVG), SEQ ID NO: 165 (SGSSGNVGYGDYVS), or SEQ ID NO: 166
- 35 (SGSTSNVSGNDVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS), SEQ ID NO: 168 (GVTERAS), SEQ ID NO: 169 (GATNLAS), or SEQ ID NO: 170 (GATNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 171 (ASFDTSSGGI), SEQ ID NO: 172 (ASYDDSSGGI), SEQ ID NO: 173 (ASYDSSSGGV), or SEQ ID NO: 174 (GSYDSNSGGI);
- 40 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1.

5

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 155 (DISSSGKAYANPALKS);

10 VHCDR3 comprises the sequence set forth in SEQ ID NO: 159 (CRDGGVSYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 163 (SGSSSNIGGGNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 171 (ASFDTSSGGI);

or for each CDR sequence, an amino acid sequence with

15 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "3aG3" herein.

20

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 155 (DISSSGKAYANPALKS);

25 VHCDR3 comprises the sequence set forth in SEQ ID NO: 159 (CRDGGVSYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 163 (SGSSSNIGGGNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 171 (ASFDTSSGGI).

30 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 156 (DISSGGKVYGHHPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 160 (CRDGGVSYGYDSDY);

35 VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 168 (GVTERAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 172 (ASYDDSSGGI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

40 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as “3aD3” herein.

- 5 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 156 (DISSGGKVYGH PALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 160 (CRDGGVSYGYDS DY);
  - 10 VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 168 (GVTERAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 172 (ASYDDSSGGI).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, 15 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);
  - 20 VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,

- 25 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as “3aH6” herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, 30 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);
  - 35 VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows: 40
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 166 (SGSTSNVGSGNDVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and  
 5 VLCDR3 comprises the sequence set forth in SEQ ID NO: 174 (GSYDSNSGGI);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino  
 10 acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule  
 comprising CDRs having 100% identity to those given above is referred to as "3bG4" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 15 VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 166 (SGSTSNVGSGNDVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and  
 20 VLCDR3 comprises the sequence set forth in SEQ ID NO: 174 (GSYDSNSGGI).

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3,  
 VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
 sequence as follows:  
 25 VHFR1 comprises the sequence set forth in SEQ ID NO: 471  
 (QVQLQESGPSLVKPSQTLSTCTISGFSLI);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 472 (WVRQAPGKVPEWVG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 473  
 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCVR);  
 30 VHFR4 comprises the sequence set forth in SEQ ID NO: 474 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 475  
 (QAVLTQPSSVSKSLGQSVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 476 (WFQQVPGSAPKLLFY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 477  
 35 (GVPDRFSGSRSGNTATLTITSLQAEDADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 478 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto.

40



The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 471  
 5 (QVQLQESGPSLVKPSQTLSTCTISGFSLI);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 472 (WVRQAPGKVPEWVG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 473  
 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCVR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 474 (WGPGLLVTVSS);  
 10 VLFR1 comprises the sequence set forth in SEQ ID NO: 475  
 (QAVLTQPSSVSKSLGQSVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 476 (WFQQVPGSAPKLLFY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 477  
 (GVPDRFSGSRSGNTATLTITSLQAEDEADYYC);  
 15 VLFR4 comprises the sequence set forth in SEQ ID NO: 478 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 20 an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. A specific binding molecule  
 comprising FRs having 100% identity to those given above is referred to as "3bG4" herein.

The specific binding molecule may comprise:

- (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
 25 wherein each of said FRs comprises an amino acid sequence as follows:  
 VHFR1 comprises the sequence set forth in SEQ ID NO: 471  
 (QVQLQESGPSLVKPSQTLSTCTISGFSLI);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 472 (WVRQAPGKVPEWVG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 473  
 30 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCVR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 474 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO:  
 475(QAVLTQPSSVSKSLGQSVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 476 (WFQQVPGSAPKLLFY);  
 35 VLFR3 comprises the sequence set forth in SEQ ID NO: 477  
 (GVPDRFSGSRSGNTATLTITSLQAEDEADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 478 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 40 (ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);

5 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 166 (SGSTSNVGSGNDVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 174 (GSYDSNSGGI);

or for each CDR sequence, an amino acid sequence with

10 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "3bG4" herein.

15

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

20 VHFR1 comprises the sequence set forth in SEQ ID NO: 471 (QVQLQESGPSLVKPSQTLSTCTISGFSLI);

VHFR2 comprises the sequence set forth in SEQ ID NO: 472 (WVRQAPGKVPPEWVG);

VHFR3 comprises the sequence set forth in SEQ ID NO: 473 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCVR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 474 (WGPGLLVTVSS);

25 VLFR1 comprises the sequence set forth in SEQ ID NO: 475 (QAVLTQPSSSVSKSLGQSVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 476 (WFQQVPGSAPKLLFY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 477 (GVPDRFSGSRSGNTATLTITSLQAEDEADYYC);

30 VLFR4 comprises the sequence set forth in SEQ ID NO: 478 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said

35 CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 166 (SGSTSNVGSGNDVS);

40 VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 174 (GSYDSNSGGI);

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "3bG4" herein.

5

The specific binding molecule may comprise:

(a) A VH domain comprising the sequence set forth in SEQ ID NO: 479 (QVQLQESGPSLVKPSQTLSTCTISGFSLSINGVGWRQAPGKVPEWVGDIASSGKAYS NPALKSRLSITRDTSKSQVLSLRSVTTEDTAVYYCVRCRDGGVITYGYDIDYWGPGLLVT VSS); and/or

10

(b) a VL domain comprising the sequence set forth in SEQ ID NO: 480 (QAVLTQPSSVSKSLGQSVSITCSGSTSNVGSGNDVSWFQQVPGSAPKLLFYGATNRAS GVPDRFSGSRSGNTATLTITSLQAEDEADYYCGSYDSNSGGIFGSGTRLTVLG);

or a humanized variant thereof.

15

The specific binding molecule may comprise:

(a) A heavy chain comprising the sequence set forth in SEQ ID NO: 481 (QVQLQESGPSLVKPSQTLSTCTISGFSLSINGVGWRQAPGKVPEWVGDIASSGKAYS NPALKSRLSITRDTSKSQVLSLRSVTTEDTAVYYCVRCRDGGVITYGYDIDYWGPGLLVT VSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKIEPRGPTIKPCPPCKCPAPNLL GGPSVFIFPPKIKDVLMISSLPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDY NSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEE EMTKKQVTLTCMVTDMPEDIYVEWTNNGKTELNYKNTEPVLSDGSYFMYSKLRVEKK NWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or

20

(b) a light chain comprising the sequence set forth in SEQ ID NO: 482 (QAVLTQPSSVSKSLGQSVSITCSGSTSNVGSGNDVSWFQQVPGSAPKLLFYGATNRAS GVPDRFSGSRSGNTATLTITSLQAEDEADYYCGSYDSNSGGIFGSGTRLTVLGGQPKSSP SVTLFPPSSEETNKATLVCTITDFYPGVVTVDWKVDGTPVTQGMETTQPSKQSNNKYM ASSYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);

25

30

or a humanized variant thereof.

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 6 below. The epitope may be within residues 1 to 49 of SEQ ID NO: 1.

Table 6

| Clone name | VH                     |                                                      |                                          | VL                                                                           |                                   |                                               | Epitope |
|------------|------------------------|------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------|---------|
|            | CDR1                   | CDR2                                                 | CDR3                                     | CDR1                                                                         | CDR2                              | CDR3                                          |         |
| 3aD3       | SNGVG (SEQ ID NO: 149) | DISSGGK <b>V</b> YGHP ALKS (SEQ ID NO: 156)          | CRDGGVSYGYD <b>S</b> DY (SEQ ID NO: 160) | SGSSSNVGYG <b>D</b> YV <b>G</b> (SEQ ID NO: 138)                             | GV <b>T</b> ERAS (SEQ ID NO: 168) | ASYD <b>D</b> SSGGI (SEQ ID NO: 172)          | 1-49    |
| 3aH6       | SNGVG (SEQ ID NO: 149) | DISS <b>V</b> GK <b>K</b> YANP ALKS (SEQ ID NO: 157) | CRDGGV <b>T</b> YGYDIDY (SEQ ID NO: 161) | SGSS <b>G</b> NVGYG <b>D</b> YV S (SEQ ID NO: 165)                           | GATN <b>L</b> AS (SEQ ID NO: 169) | ASYDSSSG <b>V</b> (SEQ ID NO: 173)            | 1-49    |
| 3aG3       | SNGVG (SEQ ID NO: 149) | DISSSGKAYANP ALKS (SEQ ID NO: 155)                   | CRDGGVSYGYDIDY (SEQ ID NO: 159)          | SGSSSN <b>I</b> G <b>G</b> GN <b>L</b> S (SEQ ID NO: 163)                    | GAT <b>S</b> RAS (SEQ ID NO: 141) | AS <b>F</b> D <b>I</b> SSGGI (SEQ ID NO: 171) | 1-49    |
| 3bG4       | SNGVG (SEQ ID NO: 149) | D <b>I</b> ASSGKAY <b>S</b> NP ALKS (SEQ ID NO: 158) | CRDGGV <b>T</b> YGYDIDY (SEQ ID NO: 161) | SG <b>S</b> T <b>S</b> NV <b>G</b> SG <b>N</b> D <b>V</b> S (SEQ ID NO: 166) | GAT <b>N</b> RAS (SEQ ID NO: 170) | <b>G</b> SYDSNSGGI (SEQ ID NO: 174)           | 1-49    |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 6;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 6;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 6;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 6;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 6; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 6;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM. The  $K_D$  may be less than around 20 nM, less than around 15 nM, or less than around 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 148. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1 nM to around 20 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1
- 20 nM to around 10 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 19.1 nM, optionally wherein the specific binding molecule comprises the CDRs of 3aD3. The  $K_D$  for binding to SEQ ID NO: 1 may be around 3.6 nM, optionally wherein the specific binding molecule comprises the CDRs of 3aH6. The  $K_D$  for binding to SEQ ID NO: 1 may be around 6.1 nM, optionally wherein the specific binding molecule comprises the CDRs of 3aG3. The  $K_D$  for binding to SEQ ID NO: 1 may be around 8.9 nM,
- 25 optionally wherein the specific binding molecule comprises the CDRs of 3bG4.

- The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 422 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid
- 30 sequence comprising residues 1 to 49 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 422. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 422. The specific binding molecule may comprise an amino acid sequence
- 35 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 422 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 422. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 422.

SEQ ID NO: 422 (3aD3 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNGVGWVRRAPGKVPEWVGDISSGGKVYGHFALK  
SRLSITRDTSKSQVSLSVSSVTSEDVAVYYCVRCRDGGVSYGYDSDYWGPGLLTVSSSEGKSSG  
ASGESKVDDQAVVTQPSSVSKSLGQSVSITCSGSSSNVGYGDYVWGFQVPGSAPKLLIYGVTE  
5 RASGVPDRFSGSRSGNTATLTISSIAEADYCYASYDDSSGGIFGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 423 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid  
10 sequence comprising residues 1 to 49 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 423. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 423. The specific binding molecule may comprise an amino acid sequence  
15 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 423 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 423. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 423.

SEQ ID NO: 423 (3aH6 amino acid sequence)

20 QVQLQESGPSLVKPSQTLSTCTVSGFSLSSNGVGWVRQAPGKVPEWLGDIVSGKKYANPALK  
SRLSFTRDTSKSQVSLSLSSVTEDTAVYYCVKCRDGGVTYGYDIDYWGPGLLVTSSEGKSSGA  
SGESKVDDQAVVTQPSSVSGSLGQSVSITCSGSSGNVGYGDYVSWFQQFHGSAPKLLIYGATNL  
ASGVPARFSGSRSGNTATLTISSLHADEADYCYASYDSSSGGVFGSGTRLTVLG

25 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 424 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 424. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 424. The specific binding molecule may comprise an amino acid sequence  
30 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 424 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 424. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 424.  
35

SEQ ID NO: 424 (3aG3 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSSNGVGWVRQAPGKVPEWVGDISSSGKAYANPALK  
SRLSITRDTAKTQVFLSLSSVTEDTAVYYCVRCRDGGVSYGYDIDYWGPGLLTVSSSEGKSSGA

SGESKVDDQAVLTQPPSVSGSPGQRV SITCSGSSSNIGGGNYLSWFQQVPGSAPKLLIYGATSRA  
SGVPDRFSGSRSGNTATLTISLQAEDADYYCASFDTS SGGIFGAGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 425 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 425. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 425. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 425 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 425. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 425.

15

SEQ ID NO: 425 (3bG4 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTISGFSLISNGVGVWRQAPGKVPEWVGDIASSGKAYSNPALKS  
RLSITRDTSKSQVSLRLSVTTEDTAVYYCVRCDGGVTYGYDIDYWGPGLLVTVSSEGKSSGAS  
GESKVDDQAVLTQPSSVSKSLGQSVSITCSGSTSNVGSNDVSWFQQVPGSAPKLLFYGATNRA  
SGVPDRFSGSRSGNTATLTITSLQAEDADYYCGSYDSNSGGIFGSGTRLTVLG

20

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of

| SEQ                                                                | ID | NO: | 175 |
|--------------------------------------------------------------------|----|-----|-----|
| (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDT). |    |     |     |

25

The epitope may be within an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "3bF4" herein.

30

The epitope may comprise the amino acid sequence of SEQ ID NO: 175 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDT).

The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 175 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDT).

35

The epitope may consist of the amino acid sequence of SEQ ID NO: 175 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDT).

The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 175 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDT).

40

- The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each
- 5 of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (S N G V G);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 176 (D I/K S S V/A G K K/T Y A/G N P A L K S);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 177 (C R D G G V T Y G Y D I/V
- 10 D Y);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 178 (S G S S S N V G L/Y R/G N/D Y/V V T/S);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 179 (G A/T T S/T R A S); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 180 (A S A/F D T/S N/D D/S G G
- 15 V/I);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto.
- 20 Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.
- 25 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS), or SEQ ID NO: 182 (DKSSAGKTYGNPALKS);
- 30 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY), or SEQ ID NO: 184 (CRDGGVTYGYDVDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 185 (SGSSSNVGLRNYVT), or SEQ ID NO: 186 (SGSSSNVGYGDVVS);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS), or SEQ ID NO:
- 35 188 (GTTTRAS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 189 (ASADTNDGGV), or SEQ ID NO: 190 (ASFDSDSGGI);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
- 40 (ii) one, two, or three amino acid substitutions relative thereto,



wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, 5 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 185 (SGSSSNVGLRNYVT);  
 10 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 189 (ASADTNDGGV);  
 or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,
- 15 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "3bF4" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, 20 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 186 (SGSSSNVGYGDVVS);  
 25 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 189 (ASADTNDGGV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- 30 VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 184 (CRDGGVTYGYDVVDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 186 (SGSSSNVGYGDVVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and  
 35 VLCDR3 comprises the sequence set forth in SEQ ID NO: 190 (ASFDSDSGGI);  
 or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as “3aB7” herein.

- 5 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 184 (CRDGGVTYGYDVDY);
  - 10 VLCDR1 comprises the sequence set forth in SEQ ID NO: 186 (SGSSSNVGYGDVVS);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 190 (ASFDSDSGGI).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 7 below. The epitope may be within residues 49 to 111 of SEQ ID NO: 1.

Table 7

| Clone name | VH                        |                                      |                                                  | VL                                 |                             |                                             | Epitope |
|------------|---------------------------|--------------------------------------|--------------------------------------------------|------------------------------------|-----------------------------|---------------------------------------------|---------|
|            | <u>CDR1</u>               | <u>CDR2</u>                          | <u>CDR3</u>                                      | <u>CDR1</u>                        | <u>CDR2</u>                 | <u>CDR3</u>                                 |         |
| 3aB7       | SNGVG<br>(SEQ ID NO: 149) | DKSSAGKTYGNPALKS<br>(SEQ ID NO: 182) | CRDGGVTYGYD <sup>1</sup> VDY<br>(SEQ ID NO: 184) | SGSSSNVGYGDVVS<br>(SEQ ID NO: 186) | GTTTRAS<br>(SEQ ID NO: 188) | ASFDS <sup>2</sup> SGGI<br>(SEQ ID NO: 190) | 49-111  |
| 3bF4       | SNGVG<br>(SEQ ID NO: 149) | DISSVGKKYANPALKS<br>(SEQ ID NO: 157) | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)               | SGSSSNVGLRNYVT<br>(SEQ ID NO: 185) | GATSRAS<br>(SEQ ID NO: 141) | ASADTNDGGV<br>(SEQ ID NO: 189)              | 49-111  |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 7;
- 5 VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 7;
- VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 7;
- VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 7;
- VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 7; and
- VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 7;

10 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1.

15

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1 with a  $K_D$  of less than around 250 nM. The  $K_D$  may be less than around 200 nM, less than around 150 nM, or less than around 100 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 175. The  $K_D$  for binding to  
 20 SEQ ID NO: 1 may be around 1 nM to around 20 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 50 nM to around 150 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 69 nM, optionally wherein the specific binding molecule comprises the CDRs of 3aB7. The  $K_D$  for binding to SEQ ID NO: 1 may be around 140 nM, optionally wherein the specific binding molecule comprises the CDRs of 3bF4.

25

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 420 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. The CDRs of the specific binding molecule  
 30 may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 420. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 420. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
 35 to SEQ ID NO: 420 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 420. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 420.

SEQ ID NO: 420 (3aB7 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNGVGWVRQAPGKVPPEWVGDKSSAGKTYGNPAL

40 KSRLSITRDTSKSQVSLSLSSVTTEDTAVYYCVRCRDGGVTYGYDVDYWGPGLLVTVSSEGKSSG

ASGESKVDDQAVLTQPSSVSKSLGQSVSITCSGSSSNVGYGDVVSWFQQFPGSAPKLLIFGTTTR  
 ASGVPDRFSGSRSGNAATLTINSLQAEDEADYYCASFDSDSGGIAGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 421 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 421. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 421. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 421 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 421. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 421.

15

SEQ ID NO: 421 (3bF4 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSSNGVGWVRQAPGKVPEWLGDISSVGKKYANPALK  
 SRLSFTTRDTSKSQVSLSLSSVTEDTAVYYCVKCRDGGVTYGYDIDYWGPGLLVTVSSEKSSGA  
 SGESKVDDQAVLTQPSSVSKSTGQTVSITCSGSSSNVGLRNYVTWFQQVPGSAPKLLIYGATSRA  
 SGIPDRFSGSRSGNTATLISSLQAEDEADYYCASADTNDGGVFGSGTRLTVLG

20

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 146 to 157 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 191 (GKTKIATPRGA).

25

The epitope may be within an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "3aD6" herein.

30 The epitope may comprise the amino acid sequence of SEQ ID NO: 191 (GKTKIATPRGA). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 191 (GKTKIATPRGA).

35 The epitope may consist of the amino acid sequence of SEQ ID NO: 191 (GKTKIATPRGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 191 (GKTKIATPRGA).

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1. Said specific binding molecule may 40 comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 192 (S N A V I/G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 193 (L I D V/I D G D A/T A Y D/N P A L K/E S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 194 (D/H Y G/D S/K W G Y V/A S/D D/S I D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 195 (S G S D/S -/S -/N -/V I/G G/Y G A/D D/Y V G);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 196 (D N/A D/T N/T R P/A S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 197 (G/A T/S Y S/Q G/N A/E N/R Y/S G I/V);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

15

Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

20

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI), or SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS), or SEQ ID NO: 201 (LIDIDGDTAYNPALES);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY), or SEQ ID NO: 203 (HYDKWGYADSIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 204 (SGSDIGGADVG), or SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 206 (DNDNRPS), or SEQ ID NO: 207 (DATTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 208 (GTYSGANYGI), or SEQ ID NO: 209 (ASYQNERSGV);

35

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1.

40

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);

5 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 204 (SGSDIGGADVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 206 (DNDNRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 208 (GTYSGANYGI);

or for each CDR sequence, an amino acid sequence with

10 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "3aD6" herein.

15

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);

20 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 204 (SGSDIGGADVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 206 (DNDNRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 208 (GTYSGANYGI).

25 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 201 (LIDIDGDTAYNPALES);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 203 (HYDKWGYADSIDY);

30 VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 207 (DATTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 209 (ASYQNERSGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

35 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "3aA6" herein.

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 8 below. The epitope may be within residues 147 to 157 of SEQ ID NO: 1.

5 **Table 8**

| Clone name | VH                        |                                                   |                                           | VL                                 |                             |                                | Epitope |
|------------|---------------------------|---------------------------------------------------|-------------------------------------------|------------------------------------|-----------------------------|--------------------------------|---------|
|            | <u>CDR1</u>               | <u>CDR2</u>                                       | <u>CDR3</u>                               | <u>CDR1</u>                        | <u>CDR2</u>                 | <u>CDR3</u>                    |         |
| 3aA6       | SNAVG<br>(SEQ ID NO: 17)  | LIDIDGDTAYNPAL <del>E</del> S<br>(SEQ ID NO: 201) | <u>H</u> YDKWGYADSIDY<br>(SEQ ID NO: 203) | SGSSSNVGYGDYVG<br>(SEQ ID NO: 138) | DATTRAS<br>(SEQ ID NO: 207) | ASYQNERSGV<br>(SEQ ID NO: 209) | 147-157 |
| 3aD6       | SNAVI<br>(SEQ ID NO: 198) | LIDVDGDAAYDPALKS<br>(SEQ ID NO: 200)              | DYGSWGYVSDIDY<br>(SEQ ID NO: 202)         | SGSD---IGGADV<br>(SEQ ID NO: 204)  | DNDNRPS<br>(SEQ ID NO: 206) | GTYSGANYGI<br>(SEQ ID NO: 208) | 147-157 |



The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 8;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 8;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 8;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 8;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 8; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 8;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1 with a  $K_D$  of less than around 50 nM. The  $K_D$  may be less than around 40 nM, less than around 30 nM, or less than around 20 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 191. The  $K_D$  for binding to SEQ ID NO: 1 may be around 10 nM to around 20 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be
- 20 around 16.5 nM, optionally wherein the specific binding molecule comprises the CDRs of 3aD6.

- The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 418 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid
- 25 sequence comprising residues 147 to 157 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 418. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 418. The specific binding molecule may comprise an amino
- 30 acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 418 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 418. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 418.

SEQ ID NO: 418 (3aA6 amino acid sequence)

- 35 QVRLQESGSSLVKPSQTLVCTVSGFPLTSNAVGVWRQAPGKAPEWLGLIDIDGDTAYNPALES  
 RLSITRDTSKSQVSLSLSSVAIEDTAVYYCARHYDKWGYADSIDYWGPGLLVTVSSEGKSSGASG  
 ESKVDDQALLTQPSSVFGSLGQQRVSITCSGSSSNVGYGDYVGWYQQVPGSAPKLLIYDATTRASG  
 VPDRFSGSRSGNTATLTISLQAEDADYYCASYQNERSGVFGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 419 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 419. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 419. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 419 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 419. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 419.

SEQ ID NO: 419 (3aD6 amino acid sequence)  
 QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNAVIWVRQAPGKAPEWVALIDVDGDAAYDPALKS  
 RLSITRDTSKQVSLSLRSVTEDTAVYYCARDYGSWGYVSDIDYWGPGLLVTVSSEKSSGASG  
 ESKVDDQAVLTQPSSVSGSLGQRVSITCSGSDIGGADVGFQVPGSGLRTLIDNDNRPSGVP  
 DRFSGSKSGNTATLTISLQPEADYFCGTYSYGANYGIFGSGTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 221 (RENAKAKTDHGAE).

The epitope may comprise the amino acid sequence of SEQ ID NO: 221 (RENAKAKTDHGAE). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 221 (RENAKAKTDHGAE). The epitope may be within an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "E2E8" herein. Critical residues of the epitope may be residue 391 (E) (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 222 (XXXXXXXXXXXXXE, wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO: 8, wherein any one or more residue other than residue number 391 (E) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 221, wherein any one or more residue other than residue number 391 (E) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 221, wherein any one or more residue other than residue number 391 (E) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and any one or more residue other than residue number 391 (E) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1).

40

The epitope may comprise the amino acid sequence of SEQ ID NO: 221 (RENAKAKTDHGAE). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 221 (RENAKAKTDHGAE).

- 5 The epitope may consist of the amino acid sequence of SEQ ID NO: 221 (RENAKAKTDHGAE). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 221 (RENAKAKTDHGAE).

- The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. Said specific binding molecule may  
10 comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 223 (D/S R/W G V A);

- VHCDR2 comprises the sequence set forth in SEQ ID NO: 224 (T M R S G G T/G I/T D/E  
15 Y/D N P A L K S);

VHCDR3 comprises the sequence set forth SEQ ID NO: 225 (G Y L S G D/I/V R/H Y A);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 226 (S G S R/S S D/N I/V G Y/D/A  
G N/D/R Y V S/G);

- VLCDR2 comprises the sequence set forth in SEQ ID NO: 227 (D/S/G T/A N/R/T T/N/S R A  
20 S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 228 (A N/S I D S/T S/G R/N S/N  
H/L L/I);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or  
25 (ii) one, two, or three amino acid substitutions relative thereto.

- Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%  
30 identity. Preferably said sequence identity is at least 90% or at least 95%.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA), SEQ ID NO: 230  
35 (DWGVA), or SEQ ID NO: 231 (SWGVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS), SEQ ID NO: 233 (TMRSGGGTEYNPALKS), or SEQ ID NO: 234 (TMRSGGTTDDNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA), SEQ ID NO: 236 (GYLSGIHYA), or SEQ ID NO: 237 (GYLSGVHYA);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNVVS), SEQ ID NO: 239 (SGSSSNVGAGNYVG), SEQ ID NO: 240 (SGSSSNVGDGDYVG), or SEQ ID NO: 241 (SGSSSNVGDGRYVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS), SEQ ID NO: 243 (DTTSRAS), SEQ ID NO: 170 (GATNRAS), or SEQ ID NO: 244 (SARNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRS HL), SEQ ID NO: 246 (ASIDSGNNLL), or SEQ ID NO: 247 (ASIDTSRSHI);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNVVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRS HL);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "E2E8" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNVVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRS HL).

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 483  
 5 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 484 (WVRQAPGKALEWVG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 485  
 (RLSITRDTSKSQVFLSLSSVTEDMAMYYCAR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 486 (WGRGLLVTVSS);  
 10 VLFR1 comprises the sequence set forth in SEQ ID NO: 487  
 (QAVLTQPSSVSKSLGQSVSIAC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 488 (WFQQIPGSAPKLLIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 489  
 (GVPDRFSGARSGNTATLTINSLQAEDEADYYC);  
 15 VLFR4 comprises the sequence set forth in SEQ ID NO: 490 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto.
- 20 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- VHFR1 comprises the sequence set forth in SEQ ID NO: 483  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 25 VHFR2 comprises the sequence set forth in SEQ ID NO: 484 (WVRQAPGKALEWVG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 485  
 (RLSITRDTSKSQVFLSLSSVTEDMAMYYCAR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 486 (WGRGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 487  
 30 (QAVLTQPSSVSKSLGQSVSIAC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 488 (WFQQIPGSAPKLLIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 489  
 (GVPDRFSGARSGNTATLTINSLQAEDEADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 490 (FGSGTRLTVLG);  
 35 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. A specific binding  
 40 molecule comprising FRs having 100% identity to those given above is referred to as "E2E8" herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

5 VHFR1 comprises the sequence set forth in SEQ ID NO: 483  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 484 (WVRQAPGKALEWVG);

VHFR3 comprises the sequence set forth in SEQ ID NO: 485  
(RLSITRDTSKSQVFLSLSSVTEDMAMYYCAR);

10 VHFR4 comprises the sequence set forth in SEQ ID NO: 486 (WGRGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 487  
(QAVLTQPSSVSKSLGQSVSIAC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 488 (WFQQIPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 489  
15 (GVPDRFSGARSGNTATLTINSLQAEDYDYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 490 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

20 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA);

25 VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNVYS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRSHL);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

30 (ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "E2E8" herein.

35

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 483  
40 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

- VHFR2 comprises the sequence set forth in SEQ ID NO: 484 (WVRQAPGKALEWVG);
- VHFR3 comprises the sequence set forth in SEQ ID NO: 485 (RLSITRDTSKSQVFLSLSSVTEDMAMYYCAR);
- VHFR4 comprises the sequence set forth in SEQ ID NO: 486 (WGRGLLTVSS);
- 5 VLFR1 comprises the sequence set forth in SEQ ID NO: 487 (QAVLTQPSSVSKSLGQSVSIAC);
- VLFR2 comprises the sequence set forth in SEQ ID NO: 488 (WFQQIPGSAPKLLIY);
- VLFR3 comprises the sequence set forth in SEQ ID NO: 489 (GVPDRFSGARSGNTATLTINSLQAEDEADYYC);
- 10 VLFR4 comprises the sequence set forth in SEQ ID NO: 490 (FGSGTRLTVLG);
- or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
- (ii) one, two, three, four or five amino acid substitutions relative thereto; and
- (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said
- 15 CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNYVS);
- 20 VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRSHL);
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as
- 25 "E2E8" herein.

The specific binding molecule may comprise:

- (a) A VH domain comprising the sequence set forth in SEQ ID NO: 491 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTDRGVAWVRQAPGKALEWVGTMRSRGGTID
- 30 YNPALKSRLSITRDTSKSQVFLSLSSVTEDMAMYYCARGYLSGDRYAWGRGLLTVSS);
- and/or
- (b) a VL domain comprising the sequence set forth in SEQ ID NO: 492 (QAVLTQPSSVSKSLGQSVSIACSGSRSDIGYGNYVSWFQQIPGSAPKLLIYDTNTRASGV
- PDRFSGARSGNTATLTINSLQAEDEADYYCANIDSSRSHLFGSGTRLTVLG);
- 35 or a humanized variant thereof.

The specific binding molecule may comprise:

- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 493 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTDRGVAWVRQAPGKALEWVGTMRSRGGTID
- 40 YNPALKSRLSITRDTSKSQVFLSLSSVTEDMAMYYCARGYLSGDRYAWGRGLLTVSSA

KTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDL  
 YTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPS  
 VFIFPPKIKDVLMSLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDYNSTLR  
 VVSALPIQHQQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEEEMTKK  
 5 QVTLTCTMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVER  
 NSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or  
 (b) a light chain comprising the sequence set forth in SEQ ID NO: 494  
 (QAVLTQPSSSVSKSLGQSVSIACSGSRSDIGYGNVSWFQQIPGSAPKLLIYDTNTRASGV  
 PDRFSGARSGNTATLTINSLQAEDEADYYCANIDSSRSHLFGSGTRLTVLGGQPKSSPSV  
 10 TLFPPSSEETNKATLVCTITDFYPGVVTVDWKVDGTPVTQGMETTQPSKQSNNKYMAS  
 SYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);  
 or a humanized variant thereof.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 15 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTTDDNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 241 (SGSSSNVGDGRYVS);  
 20 VLCDR2 comprises the sequence set forth in SEQ ID NO: 243 (DTTSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 246 (ASIDSGNNLL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 25 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "E1E8"  
 herein.

30 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTTDDNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
 35 VLCDR1 comprises the sequence set forth in SEQ ID NO: 241 (SGSSSNVGDGRYVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 243 (DTTSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 246 (ASIDSGNNLL).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 40 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:



- VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTTDDNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 239 (SGSSSNVGAGNYVG);  
 5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (GATNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "E2A6" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 15 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTTDDNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 239 (SGSSSNVGAGNYVG);  
 20 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (GATNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 25 VHCDR1 comprises the sequence set forth in SEQ ID NO: 231 (SWGVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 233 (TMRSGGGTEYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 236 (GYLSGIHYA);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 240 (SGSSSNVGDDYVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 244 (SARNRAS); and  
 30 VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino  
 35 acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "E2B7" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 40 VHCDR1 comprises the sequence set forth in SEQ ID NO: 231 (SWGVA);

- VHCDR2 comprises the sequence set forth in SEQ ID NO: 233 (TMRSGGGTEYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 236 (GYLSGIHYA);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 240 (SGSSSNVGDGDYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 244 (SARNRAS); and  
5 VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 9 below. The epitope may be within residues 379 to 391 of SEQ ID NO: 1.

Table 9

| Clone name | VH                        |                                   |                               | VL                                 |                             |                                | Epitope |
|------------|---------------------------|-----------------------------------|-------------------------------|------------------------------------|-----------------------------|--------------------------------|---------|
|            | <u>CDR1</u>               | <u>CDR2</u>                       | <u>CDR3</u>                   | <u>CDR1</u>                        | <u>CDR2</u>                 | <u>CDR3</u>                    |         |
| E1E8       | DWGVA<br>(SEQ ID NO: 230) | TMRSGGTTDDNPALKS (SEQ ID NO: 234) | GYLSGVHYA<br>(SEQ ID NO: 237) | SGSSNVGDGRVVS<br>(SEQ ID NO: 241)  | DTTSRAS<br>(SEQ ID NO: 243) | ASIDSGNNLL<br>(SEQ ID NO: 246) | 391'E'  |
| E2A6       | DWGVA<br>(SEQ ID NO: 230) | TMRSGGTTDDNPALKS (SEQ ID NO: 234) | GYLSGVHYA<br>(SEQ ID NO: 237) | SGSSNVGAGNYVG<br>(SEQ ID NO: 239)  | GATNRAS<br>(SEQ ID NO: 70)  | ASIDTSRSHI<br>(SEQ ID NO: 247) | 391'E'  |
| E2B7       | SWGVA<br>(SEQ ID NO: 231) | TMRSGGTEYNPALKS (SEQ ID NO: 233)  | GYLSGIHYA<br>(SEQ ID NO: 236) | SGSSNVGDGDYVG<br>(SEQ ID NO: 240)  | SARNRAS<br>(SEQ ID NO: 244) | ASIDTSRSHI<br>(SEQ ID NO: 247) | 391'E'  |
| E2E8       | DRGVA<br>(SEQ ID NO: 229) | TMRSGGTIDYNPALKS (SEQ ID NO: 232) | GYLSGDRYA<br>(SEQ ID NO: 235) | SGSRSDIGYGNVVS<br>(SEQ ID NO: 238) | DTNTRAS<br>(SEQ ID NO: 242) | ANIDSSRSHL<br>(SEQ ID NO: 245) | 391'E'  |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 9;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 9;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 9;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 9;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 9; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 9;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1.

- 15 The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM. The  $K_D$  may be less than around 20 nM, less than around 15 nM, or less than around 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 4. The specific binding molecule may have no detectable binding to SEQ ID NO: 1. The  $K_D$  for binding to SEQ ID NO: 4 may be around 300 pM to
- 20 around 10 nM. The  $K_D$  for binding to SEQ ID NO: 4 may be around 300 pM to around 500 pM. The  $K_D$  for binding to SEQ ID NO: 4 may be around 1 nM to around 10 nM. The  $K_D$  for binding to SEQ ID NO: 4 may be around 401 pM, optionally wherein the specific binding molecule comprises the CDRs of E1E8. The  $K_D$  for binding to SEQ ID NO: 4 may be around 6.3 nM, optionally wherein the specific binding molecule comprises the CDRs of E1E8.

- 25 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 248 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The CDRs of the specific binding
- 30 molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 248. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 248. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least
- 35 99% identity to SEQ ID NO: 248 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 248. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 248.

SEQ ID NO: 248 (E2E8 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTDRGVAVWRQAPGKALEWVGTMRSGGTIDYNPALK  
 40 SRLSITRDTSKSQVFLSLSSVTTEDMAMYYCARGYLSGDRYAWGRGLLVTSSEGGKSSGASGES

KVDDQAVLTQPSSVSKSLGQSVSIACSGSRSDIGYGNVSWFQQIPGSAPKLLIYDTNTRASGVDP  
RFSGARSGNTATLTINSLQAEDEADYYCANIDSSRSHLFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 250 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 250. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 250. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 250 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 250. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 250.

15

SEQ ID NO: 250 (E1E8 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTDWGVAVWRQAPGKALEWLGTMRSGGTTDDNPAL  
KSRLSITRDTSKSQVSLSLSSVTTEDMAMYYCARGYLSGVHYAWGRGLLVTVSSEKSSGASGE  
SKVDDQAVLTQPSSVSGSLGQSVSITCSGSSSNVGDGRYVSWFQQVPGSAPKLLIYDTSRASGV  
PDRFSGSRSGNTATLIITSLQAEDEADYYCASIDSGNNLLFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 252 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 252. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 252. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 252 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 252. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 252.

SEQ ID NO: 252 (E2A6 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTDWGVAVWRQAPGKALEWLGTMRSGGTTDDNPAL  
KSRLSITRDTSKSQVSLSLSSVTTEDMAMYYCARGYLSGVHYAWGRGLLVTVSSEKSSGASGE  
SKVDDRVRTQPSSVSKSLGQSVSITCSGSSSNVAGNYVGWFQQVPGSAPKLLIYGATNRASG  
VPARFSGSKSGVTATLTITSLQAEDEADYYCASIDTSRSHIFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 254 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 254. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 254. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 254 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 254. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 254.

SEQ ID NO: 254 (E2B7 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSWGVAVWRQAPGKALEWLGTMRSGGGTEYNPAL  
 15 KSRLSITRDTSKSQVSLSLSSVTEDMAMYYCARGYLSGIHYAWGRLLVSVSSEKSSGASGES  
 KVDDQAVLTQLSSVSGSLGQRVSITCSGSSSNVGDGDYVGWVFQQLPGSAPKLLIYSARNRASGV  
 PDRFSGSRSGNTATLTITSLQAEDEADYYCASIDTSRSHIFGSGTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 113 to 238 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 255 (SLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQGKGQANATRIP AKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTP PKSPSS).

25 The epitope may be within an amino acid sequence comprising residues 113 to 238 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB11" herein.

30 The epitope may comprise the amino acid sequence of SEQ ID NO: 255 (SLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQGKGQANATRIP AKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTP PKSPSS). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 255  
 35 (SLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQGKGQANATRIP AKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTP PKSPSS).

The epitope may consist of the amino acid sequence of SEQ ID NO: 255  
 40 (SLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQGKGQANATRIP

AKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTP  
 PKSPSS). The epitope may consist of an amino acid sequence having at least 70%, at least 75%,  
 at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 255  
 (SLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPQKQGANATRIP  
 5 AKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTP  
 PKSPSS).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

10 VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 256 (SGSNIGSNDVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 257 (DNNNRPS); and  
 15 VLCDR3 comprises the sequence set forth in SEQ ID NO: 258 (GGYAGSSSNFL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 20 an amino acid sequence comprising residues 113 to 238 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CB11"  
 herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 25 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 256 (SGSNIGSNDVG);  
 30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 257 (DNNNRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 258 (GGYAGSSSNFL).

The epitope of the specific binding molecule may be within an amino acid sequence comprising  
 residues 1 to 155 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence  
 35 of                                      SEQ                                      ID                                      NO:                                      293  
 (MAEPRQEFEVMEHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPR).

The epitope may be within an amino acid sequence comprising residues 1 to 155 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA2" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 293  
 5 (MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPR). The epitope may comprise an amino acid sequence  
 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
 to SEQ ID NO: 293  
 10 (MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPR).

The epitope may consist of the amino acid sequence of SEQ ID NO: 293  
 15 (MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPR). The epitope may consist of an amino acid sequence  
 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
 to SEQ ID NO: 293  
 20 (MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPR).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 25 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);  
 30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 35 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 1 to 155 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CA2" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 40 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:



VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);  
 5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV).

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 1 to 238 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence  
 10 of SEQ ID NO: 260  
 (MAEPRQEFVMEFHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSG  
 DRSGYSSPGSPGTPGSRSRTPSLPTPPTREP KKVAVVRTPPKSPSS).

15 The epitope may be within an amino acid sequence comprising residues 1 to 238 of SEQ ID NO: 1.  
 This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB6" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 260  
 20 (MAEPRQEFVMEFHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSG  
 DRSGYSSPGSPGTPGSRSRTPSLPTPPTREP KKVAVVRTPPKSPSS). The epitope may comprise  
 an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%  
 25 or at least 99% identity to SEQ ID NO: 260  
 (MAEPRQEFVMEFHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSG  
 DRSGYSSPGSPGTPGSRSRTPSLPTPPTREP KKVAVVRTPPKSPSS).

30 The epitope may consist of the amino acid sequence of SEQ ID NO: 260  
 (MAEPRQEFVMEFHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM  
 VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSG  
 35 DRSGYSSPGSPGTPGSRSRTPSLPTPPTREP KKVAVVRTPPKSPSS). The epitope may consist of  
 an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95%  
 or at least 99% identity to SEQ ID NO: 260  
 (MAEPRQEFVMEFHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM

VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG  
DRSGYSSPGSPGTPGSRSRTPSLPTPTREPKKVAVVRTPPKSPSS).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
5 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 261 (SGSSSNIGTGNYVG);  
10 VLCDR2 comprises the sequence set forth in SEQ ID NO: 262 (GAVTRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV);  
or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,
- 15 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 1 to 238 of SEQ ID NO: 1. The specific binding  
molecule comprising CDRs having 100% identity to those given above is referred to as "CB6" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
20 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 261 (SGSSSNIGTGNYVG);  
25 VLCDR2 comprises the sequence set forth in SEQ ID NO: 262 (GAVTRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV).

- The epitope of the specific binding molecule may be within an amino acid sequence comprising  
residues 1 to 319 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence  
30 of SEQ ID NO: 264  
(MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE  
TSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM  
VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG  
DRSGYSSPGSPGTPGSRSRTPSLPTPTREPKKVAVVRTPPKSPSSAKSRLQTAPVMPDLKNVK  
35 SKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL SKVT).

- The epitope may be within an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1.  
This epitope may be bound by the CDRs of the specific binding molecules referred to as "CA7",  
"CA8", and "CB10" herein.

40

The epitope within an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1 may preferably be within an amino acid sequence comprising residues 37 to 49 of SEQ ID NO: 1. This epitope may be bound by the CDRs of at least the specific binding molecule referred to as "CA7" herein.

5

The epitope may comprise the amino acid sequence of SEQ ID NO: 264 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG

10 DRSGYSSPGSPGTPGSRSRTPSLPTPTREP KKVAVVRTPPKSPSSAKSRLQTAPVMPDLKNVK SKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 264 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE

15 TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG DRSGYSSPGSPGTPGSRSRTPSLPTPTREP KKVAVVRTPPKSPSSAKSRLQTAPVMPDLKNVK SKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT).

20 The epitope may consist of the amino acid sequence of SEQ ID NO: 264 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG

25 SKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHV PGGGSVQIVYKPVDSLKVT). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 264 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGSEEPGSE TSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAGHVTQARM

30 VSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSG DRSGYSSPGSPGTPGSRSRTPSLPTPTREP KKVAVVRTPPKSPSSAKSRLQTAPVMPDLKNVK SKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 35 VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYVVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 265 (GSYYHGGGNGMVDFDY);
- 40 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

- VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV);  
 or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - 5 (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CA7" herein.
- 10 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 265
- 15 (GSYYHGGGNGMVDFDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV).
- 20 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- VHFR1 comprises the sequence set forth in SEQ ID NO: 495 (RVRLQGSGPSLVKPSQTLSTCTVSGFSFD);
  - 25 VHFR2 comprises the sequence set forth in SEQ ID NO: 496 (WVRQAPGKALEWLG);
  - VHFR3 comprises the sequence set forth in SEQ ID NO: 497 (RLSITRDTSKSQVSLSVSSVTIEDTALYYCVR);
  - VHFR4 comprises the sequence set forth in SEQ ID NO: 498 (WSPGLLVTVSS);
  - VLFR1 comprises the sequence set forth in SEQ ID NO: 499
- 30 (QVVVRTQPSSVSGSLGQRVSITC);
- VLFR2 comprises the sequence set forth in SEQ ID NO: 500 (WFQQVPGSAPKLLIY);
  - VLFR3 comprises the sequence set forth in SEQ ID NO: 501 (GVPDRFSGSRSGNTATLTIDSLQAEDADYYC);
  - VLFR4 comprises the sequence set forth in SEQ ID NO: 502 (FGSGTRLTVLG);
- 35 or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
  - (ii) one, two, three, four or five amino acid substitutions relative thereto.

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 495  
 5 (RVRLQGSGPSLVKPSQTLSTCTVSGFSFD);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 496 (WVRQAPGKALEWLG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 497  
 (RLSITRDTSKSQVSLSVSSVTIEDTALYYCVR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 498 (WSPGLLVTVSS);  
 10 VLFR1 comprises the sequence set forth in SEQ ID NO: 499  
 (QVVRTQPSSVSGSLGQRVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 500 (WFQQVPGSAPKLLIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 501  
 (GVPDRFSGSRSGNTATLTIDSLQAEDEADYYC);  
 15 VLFR4 comprises the sequence set forth in SEQ ID NO: 502 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 20 an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. A specific binding molecule  
 comprising FRs having 100% identity to those given above is referred to as "CA7" herein.

The specific binding molecule may comprise:

- (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
 25 wherein each of said FRs comprises an amino acid sequence as follows:  
 VHFR1 comprises the sequence set forth in SEQ ID NO: 495  
 (RVRLQGSGPSLVKPSQTLSTCTVSGFSFD);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 496 (WVRQAPGKALEWLG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 497  
 30 (RLSITRDTSKSQVSLSVSSVTIEDTALYYCVR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 498 (WSPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 499  
 (QVVRTQPSSVSGSLGQRVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 500 (WFQQVPGSAPKLLIY);  
 35 VLFR3 comprises the sequence set forth in SEQ ID NO: 501  
 (GVPDRFSGSRSGNTATLTIDSLQAEDEADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 502 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 40 (ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);

5 VHCDR3 comprises the sequence set forth in SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV).

10 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. The specific binding  
15 molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CA7" herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,

20 wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 495 (RVRLQGSGPSLVKPSQTLSTCTVSGFSD);

VHFR2 comprises the sequence set forth in SEQ ID NO: 496 (WVRQAPGKALEWLG);

25 VHFR3 comprises the sequence set forth in SEQ ID NO: 497 (RLSITRDTSKSQVSLSVSSVTIEDTALYYCVR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 498 (WSPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 499 (QVVRTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 500 (WFQQVPGSAPKLLIY);

30 VLFR3 comprises the sequence set forth in SEQ ID NO: 501 (GVPDRFSGSRSGNTATLTIDSLQAEDYDYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 502 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

35 (ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);

- VHCDR3 comprises the sequence set forth in SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and
- 5 VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV).
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CA7" herein.
- 10 The specific binding molecule may comprise:
- (a) A VH domain comprising the sequence set forth in SEQ ID NO: 503  
(RVRLQGSGPSLVKPSQTLSTCTVSGFSFDSYYVGWVRQAPGKALEWLGNIYSTGRAFY  
NPALKSRLSITRDTSKSQVSLSVSSVTIEDTALYYCVRGSYYHGGGNGMVDFFDYWSPGL  
LTVSS); and/or
- 15 (b) a VL domain comprising the sequence set forth in SEQ ID NO: 504  
(QVVRTQPSSVSGSLGQRVSITCSGSSSNVGYGNYVGWFQQVPGSAPKLLIYAATSRAS  
GVPDRFSGSRSGNTATLTIDSLQAEDEADYYCSSYQRGNTGVFGSGTRLTVLG);
- or a humanized variant thereof.
- 20 The specific binding molecule may comprise:
- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 505  
(RVRLQGSGPSLVKPSQTLSTCTVSGFSFDSYYVGWVRQAPGKALEWLGNIYSTGRAFY  
NPALKSRLSITRDTSKSQVSLSVSSVTIEDTALYYCVRGSYYHGGGNGMVDFFDYWSPGL  
LTVSSAKTTAPSVYPLAPVCGDGTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFP  
25 AVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAP  
NLLGGPSVFIFPPKIKDVLMSLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHRE  
DYNSTLRVVSALPIQHQDWMGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLP  
EEEMTKKQVTLTCMVTDMPEDIVYEWNTNNGKTELNYKNTEPVLDSDGSYFMYSKL  
RVE KKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or
- 30 (b) a light chain comprising the sequence set forth in SEQ ID NO: 506  
(QVVRTQPSSVSGSLGQRVSITCSGSSSNVGYGNYVGWFQQVPGSAPKLLIYAATSRAS  
GVPDRFSGSRSGNTATLTIDSLQAEDEADYYCSSYQRGNTGVFGSGTRLTVLGGQPKSS  
PSVTLFPPSSEELETNKATLVCTITDFYPGVTVDWKVDGTPVTQGMETTQPSKQSNNKY  
MASSYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);
- 35 or a humanized variant thereof.
- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 266 (SNAVV);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 267 (AIDKDGDTIYNPALKS);
- 40 VHCDR3 comprises the sequence set forth in SEQ ID NO: 268 (DPSGWGYPDVDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 269 (SGTYIGSSDVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 270 (GTSSRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 271 (ATYESSYHNSV);  
 or for each CDR sequence, an amino acid sequence with

- 5 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CA8" herein.

10

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 266 (SNAVV);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 267 (AIDKDGDTIYNPALKS);  
 15 VHCDR3 comprises the sequence set forth in SEQ ID NO: 268 (DPSGWGYPDVDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 269 (SGTYIGSSDVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 270 (GTSSRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 271 (ATYESSYHNSV).

- 20 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 272 (SNTVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 273 (EINSGGSTYYPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 274 (GARSTYAAAY);  
 25 VLCDR1 comprises the sequence set forth in SEQ ID NO: 275 (SGSSSDVGYSTWVY);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 276 (HISNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 277 (AAYDSSNNVWI);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or  
 30 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 1 to 319 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CB10"  
 herein.

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The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 272 (SNTVA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 273 (EINSGGSTYYPALKS);  
 40 VHCDR3 comprises the sequence set forth in SEQ ID NO: 274 (GARSTYAAAY);



VLCDR1 comprises the sequence set forth in SEQ ID NO: 275 (SGSSSDVGYSTWVY);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 276 (HISNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 277 (AAYDSSNNVWI).

- 5 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 278 (DHAGTYGLGDRKD).

The epitope may be within an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1.

- 10 This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB7" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 278 (DHAGTYGLGDRKD). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 278 (DHAGTYGLGDRKD).

15

The epitope may consist of the amino acid sequence of SEQ ID NO: 278 (DHAGTYGLGDRKD). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 278 (DHAGTYGLGDRKD).

- 20 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLAYDY);

- 25 VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMYA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

- 30 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB7" herein.

- 35 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLAYDY);

- 40 VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMYA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV).

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3,  
 5 VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
 sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 507  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 508 (WVRQAPGKALEWVS);  
 10 VHFR3 comprises the sequence set forth in SEQ ID NO: 509  
 (RLSITADTSKQVSLSLSSVTTEDTAVYYCAR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 510 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 511  
 (QAVLTQPSSVSRSLGQSVSMTC);  
 15 VLFR2 comprises the sequence set forth in SEQ ID NO: 512 (WFQQVPGSAPKLLIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 513  
 (GVPDRFSGSRSGNTATLTISLQAEDADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 514 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 20 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto.

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3,  
 VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
 25 sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 507  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 508 (WVRQAPGKALEWVS);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 509  
 30 (RLSITADTSKQVSLSLSSVTTEDTAVYYCAR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 510 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 511  
 (QAVLTQPSSVSRSLGQSVSMTC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 512 (WFQQVPGSAPKLLIY);  
 35 VLFR3 comprises the sequence set forth in SEQ ID NO: 513  
 (GVPDRFSGSRSGNTATLTISLQAEDADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 514 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 40 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1. A specific binding molecule comprising FRs having 100% identity to those given above is referred to as "CB7" herein.

5 The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 507  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

10 VHFR2 comprises the sequence set forth in SEQ ID NO: 508 (WVRQAPGKALEWVS);

VHFR3 comprises the sequence set forth in SEQ ID NO: 509  
(RLSITADTSKSQVSLSLSSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 510 (WGPGLLVTVSS);

15 VLFR1 comprises the sequence set forth in SEQ ID NO: 511  
(QAVLTQPSSVSRSLGQSVSMTC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 512 (WFQQVPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 513  
(GVPDRFSGSRSGNTATLTISLQAEDYDY);

VLFR4 comprises the sequence set forth in SEQ ID NO: 514 (FGSGTRLTVLG);

20 or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

25 VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLYAYDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

30 VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto

35 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CB7" herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 507 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

5 VHFR2 comprises the sequence set forth in SEQ ID NO: 508 (WVRQAPGKALEWVS);

VHFR3 comprises the sequence set forth in SEQ ID NO: 509 (RLSITADTSKQVSLSLSSVTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 510 (WGPGLLVTVSS);

10 VLFR1 comprises the sequence set forth in SEQ ID NO: 511 (QAVLTQPSSVSRSLGQSVSMTC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 512 (WFQQVPGSAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 513 (GVPDRFSGSRSGNTATLTISLQAEDEADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 514 (FGSGTRLTVLG);

15 or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLAYDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMYA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV);

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CB7" herein.

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The specific binding molecule may comprise:

(a) A VH domain comprising the sequence set forth in SEQ ID NO: 515 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTNYRVGWVRQAPGKALEWVSNIRSGGTTWYNPALKSRLSITADTSKQVSLSLSSVTEDTAVYYCARDSSGDLAYDYWGPGLLVTVS

35 S); and/or

(b) a VL domain comprising the sequence set forth in SEQ ID NO: 516 (QAVLTQPSSVSRSLGQSVSMTCGSSSNVGYGNMYMAWFQQVPGSAPKLLIYGATSRASGVPDRFSGSRSGNTATLTISLQAEDEADYYCASYDSTSGGVFGSGTRLTVLG);

or a humanized variant thereof.

40

The specific binding molecule may comprise:

- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 517  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLTNYRVGWWRQAPGKALEWVSNIRSGGTTW  
YNPALKSRLSITADTSKSQVLSLSSVTTEDTAVYYCARDSSGDLYAYDYWGPGLLVTVS  
5 SAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQS  
DLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKCPPCKCPAPNLLGG  
PSVFIFPPKIKDVLMISSLPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDYNST  
LRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSRAPQVYVLPPEEEMT  
KKQVTLTCMVTDMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWV  
10 ERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or  
(b) a light chain comprising the sequence set forth in SEQ ID NO: 518  
(QAVLTQPSSVSRSLGQSVSMTCSSSSNVGYGNMAWFQQVPGSAPKLLIYGATSRAS  
GVPDRFSGSRSGNTATLTISLQAEDEADYYCASYDSTSGGVFGSGTRLTVLGGQPKSS  
PSVTLFPPSSEELETNKATLVCTITDFYPGVTVDWKVDGTPVTQGMETTQPSKQSNNKY  
15 MASSYLTLTARAWERHSSYSCQVTHEGHTVEKSLRADCS);

or a humanized variant thereof.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
20 sequence of SEQ ID NO: 283 (ADGKTKIATPRGA).

The epitope may be within an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CC7" herein.  
25

The epitope may comprise the amino acid sequence of SEQ ID NO: 283 (ADGKTKIATPRGA). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 283 (ADGKTKIATPRGA).

30 The epitope may consist of the amino acid sequence of SEQ ID NO: 283 (ADGKTKIATPRGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 283 (ADGKTKIATPRGA).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
35

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAAYDPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);  
40 VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL);  
or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

- 5           wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CC7" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
10   VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYPDALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);

15   VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL).

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
20   sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 519  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 520 (WVRQAPGKAPEWVA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 521  
25   (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 522 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 523  
(RVVVRTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 524 (WFQQVPGSGLKTVIY);

30   VLFR3 comprises the sequence set forth in SEQ ID NO: 525  
(GVPDRFSGSKSGDTATLTISLQAEDADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 526 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

35           (ii) one, two, three, four or five amino acid substitutions relative thereto.

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 519 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);
- VHFR2 comprises the sequence set forth in SEQ ID NO: 520 (WVRQAPGKAPEWVA);
- VHFR3 comprises the sequence set forth in SEQ ID NO: 521 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCAR);
- VHFR4 comprises the sequence set forth in SEQ ID NO: 522 (WGPGLLVTVSS);
- VLFR1 comprises the sequence set forth in SEQ ID NO: 523 (RVVVRTQPSSVSGSLGQRVSITC);
- VLFR2 comprises the sequence set forth in SEQ ID NO: 524 (WFQQVPGSGLKTVIY);
- VLFR3 comprises the sequence set forth in SEQ ID NO: 525 (GVPDRFSGSKSGDTATLTISLQAEDADYYC);
- VLFR4 comprises the sequence set forth in SEQ ID NO: 526 (FGSGTRLTVLG);
- or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
  - (ii) one, two, three, four or five amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. A specific binding molecule comprising FRs having 100% identity to those given above is referred to as "CC7" herein.
- The specific binding molecule may comprise:
- (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
 

VHFR1 comprises the sequence set forth in SEQ ID NO: 519 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 520 (WVRQAPGKAPEWVA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 521 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 522 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 523 (RVVVRTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 524 (WFQQVPGSGLKTVIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 525 (GVPDRFSGSKSGDTATLTISLQAEDADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 526 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

    - (i) at least 50% identity thereto, and/or
    - (ii) one, two, three, four or five amino acid substitutions relative thereto; and
  - (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
 

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

- VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYPDALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and  
 5 VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 10 an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. The specific binding  
 molecule comprising FRs and CDRs having 100% identity to those given above is referred to as  
 "CC7" herein.

The specific binding molecule may comprise:

- 15 (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
 wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 519  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 520 (WVRQAPGKAPEWVA);

- 20 VHFR3 comprises the sequence set forth in SEQ ID NO: 521  
 (RLSITRDTSKSQVSLSLRSVTTEDTAVYYCAR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 522 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 523  
 (RVVVRTQPSSVSGSLGQRVSITC);

- 25 VLFR2 comprises the sequence set forth in SEQ ID NO: 524 (WFQQVPGSGLKTVIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 525  
 (GVPDRFSGSKSGDTATLTISLQAEDADYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 526 (FGSGTRLTVLG);

- or for each FR sequence, an amino acid sequence with

- 30 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
 CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

- 35 VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYPDALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL);



wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CC7" herein.

5

The specific binding molecule may comprise:

(a) A VH domain comprising the sequence set forth in SEQ ID NO: 527 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNAVIWVRQAPGKAPEWVALIDVDGDAAY DPALKSRLSITRDTSKSQVSLSLRSVTTEDTAVYYCARDYGSWGYVSDIDYWGPGLLTV

10

SS); and/or

(b) a VL domain comprising the sequence set forth in SEQ ID NO: 528 (RVVVRTQPSSVSGSLGQRVISITCSGSYITGSSVGWFQQVPGSGLKTVIYDNNDRPSGVPD RFSGSKSGDTATLTISLQAEDADYYCASYDTSNIGLFGSGTRLTVLG);

or a humanized variant thereof.

15

The specific binding molecule may comprise:

(a) A heavy chain comprising the sequence set forth in SEQ ID NO: 529 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNAVIWVRQAPGKAPEWVALIDVDGDAAY DPALKSRLSITRDTSKSQVSLSLRSVTTEDTAVYYCARDYGSWGYVSDIDYWGPGLLTV

20

SSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQ SDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKCPPCKCPAPNLLG GPSVFIFPPKIKDVLMSLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDYN STLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPEEE MTCKQVTLTCMVTDMPEDIYVEWTNNGKTELNYKNTEPVLDSGYSFMYSKLRVEKKN

25

WVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or

(b) a light chain comprising the sequence set forth in SEQ ID NO: 530 (RVVVRTQPSSVSGSLGQRVISITCSGSYITGSSVGWFQQVPGSGLKTVIYDNNDRPSGVPD RFSGSKSGDTATLTISLQAEDADYYCASYDTSNIGLFGSGTRLTVLGGQPKSSPSVTLF PPSSEELETNKATLVCTITDFYPGVVTDWKVDGTPVTQGMETTQPSKQSNNKYMASSY

30

LTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);

or a humanized variant thereof.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 155 to 227 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid

35

sequence of SEQ ID NO: 294 (RGAAPPQGKQGANATRIPAKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP PTREPKKVA).

The epitope may be within an amino acid sequence comprising residues 155 to 227 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecules referred to as "CB12" and "CC3" herein.

- 5 The epitope may comprise the amino acid sequence of SEQ ID NO: 294 (RGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP PTREPKKVA). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 294 (RGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP  
10 PTREPKKVA).

- The epitope may consist of the amino acid sequence of SEQ ID NO: 294 (RGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP PTREPKKVA). The epitope may consist of an amino acid sequence having at least 70%, at least  
15 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 294 (RGAAPPGQKGQANATRIPAKTPPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP PTREPKKVA).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
20 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 286 (CRDGGVSYGYDVDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 287 (SGSSSNVGGDYVG);

- 25 VLCDR2 comprises the sequence set forth in SEQ ID NO: 288 (DTTSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 289 (ASVDKTTGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

- 30 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 155 to 227 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB12" herein.

- 35 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 286 (CRDGGVSYGYDVDY);

- 40 VLCDR1 comprises the sequence set forth in SEQ ID NO: 287 (SGSSSNVGGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 288 (DTTSRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 289 (ASVDKTTGGV).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 5 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 286 (CRDGGVSYGYDVDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 290 (SGSSSNVGYGTYVS);  
 10 VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 291 (ASYDTGSGGV);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 15 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 155 to 227 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CC3" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 20 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 286 (CRDGGVSYGYDVDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 290 (SGSSSNVGYGTYVS);  
 25 VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 291 (ASYDTGSGGV).

- The epitope of the specific binding molecule may be within an amino acid sequence comprising  
 residues 155 to 238 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
 30 sequence of SEQ ID NO: 295  
 (RGAAPPQKQGQANATRIPAKTPPAPKTPSSGEPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP  
 PTREPKKVAVVRTPPKSPSS).

- The epitope may be within an amino acid sequence comprising residues 155 to 238 of SEQ ID NO:  
 35 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA1"  
 herein.

- The epitope may comprise the amino acid sequence of SEQ ID NO: 295  
 (RGAAPPQKQGQANATRIPAKTPPAPKTPSSGEPKSGDRSGYSSPGSPGTPGSRSRTPSLPTP  
 40 PTREPKKVAVVRTPPKSPSS). The epitope may comprise an amino acid sequence having at least

70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 295

(RGAAPPQGKGQANATRIAPAKTPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSS).

5

The epitope may consist of the amino acid sequence of SEQ ID NO: 295 (RGAAPPQGKGQANATRIAPAKTPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSS). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO:

10 295

(RGAAPPQGKGQANATRIAPAKTPAPKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSS).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

15

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 296 (DIRADGATNYNAALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 297 (PGNYYYGAGRDVARLAD);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 298 (SGSSSNIGGGNAVG);

20

VLCDR2 comprises the sequence set forth in SEQ ID NO: 288 (DTTSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 299 (AAMDSSSLIGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

25

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 155 to 238 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CA1" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 186 to 263 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid

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sequence of SEQ ID NO: 300 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPLKNVKSIGST).

The epitope may be within an amino acid sequence comprising residues 186 to 263 of SEQ ID NO:

35

1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA3" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 300 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQT

40

APVPMPLKNVKSIGST). The epitope may comprise an amino acid sequence having at least

70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 300 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPLDKNVKSKIGST).

- 5 The epitope may consist of the amino acid sequence of SEQ ID NO: 300 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPLDKNVKSKIGST). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 300 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQT  
10 APVPMPLDKNVKSKIGST).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
15 VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 184 (CRDGGVTYGYDVDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 301 (SGSSGNIGYDDYVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 302 (GATRRSS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 303 (ASYDSSGGGV);  
20 or for each CDR sequence, an amino acid sequence with  
(i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 186 to 263 of SEQ ID NO: 1. The specific binding  
25 molecule comprising CDRs having 100% identity to those given above is referred to as "CA3" herein.

- The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 186 to 350 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 304  
30 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPLDKNVKSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDFKDRV).

- The epitope may be within an amino acid sequence comprising residues 186 to 350 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CD2" herein.  
35

- The epitope may comprise the amino acid sequence of SEQ ID NO: 304 (GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPLDKNVKSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL  
40

SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRV). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 304

(GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVP  
5 MPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL  
SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRV).

The epitope may consist of the amino acid sequence of SEQ ID NO: 304  
(GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVP  
10 MPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL  
SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRV). The epitope may consist of an amino acid  
sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99%  
identity to SEQ ID NO: 304

(GEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVP  
15 MPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL  
SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRV).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 305 (SGSNIGDADVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 306 (YNENRPS); and  
25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 307 (GSYAGDTYNHGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino  
30 acid sequence comprising residues 186 to 350 of SEQ ID NO: 1. The specific binding molecule  
comprising CDRs having 100% identity to those given above is referred to as "CD2" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising  
residues 239 to 348 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
35 sequence of SEQ ID NO: 308  
(AKSRLQTAPVPMPLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGG  
GSVQIVYKPVDL SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDV).

The epitope may be within an amino acid sequence comprising residues 239 to 348 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB9" herein.

5 The epitope may comprise the amino acid sequence of 308 (AKSRLQTAPVPMPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGG GSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKFD). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to 308  
10 (AKSRLQTAPVPMPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGG GSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKFD).

The epitope may consist of the amino acid sequence of 308 (AKSRLQTAPVPMPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGG GSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKFD). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to 308  
15 (AKSRLQTAPVPMPDLKNVSKIGSTENLKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGG GSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKFD).

20 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 48 (GIDSDGEEGYNPALNS);  
25 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 67 (SGRFIGISSVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);

or for each CDR sequence, an amino acid sequence with  
30 (i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 239 to 348 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB9" herein.

35 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 266 to 359 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 309 (LKHQPGGGKVQIINKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHH  
40 KPGGGQVEVKSEKLDKFDKRVQSKIGSLDN).

The epitope may be within an amino acid sequence comprising residues 266 to 359 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CG11" herein.

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The epitope may comprise the amino acid sequence of SEQ ID NO: 309 (LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHH KPGGGQVEVKSEKLDKDRVQSKIGSLDN). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to

|    |    |     |    |     |     |
|----|----|-----|----|-----|-----|
| 10 | to | SEQ | ID | NO: | 309 |
|----|----|-----|----|-----|-----|

(LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHH KPGGGQVEVKSEKLDKDRVQSKIGSLDN).

The epitope may consist of the amino acid sequence of SEQ ID NO: 309 (LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHH KPGGGQVEVKSEKLDKDRVQSKIGSLDN). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to

|    |    |     |    |     |     |
|----|----|-----|----|-----|-----|
| 15 | to | SEQ | ID | NO: | 309 |
|----|----|-----|----|-----|-----|

(LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHH KPGGGQVEVKSEKLDKDRVQSKIGSLDN).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);

25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNYVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);

30 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 266 to 359 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CG11" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 277 to 319 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 315 (IINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSK).

40



The epitope may be within an amino acid sequence comprising residues 277 to 319 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA10" herein.

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The epitope may comprise the amino acid sequence of SEQ ID NO: 315 (IINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 315 (IINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT).

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The epitope may consist of the amino acid sequence of SEQ ID NO: 315 (IINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 315 (IINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDSLKVT).

15

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

20

VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 316 (SGSSSNVGYGNYVT);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 317 (DATTRVS); and

25

VLCDR3 comprises the sequence set forth in SEQ ID NO: 318 (AAHDSSSGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising

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an amino acid sequence comprising residues 277 to 319 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CA10" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 5 (IKHVPGGGSVQIVYKPVDSLKVTSCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGA).

35

The epitope may be within an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CC12" herein.

5 The epitope may comprise the amino acid sequence of SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to  
 10 SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA).

The epitope may consist of the amino acid sequence of SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH  
 15 VPGGGNKKIETHKLTFRNAKAKTDHGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to  
 SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA).

20

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 48 (GIDSDGEEGYNPALNS);  
 25 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 67 (SGRFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);

or for each CDR sequence, an amino acid sequence with

30 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CC12" herein.

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The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 319 (TSKCGSLGNIHHK).

The epitope may be within an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CE2" or "E1B8" herein. Critical residues of the epitope may be residues 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 320 (XXXXGSLGNIXXX, wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO: 319, wherein any one or more residue other than residue number 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 319, wherein any one or more residue other than residue number 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 319, wherein any one or more residue other than residue number 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and any one or more residue other than residue number 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1).

The epitope may comprise the amino acid sequence of SEQ ID NO: 319 (TSKCGSLGNIHHK). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 319 (TSKCGSLGNIHHK).

The epitope may consist of the amino acid sequence of SEQ ID NO: 319 (TSKCGSLGNIHHK). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 319 (TSKCGSLGNIHHK).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNVVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CE2" or "E1B8" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);  
 5 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNVYS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV).

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The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 531  
 15 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 532 (WVRQAPGKALEWIG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 533  
 (RLSITRDTSKNQVSLSLSSATTEDTAVYYCGR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 534 (WGPGLLVTVSS);  
 20 VLFR1 comprises the sequence set forth in SEQ ID NO: 535  
 (QAVLTQPSSVSKSLGQSVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 536 (WFQQVPGSAPKILIIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 537  
 (GVPDRFSGSRSGNTATLTITSLQAEDYDYC);  
 25 VLFR4 comprises the sequence set forth in SEQ ID NO: 538 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto.

- 30 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

- VHFR1 comprises the sequence set forth in SEQ ID NO: 531  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 35 VHFR2 comprises the sequence set forth in SEQ ID NO: 532 (WVRQAPGKALEWIG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 533  
 (RLSITRDTSKNQVSLSLSSATTEDTAVYYCGR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 534 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 535  
 40 (QAVLTQPSSVSKSLGQSVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 536 (WFQQVPGSAPKILIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: n537  
 (GVPDRFSGSRSGNTATLTITSLQAEDEADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 538 (FGSGTRLTVLG);  
 5 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. A specific binding  
 10 molecule comprising FRs having 100% identity to those given above is referred to as "CE2" herein.

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
 wherein each of said FRs comprises an amino acid sequence as follows:  
 15 VHFR1 comprises the sequence set forth in SEQ ID NO: 531  
 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 532 (WVRQAPGKALEWIG);  
 VHFR3 comprises the sequence set forth in SEQ ID NO: 533  
 (RLSITRDTSKNQVSLSLSSATTEDTAVYYCGR);  
 20 VHFR4 comprises the sequence set forth in SEQ ID NO: 534 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 535  
 (QAVLTQPSSSVKSLGQSVSITC);  
 VLFR2 comprises the sequence set forth in SEQ ID NO: 536 (WFQQVPGSAPKILIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 537  
 25 (GVPDRFSGSRSGNTATLTITSLQAEDEADYYC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 538 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with  
 (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto; and  
 30 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
 CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);  
 35 VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNYVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 40 (ii) one, two, or three amino acid substitutions relative thereto

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CE2" herein.

5

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 531  
10 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 532 (WVRQAPGKALEWIG);

VHFR3 comprises the sequence set forth in SEQ ID NO: 533  
(RLSITRDTSKNQVLSLSSATTEDTAVYYCGR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 534 (WGPGLLVTVSS);

15 VLFR1 comprises the sequence set forth in SEQ ID NO: 535  
(QAVLTQPSSVSKSLGQSVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 536 (WFQQVPGSAPKILIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 537  
(GVPDRFSGSRSGNTATLTITSLQAEDADYYC);

20 VLFR4 comprises the sequence set forth in SEQ ID NO: 538 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto; and

(b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
25 CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNYVS);

30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as

35 "CE2" herein.

The specific binding molecule may comprise:

(a) A VH domain comprising the sequence set forth in SEQ ID NO: 539  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLTNYPVGWVRQAPGKALEWIGNIENDGSANY

ASALKSRLSITRDTSKNQVSLSLSSATTEDTAVYYCGREFGGSDGYTYFVDIDYWGPGLL  
VTVSS); and/or

- (b) a VL domain comprising the sequence set forth in SEQ ID NO: 540  
(QAVLTQPSSVSKSLGQSVSITCSGSSSNVGYGNYVSWFQQVPGSAPKILYIGATSRAS  
5 GVPDRFSGSRSGNTATLTITSLQAEDEADYYCASYDGSSSGVFGSGTRLTVLG);  
or a humanized variant thereof.

The specific binding molecule may comprise:

- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 541  
10 (QVQLQESGPSLVKPSQTLSTCTVSGFSLTNYPVGWVRQAPGKALEWIGNIENDGSANY  
ASALKSRLSITRDTSKNQVSLSLSSATTEDTAVYYCGREFGGSDGYTYFVDIDYWGPGLL  
VTVSSAKTTAPSVYPLAPVCGDGTGSSVTGLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPA  
VLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKIEPRGPTIKPCPPCKCPAPN  
LLGGPSVFIFPPKIKDVLMIPLSPITCVVVDVSEDDPDVQISWVNNVEVHTAQTQTHRED  
15 YNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPE  
EEMTKKQVTLTCMVTDMPEDIYVEWTNNGKTELNYKNTEPVLDSGSYFMYSKLRVEK  
KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or  
(b) a light chain comprising the sequence set forth in SEQ ID NO: 542  
(QAVLTQPSSVSKSLGQSVSITCSGSSSNVGYGNYVSWFQQVPGSAPKILYIGATSRASG  
20 VPDRFSGSRSGNTATLTITSLQAEDEADYYCASYDGSSSGVFGSGTRLTVLGGQPKSSP  
SVTLFPPSSEETNKATLVCTITDFYPGVVTVDWKVDGTPVTQGMETTQPSKQSNNKYM  
ASSYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);  
or a humanized variant thereof.

- 25 The epitope of the specific binding molecule may be within an amino acid sequence comprising  
residues 331 to 360 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
sequence of SEQ ID NO: 321 (KPGGGQVEVKSEKLDKDRVQSKIGSLDNI).

- The epitope may be within an amino acid sequence comprising residues 331 to 360 of SEQ ID NO:  
30 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CE3"  
herein.

- The epitope may comprise the amino acid sequence of SEQ ID NO: 321  
(KPGGGQVEVKSEKLDKDRVQSKIGSLDNI). The epitope may comprise an amino acid sequence  
35 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
to SEQ ID NO: 321 (KPGGGQVEVKSEKLDKDRVQSKIGSLDNI).

The epitope may consist of the amino acid sequence of SEQ ID NO: 321  
(KPGGGQVEVKSEKLDKDRVQSKIGSLDNI). The epitope may consist of an amino acid sequence

having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 321 (KPGGGQVEVKSEKLDKDRVQSKIGSLDNI).

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGIDYLGITIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI);
- or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CE3" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGIDYLGITIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);
  - VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI).

- The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- VHFR1 comprises the sequence set forth in SEQ ID NO: 543 (QVRLQESGPSLVKPSQTLSTCTVSGFSLI);
  - VHFR2 comprises the sequence set forth in SEQ ID NO: 544 (WVRQAPGKVPESLA);
  - VHFR3 comprises the sequence set forth in SEQ ID NO: n545 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);
  - VHFR4 comprises the sequence set forth in SEQ ID NO: 546 (WGPGLLVTVSS);
  - VLFR1 comprises the sequence set forth in SEQ ID NO: 547 (QAVLTQPSSVSGSLGQRVSITC);
  - VLFR2 comprises the sequence set forth in SEQ ID NO: 548 (WFQQLPGSGLRTIY);



VLFR3 comprises the sequence set forth in SEQ ID NO: 549  
(GIPDRFSGSKSGVTATLTIDSLQAEDEADYFC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 550 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

- 5 (i) at least 50% identity thereto, and/or  
(ii) one, two, three, four or five amino acid substitutions relative thereto.

The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid  
10 sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 543  
(QVRLQESGPSLVKPSQTLSTCTVSGFSLI);

VHFR2 comprises the sequence set forth in SEQ ID NO: 544 (WVRQAPGKVPESLA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 545  
15 (RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 546 (WGPGLLVTVSS);

VLFR1 comprises the sequence set forth in SEQ ID NO: 547  
(QAVLTQPSSVSGSLGQRVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 548 (WFQQLPGSGLRTIY);

20 VLFR3 comprises the sequence set forth in SEQ ID NO: 549  
(GIPDRFSGSKSGVTATLTIDSLQAEDEADYFC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 550 (FGSGTRLTVLG);

or for each FR sequence, an amino acid sequence with

- 25 (i) at least 50% identity thereto, and/or  
(ii) one, two, three, four or five amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1. A specific binding molecule comprising FRs having 100% identity to those given above is referred to as "CE3" herein.

30 The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 543  
(QVRLQESGPSLVKPSQTLSTCTVSGFSLI);

35 VHFR2 comprises the sequence set forth in SEQ ID NO: 544 (WVRQAPGKVPESLA);

VHFR3 comprises the sequence set forth in SEQ ID NO: 545  
(RLDITRDTSKNQISLSLSSVTDDAAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 546 (WGPGLLVTVSS);

40 VLFR1 comprises the sequence set forth in SEQ ID NO: 547  
(QAVLTQPSSVSGSLGQRVSITC);

- VLFR2 comprises the sequence set forth in SEQ ID NO: 548 (WFQQLPGSGLRTIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 549  
 (GIPDRFSGSKSGVTATLTIDSLQAEDEADYFC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 550 (FGSGTRLTVLG);
- 5 or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
  - (ii) one, two, three, four or five amino acid substitutions relative thereto; and
- (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- 10 VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGYDYLGTIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and
- 15 VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI);  
 or for each CDR sequence, an amino acid sequence with
- (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising
- 20 an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CE3" herein.
- The specific binding molecule may comprise:
- 25 (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:
- VHFR1 comprises the sequence set forth in SEQ ID NO: 543  
 (QVRLQESGPSLVKPSQTLSTCTVSGFSLI);  
 VHFR2 comprises the sequence set forth in SEQ ID NO: 544 (WVRQAPGKVPESLA);
- 30 VHFR3 comprises the sequence set forth in SEQ ID NO: 545  
 (RLDITRDTSKNQISLSLSSVTDDAAVYCTR);  
 VHFR4 comprises the sequence set forth in SEQ ID NO: 546 (WGPGLLVTVSS);  
 VLFR1 comprises the sequence set forth in SEQ ID NO: 547  
 (QAVLTQPSSVSGSLGQRVSITC);
- 35 VLFR2 comprises the sequence set forth in SEQ ID NO: 548 (WFQQLPGSGLRTIY);  
 VLFR3 comprises the sequence set forth in SEQ ID NO: 549  
 (GIPDRFSGSKSGVTATLTIDSLQAEDEADYFC);  
 VLFR4 comprises the sequence set forth in SEQ ID NO: 550 (FGSGTRLTVLG);  
 or for each FR sequence, an amino acid sequence with
- 40 (i) at least 50% identity thereto, and/or

- (ii) one, two, three, four or five amino acid substitutions relative thereto; and
- (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAV G);
- 5 VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGYDYLGTIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI);
- 10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CE3" herein.
- 15 The specific binding molecule may comprise:
- (a) A VH domain comprising the sequence set forth in SEQ ID NO: 551 (QVRLQESGPSLVKPSQTLSTCTVSGFSLISNAVGVWRQAPGKVPESLAGCSDGKCY NSALKSRDLITRDTSKNQISLSLSSVTDDAAVYYCTRGYYPVYGYDYLGTIDYWGPGLLV TVSS); and/or
- 20 (b) a VL domain comprising the sequence set forth in SEQ ID NO: 552 (QAVLTQPSSVSGSLGQRVSITCSGSSSNVGRNDVAWFQQLPGSGLRTIYGTTSRPSGIP DRFSGSKSGVTATLTIDSLQAEDEADYFCASGDSSAINDIFGSGTRLTVLG);
- or a humanized variant thereof.
- 25 The specific binding molecule may comprise:
- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 553 (QVRLQESGPSLVKPSQTLSTCTVSGFSLISNAVGVWRQAPGKVPESLAGCSDGKCY NSALKSRDLITRDTSKNQISLSLSSVTDDAAVYYCTRGYYPVYGYDYLGTIDYWGPGLLV TVSSAKTTAPSVYPLAPVCGD TTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAV
- 30 LQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNL LGGPSVFIFPPKIKDVLMSLSPIVTCVVDVSEDDPDVQISWFVNNVEVHTAQTQTHRED YNSTLRVVSALPIQHQDWMMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPE EEMTKKQVTLTCMVTD FMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEK KNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK); and/or
- 35 (b) a light chain comprising the sequence set forth in SEQ ID NO: 554 (QAVLTQPSSVSGSLGQRVSITCSGSSSNVGRNDVAWFQQLPGSGLRTIYGTTSRPSGIP DRFSGSKSGVTATLTIDSLQAEDEADYFCASGDSSAINDIFGSGTRLTVLGGQPKSSPSVT LFPPSSEELETNKATLVCTITDFYPGVTVVDWKVDGTPVTQGMETTQPSKQSNKMYMAS SYLTLTARAWERHSSYSCQVTHEGHTVEKSLSRADCS);
- 40 or a humanized variant thereof.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 348 to 390 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 322 (DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

5

The epitope may be within an amino acid sequence comprising residues 348 to 390 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA6" herein.

10 The epitope may comprise the amino acid sequence of SEQ ID NO: 322 (DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGA). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 322 (DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

15

The epitope may consist of the amino acid sequence of SEQ ID NO: 322 (DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 322

20 (DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);

25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 323 (DKSSGGKTYGNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 324 (SGSRNNIGYGNHVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 207 (DATTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 325 (ASFDRGSGGI);

30 or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 348 to 390 of SEQ ID NO: 1. The specific binding

35 molecule comprising CDRs having 100% identity to those given above is referred to as "CA6" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 348 to 441 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 326

(DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGAEIVYKSPVVSGDTSRHLNSNVSS  
TGSIDMVDSPQLATLADEVASLAKQGL).

The epitope may be within an amino acid sequence comprising residues 348 to 441 of SEQ ID NO:

- 5 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA11" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 326  
(DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGAEIVYKSPVVSGDTSRHLNSNVSS  
10 TGSIDMVDSPQLATLADEVASLAKQGL). The epitope may comprise an amino acid sequence  
having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
to SEQ ID NO: 326  
(DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGAEIVYKSPVVSGDTSRHLNSNVSS  
TGSIDMVDSPQLATLADEVASLAKQGL).

15

The epitope may consist of the amino acid sequence of SEQ ID NO: 326  
(DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGAEIVYKSPVVSGDTSRHLNSNVSS  
TGSIDMVDSPQLATLADEVASLAKQGL). The epitope may consist of an amino acid sequence  
having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity  
20 to SEQ ID NO: 326  
(DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAAKAKTDHGAEIVYKSPVVSGDTSRHLNSNVSS  
TGSIDMVDSPQLATLADEVASLAKQGL).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
25 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 272 (SNTVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 273 (EINSGGSTYYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 274 (GARSTYAAAY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 327 (SGSGSNIGAGNWVS);

30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 328 (GATSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 329 (AAYDSGSSIV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

- 35 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino  
acid sequence comprising residues 348 to 441 of SEQ ID NO: 1. The specific binding molecule  
comprising CDRs having 100% identity to those given above is referred to as "CA11" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 330 (GSLDNITHVPGGG).

- 5 The epitope may be within an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CA4" herein. Critical residues of the epitope may be residues 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 331 (XXXDXITHXPXXX, wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO: 330, wherein any one or more residue other than residue number 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) (numbering according to SEQ ID NO: 1) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 330, wherein any one or more residue other than residue number 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) (numbering according to SEQ ID NO: 1) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 330, wherein any one or more residue other than residue number 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) (numbering according to SEQ ID NO: 1) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and any one or more residue other than residue number 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) (numbering according to SEQ ID NO: 1) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1).

The epitope may comprise the amino acid sequence of SEQ ID NO: 330 (GSLDNITHVPGGG). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 330 (GSLDNITHVPGGG).

The epitope may consist of the amino acid sequence of SEQ ID NO: 330 (GSLDNITHVPGGG). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 330 (GSLDNITHVPGGG).

30

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);  
 35 VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);

or for each CDR sequence, an amino acid sequence with

- 40 (i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CA4" herein.

5

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

10 VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA).

15 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 555 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

20 VHFR2 comprises the sequence set forth in SEQ ID NO: 556 (WVRQAPGQALEWIS);

VHFR3 comprises the sequence set forth in SEQ ID NO: 557 (RLSITRDTSKSQFSLSLSSVTEDTAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 558 (WGPGLLVTVSS);

25 VLFR1 comprises the sequence set forth in SEQ ID NO: 559 (DIQVTQSPSSLSASLTERVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 560 (WYQQKPGQAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 561 (DVPSRFSGSGSGTDYTLTITSLEADDTATYYC);

VLFR4 comprises the sequence set forth in SEQ ID NO: 562 (FGGGTNVEIK);

30 or for each FR sequence, an amino acid sequence with

(i) at least 50% identity thereto, and/or

(ii) one, two, three, four or five amino acid substitutions relative thereto.

35 The specific binding molecule may comprise framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 555 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 556 (WVRQAPGQALEWIS);

- VHFR3 comprises the sequence set forth in SEQ ID NO: 557  
(RLSITRDTSKSQFSLSLSSVTTEDTAVYYCTR);
- VHFR4 comprises the sequence set forth in SEQ ID NO: 558 (WGPGLLVTVSS);
- VLFR1 comprises the sequence set forth in SEQ ID NO: 559  
5 (DIQVTQSPSSLSASLTERVSITC);
- VLFR2 comprises the sequence set forth in SEQ ID NO: 560 (WYQQKPGQAPKLLIY);
- VLFR3 comprises the sequence set forth in SEQ ID NO: 561  
(DVPSRFSGSGSGTDYTLTITSLEADDTATYYC);
- VLFR4 comprises the sequence set forth in SEQ ID NO: 562 (FGGGTNVEIK);
- 10 or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
- (ii) one, two, three, four or five amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. A specific binding  
15 molecule comprising FRs having 100% identity to those given above is referred to as "CA4" herein.
- The specific binding molecule may comprise:
- (a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4,  
wherein each of said FRs comprises an amino acid sequence as follows:
- 20 VHFR1 comprises the sequence set forth in SEQ ID NO: 555  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLT);
- VHFR2 comprises the sequence set forth in SEQ ID NO: 556 (WVRQAPGQALEWIS);
- VHFR3 comprises the sequence set forth in SEQ ID NO: 557  
(RLSITRDTSKSQFSLSLSSVTTEDTAVYYCTR);
- 25 VHFR4 comprises the sequence set forth in SEQ ID NO: 558 (WGPGLLVTVSS);
- VLFR1 comprises the sequence set forth in SEQ ID NO: 559  
(DIQVTQSPSSLSASLTERVSITC);
- VLFR2 comprises the sequence set forth in SEQ ID NO: 560 (WYQQKPGQAPKLLIY);
- VLFR3 comprises the sequence set forth in SEQ ID NO: 561  
30 (DVPSRFSGSGSGTDYTLTITSLEADDTATYYC);
- VLFR4 comprises the sequence set forth in SEQ ID NO: 562 (FGGGTNVEIK);
- or for each FR sequence, an amino acid sequence with
- (i) at least 50% identity thereto, and/or
- (ii) one, two, three, four or five amino acid substitutions relative thereto; and
- 35 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);
- 40 VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);



VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);  
 or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or  
 5 (ii) one, two, or three amino acid substitutions relative thereto  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as "CA4" herein.

10

The specific binding molecule may comprise:

(a) framework regions (FRs) VHFR1, VHFR2, VHFR3, VHFR4, VLFR1, VLFR2, VLFR3 and VLFR4, wherein each of said FRs comprises an amino acid sequence as follows:

VHFR1 comprises the sequence set forth in SEQ ID NO: 555  
 15 (QVQLQESGPSLVKPSQTLSTCTVSGFSLT);

VHFR2 comprises the sequence set forth in SEQ ID NO: 556 (WVRQAPGQALEWIS);

VHFR3 comprises the sequence set forth in SEQ ID NO: 557  
 (RLSITRDTSKSQFSLSLSSVTEDTAVYYCTR);

VHFR4 comprises the sequence set forth in SEQ ID NO: 558 (WGPGLLVTVSS);

20 VLFR1 comprises the sequence set forth in SEQ ID NO: 559  
 (DIQVTQSPSSLSASLTERVSITC);

VLFR2 comprises the sequence set forth in SEQ ID NO: 560 (WYQQKPGQAPKLLIY);

VLFR3 comprises the sequence set forth in SEQ ID NO: 561  
 (DVPSRFSGSGSGTDYTLTITSLEADDTATYYC);

25 VLFR4 comprises the sequence set forth in SEQ ID NO: 562 (FGGGTNVEIK);

or for each FR sequence, an amino acid sequence with

- (i) at least 50% identity thereto, and/or  
 (ii) one, two, three, four or five amino acid substitutions relative thereto; and  
 (b) the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said  
 30 CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);

35 VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. The specific binding molecule comprising FRs and CDRs having 100% identity to those given above is referred to as  
 40 "CA4" herein.

The specific binding molecule may comprise:

- (a) A VH domain comprising the sequence set forth in SEQ ID NO: 563  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLTSYSVYWRQAPGQALEWISIMYASGRVDY  
5 NPALKSRLSITRDTSKSQFSLSLSSVTTEDTAVYYCTRG IENWGPGLLVTVSS); and/or  
(b) a VL domain comprising the sequence set forth in SEQ ID NO: 564  
(DIQVTQSPSSLSASLTERVSITCRTSQSVNNYLSWYQQKPGQAPKLLIYYATRLYTDVPS  
RFGSGSGSDYTLTITSLEADDTATYYCLQYDSTPLAFGGGTNVEIK);  
or a humanized variant thereof.

The specific binding molecule may comprise:

- (a) A heavy chain comprising the sequence set forth in SEQ ID NO: 565  
(QVQLQESGPSLVKPSQTLSTCTVSGFSLTSYSVYWRQAPGQALEWISIMYASGRVDY  
NPALKSRLSITRDTSKSQFSLSLSSVTTEDTAVYYCTRG IENWGPGLLVTVSSAKTTAPSV  
15 YPLAPVCGDTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSV  
TVTSSTWPSQSITCNVAHPASSTKVDKKIEPRGPTIKCPPCKCPAPNLLGGPSVFIFPPKI  
KDVLMISLSPIVTCVVVDVSEDDPDVQISWVFNNEVHTAQTQTHREDYNSTLRVVSALPI  
QHGDWMSGKEFKCKVNNKDLPAPIERTISKPKGSRAPQVYVLPPEEEMTKKQVTLTC  
MVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSGYSFMYSKLRVEKKNWVERNSYSCS  
20 VVHEGLHNHHTTKSFSRTPGK); and/or  
(b) a light chain comprising the sequence set forth in SEQ ID NO: 566  
(DIQVTQSPSSLSASLTERVSITCRTSQSVNNYLSWYQQKPGQAPKLLIYYATRLYTDVPS  
RFGSGSGSDYTLTITSLEADDTATYYCLQYDSTPLAFGGGTNVEIKGQPKSSPSVTLFPP  
SSEELTNKATLVCTITDFYPGVTVTDWKVDGTPVTQGMETTQPSKQSNNKYMSSYLTL  
25 TARAWEHRHSSYSCQVTHEGHTVEKSLSRADCS);  
or a humanized variant thereof.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 359 to 391 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
30 sequence of SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFR ENAKAKTDHGAE).

The epitope may be within an amino acid sequence comprising residues 359 to 391 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB2" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFR ENAKAKTDHGAE). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFR ENAKAKTDHGAE).

The epitope may consist of the amino acid sequence of SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFRNAAKAKTDHGAE). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFRNAAKAKTDHGAE).

5

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

10 VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL);

or for each CDR sequence, an amino acid sequence with

15

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 359 to 391 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB2" herein.

20

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

25 VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL).

30 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 360 to 390 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 333 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

The epitope may be within an amino acid sequence comprising residues 360 to 390 of SEQ ID NO:

35 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB3" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 333 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA). The epitope may comprise an amino acid sequence

having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 333 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

The epitope may consist of the amino acid sequence of SEQ ID NO: 333  
 5 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 333 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 10 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 334 (SVAVN);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 335 (GIISNGGTGYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 336 (GVEWEGSMDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 337 (SGSSSNVGAGSYVG);

15 VLCDR2 comprises the sequence set forth in SEQ ID NO: 338 (GATKRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 339 (VSYQTDFTLV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

20 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 360 to 390 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB3" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1,  
 25 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 334 (SVAVN);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 335 (GIISNGGTGYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 336 (GVEWEGSMDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 337 (SGSSSNVGAGSYVG);

30 VLCDR2 comprises the sequence set forth in SEQ ID NO: 338 (GATKRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 339 (VSYQTDFTLV).

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid  
 35 sequence of SEQ ID NO: 33 (GNKKIETHKLTFR).

The epitope may be within an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecules referred to as "CA9" and "CA12" herein. Critical residues of the epitope may be residues 370 (K), and/or 374 (H)  
 40 (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of

SEQ ID NO: 34 (XXXKXXHXHXXXX, wherein X is any amino acid). The epitope may comprise the amino acid sequence of SEQ ID NO: 33, wherein any one or more residue other than residue number 370 (K), and/or 374 (H) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 33, wherein any one or more residue other than residue number 370 (K), and/or 374 (H) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1). The epitope may comprise the amino acid sequence of SEQ ID NO: 33, wherein any one or more residue other than residue number 370 (K), and/or 374 (H) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1) and any one or more residue other than residue number 370 (K), and/or 374 (H) is replaced by a non-conservative amino acid substitution (numbering according to SEQ ID NO: 1).

The epitope may comprise the amino acid sequence of SEQ ID NO: 33 (GNKKIETHKLTFR). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 33 (GNKKIETHKLTFR).

The epitope may consist of the amino acid sequence of SEQ ID NO: 33 (GNKKIETHKLTFR). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 33 (GNKKIETHKLTFR).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 58 (SYRSDGLAYGYVQAIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTG);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CA9" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 58 (SYRSDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

- 5 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 265  
 10 (GSYYHGGGNGMVDFFDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV);  
 or for each CDR sequence, an amino acid sequence with  
 15 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The specific binding  
 molecule comprising CDRs having 100% identity to those given above is referred to as "CA12"  
 20 herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);  
 25 VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 265  
 (GSYYHGGGNGMVDFFDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and  
 30 VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV).

- The epitope of the specific binding molecule may be within an amino acid sequence comprising  
 residues 49 to 113 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence  
 of
- |    | SEQ                                                               | ID | NO: | 340 |
|----|-------------------------------------------------------------------|----|-----|-----|
| 35 | (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS |    |     |     |
|    | )                                                                 |    |     |     |

- The epitope may be within an amino acid sequence comprising residues 49 to 113 of SEQ ID NO:  
 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CB5"  
 40 herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 340 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 340 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS).

The epitope may consist of the amino acid sequence of SEQ ID NO: 340 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 340 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 341 (DITSGGRITYGNLALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 160 (CRDGGVSYGYDSY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 342 (SGSSSNVSGSDHVN);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 343 (RTTNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 344 (ASHDNNSGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 113 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CB5" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 49 to 155 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 345 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPR).

The epitope may be within an amino acid sequence comprising residues 49 to 155 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecules referred to as "CC4" and "CD1" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 345 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPR). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or  
 5 at least 99% identity to SEQ ID NO: 345 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPR).

The epitope may consist of the amino acid sequence of SEQ ID NO: 345  
 10 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPR). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 345 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPS  
 15 LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPR).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 20 VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 346 (SGSSSNVGYTNLGYSNLVT);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and  
 25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 347 (ASYDSSNGGI);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino  
 30 acid sequence comprising residues 49 to 155 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CC4" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 35 VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 286 (CRDGGVSYGYDVDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 290 (SGSSSNVGYGTIVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and  
 40 VLCDR3 comprises the sequence set forth in SEQ ID NO: 291 (ASYDTGSGGV);



or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 155 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CD1" herein.

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 49 to 238 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 348 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPP APKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREP KKVAVVRTPPKSPSS).

The epitope may be within an amino acid sequence comprising residues 49 to 238 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "CC5" herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 348 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPP APKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREP KKVAVVRTPPKSPSS). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 348 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPP APKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREP KKVAVVRTPPKSPSS).

The epitope may consist of the amino acid sequence of SEQ ID NO: 348 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPP APKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREP KKVAVVRTPPKSPSS). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 348 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPS LEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPP APKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREP KKVAVVRTPPKSPSS).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 349 (DISSVGKKYASPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);  
 5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 350 (ASYDSSNGGV);  
 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
     (ii) one, two, or three amino acid substitutions relative thereto,  
 10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 238 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "CC5" herein.
- The epitope of the specific binding molecule may be within an amino acid sequence comprising  
 15 residues 373 to 385 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 351 (THKLTFRENAKAK).
- The epitope may be within an amino acid sequence comprising residues 373 to 385 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "MD9" or  
 20 "MoD9" herein.
- The epitope may comprise the amino acid sequence of SEQ ID NO: 351 (THKLTFRENAKAK). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 351 (THKLTFRENAKAK).  
 25
- The epitope may consist of the amino acid sequence of SEQ ID NO: 351 (THKLTFRENAKAK). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 351 (THKLTFRENAKAK).
- 30 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
     VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);  
     VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYSPALKS);  
     VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);  
 35 VLCDR1 comprises the sequence set forth in SEQ ID NO: 352 (SGSSSNVGIYDVS);  
     VLCDR2 comprises the sequence set forth in SEQ ID NO: 353 (GTNNRPS); and  
     VLCDR3 comprises the sequence set forth in SEQ ID NO: 354 (AAGDSSTIAV);  
 or for each CDR sequence, an amino acid sequence with  
     (i) at least 85% identity thereto, and/or  
 40      (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 373 to 385 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "MD9" or "MoD9" herein.

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The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYSPALKS);

10 VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 352 (SGSSSNVGIYDVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 353 (GTNNRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 354 (AAGDSSTIAV).

15 The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 275 to 305 and/or residues 337 to 368 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

20 The epitope may be within an amino acid sequence comprising residues 275 to 305 and/or residues 337 to 368 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "NS1G7" herein.

25 The epitope may comprise the amino acid sequence of SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN). The epitope may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

30

35 The epitope may consist of the amino acid sequence of SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN). The epitope may consist of an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDKDRVQSKIGSLDNITHVPGGGN).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

40 VHCDR1 comprises the sequence set forth in SEQ ID NO: 357 (SYGVG);

- VHCDR2 comprises the sequence set forth in SEQ ID NO: 358 (SISSGGTTFYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 359 (DVHIYYNDYGAAYGDRDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 360 (SGSSSNIGGGNYVS);  
5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 361 (GTTSRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 362 (ASYDTNSGSV);  
or for each CDR sequence, an amino acid sequence with  
(i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
10 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 275 to 305 and/or residues 337 to 368 of SEQ ID NO: 1. The specific binding molecule comprising CDRs having 100% identity to those given above is referred to as "NS1G7" herein.
- 15 The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
VHCDR1 comprises the sequence set forth in SEQ ID NO: 357 (SYGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 358 (SISSGGTTFYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 359  
20 (DVHIYYNDYGAAYGDRDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 360 (SGSSSNIGGGNYVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 361 (GTTSRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 362 (ASYDTNSGSV).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 10 below.

**Table 10**

| Clone name | VH                        |                                       |                                       | VL                                 |                              |                                 | Epitope |
|------------|---------------------------|---------------------------------------|---------------------------------------|------------------------------------|------------------------------|---------------------------------|---------|
|            | CDR1                      | CDR2                                  | CDR3                                  | CDR1                               | CDR2                         | CDR3                            |         |
| CB11       | SNAVI<br>(SEQ ID NO: 198) | LIDVDGDAAYDPALKS<br>(SEQ ID NO: 200)  | DYGSWGYVSDIDY<br>(SEQ ID NO: 202)     | SGSNIGSNDVG (SEQ ID NO: 256)       | DNNRNP<br>S (SEQ ID NO: 257) | GGYAGSSSNFL<br>(SEQ ID NO: 258) | 113-238 |
| CA2        | SNGVG<br>(SEQ ID NO: 259) | DISSVGKKYANPALKS<br>(SEQ ID NO: 157)  | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)    | SGSSGNVGYGDYVS<br>(SEQ ID NO: 165) | GATNLAS<br>(SEQ ID NO: 169)  | ASYDSSSGGV<br>(SEQ ID NO: 173)  | 1-155   |
| CB6        | SNGVG<br>(SEQ ID NO: 259) | DISSVGKKYANPALKS<br>(SEQ ID NO: 157)  | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)    | SGSSNIGTGNVVG (SEQ ID NO: 261)     | GAVTRA<br>S (SEQ ID NO: 262) | ASYDSTSGGV<br>(SEQ ID NO: 263)  | 1-238   |
| CA7        | SYVVG<br>(SEQ ID NO: 44)  | NIYSTGRAFYNPALKS<br>(SEQ ID NO: 52)   | GSYYHGGNGMVDFFD<br>Y (SEQ ID NO: 265) | SGSSSNVGYGNYVG<br>(SEQ ID NO: 39)  | AATSRAS<br>(SEQ ID NO: 72)   | SSYQRGNTGV<br>(SEQ ID NO: 78)   | 1-319   |
| CA8        | SNAV<br>(SEQ ID NO: 266)  | AIDKDGDTIYNPALKS<br>(SEQ ID NO: 267)  | DPSGWGYPDVY (SEQ ID NO: 268)          | SGTYIGSSDVVG (SEQ ID NO: 269)      | GTSSRP<br>S (SEQ ID NO: 270) | ATYESSYHNSV<br>(SEQ ID NO: 271) | 1-319   |
| CB10       | SNTVA<br>(SEQ ID NO: 272) | EINSGGSTYINPALK<br>S (SEQ ID NO: 273) | GARSTYAA (SEQ ID NO: 274)             | SGSSSDVGYSTWY<br>(SEQ ID NO: 275)  | HISNRAS<br>(SEQ ID NO: 276)  | AAVDSSNNVWI<br>(SEQ ID NO: 277) | 1-319   |

|      |                           |                                       |                                        |                                     |                               |                                   |         |
|------|---------------------------|---------------------------------------|----------------------------------------|-------------------------------------|-------------------------------|-----------------------------------|---------|
| CB7  | NYRVG<br>(SEQ ID NO: 279) | NIRSGGTTWYNPALK<br>S (SEQ ID NO: 280) | DSSGDLAYDY (SEQ ID NO: 281)            | SGSSSNVGYGNMYMA<br>(SEQ ID NO: 282) | GATSRA<br>S (SEQ ID NO: 141)  | ASYDSTSGGV<br>(SEQ ID NO: 263)    | 13-25   |
| CC7  | SNAVI<br>(SEQ ID NO: 198) | LIDVDGDAAYDPALKS<br>(SEQ ID NO: 200)  | DYGSWGYVSDIDY<br>(SEQ ID NO: 202)      | SGSYITGSSVG (SEQ ID NO: 292)        | DNNDRLP<br>S (SEQ ID NO: 284) | ASYDTSNIGL<br>(SEQ ID NO: 285)    | 145-157 |
| CB12 | SNGVG<br>(SEQ ID NO: 259) | DKSSAGKTYGNPALK<br>S (SEQ ID NO: 182) | CRDGGVSYGYDVDY<br>(SEQ ID NO: 286)     | SGSSSNVGGDYVG (SEQ ID NO: 287)      | DTTSRPS<br>(SEQ ID NO: 288)   | ASVDKTTGGV<br>(SEQ ID NO: 289)    | 155-227 |
| CC3  | SNGVG<br>(SEQ ID NO: 259) | DKSSAGKTYGNPALK<br>S (SEQ ID NO: 182) | CRDGGVSYGYDVDY<br>(SEQ ID NO: 286)     | SGSSSNVGYGTYS<br>(SEQ ID NO: 290)   | GTTTRAS<br>(SEQ ID NO: 188)   | ASYDTGSGGV<br>(SEQ ID NO: 291)    | 155-227 |
| CA1  | SNAVI<br>(SEQ ID NO: 198) | DIRADGATNYNAALK<br>S (SEQ ID NO: 296) | PGNYYYGAGRDVARLA<br>D (SEQ ID NO: 297) | SGSSSNIGGGNAV<br>(SEQ ID NO: 298)   | DTTSRPS<br>(SEQ ID NO: 288)   | AAMDSSSLIGV<br>(SEQ ID NO: 299)   | 155-238 |
| CA3  | SNGVG<br>(SEQ ID NO: 259) | DKSSAGKTYGNPALK<br>S (SEQ ID NO: 182) | CRDGGVTYGYDVDY<br>(SEQ ID NO: 184)     | SGSSGNIGYDDYVS (SEQ ID NO: 301)     | GATRRS<br>S (SEQ ID NO: 302)  | ASYDSSGGGV<br>(SEQ ID NO: 303)    | 186-263 |
| CD2  | SNAVI<br>(SEQ ID NO: 198) | LIDVDGDAAYDPALKS<br>(SEQ ID NO: 200)  | DYGSWGYVSDIDY<br>(SEQ ID NO: 202)      | SGSNIGDADVG (SEQ ID NO: 305)        | YNENRP<br>S (SEQ ID NO: 306)  | GSYAGDTYNHG<br>V (SEQ ID NO: 307) | 186-350 |
| CB9  | SNSVG<br>(SEQ ID NO: 42)  | GIDSDGEEGYNPALN<br>S (SEQ ID NO: 48)  | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54)   | SGRFIGISSVG (SEQ ID NO: 67)         | ASDGRP<br>S (SEQ ID NO: 70)   | GSSDRTQYTG<br>(SEQ ID NO: 74)     | 239-348 |

|          |                           |                                       |                                      |                                     |                              |                                |         |
|----------|---------------------------|---------------------------------------|--------------------------------------|-------------------------------------|------------------------------|--------------------------------|---------|
| CG11     | NYPVG<br>(SEQ ID NO: 310) | NIENDGSANYASALK<br>S (SEQ ID NO: 311) | EFGGSDGYTYFVDIDY<br>(SEQ ID NO: 312) | SGSSSNVGYGNYVS<br>(SEQ ID NO: 313)  | GATSRA<br>S (SEQ ID NO: 141) | ASYDGSSSGV<br>(SEQ ID NO: 314) | 266-359 |
| CA10     | SNGVG<br>(SEQ ID NO: 259) | DISSVGKKYANPALKS<br>(SEQ ID NO: 157)  | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)   | SGSSSNVGYGNYVT<br>(SEQ ID NO: 316)  | DATTRVS<br>(SEQ ID NO: 317)  | AAHDSGSGV<br>(SEQ ID NO: 318)  | 277-319 |
| CC12     | SNSVG<br>(SEQ ID NO: 42)  | GIDSDGEEGYNPALN<br>S (SEQ ID NO: 48)  | SYRADGLAYGYVQAIDY<br>(SEQ ID NO: 54) | SGRFIGISSVG (SEQ ID NO: 67)         | ASDGRP<br>S (SEQ ID NO: 70)  | GSSDRTQYTG<br>(SEQ ID NO: 74)  | 297-390 |
| CE2/E1B8 | NYPVG<br>(SEQ ID NO: 310) | NIENDGSANYASALK<br>S (SEQ ID NO: 311) | EFGGSDGYTYFVDIDY<br>(SEQ ID NO: 312) | SGSSSNVGYGNYVS<br>(SEQ ID NO: 313)  | GATSRA<br>S (SEQ ID NO: 141) | ASYDGSSSGV<br>(SEQ ID NO: 314) | 319-331 |
| CE3      | SNAV<br>(SEQ ID NO: 17)   | GCSSDGKCYNSALK<br>S (SEQ ID NO: 20)   | GYYPVYGYDYLGTIDY<br>(SEQ ID NO: 23)  | SGSSSNVGRNDVA (SEQ ID NO: 25)       | GTTSRP<br>S (SEQ ID NO: 28)  | ASGDSSAINDI<br>(SEQ ID NO: 31) | 331-360 |
| CA6      | SNGVG<br>(SEQ ID NO: 259) | DKSSGGKTYGNPALK<br>S (SEQ ID NO: 323) | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)   | SGSRNNIGYGNHVG<br>(SEQ ID NO: 324)  | DATTRAS<br>(SEQ ID NO: 207)  | ASFDRGSGGI<br>(SEQ ID NO: 325) | 348-390 |
| CA11     | SNTVA<br>(SEQ ID NO: 272) | EINSGGSTYYPALK<br>S (SEQ ID NO: 273)  | GARSTYAA (SEQ ID NO: 274)            | SGSGSNIGAGNWWVS<br>(SEQ ID NO: 327) | GATSRP<br>S (SEQ ID NO: 328) | AAYDSGSSIV<br>(SEQ ID NO: 329) | 348-441 |
| CA4      | SYSVY<br>(SEQ ID NO: 83)  | IMYASGRVDYNPALK<br>S (SEQ ID NO: 84)  | GIEN (SEQ ID NO: 89)                 | RTSQSVNNYLS (SEQ ID NO: 91)         | YATRLYT<br>(SEQ ID NO: 95)   | LQYDSTPLA<br>(SEQ ID NO: 97)   | 355-367 |

|      |                           |                                       |                                       |                                          |                              |                                |         |
|------|---------------------------|---------------------------------------|---------------------------------------|------------------------------------------|------------------------------|--------------------------------|---------|
| CB2  | TNSVG<br>(SEQ ID NO: 45)  | GIDTDGEEGNPVLK<br>S (SEQ ID NO: 53)   | SYRTDGLAYGYVQAIDY<br>(SEQ ID NO: 55)  | SGSYIGSSGVG (SEQ ID NO: 68)              | ASDGRP<br>S (SEQ ID NO: 70)  | GSSDRTQYTGL<br>(SEQ ID NO: 79) | 359-391 |
| CB3  | SVAVN<br>(SEQ ID NO: 334) | GIISNGGTGYNPALKS<br>(SEQ ID NO: 335)  | GVEWEGSMDY (SEQ ID NO: 336)           | SGSSSNVAGGSYVG<br>(SEQ ID NO: 337)       | GATKRA<br>S (SEQ ID NO: 338) | VSYQTDFTLV<br>(SEQ ID NO: 339) | 360-390 |
| CA9  | SNSVG<br>(SEQ ID NO: 42)  | GIDTDGEEGNPALN<br>S (SEQ ID NO: 46)   | SYRSDGLAYGYVQAIDY<br>(SEQ ID NO: 58)  | SGSFIGISSVG (SEQ ID NO: 63)              | ASDGRP<br>S (SEQ ID NO: 70)  | GSSDRTQYTGV<br>(SEQ ID NO: 74) | 367-379 |
| CA12 | SYVVG<br>(SEQ ID NO: 44)  | NIYSTGRAFYNPALKS<br>(SEQ ID NO: 52)   | GSYYHGGNGMVDFFD<br>Y (SEQ ID NO: 265) | SGSSSNVGYGNYVG<br>(SEQ ID NO: 39)        | AATSRAS<br>(SEQ ID NO: 72)   | SSYQRGNTGV<br>(SEQ ID NO: 78)  | 367-379 |
| CB5  | SNGVG<br>(SEQ ID NO: 259) | DITSGGRTYGNLALK<br>S (SEQ ID NO: 341) | CRDGGVSYGYDSDY<br>(SEQ ID NO: 160)    | SGSSSNVGS GDHVN<br>(SEQ ID NO: 342)      | RTTNRA<br>S (SEQ ID NO: 343) | ASHDNNSGGV<br>(SEQ ID NO: 344) | 49-113  |
| CC4  | SNGVG<br>(SEQ ID NO: 259) | DIASSGKAYSNPALKS<br>(SEQ ID NO: 158)  | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)    | SGSSSNVGYTNLGYSNL<br>VT (SEQ ID NO: 346) | GATNRA<br>S (SEQ ID NO: 170) | ASYDSSNGGI<br>(SEQ ID NO: 347) | 49-155  |
| CD1  | SNGVG<br>(SEQ ID NO: 259) | DKSSAGKTYGNPALK<br>S (SEQ ID NO: 182) | CRDGGVSYGYDVDY<br>(SEQ ID NO: 286)    | SGSSSNVGYGTYVS<br>(SEQ ID NO: 290)       | GTTTRAS<br>(SEQ ID NO: 188)  | ASYDTGSGGV<br>(SEQ ID NO: 291) | 49-155  |
| CC5  | SNGVG<br>(SEQ ID NO: 259) | DISSVGKKYASPALKS<br>(SEQ ID NO: 349)  | CRDGGVTYGYDIDY<br>(SEQ ID NO: 161)    | SGSSSNVGYGNYVG<br>(SEQ ID NO: 39)        | GATSRA<br>S (SEQ ID NO: 141) | ASYDSSNGGV<br>(SEQ ID NO: 350) | 49-238  |



|              |                              |                                       |                                         |                                   |                                  |                                |                     |
|--------------|------------------------------|---------------------------------------|-----------------------------------------|-----------------------------------|----------------------------------|--------------------------------|---------------------|
| MD9/MoD<br>9 | RESIA<br>(SEQ ID<br>NO: 102) | GVGIDGTSYYSPALK<br>S (SEQ ID NO: 103) | NYIDFEY (SEQ ID NO:<br>104)             | SGSSSNVGIYDVS (SEQ<br>ID NO: 352) | GTNNRP<br>S (SEQ ID<br>NO: 353)  | AAGDSSTIAV<br>(SEQ ID NO: 354) | 373-385             |
| NS1G7        | SYGVG<br>(SEQ ID<br>NO: 357) | SISGGTTFYNPALKS<br>(SEQ ID NO: 358)   | DVHIYYNDYGAAYGDRD<br>Y (SEQ ID NO: 359) | SGSSNIGGGNYVS (SEQ<br>ID NO: 360) | GTTSTRA<br>S (SEQ ID<br>NO: 361) | ASYDTNSGSV<br>(SEQ ID NO: 362) | 275-305,<br>337-368 |

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 10;
  - VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 10;
  - 5 VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 10;
  - VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 10;
  - VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 10; and
  - VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 10;
- or for each CDR sequence, an amino acid sequence with
- 10 (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
- wherein the specific binding molecule binds to an epitope within SEQ ID NO: 1, optionally wherein the specific binding molecule has a  $K_D$  of less than around 25 nM.

- 15 The  $K_D$  may be less than around 20 nM, less than around 15 nM, or less than around 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or to SEQ ID NO: 5. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1 nM to around 20 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1 nM to around 10 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1.23 nM to 6.9 nM, optionally wherein the specific binding molecule comprises the CDRs of CC7. The  $K_D$  for binding to SEQ ID
- 20 NO: 1 may be around 1.3 nM to 3.61 nM, optionally wherein the specific binding molecule comprises the CDRs of CA4. The  $K_D$  for binding to SEQ ID NO: 1 may be around 3.79 nM to 16.7 nM, optionally wherein the specific binding molecule comprises the CDRs of CE3. The  $K_D$  for binding to SEQ ID NO: 1 may be around 5.03 nM to 11 nM, optionally wherein the specific binding molecule comprises the CDRs of CE2. The  $K_D$  for binding to SEQ ID NO: 1 may be around 3.7 nM to 5.19 nM, optionally
- 25 wherein the specific binding molecule comprises the CDRs of CB7.

- The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 363 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid
- 30 sequence comprising residues 1-155 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 363. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 363. The specific binding molecule may comprise an amino acid sequence
  - 35 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 363 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 363. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 363.

SEQ ID NO: 363 (CA2 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSSVAVNWVRQAPGKVPEWLGGIISNGGTGYNPALKS  
RLSITRDTSKSQVSLALHTVTEDTAVYYCGRGVEWEGSMDYLGPGLLVTVSSEKSSSGSGSETK  
VDDQSVLTQPSSVSGFLGQRTITCSGSSSNVAGSYVGWYQQVPGSGLRILYIGATKRASGLPD

5 RFSGSRSGNTATLTISLQAEDEADYYCVSYQTDFTLVFGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 364 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid  
10 sequence comprising residues 13-25 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 364. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 364. The specific binding molecule may comprise an amino acid sequence  
15 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 364 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 364. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 364.

SEQ ID NO: 364 (CB7 amino acid sequence)

20 QVQLQESGPSLVKPSQTLSTCTVSGFSLTNRYVGWVRQAPGKALEWVSNIRSGGTTWYNPALK  
SRLSITADTSKSQVSLSLSSVTEDTAVYYCARDSSGDLAYDYWGPGLLVTVSSEKSSSGASGE  
SKVDDQAVLTQPSSVSRSLGQSVSMTCGSSSNVGYGNMAWFQQVPGSAPKLLIYGATSRAS  
GVPDRFSGSRSGNTATLTISLQAEDEADYYCASYDSTSGGVFGSGTRLTVLG

25 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 365 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,  
30 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 365. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 365. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 365 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 365.  
35 The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 365.

SEQ ID NO: 365 (CC7 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNAVIWVRQAPGKAPEWVALIDVDGDAAYDPALKS  
RLSITRDTSKSQVSLSLRSVTEDTAVYYCARDYGSWGYVSDIDYWGPGLLVTVSSEKSSSGASG

ESKVDDRVVRTQPSSVSGSLGQRV SITCSGSYITGSSVGVWFQQVPGSGLKTVIYDNNDRPSGVP  
DRFSGSKSGDTATLTISLQAED EADYYCASYDTSNIGLFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 366 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 366. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 366. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 366 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 366. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 366.

15

SEQ ID NO: 366 (CE2/E1B8 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTNYPVGWVRQAPGKALEWIGNIENDGSANYASALKS  
RLSITRDTSKNQVSLSLSSATTEDTAVYYCGREFGGSDGYTYFVDIDYWGPGLLVTSSEKSSG  
ASGESKVDDQAVLTQPSSVSKSLGQSVSITCSGSSSNVGYGNYVSWFQQVPGSAPKILIYGATSR  
ASGVDPDRFSGSRSGNTATLTITSLQAED EADYYCASYDGSSSGVFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 367 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 367. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 367. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 367 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 367. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 367.

SEQ ID NO 367: (CE3 amino acid sequence)

QVRLQESGPSLVKPSQTLSTCTVSGFSLISNAVGWVRQAPGKVPESLAGCSDGKCYNSALKS  
RLDITRDTSKNQISLSLSSVTDDAAVYYCTRGYYPVYGYDYLGTIDYWGPGLLVTSSEKSSGA  
SGESKVDDQAVLTQPSSVSGSLGQRV SITCSGSSSNVGRNDVAWFQQLPGSGLRTIYGTTSRPS  
GIPDRFSGSKSGVTATLTIDSLQAED EADYFCASGDSSAINDIFGSGTRTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 368 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 368. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 368. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 368 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 368. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 368.

SEQ ID NO: 368 (CA4 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSYSVYVWRQAPGQALEWISIMYASGRVDYNPALKS  
 RLSITRDTSKSQFSLSLSSVTEDTAVYYCTRGLENWGPGLLVTSSEKSSGASGESKVDDDIQV  
 TQSPSSLSASLTERVSITCRISQSVNNYLSWYQQKPGQAPKLLIYYATRLYTDVPSRFSGSGSGTD  
 YTLTITSLEADDTATYYCLQYDSTPLAFGGGTNVEIK

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 369 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 359 to 391 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 369. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 369. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 369 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 369. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 369.

SEQ ID NO: 369 (CB2 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSTNSVGWVRQAPGKAPEWVAGIDTDGEEGFNPVLK  
 SRLSITRDTSKSQVSLSLSNVTSEDVAVYYCGRSYRTDGLAYGYVQAIDYWGPGLLVTSSEKSS  
 GASGESKVDDQSVLTQPSSVSGSPGQTVSITCSGSYIGSSGVGWFGQLPGSGLRITIVASDGRPS  
 GVPDRFMSKSGNTATLTISLQAEDEADYFCGSSDRTQYTGLFGSGTRLTLVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 370 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 360 to 390 of SEQ ID NO: 1. The CDRs of the specific binding

- molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 370. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 370. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 370 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 370. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 370.

SEQ ID NO: 370 (CB3 amino acid sequence)

10 QVQLQESGPSLVKPSQTLSTCTVSGFSLSSVAVNWVRQAPGKVPEWLGGIISNGGTGYNPALKS  
RLSITRDTSKSQVSLALHTVTTEDTAVYYCGRGVEWEGSMDYLGPGLLVTVSSEGKSSGSGSETK  
VDDQSVLTQPSSVSGFLGQRVTITCSGSSSNVAGSYVGWYQQVPGSGLRILIYGATKRASGLPD  
RFGSGRSGNTATLTISSLQAEDEADYYCVSYQTDFTLVFGSGTRLTVLG

- 15 The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 371 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%,  
20 at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 371. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 371. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 371 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 371.  
25 The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 371.

SEQ ID NO: 371 (CA9 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLTSNSVGWVRQAPGKAPWVAGIDTDGEEGYNPALN  
SRLSITRDTSKSQVSLSLSSVTSEDVAVYYCGRSYRSDGLAYGYVQAIDYWGPGLLVTVSSEGKS  
30 SGASGESKVDDQAVLTQPASVSGSLGQRVSITCSGSGFIGISSVGWFQQLPGSGLRITIVASDGRPS  
GVPDRFSMSKSGNTATLTISSLQAEDEADYFCGSSDRTQYTG VFGSGTRLTVLG

- The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 372 wherein  
35 the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 372. The CDRs may be 100%  
40 identical to the CDRs of SEQ ID NO: 372. The specific binding molecule may comprise an amino

acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 372 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 372. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 372.

5 SEQ ID NO: 372 (CA12 amino acid sequence)

QVQLQGSGPSLVKPSQTLSTCTVSGFSFDSYYVGWVRQAPGKALEWLGNIYSTGRAFYNPALK  
SRLSITRDTSKSQVSLSVSSVTIEDTALYYCVRGSYYHGGNGMVDFFDYWSPGLLVTVSSEGKS  
SGASGESKVDDQVVRTQPSSVSGSLGQQRVSITCSGSSSNVGYGNYVGVWFQQVPGSAPKLLIYAA  
TSRASGVDPDRFSGSRSGNTATLTIDSLQAEDEADYYCSSYQRGNTGVFGSGTRLTVLG

10

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 373 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 373 to 385 of SEQ ID NO: 1. The CDRs of the specific binding  
15 molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 373. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 373. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least  
20 99% identity to SEQ ID NO: 373 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 373. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 373.

SEQ ID NO: 373 (MD9/MoD9 amino acid sequence)

QVRLQESGPSLVKSSQTLSTCTVSGFSLTRESIAWVRQAPGKVPEWLGGVGIDGTSYYSPALKS  
25 RLSITRDTSKSQASLSLSSVATEDTAMYYCARNYIDFEYWGPGLLVTVSSEGKSSGASGESKVDD  
QAVLTQLSSVSGSLGQQRISITCSGSSSNVGIYDVSWFQQLPGSGLRTVIYGTNNRPSGVPDRFSG  
SRSGNTATLTISLQSEDAIYYCAAGDSSTIAVFGSGTRLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least  
30 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 374 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 275 to 305 and/or 337 to 368 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%,  
35 at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 374. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 374. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 374 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 374. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 374.

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SEQ ID NO: 374 (NS1G7 amino acid sequence)  
 QVQLQESGPSLVKPSQTLSTCTVSGFSLTSYGVGWRQAPGKTLEWISSISSGGTTFFYNPALKS  
 RLSITRDTSESQVSLSLSSVTTEDTAVYYCTRDVHIYYNDYGAAYGDRDYWGPGLLVTVSSEGKS  
 SGASGESKVDDQAVVTQPPSVSGSPGQRVSITCSGSSSNIGGGNYVSWYQQLPGSGLRTLIIYGT  
 5 TSRASGVPDFRSGSGSGNTATLTISLQAEDEADYYCASYDTNSGVSFVSGSTRLTVLG

The epitope of the specific binding molecule may be within an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. Accordingly, the epitope may be within the amino acid sequence of SEQ ID NO: 5  
 10 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA).

The epitope may be within an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. This epitope may be bound by the CDRs of the specific binding molecule referred to as "S1E12"  
 15 herein.

The epitope may comprise the amino acid sequence of SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA). The epitope may comprise an amino acid sequence  
 20 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA).

The epitope may consist of the amino acid sequence of SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA). The epitope may consist of an amino acid sequence  
 25 having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 5 (IKHVPGGGQSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITH VPGGGNKKIETHKLTFRNAKAKTDHGA).  
 30

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. Said specific binding molecule may  
 35 comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 136 (S/R/D/T N/E/Y/H S/G V/I G/A);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 162 (G I/V D/G/N T/I/Y/S D G  
 40 E/T/R E/S/T G/Y/E Y/F N/S P/S A/V L N/K S);



VHCDR3 comprises the sequence set forth in SEQ ID NO: 164 (S/N/D/T Y/-/S R/-/K A/-/G/S/T D/- G/- L/-/Y A/-/G Y/-/W G/- Y/-/H V/Y Q/I/Y A/D/Q I/F D/E Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 167 (S G S F/N/S/Y I/S G/N I/S/V S/A/G S/Y/G -/G -/D -/Y V G/T/S);

5 VLCDR2 comprises the sequence set forth in SEQ ID NO: 181 (A/R/D S/N/A D/R/T G/N R P/A S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 183 (G/A S S/Y/H D/- R/Q/D T/S/N Q/W/R Y/G/I T/S G/A V/L);

or for each CDR sequence, an amino acid sequence with

- 10 (i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto.

Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at  
15 least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG), SEQ ID NO: 187 (SHSVG), SEQ ID NO: 45 (TNSVG), SEQ ID NO: 102 (RESIA), or SEQ ID NO: 199 (DYGIG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS), SEQ ID NO: 205 (GINYDGRTEYNSALKS), SEQ ID NO: 103 (GVGIDGTSYSPALKS), SEQ ID NO: 53 (GIDTDGEEGFNPVLKS), or SEQ ID NO: 48 (GIDSDGEEGYNPALNS);

25 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY), SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY), SEQ ID NO: 210 (TYRSDGYAYGYVQAIDY), SEQ ID NO: 104 (NYIDFEY), or SEQ ID NO: 211 (DSKGGWGHVYQFDY);

30 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG), SEQ ID NO: 68 (SGSYIGSSGVG), SEQ ID NO: 212 (SGSNIGSASVT), or SEQ ID NO: 213 (SGSSSNVGYGDYVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS), SEQ ID NO: 214 (RNRNRPS), or SEQ ID NO: 215 (DATNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV), SEQ ID NO: 79 (GSSDRTQYTGL), SEQ ID NO: 216 (ASHDNRISAV), or SEQ ID NO: 217 (GSYQSWGSGV);

35 or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1.

40

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 5 VHCDR1 comprises the sequence set forth in SEQ ID NO: 426 (S/T N/H S V G);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 427 (G I D T/S D G E E G Y/F N P A/V L N/K S);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 428 (S/T Y R A/T/S D G L/Y G Y V Q A I D Y);
- 10 VLCDR1 comprises the sequence set forth in SEQ ID NO: 429 (S G S F/Y I G I/S S S/G V G);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (A S D G R P S); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 432 (G S S D R T Q Y T G V/L);  
 or for each CDR sequence, an amino acid sequence with
- 15 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto.

Said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at  
 20 least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 25 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG), SEQ ID NO: 187 (SHSVG) or SEQ ID NO: 45 (TNSVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS), SEQ ID NO: 53 (GIDTDGEEGFNPVLKS), or SEQ ID NO: 48 (GIDSDGEEGYNPALNS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY),  
 30 SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY), or SEQ ID NO: 210 (TYRSDGYAYGYVQAIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG), or SEQ ID NO: 68 (SGSYIGSSGVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV), or SEQ  
 35 ID NO: 79 (GSSDRTQYTGL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule  
 40 comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
- 5 VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV);
- 10 or for each CDR sequence, an amino acid sequence with
  - (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. The specific binding
- 15 molecule comprising CDRs having 100% identity to those given above is referred to as "S1E12" herein.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- 20 VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
- 25 VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);
- 30 VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL);
- 35 or for each CDR sequence, an amino acid sequence with
  - (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto,
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. The specific binding

molecule comprising CDRs having 100% identity to those given above is referred to as "NS2A1" herein.

- The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, 5 VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
- VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);
  - VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);
  - VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);
  - VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);
  - 10 VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and
  - VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL).

The specific binding molecule may comprise the CDR sequences of a clone set out in Table 11 below. The epitope may be within residues 297 to 390 of SEQ ID NO: 1.

Table 11

| Clone name | VH                               |                                              |                                                      | VL                                                |                                    |                                                   | Epitope        |
|------------|----------------------------------|----------------------------------------------|------------------------------------------------------|---------------------------------------------------|------------------------------------|---------------------------------------------------|----------------|
|            | CDR1                             | CDR2                                         | CDR3                                                 | CDR1                                              | CDR2                               | CDR3                                              |                |
| NS2B6      | <u>RESIA</u><br>(SEQ ID NO: 102) | <u>GVGIDGTSYYSPALK</u><br>S (SEQ ID NO: 103) | <u>N-----YIDFEY</u> (SEQ ID NO: 104)                 | <u>SGSNIGSAS---VT</u><br>(SEQ ID NO: 212)         | <u>RNRNRPS</u><br>(SEQ ID NO: 214) | <u>GSY-</u><br><u>QSWGSGV</u><br>(SEQ ID NO: 217) | <u>297-390</u> |
| NS1B2      | <u>DYGIG</u><br>(SEQ ID NO: 199) | <u>GINYDGRTEYNALK</u><br>S (SEQ ID NO: 205)  | <u>DSKG---</u><br><u>GWGHVYQFDY</u> (SEQ ID NO: 211) | <u>SGSSSNVGYGDYV</u><br><u>S</u> (SEQ ID NO: 213) | <u>DATNRAS</u><br>(SEQ ID NO: 215) | <u>ASH-DNRISAV</u><br>(SEQ ID NO: 216)            | 297-390        |
| S1A5       | <u>SNSVG</u><br>(SEQ ID NO: 42)  | <u>GIDTDGEEGYNPALN</u><br>S (SEQ ID NO: 46)  | <u>TYRSDGYAYGYVQAID</u><br>Y (SEQ ID NO: 210)        | NA                                                | NA                                 | NA                                                | 297-390        |
| S1A12      | <u>SNSVG</u><br>(SEQ ID NO: 42)  | <u>GIDTDGEEGYNPALN</u><br>S (SEQ ID NO: 46)  | <u>TYRSDGYAYGYVQAID</u><br>Y (SEQ ID NO: 210)        | <u>SGSFIGISS---VG</u><br>(SEQ ID NO: 63)          | <u>ASDGRPS</u><br>(SEQ ID NO: 70)  | <u>GSSDRTQYTG</u><br>V (SEQ ID NO: 74)            | 297-390        |
| S1E12      | <u>SNSVG</u><br>(SEQ ID NO: 42)  | <u>GIDTDGEEGYNPALN</u><br>S (SEQ ID NO: 46)  | <u>SYRADGLAYGYVQAID</u><br>Y (SEQ ID NO: 54)         | <u>SGSFIGISS---VG</u><br>(SEQ ID NO: 63)          | <u>ASDGRPS</u><br>(SEQ ID NO: 70)  | <u>GSSDRTQYTG</u><br>V (SEQ ID NO: 74)            | 297-390        |
| S1D5       | <u>SHSVG</u><br>(SEQ ID NO: 187) | <u>GIDSDGEEGYNPALN</u><br>S (SEQ ID NO: 48)  | <u>SYRADGLAYGYVQAID</u><br><u>Y</u> (SEQ ID NO: 54)  | <u>SGSFIGISS---VG</u><br>(SEQ ID NO: 63)          | <u>ASDGRPS</u><br>(SEQ ID NO: 70)  | <u>GSSDRTQYTG</u><br>V (SEQ ID NO: 74)            | 297-390        |

|       |                          |                                      |                                       |                                 |                            |                                 |         |
|-------|--------------------------|--------------------------------------|---------------------------------------|---------------------------------|----------------------------|---------------------------------|---------|
| NS2A1 | TNSVG<br>(SEQ ID NO: 45) | GIDTDGEEGFNPVLK<br>S (SEQ ID NO: 53) | SYRTDGLAYGYVQAID<br>Y (SEQ ID NO: 55) | SGSYIGSSG—VG<br>(SEQ ID NO: 68) | ASDGRPS<br>(SEQ ID NO: 70) | GSSDRTQYTG<br>L (SEQ ID NO: 79) | 297-390 |
|-------|--------------------------|--------------------------------------|---------------------------------------|---------------------------------|----------------------------|---------------------------------|---------|

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises a VHCDR1 amino acid sequence set forth in table 11;

VHCDR2 comprises a VHCDR2 amino acid sequence set forth in table 11;

VHCDR3 comprises a VHCDR3 amino acid sequence set forth in table 11;

VLCDR1 comprises a VLCDR1 amino acid sequence set forth in table 11;

VLCDR2 comprises a VLCDR2 amino acid sequence set forth in table 11; and

VLCDR3 comprises a VLCDR3 amino acid sequence set forth in table 11;

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1.

The specific binding molecule may bind to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM. The  $K_D$  may be less than around 20 nM, less than around 15 nM, or less than around 10 nM. The  $K_D$  may preferably be for binding to SEQ ID NO: 1 or SEQ ID NO: 5. The  $K_D$  for binding to SEQ ID NO: 1 may be around 500 pM to around 15 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 500 pM to around 1 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 829 pM, optionally wherein the specific binding molecule comprises the CDRs of S1E12. The  $K_D$  for binding to SEQ ID NO: 1 may be around 1 nM to around 15 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 2.9 nM to 10 nM, optionally wherein the specific binding molecule comprises the CDRs of NS2A1. The  $K_D$  for binding to SEQ ID NO: 5 may be around 1 nM to around 15 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 3 nM to 8 nM. The  $K_D$  for binding to SEQ ID NO: 1 may be around 5.4 nM, optionally wherein the specific binding molecule comprises the CDRs of NS2A1.

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 218 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 218. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 218. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 218 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 218. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 218.

SEQ ID NO: 218 (S1E12 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLGSNSVGWVRQAPGKAPEWVAGIDTDGEEGYNPALNSR  
LSITRDTSKSQVLSLSSVTSEDVAVYYCGRSYRADGLAYGYVQAIDYWGPGLLTVTSSEKSSGAS  
GESKVDDRVRTQPSSVSGSLGQRVSITCSGSGFIGISSVGWFQQLPGSGLRTIIVASDGRPSGVPDR  
FSMSKSGNTATLTISLQAEDEADYFCGSSDRTQYTGVFSGSGLTLTVLG

The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 220 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1. The CDRs of the specific binding molecule may be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to the CDRs of SEQ ID NO: 220. The CDRs may be 100% identical to the CDRs of SEQ ID NO: 220. The specific binding molecule may comprise an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 220 wherein CDRs are 100% identical to the CDRs of SEQ ID NO: 220. The specific binding molecule may comprise the amino acid sequence of SEQ ID NO: 220.

SEQ ID NO: 220 (NS2A1 amino acid sequence)

QVQLQESGPSLVKPSQTLSTCTVSGFSLSTNSVGWVRQAPGKAPEWVAGIDTDGEEGFNPVLKSR  
LSITRDTSKSQVLSLSNVTSEDVAVYYCGRSYRTDGLAYGYVQAIDYWGPGLLVTISSEKSSGASG  
ESKVDDQSVLTQPSSVSGSPGQTVSITCSGSGYIGSSGVGWFQQLPGSGLRTIIVASDGRPSGVPDGF  
SMKSGNTATLTISLQAEDEADYFCGSSDRTQYTGFLFGSGLTLTVLG

CDRs disclosed herein in connection with different clones may be combined into a specific binding molecule.

The specific binding molecule may comprise one or more CDR sequences disclosed herein in connection a clone identified in any one of tables 1 to 11 wherein the remaining CDR sequences are disclosed herein in connection one or more other clones identified in any one of tables 1 to 11. The specific binding molecule may comprise CDRs from two, three, four, five or six clones identified in any one of tables 1 to 11.

The specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises a VHCDR1 amino acid sequence set forth in any one of tables 1 to 11;

VHCDR2 comprises a VHCDR2 amino acid sequence set forth in any one of tables 1 to 11;

VHCDR3 comprises a VHCDR3 amino acid sequence set forth in any one of tables 1 to 11;

VLCDR1 comprises a VLCDR1 amino acid sequence set forth in any one of tables 1 to 11;

VLCDR2 comprises a VLCDR2 amino acid sequence set forth in any one of tables 1 to 11; and

VLCDR3 comprises a VLCDR3 amino acid sequence set forth in any one of tables 1 to 11;

or for each CDR sequence, an amino acid sequence with



- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to an epitope within SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs of a clone selected from the group consisting of S1D12, E2E8, E1E8, E2A6, E2B7, NS2A1, S1E12, S1B1, S1D9, S1F4, S1G2, S1G10, S2C6, MD9, 412E10, 412B9, 412E6, 412G11, CA2, CA4, CA9, CA12, CB2, CB3, CB7, CC7, CE2, CE3, 3aA6, 3aD6, 3aB7, 3bF4, 3aD3, 3aH6, 3aG3, 3bG4 and NS1G7;

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to an epitope within SEQ ID NO: 1.

The specific binding molecule may comprise the CDRs of a clone selected from the group consisting of S1D12, E2E8, E1E8, E2A6, E2B7, NS2A1, S1E12, S1B1, S1D9, S1F4, S1G2, S1G10, S2C6, MD9, 412E10, 412B9, 412E6, 412G11, CA2, CA4, CA9, CA12, CB2, CB3, CB7, CC7, CE2, CE3, 3aA6, 3aD6, 3aB7, 3bF4, 3aD3, 3aH6, 3aG3, 3bG4 and NS1G7.

Without being bound by theory, the specific binding molecule is thought to bind to its target monovalently. The specific binding molecule may be a monovalent binder.

The specific binding molecule may bind to SEQ ID NO: 1 or a fragment thereof with a  $K_D$  of less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 8 nM, less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1 nM, less than 0.5 nM, less than 0.4 nM, less than 0.3 nM, less than 0.2 nM or less than 0.15 nM.

The specific binding molecule may bind to SEQ ID NO: 1 or a fragment thereof with a  $K_D$  of less than 10 nM.

The specific binding molecule may have a  $K_D$  of 5 to 25 nM. The specific binding molecule may have a  $K_D$  of 5 to 20 nM. The specific binding molecule may have a  $K_D$  of 6 to 25 nM. The specific binding molecule may have a  $K_D$  of 6 to 20 nM.

The specific binding molecule may compete for binding to the same epitope as the epitope bound by mAb423. Without being bound by theory, the epitope of mAb423 is thought to be DHGAE, corresponding to residues 387-391 of SEQ ID NO: 1. It is thought that the binding of mAb423 is Glu-391 specific. Accordingly, mAb423 does not bind to DHGA, corresponding to residues 387-390 of SEQ ID NO: 1. The specific binding molecule may therefore compete for binding to DHGAE, corresponding to residues 387 to 391 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope comprising one or more of residues 387 to 391 of SEQ ID NO:1 may therefore compete for binding to

the same epitope as the epitope bound by mAb423. For example, a specific binding molecule with an epitope within an amino acid sequence comprising residues 369 to 390 of SEQ ID NO: 1 may compete for binding to the same epitope as the epitope bound by mAb423. Preferably, the specific binding molecules that compete for binding to the same epitope as the epitope bound by mAb423 are Glu-391 specific. The specific binding molecule that competes for binding to the same epitope as the epitope bound by mAb423 may therefore be selected from the group consisting of E1E8, E2A6, E2B7, E2E8 and E1B8.

The epitopes of clones directed to the dGAE fragment may include residues thought to be involved in the formation of the "C shaped" architecture of the PHF core (see Figures 2 to 4). The binding of such clones may impair the formation of the "C shaped" architecture of the PHF core or inhibit binding of subunits to existing oligomers by steric hinderance and/or inhibiting the association of key residues.

The specific binding molecule may compete with the binding of a first region within residues 296 to 391 of SEQ ID NO: 1 to a second region within residues 296 to 391 of SEQ ID NO: 1. Accordingly, the specific binding molecule may compete with the binding of a first region within the dGAE fragment to a second region within the dGAE fragment.

The specific binding molecule may compete with the binding of a first region within residues 296 to 390 of SEQ ID NO: 1 to a second region within residues 296 to 390 of SEQ ID NO: 1. Accordingly, the specific binding molecule may compete with the binding of a first region within the dGA fragment to a second region within the dGA fragment.

The specific binding molecule may compete with the binding of a first region within residues 308 to 378 of SEQ ID NO: 1 to a second region within residues 308 to 378 of SEQ ID NO: 1. Accordingly, the specific binding molecule may compete with the binding of a first region within dGAE73 and/or dGAE71 to a second region within dGAE73 and/or dGAE71.

The specific binding molecule may compete with the binding of a first region within residues 296 to 386 of SEQ ID NO: 1 to a second region within residues 296 to 386 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first region within residues 306 to 391 of SEQ ID NO: 1 to a second region within residues 306 to 391 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first region within residues 306 to 386 of SEQ ID NO: 1 to a second region within residues 306 to 386 of SEQ ID NO: 1.

The first and second region may be within the same polypeptide molecule. Accordingly, the specific binding molecule may inhibit the formation of a hairpin structure of the PHF core. The specific binding molecule may inhibit the folding of the PHF core.

The PHF core is composed of eight  $\beta$ -sheets ( $\beta$  1–8) that run along the length of the protofilament, adopting a C-shaped architecture.

Starting from the termini of the PHF, there is a heterotypic cross- $\beta$  interface formed between  $\beta$  1–2 and  $\beta$  8. The N-terminal end of the ordered core is formed by the hexapeptide <sub>306</sub>VQIVYK<sub>311</sub>, (SEQ ID NO: 430) which forms a complementary packing interface with residues 373–378 from the opposing  $\beta$  8 by face-to-face packing of hydrophobic groups. The specific binding molecule may compete with the binding of residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping either 306 to 311 of SEQ ID NO: 1 or residues 373 to 378 of SEQ ID NO: 1 may compete with the binding of residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 367 to 379 of SEQ ID NO: 1 may compete with the binding of residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of S1G2 (or a derivative thereof) may compete with the binding of residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1.

Strands  $\beta$  2 (residues 313–322 of SEQ ID NO: 1) and  $\beta$  8 (residues 368–378 of SEQ ID NO: 1) pack against each other through a polar-zipper motif. The specific binding molecule may compete with the binding of residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping either 313 to 322 of SEQ ID NO: 1 or residues 368 to 378 of SEQ ID NO: 1 may compete with the binding of residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 367 to 379 of SEQ ID NO: 1 may compete with the binding of residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of S1G2 (or a derivative thereof) may compete with the binding of residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1.

A hydrophobic cluster of L324, I326 and V363 stabilizes the region immediately after a turn in the PHF core and the cross- $\beta$  interface between  $\beta$  3 and  $\beta$  7 is further cemented by hydrogen bonds between the sidechains of H328 and T361. The specific binding molecule may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping either 324 to 331 of SEQ ID NO: 1 or residues 356 to 363 of SEQ ID NO: 1 may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1.

For example, a specific binding molecule with an epitope within residues 319 to 331 of SEQ ID NO: 1 may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of CE2 (or a derivative thereof)

may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1.

As a further example, a specific binding molecule with an epitope within residues 355 to 367 of SEQ ID NO: 1 may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of CA4 (or a derivative thereof) may compete with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1.

The two “sides” of the PHF core meet through a  $\beta$ -helix structure that is defined by three  $\beta$ -strands in residues 337 to 368 of SEQ ID NO: 1 ( $\beta$  4–6). The “hinge” region of the PHF core may be defined as residues 337 to 355 of SEQ ID NO: 1 and may alternatively be defined as the “critical abnormal fold”. Two-residue (E342, K343) and three-residue (<sup>347</sup>KDR<sub>349</sub>)  $\beta$ -arc corners punctuate the triangular  $\beta$ -helix geometry, which is closed with a pivotal  $\sim 70^\circ$  glycine conformation (G355). Hydrophobic clustering, aliphatic stacking (V339, L344, V350 and I354) and aromatic stacking (F346) stabilize the interior of the  $\beta$ -helix. Any specific binding molecule disclosed herein with an epitope overlapping residues 337 to 355 of SEQ ID NO: 1 may compete with the binding of residues 337 to 355 of SEQ ID NO: 1 to residues 337 to 355 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 337 to 355 of SEQ ID NO: 1 may compete with the binding of residues 337 to 355 of SEQ ID NO: 1 to residues 337 to 355 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of S1D12 (or a derivative thereof) may compete with the binding of residues 337 to 355 of SEQ ID NO: 1 to residues 337 to 355 of SEQ ID NO: 1.

Specific binding molecules competing for binding of regions described above may have utility in preventing the formation of the PHF core structure and therefore inhibiting tau aggregation. A combination of specific binding molecules competing for binding of multiple regions described above may have increased utility in preventing the formation of the PHF core structure and therefore inhibiting tau aggregation.

Alternatively, the first and second region may be within different polypeptide molecules. Accordingly, the specific binding molecule may inhibit the binding of a first polypeptide to a second polypeptide. The first and second polypeptides may comprise the PHF core.

As illustrated in Figures 5 and 6, a new dGAE unit progressively unfolds and becomes aligned with the structure of an existing oligomer. This attachment sequence may be understood in terms of 3 stages corresponding to progressive binding of key segments of dGAE and their epitopes into the oligomer. As can be seen, the hinge region recognised by S1D12 is the primary site of attachment, followed by progressive symmetrical binding of the other domains.

The specific binding molecule may compete with the binding of a first polypeptide comprising the amino acid sequence GGGQVEVKSEKLDKDRVQSK (SEQ ID NO: 375 – corresponding to residues 333 to 353 of SEQ ID NO: 1) to a second polypeptide comprising the PHF core. The specific binding molecule may compete with the binding of a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising residues 333 to 353 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping residues 333 to 353 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 333 to 353 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 337 to 355 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 333 to 353 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of S1D12 (or a derivative thereof) may compete with the binding of a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 333 to 353 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first polypeptide comprising the amino acid sequence CGSLGNIHHKPG (SEQ ID NO: 376 – corresponding to residues 322 to 333 of SEQ ID NO: 1) to a second polypeptide comprising the PHF core. The specific binding molecule may compete with the binding of a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising residues 322 to 333 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping residues 322 to 333 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 322 to 333 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 319 to 331 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 322 to 333 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of CE2 (or a derivative thereof) may compete with the binding of a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 322 to 333 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first polypeptide comprising the amino acid sequence SLDNITHVP (SEQ ID NO: 377 – corresponding to residues 356 to 364 of SEQ ID NO: 1) to a second polypeptide comprising the PHF core. The specific binding molecule may compete with the binding of a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising residues 356 to 364 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping residues 356 to 364 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 356 to 364 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 355 to 367 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising

the PHF core and/or residues 356 to 364 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of CA4 (or a derivative thereof) may compete with the binding of a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 356 to 364 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first polypeptide comprising the amino acid sequence VQIVYKPVD (SEQ ID NO: 378 – corresponding to residues 306 to 314 of SEQ ID NO: 1) to a second polypeptide comprising the PHF core. The specific binding molecule may compete with the binding of a first polypeptide comprising residues 306 to 314 of SEQ ID NO: 1 to a second polypeptide comprising residues 306 to 314 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping residues 306 to 314 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 306 to 314 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 306 to 314 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope comprising residues 306 to 314 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 306 to 314 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 306 to 314 of SEQ ID NO: 1.

The specific binding molecule may compete with the binding of a first polypeptide comprising the amino acid sequence KKIETHKLTF (SEQ ID NO: 379 – corresponding to residues 369 to 378 of SEQ ID NO: 1) to a second polypeptide comprising the PHF core. The specific binding molecule may compete with the binding of a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising residues 369 to 378 of SEQ ID NO: 1. Any specific binding molecule disclosed herein with an epitope overlapping residues 369 to 378 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 369 to 378 of SEQ ID NO: 1. For example, a specific binding molecule with an epitope within residues 367 to 379 of SEQ ID NO: 1 may compete with the binding of a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 369 to 378 of SEQ ID NO: 1. For instance, a specific binding molecule comprising the CDRs of S1G2 (or a derivative thereof) may compete with the binding of a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising the PHF core and/or residues 369 to 378 of SEQ ID NO: 1.

Without being bound by theory, in any embodiment where the binding of a specific binding molecule competes with the binding of a first region within residues 296 to 391 of SEQ ID NO: 1 to a second region within residues 296 to 391 of SEQ ID NO: 1 (or within the other ranges or residues of SEQ ID NO: 1 set out above), the specific binding molecule may inhibit the tau aggregation. This applies whether the first and second region are within the same or different polypeptide molecules. Any suitable test for determining competitive binding or for screening inhibitors of tau aggregation may therefore be used to confirm that a specific binding molecule competes with the binding of a first region within residues 296 to 391 of SEQ ID NO: 1 to a second region within residues 296 to 391 of SEQ ID NO: 1.

Suitable screening methods include a thioflavin T-assay, a tau-tau immunoassay and an assay for assessing the effects of aggregated tau in cell culture. A suitable assay for assessing the effects of aggregated tau in cell culture is disclosed in UK application no. GB2010620.9 filed on 10 July 2020, and in international (PCT) application no. PCT/EP2021/069138 filed on 9 July 2021 and claiming priority to UK application no. GB2010620.9, both of which are hereby incorporated by reference in their entirety.

The invention provides specific binding molecules with high affinities for their ligands. A specific binding molecule with high affinity for its ligand is advantageous in the present invention, as, generally, less of a specific binding molecule with high affinity for its ligand is required to achieve a particular effect than of a specific binding molecule with lower affinity for the same ligand. For instance, if the specific binding molecule is for therapeutic use, it can be expected that a lower dosage would be required of a specific binding molecule with high affinity for its ligand than of a specific binding molecule with lower affinity for the same ligand. This may be advantageous for the patient, who might require fewer or smaller doses of the specific binding molecule, e.g. antibody, and would also be more economical, as less of the specific binding molecule would be required for the therapy.

The affinity of a binding molecule for its ligand (or binding partner), such as the affinity of an antibody for its target antigen, can be quantitatively defined by the dissociation constant ( $K_D$ ) for a complex of the binding molecule and ligand. The  $K_D$  value of a specific binding molecule, e.g. an antibody, corresponds to the ratio of the binding molecule dissociation rate (i.e. how quickly it dissociates from its ligand) to the binding molecule association rate (i.e. how quickly it binds its ligand). A lower  $K_D$  value corresponds to a higher binding affinity of the binding molecule for its ligand.  $K_D$  may be measured under any suitable conditions for binding of specific binding molecule to its ligand, preferably under conditions identified as optimal. Methods as described in the Examples may be used. Alternatively, any other conditions identified as promoting the binding of the specific binding molecule of the invention to a peptide comprising the epitope within SEQ ID NO: 1 bound by the specific binding molecule may be used. A number of methods by which the  $K_D$  of an interaction between a specific binding molecule and its ligand may be calculated are well-known in the art. Known techniques include SPR (e.g. Biacore) and polarization-modulated oblique-incidence reflectivity difference (OI-RD).

The specific binding molecule may be an isolated specific binding molecule.

As indicated, the specific binding molecule of the invention comprises 6 CDRs consisting of polypeptide sequences. As used herein, "protein" and "polypeptide" are interchangeable, and each refer to a sequence of 2 or more amino acids joined by one or more peptide bonds. Thus, the specific binding molecule may be a polypeptide. Alternatively, the specific binding molecule may comprise one or more polypeptides which comprise the CDR sequences. Preferably, the specific binding molecule of the invention is an antibody or an antibody fragment.

When a CDR sequence is modified by substitution of a particular amino acid residue, the substitution may be a conservative amino acid substitution. However, a substitution of a CDR residue may equally be a non-conservative substitution, in which one amino acid is substituted for another with a side-chain belonging to a different family.

Wherever the invention provides a CDR sequence comprising one, two, or three amino acid substitutions relative to a specified CDR sequence, said one, two, or three amino acid substitutions may be conservative amino acid substitutions. Preferably the CDR sequence comprises two conservative amino acid substitutions. More preferably the CDR sequence comprises one conservative amino acid substitution.

When a FR sequence is modified by substitution of a particular amino acid residue, the substitution may be a conservative amino acid substitution. However, a substitution of a FR residue may equally be a non-conservative substitution, in which one amino acid is substituted for another with a side-chain belonging to a different family.

Wherever the invention provides a FR sequence comprising one, two, three, four or five amino acid substitutions relative to a specified FR sequence, said one, two, three, four or five amino acid substitutions may be conservative amino acid substitutions. Preferably the FR sequence comprises four conservative amino acid substitutions. Preferably the FR sequence comprises three conservative amino acid substitutions. Preferably the FR sequence comprises two conservative amino acid substitutions. More preferably the FR sequence comprises one conservative amino acid substitution.

Amino acid substitutions or additions in the scope of the invention may be made using a proteinogenic amino acid encoded by the genetic code, a proteinogenic amino acid not encoded by the genetic code, or a non-proteinogenic amino acid. Preferably any amino acid substitution or addition is made using a proteinogenic amino acid. The amino acids making up the sequence of the CDRs may include amino acids which do not occur naturally, but which are modifications of amino acids which occur naturally. Providing these non-naturally occurring amino acids do not alter the sequence and do not affect specificity, they may be used to generate CDRs described herein without reducing sequence identity, i.e. are considered to provide an amino acid of the CDR. For example derivatives of the amino acids such as methylated amino acids may be used. The specific binding molecule of the invention be a non-natural molecule, i.e. not a molecule found in nature.

Modifications to the amino acid sequences of the CDRs set out in herein may be made using any suitable technique, such as site-directed mutagenesis of the encoding DNA sequence or solid state synthesis.

Specific binding molecules of the invention comprise CDRs as described herein. Additionally, such molecules may contain linker moieties or framework sequences to allow appropriate presentation of the



CDRs. Additional sequences may also be present which may conveniently confer additional properties, e.g. peptide sequences which allow isolation or identification of the molecules containing the CDRs such as those described hereinbefore. In such cases a fusion protein may be generated.

The CDRs of the specific binding molecule of the invention may be defined as having a certain percentage sequence identity to one or more SEQ ID NOs described herein. Sequence identity may be assessed by any convenient method. However, for determining the degree of sequence identity between sequences, computer programmes that make pairwise or multiple alignments of sequences are useful, for instance EMBOSS Needle or EMBOSS stretcher (both Rice, P. et al., Trends Genet., 16, (6) pp276-277, 2000) may be used for pairwise sequence alignments while Clustal Omega (Sievers F et al., Mol. Syst. Biol. 7:539, 2011) or MUSCLE (Edgar, R.C., Nucleic Acids Res. 32(5):1792-1797, 2004) may be used for multiple sequence alignments, though any other appropriate programme may be used. Whether the alignment is pairwise or multiple, it must be performed globally (i.e. across the entirety of the reference sequence) rather than locally.

Sequence alignments and % identity calculations may be determined using for instance standard Clustal Omega parameters: matrix Gonnet, gap opening penalty 6, gap extension penalty 1. Alternatively, the standard EMBOSS Needle parameters may be used: matrix BLOSUM62, gap opening penalty 10, gap extension penalty 0.5. Any other suitable parameters may alternatively be used.

For the purposes of this application, where there is dispute between sequence identity values obtained by different methods, the value obtained by global pairwise alignment using EMBOSS Needle with default parameters shall be considered valid.

Wherever the invention provides a CDR sequence with at least 85% identity to a specified CDR sequence, said sequence identity is at least about 85% sequence identity and may therefore be at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity. Preferably said sequence identity is at least 90% or at least 95%.

As stated above, the specific binding molecule of the invention is preferably an antibody or an antibody fragment. An "antibody" is an immunoglobulin having the features described hereinbefore. Also contemplated by the invention are variants of naturally occurring antibodies which retain the CDRs but are presented in a different framework, as discussed hereinafter and which function in the same way, i.e. retain specificity for the antigen. Thus, antibodies include functional equivalents or homologues in which naturally occurring domains have been replaced in part or in full with natural or non-natural equivalents or homologues which function in the same way.

When the specific binding molecule of the invention is an antibody, it is preferably a monoclonal antibody. By "monoclonal antibody" is meant an antibody preparation consisting of a single antibody

species, i.e. all antibodies in the preparation have the same amino acid sequences, including the same CDRs, and thus bind the same epitope on their target antigen (by "target antigen" is meant the antigen containing the epitope bound by a particular antibody, i.e. the target antigen of an anti-2N4R antibody is 2N4R) with the same effect. In other words, the antibody of the invention is preferably not part of a polyclonal mix of antibodies.

In an antibody, as described above, the CDR sequences are located in the variable domains of the heavy and light chains. The CDR sequences sit within a polypeptide framework, which positions the CDRs appropriately for antigen binding. Thus, the remainder of the variable domains (i.e. the parts of the variable domain sequences which do not form a part of any one of the CDRs) constitute framework regions. The N-terminus of a mature variable domain forms framework region 1 (FR1); the polypeptide sequence between CDR1 and CDR2 forms FR2; the polypeptide sequence between CDR2 and CDR3 forms FR3; and the polypeptide sequence linking CDR3 to the constant domain forms FR4. In an antibody of the invention the variable region framework regions may have any appropriate amino acid sequence such that the antibody binds to SEQ ID NO: 1 or a fragment thereof via its CDRs. The constant regions may be the constant regions of any mammalian (preferably human) antibody isotype.

In certain embodiments of the invention the specific binding molecule may be multi-specific, e.g. a bi-specific monoclonal antibody. A multi-specific binding molecule contains regions or domains (antigen-binding regions) which bind to at least two different molecular binding partners, e.g. bind to two or more different antigens or epitopes. In the case of a bi-specific antibody, the antibody comprises two heavy and light chains, in the formation as described above, except that the variable domains of the two heavy chains and the two light chains, respectively, are different, and thus form two different antigen-binding regions. In a multi-specific (e.g. bi-specific) binding molecule, e.g. monoclonal antibody, of the invention, one of the antigen-binding regions has the CDR sequences of a specific binding molecule of the invention as defined herein, and thus binds SEQ ID NO: 1 or a fragment thereof. The other antigen-binding region(s) of the multi-specific binding molecule of the invention are different to the antigen-binding regions formed by CDRs of the invention, e.g. have CDRs with sequences different to those defined herein for the specific binding molecule of the invention. The additional (e.g. second) antigen-binding region(s) of the specific binding molecule, e.g. in the bi-specific antibody, may also bind SEQ ID NO: 1 or a fragment thereof, but at a different epitope to the first antigen-binding region which binds to SEQ ID NO: 1 or a fragment thereof (which has the CDRs of the specific binding molecule of the invention). Alternatively, the additional (e.g. second) antigen-binding region(s) may bind additional (e.g. a second), different antigen(s) which is(are) not SEQ ID NO: 1 or a fragment thereof. In an alternative embodiment, the two or more antigen-binding regions in the specific binding molecule, e.g. in an antibody, may each bind to the same antigen, i.e. provide a multivalent (e.g. bivalent) molecule.

The specific binding molecule may be an antibody fragment or synthetic construct capable of binding human SEQ ID NO: 1 or a fragment thereof. Antibody fragments are discussed in Rodrigo et al., *Antibodies*, Vol. 4(3), p. 259-277, 2015. Antibody fragments of the invention are preferably monoclonal

(i.e. they are not part of a polyclonal mix of antibody fragments). Antibody fragments include, for example, Fab, F(ab')<sub>2</sub>, Fab' and Fv fragments. Fab fragments are discussed in Roitt et al, Immunology second edition (1989), Churchill Livingstone, London. A Fab fragment consists of the antigen-binding domain of an antibody, i.e. an individual antibody may be seen to contain two Fab fragments, each consisting of a light chain and its conjoined N-terminal section of the heavy chain. Thus, a Fab fragment contains an entire light chain and the VH and CH1 domains of the heavy chain to which it is bound. Fab fragments may be obtained by digesting an antibody with papain.

F(ab')<sub>2</sub> fragments consist of the two Fab fragments of an antibody, plus the hinge regions of the heavy domains, including the disulphide bonds linking the two heavy chains together. In other words, a F(ab')<sub>2</sub> fragment can be seen as two covalently joined Fab fragments. F(ab')<sub>2</sub> fragments may be obtained by digesting an antibody with pepsin. Reduction of F(ab')<sub>2</sub> fragments yields two Fab' fragments, which can be seen as Fab fragments containing an additional sulfhydryl group which can be useful for conjugation of the fragment to other molecules.

Fv fragments consist of just the variable domains of the light and heavy chains. These are not covalently linked and are held together only weakly by non-covalent interactions. Fv fragments can be modified to produce a synthetic construct known as a single chain Fv (scFv) molecule. Such a modification is typically performed recombinantly, by engineering the antibody gene to produce a fusion protein in which a single polypeptide comprises both the VH and VL domains. scFv fragments generally include a peptide linker covalently joining the VH and VL regions, which contributes to the stability of the molecule. The linker may comprise from 1 to 20 amino acids, such as for example 1, 2, 3 or 4 amino acids, 5, 10 or 15 amino acids, or other intermediate numbers in the range 1 to 20 as convenient. The peptide linker may be formed from any generally convenient amino acid residues, such as glycine and/or serine. One example of a suitable linker is Gly<sub>4</sub>Ser. Multimers of such linkers may be used, such as for example a dimer, a trimer, a tetramer or a pentamer, e.g. (Gly<sub>4</sub>Ser)<sub>2</sub>, (Gly<sub>4</sub>Ser)<sub>3</sub>, (Gly<sub>4</sub>Ser)<sub>4</sub> or (Gly<sub>4</sub>Ser)<sub>5</sub>. However, it is not essential that a linker be present, and the VL domain may be linked to the VH domain by a peptide bond. An scFv is herein defined as an antibody fragment.

The specific binding molecule may be an analogue of an scFv. For example, the scFv may be linked to other specific binding molecules (for example other scFvs, Fab antibody fragments and chimeric IgG antibodies (e.g. with human frameworks)). The scFv may be linked to other scFvs so as to form a multimer which is a multi-specific binding protein, for example a dimer, a trimer or a tetramer. Bi-specific scFvs are sometimes referred to as diabodies, tri-specific scFvs as triabodies and tetra-specific scFvs as tetrabodies. In other embodiments the scFv of the invention may be bound to other, identical scFv molecules, thus forming a multimer which is mono-specific but multi-valent, e.g. a bivalent dimer or a trivalent trimer may be formed. Synthetic constructs that can be used include CDR peptides. These are synthetic peptides comprising antigen-binding determinants. Peptide mimetics can also be used. These molecules are usually conformationally-restricted organic rings that mimic the structure of a CDR loop and that include antigen-interactive side chains.

The specific binding molecule may be a scAb (single-chain antibody). A scAb may comprise an scFv. The scFv may comprise a variable heavy domain and a variable light domain optionally joined by a flexible protein linker as described above. A scAb may further comprise a light chain constant domain. The light chain constant domain may be human, such as a human C $\kappa$  domain.

The antibody or antibody fragment of the invention may be a chimeric antibody, or preferably may be humanised. This is particularly the case for monoclonal antibodies and antibody fragments. Humanised or chimeric antibodies or antibody fragments are desirable when the molecule is to be used as a human therapeutic. Therapeutic treatment of humans with murine antibodies can be ineffective for a number of reasons, e.g. a short *in vivo* half-life of the antibody; weak effector functions mediated by the mouse heavy chain constant region due to low recognition of the murine heavy chain constant region by Fc receptors on human immune effector cells; patient sensitisation to the antibody, and generation of a human anti-mouse antibody (HAMA) response; and neutralisation of the mouse antibody by HAMA leading to loss of therapeutic efficacy.

As detailed above, the isotype of an antibody is defined by the sequence of its heavy chain constant regions. The chimeric antibody of the invention may have the constant regions of any human antibody isotype, and any sub-class within each isotype. For instance, the chimeric antibody may have the Fc regions of an IgA, IgD, IgE, IgG or IgM antibody (i.e. the chimeric antibody may comprise the constant domains of heavy chains  $\alpha$ ,  $\delta$ ,  $\epsilon$ ,  $\gamma$ , or  $\mu$ , respectively), though preferably the antibody of the invention is of the IgG isotype. Thus, the chimeric antibody of the invention may be of any isotype. The light chain of the chimeric antibody may be either a  $\kappa$  or  $\lambda$  light chain, i.e. it may comprise the constant region of a human  $\lambda$  light chain or a human  $\kappa$  light chain. A chimeric antibody fragment is, correspondingly, an antibody fragment comprising constant domains (e.g. an Fab, Fab' or F(ab')<sub>2</sub> fragment). The constant domains of a chimeric antibody fragment of the invention may be as described above for a chimeric monoclonal antibody.

Chimeric antibodies may be generated using any suitable technique, e.g. recombinant DNA technology in which the DNA sequence of the murine variable domain is fused to the DNA sequence of the human constant domain(s) so as to encode a chimeric antibody. A chimeric antibody fragment may be obtained either by using recombinant DNA technology to produce a DNA sequence encoding such a polypeptide, or by processing a chimeric antibody of the invention to produce the desired fragments, as described above. Chimeric antibodies can be expected to overcome the problems of a short *in vivo* half-life and weak effector functions associated with using a murine antibody in human therapy, and may reduce the probability of patient sensitisation and HAMA occurring. However, patient sensitisation and HAMA may still occur when a chimeric antibody is administered to a human patient, due to the presence of murine sequences in the variable domains.

Preferably the antibody or antibody fragment of the invention is therefore fully humanised. A humanised antibody is an antibody derived from another species, e.g. a mouse, in which not only are the constant domains of the antibody chains replaced with human constant domains, but the amino acid sequences of the variable regions are modified, in particular to replace the foreign (e.g. murine) framework sequences with human framework sequences, such that, preferably, the only non-human sequences in the antibody are the CDR sequences. A humanised antibody can overcome all the problems associated with therapeutic use of a non-human antibody in a human, including avoiding or minimising the probability of patient sensitisation and HAMA occurring.

Antibody humanisation is generally performed by a process known as CDR grafting, though any other technique in the art may be used. CDR grafting is well described in Williams, D.G. et al., *Antibody Engineering* Vol. 1, edited by R. Kontermann and S. DObel, Chapter 21, pp. 319-339. In this process, a chimeric antibody as described above is first generated. Subsequent humanisation of the foreign, e.g. murine, variable domains involves intercalating the murine CDRs from each immunoglobulin chain within the FRs of the most appropriate human variable region. This is done by aligning the murine variable domains with databases of known human variable domains (e.g. IMGT or Kabat). Appropriate human framework regions are identified from the best aligned variable domains, e.g. domains with high sequence identity between the human and murine framework regions, domains containing CDRs of the same length, domains having the most similar structures (based on homology modelling), etc. The murine CDR sequences are then grafted into the lead human framework sequences at the appropriate locations using recombinant DNA technology, and the humanised antibodies then produced and tested for binding to the target antigen. The process of antibody humanisation is known and understood by the skilled individual, who can perform the technique without further instruction. Antibody humanisation services are also offered by a number of commercial companies, e.g. GenScript (USA/China) or MRC Technology (UK). Humanised antibody fragments can be easily obtained from humanised antibodies, as described above.

Thus, the antibody or antibody fragment of the invention may be derived from any species, e.g. it may be a murine antibody or antibody fragment. It is preferred, however, that the antibody or antibody fragment is a chimeric antibody or antibody fragment, i.e. that only the variable domains of the antibody or antibody fragment are non-human, and the constant domains are all human. Optimally, the antibody or antibody fragment of the invention is a humanised antibody or antibody fragment.

The invention also provides a composition comprising the specific binding molecule described above. At least 90 % of the specific binding molecules in the composition that bind to an epitope within SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM. Techniques by which  $K_D$  of the binding molecule may be measured, and conditions under which the  $K_D$  may be measured, are described above. In an alternative embodiment, a composition is provided comprising the specific binding molecule of the invention in which at least 90% of the specific binding molecules in the composition that bind to an epitope within SEQ ID NO: 1 have the CDRs as described hereinbefore,

and preferably contain two copies of the CDRs in each molecule (e.g. in an antibody). In a yet further embodiment, a composition is provided comprising the specific binding molecule of the invention in which the specific binding molecule is an antibody or fragment thereof and at least 90% of the antibodies or fragments in said composition are said antibodies or fragments of the invention (i.e. contain the CDRs as described hereinbefore, preferably contain two copies of the CDRs described hereinbefore). Further preferred compositions according to the invention comprise antibody fragments, monoclonal antibodies or their fragments, chimeric antibodies or their fragments, or humanized antibodies or their fragments, of the invention.

In an alternative statement of the first aspect of the invention, the invention provides a specific binding molecule that binds to an epitope within SEQ ID NO: 1. In this alternative first aspect, the specific binding molecule of the invention is defined without reference to the binding affinity with which antibody mAb423. This alternative first aspect of the invention is disclosed in combination with any and all of the features identified above in relation to the first aspect of the invention and any and all of the features identified below in relation to subsequent aspects of the invention.

According to a second aspect, the invention provides a composition comprising a specific binding molecule according to the first aspect of the invention, wherein at least 90% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM.

The term "composition" as used herein means a product (e.g. a solution or preparation) containing at least the specific binding molecule of the invention. The composition should be made up in a form in which the specific binding molecule may be stably stored, i.e. a form in which the specific binding molecule does not degrade or become denatured, or lose its structure or activity. Suitable conditions in which an antibody may be stored are well known to the skilled person. The composition of the invention may be a liquid composition (i.e. a solution), such as an aqueous composition (i.e. a solution made up in water) or a composition made up in solvent, such as one or more organic solvents, or primarily in a solvent. Such a solvent may be polar or non-polar. Alternatively, the composition may be a powder, such as a lyophilised powder, or may be in any other suitable form for the storage of a specific binding molecule.

At least 90% of the specific binding molecules in the composition that bind to SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM. Preferably at least 95%, 96%, 97%, 98% or 99% of the specific binding molecules in the composition that bind to SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM, 20 nM, 15 nM or 10 nM. In this embodiment the specific binding molecule has the definition described hereinbefore but is not necessarily a specific binding molecule of the invention, i.e. all specific binding molecules which bind SEQ ID NO: 1 are assessed to determine if at least 90% have the required  $K_D$ . Preferably the specific binding molecules to be assessed are antibodies or their fragments. The skilled person is able to calculate the  $K_D$  of the binding of a specific binding

molecule to its ligand. Conditions under which the  $K_D$  of specific binding molecules of the invention may be calculated, and methods by which this may be achieved, are mentioned above. By 90% is meant 90% of the number of specific binding molecules which bind SEQ ID NO: 1 (i.e. 9 out of 10 specific binding molecules which bind SEQ ID NO: 1), not 90% w/w. As noted, at least 90% of the specific binding molecules which bind SEQ ID NO: 1 bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM. This does not preclude that the composition contains any concentration of specific binding molecules which bind other antigens. This provides a composition in which the molecules which bind to SEQ ID NO: 1 are largely uniform, i.e. have similar functionality.

At least 90% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 may bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM.

At least 95% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 may bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM.

At least 99% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 may bind with a  $K_D$  of less than 25 nM, preferably less than 20 nM, 15 nM or 10 nM.

The composition (and preparation) of the invention may contain additives, which may be advantageous for storage of a specific binding molecule such as an antibody or antibody fragment. For instance, if the composition is a liquid, the composition may advantageously comprise a high concentration of a cryoprotective agent, such as glycerol or ethylene glycol, e.g. at least 20%, at least 25%, at least 30%, at least 40% or at least 50% glycerol or ethylene glycol. Percentages may be expressed as w/w or v/v. A cryoprotective agent prevents the composition from freezing at low temperature, protecting the specific binding molecule from ice damage during storage. Concentrated sucrose (e.g. at least 250 mM, at least 500 mM, at least 750 mM or at least 1M sucrose) may advantageously be comprised within a liquid composition. Liquid compositions may also comprise one or more antioxidants, e.g. 3-mercaptoethanol or dithiothreitol, one or more metal chelating agents, e.g. ethylenediaminetetraacetic acid (EDTA), and one or more carrier proteins, particularly bovine serum albumin (BSA). The liquid composition may preferably comprise up to 1% BSA, e.g. 0.1-0.5% BSA. The composition of the invention may be at a pH of 5-8, e.g. 6-8, 7-8 or 7-7.5. The pH may be maintained by addition of a buffer to the composition, e.g. Tris (i.e. tris(hydroxymethyl)aminomethane), HEPES or MOPS. For instance, the composition may contain 5-50 mM HEPES, e.g. 10-20 mM HEPES. Lyophilised compositions (or compositions) of the invention may contain one or more stabilisers, such as a polyol, e.g. glycerol or sorbitol, and/or a sugar, e.g. sucrose, trehalose or mannitol. The composition may also contain additional components as described for compositions described hereinafter.

According to a third aspect, the invention provides a nucleic acid molecule comprising a nucleic acid sequence encoding a specific binding molecule according to the first aspect of the invention.

The nucleic acid sequence may be selected from the group consisting of SEQ ID NOs: 43, 219, 249, 251, 253, 380 to 411, and 431 or a nucleic acid sequence with at least 70% identity to any one of SEQ ID NOs: 43, 219, 249, 251, 253, 380 to 411, and 431. Preferably the nucleic acid sequence may have at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to any one of SEQ ID NOs: 43, 219, 249, 251, 253, 380 to 411, and 431.

SEQ ID NO: 380 (S1D12 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTGAACAACAATGCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTCGCTTGTGGGTTGTAGCAGTGATGGAACGTGTTACTATAATTCGGCCCTGAA  
ATCCCGGCTCGACATCACCAGGGACACCTCCAAGAACCAGATCTCCCTGTCACTGAGCAGCGTT  
ACAACGTACGACGCGGCCGTGTACTATTGTACAAGAGGCCATTATAGTATTTATGGTTATGACTA  
TCTTGGCACTATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCT  
TCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGT  
CCGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTCCGGGGGTG  
GTAATAGTGTGGGCTGGTACCAACACCTCCCAGGCTCAGGCCTCAAAACCATCATCTATGATACT  
AACAGTCGACCCTCGGGGGTCCCGGACCGATTCTCTGGCTCCAGGTCTGGCAACACGGCCACC  
CTAACCATCAACTCGCTCCAGGCTGAGGACGAGGGTGATTATTACTGTGTAACGGGTGACAGCA  
CTACTCATGATGATCTTGTCTGGCAGCGGGACCAGGCTGACCGTCTGCGG

SEQ ID NO: 219 (S1E12 nucleotide sequence)

CAGGTGCAGTTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCCGGATTCTCATTAGGCAGCAATTCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAGGTCTCTTTGTCAATTGAGCAGCGTG  
ACAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGGCTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAA  
ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACAGGGTCGTGCGGACTCAACCGTCTCC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTTCATCGGTATTAGTA  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCTCAGAACCATCATCGTGCGGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAA  
TATACTGGAGTTTTCTGGCAGCGGGACCAGGCTGACCGTCTGCGG

SEQ ID NO: 381 (S1G2 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCAATTGAGCAGCGTG  
ACAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGGCTGATGGTCTTGCTTACG



GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAA  
ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCCGTGGTGAAGCTTCTCAGCCGTCTCC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTTCATCGGTATTAGTA  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCCT  
TATACTGGGGTCTTCGGCAGCGGGACCAGGCTGACCGTCTGGGT

SEQ ID NO: 388 (S1B1 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTGTCCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCATTGAGCAGCGTG  
ACAAGTGAGGACACGGCCGTGTACTACTGTGTAAGAAGTTATAGGACTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAA  
ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGAAGCTTCTCAGCCGTCTCC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTTCATCGGTATTAGTA  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCCTCATCGTTGCGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACCGATTCTCTAACTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAA  
TATACTGGAGTTTTTCGGCAGCGGGACCAGGCTGACCGTCTGGT

SEQ ID NO: 382 (CA4 nucleotide sequence)

CAGGTTTCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAGCTATTCCGTATACTGGGTCCGCCAGGCTCCAGGCC  
AGGCACTGGAGTGGATTAGTATTATGTATGCTAGTGGAAGAGTAGACTATAACCCGGCCCTGAAA  
TCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAATTCTCCCTGTCTATTGAGCAGCGTGA  
CAACTGAGGACACGGCCGTCTACTACTGTACAAGAGGAATCGAAAACCTGGGGCCCCGGACTCCT  
GGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACGAC  
ATCCAGGTGACCCAGTCTCCGTCCCTGTCTGCATCTCTAACAGAGAGAGTCTCCATCACTTG  
CCGGACCAGTCAGAGCGTTAACAATTACTTAAGCTGGTATCAGCAGAAACCAGGGCAAGCTCCT  
AAGCTCCTGATCTATTATGCAACCAGATTGTACACCGATGTCCCATCCCGTTTCAAGTGGCAGTGG  
ATCTGGGACAGATTACACCCTCACCATCACCAGCCTGGAGGCGGACGACACTGCAACTTATTAC  
TGTCTACAATATGATAGTACACCTCTTGCAATTCGGCGGTGGGACCAACGTGGAAATCAAACGG

SEQ ID NO: 383 (CE2/E1B8 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAACTATCCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGATTGGTAACATAGAAAATGATGGAAGTGCGAAGTATGCCTCGGCCCTGAA  
ATCCCCGACTCAGCATCACCAGGGACACCTCCAAGAACCAAGTCTCCCTGTCACTGAGCAGCGCG  
ACAACTGAGGACACGGCCGTTTACTACTGTGGAAGAGAATTCCGTGGGAGTGATGGTTATACTT  
ATTCGTTGATATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCT  
TCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGT  
CCAAGTCCCTGGGCCAGAGTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGG  
TAATTATGTGAGCTGGTTCCAACAGGTCCCAGGATCAGCCCCCAAATCCTCATCTATGGTGCAA  
CCAGTCGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTC  
TGACCATCACCTCGCTCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTATGACGGCAG  
TAGCAGTGGTGTTCGCGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 249 (E2E8 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCGACCGTGGTGTAGCCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGGTTGGTACTATGCGTAGTGGTGGAAACGATAGACTATAACCCGGCCCTGAA  
ATCCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTTTTCTGTCACTGAGCAGCGTC  
ACAACTGAGGACATGGCCATGTACTACTGTGCCAGAGGTTATTTGAGCGGTGATCGTTATGCCT  
GGGGCCGAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGT  
CTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCCAAGTCCCTGGGCCAGA  
GTGTCTCCATCGCCTGCTCTGGAAGCAGGAGCGACATTGGATATGGTAATTATGTGAGCTGGTT  
CCAACAGATCCCAGGATCAGCCCCCAAATCCTTATTTATGATACAAACACTCGGGCCTCGGGG  
GTCCCCGACCGATTCTCCGGCGCCAGGTCTGGCAACACAGCAAACTGACCATCAACTCGCTCC  
AGGCTGAGGACGAGGCCGATTATTACTGTGCAAATATTGACAGTAGTCGCAGTCATCTTTTCGGC  
AGTGGCACCAGACTGACCGTCCTGGGT

SEQ ID NO: 251 (E1E8 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACTGACTGGGGTGTAGCTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTACGATGCGTAGTGGTGGGACTACAGACGATAACCCGGCCCTGA  
AATCCCGCCTCAGCATCACCAGGGACACCTCTAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACATGGCCATGTACTACTGTGCCAGAGGTTATTTGAGTGGTGTGCATTATGCCT  
GGGGCCGAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGT  
CTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTATCTGGGTCCCTGGGCCAGA  
GTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTGGGAGATGGTAGATATGTGAGCTGGTT  
CCAACAGGTCCCAGGATCAGCCCCCAAATCCTCATCTATGATACAACCAGTCGAGCCTCGGGG  
GTTCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTCATCATCACCTCGCTCC

AGGCTGAGGACGAGGCCGATTATTACTGTGCATCTATTGACAGCGGTAACAATCTTCTTTTCGGC  
AGCGGCACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 431 (NS2A1 nucleotide sequence)

CAGGTGCAGTTGCAGGAGTCGGGACCCAGCCTCGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAAGCACTAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTTTAATCCAGTCCTTAA  
GTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCAATTGAGCAACGTG  
ACAAGTGAAGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGACTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACTATCTCCTCAGAAGGTAA  
ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCACTGTGCTGACTCAGCCGTCTCC  
GTGTCCGGGTCCCCGGGCCAGACAGTCTCCATCACCTGCTCTGGAAGCTATATCGGTAGTAGTG  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACGGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAA  
TATACTGGACTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 384 (CE3 nucleotide sequence)

CAGGTGCGACTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCGTCACC  
TGCACGGTCTCTGGATTCTCATTGATCAGCAATGCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTCGCTTGCTGGTTGTAGCAGTGATGAAAAGTGTTACTATAACTCGGCCCTGAA  
ATCCCGGCTCGACATCACCAGGGACACCTCGAAGAACCAGATCTCCCTGTCACTGAGCAGCGTC  
ACAAGTACGACGCGGCCGTGTACTACTGTACAAGAGGCTATTATCCTGTTTATGGTTATGACTA  
TCTTGGCACTATCGACTACTGGGGCCCCGGACTCCTGGTCAACCGTCTCCTCAGAAGGTAAATCT  
TCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAAGCTGTGCTGACTCAACCGTCTCCGTGT  
CTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGTAGAA  
ATGATGTAGCCTGGTTCCAACAACTCCCAGGATCAGGCCTCAGAACCATCATCTATGGTACTACC  
AGTCGACCCTCAGGTATCCCGGACCGATTCTCCGGCTCCAAGTCTGGCGTTACGGCCACCCTGA  
CCATCGACTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGCCTCTGGTGACAGTAGTGC  
CATTAATGATATTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 385 (CB7 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACTAATCTCGTGTAGGTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGGTTAGTAACATACGGAGTGGTGGAACATACATGGTATAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACCAGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACACGGCCGTATATTATTGTGCAAGAGATTCTCTGGTGATCTTTATGCGTATG  
ATTACTGGGGCCCAGGACTCCTGGTCAACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGG  
CGAGTCTAAAGTGGATGACCAAGCCGTGCTGACTCAGCCGTCTCCGTGTCCAGGTCCCTGGG  
CCAGAGTGTCTCCATGACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATATGGCCT

GGTTCCAACAGGTTCCAGGATCAGCCCCAACTCCTCATCTATGGTGCAACCAGTCGAGCCTC  
GGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCAGCTC  
GCTCCAGGCTGAGGACGAGGCCGATTACTACTGTGCATCTTATGACAGCACTAGCGGGGGTGTCT  
TTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 386 (CC7 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCACTAACCAGCAATGCTGTGATCTGGGTCCGGCAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTTTGATAGATGTTGATGGAGATGCAGCCTATGACCCAGCCCTTAA  
GTCCCGCCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCCCTTTCACTGCGCAGCGTG  
ACAACTGAGGACACGGCCGTGTACTACTGTGCAAGAGACTATGGTAGTTGGGGTTATGTTCCG  
ACATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGC  
GTCTGGCGAGTCTAAAGTGGATGACAGGGTCGTGCGGACTCAACCGTCCTCCGTGTCTGGGTC  
CCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTACATCACTGGTAGTTCTGTAGGCTGG  
TTCCAACAGGTCCCAGGATCGGGCCTCAAACCGTCATCTATGACAATAACGATCGACCCTCAG  
GGGTCCCCGACCGATTCTCTGGCTCCAAGTCGGGCGACACAGCCACCCTGACCATCAGCTCGC  
TCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTATGACACCAGTAACATTGGTCTTTTC  
GGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 387 (412E10 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGCTTCTCTGTAATAAGCGATTCTGTAGCCTGGGTCCGCCAGGCTCCAGGAA  
AAGTGCCGGAGTGGCTTGGTGCTAGCGGCAGTTCTGGAACAAATACTATAACCCGGCCCTAA  
ATCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGATACGGCCGTGTACTACTGTGCGAGAGGTATTATCGCCGGTGTAGATGTCTGGG  
GCCGAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAA  
AGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCTGGGTCCCTGGGCCAGAGGGT  
CTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATGTGGGCTGGTACCAA  
CAGGTCCCAGGATCAGCCCCAACTCCTCATCTATGGTACAGCCATTCGAGCCTCGGGGGTCC  
CCGACCGATTCTCCGGCTCCAGGTCTGGGGACACAGCCACCCTTACCATCACCTCGCTCCAGG  
CTGAGGACGAGGCCGATTACTACTGTGCATCTTATCAGAGTAATTACGCTTTTTTCGGCAGCGGG  
ACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 43 (E2B7 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACAGCTGGGGTGTAGCTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTACCATGCGTAGTGGTGGTGGTACAGAATATAATCCGGCCCTGAA  
ATCCCGCCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGACATGGCCATGTACTACTGTGCCAGAGGTTATTTGAGTGGTATTATTATGCCTG

GGGCCGAGGACTCCTAGTCTCCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCT  
AAAGTGGATGACCAGGCTGTGCTGACTCAGCTGTCTCCGTGTCTGGGTCCCTGGGCCAGAGG  
GTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGAGATGGTGATTATGTGGGCTGGTTCC  
AACAGCTCCCAGGATCAGCCCCCAAACCTCTCATCTATAGTGCGCGCAATCGAGCCTCGGGGT  
CCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTAACCATCACCTCGCTCCAG  
GCTGAGGACGAGGCCGATTATTACTGTGCATCTATTGACACCAGTCGCTCTCACATTTTCGGCAG  
CGGGACCAGACTGACCGTCTGGGT

SEQ ID NO: 253 (E2A6 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACTGACTGGGGTGTAGCTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTACGATGCGTAGTGGTGGGACTACAGACGATAACCCGGCCCTGA  
AATCCCGCCTCAGCATCACCAGGGACACCTCTAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACATGGCCATGTACTACTGTGCCAGAGGTTATTTGAGTGGTGTGCATTATGCCT  
GGGGCCGAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGT  
CTAAAGTGGATGACCGGGTCGTGCGGACTCAGCCGTCTCCGTGTCCAAGTCCCTGGGCCAGA  
GTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGAGCTGGTAATTATGTGGGCTGGTT  
CCAACAGGTCCCAGGATCAGCCCCCAAACCTCTCATCTATGGTGCAACCAATCGAGCCTCGGGG  
GTCCCCGCCCGATTCTCAGGCTCCAAGTCTGGCGTCACAGCGACTCTAACCATCACCTCGCTCC  
AGGCTGAGGACGAGGCCGATTATTACTGTGCATCTATTGACACCAGTCGCTCTCACATTTTCGGC  
AGCGGGACCAGGCTGACCGTCTGGGT

SEQ ID NO: 389 S1D9 nucleotide sequence

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATAGTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAATCAAGTCTCTTTGTCAATTGAGCAGAGTG  
ACAAGTGAGGACACGGCCGTTTACTACTGTGGAAGAACTTATAGGACTGATGGTTATGCTTACGG  
TTATGTCCAAGCCATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAA  
TCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCGGGTCATGCTGACTCAGCCACCCTCCG  
TGTCGGGTCCCCGGGCCAGACGGTATCCATCACCTGCTCTGGAAGCTTCATCGGTATTAGTAG  
TGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCCTCATTTTTGCGAGTGACGGT  
CGACCCTCAGGGGTCCCCGATCGATTCTCTAACTCCAAATCGGGCAACACAGCCACCCTGACCA  
TCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAATA  
TACTGGAGTTTTTCGGCAGCGGGACCAGGCTGACCGTCTGAGT

SEQ ID NO: 390 (S1F4 nucleotide sequence)

CAGGTGCAGTTGCAAGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAAGTAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAAGTCTCATTGTCATTGAGCAGCGTT  
ACAAGTGAGGACACGGCCGTGTACTACTGTGTAAGAAGTTATAGAGCTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGCTCACCATCTCCTCAGAAGGTAA  
ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCCGTGGTGAAGTCAAGCGTCTCCTC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTTCATCGGTATTAGTA  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCGTCATCGTGGCGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACCGATTCTCTAACTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAA  
TATACTGGAGTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 391 (S1G10 nucleotide sequence)

CAGGTTCAAGTTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACCT  
GCACGGTCTCTGGATTCTCATTAAACCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAAA  
GGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
TCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAAGTCTCATTGTCATTGAGCAGCGTGA  
CAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGAGCTGATGGTCTTGCTTACGG  
TTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAA  
TCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCTCA  
TGTCCGGGTCCCTGGGCcAGAGGGTCTCCATCACCTGTTCTGGAAGCTTCATCGGTATTAGTAGT  
GTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGACGGT  
CGACCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGACCA  
TCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAATA  
TACTGGAGTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 392 (S2C6 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAATCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
GTCCCAATATGCAGCTAGTGATCCGGACACCTCCAAGAGTCAAGTCTCCTTGTCATTGAGCAGC  
GTGACAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAACTTATAGGACTGATGGTTTTGCTTA  
TGGTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGCTCACTATCTCCTCAGAAGGT  
AAATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTT  
CCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTTTATTGGTATTAG  
TAGTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGAC  
GGTCGACCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGA

CCATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCA  
ATATACTGGAGTTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 393 (MD9/MoD9 nucleotide sequence)

CAGGTGCGGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGTCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAGGGAATCTATAGCCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGCTTGGTGGTGTAGGCATTGATGGAACCTCATACTATAGCCCGGCCCTGAA  
ATCCCGGCTCAGTATCACGAGGGACACCTCCAAGAGCCAAGCCTCCCTGTCACTGAGCAGCGT  
GGCAACTGAGGACACGGCCATGTATTACTGTGCACGTAATTATATTGATTTTCGAGTACTGGGGCC  
CAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAAAGT  
GGATGACCAGGCTGTGCTGACTCAACTGTCCTCCGTATCTGGGTCCCTGGGCCAGAGGATCTCC  
ATCACCTGCTCTGGAAGCAGCAGCAACGTTGGTATATATGATGTGTCTTGGTTCCAACAACCTCCC  
AGGATCAGGCCTCAGAACCGTCATCTATGGTACTAACAATCGACCCTCGGGTGTCCCGGACCGA  
TTCTCCGGCTCCAGGTCTGGCAACACGGCCACCCTGACTATCAGCTCTCTCCAGTCTGAGGACG  
AGGCCATTTATTACTGTGCTGCTGGTGACAGCAGTACTATTGCTGTTTTTCGGCAGCGGGACCAG  
GCTGACCGTCCTGGGT

SEQ ID NO: 394 (412B9 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCTGTAATAAGCGATTCTGTAGCCTGGGTCCGCCAGGCTCCAGGAA  
AAGTGCCGGAGTGGCTTGGTGTAGCGGCAGTTCTGGAACAAAATACTATAACCCGGCCCTAAA  
ATCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGATACGGCCGTGTACTACTGTGCGAGAGGTATTATCGCCGGTGTAGATGTCTGGG  
GCCGAGGACTCCTGGTCTCCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAA  
AGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCTGGGGCCCTGGGCCAGAGGGT  
CTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTGATTATGTGGGCTGGTACCAA  
CAGGTCCCAGGATCAGCCCCAACTCCTCATCTATGGTGCAGCCAGTCGAGCCTCGGGGGTC  
CCCAGCCGATTCTCTGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCAGCTCGCTCCAGG  
CTGAGGACGAGGCCGATTATTACTGTGCATCTTATGACAGCAGTGACGGTGGTGTTCGCGAG  
CGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 395 (412E6 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCAGAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACTATGGTGTGGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTAACATATATAGTGGTGGGTCTACATACTATAACCCGGCCCTGAA  
ATCCCGACTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAACAGCGTG  
ACACTTGAGGACACGGCCGTTTATTACTGTGGAAGAGGAGGTGTTGGGAGTGTGACGTCTGGG  
GCCGAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAA  
AGTGGATGACCAGGCTGTGCTGACTCAGCCGCCCTCCGTGTCCGGTTCGCCAGGCCAGAGGGT  
CTCCATCACCTGCTCTGGAGGCAGGAATAACATCGGGCGTGGTACCTTTGTGGAAGTGGTACCAG

CAACTCCCAGGATCAGGCCTCAAAACCGTCATCTATGGTACTGACCGTCGACCACCGGGGGTCC  
CGGACCGATTCTCCGGCTCCAAGACTGGCAACGCGGCCACCCTGACCATCACCTCCCTCCAGG  
CTGAGGACGAGGCCGATTATTGGTGTGCTACTTATGATTACAGTAATGATATGATTATTCTCGGC  
AGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 396 (412G11 nucleotide sequence)

CAGGTGCGGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGTACGGTCTCTGGATTCTCATTAACCAGCTATGCTTTAGGCTGGGTCCGCCAGGCTCCAGGAA  
GGGCTCCGGAGTGGATTGGTAACATATGGAGGGGTGGACGAATAGAATATAACCCGGCCCTGA  
AATCCCGGCTCAGCATCACTAGGGACACCTCCAAGAGCCAAGTCTCGCTGTCACTGAGCAGCGT  
GACAACTGAGGATACGGCCGTGTACTACTGTTCAAGAAGTGGCGGCGACTGGGGCCCAGGACT  
CCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGAC  
CAGGCTGTGCTGACTCAGCCGTCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
TGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATGTGGGCTGGTACCAACAGGTCCCAG  
GATCAGCCCCCAAACCTCCTCATCTATGGTGCAACCAGTCGAGCCTCGGGGGTCCCCGACCGATT  
CTCCGGCTCCAGGTCTGAGAACACAGCCACCCTGACCATCAGCTCCCTCCAGGCTGAGGACGA  
GGCCGATTATTACTGTGCGTCTTATGATAGGAGTGAGAGTGTTGTGTTTCGGCAGCGGGACCAGA  
CTGACCGTCCTGGGT

SEQ ID NO: 397 (CA2 nucleotide sequence)

CAGGTTGAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAGCAGCGTCGCTGTAACTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGCTTGGTGGCATTATTAGTAATGGAGGCACAGGCTATAATCCGGCCCTGAA  
ATCTCGGCTGAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGGCACTGACCCACGTG  
ACAACTGAGGACACGGCCGTGTACTACTGTGGAAGGGGAGTTGAATGGGAGGGCTCTATGGAC  
TACTTGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCTCTGGCTCTG  
AGACTAAAGTGGATGACCAGTCTGTGCTGACTCAGCCGTCTCCGTGTCCGGGTTCTGGGCCA  
GAGGGTCACCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGAGCTGGTAGTTATGTGGGCTG  
GTACCAGCAGGTCCCAGGATCGGGCCTCAGAATCCTCATCTATGGTGCAACCAAGCGAGCCTCG  
GGACTCCCCGACCGATTCTCCGGCTCCAGGTCTGGGAACACAGCCACCCTGACCATCAGCTCG  
CTCCAGGCTGAGGACGAGGCCGATTATTACTGCGTATCTTATCAGACTGATTTTACTTTAGTTTC  
GGCAGCGGGACCAGGCTGACCGTCCTAGGT

SEQ ID NO: 398 (CA9 nucleotide sequence)

CAGGTGACGCTTCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCAATTGAGCAGCGTG  
ACAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGAGTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAA



ATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAAGCTGTGCTGACTCAGCCGGCCTCC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGTTCTGGAAGCTTCATCGGTATTAGTA  
GTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGACG  
GTGACCCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGAC  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAA  
TATACTGGAGTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 399 (CA12 nucleotide sequence)

CAGGTGCAGCTGCAGGGGTGCGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCTTTTGACAGCTATTATGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTAATATATAGTACTGGAAGGGCATTCTATAACCCGGCCCTGAAA  
TCCCGGCTCAGCATCACAGGGACACCTCCAAGAGCCAAGTCTCCCTATCAGTGAGCAGCGTGA  
CAATTGAGGACACGGCCCTGTACTACTGTGTCAGAGGCTCGTATTATCACGGTGGTGGCAATGG  
GATGGTCGACTTTTTCGACTACTGGAGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAA  
TCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGTCGTGCGGACTCAGCCGTCCTCC  
GTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCAGCAGCAATGTTGGAT  
ATGGTAATTATGTGGGCTGGTTCCAACAGGTGCCAGGGTCAGCCCCCAAACCTCCTCATCTATGC  
TGCAACCAGTCGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGGAATACAGC  
CACCTGACCATCGACTCGCTCCAGGCTGAGGACGAGGCCGATTATTACTGTTTCATCTTATCAAC  
GCGGTAACACTGGTGTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 400 (CB2 nucleotide sequence)

CAGGTTTCAGCTTCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACCT  
GCACGGTCTCTGGATTCTCATTAAGCACTAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAAA  
GGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTTTAATCCAGTCCTTAAG  
TCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCATTGAGCAACGTGA  
CAAGTGAAGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGACTGATGGTCTTGCTTACGG  
TTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACTATCTCCTCAGAAGGTAAAT  
CTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGTCTGTGCTGACTCAGCCGTCCTCCGT  
GTCCGGGTCCCCGGGCCAGACAGTCTCCATCACCTGCTCTGGAAGCTATATCGGTAGTAGTGGT  
GTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCCTCAGAACCATCATCGTGGCGAGTGACGGT  
CGACCCTCAGGGGTCCCCGACCGATTCTCTATGTCCAAATCGGGCAACACAGCCACCCTGACCA  
TCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTTCTGTGGAAGTAGTGATAGGACTCAATA  
TACTGGACTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 401 (CB3 nucleotide sequence)

CAGGTTGAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAAGCAGCGTCGCTGTAACTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGCTTGGTGGCATTATTAGTAATGGAGGCACAGGCTATAATCCGGCCCTGAA  
ATCTCGGCTGAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGGCACTGACCCACGTG  
ACAACTGAGGACACGGCCGTGTACTACTGTGGAAGGGGAGTTGAATGGGAGGGCTCTATGGAC  
TACTTGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCTCTGGCTCTG  
AGACTAAAGTGGATGACCAGTCTGTGCTGACTCAGCCGTCTCCGTGTCCGGGTTCTGGGCCA  
GAGGGTCACCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGAGCTGGTAGTTATGTGGGCTG  
GTACCAGCAGGTCCCAGGATCGGGCCTCAGAATCCTCATCTATGGTGCAACCAAGCGAGCCTCG  
GGACTCCCCGACCGATTCTCCGGCTCCAGGTCTGGGAACACAGCCACCCTGACCATCAGCTCG  
CTCCAGGCTGAGGACGAGGCCGATTATTACTGCGTATCTTATCAGACTGATTTTACTTTAGTTTTC  
GGCAGCGGGACCAGGCTGACCGTCCTAGGT

SEQ ID NO: 402 (CB7 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAACTATCGTGTAGGTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGGTTAGTAACATACGGAGTGGTGGAACTACATGGTATAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACCGCGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACACGGCCGTATATTATTGTGCAAGAGATTCTCTGGTGATCTTTATGCGTATG  
ATTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCGTCTGG  
CGAGTCTAAAGTGGATGACCAGGCCGTGCTGACTCAGCCGTCTCCGTGTCCAGGTCCCTGGG  
CCAGAGTGTCTCCATGACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATATGGCCT  
GGTTCCAACAGGTTCCAGGATCAGCCCCAACTCCTCATCTATGGTGCAACCAGTCGAGCCTC  
GGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCAGCTC  
GCTCCAGGCTGAGGACGAGGCCGATTACTACTGTGCATCTTATGACAGCACTAGCGGGGGTGTCT  
TTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 403 (CC7 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCACTAACCAGCAATGCTGTGATCTGGGTCCGGCAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTTTGATAGATGTTGATGGAGATGCAGCCTATGACCCAGCCCTTAA  
GTCCCGCCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCCCTTTCACTGCGCAGCGTG  
ACAACTGAGGACACGGCCGTGTACTACTGTGCAAGAGACTATGGTAGTTGGGGTTATGTTCCG  
ACATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGC  
GTCTGGCGAGTCTAAAGTGGATGACAGGGTCGTGCGGACTCAACCGTCCTCCGTGTCTGGGTC  
CCTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCTACATCACTGGTAGTTCTGTAGGCTGG  
TTCCAACAGGTCCCAGGATCGGGCCTCAAACCGTCATCTATGACAATAACGATCGACCCTCAG  
GGGTCCCCGACCGATTCTCTGGCTCCAAGTCGGGCGACACAGCCACCCTGACCATCAGCTCGC

TCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTATGACACCAGTAACATTGGTCTTTTC  
GGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 404 (3aA6 nucleotide sequence)

CAGGTGCGGCTGCAGGAGTCGGGATCCAGTCTGGTGAAGCCCTCACAGACCCTCTCCCTCGTC  
TGCACGGTCTCTGGATTCCCATTAACCAGCAATGCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCGCCGGAGTGGCTAGGTCTCATAGATATTGATGGAGACACAGCCTATAACCCAGCCCTTGA  
GTCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCCCTGTCACTGAGCAGCGTG  
GCAATTGAGGACACGGCCGTGTACTATTGTGCTCGTCATTATGATAAATGGGGTTATGCTGATTG  
GATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGCG  
TCTGGCGAGTCTAAAGTGGATGACCAGGCCCTGTGACTCAGCCGTCTCCGTGTTTGGTTCCC  
TGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTGATTATGT  
AGGCTGGTACCAACAGGTCCCAGGATCAGCCCCCAAACCTCCTCATCTATGATGCAACCACTCGA  
GCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGGAACACAGCCACCCTGACCATC  
AGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTATCAGAATGAAAGAAGTG  
GTGTTTTCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 405 (3aD6 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCACTAACCAGCAATGCTGTGATCTGGGTCCGGCAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTTTGATAGATGTTGATGGAGATGCAGCCTATGACCCAGCCCTTAA  
GTCCCGCCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCCCTTTCACTGCGCAGCGTG  
ACAACCTGAGGACACGGCCGTGTACTACTGTGCAAGAGACTATGGTAGTTGGGGTTATGTTTCCG  
ACATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGGCGC  
GTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCTGGGTCC  
CTGGGCCAGAGGGTCTCCATCACCTGCTCTGGAAGCGACATCGGTGGTGCTGATGTAGGCTGG  
TTCCAACAGGTCCCAGGATCGGGCCTCAGAACCCTCATCTATGATAATGACAATCGACCCTCAG  
GGGTCCCCGACCGATTCTCTGGCTCCAAGTCGGGCAACACAGCCACCCTGACCATCAGCTCGC  
TCCAGCCTGAGGATGAGGCCGATTATTTCTGTGGCACTTATTCTGGTGCTAACTATGGTATTTTT  
GGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 406 (3aB7 nucleotide sequence)

CAGGTTGAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAGCAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGGTTGGTGATAAAGCAGTGCTGGAAAGACATACGGTAACCCGGCCCTGA  
AATCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACACGGCCGTGTACTACTGTGTAAGATGCAGGGATGGTGGTGTGACTTATGGT  
TATGACGTGCACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTG  
GCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCCA  
AGTCCCTGGGCCAGAGTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTGA

TGTTGTGAGCTGGTTCCAACAGTTCCCAGGATCAGCCCCAACTCCTCATTTTCGGTACAACGA  
CTCGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACGCAGCGACTCTAA  
CCATCAACTCTCTCCAGGCTGAGGACGAGGCCGACTATTACTGTGCGTCTTTTGATAGTGATAGC  
GGTGAATTGCCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 407 (3bF4 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCCTTGAGTAGCAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGCTTGGTGATATAAGCAGTGTTGGAAAAAATACGCTAACCCGGCCCTGAA  
ATCTCGGCTCAGCTTCACTAGGGACACCTCCAAGAGCCAAGTGTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGACACGGCCGTGTACTATTGTGTAAAATGCAGGGATGGTGGTGTGACTTATGGTT  
ATGATATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGG  
CGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCTCGTGTCTAAG  
TCCACGGGCCAGACTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGGTACGTAATT  
ATGTGACCTGGTTCCAACAGGTCCCAGGATCAGCCCCAACTCCTCATCTATGGTGCAACCAG  
TCGAGCCTCGGGGATCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTGAT  
CATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTGCTGACACCAATGAC  
GGTGGTGTTCGCGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 408 (3aD3 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACTAGCAATGGTGTAGGCTGGGTCCGCCGGGCTCCAGGAA  
AGGTGCCGGAGTGGGTTGGTGATATAAGCAGTGTTGGAAAAGTATACGGGCACCCGGCCCTGA  
AATCCCGGCTCAGCATCACAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAAGTGAGGACACGGCCGTGTACTACTGTGTAAGATGCAGGGATGGTGGTGTGAGTTATGGT  
TATGATAGCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTG  
GCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGGTGAAGTCAAGCAGCAACGTTGGATATGGTGA  
AGTCCCTGGGCCAGAGTGTCTCCATCACCTGCTCTGGAAGCAGCAGCAACGTTGGATATGGTGA  
TTATGTGGGCTGGTTCCAACAGGTCCCAGGATCAGCCCCAACTCCTCATCTATGGTGTAACC  
GAGCGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTG  
ACCATCAGCTCGATCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTATGACGACAGTA  
GCGGTGGTATTTTCGCGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 409 (3aH6 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCCTTGAGTAGCAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGCTTGGTGATATAAGCAGTGTTGGAAAAAATACGCTAACCCGGCCCTGAA  
ATCTCGGCTCAGCTTCACTAGGGACACCTCCAAGAGCCAAGTGTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGACACGGCCGTGTACTATTGTGTAAAATGCAGGGATGGTGGTGTGACTTATGGTT  
ATGATATCGACTACTGGGGCCCAGGACTACTGGTCACCGCCTCCTCAGAAGGTAAATCTTCTGG

CGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCCGTGGTGACTCAGCCGTCTCCGTGTCTGG  
GTCCCTGGGCCAGAGTGTCTCCATCACCTGCTCCGGAAGCTCCGGCAACGTTGGCTATGGCGA  
TTATGTGAGTTGGTTCCAACAATTCCACGGATCGGCCCCCAAACCTCCTCATCTATGGTGCAACCA  
ATCTTGCCTCGGGAGTTCCCGCCCGATTCTCCGGCTCCAGGTCTGGCAACACGGCCACCCTTAC  
TATCAGCTCGCTCCACGCTGAGGACGAGGCCGATTACTATTGTGCATCTTATGACAGCAGTAGC  
GGCGGTGTGTTCCGGCAGCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 410 (3aG3 nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAAGTAGTAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGGTTGGTGATATAAGTAGTAGTGGAAGGCATACGCTAATCCGGCCCTGAA  
ATCCCGGCTCAGCATCACAGGGACACCGCCAAGACCCAAGTCTTCCTGTCACTGAGCAGCGTG  
ACAACCTGAGGACACGGCCGTGTACTACTGTGTAAGATGCAGGGATGGTGGTGTAAATTATGGTT  
ATGATATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTGG  
CGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCACCCTCCGTGTCCGG  
GTCCCCGGGCCAGAGGGTATCCATTACCTGCTCTGGAAGCAGCAGCAACATCGGGGGTGGTAA  
TTATCTGAGCTGGTTCCAACAGGTCCCAGGATCAGCCCCCAAACCTCCTCATCTATGGTGCAACCA  
GTGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGATCTGGCAACACAGCGACTCTGA  
CAATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTATTACTGTGCATCTTTTGACACCAGTAG  
CGGTGGTATTTTCGGCGCCGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 411 (3bG4 nucleotide sequence)

CAGGTGCAGCTTCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGACAATCTCTGGATTCTCATTAAATCAGCAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCGGAGTGGGTTGGTGATATTGCTAGTAGTGGAAGGCATACAGTAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGGAGCGT  
GACAACCTGAGGACACGGCCGTGTACTACTGTGTAAGATGCAGGGATGGTGGTGTGACTTATGGT  
TATGATATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGTAAATCTTCTG  
GCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGCTGACTCAGCCGTCTCCGTGTCCAA  
GTCCCTGGGCCAGAGTGTCTCCATCACCTGCTCCGGAAGCACTAGCAACGTTGGAAGTGGTAAT  
GATGTGAGCTGGTTCCAACAGGTCCCAGGATCAGCCCCCAAACCTCCTTCTACGGTGCAACCA  
ACCGAGCCTCGGGGGTCCCCGACCGATTCTCCGGCTCCAGGTCTGGCAACACAGCGACTCTGA  
CCATCACCTCGCTTCAGGCTGAGGACGAGGCCGATTATTACTGTGGATCTTATGACAGCAATAG  
CGGTGGTATTTTCGGCAGTGGGACCAGGCTGACCGTCCTGGGT

SEQ ID NO: 412 (NS1G7 nucleotide sequence)

CAGGTGCAGCTGCAGGAATCAGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACAGCTATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGACACTGGAGTGGATTAGTAGCATATCTAGTGGTGGAACTACTTTCTATAACCCGGCCCTGAAA  
TCCCGCCTCAGCATCACAGGGACACCTCCGAGAGCCAAGTCTCCCTGTCACTGAGCAGCGTG

ACGACTGAGGACACGGCCGTGTACTACTGTACAAGAGACGTGCATATTTACTATAATGATTATGG  
 TGCTGCTTATGGTGACAGGGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCAGAAGGT  
 AAATCTTCTGGCGCGTCTGGCGAGTCTAAAGTGGATGACCAGGCTGTGGTGACTCAGCCACCCT  
 CCGTGTCCGGGTCCCCGGGCCAGAGGGTATCCATCACCTGCTCTGGAAGCAGCAGCAACATCG  
 GGGGTGGTAATTATGTGAGCTGGTACCAACAACCTCCAGGATCGGGCCTCAGAACCCTCATCTA  
 TGGTACAACCAGTCGAGCCTCGGGGGTCCCCGACCGGTTTTCCGGCTCCGGATCTGGCAACAC  
 AGCGACTCTGACCATCAGCTCGCTCCAAGCTGAAGACGAGGCCGATTATTACTGTGCATCTTATG  
 ACACGAATAGCGGTAGTGTTCGGCAGTGGGACCAGGCTGACCGTCCTGGGT

The nucleic acid sequence may comprise a nucleic acid sequence encoding a variable domain disclosed herein. The variable domain may be a VH domain and/or a VL domain. Typically, the nucleic acid sequence comprises a nucleic acid sequence encoding a VH domain and a nucleic acid sequence encoding a VL domain. The nucleic acid sequence encoding a VH domain may be a nucleic acid sequence encoding a VH domain of any of SEQ ID NOs: 43, 219, 249, 251, 253, 380 to 411, and 431. The nucleic acid sequence encoding a VH domain may be selected from the group consisting of SEQ ID NOs: 567, 569, 571, 573, 575, 577, 579, 581, 583, 585 and 587 or a nucleic acid sequence with at least 70% identity to any one of SEQ ID NOs: 567, 569, 571, 573, 575, 577, 579, 581, 583, 585 and 587. Preferably the nucleic acid sequence may have at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to any one of SEQ ID NOs: 567, 569, 571, 573, 575, 577, 579, 581, 583, 585 and 587. The nucleic acid sequence encoding a VL domain may be a nucleic acid sequence encoding a VL domain of any of SEQ ID NOs: 43, 219, 249, 251, 253, 380 to 411, and 431. The nucleic acid sequence encoding a VL domain may be selected from the group consisting of SEQ ID NOs: 568, 570, 572, 574, 576, 578, 580, 582, 584, 586 and 588 or a nucleic acid sequence with at least 70% identity to any one of SEQ ID NOs: 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, and 588. Preferably the nucleic acid sequence may have at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to any one of SEQ ID NOs: 568, 570, 572, 574, 576, 578, 580, 582, 584, 586 and 588.

SEQ ID NO: 567 (S1D12 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
 TGCACGGTCTCTGGATTCTCATTGAACAACAATGCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
 AGGTGCCGGAGTCGCTTGTGGGTTGTAGCAGTGATGGAACGTGTTACTATAATTCGGCCCTGAA  
 ATCCCGGCTCGACATCACCAGGGACACCTCCAAGAACCAGATCTCCCTGTCACTGAGCAGCGTT  
 ACAACTGACGACGCGGCCGTGTACTATTGTACAAGAGGCCATTATAGTATTTATGGTTATGACTA  
 TCTTGGCACTATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 568 (S1D12 VL nucleotide sequence)

CAGGCTGTGCTGACTCAGCCGTCTCCGTGTCCGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
 TGCTCTGGAAGCAGCAGCAACGTCGGGGTGGTAATAGTGTGGGCTGGTACCAACACCTCCCA  
 GGCTCAGGCCTCAAAACCATCATCTATGATACTAACAGTCGACCCTCGGGGGTCCCCGGACCGAT

TCTCTGGCTCCAGGTCTGGCAACACGGCCACCCTAACCATCAACTCGCTCCAGGCTGAGGACGA  
GGGTGATTATTACTGTGTAACGGGTGACAGCACTACTCATGATGATCTTGTCTGGCAGCGGGACC  
AGGCTGACCGTCCTGGGG

SEQ ID NO: 569 (S1G2 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACCAGCAATTCTGTGGGCTGGGTCCGACAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTGGTATAGATACTGATGGAGAAGAAGGCTATAATCCAGCCCTTAA  
CTCCCGGCTCAGCATCACAGGGACACCTCCAAGAGTCAAGTCTCTTTGTCATTGAGCAGCGTG  
ACAAGTGAGGACACGGCCGTGTACTACTGTGGAAGAAGTTATAGGGCTGATGGTCTTGCTTACG  
GTTATGTCCAAGCCATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 570 (S1G2 VL nucleotide sequence)

CAGGCCGTGGTGACTCAGCCGTCCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
TGCTCTGGAAGCTTCATCGGTATTAGTAGTGTAGGCTGGTTCCAACAGCTCCCAGGATCGGGCC  
TCAGAACCATCATCGTGGCGAGTGACGGTCGACCCTCAGGGGTCCCCGACCGATTCTCTATGTC  
CAAATCGGGCAACACAGCCACCCTGACCATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTA  
TTTCTGTGGAAGTAGTGATAGGACTCCTTATACTGGGGTCTTCGGCAGCGGGACCAGGCTGACC  
GTCCTGGGT

SEQ ID NO: 571 (CB7 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACCAACTATCGTGTAGGTTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGGTTAGTAACATACGGAGTGGTGGAACATACATGGTATAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACCGCGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGT  
GACAACTGAGGACACGGCCGTATATTATTGTGCAAGAGATTCTCTGGTGATCTTTATGCGTATG  
ATTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 572 (CB7 VL nucleotide sequence)

CAGGCCGTGCTGACTCAGCCGTCCTCCGTGTCCAGGTCCCTGGGCCAGAGTGCTCTCCATGACC  
TGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATATGGCCTGGTTCCAACAGGTTCCAG  
GATCAGCCCCCAAACCTCCTCATCTATGGTGCAACCAGTCGAGCCTCGGGGGTCCCCGACCGATT  
CTCCGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCAGCTCGCTCCAGGCTGAGGACGA  
GGCCGATTACTACTGTGCATCTTATGACAGCACTAGCGGGGGTGTCTTCGGCAGCGGGACCAG  
GCTGACCGTCCTGGGT

SEQ ID NO: 573 (CC7 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCACTAACCAGCAATGCTGTGATCTGGGTCCGGCAGGCTCCAGGAA  
AGGCGCCGGAGTGGGTTGCTTTGATAGATGTTGATGGAGATGCAGCCTATGACCCAGCCCTTAA

GTCCCGCCTCAGCATCACCAGGGACACCTCCAAGAGTCAAGTCTCCCTTTCACTGCGCAGCGTG  
ACAACTGAGGACACGGCCGTGTACTACTGTGCAAGAGACTATGGTAGTTGGGGTTATGTTTCCG  
ACATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 574 (CC7 VL nucleotide sequence)

AGGGTCGTGCGGACTCAACCGTCCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
TGCTCTGGAAGCTACATCACTGGTAGTTCTGTAGGCTGGTTCCAACAGGTCCCAGGATCGGGCC  
TCAAACCGTCATCTATGACAATAACGATCGACCCTCAGGGGTCCCCGACCGATTCTCTGGCTC  
CAAGTCGGGCGACACAGCCACCCTGACCATCAGCTCGCTCCAGGCTGAGGACGAGGCCGATTA  
TACTGTGCATCTTATGACACCAGTAACATTGGTCTTTTCGGCAGCGGGACCAGGCTGACCGTCC  
TGGGT

SEQ ID NO: 575 (CA4 VH nucleotide sequence)

CAGGTTTCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCAGCTATTCCGTATACTGGGTCCGCCAGGCTCCAGGCC  
AGGCACTGGAGTGGATTAGTATTATGTATGCTAGTGGAAGAGTAGACTATAACCCGGCCCTGAAA  
TCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGTCAATTCTCCCTGTCATTGAGCAGCGTGA  
CAACTGAGGACACGGCCGTCTACTACTGTACAAGAGGAATCGAAAACCTGGGGCCCCGACTCCT  
GGTCACCGTCTCCTCA

SEQ ID NO: 576 (CA4 VL nucleotide sequence)

GACATCCAGGTGACCCAGTCTCCGTCCCTCCCTGTCTGCATCTCTAACAGAGAGAGTCTCCATCA  
CTTGCCCGGACCAGTCAGAGCGTTAACAATTACTTAAGCTGGTATCAGCAGAAACCAGGGCAAAGC  
TCCTAAGCTCCTGATCTATTATGCAACCAGATTGTACACCGATGTCCCATCCCGGTTCACTGGCA  
GTGGATCTGGGACAGATTACACCCTCACCATCACCAGCCTGGAGGCGGACGACACTGCAACTTA  
TACTGTCTACAATATGATAGTACACCTCTTGCAATTCGGCGGTGGGACCAACGTGGAATCAAAC  
GG

SEQ ID NO: 577 (3bG4 VH nucleotide sequence)

CAGGTGCAGCTTCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGACAATCTCTGGATTCTCATTAAATCAGCAATGGTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCCGAGTGGGTTGGTGATATTGCTAGTAGTGGAAGGCATACAGTAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGGAGCGT  
GACAACTGAGGACACGGCCGTGTACTACTGTGTAAGATGCAGGGATGGTGGTGTGACTTATGGT  
TATGATATCGACTACTGGGGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 578 (3bG4 VL nucleotide sequence)

CAGGCTGTGCTGACTCAGCCGTATCCGTGTCCAAGTCCCTGGGCCAGAGTGTCTCCATCACCT  
GCTCCGGAAGCACTAGCAACGTTGGAAGTGGAATGATGTGAGCTGGTTCCAACAGGTCCCAGG  
ATCAGCCCCCAAACCTCTCTTCTACGGTGCAACCAACCGAGCCTCGGGGTCCCCGACCGATTG



TCCGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCACCTCGCTTCAGGCTGAGGACGAG  
GCCGATTATTACTGTGGATCTTATGACAGCAATAGCGGTGGTATTTTCGGCAGTGGGACCAGGC  
TGACCGTCCTGGGT

SEQ ID NO: 579 (CA7 VH nucleotide sequence)

CGGGTGCGGCTGCAGGGGTCGGGACCCAGCCTGGTGAAACCtCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCTTTTGACAGCTATTATGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGCTTGGTAATATATATAGTACTGGAAGGGCATTCTATAACCCGGCCCTGAAA  
TCCCGGCTCAGCATCACCAAGGACACCTCCAAGAGCCAAGTCTCCCTATCAGTGAGCAGCGTGA  
CAATTGAGGACACGGCCCTGTACTACTGTGTGACAGGCTCGTATTATCACGGTGGTGGCAATGG  
GATGGTGCAGTTTTTCGACTACTGGAGCCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 580 (CA7 VL nucleotide sequence)

CAGGTCTGTGCGACTCAGCCGTCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
TGCTCTGGAAGCAGCAGCAATGTTGGATATGGTAATTATGTGGGCTGGTTCCAACAGGTGCCAG  
GGTCAGCCCCCAAACCTCCTCATCTATGCTGCAACCAGTCGAGCCTCGGGGGTCCCCGACCGATT  
CTCCGGCTCCAGGTCTGGGAATACAGCCACCCTGACCATCGACTCGCTCCAGGCTGAGGACGA  
GGCCGATTATTACTGTTTCATCTTATCAACGCGGTAACACTGGTGTTTTTCGGCAGCGGGACCAGG  
CTGACCGTCCTGGGT

SEQ ID NO: 581 (E2E8 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAAACCGACCGTGGTGTAGCCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGGTTGGTACTATGCGTAGTGGTGAACGATAGACTATAACCCGGCCCTGAA  
ATCCCGGCTCAGCATCACCAAGGACACCTCCAAGAGCCAAGTTTTCTGTCACTGAGCAGCGTC  
ACAACTGAGGACATGGCCATGTACTACTGTGCCAGAGGTTATTTGAGCGGTGATCGTTATGCCT  
GGGGCCGAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 582 (E2E8 VL nucleotide sequence)

CAGGCTGTGCTGACTCAGCCGTCTCCGTGTCCAAGTCCCTGGGCCAGAGTGTCTCCATCGCCT  
GCTCTGGAAGCAGGAGCGACATTGGATATGGTAATTATGTGAGCTGGTTCCAACAGATCCCAGG  
ATCAGCCCCCAAACCTCCTTATTTATGATACAAACACTCGGGCCTCGGGGGTCCCCGACCGATTCT  
CCGGCGCCAGGTCTGGCAACACAGCAACACTGACCATCAACTCGCTCCAGGCTGAGGACGAGG  
CCGATTATTACTGTGCAAATATTGACAGTAGTCGCAGTCATCTTTTCGGCAGTGGCACCAGACTG  
ACCGTCCTGGGT

SEQ ID NO: 583 (412E10 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGCTTCTCTGTAATAAGCGATTCTGTAGCCTGGGTCCGCCAGGCTCCAGGAA  
AAGTGCCGGAGTGGCTTGGTGTAGCGGCAGTTCTGGAAACAAATACTATAACCCGGCCCTAAA

ATCCCGGCTCAGCATCACCAGGGACACCTCCAAGAGCCAAGTCTCCCTGTCACTGAGCAGCGTG  
ACAACTGAGGATACGGCCGTGTACTACTGTGCGAGAGGTATTATCGCCGGTGTAGATGTCTGGG  
GCCGAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 584 (412E10 VL nucleotide sequence)

CAGGCTGTGCTGACTCAGCCGTCCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACC  
TGCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATGTGGGCTGGTACCAACAGGTCCCAG  
GATCAGCCCCCAAACCTCCTCATCTATGGTACAGCCATTCGAGCCTCGGGGGTCCCCGACCGATT  
CTCCGGCTCCAGGTCTGGGGACACAGCCACCCCTTACCATCACCTCGCTCCAGGCTGAGGACGA  
GGCCGATTACTACTGTGCATCTTATCAGAGTAATTACGCTTTTTTCGGCAGCGGGACCAGGCTGA  
CCGTCCTGGGT

SEQ ID NO: 585 (CE2 VH nucleotide sequence)

CAGGTGCAGCTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCCTCACC  
TGCACGGTCTCTGGATTCTCATTAACCAACTATCCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGCACTGGAGTGGATTGGTAACATAGAAAATGATGGAAGTGCGAAGTATGCCTCGGCCCTGAA  
ATCCCGACTCAGCATCACCAGGGACACCTCCAAGAACCAAGTCTCCCTGTCACTGAGCAGCGCG  
ACAACTGAGGACACGGCCGTTTACTACTGTGGAAGAGAATTCGGTGGGAGTGATGGTTATACTT  
ATTCGTTGATATCGACTACTGGGGCCAGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 586 (CE2 VL nucleotide sequence)

CAGGCTGTGCTGACTCAGCCGTCCTCCGTGTCCAAGTCCCTGGGCCAGAGTGTCTCCATCACCT  
GCTCTGGAAGCAGCAGCAACGTTGGATATGGTAATTATGTGAGCTGGTTCCAACAGGTCCCAGG  
ATCAGCCCCCAAATCCTCATCTATGGTGCAACCAGTCGAGCCTCGGGGGTCCCCGACCGATTG  
TCCGGCTCCAGGTCTGGCAACACAGCGACTCTGACCATCACCTCGCTCCAGGCTGAGGACGAG  
GCCGATTATTACTGTGCATCTTATGACGGCAGTAGCAGTGGTGTTCGGCAGCGGGACCAGGC  
TGACCGTCCTGGGT

SEQ ID NO: 587 (CE3 VH nucleotide sequence)

CAGGTGCGACTGCAGGAGTCGGGACCCAGCCTGGTGAAGCCCTCACAGACCCTCTCCGTCACC  
TGCACGGTCTCTGGATTCTCATTGATCAGCAATGCTGTAGGCTGGGTCCGCCAGGCTCCAGGAA  
AGGTGCCCGAGTCGCTTGCTGGTTGTAGCAGTGATGAAAAGTGTTACTATAACTCGGCCCTGAA  
ATCCCGGCTCGACATCACCAGGGACACCTCGAAGAACCAGATCTCCCTGTCACTGAGCAGCGTC  
ACAACTGACGACGCGGCCGTGTACTACTGTACAAGAGGCTATTATCCTGTTTATGGTTATGACTA  
TCTTGGCACTATCGACTACTGGGGCCCCGGACTCCTGGTCACCGTCTCCTCA

SEQ ID NO: 588 (CE3 VL nucleotide sequence)

CAAGCTGTGCTGACTCAACCGTCCTCCGTGTCTGGGTCCCTGGGCCAGAGGGTCTCCATCACCT  
GCTCTGGAAGCAGCAGCAACGTTGGTAGAAATGATGTAGCCTGGTTCCAACAACTCCCAGGATC  
AGGCCTCAGAACCATCATCTATGGTACTACCAGTCGACCCTCAGGTATCCCGGACCGATTCTCC

GGCTCCAAGTCTGGCGTTACGGCCACCCTGACCATCGACTCGCTCCAGGCTGAGGACGAGGCC  
GATTATTTCTGTGCCTCTGGTGACAGTAGTGCCATTAATGATATTTTCGGCAGCGGGACCAGGCT  
GACCGTCCTGGGT

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that may encode any given amino acid sequences, such as a CDR as described herein. By degenerate nucleotide sequences is meant two (or more) nucleotide sequences which encode the same protein (or protein sequence), specifically in the open reading frame of the reference nucleotide sequence which begins at position 1 (i.e. in which codon 1 of the encoding sequence corresponds to positions 1-3 of the reference nucleotide sequence).

The nucleic acid molecule of the invention may be an isolated nucleic acid molecule and may further include DNA or RNA or chemical derivatives of DNA or RNA. The term "nucleic acid molecule" specifically includes single and double stranded forms of DNA and RNA.

Methods for preparing a nucleic acid molecule encoding a specific binding molecule of the invention are well known in the art, e.g. conventional polymerase chain reaction (PCR) cloning techniques can be used to construct the nucleic acid molecule of the invention. The nucleotide sequence encoding the specific binding molecule of the invention may be codon-optimised for expression in cells of a particular type or origin, e.g. the sequence may be hamster-optimised for expression in CHO cells.

According to a fourth aspect, the invention provides a construct comprising a nucleic acid molecule of the third aspect of the invention.

The construct is conveniently a recombinant construct comprising the nucleic acid molecule of the invention. In the construct, the nucleic acid molecule of the invention may be flanked by restriction sites (i.e. nucleotide sequences recognised by one or more restriction enzymes) to enable easy cloning of the nucleic acid molecule of the invention. In the construct of the invention the nucleotide sequence encoding the specific binding molecule of the invention may conveniently be operably linked within said construct to an expression control sequence, which may be heterologous to the nucleic acid molecule, i.e. non-native. Such an expression control sequence is typically a promoter, though the nucleotide sequence encoding the specific binding molecule may alternatively or additionally be operably linked to other expression control sequences such as a terminator sequence, an operator sequence, an enhancer sequence or suchlike. Accordingly, the construct may comprise a native or non-native promoter.

The term "operably linked" refers to the association of two or more nucleic acid molecules on a single nucleic acid fragment so that the function of one is affected by the other. For example, a promoter is operably linked to a coding sequence when it is capable of affecting the expression of that coding

sequence (i.e. the coding sequence is under the transcriptional control of the promoter). Coding sequences may be operably linked to regulatory sequences in sense or antisense orientation.

The term "expression control sequence" refers to nucleotide sequences located upstream (5' non-coding sequences), within, or downstream (3' non-coding sequences) of a coding sequence, and which influence transcription, RNA processing or stability, or translation of the associated coding sequence. Expression control sequences may include promoters, operators, enhancers, translation leader sequences, a TATA box, a B recognition element and suchlike. As used herein, the term "promoter" refers to a nucleotide sequence capable of controlling the expression of a coding sequence or RNA. Suitable examples are provided hereinafter. In general, a coding sequence is located 3' to a promoter sequence. Promoters may be derived in their entirety from a native gene, or be composed of different elements derived from different promoters found in nature, or even comprise synthetic nucleotide segments. It is further recognised that since in most cases the exact boundaries of regulatory sequences have not been completely defined, nucleic acid fragments of different lengths may have identical regulatory activity.

Methods for preparing a construct of the invention are well known in the art, e.g. conventional polymerase chain reaction (PCR) cloning techniques can be used to construct the nucleic acid molecule of the invention which may be inserted into suitable constructs (e.g. containing an expression control sequence) using known methods.

According to a fifth aspect, the invention provides a vector comprising a nucleic acid molecule of the third aspect of the invention or a construct of the fourth aspect of the invention.

The term "vector" as used herein refers to a vehicle into which the nucleic acid molecule or construct of the invention may be introduced (e.g. be covalently inserted) from which the specific binding molecule or mRNA encoding it may be expressed and/or the nucleic acid molecule/construct of the invention may be cloned. The vector may accordingly be a cloning vector or an expression vector.

The nucleic acid molecule or construct of the invention may be inserted into a vector using any suitable methods known in the art, for example, without limitation, the vector and nucleic acid molecule may be digested using appropriate restriction enzymes and then may be ligated with the nucleic acid molecule having matching sticky ends, or as appropriate the digested nucleic acid molecule may be ligated into the digested vector using blunt-ended cloning.

The vector may be a bacterial or prokaryotic vector, or it may be a eukaryotic vector, particularly a mammalian vector. The nucleic acid molecule or construct of the invention may be produced in or introduced into a general purpose cloning vector, particularly a bacterial cloning vector, e.g. an Escherichia coli cloning vector. Examples of such vectors include pUC19, pBR322, pBluescript vectors (Stratagene Inc.) and pCR TOPO® from Invitrogen Inc., e.g. pCR2.1-TOPO.

The nucleic acid molecule or construct of the invention may be sub-cloned into an expression vector for expression of the specific binding molecule of the invention, particularly a mammalian expression vector. Expression vectors can contain a variety of expression control sequences. In addition to control sequences that govern transcription and translation, vectors may contain additional nucleic acid sequences that serve other functions, including for example vector replication, selectable markers etc.

The expression vector should have the necessary 5' upstream and 3' downstream regulatory elements such as promoter sequences, e.g. the cytomegalovirus (CMV), PGK or EF1a promoter, particularly the human CMV (HCMV) promoter, ribosome recognition and binding TATA box, a Kozak sequence at the translation start site, and the 3' UTR AATAAA transcription termination sequence for efficient gene transcription and translation in its respective host cell. Other promoters include the constitutive simian virus 40 (SV40) early promoter, the mouse mammary tumour virus (MMTV) promoter, the HIV LTR promoter, the MoMuLV promoter, the avian leukaemia virus promoter, the EBV immediate early promoter, and the Rous sarcoma virus promoter. Human gene promoters may also be used, including, but not limited to the actin promoter, the myosin promoter, the haemoglobin promoter, and the creatine kinase promoter. In certain embodiments inducible promoters may be used. These provide a molecular switch capable of turning expression of the nucleic acid molecule on or off. Examples of inducible promoters include, but are not limited to, a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, or a tetracycline promoter. Further, the expression vector may contain 5' and 3' untranslated regulatory sequences that may function as enhancer sequences, and/or terminator sequences that can facilitate or enhance efficient transcription of the nucleic acid molecule.

Examples of vectors are plasmids, autonomously replicating sequences, and transposable elements. Additional exemplary vectors include, without limitation, phagemids, cosmids, artificial chromosomes such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), or P1-derived artificial chromosome (PAC), bacteriophages such as lambda phage or M13 phage, and animal viruses. Examples of categories of animal viruses useful as vectors include, without limitation, retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpesvirus (e.g. herpes simplex virus), poxvirus, baculovirus, papillomavirus, and papovavirus (e.g. SV40).

Particularly preferred expression vectors are those disclosed in Kettleborough et al. (Protein Eng, Vol. 4(7): 773-783, 1991), which were specifically designed to express chimeric or reshaped human light and heavy chains in mammalian cells. These vectors contain the human cytomegalovirus (HCMV) enhancer and promoter for transcription, an appropriate human light or heavy chain constant region, a gene such as neomycin resistance (neo) for selection of transformed cells, and the SV40 origin of replication for DNA replication in host cells.

According to a sixth aspect, the invention provides a host cell comprising a nucleic acid molecule of the third aspect of the invention, a construct of the fourth aspect of the invention or a vector of the fifth aspect of the invention.

The host cell may be a prokaryotic (e.g. bacterial) or eukaryotic (e.g. mammalian) cell. A prokaryotic cell may in particular be used as a cloning host for the nucleic acid molecule, construct or vector of the invention. Suitable prokaryotic cells for use as cloning hosts include without limitation, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia*, in particular *E. coli*, and Bacilli such as *B. subtilis*. The cloning host may alternatively be a eukaryotic cell such as a fungal cell, e.g. *Pichia pastoris*, or a yeast cell, or even a higher eukaryotic cell such as a mammalian cell.

The host cell of the invention may alternatively be a production host, i.e. a cell used to express and produce the specific binding molecule of the invention. The production host cell may be a prokaryotic cell, as defined above, but is preferably a eukaryotic cell. The production host may be a fungal cell, such as *Pichia pastoris* or a yeast cell, but is preferably a mammalian cell, particularly a rodent cell, a human cell or a cell of an alternative primate.

Particular examples of cells which may constitute a production host according to the invention include Cos cells, such as COS-7 cells, HEK293 cells, CHO cells, though any suitable cell type or line may be used.

The nucleic acid molecule, construct or vector of the invention may be integrated into the host cell chromosome or may be maintained extra-chromosomally. The nucleic acid molecule, construct or vector may be introduced into a host cell by any method known in the art. Such methods include, in particular, for prokaryotic cells transformation, transduction and conjugation. Transformation refers to the genetic alteration of a competent bacterium by direct uptake of DNA. Transduction refers to infection of a bacterium using a bacteriophage in order to introduce DNA of interest. Conjugation refers to the direct transfer of genetic material between bacterial cells in direct contact.

For eukaryotic cells, nucleic acid molecules, constructs and vectors may be introduced by transfection or transduction. Transfection may be accomplished by a variety of means known in the art including but not limited to calcium phosphate-DNA co-precipitation, DEAE-dextran-mediated transfection, polybrene-mediated transfection, electroporation, microinjection, liposome fusion, lipofection, protoplast fusion, retroviral infection, and biolistics. Transduction refers to the delivery of a gene(s) using a viral or retroviral vector by means of viral infection rather than by transfection. In certain embodiments, retroviral vectors are transduced by packaging the vectors into viral particles or virions prior to contact with a cell. The skilled person is well aware of appropriate methods for introducing such genetic material into a host cell.

According to a seventh aspect, the invention provides a method of preparing a specific binding molecule according to the first aspect of the invention comprising:

- i) introducing into a host cell a nucleic acid molecule of the third aspect of the invention, a construct of the fourth aspect of the invention or a vector of the fifth aspect of the invention;
- ii) expressing the nucleic acid molecule such that the specific binding molecule is produced; and
- iii) collecting the specific binding molecule, preferably by purification.

The host cell used in the method is as described above with reference to a host cell provided by the invention. Methods of introducing a nucleic acid molecule, construct or vector of the invention into a host cell are as described above. Advantageously, the nucleic acid molecule, construct or vector of the invention comprises a selectable marker such that host cells into which it has been introduced may be selected. Examples of selectable markers include antibiotic resistance genes, such as an ampicillin resistance gene (e.g. 13-lactamase), a kanamycin resistance gene or a chloramphenicol resistance gene (e.g. chloramphenicol acetyl transferase). Selectable markers particularly suitable for use in mammalian host cells include hygromycin-B phosphotransferase gene (hph) which confers resistance to hygromycin B, the amino glycoside phosphotransferase gene (neo or aph) from Tn5 which codes for resistance to the antibiotic G418, the dihydrofolate reductase (DHFR) gene, the adenosine deaminase gene (ADA), and the multi-drug resistance (MDR) gene.

Cells into which a nucleic acid molecule, construct or vector have been introduced may then be easily selected as appropriate, e.g. by exposure to the compound to which the selectable marker confers resistance. In a particular embodiment of the invention CHO cells lacking the DHFR genes are transfected or transduced with a vector of the invention carrying a DHFR gene, restoring DHFR function in the cells. Transfected cells are then selected by culture in medium lacking thymidine, which DHFR is required to synthesise. By "expression" of the nucleic acid molecule of the invention is meant that the gene, i.e. the nucleotide sequence, within the nucleic acid molecule, which encodes the specific binding molecule of the invention, is transcribed and translated so as to produce the specific binding molecule of the invention. Expression of the nucleic acid molecule, to produce the specific binding molecule of the invention, may be constitutive or inducible, depending on the promoter used to drive expression of the gene. It is straightforward for the skilled person to express a gene in a host cell, though it may be necessary for expression conditions to be optimised. This is well within the ability of the skilled person.

The specific binding molecule produced by the production host is finally collected. "Collection" of the specific binding molecule produced by this method simply means that it is separated from the production host cells. Collection does not necessarily entail isolation of the specific binding molecule, though preferably the specific binding molecule is isolated by purification. The specific binding molecule may be produced, such that it is secreted from the host cells, e.g. the specific binding molecule may be produced with a signal sequence. If the specific binding molecule is secreted by the host cells it can, at its most simple, be collected simply by isolating the culture supernatant by e.g. centrifugation of the

culture. The specific binding molecule would thus be collected as it would be separated from the production host cells. Antibody heavy and light chains are natively encoded with N-terminal signal sequences, and are thus secreted from cells which produce them. Preferably, the specific binding molecule of the invention is produced such that it is secreted from the host cells, e.g. it may be produced with a signal sequence (and thus the nucleic acid molecule of the invention may encode a specific binding molecule with a signal sequence). Upon translocation of the polypeptide chains across the relevant membrane (the cell surface membrane in bacteria, the ER membrane in eukaryotes), the signal sequence is cleaved, yielding a mature polypeptide sequence. Specific binding molecules with and without signal sequences fall under the scope of this invention.

If the specific binding molecule of the invention is not produced such that it is secreted from the host cells, the specific binding molecule may be collected by harvesting and lysing the host cells producing the molecule. The individual skilled in the art can readily perform this task. Host cells may be harvested by centrifugation, and lysed by e.g. sonication, French Press, chemical lysis using a protein extraction reagent (e.g. BugBuster®, EMD Millipore (USA)), or a mammalian cell lysis kit as produced by e.g. AbCam (UK) or Sigma-Aldrich (USA)). The specific binding molecule of the invention is preferably then purified. Methods for purification of specific binding molecules are described earlier. Purification is preferably achieved such that the specific binding molecule is at least 50% (e.g. 60%, 70%, 80%, 90%, 95%) pure, when assessed on a w/w basis relative to other components present in the solution or composition (excluding the solvent).

Alternatively, the specific binding molecule may be prepared by any suitable method of cell-free synthesis.

According to an eighth aspect, the invention provides a specific binding molecule obtainable by a method according to the seventh aspect of the invention.

A specific binding molecule obtainable by the above method falls under the scope of this invention (i.e. which has the characteristics of a molecule obtained when such a method is used, even if that specific method is not used). The invention also extends to specific binding molecules which are obtained by using that method. Such a specific binding molecule has the characteristics of the specific binding molecule provided by the invention which is described above. A specific binding molecule obtainable by the above method is a polypeptide, preferably an antibody or a fragment of an antibody.

According to a ninth aspect, the invention provides a pharmaceutical composition comprising a specific binding molecule according to the first aspect of the invention or a composition according to a second aspect of the invention and one or more pharmaceutically acceptable diluents, carriers or excipients.

The compositions of the invention may be formulated in any convenient manner according to techniques and procedures known in the pharmaceutical art. The specific binding molecule may be presented in



the form of a pharmaceutically acceptable salt and in such cases the compositions are prepared accordingly. "Pharmaceutically acceptable" as used herein refers to ingredients that are compatible with other ingredients of the compositions as well as physiologically acceptable to the recipient. The nature of the composition and carriers or excipient materials, dosages etc. may be selected in routine manner according to choice and the desired route of administration, purpose of treatment etc. Dosages may likewise be determined in routine manner and may depend upon the nature of the molecule, purpose of treatment, age of patient, mode of administration etc.

The pharmaceutical composition may be prepared for administration to a subject by any suitable means. Such administration may be e.g. oral, rectal, nasal, topical, vaginal or parenteral. Oral administration as used herein includes buccal and sublingual administration. Topical administration as used herein includes transdermal administration. Parenteral administration as defined herein includes subcutaneous, intramuscular, intravenous, intraperitoneal and intradermal administration.

Pharmaceutical compositions as disclosed herein include liquid solutions or syrups, solid compositions such as powders, granules, tablets or capsules, creams, ointments and any other style of composition commonly used in the art. Suitable pharmaceutically acceptable diluents, carriers and excipients for use in such compositions are well known in the art.

For instance, suitable excipients include lactose, maize starch or derivatives thereof, stearic acid or salts thereof, vegetable oils, waxes, fats and polyols. Suitable carriers or diluents include carboxymethylcellulose (CMC), methylcellulose, hydroxypropylmethylcellulose (HPMC), dextrose, trehalose, liposomes, polyvinyl alcohol, pharmaceutical grade starch, mannitol, lactose, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose (and other sugars), magnesium carbonate, gelatin, oil, alcohol, detergents and emulsifiers such as polysorbates. Stabilising agents, wetting agents, emulsifiers, sweeteners etc. may also be used.

Liquid pharmaceutical compositions, whether they be solutions, suspensions or other like form, may include one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono- or diglycerides which may serve as a solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. An injectable pharmaceutical composition is preferably sterile.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented). The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's

disease, although appropriate dosages may be determined by clinical trials. Conveniently a specific binding molecule of the invention may be provided to a subject in a daily, weekly or monthly dose, or a dose in an intermediate frequency, e.g. a dose may be provided every 2, 3, 4, 5 or 6 days, every 2, 3, 4, 5 or 6 weeks, every 2, 3, 4, 5 or 6 months, annually or biannually. The dose may be provided in the amount of from 10 ng/kg to 100 mg/kg, e.g. 1 pg/kg to 10 mg/kg body weight, for example from 10 pg/kg to 1 mg/kg. The skilled clinician will be able to calculate an appropriate dose for a patient based on all relevant factors, e.g. age, height, weight, the condition to be treated and its severity. The pharmaceutical composition of the invention may further comprise at least one second therapeutically active agent, i.e. the composition may comprise both the specific binding molecule of the invention and another therapeutic agent. The second therapeutically active agent may be e.g. a drug molecule or a second specific binding molecule. The second specific binding molecule may bind a ligand which is not human tau or to a different epitope on human tau. The second therapeutically active agent may be a second agent for treatment of the condition during the treatment of which the specific binding molecule of the invention is administered to a subject, i.e. the specific binding molecule of the invention and the second therapeutic agent in the composition are both intended to treat the same illness or condition.

The pharmaceutical composition may further comprise at least one second therapeutically active agent.

The at least one second therapeutically active agent may comprise at least one second specific binding molecule according to the invention. A combination of specific binding molecules competing for binding of multiple regions described above may have increased utility in preventing the formation of the PHF core structure and therefore inhibiting tau aggregation.

In a particular embodiment the pharmaceutical composition may comprise a specific binding molecule that competes with the binding of residues 337 to 355 of SEQ ID NO: 1 to residues 337 to 355 of SEQ ID NO: 1.

The pharmaceutical composition may further comprise one or more specific binding molecules selected from the group consisting of:

- a specific binding molecule that competes with the binding of residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1;
- a specific binding molecule that competes with the binding of residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1; and
- a specific binding molecule may compete with the binding of residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1.

In a particular embodiment the pharmaceutical composition may comprise a specific binding molecule that competes with the binding of a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising residues 333 to 353 of SEQ ID NO: 1.

The pharmaceutical composition may further comprise one or more specific binding molecules selected from the group consisting of:

- a specific binding molecule that competes with the binding of a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising residues 369 to 378 of SEQ ID NO: 1;
- a specific binding molecule that competes with the binding of a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising residues 322 to 333 of SEQ ID NO: 1; and
- a specific binding molecule may compete with the binding of a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising residues 356 to 364 of SEQ ID NO: 1.

The pharmaceutical composition may therefore comprise:

- i. a first specific binding molecule comprising the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCTYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGYDYLGTIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGNSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1; and

one or more further specific binding molecules selected from the group consisting of:

- ii. a specific binding molecule comprising the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTG);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

- (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1;
- iii. a specific binding molecule comprising the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNVVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1; and
- iv. a specific binding molecule comprising the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:  
 VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1

The pharmaceutical composition may comprise a specific binding molecule comprising the CDRs of S1D12 and one or more further specific binding molecules comprising the CDRs of a specific binding molecule selected from the group consisting of S1G2, CE2 and CA4.

The at least one second therapeutically active agent may be any suitable symptomatic treatment for a tauopathy, such as any suitable symptomatic treatment for AD. The at least one second therapeutically active agent may be selected from the group consisting of an acetylcholinesterase (ACE) inhibitor, an NMDA receptor antagonist, a tau aggregation inhibitor and a  $\beta$ -amyloid aggregation inhibitor.

The acetylcholinesterase inhibitor (AChEI) may be selected from the group consisting of rivastigmine, galantamine, donepezil and tacrine.

Rivastigmine is a non-selective pseudoreversible acetylcholinesterase inhibitor that inhibits both butyrylcholinesterase (BuChE) and acetylcholinesterase (unlike donepezil, which selectively inhibits acetylcholinesterase). It is thought to work by inhibiting these cholinesterase enzymes, which would otherwise break down the brain neurotransmitter acetylcholine.

Galantamine is a weak competitive and reversible cholinesterase inhibitor in all areas of the body and also a potent allosteric potentiating ligand of human nicotinic acetylcholine receptors (nAChRs)  $\alpha 4\beta 2$ ,  $\alpha 7/5$ -HT<sub>3</sub>,  $\alpha 3\beta 4$ , and  $\alpha 6\beta 4$  in certain areas of the brain. It increases the concentration and thereby action of acetylcholine in certain parts of the brain. It has shown activity in modulating the nicotinic cholinergic receptors on cholinergic neurons to increase acetylcholine release.

Donepezil binds and inactivates reversibly and non-competitively the cholinesterases, thus inhibiting hydrolysis of acetylcholine. It is selective for AChE over BuChE. This results in increased acetylcholine concentrations at cholinergic synapses. In addition to its actions as an acetylcholinesterase inhibitor, donepezil has been found to act as a potent agonist of the  $\alpha 1$  receptor ( $K_i = 14.6$  nM), and has been shown to produce specific anti-amnesic effects in animals mainly via this action.

Tacrine is not preferred because it is associated with significant liver toxicity.

The NMDA receptor antagonist may be memantine. Memantine is an NMDA receptor antagonist, which reduces certain types of brain activity by binding to NMDA receptors on brain cells and blocking the activity of the neurotransmitter glutamate. At normal levels, glutamate aids in memory and learning, but if levels are too high, glutamate appears to overstimulate nerve cells, killing them through excitotoxicity. Memantine is a low-affinity voltage-dependent uncompetitive antagonist at glutamatergic NMDA receptors. By binding to the NMDA receptor with a higher affinity than  $Mg^{2+}$  ions, memantine is able to inhibit the prolonged influx of  $Ca^{2+}$  ions, particularly from extrasynaptic receptors, which forms the basis of neuronal excitotoxicity. Memantine acts as a non-competitive antagonist at different neuronal nicotinic acetylcholine receptors (nAChRs) at potencies possibly similar to the NMDA and 5-HT<sub>3</sub> receptors, but this is difficult to ascertain with accuracy because of the rapid desensitization of nAChR responses in these experiments. It has also been reported that memantine can increase extracellular acetylcholine in the nucleus accumbens and the ventral tegmental areas (see Shearman, E, Rossi, S, Szasz, B, Juranyi, Z, Fallon, S et al. (2006) Changes in cerebral neurotransmitters and metabolites induced by acute donepezil and memantine administrations: A microdialysis study. Brain Research Bulletin 69:204-213).

The tau aggregation inhibitor may be a methylthioninium (MT)-containing compound. W096/30766 describes MT-containing compounds for use in the treatment and prophylaxis of various "tauopathy" diseases. One example compound was methylthioninium chloride ("MTC") commonly known as methylene blue, which is the chloride salt of the oxidized form of methylthioninium (MT) i.e. MT<sup>+</sup>. MT is a redox molecule and, depending on environmental conditions (e.g., pH, oxygen, reducing agents), exists in equilibrium between a reduced [leucomethylthioninium (LMT)] and an oxidized form (MT<sup>+</sup>).

The MT containing compound may be an LMT compound. Preferably the LMT compound is an "LMTX" compound of the type described in W02007/110627 or W02012/107706.

The MT containing compound may be an MT<sup>+</sup> compound. Preferably the MT compound is an MT<sup>+</sup> compound of the type described in W096/30766 or W02007/110630.

Without being bound by theory, an MT containing compound may enhance the activity of a specific binding molecule of the invention by increasing the availability of the epitope bound by the specific binding molecule.

The  $\beta$ -amyloid aggregation inhibitor may be any suitable substance that inhibits the aggregation of  $\beta$ -amyloid. For instance, it may be a molecule that can interact with  $\beta$ -amyloid to block aggregation of  $\beta$ -amyloid. The  $\beta$ -amyloid aggregation inhibitor may bind to A $\beta$  (1-42).

According to a tenth aspect, the invention provides a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention for use in therapy.

By therapy is meant the treatment of a subject. By "therapy" as used herein is meant the treatment of any medical condition. Such treatment may be prophylactic (i.e. preventative), curative (or treatment intended to be curative), or palliative (i.e. treatment designed merely to limit, relieve or improve the symptoms of a condition). A subject, as defined herein, refers to any mammal, e.g. a farm animal such as a cow, horse, sheep, pig or goat, a pet animal such as a rabbit, cat or dog, or a primate such as a monkey, chimpanzee, gorilla or human. Most preferably the subject is a human.

The invention therefore has general use in medicine. Accordingly, the invention provides a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention for use in medicine or for use as a medicament.

Preferably, the specific binding molecule of the first aspect of the invention binds to an epitope within residues 296 to 391 of SEQ ID NO: 1.

Most preferably, the specific binding molecule comprises the CDRs of a specific binding molecule selected from the group consisting of S1D12, S1G2, CE2 and CA4.

According to an eleventh aspect, the invention provides a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention for use in treatment of a tauopathy.

Preferably, the specific binding molecule of the first aspect of the invention binds to an epitope within residues 296 to 391 of SEQ ID NO: 1.

Most preferably, the specific binding molecule comprises the CDRs of a specific binding molecule selected from the group consisting of S1D12, S1G2, CE2 and CA4.

Aggregation of the tau protein is a hallmark of diseases referred to as "tauopathies". Various tauopathy disorders that have been recognized which feature prominent tau pathology in neurons and/or glia and this term has been used in the art for several years. The similarities between these pathological inclusions and the characteristic tau inclusions in diseases such as AD indicate that the structural features are shared and that it is the topographic distribution of the pathology that is responsible for the different clinical phenotypes observed. In particular, cryo-electron microscope structures of aggregated Tau in AD, Pick's disease (a subtype of Frontotemporal Dementia), chronic traumatic encephalopathy (CTE) and cortico-basal degeneration (CBD) have been obtained previously, and all show common conformational features, indicating that compounds that have the ability to modulate Tau aggregation in e.g. PHFs (as observed in AD), may also modulate aggregation of Tau in other tauopathies. In addition to specific diseases discussed below, those skilled in the art can identify tauopathies by combinations of cognitive or behavioural symptoms, plus additionally through the use of appropriate ligands for aggregated tau as visualised using PET or MRI, such as those described in WO02/075318.

Aspects of the present invention relate to "tauopathies". As well as Alzheimer's disease (AD), the pathogenesis of neurodegenerative disorders such as Pick's disease and Progressive Supranuclear Palsy (PSP) appears to correlate with an accumulation of pathological truncated tau aggregates in the dentate gyrus and stellate pyramidal cells of the neocortex, respectively. Relevant dementias include fronto-temporal dementia (FTD); parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-lusian degeneration (PNLD); cortico-basal degeneration (CBD); Dementia with Argrophilic grains (AgD); Dementia pugilistica (DP) wherein despite different topography, NFTs are similar to those observed in AD ( Bouras et al., 1992); Chronic traumatic encephalopathy (CTE), a tauopathy including DP as well as repeated and sports-related concussion (

McKee, et al., 2009 ). Others are discussed in Wischik et al. 2000, for detailed discussion - especially Table 5.1).

Abnormal tau in NFTs is found also in Down's Syndrome (DS) (Flament et al., 1990), and in dementia with Lewy bodies (DLB) (Harrington et al., 1994). Tau-positive NFTs are also found in Postencephalitic parkinsonism (PEP) (Charpiot et al., 1992). Glial tau tangles are observed in Subacute sclerosing panencephalitis (SSPE) (Ikeda et al., 1995). Other tauopathies include Niemann-Pick disease type C (NPC) (Love et al., 1995); Sanfilippo syndrome type B (or mucopolysaccharidosis III B, MPS III B) (Ohmi, et al., 2009); myotonic dystrophies (DM), DM1 (Sergeant, et al., 2001 and references cited therein) and DM2 (Maurage et al., 2005). Additionally, there is a growing consensus in the literature that a tau pathology may also contribute more generally to cognitive deficits and decline, including in mild cognitive impairment (MCI) (see e.g. Braak, et al., 2003, Wischik et al., 2018).

All of these diseases, which are characterized primarily or partially by abnormal tau aggregation, are referred to herein as "tauopathies" or "diseases of tau protein aggregation". In aspects of the invention relating to tauopathies, the tauopathy may be selected from any tauopathy defined herein. Without wishing to be bound by theory, the present inventors believe that all structures solved for tauopathies encompass the dGAE region of Tau. As such, specific binding molecules that stabilise a conformation of dGAE that is not prone to assembly by binding to dGAE can reasonably be expected to apply to all tau diseases including but not limited to AD.

The tauopathy may be selected from the group consisting of Alzheimer's disease, Primary age-related tauopathy (PART), Neurofibrillary tangle-predominant senile dementia, Chronic traumatic encephalopathy (CTE), Progressive supranuclear palsy (PSP), Corticobasal degeneration (CBD), Frontotemporal dementia (FTD), Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Pick disease, disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), pallido-ponto-nigral degeneration (PPND), Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD), Dementia with Argrophilic grains (AgD), Down's Syndrome (DS), dementia with Lewy bodies (DLB), Postencephalitic parkinsonism (PEP), Dementia pugilistica (DP), traumatic brain injury (TBI), stroke, ischemia, Lytico-bodig disease (Parkinson-dementia complex of Guam), Ganglioglioma, Gangliocytoma, Meningioangiomas, Postencephalitic parkinsonism, Subacute sclerosing panencephalitis (SSPE), Lead encephalopathy, tuberous sclerosis, Pantothenate kinase-associated neurodegeneration, lipofuscinosis and mild cognitive impairment (MCI).

The tauopathy may be Alzheimer's disease.

The invention also embraces treatment as a prophylactic measure. The treatment may be prophylactic treatment. The treatment may be by active immunization or passive immunization.



Active tau immunization has been shown to reduce tau pathology by targeting single or multiple phospho-epitopes, the amino terminus, full-length normal and mutant tau or aggregated tau. Reductions in pathological tau are achieved with few reported adverse effects, and the long-lasting immune response makes active immunization a promising option. However, elicitation of antibodies against a native protein always carries the risk of adverse immune reactions and detrimental targeting of the normal protein.

Passive immunization offers a potential solution to the safety concerns that arise from active strategies. Patients will not develop their own antibodies, and the effects of immunization are likely to be transient, which reduces the risk of immunological adverse effects. Passive immunization also offers greater specificity for the epitope that is being targeted.

Antibodies could also modify disease progression by blocking the spread of tau pathology.

The specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention may therefore be for use in treatment of an early stage tauopathy and/or a tauopathy characterised by mild symptoms. The specific binding molecule may be for use in treatment of mild cognitive impairment (MCI).

The specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention may be for use in treatment of a tauopathy in a subject at risk of developing a tauopathy. The subject at risk of developing a tauopathy may be identified by any suitable means, such as one or more of medical history, physical examination, neurological examination, brain imaging, mental status tests (such as the Mini-Mental State Exam (MMSE) and the Mini-Cog test), computerised cognitive tests (such as the Cantab Mobile, Cognigram, Cognivue, Cognision and Automated Neuropsychological Assessment Metrics (ANAM) devices), mood assessment and genetic testing.

The skilled person is aware that a tauopathy diagnosis may not always be definitive until post-mortem. Accordingly, the specific binding molecule may be for use in treatment of a tauopathy in a subject at risk of developing a tauopathy. The subject may be suspected of having a tauopathy. The subject may have one or more symptoms of a tauopathy. The specific binding molecule may be for use in slowing progression of a tauopathy or suspected tauopathy.

The term "treatment" includes "combination" treatments and therapies, in which two or more treatments or therapies for the same tauopathy, are combined, for example, sequentially or simultaneously. These may be symptomatic or disease modifying treatments.

The particular combination would be at the discretion of the physician. In combination treatments, the therapeutically active substances (i.e., a specific binding molecule, composition or pharmaceutical composition as described herein, plus one or more other therapeutically active substances) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes. For example, when administered sequentially, the therapeutically active substances can be administered at closely spaced intervals (e.g., over a period of 5-10 minutes) or at longer intervals (e.g., 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutically active substances.

An example of a combination treatment of the invention would be a specific binding molecule in combination with an ACE inhibitor, an NMDA receptor antagonist or a tau aggregation inhibitor.

A further example of a combination treatment of the invention would be a specific binding molecule comprising the CDRs of S1D12 and one or more further specific binding molecules comprising the CDRs of a specific binding molecule of the invention. The further specific binding molecule may for example be selected from the group consisting of S1G2, CE2 and CA4.

In other embodiments the treatment is a "monotherapy", which is to say that the specific binding molecule is not used in combination (within the meaning discussed above) with another active agent for treating the same tauopathy in the subject.

According to a twelfth aspect, the invention provides a method of treating a tauopathy, comprising administering to a subject in need thereof a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention.

Preferably, the specific binding molecule of the first aspect of the invention binds to an epitope within residues 296 to 391 of SEQ ID NO: 1.

Most preferably, the specific binding molecule comprises the CDRs of a specific binding molecule selected from the group consisting of S1D12, S1G2, CE2 and CA4.

The term "therapeutically-effective amount," where used herein, pertains to that amount of an agent used in the practice of the combination methodologies of the invention which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

As explained above the invention also embraces treatment as a prophylactic measure. For example, the invention provides a method of prophylactic treatment of a tauopathy in a subject, which method

comprises administering to said subject a specific binding molecule according to the first aspect of the invention, a composition according to the second aspect of the invention or a pharmaceutical composition according to the ninth aspect of the invention.

The term "prophylactically effective amount" where used herein, pertains to that amount of a compound of the invention, or a material, composition or dosage from comprising said compound, which is effective for producing some desired prophylactic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen. "Prophylaxis" in the context of the present specification should not be understood to circumscribe complete success i.e. complete protection or complete prevention. Rather prophylaxis in the present context refers to a measure which is administered in advance of detection of a symptomatic condition with the aim of preserving health by helping to delay, mitigate or avoid that particular condition.

According to a thirteenth aspect, the invention provides an *in vitro* method of inhibiting aggregation of a tau protein or a fragment thereof comprising contacting the tau protein or a fragment thereof with a specific binding molecule according to the first aspect of the invention.

Preferably, the specific binding molecule of the first aspect of the invention binds to an epitope within residues 296 to 391 of SEQ ID NO: 1.

Most preferably, the specific binding molecule comprises the CDRs of a specific binding molecule selected from the group consisting of S1D12, S1G2, CE2 and CA4.

The method may be selected from the group consisting of a thioflavin T-assay, a tau-tau immunoassay and an assay for assessing the effects of aggregated tau in cell culture. A suitable assay for assessing the effects of aggregated tau in cell culture is disclosed in UK application no. GB2010620.9 filed on 10 July 2020, and in international (PCT) application no. PCT/EP2021/069138 filed on 9 July 2021 and claiming priority to UK application no. GB2010620.9, both of which are hereby incorporated by reference in their entirety.

The invention therefore provides a screening method for measuring the effect of a specific binding molecule on the aggregation of tau protein. The tau protein may be human tau. The human tau may comprise the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

In this context, by "fragment" is meant any region of the tau protein capable of aggregation *in vitro*. For example, tau protein fragments include SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

In this context, by “contacting” is meant “exposing to”. It does not require directionality; the tau protein or a fragment thereof may be exposed to the specific binding molecule or the specific binding molecule may be exposed to the tau protein or a fragment thereof. The contacting occurs under conditions permissive for aggregation of the tau protein or fragment thereof.

According to a fourteenth aspect, the invention provides an *in vitro* method for detecting a tau protein or a fragment thereof in a sample comprising contacting the sample with a specific binding molecule of the first aspect of the invention.

In a preferred embodiment, the specific binding molecule may comprise the CDRs of a specific binding molecule selected from the group consisting of S1D12, S1G2 and E2E8.

The sample may be defined as a “patient sample” or a “biological sample”. The sample may be from a subject suffering from or at risk of a tauopathy.

Samples are typically obtained prior to the methods of the invention being performed. The methods of the invention are *in vitro* or *ex vivo* methods accordingly. In some alternative embodiments, the method may further comprise a step or steps of sample collection.

The sample may be a plasma, a whole blood sample, a brain lysate or cerebrospinal fluid (CSF) sample. Preferably, the sample is a plasma sample.

The sample may be processed in any suitable way prior to detecting the tau protein or a fragment thereof in a sample. The tau protein or fragment thereof may be isolated, extracted and/or purified from the sample. The isolation, extraction and/or purification may be performed by any suitable technique.

The method of the invention may further comprise an initial step of isolating, extracting and/or purifying the tau protein or fragment thereof from the sample. The method may therefore further comprise isolating the tau protein or fragment thereof from the sample. The method may further comprise extracting the tau protein or fragment thereof from the sample. The method may further comprise purifying the tau protein or fragment thereof from the sample.

The step of obtaining the sample and/or the step of isolating, extracting and/or purifying the tau protein or fragment thereof from the sample may occur in a different location to the subsequent steps of the method. Accordingly, the method may further comprise a step of transporting the sample and/or transporting the tau protein or fragment thereof.

The sample (the term “sample” includes the tau protein or fragment thereof isolated and/or purified therefrom) may be denatured, for example by treatment with sodium dodecyl sulphate (SDS). The method may further comprise a step of denaturing the tau protein or fragment thereof prior to contacting

the sample with the specific binding molecule. The denaturing may preferably be by contacting the sample with sodium dodecyl sulphate (SDS). The sample may therefore comprise denatured protein. The tau protein or a fragment thereof may be denatured.

The term "detecting" as used herein encompasses quantitative or qualitative detection. "Detecting" may include measuring and/or quantifying the amount (or level) of a tau protein or a fragment thereof in a sample.

The tau protein or fragment thereof may be detected using an immunoassay. Immunoassays have the potential to be miniaturised to run on a microfluidics device or test-strip and may be more suited for clinical point-of-care applications. Embodiments of the invention which incorporate an immunoassay may therefore be used *in situ* by a primary healthcare provider for assistance in prescribing a treatment for an individual patient.

The amount (or level) of a tau protein or a fragment thereof in a sample may be measured using a homogeneous or heterogeneous immunoassay.

Thus, in some embodiments, the amount (or level) of a tau protein or a fragment thereof may be measured in solution by binding to specific binding molecules of the invention that are present in excess, whereby binding alters detectable properties of the label. The amount of tau protein or a fragment thereof present will therefore affect the amount of the label with a particular detectable property. As is well known in the art, the label may comprise a radioactive label, a fluorescent label or an enzyme having a chromogenic or chemiluminescent substrate that is coloured or caused or allowed to fluoresce when acted on by the enzyme.

Alternatively, a heterogeneous format may be used in which the at least one tau protein or a fragment thereof is captured by surface-bound antibodies for separation and quantification. In some embodiments, a sandwich assay may be used in which a surface-bound tau protein or a fragment thereof is quantified by binding a labelled secondary antibody.

Suitably, the immunoassay may comprise an enzyme immunoassay (EIA) in which the label is an enzyme such, for example, as horseradish peroxidase (HRP). Suitable substrates for HRP are well known in the art and include, for example, ABTS, OPD, AmplexRed, DAB, AEC, TMB, homovanillic acid and luminol. In some embodiments, an ELISA immunoassay may be used; a sandwich ELISA assay may be particularly preferred.

The immunoassay may be competitive or non-competitive. Thus, in some embodiments, the amount of a tau protein or a fragment thereof may be measured directly by a homogeneous or heterogeneous method, as described above. Alternatively, the amount of a tau protein or a fragment thereof in the sample may be sequestered in solution with a specific binding molecule which is present in excess, and

the amount of specific binding molecule remaining then determined by binding to surface-bound tau protein or a fragment thereof to give an indirect read-out of the amount of tau protein or a fragment thereof in the original sample. In another variant, the tau protein or a fragment thereof may be caused to compete for binding to a surface bound specific binding molecule with a known amount of a labelled tau protein or a fragment thereof.

The surface bound specific binding molecule or tau protein or a fragment thereof may be immobilised on any suitable surface of the kind known in the art. For instance, the specific binding molecule or tau protein or a fragment thereof may be immobilised on a surface of a well or plate or on the surface of a plurality of magnetic or non-magnetic beads.

In some embodiments, the immunoassay may be a competitive assay, further comprising a known amount of the tau protein or a fragment thereof, which is the same as the one to be quantified in the sample, but tagged with a detectable label. The labelled tau protein or a fragment thereof may be affinity-bound to a suitable surface by a specific binding molecule to the tau protein or a fragment thereof. Upon adding the sample, a proportion of the labelled tau protein or a fragment thereof may be displaced from the surface-bound specific binding molecule, thereby providing a measure of the level of tau protein or a fragment thereof in the sample.

In some embodiments, the immunoassay may comprise surface-bound tau protein or a fragment thereof, which is the same as the tau protein or a fragment thereof that is to be quantitated in the sample, and a known amount of specific binding molecule to the tau protein or a fragment thereof in solution in excess. The sample is first mixed with the specific binding molecule in solution such that a proportion of the specific binding molecules bind with the tau protein or a fragment thereof in the sample. The amount of unbound specific binding molecules remaining can then be measured by binding to the surface-bound tau protein or a fragment thereof.

In some embodiments, the immunoassay may comprise a labelled secondary antibody to the tau protein or a fragment thereof or to a primary antibody to the tau protein or a fragment thereof for quantifying the amount of the tau protein or a fragment thereof bound to surface-bound antibodies or the amount of primary antibody bound to the tau protein or a fragment thereof immobilised on a surface.

Measuring the level of a tau protein or a fragment thereof may be by equipment for measuring the level of a tau protein or a fragment thereof in a sample comprising a sample collection device and an immunoassay. The equipment may further comprise a detector for detecting labelled tau protein or a fragment thereof or labelled antibodies to the tau protein or a fragment thereof in the immunoassay. Suitable labels are mentioned above, but in a preferred embodiment, the label may be an enzyme having a chromogenic or chemiluminescent substrate that is coloured or caused or allowed to fluoresce when acted on by the enzyme.

The immunoassay or equipment may be incorporated into a miniaturised device for measuring the level of a tau protein or a fragment thereof in a biological sample. Suitably, the device may comprise a lab-on-a-chip.

Measuring levels of tau protein or a fragment thereof may be by a device for measuring the level of at least one tau protein or a fragment thereof in a sample obtained from a patient, the device comprising one or more parts defining an internal channel having an inlet port and a reaction zone, in which a tau protein or a fragment thereof in a sample may be reacted with an immobilised primary antibody for the tau protein or a fragment thereof for capturing the tau protein or a fragment thereof, or a primary antibody for the tau protein or a fragment thereof in excess in solution after mixing with the sample upstream of the reaction zone may be reacted with tau protein or a fragment thereof, which is the same as the one to be measured in the sample, but immobilised on a surface within the reaction zone, for quantifying directly or indirectly the amount of the tau protein or a fragment thereof in the sample.

The captured tau protein or a fragment thereof or primary antibody may then be detected using a secondary antibody to the tau protein or a fragment thereof or primary antibody, which is tagged with an enzyme.

As described above, the enzyme may have a chromogenic or chemiluminescent substrate that is coloured or caused or allowed to fluoresce when acted on by the enzyme. Suitably, the one or more parts of the device defining the channel, at least adjacent the reaction zone, may be transparent to light, at least in a range of wavelengths encompassing the colour or fluorescence of the substrate to allow detection of a reaction between the tau protein or a fragment thereof or primary antibody and the secondary antibody using a suitable detector such, for example, as a photodiode, positioned outside the channel or further channel.

In some embodiments, the device may comprise a plurality of channels, each with its own inlet port, for measuring the levels of a plurality of different tau protein or a fragments thereof in the sample in parallel. Therefore, each channel may include a different respective immobilised primary antibody or tau protein or a fragment thereof.

Suitably, the device may comprise one or more selectively operable valves associated with the one or more inlet ports for controlling the admission of a sequence of different reagents into to the channels such, for example, as the sample, wash solutions, primary antibody, secondary antibody and enzyme substrate.

The device therefore may comprise a microfluidics device. The channel may include a reaction zone. Microfluidics devices are known to those skilled in the art. A review of microfluidic immunoassays or protein diagnostic chip microarrays is provided by Chin et al. 2012. *Lab on a Chip*. 2012; 12:2118-2134. A microfluidics device suitable for carrying out an ELISA immunoassay at a point-of-care is disclosed

by Chan CD, Laksanasopin T, Cheung YK, Steinmiller D et al. "Microfluidics-based diagnostics of infectious diseases in the developing world". *Nature Medicine*. 2011;17(8):1015-1019, the contents of which are incorporated herein by reference.

The specific binding molecule may be a specific binding molecule according to the first aspect of the invention. The epitope of the specific binding molecule may be within SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7. The specific binding molecule may bind to SEQ ID NO:1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.

The specific binding molecule may bind to an epitope within residues 296 to 391 of SEQ ID NO: 1 wherein the sample is a plasma sample.

The method may comprise contacting a sample with at least one specific binding molecule of the first aspect of the invention. The method may comprise contacting the sample with a first specific binding molecule that binds to an epitope within residues 296 to 391 of SEQ ID NO: 1 and contacting the sample with a second specific binding molecule that binds to an epitope within SEQ ID NO: 1.

The first and/or second specific binding molecule may be a specific binding molecule according to the first aspect of the invention. The first or second specific binding molecule may be a known specific binding molecule such as HT7, BT2, Tau12 or Tau146.

The first specific binding molecule may bind to SEQ ID NO: 1 or a fragment thereof with a  $K_D$  of less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 8 nM, less than 6 nM, less than 5 nM, less than 4 nM, less than 3 nM, less than 2 nM, less than 1 nM, less than 0.5 nM, less than 0.4 nM, less than 0.3 nM, less than 0.2 nM or less than 0.15 nM. A high affinity first specific binding molecule may be especially advantageous in embodiments where the first specific binding molecule is a surface bound specific binding molecule. A preferred high affinity first specific binding molecule is a specific binding molecule comprising the CDRs of S1D12.

The first specific binding molecule may bind to an epitope within residues 296 to 391 of SEQ ID NO: 1. Preferably, the first specific binding molecule binds to an epitope within residues 337 to 355 of SEQ ID NO: 1.

The second specific binding molecule may bind to the same epitope or to a different epitope than the first specific binding molecule. The skilled person will understand that an appropriate pair of antibodies may permit detection of particular tau fragments of interest. For instance, where the epitope of the first specific binding molecule and the second specific binding molecule are widely spaced across the sequence of SEQ ID NO:1 (such as binding to an N-terminal region and to a C-terminal region respectively), the method may selectively detect full length and longer fragments of tau; shorter



fragments of tau that are only bound by one of the specific binding molecules (or by neither) will not be detected.

The ability to interrogate and determine the levels of various tau species or fragments in patient samples is crucial in early AD diagnosis. The invention provides a method for determining the concentrations of different tau species accordingly. The method may use spiked samples. The method may use pairings of specific binding molecules directed towards selected epitopes of the tau protein. Accordingly, the method may be a sandwich ELISA assay.

The second specific binding molecule may bind to an epitope within residues 367 to 379 of SEQ ID NO: 1. A preferred second specific binding molecule is a specific binding molecule comprising the CDRs of S1G2.

When the first specific binding molecule binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and the second specific binding molecule binds to an epitope within residues 367 to 379 of SEQ ID NO: 1, the method may detect SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7. Since cleavage within the from proteolytically stable core of the paired helical filament (PHF) is thought to be uncommon, this embodiment may therefore detect total tau comprising the PHF.

The second specific binding molecule may bind to an epitope within residues 379 to 391 of SEQ ID NO: 1. A preferred second specific binding molecule is a specific binding molecule comprising the CDRs of E2E8.

As described herein, specific binding molecules that bind to an epitope within residues 379 to 391 of SEQ ID NO: 1 may be "E-specific"; that E391 may be critical for binding. When the first specific binding molecule binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and the second specific binding molecule binds to an epitope within residues 379 to 391 of SEQ ID NO: 1, the method may detect SEQ ID NO: 1, SEQ ID NO: 3 and SEQ ID NO: 4. Since E-specific specific binding molecules do not detect SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, this embodiment may therefore detect dGAE and full length tau but not fragments lacking E391 such as dGA.

The second specific binding molecule may bind to an epitope within residues 13 to 25 of SEQ ID NO: 1. A preferred second specific binding molecule is a specific binding molecule comprising the CDRs of CB7.

When the first specific binding molecule binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and the second specific binding molecule binds to an epitope within residues 13 to 25 of SEQ ID NO: 1, the method may detect SEQ ID NO: 1. However, this embodiment will not detect isolated SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7 as these fragments omit residues

13 to 25 of SEQ ID NO: 1. Since the epitopes used in this embodiment are spaced widely apart, this embodiment may therefore detect full-length tau.

The method may comprise contacting the sample with at least one pair of first and second specific binding molecules, wherein the pair of first and second specific binding molecules may be any two specific binding molecules of the invention. Preferred pairs of first and second specific binding molecule include:

- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 367 to 379 of SEQ ID NO: 1;
- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 379 to 391 of SEQ ID NO: 1; and
- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 13 to 25 of SEQ ID NO: 1.

The method may comprise contacting the sample with at least two or at least three pairs of first and second specific binding molecules. For instance, the method may comprise contacting the sample with:

- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 367 to 379 of SEQ ID NO: 1;
- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 379 to 391 of SEQ ID NO: 1; and
- A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 13 to 25 of SEQ ID NO: 1.

Where the method comprises contacting the sample with two or more pairs of specific binding molecules, each pair of specific binding molecules is typically contacted to the sample separately and/or in parallel. The sample may therefore be aliquoted prior to contacting the sample with the pairs of specific binding molecules. A separate aliquot may be contacted with each pair of specific binding molecules. Contacting in parallel may be contacting at the same time or simultaneously. Contacting in parallel may be contacting at essentially the same time or essentially simultaneously. Contacting in parallel may be not contacting sequentially or contacting one after another. Contacting in parallel typically means each pair of specific binding molecules is contacted to the sample in a separate vessel. Contacting in parallel typically means that each pair of specific binding molecules may independently interact with the sample.

Each pair of specific binding molecules may be configured to detect a different tau protein or a fragment thereof. For example:

- A first pair of specific binding molecules that bind to an epitope within residues 337 to 355 of SEQ ID NO: 1 and to an epitope within residues 367 to 379 of SEQ ID NO: 1, respectively, may be configured to detect total tau comprising the PHF;
- A second pair of specific binding molecules that bind to an epitope within residues 337 to 355 of SEQ ID NO: 1 and to an epitope within residues 379 to 391 of SEQ ID NO: 1, respectively, may be configured to detect dGAE and full length tau but not fragments lacking E391 such as dGA; and
- A third pair of specific binding molecules that bind to an epitope within residues 337 to 355 of SEQ ID NO: 1 and to an epitope within residues 13 to 25 of SEQ ID NO: 1, respectively, may be configured to detect full-length tau.

The method may further comprise a step of determining the levels of the different tau proteins or a fragment(s) thereof. The method may further comprise a step of comparing the levels of the different tau proteins or a fragment(s) thereof.

In a specific embodiment, the method comprises detecting a tau protein or a fragment thereof in a sample comprising:

- a) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule comprising the CDRs of S1D12 and a specific binding molecule comprising the CDRs of S1G2;
- b) contacting the sample with a second pair of specific binding molecules comprising a specific binding molecule comprising the CDRs of S1D12 and a specific binding molecule comprising the CDRs of E2E8; and
- c) contacting the sample with a third pair of specific binding molecules comprising a specific binding molecule comprising the CDRs of S1D12 and a specific binding molecule comprising the CDRs of CB7;

wherein each pair of specific binding molecules is contacted to the sample in parallel.

The invention provides distinguishing and/or determining the levels of hT40, dGAE and dGA in a sample accordingly.

According to a fifteenth aspect, the invention provides a diagnostic method comprising contacting a sample with a specific binding molecule of the first aspect of the invention.

The diagnostic method may comprise the *in vitro* method for detecting a tau protein or a fragment thereof in a sample according to the fourteenth aspect.

The method may further comprise diagnosing a tauopathy if a tau protein or a fragment thereof is detected.

The specific binding molecule may bind to an epitope within residues 296 to 391 of SEQ ID NO: 1. Preferably, the specific binding molecule binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 or to an epitope within residues 367 to 379 of SEQ ID NO: 1

An advantage of the present invention is the provision of a diagnostic test for a tauopathy which can be performed using a plasma sample. Plasma samples are easier, faster and safer to obtain than CSF samples. However, very limited published data are available supporting a diagnostic test for a tauopathy, particularly Alzheimer's disease, in a plasma sample. The complexities of extracellular tau and the limited progress towards developing a blood-based screen for Alzheimer's disease are reviewed in Chen *et al* (2019) *Alzheimers Dement.* 15(3): 487–496. Chen *et al* concluded that “most plasma tau is full length”. None of the antibodies described targeted residues 296 to 391 of full-length Tau (see Figure 1A). The authors suggest using N-terminal assays in a diagnostic context. Two N-terminal assays are described:

- NT1 requires a minimal sequence of residues 6 to 198 of full-length tau.
- NT2 requires a longer sequence of residues 6 to 224 of full-length tau.

Chen *et al* suggest use of the NT1 assay, rather than the NT2 assay is preferred in a diagnostic context. Chen *et al* therefore teach away from using a specific binding molecule that binds to an epitope within residues 296 to 391 of SEQ ID NO: 1.

The levels of tau measured when using our core capture antibody S1D12 as part of an antibody pair is 1,000-fold more than the typical values seen for the existing NT1 assay in human plasma. In contrast to the reported NT1 assay, where AD/MCI patients typically show higher assay values than healthy controls, for assays using S1D12 capture this pattern is surprisingly reversed with health control samples showing higher tau fragment values than AD/MCI patients. The levels of tau detected using the core capture antibody are significantly greater than previously reported and suggests that the use of S1D12 reveals large amounts of previously undetected tau fragments in biological samples. The use of a specific binding molecule comprising the CDRs of S1D12 therefore provides a surprisingly sensitive AD / MCI diagnostic assay with improved performance over the existing NT1 assay in human plasma samples. These findings translate to higher levels of core-proline fragments in healthy control and form the basis of a regular monitoring test to identify patients worthy of additional screening, i.e. a potential predictor of early onset of disease.

The method may comprise contacting the sample with a pair of specific binding molecules that bind to an epitope within residues 337 to 355 of SEQ ID NO: 1 and to an epitope within residues 367 to 379 of SEQ ID NO: 1, respectively.

Preferably, the method comprises contacting the sample with a pair of specific binding molecules comprising a first specific binding molecule comprising the CDRs of S1D12 and a second specific binding molecule comprising the CDRs of S1G2.

In a study using human plasma samples disclosed herein, the inventors have unexpectedly shown an ability to discriminate between AD patients and healthy controls using a combination of S1D12 and S1G2. While the combination of S1D12 and CB7 (which binds an N-terminal epitope of Tau13-25) does not show an overall difference in values between AD and healthy control groups. CB7 binds within the NT1 region of Chen *et al* (2019) and overlaps with the epitope of the Tau12 antibody (6-18) used in NT1. These data therefore show an unexpected advantage of using a first specific binding molecule comprising the CDRs of S1D12 and a second specific binding molecule comprising the CDRs of S1G2 to diagnose Alzheimer's disease.

The diagnostic method may comprise contacting a plasma sample with a pair of specific binding molecules comprising a first specific binding molecule comprising the CDRs of S1D12 and a second specific binding molecule comprising the CDRs of S1G2, wherein the tauopathy is Alzheimer's disease.

A specific binding molecule used in the method of the fourteenth of the fifteenth aspects of the invention may be a specific binding molecule comprising the CDRs of CB7 and/or CC7. The epitopes of CB7 and CC7 fall in regions of tau with no homology between the human and mouse tau sequences. The diagnostic utility of these specific binding molecules is demonstrated by their ability to recognise the presence of pathologic human tau in a transgenic mouse brain against a background of endogenous mouse tau protein. These specific binding molecules may therefore be utilised to track the fragmentation patterns of pathologic tau species during aging and in relation to any pharmacologic treatments that may affect the (human) tau protein, its aggregation, movement between compartments in the body (e.g. between brain and blood) and its pattern of fragmentation.

The *in vitro* method for detecting a tau protein or a fragment thereof according to the fifteenth aspect of the invention, or the diagnostic method according to the sixteenth aspect of the invention may comprise contacting the sample with a pair of first and second specific binding molecules, wherein the pair of first and second specific binding molecules wherein the first specific binding molecule binds within the core region of tau (such as to an epitope within residues 337 to 355 or 367 to 379 of SEQ ID NO: 1) and the second specific binding molecule binds to an epitope within residues 13 to 25 of SEQ ID NO: 1. The first specific binding molecule may comprise the CDRs of S1D12 or S1G2. The second specific binding molecule may comprise the CDRs of CB7. Such pairings have the advantage of detecting tau fragments that contain the amino acids spanning from 13-379 of SEQ ID NO:1. The inventors have shown that such fragments decrease with aging in L66 <sup>+/+</sup> mice, suggesting that either a truncation or epitope occlusion event is occurring or that multiple events of this nature are occurring during the aging of L66 <sup>+/+</sup> mice. Methods enabling detection of tau fragments that contain the amino acids spanning from 13-379 of SEQ ID NO:1 may therefore provide an early marker for pathology associated events.

The *in vitro* method for detecting a tau protein or a fragment thereof according to the fifteenth aspect of the invention, or the diagnostic method according to the sixteenth aspect of the invention may comprise contacting the sample with a pair of first and second specific binding molecules, wherein the pair of first and second specific binding molecules wherein the first specific binding molecule binds N-terminally to the core region of tau (such as to an epitope within residues 147 to 163, residues 159 to 163, or 147 to 157 of SEQ ID NO: 1) and the second specific binding molecule binds to an epitope within residues 13 to 25 of SEQ ID NO: 1. The first specific binding molecule may comprise the CDRs of HT7, or an alternative specific binding molecule disclosed herein with a nearby or overlapping epitope, such as 3aA6 and 3aD6 which bind to the adjacent epitope within residues 147 to 157 of SEQ ID NO: 1. The second specific binding molecule may comprise the CDRs of CB7. Such pairings have the advantage of detecting tau fragments that contain the amino acids spanning from 13-163 or 13-157 of SEQ ID NO:1. The inventors have shown that such fragments increase with aging in L66 <sup>+/+</sup> mice, suggesting that levels of smaller, truncated fragments of human tau increase during the aging of L66 <sup>+/+</sup> mice. Methods enabling detection of tau fragments that contain the amino acids spanning from 13-163 or 13-157 of SEQ ID NO:1 may therefore provide an early marker for pathology associated events.

The *in vitro* method for detecting a tau protein or a fragment thereof according to the fifteenth aspect of the invention, or the diagnostic method according to the sixteenth aspect of the invention may comprise contacting the sample with a pair of first and second specific binding molecules, wherein the pair of first and second specific binding molecules are a pair identified in Table 26 or 27, or a pair comprising the CDRs of each of a pair of antibodies identified in Table 26 or 27 or are a pair of antibodies targeting the same, adjacent or overlapping epitopes as a pair of antibodies identified in Table 26 or 27.

According to a sixteenth aspect, the invention provides a diagnostic device for use in a method according to the fifteenth aspect of the invention.

The device may comprise any suitable components described in connection with the fourteenth aspect of the invention.

The device may comprise equipment for measuring the level of a tau protein or a fragment thereof in a sample comprising a sample collection device and an immunoassay. The equipment may further comprise a detector for detecting labelled tau protein or a fragment thereof or labelled antibodies to the tau protein or a fragment thereof in the immunoassay.

The immunoassay or equipment may be incorporated into a miniaturised device for measuring the level of a tau protein or a fragment thereof in a biological sample. Suitably, the device may comprise a lab-on-a-chip.

The device may comprise one or more parts defining an internal channel having an inlet port and a reaction zone.

In some embodiments, the device may comprise a plurality of channels, each with its own inlet port, for measuring the levels of a plurality of different tau protein or a fragment(s) thereof in the sample in parallel. Therefore, each channel may include a different respective immobilised primary antibody or tau protein or a fragment thereof.

Suitably, the device may comprise one or more selectively operable valves associated with the one or more inlet ports for controlling the admission of a sequence of different reagents into the channels such, for example, as the sample, wash solutions, primary antibody, secondary antibody and enzyme substrate.

The device therefore may comprise a microfluidics device. The channel may include a reaction zone. Microfluidics devices are known to those skilled in the art. A review of microfluidic immunoassays or protein diagnostic chip microarrays is provided by Chin et al. 2012. *Lab on a Chip*. 2012; 12:2118-2134. A microfluidics device suitable for carrying out an ELISA immunoassay at a point-of-care is disclosed by Chan CD, Laksanasopin T, Cheung YK, Steinmiller D et al. "Microfluidics-based diagnostics of infectious diseases in the developing world". *Nature Medicine*. 2011;17(8):1015-1019, the contents of which are incorporated herein by reference.

According to a seventeenth aspect, the invention provides a kit comprising a specific binding molecule according to the first aspect of the invention and reagents for detecting a tau protein or a fragment thereof in a sample.

The kit may comprise a first specific binding molecule that binds to an epitope within residues 296 to 391 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within SEQ ID NO: 1.

The kit may comprise any suitable components described in connection with the fourteenth aspect of the invention.

The kit may comprise an enzyme such, for example, as horseradish peroxidase (HRP). Suitable substrates for HRP are well known in the art and include, for example, ABTS, OPD, AmplexRed, DAB, AEC, TMB, homovanillic acid and luminol.

The kit may comprise one or more specific binding molecules or tau protein or a fragment thereof immobilised on a surface of a well or plate or on the surface of a plurality of magnetic or non-magnetic beads.

The kit may comprise a labelled secondary antibody to the tau protein or a fragment thereof or to a primary antibody to the tau protein or a fragment thereof for quantifying the amount of the tau protein or a fragment thereof bound to surface-bound antibodies or the amount of primary antibody bound to the tau protein or a fragment thereof immobilised on a surface.

The present invention will now be described by way of reference to the following Examples and accompanying Drawings which are present for the purposes of illustration only and are not to be construed as being limiting on the invention.

Example 1: Sheep Immunisation using tau protein antigens and analysis of antigen specific immune response

Two Welsh bred sheep were hyperimmunised with full length tau protein (2N4R, referred as hT40 in this study) and truncated tau (dGAE, representing the core repeat region corresponding to amino acids 297-391 of hT40) separately to generate antigen specific immune response. For primary immunisation, 500 µg of hT40 or dGAE was mixed with Freund's complete adjuvant in a final volume of up to 2 ml and administered per sheep. For subsequent boosts at 4 weeks intervals, 250 µg of each antigen was mixed with Freund's incomplete adjuvant and administered per sheep. The immune responses were monitored by performing binding ELISA using polyclonal sera collected after 10-14 days of subsequent boosts (Figure 7).

ELISA plates were coated with 1 µg/ml hT40 or dGAE by incubation at 37°C for 1 h or 4°C overnight, followed by blocking with PBS containing 2% Marvel (MPBS) at 37°C for 1 h. After each step the plates were washed three times with PBS containing 0.1% tween 20 (PBST) and three times with PBS. Sheep polyclonal sera was added to designated wells (pre-immune and subsequent boost samples), double diluted in PBS across the plate and incubated at room temperature for 1 h. Anti-sheep IgG HRP conjugated secondary antibody (Sigma A3415,) was added to the wells and incubated as before. The resulting immunoreaction was developed by adding SureBlue TMB substrate solution, the reaction was stopped using 1 M H<sub>2</sub>SO<sub>4</sub> and the absorbance values measured using a microplate reader at absorbance 450 nm.

Antigen specific immune response was achieved after the first boost for both hT40 and dGAE immunised sheep (Figure 7a and 7b) and the levels peaked at boost 2, 3 and 4 without any further improvement in antibody titre. Therefore after 4th boost immunisation, approx. 350 ml of blood was collected from each sheep, PBLs separated using standard techniques and stored in RNA later solution for the extraction of mRNA and further amplification of antibody genes for library construction.

Example 2: Construction of phage display antibody libraries from the immunorepertoire of sheep



Peripheral blood lymphocytes (PBLs) were prepared from sheep blood using Accuspin system Histopaque 1077 columns (Sigma, Cat No: A7054) according to manufacturer's instructions. Total RNA was extracted using RNeasy midi kit (QIAGEN) and cDNA was synthesised by RT-PCR using sheep antibody constant region-specific primers (OvCHFOR 5'-GAC TTT CGG GGC TGT GGT GGA GGC-3', OvCKFOR 5'-GA TGG TTT GAA GAG GGA GAC GGA TGG CTG AGC-3', OvCLFOR 5'-A CAG GGT GAC CGA GGG TGC GGA CTT GG-3'). Sheep IgG VH and V $\lambda$ /Vk repertoires were created by PCR amplification as per published methods using V region specific primers (Charlton et al., 2000). For joining of antibody genes, PCR products were enzymatically digested and ligated using the restriction sites Ascl for heavy chain and Mlul for light chain at the 15 amino acid cellulase linker region incorporated through PCR design. The cloning sites NcoI and NotI were incorporated to the ligated DNA through PCR and the resultant scFv DNA fragments were cloned into a phagemid vector pHEN 2a (Hoogenboom et al 1991). Separate VH-V $\lambda$  and VH-Vk antibody phage display libraries were created by transformation of electrocompetent E. coli TG1 cells (Lucigen Corp).

Two separate phage display libraries were constructed for dGAE and hT40 immunisation hereby referred to as tau antibody library 1 and library 2 respectively. These resultant VH-V $\lambda$  and VH-Vk libraries were rescued separately through helper phage infection following published methods (Charlton et al., 2001) and subjected to biopanning including forced epitope selection for the isolation of phage binders with desired specificity and binding affinity.

### Example 3: Selection and screening of dGAE and hT40 phage display antibody libraries

Several biopanning strategies were employed to isolate tau protein specific binders from Library 1 and Library 2.

Helper phage rescued Library 1 was subjected to three selection campaigns as outlined in Table 11. Screening of phage monoclonals using ELISA identified several phage binders, which showed specific binding to the antigens used for selection namely dGA (representing amino acid sequences 297-390 of hT40) and dGAE. These phage binders were grouped into two – (1) dGAE specific binders - (2) dGAE cross reactive binders which recognised dGAE, dGA and hT40. DNA sequencing revealed rich diversity in the selected positive phage population and unique phage clones were reformatted into single chain antibodies (scAbs) by cloning the respective scFv gene (VH-linker-VL) into the bacterial expression vector pIMS147 (reference) using NcoI and NotI restriction enzymes. Unique sequences from these selections were given in a separate document along with sequence IDs.

In order to distinguish between positive clones arising from different selection strategies, the following nomenclature was used.

All positive clones from Library 1 selection 1 were given a prefix 'E' (dGAE panning)

All positive clones from Library 1 selection 2 were given a prefix 'NS' (non-stringent dGA panning)

All positive clones from Library 1 selection 2 were given a prefix 'S' (stringent dGA panning)

All positive clones from Library 1 where a repeat of selection 2 strategy was performed were given a prefix 'M'

*Table 12: Showing the three different selection strategies for Library 1 and the concentrations of dGA or dGAE antigen used for different rounds of panning.*

|                                  |                        |                       |                       |
|----------------------------------|------------------------|-----------------------|-----------------------|
| <b>Library 1<br/>Selection 1</b> | Pan 1 - 50 µg/ml dGAE  | Pan 2 - 10 µg/ml dGAE | Pan 2 - 1 µg/ml dGAE  |
| <b>Library 1<br/>Selection 2</b> | Pan 1 - 100 µg/ml dGA  | Pan 2 - 50 µg/ml dGAE | Pan 2 - 10 µg/ml dGAE |
| <b>Library 1<br/>Selection 3</b> | Pan 1 - 100 µg/ml dGAE | Pan 2 - 10 µg/ml dGAE | Pan 2 - 1 µg/ml dGAE  |

Similarly, helper phage rescued Library 2 was subjected to five different selection campaigns using the following antigens as outlined in Table 2 and unique phage binders to respective antigens were reformatted into scAbs as described previously. Antigens used for selection are - hT40, R1-3 (representing amino acids in the region 266-359 on hT40) and biotinylated 412-441 (representing amino acids in the region 412-441 on hT40). In selection strategies 4 and 5, a step to deselect dGA binding phage population was introduced to encourage the enrichment of clones outside of 297-390 region on the tau protein.

Table 13: Showing the five different selection strategies for Library 2 and the concentrations of various antigens used for different rounds of panning.

|                                  |                           |                                          |                         |
|----------------------------------|---------------------------|------------------------------------------|-------------------------|
| <b>Library 2<br/>Selection 1</b> | Pan 1 - 100 µg/ml hT40    | Pan 2 - 10 µg/ml hT40                    | Pan 2 - 1 µg/ml hT40    |
| <b>Library 2<br/>Selection 2</b> | Pan 1 - 100 µg/ml R1-3    | Pan 2 - 50 µg/ml R1-3                    | Pan 2 - 10 µg/ml R1-3   |
| <b>Library 2<br/>Selection 3</b> | Pan 1 - 100 µg/ml 412-441 | Pan 2 - 10 µg/ml 412-441                 | Pan 2 - 1 µg/ml 412-441 |
| <b>Library 2<br/>Selection 4</b> | Pan 1 - 100 µg/ml hT4Z    | Pan 2 - 50 µg/ml hT40<br>dGA deselection | Pan 2 - 10 µg/ml hT40   |
| <b>Library 2<br/>Selection 5</b> | Pan 1 - 100 µg/ml hT40    | Pan 2 - 10 µg/ml hT40<br>dGA deselection | Pan 2 - 0.1 µg/ml hT40  |

In order to distinguish between positive clones arising from different selection strategies, the following nomenclature was used.

All positive clones from Library 2 selection 1 and selection 2 were given a prefix 'C'

All positive clones from Library 2 selection 3 were given a prefix '412'

All positive clones from Library 2 selection 4 and selection 5 were given prefixes '3a' and '3b' respectively

#### Example 4: Expression of reformatted scAbs in bacterial system and purification using affinity chromatography

Bacterial stocks of positive clones were grown in Terrific Broth (TB) medium supplemented with PO<sub>4</sub> salts, 100 µg/ml ampicillin and 1% w/v glucose to reach desired cell density, induced with 1 mM IPTG and expressed scAbs in the periplasm was released using the osmotic shock solution (100 ml 200 mM Tris-HCl-20% sucrose, 200 µl 0.5 M EDTA and 0.5 mg lysozyme followed by 5Mm MgSO<sub>4</sub>) and incubating on ice for 15 minutes each. Recombinant anti-tau scAbs present in crude periplasmic extracts were purified using IMAC columns via binding of hexa Histidine tagged protein to activated Ni-sepharose beads and elution using 200 mM Imidazole. Eluted protein samples were dialysed against 1 x PBS pH 7.4 and purity analysed on 4-12% Bis-Tris gels using SDS-PAGE. All expressed scAbs were found to be 90% pure. Protein concentrations were determined by running a standard scAb of known concentration alongside unknown samples using SDS-PAGE and comparing the intensities of the protein bands using ImageJ. Alternatively, absorbance values at 280 nm were measured using

Ultraspec 6300 pro UV/Visible spectrophotometer (Amersham, Biosciences) and final scAb concentrations determined from the values obtained.

Example 5: Mapping of specific binding regions and affinity ranking of anti-tau scAbs

A series of binding ELISA was performed using various truncated versions of the tau protein and 13mer peptide libraries spanning the entire hT40 molecule for mapping the epitopes of anti-tau scAbs (Full list of protein antigens used is given in Table 14). In general, ELISA plates were coated with 1 ug/ml hT40 or dGA or dGAE or other truncated versions of the protein and in the case of biotinylated peptides, plates were coated with 5 µg/ml Streptavidin followed by 1 µg/ml biotinylated peptide. The plates were blocked with 2% MPBS and scAb samples added at desired starting concentrations and double diluted across the plate. Binding was detected using anti-Human C Kappa HRP conjugated secondary antibody and the resulting immunoreaction was developed and absorbance values measured as described above.

For affinity ranking ELISA, plates were coated with 1 µg/ml hT40 or dGA or dGAE as before and blocked as normal. Anti-tau scAbs at a starting concentration of 25 ug/ml or 1 µg/ml was added to designated wells and a serial dilution in 1 x PBS was performed for each sample. Binding reaction was determined as before, and the scAbs were ranked based on their absorbance values and top binding scAbs were selected for affinity studies using Surface Plasmon Resonance technology.

*Table 14: Listing various truncated versions of hT40 and biotinylated peptide antigens used for epitope mapping of anti-tau scAbs.*

|           |                 |                |                  |
|-----------|-----------------|----------------|------------------|
| Tau 1-49  | m186-350        | m268-391       | N biotin 306-323 |
| Tau 1-201 | C2 -186-319     | m352-441       | N biotin 301-325 |
| Tau 1-227 | 42a- 186-350    | m348-441       | N biotin 331-360 |
| B1- 1-391 | m113-319        | Tau 275-305    | N biotin 301-359 |
| Tau 1-251 | m113-201        | Tau 323-335    | N biotin 337-355 |
| Tau 1-319 | m113-251        | Tau 297-315    | C biotin 337-355 |
| Tau 1-155 | m186-251        | dGAE (297-391) | N biotin 339-351 |
| Tau 1-286 | m186-390+D/GA/S | dGA (297-390)  | N biotin 341-353 |

|           |                     |                  |                                            |
|-----------|---------------------|------------------|--------------------------------------------|
| Tau 1-391 | m186-319/+GAE/DHGAE | Tau 337-368      | N biotin 379-390                           |
| Tau 1-238 | m221-441            | Tau 377-390      | N biotin 390-414                           |
| m113-238  | m239-441            | Tau 306-336      | hT40 13mer library N terminal biotinylated |
| m113-155  | m221-319            | Tau 377-391      |                                            |
| m186-441  | m239-319            | Tau 360-378      |                                            |
| m186-391  | m268-441            | N biotin 412-441 |                                            |

**Example 6: Detailed mapping of core region binding anti-tau scAbs**

Positive scAbs from Library 1 selections - 'E', 'NS', 'S' and 'M' clones (as described previously) were checked for hT40, dGA and dGAE binding using direct binding ELISA. scAbs specifically binding to dGAE were grouped as 'E' dependant and showed no cross reactivity towards hT40. Selected E specific scAbs and their specific binding to dGAE is shown below (Fig 8 A-E).

*Table 15: A summary of specific scAb binding to various tau truncations and protein fragments representing regions of the tau molecule. A further narrowing down of binding regions was achieved for some scAbs, including those showing positive reactivity to shorter epitopes within 13mer peptides is also shown*

| scAb clones | Tau proteins/fragments with positive scAb reactivity | Shortest region bound on hT40 |
|-------------|------------------------------------------------------|-------------------------------|
| E1E8        | 297-391 (dGAE)                                       | 391'E'                        |
| E2A6        | 297-391 (dGAE)                                       | 391'E'                        |
| E2B7        | 297-391 (dGAE)                                       | 391'E'                        |
| E2E8        | 297-391 (dGAE)                                       | 391'E'                        |
| E1B8        | 297-390 (dGA), 297-391 (dGAE), 313-336               | 313-336                       |

Similarly, dGA binding 'NS', 'S' and 'M' group scAbs were subjected to further antigen binding ELISA using shorter tau proteins and biotinylated 13mer peptides as shown below (Fig 10 A-F) and (Fig 11 A-R).

Table 16: A summary of specific scAb binding to various tau truncations and protein fragments representing regions of the tau molecule. A further narrowing down of epitopes was achieved for some scAbs, including those showing positive reactivity to shorter epitopes, contained within 13mers, or recognising two epitopes are shown.

| scAb clones | Tau proteins/fragments with positive scAb reactivity           | Shortest region bound on hT40 |
|-------------|----------------------------------------------------------------|-------------------------------|
| NS3E5       | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 369-390                       |
| NS3H4       | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 369-390                       |
| NS4F2       | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 369-390                       |
| NS4E3       | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 369-390                       |
| NS3D9       | hT40, 297-390 (dGA), 297-391 (dGAE), 266-359, 337-368          | 337-355                       |
| NS1G7       | hT40, 297-390 (dGA), 297-391 (dGAE), 275-305, 337-368          | 275-305, 337-368              |
| NS2A3       | hT40, 297-390 (dGA), 297-391 (dGAE), 337-368                   | 337-368                       |
| NS2A8       | hT40, 297-390 (dGA), 297-391 (dGAE), 337-368                   | 337-368                       |
| NS2C5       | hT40, 297-390 (dGA), 297-391 (dGAE), 337-368                   | 337-368                       |
| NS2C8       | hT40, 297-390 (dGA), 297-391 (dGAE), 337-368                   | 337-368                       |
| NS2D3       | hT40, 297-390 (dGA), 297-391 (dGAE), 337-368                   | 337-368                       |
| NS2A1       | hT40, 297-390 (dGA), 297-391 (dGAE)                            | No binding to 13mer peptides  |
| NS2B6       | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| NS1B2       | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| S1A5        | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| S1A12       | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| S1E12       | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| S1D5        | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 297-390                       |
| S1D12       | hT40, 297-390 (dGA), 297-391 (dGAE), 186-350, 266-359, 337-368 | 337-355                       |
| S2C1        | hT40, 297-390 (dGA), 297-391 (dGAE), 186-350, 266-359, 337-368 | 337-355                       |
| S1B1        | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 367-379                       |
| S1D2        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S1D9        | hT40, 297-390 (dGA), 297-391 (dGAE)                            | 367-379                       |
| S1F4        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S1G2        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S1G10       | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S1H6        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S1H9        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |
| S2C3        | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379                       |

|          |                                                                |                     |
|----------|----------------------------------------------------------------|---------------------|
| S2C6     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |
| S2C7     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |
| S2D1     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |
| S2D4     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |
| S2D3     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391, 275-305 | 367-379,<br>275-305 |
| MD9/MoD9 | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 373-385             |
| ME12     | hT40, 297-390 (dGA), 297-391 (dGAE), 341-353, 337-349, 339-351 | 337-355             |
| MC5      | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |
| MD12     | hT40, 297-390 (dGA), 297-391 (dGAE), 369-390, 369-391          | 367-379             |

**Example 7: Detailed mapping of binding of 'C', '412', '3a' and '3b' series clones**

'C', '412', '3a' and '3b' group scAbs were subjected to further antigen binding ELISA using shorter tau proteins and biotinylated 13mer peptides as shown below (Fig 12 A-F) and (Fig 13 A-R).

*Table 17: A summary of 'C' group scAb binding to various tau truncations and protein fragments representing regions of the tau molecule. A further narrow down of binding regions achieved for some scAbs, including those showing positive reactivity to shorter epitopes and 13mers peptide libraries are shown.*

| scAb clones | Tau proteins/fragments with positive scAb reactivity | Shortest region bound on hT40 |
|-------------|------------------------------------------------------|-------------------------------|
| CA1         | hT40, 1-238, 1-319, 1-155, 155-238                   | 155-238                       |
| CA2         | hT40, 1-49, 1-319, 1-155, 186-350, 348-441           | 1-155                         |
| CA3         | hT40, 1-319, 186-350                                 | 186-263                       |
| CA4         | hT40, 239-441, 297-390 (dGA)                         | 355-367                       |
| CA6         | hT40, 239-441, 348-441                               | 348-390                       |
| CA7         | hT40, 1-319                                          | 1-319                         |
| CA8         | hT40, 1-319                                          | 1-319                         |
| CA9         | hT40, 239-441, 348-441, 297-390 (dGA)                | 367-379                       |
| CA10        | hT40, 1-319                                          | 227-319                       |
| CA11        | hT40, 239-441, 348-441                               | 348-441                       |
| CA12        | hT40, 297-390 (dGA)                                  | 367-379                       |
| CB2         | hT40, 348-441                                        | 359-391                       |
| CB3         | hT40, 297-390 (dGA)                                  | 360-390                       |
| CB5         | hT40, 1-319                                          | 49-113                        |

|      |                                                                              |         |
|------|------------------------------------------------------------------------------|---------|
| CB6  | hT40, 1-49, 1-155, 1-319, 113-251                                            | 1-238   |
| CB7  | hT40, 1-49, 1-155, 1-319                                                     | 13-25   |
| CB9  | hT40, 239-441                                                                | 239-348 |
| CB10 | hT40, 1-49, 1-319                                                            | 1-319   |
| CB11 | hT40, 1-319                                                                  | 113-238 |
| CB12 | hT40, 1-49, 1-155, 1-319, 113-251, 186-350, 266-359 (R1-3), 297-441          | 115-227 |
| CC3  | hT40, 1-49, 1-155, 1-319, 186-350                                            | 155-227 |
| CC4  | hT40, 1-155, 1-319                                                           | 49-155  |
| CC5  | hT40, 1-49, 1-155, 1-319, 113-251, 186-350                                   | 49-238  |
| CC7  | hT40, 1-319                                                                  | 145-157 |
| CC12 | hT40, 239-441, 297-390 (dGA)                                                 | 297-390 |
| CD1  | hT40, 1-49, 1-155, 1-319, 113-251, 186-350, 239-441, 266-359 (R1-3), 297-441 | 49-155  |
| CD2  | hT40, 1-319, 113-319, 113-251, 186-350                                       | 186-350 |
| CE2  | hT40, 266-359 (R1-3)                                                         | 319-331 |
| CE3  | hT40, 266-359 (R1-3)                                                         | 331-360 |
| CG11 | hT40, 186-350, 266-359 (R1-3)                                                | 266-359 |

*Table 18: A summary of '3a' & '3b' series scAbs binding to various tau truncations and protein fragments representing regions of the tau molecule. A further narrow down of binding regions achieved for some scAbs, including those showing positive reactivity to shorter epitopes and 13mers peptide libraries are also shown.*

| scAb clones | Tau proteins/fragments with positive scAb reactivity | Short epitope on hT40 |
|-------------|------------------------------------------------------|-----------------------|
| 3aD3        | 1-155, 1-111, 1-49                                   | 1-49                  |
| 3aH6        | 1-155, 1-111, 1-49                                   | 1-49                  |
| 3aG3        | 1-155, 1-111, 1-49                                   | 1-49                  |
| 3bG4        | 1-155, 1-111, 1-49                                   | 1-49                  |
| 3aB7        | 1-155, 1-111                                         | 49-111                |
| 3bF4        | 1-155, 1-111                                         | 49-111                |
| 3aA6        | 1-155, 113-251, 145-157                              | 147-157               |
| 3aD6        | 1-155, 113-251, 145-157                              | 147-157               |



**Example 8: Determination of critical binding residues on selected scAbs using Alanine Scanning Mutagenesis (ASM)**

To further elucidate epitopes of the scAb panel, and identify the critical amino acids needed for binding, alanine scanning mutagenesis of the parent 13 aa peptides for scAbs CE2, S1D12, CA4 and S1G2 was performed. For clones CE2 and CA4, no reactivity was observed for the first and last three overlapping amino acids in the 13mer peptide library which was used for epitope mapping and therefore only the 7 core amino acid sequences were subjected to alanine substitution for these antibodies. Briefly, 5 µg/ml streptavidin (Thermo Fisher) was adsorbed to Nunc 96-well MaxiSorp plates and following incubation at 37 °C for 1 h, the plates were washed as normal and blocked with 2 % MPBS. N-terminally biotinylated peptides (ProlImmune Ltd) were added to the plates and incubated for 1 h at 37 °C. Subsequently, test scAbs at starting concentrations of 100-500 nM was added and double diluted across the plate for each peptide and incubated for 1 h at 37°C. Rest of the ELISA was conducted as described above and the plates were read at absorbance 450 nm. Immunoreactivity of the scAb of interest was quantified as the % of scAb was bound for each peptide at a chosen concentration (Figure 15-20).

**Example 9: CE2 Binding region on hT40: 319-331**

*Table 19 Amino acid sequences of the parent peptide and alanine substituted peptides for identifying the critical binding sequences for CE2 scAb*

| ASM positions | Peptide Sequences              |
|---------------|--------------------------------|
| Parent        | TSK <b>C</b> GSLGNIHHK         |
| 322A          | TSK <b>A</b> GSLGNIHHK         |
| 323A          | TSK <b>C</b> <b>A</b> SLGNIHHK |
| 324A          | TSKCG <b>A</b> LGNIHHK         |
| 325A          | TSKCGS <b>A</b> GNIHHK         |
| 326A          | TSKCGSL <b>A</b> NIHHK         |
| 327A          | TSKCGSLG <b>A</b> IHHK         |
| 328A          | TSKCGSLGN <b>A</b> H HK        |

**Example 10: S1D12 & ME12 Binding region on hT40: 341-353**

*Table 20: Amino acid sequences of the parent peptide and alanine substituted peptides for identifying the critical binding sequences for S1D12 scAb and ME12 scAb*

| ASM positions | Peptide Sequences |
|---------------|-------------------|
| Parent        | SEKLDFKDRVQSK     |

|      |                           |
|------|---------------------------|
| 341A | A EK L D F K D R V Q S K  |
| 342A | S A K L D F K D R V Q S K |
| 343A | S E A L D F K D R V Q S K |
| 344A | S E K A D F K D R V Q S K |
| 345A | S E K L A F K D R V Q S K |
| 346A | S E K L D A K D R V Q S K |
| 347A | S E K L D F A D R V Q S K |
| 348A | S E K L D F K A R V Q S K |
| 349A | S E K L D F K D A V Q S K |
| 350A | S E K L D F K D R A Q S K |
| 351A | S E K L D F K D R V A S K |
| 352A | S E K L D F K D R V Q A K |
| 353A | S E K L D F K D R V Q S A |

Example 11: CA4 Binding region on hT40: 355-367

*Table 21: Amino acid sequences of the parent peptide and alanine substituted peptides for identifying the critical binding sequences for CA4 scAb*

| Peptide | Sequence                  |
|---------|---------------------------|
| Parent  | G S L D N I T H V P G G G |
| 358A    | G S L A N I T H V P G G G |
| 359A    | G S L D A I T H V P G G G |
| 360A    | G S L D N A T H V P G G G |
| 361A    | G S L D N I A H V P G G G |
| 362A    | G S L D N I T A V P G G G |
| 363A    | G S L D N I T H A P G G G |
| 364A    | G S L D N I T H V A G G G |

Example 12: Clones with binding region 367-379 on hT40

Several antibody clones were shown to bind to the region 367-379 on hT40 molecule (Table 16 & 17) and were grouped together and subjected to detailed analysis of critical binding residues using ASM peptides as described above. Amino acid sequences of the parent peptide and alanine substituted mutants are given in Table 22. Binding profiles of S1G2 scAb to the parent peptide and mutants are shown in Fig 19 A-C. Similarly, percentage binding of other scAbs in the same group recognising hT40 367-379 to various alanine substituted mutants and the parent peptide are shown in Fig 20 A-J

Table 22 Amino acid sequences of the parent peptide and alanine substituted peptides for identifying the critical binding sequences for S1G2 and related scAbs binding to 367-379 region

| Peptide | Sequence               |
|---------|------------------------|
| Parent  | GNKKIETHKLTFR          |
| 367A    | <u>A</u> NKKIETHKLTFR  |
| 368A    | G <u>A</u> KKIETHKLTFR |
| 369A    | GN <u>A</u> KIETHKLTFR |
| 370A    | GNK <u>A</u> IETHKLTFR |
| 371A    | GNKK <u>A</u> ETHKLTFR |
| 372A    | GNKKI <u>A</u> THKLTFR |
| 373A    | GNKKIE <u>A</u> HKLTFR |
| 374A    | GNKKIET <u>A</u> KLTFR |
| 375A    | GNKKIETH <u>A</u> LTFR |
| 376A    | GNKKIETHK <u>A</u> TFR |
| 377A    | GNKKIETHKLA <u>F</u> R |
| 378A    | GNKKIETHKLT <u>A</u> R |
| 379A    | GNKKIETHKLT <u>F</u> A |

Example 13: Ranking of relative binding affinities of anti-tau scAbs using hT40 binding ELISA

The relative binding affinities of anti-tau scAbs were ranked by performing hT40 antigen binding ELISA as described previously.

Example 14: Analysis of the binding kinetics of anti-tau scAbs using Biacore X100™

Surface plasmon resonance (SPR) is widely regarded as the gold standard for real time measurement of protein-protein interactions such as antibody binding. All SPR experiments were carried out using a Biacore X100 machine and HBS EP+ running buffer (GE Healthcare). A 'capture' method was followed for affinity measurements, where an anti-human constant kappa chain (HuCk) antibody was conjugated to the surface of a CM5 sensor chip using an amine coupling kit and scAb molecules were immobilised via their HuCk domain. Amine coupling is a very common approach for immobilising the ligand to the chip surface. The chip surface has a dextran matrix derivatised with carboxyl groups, which after activation with N-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), form reactive succinimide esters which allows the covalent capturing of the ligand via any

available primary amine groups (e.g. Lysine) on the ligand (in this case anti-HuCk antibody). The capture antibody was diluted 1/100 in 10 mM Sodium acetate buffer pH 5.0 and passed over the activated chip surface for a period of at least 420 s. Final ligand immobilisation levels over 12,000 RU were deemed to be satisfactory.

Following immobilisation, the level of each scAb to be captured was identified using the standard SPR equation with a theoretical  $R_{\text{Max}}$  of 100 RU. Analyte MW refers to the molecular weight of hT40 or dGA/ dGAE molecules, while ligand MW refers to the molecular weight of the scAbs tested.  $R_L$  is the desired capture level and S refers to the stoichiometric ratio:

$$R_{\text{max}} = \frac{\text{Analyte MW}}{\text{ligand MW}} \times R_L \times S$$

The scAb to be tested was added only to flow cell 2 so that flow cell 1 could act as a control to subtract any interaction with the analyte and the chip surface. Both single and multi-cycle runs were utilised using wizards developed in the Biacore X100 control software which are both accepted methods of kinetic analysis (Karlsson, R., et al. Analyzing a kinetic titration series using affinity biosensors (2006) Analytical Biochemistry 349 :136-47). The multi-cycle protocol was as follows - Three start-up cycles composed of an initial capture, to the desired level, of the scAb to be tested was performed followed by a 30 s injection of glycine buffer pH 2.0 after each cycle to regenerate the chip surface. The regeneration step removed any captured scAb whilst leaving the capture antibody intact and able to repeat the capture for the next cycle. Following three start-up cycles increasing concentrations (0.15625 nM- 100 nM) of the target to be tested were added to the chip surface after the desired scAb capture. The target was added for a 120 s association period and 420 s dissociation period followed by another regeneration, 30 s injection of glycine buffer pH 2.0 in between each cycle.

The single cycle kinetics protocol was similar and utilised the same level of scAb capture. Three start-up cycles were used followed by 5 increasing concentrations of the analyte (6.25 nM - 100 nM) for an association period of 120 s followed by a dissociation period of 420 s for each concentration. In single cycle kinetics the regeneration step was performed only after the final analyte concentration was added. Binding responses were analysed in Biacore X100 evaluation software and data fitted to a 1:1 binding model to obtain kinetic and affinity characterisation. Kinetic rates and equilibrium binding constants of lead scAbs are given in Table No: 23-26.

*Table 23 Kinetic rates and equilibrium binding constants of lead scAbs for T441*

| Top clones (scAbs) | $k_a$ (1/Ms)        | $k_d$ (1/s)            | $k_D$ (M) for hT40 binding |
|--------------------|---------------------|------------------------|----------------------------|
| <b>S1D12</b>       | $1.252 \times 10^6$ | $1.5 \times 10^{-4}$   | 122 pM                     |
| <b>S1G2</b>        | $1.057 \times 10^6$ | $1.8 \times 10^{-4}$   | 170 pM                     |
| <b>S1E12</b>       | $3.85 \times 10^5$  | $3.19 \times 10^{-4}$  | 829 pM                     |
| <b>CC7</b>         | $2.957 \times 10^5$ | $3.659 \times 10^{-4}$ | 1.23 nM                    |
| <b>NS2A1</b>       | $2.521 \times 10^5$ | $7.393 \times 10^{-4}$ | 2.9 nM                     |

|                |                     |                        |         |
|----------------|---------------------|------------------------|---------|
| <b>CA4</b>     | $4.581 \times 10^5$ | $1.654 \times 10^{-3}$ | 3.61 nM |
| <b>CE3</b>     | $1.745 \times 10^5$ | $6.620 \times 10^{-4}$ | 3.79 nM |
| <b>412-E10</b> | $2.71 \times 10^5$  | $8.5 \times 10^{-4}$   | 3.16 nM |
| <b>CE2</b>     | $2.137 \times 10^5$ | $1.077 \times 10^{-3}$ | 5.03 nM |
| <b>CB7</b>     | $1.334 \times 10^5$ | $6.936 \times 10^{-4}$ | 5.19 nM |
| <b>E1B8</b>    | To be determined    |                        |         |
| <b>E2E8</b>    | No T441 binding     |                        |         |
| <b>MoD9</b>    | To be determined    |                        |         |

Table 24 - Kinetic rates and equilibrium binding constants of lead scAbs for dGA or dGAE

| Top clones (scAbs) | $k_a$ (1/Ms)        | $K_d$ (1/s)            | $k_D$ (M) for truncated tau binding |
|--------------------|---------------------|------------------------|-------------------------------------|
| <b>S1D12</b>       | $1.21 \times 10^6$  | $4.18 \times 10^{-4}$  | 344 pM (dGA)                        |
| <b>S1G2</b>        | $7.83 \times 10^5$  | $3.499 \times 10^{-4}$ | 447 pM (dGA)                        |
| <b>S1E12</b>       | $2.99 \times 10^6$  | $1.627 \times 10^{-3}$ | 543 pM (dGA)                        |
| <b>NS2A1</b>       | $1.88 \times 10^5$  | $1.02 \times 10^{-3}$  | 5.4 nM (dGA)                        |
| <b>E1B8</b>        | $1.37 \times 10^5$  | $2.42 \times 10^{-3}$  | 17.7 nM (dGA)                       |
| <b>E2E8</b>        | $4.77 \times 10^5$  | $1.915 \times 10^{-4}$ | 401 pM (dGAE)                       |
| <b>E1E8</b>        | $1.535 \times 10^5$ | $1.4 \times 10^{-3}$   | 6.3 nM (dGAE)                       |
| <b>MoD9</b>        | To be determined    |                        |                                     |
| <b>CE2</b>         | To be determined    |                        |                                     |

Table 25 - Kinetic rates and equilibrium binding constants of '3a' and '3b'scAbs for hT40

| scAb clones | $k_a$ (1/Ms)        | $k_d$ (1/s)            | $k_D$ (nM) for htau40 binding |
|-------------|---------------------|------------------------|-------------------------------|
| <b>3aA6</b> | $1.900 \times 10^4$ | $1.880 \times 10^{-2}$ | 989 nM                        |
| <b>3aB7</b> | $2.072 \times 10^5$ | $1.435 \times 10^{-2}$ | 69 nM                         |
| <b>3aD3</b> | $5.444 \times 10^5$ | $1.038 \times 10^{-2}$ | 19.1 nM                       |
| <b>3aD6</b> | $4.021 \times 10^5$ | $6.641 \times 10^{-3}$ | 16.5 nM                       |
| <b>3aH6</b> | $2.757 \times 10^6$ | $9.868 \times 10^{-3}$ | 3.6 nM                        |
| <b>3aG3</b> | $6.294 \times 10^4$ | $3.869 \times 10^{-4}$ | 6.1 nM                        |
| <b>3bA3</b> | $1.472 \times 10^4$ | $4.643 \times 10^{-3}$ | 315 nM                        |
| <b>3bC1</b> | $3.056 \times 10^4$ | $4.231 \times 10^{-3}$ | 138 nM                        |
| <b>3bF4</b> | $1.093 \times 10^5$ | $1.532 \times 10^{-2}$ | 140 nM                        |
| <b>3bG4</b> | $6.669 \times 10^6$ | $5.966 \times 10^{-2}$ | 8.9 nM                        |

Table 26 - Summary of equilibrium binding constants and binding regions of top anti-tau scAbs

| Top clones (scAbs) | Epitope | kD for hT40 binding |
|--------------------|---------|---------------------|
| CB7                | 13-25   | 5.19 nM             |
| CC7                | 145-157 | 1.23 nM             |
| NS2A1              | 297-390 | 2.9 nM              |
| S1E12              | 297-390 | 829 pM              |
| E1B8               | 316-336 | Not available       |
| CE2                | 319-331 | 5.03 nM             |
| CE3                | 331-360 | 3.79 nM             |
| S1D12              | 337-349 | 122 pM              |
| CA4                | 355-367 | 3.61 nM             |
| S1G2               | 367-379 | 170 pM              |
| MoD9               | 373-385 |                     |
| E2E8               | 391     | No hT40 binding     |
| 412-E10            | 412-441 | 3.16 nM             |

Example 15: IgG Reformating

Top anti-tau scAbs were reformatted into sheep-mouse (IgG2a) chimeric mAbs by inserting respective VH and VL genes into our dual plasmid eukaryotic vector system (pEE2a) encoding constant heavy and light chain genes of mouse IgG2a separately and expressing recombinant mAbs in a mammalian expression system. Based on the DNA sequencing data, VH and VL genes of shortlisted anti-tau scAbs were custom synthesised separately by introducing the cloning sites BssHII and BstEII (for VH genes) and BssHII and XhoI (for VL genes) at their 5' and 3' end respectively (GeneArt custom gene synthesis service by Thermofisher). Custom synthesised VH and VL genes of respective scAbs and the eukaryotic expression vectors pEE2aMH (encoding mouse IgG2a constant regions) and pEE2aML (mouse  $\lambda$ /k constant domain) were digested with restriction enzymes mentioned above. DNA bands corresponding to antibody variable regions and pEE2a heavy and light chain vector backbones were isolated and purified using DNA gel extraction and purification following QIAquick gel extraction kit manufacturer's instructions. Purified DNA fragments were ligated and used to transform electrocompetent E. coli TG1 cells for plasmid propagation. DNA sequencing of extracted plasmid confirmed successful reformating into sheep-mouse chimeric mAbs. Large scale preparation of heavy and light chain plasmids for each anti-tau mAb clone was performed (Qiagen Plasmid Mega kit) and used to transfect Human Embryonic Kidney (HEK293F) cells grown in suspension using polyethylenimine (PEI). The transfected cells were grown for 8 days before harvesting cell culture supernatants which were then purified using Protein A beads following standard protocols. Purified mAbs were confirmed for T40 binding using ELISA and their affinities (kD) values obtained by running Biacore assays as described previously, with changes as described below.

**Example 16: Analysis of the binding kinetics of anti-tau mAbs using Biacore X100™**

For anti-tau mAb SPR measurements, htau40 was conjugated to the surface of a CM5 sensor chip using amine coupling as explained previously. Briefly, 2 µg/mL htau40 in 10 mM Sodium acetate buffer (pH 4.0) was passed over the activated chip surface (EDC/NHS) in flow cell 2 for a period for 45 s followed by blocking with 1 M ethanolamine-HCl pH 8.5. Flow cell 1 was set up as reference control and blocked simultaneously. Final immobilisation level of htau40 (R<sub>max</sub>) was approximately 250 RU. Following a minimum of three start-up cycles, increasing concentrations (0.78 nM - 25 nM) of the mAb in HBS-EP+ buffer was added at a rate of 30 µL/min to the chip. The mAb was added for a 120 s association period and 600 s dissociation period followed by a regeneration cycle of 30 s injection of glycine buffer pH 1.5 in between each cycle. Binding responses were analysed in Biacore X100 evaluation software and data fitted to a 1:1 binding model to obtain kinetic and affinity characterisation. Kinetic rates and equilibrium binding constants of lead anti-tau mAbs are given in the table below

*Table 27 - Kinetic rates and equilibrium binding constants of lead anti-tau mAbs for hT40 (TBD, to be determined)*

| Top clones (mAbs) | k <sub>a</sub> (1/Ms)   | k <sub>d</sub> (1/s)     | k <sub>D</sub> (M) for hT40 binding |
|-------------------|-------------------------|--------------------------|-------------------------------------|
| S1D12             | 4.058 x 10 <sup>5</sup> | 4.093 x 10 <sup>-5</sup> | 101 pM                              |
| S1G2              | 3.398 x 10 <sup>5</sup> | 4.748 x 10 <sup>-5</sup> | 140 pM                              |
| S1E12             | TBD                     | TBD                      | TBD                                 |
| CC7               | 4.576 x 10 <sup>6</sup> | 3.164 x 10 <sup>-2</sup> | 6.9 nM                              |
| NS2A1             | 8.937 x 10 <sup>5</sup> | 2.621 x 10 <sup>-3</sup> | 10 nM                               |
| CA4               | 1.020 x 10 <sup>6</sup> | 1.276 x 10 <sup>-3</sup> | 1.3 nM                              |
| CE3               | 1.030 x 10 <sup>5</sup> | 1.718 x 10 <sup>-3</sup> | 16.7 nM                             |
| 412-E10           | 1.658 x 10 <sup>6</sup> | 1.497 x 10 <sup>-2</sup> | 9.0 nM                              |
| CE2               | 4.579 x 10 <sup>5</sup> | 5.218 x 10 <sup>-3</sup> | 11 nM                               |
| CB7               | 2.568 x 10 <sup>6</sup> | 9.451 x 10 <sup>-3</sup> | 3.7 nM                              |

**Example 17: Determination of Limits of detection (LoD) for high affinity anti-tau antibody pairs**

The diverse panel of high affinity anti-tau antibodies (scAb and mAb formats) were paired in various combinations and tested in a Sandwich (or Capture) ELISA format to calculate their limits of detection (LoD) and their ability to differentiate between different tau species. Biologically, tau exists in 6 different isoforms and is subjected to numerous post translational modifications, some of them playing a significant role in the progression of neurodegeneration.

For Sandwich ELISA using colourimetric detection, 96 well Maxisorp plates were coated with the capture antibody S1D12 mAb at 1 µg/ml for 1 h at RT followed by blocking with 2% MPBS as normal. Full length tau (hT40), at 1 µg/ml starting concentration was added to designated wells and double diluted across rest of the plates and left to incubate at R/T for 1 h. A series of detection scAbs with varying epitope recognition properties were added at 10 µg/ml to designated wells (Figure 22). For colourimetric detection HRP conjugated anti-HuCK secondary antibody was used and the resulting immunoreaction was developed and absorbance at 450 nm measured as described previously. Cut-off point for a positive binding event was an absorbance value of 0.3 following background subtraction. In order to enhance the assay sensitivity, a chemiluminescent detection method was adopted where 50 µL SuperSignal ELISA Femto Substrate (Thermo Scientific) was added to each well following incubation with anti-HuCK HRP antibody and subsequent washing. The luminescence was read using Clariostar Plus microplate reader. A further modification to this protocol was done where various detection scAbs were directly conjugated with HRP and detected using chemiluminescent protocol as before. The lowest levels of detection achieved using different detection scAbs and a comparison of colourimetric and chemiluminescent methods of detection are shown in Table 28

*Table 28. The LoDs achieved using S1D12 mAb capture and various detection scAbs and a comparison of colourimetric and chemiluminescent methods of detection*

| Detection scAb<br>(Epitope) | Tau-441<br>affinities<br>(Biacore) | LoD (ng/ml)<br>colourimetric<br>detection | LoD (ng/ml)<br>chemiluminescence<br>detection | LoD (ng/ml)<br>direct<br>conjugation<br>of<br>detection scAb &<br>chemiluminescence |
|-----------------------------|------------------------------------|-------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------|
| CB7 (13-25)                 | 5.2 (nM)                           | 15                                        | 3.33                                          |                                                                                     |
| CA2 (100-155)               | -                                  | 6                                         | 0.37                                          |                                                                                     |
| CC7 (145-157)               | 1.2 (nM)                           | 6                                         | 3.33                                          |                                                                                     |
| CA4 (355-367)               | 3.6 (nM)                           | 6                                         | 0.37                                          |                                                                                     |
| S1G10 (367-379)             | 0.4 (nM)                           | 2                                         | 0.12                                          |                                                                                     |
| CB8 (367-379)               | 0.6 (nM)                           | 2                                         | 1.11                                          |                                                                                     |
| S1G2 (367-379)              | 0.6 (nM)                           | 2                                         | 0.12                                          | 0.04                                                                                |
| 412E10 (412-441)            | 3.3 (nM)                           | 20                                        | 0.37                                          |                                                                                     |



|                    |                    |   |  |  |
|--------------------|--------------------|---|--|--|
| E2E8 (E dependant) | 0.4 (nM)<br>(dGAE) | - |  |  |
|--------------------|--------------------|---|--|--|

Similarly, a sandwich ELISA format was set up using S1G2 mAb at 1 µg/ml as the capture antibody and HRP conjugated S1D12 mAb for detection. The assay was conducted using chemiluminescent protocol described above. The assay setup and quantification of the limit of detection are shown in Fig 23 and 24

**Example 18: Interrogation of mixed samples and their quantification using antibody pairs**

The ability to interrogate and determine the levels of various tau species or fragments in patient samples is crucial in early AD diagnosis. To this end, an experiment was set up to assess whether the concentrations of different tau species could be determined in spiked samples using various antibody pairings directed towards specific regions of the tau protein. Four spiked samples were prepared with varying concentrations and types of tau species - sample A with 5 nM full length human tau (hT40), sample B with 3.3 nM dGA, 3.3 nM dGAE and 3.3 nM hT40 (9.9 nM total protein), sample C with 2 nM dGA, and sample D with 1 nM hT40 and 4 nM dGA (5 nM total protein). These samples were analysed by performing three separate 'blind' sandwich ELISAs using S1D12 mAb to capture the different species in the mixture and detection using scAbs with specific epitopes.

For ELISA #1, wells were coated with S1D12 mAb, blocked and 20 nM hT40 was added to the first well for standard curve plotting. Four spiked samples were added to the first wells of designated rows and all samples were double diluted in PBS across the plate including the standard. The samples were incubated at RT for 1 h, washed as normal and 1 µg/ml CB7 scAb was added to each well and incubated as before. Secondary antibody anti HuCk HRP was added and the reaction was developed and read as described previously. For ELISA #2, 20 nM dGAE was added to the first well and double diluted across the plate for standard curve plotting. As for ELISA #1, spiked samples of unknown protein concentrations were added to respective wells in doubling dilutions. The detection antibody used was 'E' specific E2E8 scAb and rest of the ELISA was performed as described above. For ELISA #3, a standard curve was plotted using average absorbance values obtained from binding events of hT40, dGA and dGAE all at starting concentration of 20 nM. As before, four spiked samples were tested for binding using S1D12 capture mAb and core binding S1G2 detection scAb. Based on ELISA signals of unknown spiked samples, the types of tau fragments present in the mixture and their individual concentrations were determined as shown in Figures 25, 26 and 27. A summary of tau types and their concentrations used to spike these samples and the deduced concentrations from ELISAs are given in Table 29.

*Table 28 Summary of various tau species and their concentrations in the spiked samples and their deduced concentrations and reactivity using three different antibody pairings in a sandwich ELISA format.*

| Samples | Concentrations of various tau species in the sample mix | ELISA #1<br>S1D12-CB7<br><br>Reactivity & deduced concentration of samples | ELISA #2<br>S1D12-E2E8<br><br>Reactivity & deduced concentration of samples | ELISA #3<br>S1D12-S1G2<br><br>Reactivity & deduced concentration of samples |
|---------|---------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| A       | 5 nM hT40                                               | 5 nM N terminal                                                            | None                                                                        | 3 nM core                                                                   |
| B       | 3.3 nM hT40 + 3.3 nM dGA + 3.3 nM dGAE                  | 4 nM N terminal                                                            | 3.2 nM 'E' specific                                                         | ~9 nM core                                                                  |
| C       | 2 nM dGA                                                | None                                                                       | None                                                                        | 1 nM                                                                        |
| D       | 1 nM hT40 + 4 nM dGA                                    | 1.5 nM N terminal                                                          | None                                                                        | 3.2 nM core                                                                 |

#### Example 19: SDS treatment of dGAE aggregates and restoration of immunoreactivity

The immunoreactivity of core region scAbs is lost when dGA/dGAE fragments are aggregated which could be due to the non-availability of respective epitopes in this conformation. We have noticed Sodium dodecyl sulphate (SDS) can break apart dGA/dGAE aggregates and separate them into smaller fragments by performing an SDS-PAGE. This has been replicated and tested using an ELISA as described below.

For aggregation, 1000  $\mu$ L 100  $\mu$ M dGAE + 10  $\mu$ L 10 mM DTT was added to a 'LoBind' microfuge tubes and agitated at 700 RPM /37 °C for 24 hours. Resulting sample centrifuged at 17,000 x g / 4 °C for 60 min and supernatant discarded to remove left over monomer. Pellet resuspended in half the original volume for future experiments and hereafter referred to as 'aggregates'. 1  $\mu$ L of aggregates was added to 1 ml of PBS and SDS was added to a final concentration of 1 % (w/v). This was left to incubate on lab bench for 1 h with gentle agitation every 15 minutes. In order to neutralise the SDS effect on ELISA, Triton X-100 added to a final concentration of 3 % (v/v) and mixed gently by pipetting to prevent any bubble formation. 200  $\mu$ L added of this mix was to the first well of an ELISA plate coated with 1  $\mu$ g/ml S1D12 mAb and blocked with 2 % MPBS. Similarly aggregates treated with only SDS or Triton X-100, untreated aggregates, dGAE monomers treated with only SDS or SDS+Triton X-100 were also added to designated wells as controls. All samples were then double diluted across the plate in final volumes

of 100 µl. The final column was left with no protein to act as a blank. This was allowed to stand at room temperature for 1 hour followed by the addition of detection scAb – S1G2 at 10 µg/ml. Anti-HuCk HRP labelled secondary antibody was added as described previously and ELISA data generated was represented using the graph below. In addition, limits of detection (LoD) of various core binding antibody pairing for SDS Triton X-100 treated dGAE aggregates were calculated using the above describe ELISA method and substituting capture mAbs and detection scAbs as shown in Table 30.

*Table 30 shows the limits of detection (LoD) of various capture mAb-detection scAb pairing for SDS Triton X-100 treated dGAE aggregates in a sandwich ELISA system. NB denotes no binding*

|                  | <b>Capture System</b>      |                              |                            |                              |                                                 |                              |
|------------------|----------------------------|------------------------------|----------------------------|------------------------------|-------------------------------------------------|------------------------------|
|                  | <b>S1D12 mAb</b>           |                              | <b>423 mAb</b>             |                              | <b>Direct immobilisation of dGAE aggregates</b> |                              |
|                  | <b>Untreated dGAE agg.</b> | <b>+SDS Triton dGAE agg.</b> | <b>Untreated dGAE agg.</b> | <b>+SDS Triton dGAE agg.</b> | <b>Untreated dGAE agg.</b>                      | <b>+SDS Triton dGAE agg.</b> |
| <b>S1G2 scAb</b> | 250 ng/ml                  | 2 ng/ml                      | NB                         | 30 ng/ml                     | NB                                              | 16 ng/ml                     |
| <b>CA9 scAb</b>  |                            | 4 ng/ml                      |                            |                              |                                                 | 40 ng/ml                     |
| <b>CA12 scAb</b> |                            | 2 ng/ml                      |                            |                              |                                                 | 16 ng/ml                     |
| <b>CB8 scAb</b>  |                            | 4 ng/ml                      |                            |                              |                                                 | 30 ng/ml                     |

Example 20: Antibody based detection of various tau fragments in transgenic mice brain lysate collection.

Mouse brain lysates were prepared from wildtype, Line 1, Line 66 +/+ and Line 66 +/- (Melis et al., 2015, all surplus from Charles River, part of study R0144). All animals were female, 7-8 months old except Line 66 +/+ which were 5 months old. The Line 66 mouse construct (Fig. 23) contains human tau cDNA coding for the longest human tau isoform (2N4R tau; 441 amino acids) with two point mutations at P301S and G335D. The L1 cDNA construct (Fig. 23) contains human tau cDNA coding for amino acid residues 296-390 with a signal sequence and related sequences in a murine Thy-1 expression cassette. For brain lysate preparation, half brains were sectioned into four and the individual sections were homogenised in 400 µl of ice cold RIPA buffer (Cell signalling Technology) containing protease and phosphatase inhibitors. Total protein concentrations for individual samples were established by BCA-assay and each sample was subsequently diluted to 1 mg/ml for future experiments.

For capture ELISA, 100 µL S1D12 capture mAb was used to coat a nunc 96 well Maxisorp plate at 1 µg/ml and incubated for 1 hour at 37 °C. Plate was washed as previously and then blocked for 1 hour at 37 °C in 2 % MPBS. Brain homogenate samples (50 ng total protein) from each mouse type were added to the first wells and double diluted across the plate in PBS. These samples were left to incubate at RT for 1 hour. Various detection scAbs encompassing epitopes of interest were then added to the plate at 1 µg/ml and incubated for 1 h at RT. Secondary antibody used was anti-HuCk HRP and the assays were developed as described previously. Using S1D12 mAb capture and two separate scAb detectors, S-1G2 (Fig. 24A) and C-B7 (Fig. 24B), it was possible to differentiate between L1 and L66 samples and the wild type. When s1G2 scAb was used, tau protein was detected in 50 µg of total brain protein in all four different sample types. However, with C-B7 scAb, hT40 tau was specifically detected in L66 samples and an increase was observed in L66 homozygous group compared to L66 heterozygous samples. Therefore S1D12-CB7 pair was able to differentiate L66 from L1 and wild type with the use of an N' terminally directed detection scAb which is due to a difference in sequence homology between mouse and human tau (Hernandez et al., 2019). Over the whole protein there is approximately 77% homology at the amino acid level, but the proteins differ significantly in the N'-terminal region.

#### Example 21: Antibody based detection of tau fragments in transgenic mice plasma collection

Plasma samples from WT, L1, L66 +/- and L66 +/+ of various ages (1.5 – 9 months) were taken as described. Mice were terminally anaesthetized using an overdose of sodium pentobarbital and blood was collected through cardiac puncture through a Plastipak syringe pre-rinsed with heparinised saline heparin (10 U/ml) (Heparin sodium salt; Sigma-Aldrich) and transferred into a plastic vial containing lithium heparin anticoagulant (Sarstedt Ltd.) Blood samples, kept on ice for no more than 30 minutes, were centrifuged to obtain plasma at 2000 x g for 5 minutes at 6 °C. Plasma samples were stored at -20 °C.

For mouse plasma capture ELISA, 100 µL capture mAb was coated to the bottom of a black nunc 96 well 'maxisorp' plate at 2.5 µg/ml and incubated for 1 hour at 37 °C. After washing and blocking as normal, several known standard solutions were set up in triplicate starting at 20 ng/ml of the desired protein before double diluted in the remaining wells. Mouse samples were added to wells in duplicate with a blank in between each sample group. Line1 plasma was diluted 1:10 before addition to plate to account for its high concentration while other samples were diluted 1:2 to account for potential matrix effects. These samples were left to incubate at RT for 1 hour. HRP-conjugated secondary scAb (conjugation carried out according to manufacturer's guidelines, Abcam) was added to each well and left to incubate at RT for 1 hour. The ELISA was developed using SuperSignal ELISA Femto Substrate (Thermo Scientific) and total luminescence was read on Clariostar Plus plate reader (BMG Labtech). Tau concentrations were established using a 4-parameter fit on concentration curves generated from recombinant tau protein spiked into samples at known concentration. For WT and L66 hT40 was used as a calibrator while dGA was used for L1 calibration.

Using S1D12 capture and S1G2 detection we were able to detect varying levels of 'core region' containing tau fragments in samples from WT, L1, L66 +/- and L66 +/+. In WT and L66, the levels detected were in low ng/ml (WT at 5 month: 1.947 ng/ml, WT at 9 month: 2.177 ng/ml); (L66+/- at 5 month: 0.567 ng/ml), L66+/+ at 5 month: 1.937 ng/ml). However higher concentrations of core region tau species were detected in L1 samples (5 month: 12.355 ng/ml, 9 month 13.661 ng/ml). This is in agreement with the genetic makeup of L1 mouse which contains a truncated 3 repeat fragment corresponding residues 296-390 of hT40 and a signal sequence that drives this towards the endoplasmic reticulum. This could explain the presence of elevated levels of repeat domain core containing fragments in L1 mouse plasma that was detected using our core region pair, S1D12 mAb and S1G2 scAb. This region also shares sequence homology with mouse tau protein which is reflected by base level detection of the core in WT, L66+/+ and L66+/- plasma samples.

In addition, using a second capture-detection antibody pairing, we have successfully shown the detection of human specific tau fragments in Line66 mice which express the longest tau isoform (hT40, 441 amino acids) containing 4 repeat regions with point mutations P301S and G335D (Melis et al., 2014). Using S1D12 mAb as the capture antibody and CB7 scAb detection, Line 66+/+ mouse plasma at 1.5 months showed the presence of detectable levels of human tau as compared to the wild type mouse of same age (Fig 32A). The detection scAb CB7 (epitope 13-25 on hT40) does not cross react with endogenous mouse tau protein in Line66 transgenic model since the N terminal amino acid sequences differs considerably with between human and mouse tau. In addition, using S1D12-S1G2 pairing we have shown similar levels of core repeat region tau fragments which share close sequence homology in transgenic and wild type animals (Fig 32B) This demonstrates the utility of our panel of antibody pairs in detecting various tau fragments and truncations in transgenic mice samples which can be translated into a diagnostic setting to interrogate the presence of different tau species in diseased vs cognitively normal human samples.

#### Example 22: Antibody based detection of tau fragments in plasma samples from AD patients

Six plasma samples from individuals with an AD diagnosis and 6 samples from aged matched controls were sourced (Logical Biological, Kent UK), divided into 100 µl aliquots and stored at – 80 °C (Table 31)

*Table 31 Demographic characteristics of human plasma samples used in this study including the age, sex and ethnicity of cognitively normal controls and patients with confirmed AD diagnosis. Mini-Mental State Examination (MMSE) scores of AD patients are also shown.*

|                     | <u>Donor Number</u> | <u>Age</u> | <u>MMSE</u> | <u>Sex</u> | <u>Ethnicity</u>  |
|---------------------|---------------------|------------|-------------|------------|-------------------|
| Age-Matched Control | PL 361              | 64         | -           | F          | Caucasian         |
|                     | PL 362              | 61         | -           | M          | Caucasian         |
|                     | PL 363              | 61         | -           | M          | Caucasian         |
|                     | PL 364              | 63         | -           | M          | African American  |
|                     | PL 365              | 61         | -           | F          | Caucasian         |
|                     | PL 366              | 66         | -           | F          | African American  |
| AD                  | PL 505              | 62         | 27          | F          | Caucasian         |
|                     | PL 506              | 63         | 25          | F          | Caucasian Italian |
|                     | PL 507              | 64         | 26          | M          | Hispanic          |
|                     | PL 508              | 57         | 25          | M          | African American  |
|                     | PL 509              | 64         | 21          | M          | African American  |
|                     | PL 510              | 63         | 27          | F          | Caucasian         |

For sandwich ELISA, 100 µl S1D12 capture mAb was coated to the bottom of a black nunc 96 well 'maxisorp' plate at 2.5 µg/ml and incubated for 1 hour at 37 °C. Plate was washed as previously and then blocked for 1 hour at 37 °C in 2 % MPBS. Several known hT40 standard solutions were set up in triplicate starting at 8 ng/ml and diluted 2-fold in the remaining wells using 50 % sheep plasma as a diluent to account for any plasma matrix effects. 100 µl of each human sample diluted 1:2 in PBS were added to wells in duplicate with a blank in between each sample group. Samples were diluted 1:2 to account for potential matrix effects. These samples were left to incubate at 4 °C overnight. HRP-conjugated secondary scAb ((S-1G2 and C-B7) (conjugation carried out according to manufacturer's guidelines, Abcam)) was added to each well and left to incubate at RT for 1 hour. The ELISA was developed using SuperSignal ELISA Femto Substrate (Thermo Scientific) and total luminescence was read on a plate reader (BMG Labtech). Tau concentrations were established using a 4-parameter fit on concentration curves generated from recombinant human tau protein spiked into samples at known concentration.

Tau was detected in both patient groups (Figure 33). Interestingly different levels were detected depending on the combination of capture/detection antibody used. This data provides a proof of concept that using different pairs of antibodies depending on their epitopes will allow us to detect different fragments of tau within plasma. Further antibody pairs will be used to fully interrogate the nature of tau fragments in plasma.

Table 32 Summarises plasma tau levels of individual samples in AD and control groups using the capture-detection pairs as shown (\*Below assay limit of detection, \*\*Above assay limit of detection)

|                            | <u>Donor<br/>Number</u> | <u>S1G2-HRP<br/>Detection<br/>(ng/ml)</u> | <u>CB7-HRP<br/>Detection<br/>(ng/ml)</u> |
|----------------------------|-------------------------|-------------------------------------------|------------------------------------------|
| Age-<br>Matched<br>Control | PL 361                  | *                                         | 1.89                                     |
|                            | PL 362                  | *                                         | 1.04                                     |
|                            | PL 363                  | 0.036                                     | 1.89                                     |
|                            | PL 364                  | 0.565                                     | 1.93                                     |
|                            | PL 365                  | *                                         | *                                        |
|                            | PL 366                  | 0.74                                      | 1.84                                     |
| AD                         | PL 505                  | *                                         | *                                        |
|                            | PL 506                  | *                                         | 6.75                                     |
|                            | PL 507                  | 2.13                                      | 2.7                                      |
|                            | PL 508                  | 1.83                                      | **                                       |
|                            | PL 509                  | 0.63                                      | *                                        |
|                            | PL 510                  | 1.38                                      | 1.96                                     |

Example 23: LMT mediated inhibition of dGAE aggregates and restoration of immunoreactivity

The truncated core repeat domain dGAE (297-391), is the predominant fragment that constitutes bulk of the PHF core in AD (Wischnik et al, 1988). During dGAE aggregation in vitro, scAb binding regions on dGA/dGAE are 'hidden' or 'occluded' which leads to a loss of immunoreactivity in aggregation samples. Here we have shown the occlusion of binding regions in aggregated dGAE samples and the recovery of immunoreactivity in the presence of LMTM, a tau-aggregation inhibitor. The scAbs tested for binding are core region specific S1D12, CA4, CB3, CE2, CE3 and CA9 (binding regions given in Table 22). For preparing the aggregates, 10 µl 10 mM DTT was added to 1000 µl 100 µM dGAE and agitated with/without LMTM (1:5 ratio) at 700 rpm for 24 h at 37 °C. Following overnight agitation, one third of each sample was kept aside as 'total' and the rest was spun down at 16000 x g for 30 min and separated into 'supernatant' and 'pellet'. The pellet was then resuspended in half the original volume for further experiments. The immunoreactivities of core region specific scAbs towards dGAE aggregates formed with/without LMTM was tested using a sandwich ELISA format using a 'E' specific monoclonal antibody 423 mAb. This mAb has been shown to specifically bind to the Pronase resistant core structure in the PHFs (Wischnik et al, 1988). ELISA plates were coated with 10 µg/ml 423 mAb and blocked as normal. Doubling dilutions of dGAE aggregate 'total', 'supernatant' and 'pellet' samples at 10 µg/ml starting concentration were added to designated wells in doubling dilutions in 1 x PBS. dGAE monomer (non-aggregated) was included as assay control. All double dilutions were done in final volumes of 100 µl. This was left to incubate on lab bench for 1 h followed by the addition of test scAbs at 10 µg/ml. Anti-HuCK HRP labelled secondary antibody was added as described previously and ELISA data generated is represented using the graph below.

Table 33 Core binding scAbs tested in epitope occlusion assays and their specific binding regions on Ht40

| scAbs tested | Binding regions on hT40 |
|--------------|-------------------------|
| S-1D12       | 337-355                 |
| CA4          | 355-367                 |
| C-B3         | 360-390                 |
| C-E2         | 319-331                 |
| C-E3         | 297-356                 |
| C-A9         | 367-379                 |

All scAbs tested showed increased binding to aggregated dGAE 'total' and 'supernatant' samples, when aggregation was conducted in the presence of LMTM. This proves the opening or revealing of occluded antibody binding regions on dGAE where LMTM is preventing the aggregation event, leading to an increased immunoreactivity (Fig 34).

#### Tau aggregation inhibition assays

##### Example 24: scAb-mediated dGAE Aggregation Inhibition (Thioflavin T Assay)

Antibody mediated blocking of the tau aggregation cascade and subsequently halting its associated neurodegenerative effects would be a key end point to demonstrate the therapeutic potential of these scAbs. By incubating 100  $\mu$ M dGAE and 10 mM DTT at 37°C on a thermomixer at 700 rpm for 24 hours, "pathology mimicking" aggregates which have the morphology of paired helical filaments are formed. This aggregation can be quantified by adding a final concentration of 12.5  $\mu$ M Thioflavin T (fluorescent dye) which binds to fibril-like  $\beta$ -sheets. Fluorescence was measured with a constant emission wavelength of 480 nm and a scanning excitation wavelength of 350-470 nm using a Varian Cary Eclipse fluorescence spectrophotometer. Maximal fluorescence measurements were used as an indicator of dGAE aggregation (approximately 450 nm excitation). The assay was optimised using a range of S1D12 scAb concentrations (0.04 to 25  $\mu$ M) and tested for levels of aggregation inhibition as shown in figure 35.

Based on figure 35, 10  $\mu$ M scAb was deemed an adequate concentration to compare and rank individual scAb-mediated dGAE aggregation inhibition events. This data is summarised below in figure 30: Non-binding, negative controls showed inhibition of up to 47 %. A similar inhibition (40 %) was seen using 10  $\mu$ M bovine serum albumin as a negative control (data not shown). Despite this level of non-specific



steric inhibition by controls, the anti-tau scAb panel achieved a much greater level of aggregation inhibition, statistically significant for all the anti-tau scAbs ( $P < 0.05$ ) with the exception of CA12, CB2, S1D9 and CB8.

Example 25: scAb-mediated aggregation inhibition (tau-tau immunoassay)

To further support and rank the anti-aggregation properties of the anti-tau scAb panel, an ELISA-based aggregation inhibition assay was developed (adapted from Wischik et al., 1996).

The adapted method is as follows: dGA (1000 nM) was adsorbed to a Nunc 96-well MaxiSorp plate and incubated for 1 h at 37 °C. Plates were subsequently washed 3 times with PBST which was performed after each 1 h incubation. The plates were blocked with 2 % (w/v) dried milk powder in PBS for 1 h at 37 °C. Double diluting concentrations of test scAbs were incubated with 100 nM of dGAE in binding buffer (25 mM KPIPES, 50 mM NaCl, 0.05 % Tween 20, 1 % fish skin gelatine; pH 6.8) overnight at 4 °C on a separate polypropylene plate and subsequently added to the blocked immuno-plate for 1 h at 37 °C. scAb E2E8 (dGAE-specific) was added to the plates at 1 in 250 dilution as detection antibody (1:250 dilution) and incubated for 1 h at 37 °C. The secondary antibody used was HRP-conjugated Anti-mouse IgG (1:1000 dilution, Sigma) and incubated at RT for 1 h. The plate was subsequently developed, and readings taken at absorbance 450 nm. The assay set up is summarised in figure 37.

By using a dGAE-specific antibody for detection, this allowed the quantification of the amount of scAb required to prevent 50 % of 100 nM dGAE binding to 1000 nM dGA. This quantification has been termed a  $B_{50}$  value and an example of how this is calculated is shown in Figure 38 as is a summary of the  $B_{50}$  values achieved for various scAbs. A  $B_{50}$  was achieved for all anti-tau scAbs ranging from a molar ratio of 2.2 to 1 to as low as 0.5 to 1 (scAb to tau ratio). In this assay, negative control scAbs CB7 and 3aD6 showed no inhibition with no  $B_{50}$  value achieved ( $>10000$  nM).

Example 26: Ranking of Tau mAbs based on their ability to capture dGAE aggregates

The aggregation cascade of natively unfolded tau into insoluble filaments is a defining pathological feature of AD. Therefore, it is logical to target aggregated tau filaments for both therapeutic and diagnostic purposes. The following experiment was performed to assess the ability of our dGA mAb panel to bind aggregated dGAE using a capture ELISA method. Aggregates were prepared by incubating 100  $\mu$ M dGAE and 10 mM DTT for 24 h at 37°C with shaking at 700 RPM. The following day, dGAE aggregates were centrifuged at 17,000 x g for 20 min and the supernatant was removed. The remaining pellet was washed with 10 mM phosphate buffer and centrifuged as above. Washing was repeated a further two times to remove any remaining dGAE monomer. The dGAE pellet was resuspended in 100  $\mu$ l of 10 mM phosphate buffer. (Using a separate capture ELISA based quantification, we have worked out the efficiency of our dGAE aggregation as 80%)

For assessing the mAb panel for aggregate binding, designated rows of a maxisorp plate were coated with 1 µg/ml of each of the capture mAbs (S1D12, S1G2, CA4, NS2A1, CE2, E2E8 and CB7) and blocked as before. Following washing, 800 nM aggregated dGAE was added to the designated wells, double diluted across the plate and incubated for 1 h at RT. The plate was washed again and 1 µg/ml S1G2 scAb was added as detection antibody and incubated for 1 h at RT. To the row where S1G2 mAb was used for capture, 1 µg/ml s1D12 scAb was added as capture antibody instead of S1G2. The assay was developed using HRP labelled HuCK as described previously.

Capture ELISA graph indicates that S1D12 and S1G2 mAbs are most efficient at capturing aggregated dGAE, along with E2E8 mAb which like the 423 mAb is a '391E' binder.

Prophetic Example 27: Study protocol: Effect of S1D12 treatment in the line 1 and line 66 tau transgenic mouse models

## 1. RATIONALE

The main purpose of this study will be to determine the effect of systemic administration of mAb S1D12 on tau pathology and in tau clearance in 6-month-old tau transgenic female mice.

The study will be conducted in accordance with the European Communities Council Directive (63/2010/EU) and a project licence with local ethical approval under the UK Animals (Scientific Procedures) Act (1986). GLP compliance is not claimed for this study.

## 2. MATERIALS

### 2.1. Test Item

|                  |                                                                                                                                           |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Test item</b> | S1D12<br><br>The item will be supplied by Scottish Biologics Facility (SBF); Liberty Building, Foresterhill Road, Aberdeen AB25 2ZP (UK). |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------|

### 2.2 Test Item Formulation

|                                 |                                                                                                                                         |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Doses</b>                    | Test item will be administered intraperitoneally at 10- and 50-mg/kg (injection volume: 5ml/kg).<br><br>Each dose will be prepared..... |
| <b>Frequency of preparation</b> | ....                                                                                                                                    |
| <b>Stability</b>                | ....                                                                                                                                    |

### 2.3 Vehicle for Test Item

|                           |         |
|---------------------------|---------|
| <b>Vehicle</b>            | PBS.... |
| <b>Storage conditions</b> | .....   |

### 3. TEST SYSTEM

#### 3.1 Animals and Housing

|                                |                                                                                                                  |
|--------------------------------|------------------------------------------------------------------------------------------------------------------|
| <b>Species (Strain)</b>        | Mouse (NMRI wild-type and NMRI-derived transgenic line 1 and line 66 mice)                                       |
| <b>Supplier</b>                | Charles River (UK)                                                                                               |
| <b>Number required and sex</b> | 200 (20 wild-type, 90 line 1 and 90 line 66) female mice.                                                        |
| <b>Number per cage</b>         | 5 (same genotype and treatment group)*.                                                                          |
| <b>Bedding</b>                 | Corn cob bedding, plus environmental enrichment of paperwool and cardboard tubes (supplied by DBM Scotland Ltd). |
| <b>Minimum acclimatisation</b> | 1 week prior to dosing                                                                                           |

\* Animals may be housed alternatively if it is considered necessary by the Lead Scientist, senior animal technician or a veterinary surgeon (e.g. excessive aggression, ill health). Such changes will be recorded in the study file.

#### 3.6 Randomisation

Randomisation of animals will be performed according to genotype and body weight recorded at the beginning of the study.

### 4. STUDY DESIGN

Three cohorts of animals at different ages at the start of the experiment will be used (i.e. 3-, 4- and 5-month) and will be allocated into three corresponding groups according to genotype (wild-type, WT; line 1, L1; line 66, L66), dose of S1D12 administered (0-, 10- or 50-mg/kg) and duration of treatment (12 weeks: Group 1; 8 weeks: Group 2; 4 weeks: Group 3) (see table 24 for group size).

**Table 24:** Number of animals assigned to the study (numbers may change due to potential health issues throughout the dosing phase of the experiment).

|      | Group 1 |          |          | Group 2 |          |          | Group 3 |          |          |
|------|---------|----------|----------|---------|----------|----------|---------|----------|----------|
| Dose | 0 mg/kg | 10 mg/kg | 50 mg/kg | 0 mg/kg | 10 mg/kg | 50 mg/kg | 0 mg/kg | 10 mg/kg | 50 mg/kg |
| WT   | /       | /        | /        | /       | /        | /        | 10      | /        | 10       |
| L1   | 10      | 10       | 10       | 10      | 10       | 10       | 10      | 10       | 10       |
| L66  | 10      | 10       | 10       | 10      | 10       | 10       | 10      | 10       | 10       |

The overall experimental design is outlined in figure 35.

Animals will be injected intraperitoneally (i.p.) with either vehicle or S1D12 (10- or 50-mg/kg), once per week (Tuesdays) for twelve (Group 1), eight (Group2) or four (group 3) consecutive weeks. Age of mice at the end of the experiment will be the same for all three groups (i.e. 6 months).

At the end of the study, mice will be anaesthetized using an overdose of sodium pentobarbital administered intraperitoneally. The anesthetized animal will be placed on its back on a rack and a cut along the sternum will be performed to expose the heart. Blood will be collected via cardiac puncture through a Plastipak syringe pre-rinsed with heparinized saline Heparin (10U/ml): (sodium salt from porcine intestinal mucosa; Sigma-Aldrich, CAS No. 9041-08-1) and transferred into a plastic vials containing lithium heparin anticoagulant (Sarstedt Ltd, Additive: lithium heparin; Capacity: 500 µL).

Blood samples, kept on ice for no more than 30 minutes, will be centrifuged to obtain plasma at 2000 x g for 5 min at 6 °C [Centrifuge Sigma 3-16KL (3225 RPM, rotor: 11180)]. Plasma samples will be stored at -20 °C and transferred to SBF for tau level quantification.

After blood collection, each mouse will be perfused with heparinized saline for 2-3 minutes and the entire brain removed, dissected on ice and split in two halves, one for histological characterization and the other for biochemical analyses (details of histological and biochemistry analyses will be provided in the final report).

#### 4.1 Clinical Signs

All animals will be observed for reaction to treatment during each day of dosing and throughout the week. Where possible, the onset, intensity and duration of any signs will be recorded. The cages will be inspected daily for evidence of blood and abnormal urine and/or faeces.

#### 4.2 Body Weights

Body weight of the animals will be recorded two times per week (Tuesdays and Fridays) and dosing volumes calculated accordingly.

**Example 28: Epitope mapping and binding affinities of reformatted anti-tau mAbs**

For anti-tau mAb SPR measurements (Biacore X100™) and epitope mapping, the same methodologies described above (see Example 16) were followed. Kinetic rates and equilibrium binding constants of additional anti-tau mAbs and the regions recognised on hT40 are given in the Table 25 below

| Clones (mAbs) | $k_a$ (1/Ms)           | $k_d$ (1/s)            | $K_D$ (M) for hT40 binding | hT40 binding region |
|---------------|------------------------|------------------------|----------------------------|---------------------|
| 3aH6          | $3.128 \times 10^{-6}$ | $1.522 \times 10^{-4}$ | 49 pM                      | 1-15                |
| 3bG4          | $4.540 \times 10^{-6}$ | $2.964 \times 10^{-4}$ | 65 pM                      | 1-15                |
| 3aG3          | $1.532 \times 10^{-7}$ | $4.751 \times 10^{-3}$ | 310 pM                     | 1-15                |
| 3bD11         | $2.671 \times 10^{-6}$ | $3.979 \times 10^{-3}$ | 1.490 nM                   | 37-49               |
| E1B8          | $3.238 \times 10^{-5}$ | $1.367 \times 10^{-3}$ | 4.22 nM                    | 319-331             |
| MD9           | $6.620 \times 10^{-4}$ | $1.462 \times 10^{-3}$ | 22 nM                      | 373-385             |
| *Tau12        | $1.030 \times 10^5$    | $1.718 \times 10^{-3}$ | 1.44 nM                    | 6-18                |

Table 25 - Kinetic rates, equilibrium binding constants and binding regions of newly converted anti-tau mAbs. \*Commercially sourced Tau12 mAb binding kinetics and an affinity value was also measured and included in the table.

**Example 29: Antibodies show Specificity to Human Tau in L66<sup>+/+</sup> Brain Homogenates**

Western blots with brain homogenates prepared from 3 animals of each genotype: wild-type (WT) mice; L66<sup>+/+</sup> mouse; and L1<sup>+/+</sup> mouse brain (all 5 months old) show specificity for human tau using CB7 (hT40 13-26) and CC7 (hT40 145-157) antibodies (*Genotype and phenotype descriptions for L1 and L66<sup>+/+</sup> are provided in the initial filing document*). Protein equivalent to 20 µg from each brain extract was separated using 4-20% bis-tris gels and run in 1X MES buffer. Figure 41 shows a blot stained with CB7 antibody. A clear band is visible in the lanes containing L66<sup>+/+</sup> samples, but no other bands are detectable (WT or L1<sup>+/+</sup>). Figure 42 shows a similar outcome when a blot containing the same sample preparations is interrogated with the CC7 antibody. Once again, a band having relative mobility of 65 kDa is visible in the L66 sample with no other reactive bands present.

When these results are compared with western blots obtained with the core domain antibody binders S1D12 (hT40 337-355) (Fig. 3) and S1G2 (hT40 367-379) (Fig. 44) the results are very different with

numerous bands visible in each mouse sample. A band is detected in each sample (WT, L66<sup>+/+</sup> and L1<sup>+/+</sup>) with an apparent molecular weight of approximately 55 kDa. This band most likely corresponds to endogenous mouse tau which is of a similar size. In the L66<sup>+/+</sup> samples, a second band running at approximately 68 kDa is also detected. The presence of numerous other bands indicates proteolytic truncation of tau within brain homogenates. In addition, in Fig. 44 the S1G2 antibody is able to detect the pathologic 10-kDa tau fragment that is capable of seeding disease in other cells.

The amino acid sequences of the human and mouse tau regions that contain the epitopes of CB7, CC7, S1D12 and S1G2 are superimposed for comparison (Fig 45). It is clear that both CB7 and CC7 epitopes fall in areas with no homology between the human and mouse tau sequences; however, in the core region, the sequences are identical. Together these blots and sequence analysis (Figs 41 – 45) highlight the diagnostic utility of these antibodies as they are able to recognise the presence of pathologic human tau in a transgenic mouse brain against a background of endogenous mouse tau protein. These antibodies could be utilised to track the fragmentation patterns of pathologic tau species during aging and in relation to any pharmacologic treatments that may affect the (human) tau protein, its aggregation, movement between compartments in the body (e.g. between brain and blood) and its pattern of fragmentation.

Example 30: Core and N-terminal antibody pairings detect age-related tau protein truncations or occlusion of core regions in ageing L66 mice

Brains from L66 <sup>+/+</sup> mice of various ages (1.5-month, n=11; 3-month, n=11; and 5-month, n=8) were homogenised as previously described and protein content quantified by BCA assay. These brain homogenates were then screened in paired antibody ELISAs to assess age-related changes in the tau fragmentation pattern. Brain homogenates were included in a sandwich ELISA in duplicate and tau values were determined against the linear section of an hTau40 standard curve.

When using S1D12 antibody to capture tau from these brain homogenates and CB7 as the detector antibody, a marked decrease in tau signals was observed with increasing age (Figure 46A). This finding was confirmed by changing the orientation of the assay and using CB7 as the capture antibody and S1G2 as detector (Figure 46B). Since the pairings used in this assay detect tau fragments that contain the amino acids spanning from 13-379, any truncation or occlusion of epitopes as a result of pathology-related aggregation that masks the core will result in lower tau detection. The progressive loss of signal that is observed here suggests that either a truncation or epitope occlusion event is occurring or that multiple events of this nature are occurring during the aging of L66<sup>+/+</sup> mice.

Example 31: Shorter N-terminal human tau fragments appear to increase with age in L66 <sup>+/+</sup> mice

In order to gain further insights into the protein fragmentation state of the tau matrix in the samples investigated above, the levels of a smaller N'-terminal fragment were determined using the CB7 antibody capture paired with HT7, a commercial antibody with an epitope in the region tau159-163.

Interestingly, there was a trend towards an increase in signal as the L66<sup>+/+</sup> mice aged. So, as the longer core to N'-terminal tau fragment decreases with age (Fig. 46), the levels of smaller, truncated fragments of human tau increase in this transgenic mouse line (Fig 47).

#### Example 32: Ultrasensitive Assays for the Detection of Tau fragments in Biological Fluids

Utilising Single Molecule Array (Simoa®) technology we have lowered the limit of detection of our assays substantially, in some instances to below 1 pg/ml tau protein (or protein fragment). Simoa® is a bead-based technology where a capture antibody is coated on to magnetic beads which can then be concentrated out of solution using a magnet. A biotinylated detector is added which binds to the captured molecule of interest. Streptavidin B Galactosidase (SBG) binds to the detector and subsequently hydrolyses resorufin  $\beta$ -D-galactopyranoside (RPG) into a fluorescent product that is used for detection of the immunocomplex. Table 26 summarises the antibody pairings and limits of detection for assays successfully transferred to the Simoa® system.

| Assay                                  | Capture antibody                       | Detector antibody                      | Simoa® limit of detection (pg/ml) |
|----------------------------------------|----------------------------------------|----------------------------------------|-----------------------------------|
| <b>Core</b><br>(Tau 337-379)           | S1D12<br>(Binding region hT40 337-355) | S1G2<br>(Binding region hT40 367-379)  | 0.75                              |
| <b>Core – proline</b><br>(Tau 159-379) | S1G2                                   | HT7<br>(Binding region hT40 159-163)   | 0.32                              |
|                                        | S1D12                                  | HT7                                    | 0.32                              |
|                                        | S1D12                                  | BT2<br>(Binding region hT40 194-198)   | 0.32                              |
| <b>Core - N'</b><br>(Tau 1-379)        | S1D12                                  | Tau12<br>(Binding region hT40 6-18)    | 0.75                              |
|                                        | S1G2                                   | Tau12                                  | 1.6                               |
|                                        | S1G2                                   | 3bG4<br>(Binding region hT40 1-15)     | 20                                |
| <b>Full-length</b><br>(Tau 1-441)      | CB7<br>(Binding region hT40 13-25)     | Tau46<br>(Binding region hT40 409-441) | 2.2                               |
| <b>N' – proline</b><br>(Tau 6-198)     | CB7                                    | BT2                                    | 0.75                              |
|                                        | CB7                                    | HT7                                    | 2.2                               |
|                                        | Tau12                                  | HT7                                    | 2.2                               |
| <b>Core – C'</b><br>(Tau 337-441)      | S1G2                                   | Tau46                                  | 2.2                               |

Table 26: Assays that have successfully been transferred to Simoa®. Capture antibody is coated to magnetic beads and the detector antibody is biotinylated. Limits of detection for each assay are included.

Example 33: Differing levels of tau fragmentation in post-mortem CSF



Human post-mortem CSF samples were acquired from the South West Dementia Brain Bank (SWDBB) and split into 3 groups based on histopathological diagnoses. These groups were healthy control (HC, n=6), mild/moderate AD (n=15) and severe AD (n=12). Protein content for each CSF sample was quantified by BCA assay to ensure tau levels were determined independently of total protein concentration. These samples were then screened in Simoa® experiments utilising a number of different antibody pairings as summarised in Table 27 below.

| Assay       | Capture antibody | Detector antibody | Tau protein fragment detected (numbers refer to amino acids in the hT40 protein) |
|-------------|------------------|-------------------|----------------------------------------------------------------------------------|
| Core        | S1D12            | S1G2              | 337-379                                                                          |
| NT1         | BT2              | Tau12             | 6-198                                                                            |
| Core – N'   | S1D12            | Tau12             | 6-349                                                                            |
| Full Length | CB7              | Tau46             | 13-441                                                                           |
| Core – C'   | S1D12            | Tau46             | 337-441                                                                          |
| Core - BT2' | S1D12            | BT2               | 194-359                                                                          |
| Core - HT7' | S1D12            | HT7               | 159-349                                                                          |

Table 27: Table summarising the assays used for post-mortem CSF screening. The capture and detector antibodies used in each assay are stated along with the minimum tau fragment that each assay measures.

The Simoa® experiments used for CSF screening utilised a 2-step protocol. First a standard curve of hTau40 (540 pg/ml - 0.7 pg/ml) was created by spiking recombinant hTau40 into Tau 2.0 diluent and triple diluting. CSF samples were diluted 1:10 in Tau 2.0 diluent and subsequently again 1:100 in Tau 2.0 diluent based on previous experiments which showed that a 1:2000 dilution was optimal for the standard curve. Tau levels were read from a 4-parameter-fit standard curve, multiplied by the dilution factor and analysed for statistical differences using GraphPad prism v5.

The levels of tau fragments detected by the core assay and the previously reported NT1 assay show a statistically significant increase associated with disease severity (Table 28). The NT1 assay uses a commercial antibody pairing, BT2 and Tau12, that measures the N-terminal region of the human tau protein (that encompasses hT40 6-198) in CSF and blood (Chen *et al.* 2019). Using the Simoa® NT1 assay, Chen *et al.* reported an increase in CSF tau levels in subjects with AD biomarker positive – mild cognitive impairment (AD-MCI) and AD biomarker positive – clinical AD (AD) compared to normal control (NC). However, the levels detected were in the pg/ml range, with mean values of 220-230 pg/ml in AD-MCI and AD patients (Chen *et al.* 2019). The results reported in Table 28 are similar, where an increase in the level of tau fragments detected by both the NT1 and core assays is observed in the post-mortem CSF samples of mild-moderate and severe AD groups compared to the control group. In contrast to Chen *et al.*, however, we detected ng/ml quantities of these assay-specific tau fragments. No other fragments tested showed significant differences due to the disease. Full-length tau and, to a

lesser degree, the other long fragments are present in much lower levels than those detected using either the core or NT1 assay. This provides further proof that tau exists as a matrix of small truncated fragments with very few longer or full-length fragments and our antibody pairings can differentiate these fragments in biological samples such as CSF.

| Category                | n  | Age (yr) | Sex (F) | PM Delay (h) | <u>Total Protein</u><br>(mg/ml) | <u>Assay</u>                     |                                     |                                     |                                           |                                       |                                         |                                        | P values |
|-------------------------|----|----------|---------|--------------|---------------------------------|----------------------------------|-------------------------------------|-------------------------------------|-------------------------------------------|---------------------------------------|-----------------------------------------|----------------------------------------|----------|
|                         |    |          |         |              |                                 | <u>NT1</u><br>(6-198)<br>(ng/ml) | <u>Core</u><br>(337-379)<br>(ng/ml) | <u>Core-N</u><br>(6-349)<br>(ng/ml) | <u>Full-length</u><br>(13-441)<br>(ng/ml) | <u>Core-C</u><br>(337-441)<br>(ng/ml) | <u>Core-HT7</u><br>(194-359)<br>(ng/ml) | <u>Core-F2</u><br>(159-349)<br>(ng/ml) |          |
| <u>Control</u>          | 6  | 75.33    | 50%     | 47.33 (9.8)  | 5.17 (0.7)                      | 62.66 (14.1)                     | 163.65 (33.5)                       | 40.87 (10.3)                        | 4.52 (0.6)                                | 9.29 (5.1)                            | 2.57 (1)                                | 6.46 (2.5)                             |          |
| <u>Mild/Moderate AD</u> | 15 | 87.73    | 60%     | 67.58 (12.5) | 5.44 (0.4)                      | 83.17 (22.6)                     | 184.07 (48.1)                       | 34.92 (6.9)                         | 3.99 (0.5)                                | 7.61 (2.6)                            | 4.3 (1.2)                               | 7.95 (2)                               |          |
| <u>Severe AD</u>        | 12 | 79.75    | 50%     | 44.88 (5.1)  | 5.27 (0.5)                      | 257.06 (79)                      | 542.9 (136.2)                       | 53.88 (10.7)                        | 3.85 (0.5)                                | 10.68 (2.4)                           | 6.07 (2.1)                              | 11.39 (3.6)                            |          |
| P values                |    |          |         |              |                                 | 0.0379*                          | 0.0165*                             | 0.3262                              | 0.7786                                    | 0.7491                                | 0.4894                                  | 0.5396                                 |          |

Table 28: Results of Simoa® experiments utilising 7 different antibody pairings to detect tau fragments in post-mortem CSF samples. The antibody pairings for each assay are as follows: NT1 (BT2-Tau12), Core (S1D12-S1G2), Core-N' (S1D12-Tau12), Full-length (CB7-Tau46), Core-C' (S1D12-Tau46), Core-BT2 (S1D12-BT2) and Core-HT7 (S1D12-HT7). There is a significant increase in NT1 and core tau levels in CSF samples associated with disease severity and the quantities detected in post-mortem CSF samples are greater than those in patient CSF (ng/ml levels in post-mortem samples vs pg/ml in patient CSF as reported by Chen et al. 2019). The other fragments tested did not show any differences between disease and control groups and the levels of these tau protein fragments were far lower than those measured in either the core or NT1 assays. Data presented as mean (standard error). There was no correlation detected due to age, sex, post-mortem (PM) delay or total protein.

**Example 34: Measuring tau fragment levels in AD and healthy control plasma samples**

Human plasma samples were sourced from the commercial supplier Logical Biological Ltd. Healthy control (HC, n=12) and samples from individuals with a diagnosis of AD (AD/MCI, n=42) were aliquoted into low bind microfuge tubes and stored at – 80 °C.

The Simoa® experiments used for plasma screening utilised a 3-step protocol optimised for use with plasma samples. A standard curve (540 pg/ml - 0.7 pg/ml) was created by spiking recombinant hTau40 into Tau 2.0 diluent and triple diluting. Plasma samples were diluted 1:100 and added in duplicate to the Simoa® plate followed by the addition of respective capture beads. Different antibody pairings used for plasma screening is explained in Table 5. In general, the capture antibody coated beads are mixed with diluted plasma samples, added to the plates and incubated for 30 min at 30 °C with shaking. Following the incubation, the plates were washed using the Simoa® plate washer before the addition of 0.2 µg/ml biotinylated detector antibody which was left to incubate as before for 10 min. The plates were then washed again before the addition of SBG and a final 10 min incubation. After the final incubation and wash steps the plates were transferred to the Simoa® reader and plasma tau concentrations generated against a 4-parameter fit curve.

| <b>Assay</b> | <b>Capture Antibody</b> | <b>Detector Antibody</b> | <b>Tau Protein Fragment Measured<br/>(numbers refer to amino acids in the tau protein)</b> |
|--------------|-------------------------|--------------------------|--------------------------------------------------------------------------------------------|
| Core         | S1D12                   | S1G2                     | 337-379                                                                                    |
| NT1          | BT2                     | Tau12                    | 6-198                                                                                      |
| Core-Tau12   | S1D12                   | Tau12                    | 6-349                                                                                      |
| Core - HT7   | S1D12                   | HT7                      | 159-349                                                                                    |
| Core - BT2   | S1D12                   | BT2                      | 194-359                                                                                    |
| BT2 - HT7    | BT2                     | HT7                      | 159-198                                                                                    |
| Core - C'    | S1D12                   | Tau46                    | 337-441                                                                                    |
| BT2 - S1G2   | BT2                     | 1G2                      | 194 - 379                                                                                  |

*Table 28: Table summarises the antibody pairings used for Simoa® assays for human plasma sample screening. The capture and detector antibodies used in each assay are stated along with the tau fragment each assay (the numbers refer to the amino acid positions in the full-length human tau protein hT40).*

Human plasma screening data were subsequently analysed in Graphpad Prism v5. Interestingly, we have observed significantly higher levels of plasma tau fragments in age-matched, healthy control group compared to the AD group as detected using various capture-detector antibody pairings (Table 29).

| Category                         | n  | Average Age (yr) | Average Sex (M) | Average MMSE score | NT1<br>(6-198)<br>(pg/ml) | Core<br>(337-379)<br>(pg/ml) | Core -Tau12<br>(6-349)<br>(pg/ml) | Core -HT7<br>(194-359)<br>(pg/ml) | Core -BT2<br>(159-349)<br>(pg/ml) | BT2 -HT7<br>(159-198)<br>(pg/ml) | Core -C<br>(337-441)<br>(pg/ml) | BT2 -S1G2<br>(192-379)<br>(pg/ml) |
|----------------------------------|----|------------------|-----------------|--------------------|---------------------------|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|---------------------------------|-----------------------------------|
| AD/MCI                           | 12 | 62               | 44.4 %          | 21                 | 0.19                      | n.d.                         | 0.67                              | 30.24                             | 899.6                             | 44.51                            | n.d.                            | n.d.                              |
| Healthy Control                  | 9  | 56               | 41.6%           | NA                 | 0.145                     | n.d.                         | 0.67                              | 1,802                             | 13,619                            | 123.8                            | n.d.                            | n.d.                              |
| Assay limit of detection (pg/ml) |    |                  |                 |                    | 0.25                      | 2.2                          | 0.25                              | 0.25                              | 0.75                              | 0.25                             | 2.2                             | 2.2                               |

Table 29: Results of Simoa® experiments utilising 8 different pairings detecting tau fragments in human plasma samples. Assay antibody pairings are as follows; NT1 (BT2-Tau12), Core (S1D12-S1G2), Core-Tau12 (S1D12-Tau12), Core-HT7 (S1D12-HT7), Core-BT2 (S1D12-BT2), BT2-HT7 (BT2-HT7), Core-C' (S1D12-Tau46), BT2-S1G2 (BT2-S1G2). There is a significant decrease in core-proline tau levels (measured using core-HT7 and core-BT2 assays where S1D12 is the capture antibody) in patients with an AD diagnosis (AD/MCI) compared with health control (HC) plasma. The levels of tau measured when using our core capture antibody S1D12 as part of an antibody pair is 1,000-fold more than the typical values seen for the existing NT1 assay in human plasma. In contrast to the reported NT1 assay, where AD/MCI patients typically show higher assay values than healthy controls, for assays using S1D12 capture this pattern is reversed with health control samples showing higher tau fragment values than AD/MCI patients. Data presented as mean. n.d. – not detected (signals below blank)

Example 35: Core capture antibody S1D12 can measure ng levels of tau in human plasma

When S1D12-BT2 or S1D12-HT7 pairings are used in Simoa® assay, nanogram levels of tau fragments are detected in human plasma (Table 29). All studies reported so far have measured pg/ml concentration of tau fragments in plasma with highest levels ~ 850 pg/ml (Sparks et al 2012; Rani et al 2017). Interestingly, and contrary to the NT1 assay, this core-BT2 assay measures 1,000- to 10,000-fold more tau fragments and the levels are higher in healthy controls compared to AD patients (Fig 8). Similarly, with the core-HT7 assay, ng/ml concentration of tau was detected in healthy control plasma and the levels were lower in AD/MCI plasma. Both findings translate to higher levels of core-proline fragments in healthy control and form the basis of a regular monitoring test to identify patients worthy of additional screening, i.e. a potential predictor of early onset of disease. The levels of tau detected using the core capture antibody is significantly greater than previously reported and suggests that the use of S1D12 reveals large amounts of previously undetected tau fragments in biological samples which can be considered as a tau protein mixture (full-length tau protein and populations of tau protein fragments) that can be referred to as a 'tauosome'. The decrease in tau levels in the plasma of AD/MCI patients suggests that perhaps defective clearance of tau from the brain is a critical factor in the pathogenesis of AD.

Example 36: Monitoring the "Treatment effects" of LMTM by detecting tau levels in the plasma of L66<sup>+/-</sup> mice

The effect of the tau aggregation inhibitor LMTM on the levels of plasma tau in a L66<sup>+/-</sup> mouse line was investigated with two assays, both utilising the 3-step Simoa® protocols described above. Using the human specific NT1 assay (BT2 capture with Tau12 detection), low levels of tau ( $0.41 \pm 0.09$  pg/ml) were detected in the plasma of 5-month-old L66<sup>+/-</sup> that were treated with vehicle control solution (Figure 50A). At the same time, an increase in tau levels was measured in the plasma of L66<sup>+/-</sup> mice that had received an oral administration of LMTM (15 mg/kg) during the time period ( $1.28 \pm 0.11$  pg/ml). This suggests that LMTM facilitates solubilisation of pathologic tau from the brain into the blood of mice receiving treatment.

This hypothesis was supported by our core-proline antibody assay in which S1D12 antibody coated capture beads and BT2 detector was used (Figure 50B). This assay detects both human and mouse tau which explains the higher levels of tau detected. Again, there was an increase in plasma tau in LMTM treated L66<sup>+/-</sup> mice with  $70 \pm 25$  pg/ml tau detected in the vehicle group and  $142.08 \pm 12.08$  pg/ml in the 15 mg/kg LMTM treatment group.

Example 37: S1D12 mAb as a potential therapeutic agent

Two pilot experiments were conducted in order to investigate the therapeutic effect of S1D12 mAb, its pharmacokinetic properties and potential clinical adverse events associated with antibody

administration and finally to show the mAbs efficacy and low toxicity after 1 month of repeat administration *in vivo* in a mouse model of AD.

1) **Pharmacokinetic study (PK)** to provide information about the delivery of S1D12 mAb into the brain and plasma as a measure of its bioavailability.

- 5 2) **Repeat-dosing study** to provide efficacy data and confirm no toxicity after 1-month administration of S1D12.

For the PK study, a total of 42 female NMRI mice (Swiss-type mouse, Naval Medical Research Institute) aged 6 months were allocated into six groups according to sample collection time (Table 30 for group size). Animals were injected intraperitoneally with S1D12 (30 mg/kg) and sacrificed 24-  
10 , 48-, 72-hours and 7-, 14- and 31-days after injection to collect blood and brain samples. A control group was also included in which animals were sacrificed to collect blood and brain, but no test item was administered.

| Mice (n) | Gender | Route of administration | S1D12 dose (mg.kg) | Injection volume (ml/kg) | Time point |
|----------|--------|-------------------------|--------------------|--------------------------|------------|
| 6        | F      | i.p                     | 30                 | 5                        | 24 hours   |
| 6        | F      | i.p                     | 30                 | 5                        | 48 hours   |
| 6        | F      | i.p                     | 30                 | 5                        | 72 hours   |
| 6        | F      | i.p                     | 30                 | 5                        | 7 days     |
| 6        | F      | i.p                     | 30                 | 5                        | 14 days    |
| 6        | F      | i.p.                    | 30                 | 5                        | 31 Days    |
| 6        | F      | controls                | no dose            | na                       | na         |

Table 30: Number of animals allocated in the PK study. *i.p.*, intraperitoneal; *na*, not applicable.

- 15 Blood samples were centrifuged to obtain plasma at 2000 x *g* for 5 min at 6 °C and samples were stored at -20 °C. After blood collection, each mouse was perfused with heparinized saline for 2-3 minutes and the entire brain removed rapidly and snap frozen in liquid nitrogen and stored at -80°C. Similarly, tissue samples such as the liver (right lobe), spleen, kidney (right kidney), muscle (thigh), heart and lung (right inferior lobe) were quickly snap frozen in liquid nitrogen after dissection.

20

- The concentration of S1D12 mAb in mouse plasma was determined using an antigen-capture ELISA with dGAE (representing amino acids 297-391 of hT40), as described previously. Briefly, dGAE (1 µg/mL) was used to coat ELISA plates and blocked with 2 % Marvel. For the standard curve, 5 nM S1D12 mAb was double diluted across plate in PBS and plasma samples were added to respective  
25 wells in duplicate at dilutions of 1:1000 and 1:5000. Following washing, HRP-conjugated anti-mouse IgG as detector was added, and the assay developed using TMB solution as normal. The absorbance at 450 nm was read using a Clariostar plate reader (BMG Labtech) and MARS Clariostar software used to calculate S1D12 concentration from a standard curve.



Individual mouse plasma concentrations of S1D12 mAb were determined from 4 individual experiments performed in duplicate. Average values from each group (representing a time point) was plotted (Fig 10) and the *in vivo* half-life,  $C_{max}$  and  $T_{max}$  calculated by performing a non-compartmental analysis of the plasma data using the PKSolver2.0 software (Fig 51, Table 31). Similarly, the ability of S1D12 mAb to cross the blood brain barrier (BBB) was evaluated by determining antibody levels in mouse brain homogenate by performing the dGAE ligand binding ELISA as described above. Here a higher coating concentration of dGAE at 10 ug/ml was used to compete off antibody binding to tau present in the brain. Based on the analysis of brain homogenates, between 0.2 to 0.47% of plasma S1D12 was able to cross the BBB and a  $T_{max}$  of 48 h and  $C_{max}$  of 6.2 nM was achieved in the brain.

| Parameter | Unit   | Value       |
|-----------|--------|-------------|
| $t_{1/2}$ | h      | 256.1778139 |
| $T_{max}$ | h      | 24          |
| $C_{max}$ | nmol/L | 1455.005514 |

*Table 31 Pharmacokinetic parameters of S1D12 after the administration of a single dose at 30 mg/kg in NMRI mice.  $t_{1/2}$  is the elimination half-life from plasma,  $C_{max}$  – peak plasma concentration,  $T_{max}$  – time of peak plasma concentration.*

In a six-week repeat-dose study, a total of 12 WT, 12 Line 1 (L1) and 12 Line 66 homozygotes (L66<sup>+/+</sup>) female mice aged 2-months at the beginning of the study were used (Table 32 for group size). Mice in each genotype were injected intraperitoneally (i.p.) with either vehicle or S1D12 (30 mg/kg), once per week, for six consecutive weeks.

All animals were observed for reaction to treatment during each day of dosing and throughout the week. Mice treated with S1D12 were culled seven days after the last dosing whereas vehicle-treated animals were sacrificed the following day, i.e. 8 days post-treatment. Mice were anaesthetized using an overdose of sodium pentobarbital administered intraperitoneally for blood collection. Blood was transferred to plastic vials containing lithium heparin anticoagulant, centrifuged to obtain the plasma and the entire brain was removed as described previously. Plasma and brain samples (stored at -20 °C and -80 °C respectively) were subjected to further biochemical analysis.

| Genotype (n)  | Gender | Route of administration | Treatment        | Injection volume (ml/kg) |
|---------------|--------|-------------------------|------------------|--------------------------|
| Wild type (6) | F      | i.p                     | Vehicle          | 5                        |
| Wild type (6) | F      | i.p                     | S1D12 (30 mg/kg) | 5                        |

| Genotype (n) | Gender | Route of administration | Treatment        | Injection volume (ml/kg) |
|--------------|--------|-------------------------|------------------|--------------------------|
| Line 1 (6)   | F      | i.p                     | Vehicle          | 5                        |
| Line 1 (6)   | F      | i.p                     | S1D12 (30 mg/kg) | 5                        |
| Line 66 (6)  | F      | i.p                     | Vehicle          | 5                        |
| Line 66 (6)  | F      | i.p                     | S1D12 (30 mg/kg) | 5                        |

Table 32: Animals allocated in the repeat dose study. *i.p.* intraperitoneal.

Example 38: Quantification of S1D12 mAb in the blood and brain of mice following repeat dosing

5 Free S1D12 mAb concentration in the plasma and brain homogenates of wild-type (WT), L1 and L66<sup>+/+</sup> mice was determined using dGAE ligand binding ELISA as described previously (Figures 42 and 43). More than a 3-fold increase in S1D12 concentration was achieved in WT mice plasma following repeat dosing at 30 mg/kg S1D12 once per week for 6 weeks (Fig 52). Between 0.15 –  
 10 0.3% of plasma S1D12 antibody was shown to cross the blood brain barrier and could be detected in the brain homogenates of WT, L1 and L66<sup>+/+</sup> mice (Fig 53).

Example 39: Assessment of pathologic human tau in L66<sup>+/+</sup> brain homogenates following 6-week S1D12 mAb therapy

15 A hemisphere of each Line 66<sup>+/+</sup> mouse brain was suspended in RIPA buffer and homogenised. Samples were left on ice for 1 hour and subsequently centrifuged for 10 minutes at 10,000 x g at 4°C. The supernatant was collected, and the total protein was quantified using a BCA Protein Assay Kit. Brain homogenate supernatant from each mouse was separated *via* sodium dodecyl sulphate  
 20 polyacrylamide gel electrophoresis (SDS-PAGE) with MES running buffer. Gels were subsequently transferred on to a 0.22 µm PVDF membrane, blocked in 2% Marvel before being incubated overnight at 4°C with S1G2 antibody (367-379 region of hT40) in the same blocking agent. Following washing, the secondary antibody, sheep anti-mouse IgG-HRP, was added, and the membrane was washed five times with PBST and developed with Clarity Western ECL Substrate and read using a  
 25 BioSpectrum Gel imaging System (UVP). Results were analysed using ImageJ-Fiji (NIH, Version 1.53) where densitometric analysis was performed and the ratio of human to mouse tau densities was calculated.

A decrease in the ratio of human tau to mouse tau in the brains of L66 mAb treated mice was observed compared to the vehicle control group, when a core region specific S1G2 antibody was used for detection (Fig 54).

5 Example 40: Assessment of pathologic insoluble tau in L66<sup>+/+</sup> mouse brain homogenates following 6-week S1D12 mAb therapy

For the extraction of pathology specific insoluble tau, a hemisphere of each Line 66<sup>+/+</sup> mouse brain was resuspended in TBS buffer supplemented with 1 x Halt™ Protease and Phosphatase Inhibitor  
 10 Cocktail and homogenised. Samples were processed to collect the supernatant as before and the total protein was quantified using a BCA Protein Assay Kit. Each brain homogenate supernatant was mixed with a final concentration of 1% sarkosyl, spun down at 200,000 x g for 45 min (fixed angle rotor) and the supernatants retained. Pellets were washed with TBS + 1 % sarkosyl, spun down again at 200,000 x g for 45 min and the resulting pellets were subsequently suspended in 70 % formic acid  
 15 and neutralised with 1 M Tris-base.

Formic acid extraction of sarkosyl-insoluble tau was subsequently analysed by an S1G2-BT2 chemiluminescence sandwich ELISA. Briefly, S1G2 mAb was added to a black 96 well Nunc MaxiSorp plate, and blocked with 2% Marvel. Formic acid-extracted sarkosyl insoluble tau diluted in  
 20 PBS was added to respective wells and incubated overnight at 4°C. Biotinylated-BT2 at a concentration of 50 ng/mL was used as the detector antibody, incubated for 1 h at 37°C and a streptavidin poly-HRP was added and incubated as before. For signal generation, SuperSignal™ ELISA Femto Substrate was added to the plate and read within 5 minutes of addition with a ClarioStar Plus plate reader (BMG Labtech). Mean results for L66<sup>+/+</sup> (vehicle treated) and L66<sup>+/+</sup> (S1D12 mAb  
 25 treated) are displayed as relative luminescence units.

The levels of sarkosyl-insoluble tau are reduced in L66<sup>+/+</sup> mice treated with a repeat dose of S1D12 mAb compared to the vehicle treated group (Fig 55). The core-proline region fragment is specifically detected using the antibody pairing S1G2-BT2 and a 5-6-fold decrease in mAb-treated mice  
 30 suggests antibody-mediated clearance of pathology-associated tau from the brain into the blood (further supported by plasma tau analysis data in the following section).

Example 41: Assessment of plasma tau levels in L66<sup>+/+</sup> mice following S1D12 Immunotherapy using Simoa® assays

35 In order to monitor the 'treatment effect' of S1D12 mAb, plasma tau samples from vehicle- and antibody-treated L66<sup>+/+</sup> mice were assessed via multiple Simoa® assays to fully investigate changes in the 'tauosome'. Three-step assays were performed and analysed as per previously described plasma screening methods in this document. Details of the antibody-conjugated beads, biotinylated  
 40 detectors and plasma dilutions used are shown in Table 33 below:

| Assay   | Capture antibody | Detector antibody | Tau fragment measured (represents amino acid regions on hT40) | Mouse plasma dilution |
|---------|------------------|-------------------|---------------------------------------------------------------|-----------------------|
| Assay 1 | S1G2             | BT2               | 194 - 379                                                     | 1:100                 |
| Assay 2 | BT2              | HT7               | 159-198                                                       | 1:6                   |
| Assay 3 | BT2              | Tau12             | 6-198                                                         | 1:6                   |

Table 33: Antibody pairings used for Simoa® assays for screening S1D12-treated mouse plasma samples. The capture and detector antibodies used in each assay are given together with the tau fragment that each assay measures and the dilution of mouse plasma required for each antibody pairing.

5

An increase in plasma tau was detected in mice treated with S1D12 mAb when using a core and proline region specific antibody pairing (S1G2-BT2) in the Simoa® assay. This assay can detect both human and mouse tau and a significant increase in the tau levels was observed in L66<sup>+/+</sup> mice receiving the antibody treatment ( $1438 \pm 275$  pg/ml) vs ( $425 \pm 83$  pg/ml) (Fig 56). The differences in L1 and wildtype groups were not statistically significant. Using the human specific NT1 assay (BT2 capture with Tau12 detection), a four-fold increase in tau levels was measured in the plasma of S1D12 treated L66 mice ( $3.2 \pm 0.42$  pg/ml) compared to the levels seen in vehicle-treated group ( $0.87 \pm 0.11$  pg/ml) during the same time period (Fig 57). When using a human-specific, proline region antibody pairing (BT2-HT7), a two-fold increase in plasma tau was observed with S1D12 immunotherapy, however this difference did not reach statistical significance ( $127 \pm 55$  pg/ml vs  $61 \pm 26$  pg/ml for S1D12 mAb and vehicle group, respectively) (Fig 58).

In earlier experiments both LMTM and S1D12 were shown in *in vitro* aggregation inhibition assays to prevent, block and/or slow the accumulation of potentially disease-causing tau protein aggregates (see Figures 34, 35, 36 and 38). As an extension to these *in vitro* observations and similar to the *in vivo* findings in LMTM-treated mice shown previously (see Fig 50a and 50b), the increase in N-terminal and core-proline tau in the plasma of S1D12 mAb group provides evidence of an antibody-mediated clearance of pathologic tau from the brain in these mice.

#### 25 Example 42: Tau aggregation inhibition assays *in vitro*

dGAE protein was diluted into 10 mM phosphate buffer, pH 7.4 (PB) with monoclonal antibody s1D12 at a ratio of 4:1 protein:Ab (100  $\mu$ M dGAE + 25  $\mu$ M s1D12 and 10  $\mu$ M dGAE + 2.5  $\mu$ M s1D12) or 1:1 (25  $\mu$ M dGAE + 25  $\mu$ M s1D12).

30

As a positive control, dGAE was prepared at a final concentration of 10, 25 or 100  $\mu$ M in 10 mM PB. Negative controls consisted of dGAE with a non-tau IgG antibody at a ratio of 4:1 (10  $\mu$ M dGAE +

2.5  $\mu\text{M}$  anti-ovalbumin), or antibody alone (25 or 2.5  $\mu\text{M}$  s1D12 and 2.5  $\mu\text{M}$  anti-ovalbumin). Samples were agitated at 700 rpm at 37 °C for 3 days.

5 Transmission electron microscopy (TEM), circular dichroism (CD) and Thioflavin S (ThS) assays were performed as detailed in Al-Hilaly et. al. (2018) J. Mol. Biol. 430, 4119-4131. Briefly, TEM grids were prepared by adding 4  $\mu\text{L}$  of sample to a carbon-coated grid followed by a wash with milli-Q filtered water then staining twice with 2% uranyl acetate. Grids were air dried and then imaged using a JEOL electron microscope operating at 80 kV.

For CD, 60  $\mu\text{L}$  sample was placed in a 0.1 mm quartz cuvette and placed into a JASCO spectropolarimeter. 100  $\mu\text{L}$  ThS in 20 mM MOPS buffer was added to 50  $\mu\text{L}$  of each sample to a final concentration of 20  $\mu\text{M}$ , mixed well, incubated at room temperature for 10 minutes then fluorescence intensity measured in a Cary Eclipse spectrophotometer using an excitation wavelength of 440 nm. Baseline readings from 10 mM PB were subtracted from CD and ThS measurements.

15 The findings from these three experiments indicate that s1D12 inhibits the assembly of dGAE into fibrils in vitro.

Firstly, dGAE fibrils were readily observed by TEM in samples using concentrations as low as 10  $\mu\text{M}$ ; at the same concentration in the presence of s1D12, no fibrils were present suggesting inhibition of assembly. Fibrils were present when using the same molar ratios of dGAE:Ab with a non-tau antibody, showing that the inhibitory effect is specific.

Circular dichroism reports on secondary structure characteristics of proteins in solution. Although 10 and 25  $\mu\text{M}$  dGAE were too low in concentration to be observed using CD, and the signal is dominated by the characteristic  $\beta$ -sheet signal expected from the antibody structure. At 100  $\mu\text{M}$  dGAE, a random coil confirmation is revealed when the antibody CD signal is subtracted from the dGAE signal. This further indicates that for s1D12:dGAE at a ratio of 4:1, dGAE cannot assemble into  $\beta$ -sheet rich fibrils. Finally, Thioflavin S was used to report on the presence of fibrils. ThS is a dye that binds to amyloid, the underlying structure in dGAE fibrils, and fluoresces at a characteristic wavelength of around 483 nm when excited with light of a wavelength of 440 nm. A positive signal was clearly observed for 25 and 100  $\mu\text{M}$  dGAE fibrils. However, when incubated with s1D12 at ratios of either 4:1 or 1:1, this signal was abolished, supporting the previous observations that no fibrils are present when dGAE is incubated with s1D12.

35 Collectively, these results provide evidence that (i) s1D12 specifically inhibits the assembly of dGAE into fibrils and (ii) these assays can be utilized to determine the inhibitory activity of other antibodies in disrupting formation of fibrils that strongly resemble the paired helical filaments that are present in the tau pathology characteristic of Alzheimer's disease.

CLAIMS

1. A specific binding molecule that binds to an epitope within SEQ ID NO: 1 with a binding affinity greater than the binding affinity with which antibody mAb423 binds to an epitope within SEQ ID NO: 1.
2. The specific binding molecule according to claim 1 wherein the epitope of the specific binding molecule is within SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7.
3. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises:
  - i. an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 8 (VEVKSEKLDFKDR);
  - ii. the amino acid sequence of SEQ ID NO: 9 (XXXXXXXXKXFXR, wherein X is any amino acid); or
  - iii. the amino acid sequence of SEQ ID NO: 8, optionally wherein any one or more residue other than residue number 343 (K), 346 (F) and/or 349 (R) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1).
4. The specific binding molecule according to any one of claims 1 to 3 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:
 

VHCDR1 comprises the sequence set forth in SEQ ID NO: 10 (N/S N A V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 11 (G C S S D G T/K C Y Y/H N S A L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 12 (G H/F/Y Y S/P I/V Y G Y D Y L/S G T I D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 13 (S G S S S N V G/- G G/R N S/D V G/A);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 14 (D/N/G T N/T S R P S);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 15 (V/A T/S G D S T/S T/A H/I D/N D L/I);

or for each CDR sequence, an amino acid sequence with

  - (i) at least 85% identity thereto, and/or
  - (ii) one, two, or three amino acid substitutions relative thereto.

5. The specific binding molecule according to any one of claims 1 to 4 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG) or SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCYNSALKS), SEQ ID NO: 19 (GCSSDGKCYHNSALKS) or SEQ ID NO: 20 (GCSSDGKCYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGYDYLGTIDY), SEQ ID NO: 22 (GFYSIYGYDYSGTIDY), or SEQ ID NO: 23 (GYYPVYGYDYLGTIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG) or SEQ ID NO: 25 (SGSSSNVGRNDVA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS), SEQ ID NO: 27 (NTNSRPS), or SEQ ID NO: 28 (GTTSRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL), SEQ ID NO: 30 (VTGDSSTHDDL), or SEQ ID NO: 31 (ASGDSSAINDI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1.

6. The specific binding molecule according to any one of claims 1 to 5 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 16 (NNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 18 (GCSSDGTCYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 21 (GHYSIYGYDYLGTIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 24 (SGSSSNVGGGNSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 26 (DTNSRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 29 (VTGDSTTHDDL).

7. The specific binding molecule according to any one of claims 1 to 6 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 355 of SEQ ID NO: 1 with a  $K_D$  of less than around 500 pM, optionally wherein

i. The  $K_D$  for binding to SEQ ID NO: 1 is around 50 pM to around 150 pM, and/or

ii. The  $K_D$  for binding to SEQ ID NO: 5 is around 300 pM to around 400 pM.

8. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises:

- i. an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 33 (GNKKIETHKLTFR);
- ii. the amino acid sequence of SEQ ID NO: 34 (XXXXXXXXXXXXX, wherein X is any amino acid); or
- iii. the amino acid sequence of SEQ ID NO: 33, optionally wherein any one or more residue other than residue number 370 (K) and/or 374 (H) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1).

9. The specific binding molecule according to any one of claims 1, 2 or 8 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1. Said specific binding molecule may comprise the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 35 (S/T N/Y S/A/Y V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 36 (G/S/N I/V D/Y T/S D/T G E/Y/D/R E/T/A G/Y/F Y/F N P A/V L N/K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 37 (S/T Y/V/A R/N A/T/G/S D/- G/- L/Y/F/- A/- Y/H G/P Y/D V Q/Y A/Y I D/E Y/R/K) or SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 38 (S G S/R F/Y/D I/L/V G/S I/S/R S S/R/A/G V G) or in SEQ ID NO: 39 (SGSSSNVGYGNYVG)

VLCDR2 comprises the sequence set forth in SEQ ID NO: 40 (A/D S/A D/S/T G/S R P/A S);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 41 (G/S S/I/V S/F/Y/T D/G/A/Q R/P/- T/- P/Q/D/G Y/R/H/N T/N G/Y V/I/L);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto.

10. The specific binding molecule according to any one of claims 1, 2, 8 or 9 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG), SEQ ID NO: 17 (SNAVG), SEQ ID NO: 44 (SYYVG), or SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS), SEQ ID NO: 47 (SVDSGDGYTYNPALKS), SEQ ID NO: 48 (GIDSDGEEGYNPALNS), SEQ ID NO: 49 (GIDSDGEEGYNPALKS), SEQ ID NO: 50 (SVDSGDGYTYNPALKS), SEQ ID NO: 51 (GIDTDGEEGYNPALKS), SEQ ID NO: 52 (NIYSTGRAFYNPALKS), or SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY), SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY), SEQ ID NO: 56 (SVNGHPDVYYIDR), SEQ ID NO: 57 (TYRTDGYAYGYVQAIDY), SEQ ID NO: 58 (SYRSDGLAYGYVQAIDY), SEQ ID NO: 59



(SANGHPDVYYIDK), SEQ ID NO: 60 (TYRTDGFAYGYVQAIDY), SEQ ID NO: 61 (SYRTDGLAYGYVQAIEY), or SEQ ID NO: 265 (GSYYHGGGNGMVDFFDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG); SEQ ID NO: 64 (SGSYISSSRVG); SEQ ID NO: 65 (SGSDLGSSRVG); SEQ ID NO: 66 (SGSYIGSSAVG); SEQ ID NO: 67 (SGRFIGISSVG); SEQ ID NO: 68 (SGSYIGSSGVG); or SEQ ID NO: 69 (SGSYVSRSRVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); SEQ ID NO: 71 (DSSSRPS); or SEQ ID NO: 72 (AATSRAS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGTV); SEQ ID NO: 74 (GSSDRTQYTGV); SEQ ID NO: 75 (GVFGDRNYI); SEQ ID NO: 76 (GIFGDRNYI); SEQ ID NO: 77 (GSTAPTPHTGV); SEQ ID NO: 78 (SSYQRGNTGV); SEQ ID NO: 79 (GSSDRTQYTGL); or SEQ ID NO: 80 (GIYGDRNYI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1.

11. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 73 (GSSDRTPYTGTV).

12. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

13. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 48 (GIDSDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 57 (TYRTDGAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

14. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

15. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 51 (GIDTDGEEGYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 60 (TYRTDGFAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

16. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 44 (SYYVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 52 (NIYSTGRAFYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 265 (GSYYHGGNGMVDFFDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 72 (AATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 78 (SSYQRGNTGV).

17. The specific binding molecule according to any one of claims 1, 2, or 8 to 10 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 58 (SYRSDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTGV).

18. The specific binding molecule according to any one of claims 1, 2, or 8 to 17 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 367 to 379 of SEQ ID NO: 1 with a  $K_D$  of less than around 500 pM, optionally wherein

- i. The  $K_D$  for binding to SEQ ID NO: 1 is around 100 pM to around 200 pM, and/or
- ii. The  $K_D$  for binding to SEQ ID NO: 5 is around 400 pM to around 500 pM.

19. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 82 (VEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN).

20. The specific binding molecule according to any one of claims 1, 2 or 19 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (S Y S V Y)

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (I M Y A S G R V D Y N P A L K S)

VHCDR3 comprises the sequence set forth in SEQ ID NO: 85 (G I E N/D)

VLCDR1 comprises the sequence set forth in SEQ ID NO: 86 (R T S/N Q/E S/N V/I N/G/D N/S Y/G L S/A)

VLCDR2 comprises the sequence set forth in SEQ ID NO: 87 (Y A T Y L Y/H T)

VLCDR3 comprises the sequence set forth in SEQ ID NO: 88 (L Q Y D/G/E S/T T P L A/T);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto.

21. The specific binding molecule according to any one of claims 1, 2, 19 or 20 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN) or SEQ ID NO: 90 (GIED);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS), SEQ ID NO: 92 (RTNESVGNLYLS), SEQ ID NO: 93 (RTSQNIDNGLA), or SEQ ID NO 94 (RTSQSVGSYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT) or SEQ ID NO: 96 (YATRLHT);

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA), SEQ ID NO: 98 (LQYDSTPLT), SEQ ID NO: 99 (LQYESTPLA), or SEQ ID NO: 100 (LQYGTTPLA);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1.

22. The specific binding molecule according to any one of claims 1, 2, or 19 to 21 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 337 to 368 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein

- i. The  $K_D$  for binding to SEQ ID NO: 1 is less than around 25 nM, and/or
- ii. The  $K_D$  for binding to SEQ ID NO: 5 is less than around 25 nM.

23. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 120 (SSTGSIDMVDPQLATLADEVASLAKQGL).

24. The specific binding molecule according to any one of claims 1, 2 or 23 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 121 (S/N D/Y S/G/A V/L A/G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 122 (A/N S/I G/Y/W S/R S/G G N/S/R K/T/I Y/E Y N P A L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 123 (G I/G I/V A/G G/S V D V), or SEQ ID NO: 124 (SGGD);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 125 (S G S/G S/N N V/I G Y/R G N/D/T Y/F V G/D);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 126 (G T/A A/D/T I/S/R R A/P S/P); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 127 (A S/T Y Q/D S/Y/R N/S Y/D/N/E A/G/D/S -/G/M/V -/I F/V/I);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

25. The specific binding molecule according to any one of claims 1, 2, 23 or 24 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA), SEQ ID NO: 129 (NYGVG), or SEQ ID NO: 130 (SYALG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS), SEQ ID NO: 132 (NIWRGGRIEYPALKS), or SEQ ID NO: 133 (NIYSGGSTYYPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV), SEQ ID NO: 135 (GGVGSVDV), or SEQ ID NO: 124 (SGGD);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG), SEQ ID NO: 137 (SGGRNNIGRGTFVD), and SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS), SEQ ID NO: 140 (GAASRAS), SEQ ID NO: 141 (GATSRAS), or SEQ ID NO: 142 (GTDRRPP); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF), SEQ ID NO: 144 (ASYDRSESVV), SEQ ID NO: 145 (ASYDSSDGGV), or SEQ ID NO 146 (ATYDYSNDMII);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1.

26. The specific binding molecule according to any one of claims 1, 2, or 23 to 25 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 139 (GTAIRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 143 (ASYQSNYAF).

27. The specific binding molecule according to any one of claims 1, 2, or 23 to 25 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 128 (SDSVA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 131 (ASGSSGNKYYPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 134 (GIIAGVDV);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 140 (GAASRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 145 (ASYDSSDGGV).

28. The specific binding molecule according to any one of claims 1, 2, or 23 to 25 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 129 (NYGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 133 (NIYSGGSTYYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 135 (GGVGSVDV);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 137 (SGGRNNIGRGTFFVD);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 142 (GTDRRPP); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 146 (ATYDYSNDMII).

29. The specific binding molecule according to any one of claims 1, 2, or 23 to 25 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 130 (SYALG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 132 (NIWRGGRIEYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 124 (SGGD);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 39 (SGSSSNVGYGNYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 144 (ASYDRSESVV).

30. The specific binding molecule according to any one of claims 1, 2, or 23 to 29 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 412 to 441 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein the  $K_D$  for binding to SEQ ID NO: 1 is around 1 nM to around 10 nM.

31. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 148 (MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQ).

32. The specific binding molecule according to any one of claims 1, 2 or 31 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (S N G V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 150 (D I S/A S S/V/G G K A/K/V Y A/S/G N/H P A L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 151 (C R D G G V S/T Y G Y D I/S D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 152 (S G S S/T S/G N I/V G G/S/Y G N/D Y/D L/V S/G);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 153 (G A/V T S/N/E R/L A S);

and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 154 (A/G S F/Y D T/S/D S/N S G G I/V);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

33. The specific binding molecule according to any one of claims 1, 2, 31 or 32 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 155 (DISSSGKAYANPALKS), SEQ ID NO: 156 (DISSGGKVYGHHPALKS), SEQ ID NO: 157 (DISSVGKKYANPALKS), or SEQ ID NO: 158 (DIASSGKAYSNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 159 (CRDGGVSYGYDIDY), SEQ ID NO: 160 (CRDGGVSYGYDSDY), or SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 163 (SGSSSNIGGGNYLS), SEQ ID NO: 138 (SGSSSNVGYGDYVG), SEQ ID NO: 165 (SGSSGNVGYGDYVS), or SEQ ID NO: 166 (SGSTSNVGSNDVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS), SEQ ID NO: 168 (GVTERAS), SEQ ID NO: 169 (GATNLAS), or SEQ ID NO: 170 (GATNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 171 (ASFDTSSGGI), SEQ ID NO: 172 (ASYDDSSGGI), SEQ ID NO: 173 (ASYDSSSGGV), or SEQ ID NO: 174 (GSYDSNSGGI); or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1.

34. The specific binding molecule according to any one of claims 1, 2, or 31 to 33 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 155 (DISSSGKAYANPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 159 (CRDGGVSYGYDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 163 (SGSSSNIGGGNYLS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 171 (ASFDTSGGI).

35. The specific binding molecule according to any one of claims 1, 2, or 31 to 33 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 156 (DISSGGKVYGH PALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 160 (CRDGGVSYGYDSDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 168 (GVTERAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 172 (ASYDDSSGGI).

36. The specific binding molecule according to any one of claims 1, 2, or 31 to 33 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV).

37. The specific binding molecule according to any one of claims 1, 2, or 31 to 33 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 158 (DIASSGKAYSNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 166 (SGSTSNVGSNDVS);



VLCDR2 comprises the sequence set forth in SEQ ID NO: 170 (GATNRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 174 (GSYDSNSGGI).

38. The specific binding molecule according to any one of claims 1, 2, or 31 to 37 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 49 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein the  $K_D$  for binding to SEQ ID NO: 1 is around 1 nM to around 20 nM.

39. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 175 (QTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDT).

40. The specific binding molecule according to any one of claims 1, 2 or 39 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (S N G V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 176 (D I/K S S V/A G K K/T Y A/G N P A L K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 177 (C R D G G V T Y G Y D I/V D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 178 (S G S S S N V G L/Y R/G N/D Y/V V T/S);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 179 (G A/T T S/T R A S); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 180 (A S A/F D T/S N/D D/S G G V/I);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

41. The specific binding molecule according to any one of claims 1, 2, 39 or 40 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS), or  
 SEQ ID NO: 182 (DKSSAGKTYGNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVITYGYDIDY), or  
 SEQ ID NO: 184 (CRDGGVITYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 185 (SGSSSNVGLRNYVT), or SEQ ID NO: 186 (SGSSSNVGYGDVVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS), or SEQ ID NO: 188 (GTTTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 189 (ASADTNDGGV), or SEQ ID NO: 190 (ASFDSDSGGI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1.

42. The specific binding molecule according to any one of claims 1, 2, or 39 to 41 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 185 (SGSSSNVGLRNYVT);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 189 (ASADTNDGGV).

43. The specific binding molecule according to any one of claims 1, 2, or 39 to 41 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 149 (SNGVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 182 (DKSSAGKTYGNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 184 (CRDGGVTYGYDVDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 186 (SGSSSNVGYGDVVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 188 (GTTTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 190 (ASFDSDSGGI).

44. The specific binding molecule according to any one of claims 1, 2, or 39 to 43 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 49 to 111 of SEQ ID NO: 1 with a  $K_D$  of less than around 250 nM, optionally wherein the  $K_D$  for binding to SEQ ID NO: 1 is around 50 nM to around 150 nM.

45. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 191 (GKTKIATPRGA).

46. The specific binding molecule according to any one of claims 1, 2 or 45 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 146 to 157 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 192 (S N A V I/G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 193 (L I D V/I D G D A/T A Y D/N P A L K/E S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 194 (D/H Y G/D S/K W G Y V/A S/D D/S I D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 195 (S G S D/S -/S -/N -/V I/G G/Y G A/D D/Y V G);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 196 (D N/A D/T N/T R P/A S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 197 (G/A T/S Y S/Q G/N A/E N/R Y/S G I/V);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

47. The specific binding molecule according to any one of claims 1, 2, 45 or 46 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI), or SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS), or SEQ ID NO: 201 (LIDIDGDTAYNPALES);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY), or SEQ ID NO: 203 (HYDKWGYADSIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 204 (SGSDIGGADV), or SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 206 (DNDNRPS), or SEQ ID NO: 207 (DATTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 208 (GTYSGANYGI), or SEQ ID NO: 209 (ASYQNERSGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1.

48. The specific binding molecule according to any one of claims 1, 2, or 45 to 47 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 204 (SGSDIGGADVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 206 (DNDNRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 208 (GTYSGANYGI).

49. The specific binding molecule according to any one of claims 1, 2, or 45 to 47 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 201 (LIDIDGDTAYNPALES);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 203 (HYDKWGYADSIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 138 (SGSSSNVGYGDYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 207 (DATTRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 209 (ASYQNERSGV).

50. The specific binding molecule according to any one of claims 1, 2, or 45 to 49 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 147 to 157 of SEQ ID NO: 1 with a  $K_D$  of less than around 50 nM, optionally wherein the  $K_D$  for binding to SEQ ID NO: 1 is around 10 nM to around 20 nM.

51. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises:

- i. an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 221 (RENAKAKTDHGAE);
- ii. the amino acid sequence of SEQ ID NO: 222 (XXXXXXXXXXXXE, wherein X is any amino acid); or
- iii. the amino acid sequence of SEQ ID NO: 221, optionally wherein any one or more residue other than residue number 391 (E) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1).

52. The specific binding molecule according to any one of claims 1, 2 or 51 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence

comprising residues 379 to 391 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 223 (D/S R/W G V A);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 224 (T M R S G G T/G I/T D/E Y/D N P A L K S);

VHCDR3 comprises the sequence set forth SEQ ID NO: 225 (G Y L S G D/I/V R/H Y A);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 226 (S G S R/S S D/N I/V G Y/D/A G N/D/R Y V S/G);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 227 (D/S/G T/A N/R/T T/N/S R A S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 228 (A N/S I D S/T S/G R/N S/N H/L L/I));

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

53. The specific binding molecule according to any one of claims 1, 2, 51 or 52 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA), SEQ ID NO: 230 (DWGVA), or SEQ ID NO: 231 (SWGVA);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS), SEQ ID NO: 233 (TMRSGGGTEYNPALKS), or SEQ ID NO: 234 (TMRSGGTTDDNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA), SEQ ID NO: 236 (GYLSGIIHYA), or SEQ ID NO: 237 (GYLSGVHYA);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNVVS), SEQ ID NO: 239 (SGSSSNVGAGNYVG), SEQ ID NO: 240 (SGSSSNVGDGDYVG), or SEQ ID NO: 241 (SGSSSNVGDGRYVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS), SEQ ID NO: 243 (DTTSRAS), SEQ ID NO: 170 (GATNRAS), or SEQ ID NO: 244 (SARNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRSHL), SEQ ID NO: 246 (ASIDSGNNLL), or SEQ ID NO: 247 (ASIDTSRSHI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1.

54. The specific binding molecule according to any one of claims 1, 2, or 51 to 53 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 229 (DRGVA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 232 (TMRSGGTIDYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 235 (GYLSGDRYA);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 238 (SGSRSDIGYGNYVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 242 (DTNTRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 245 (ANIDSSRS HL).

55. The specific binding molecule according to any one of claims 1, 2, or 51 to 53 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTDDNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 241 (SGSSSNVGDGRYVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 243 (DTTSRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 246 (ASIDSGNNLL).

56. The specific binding molecule according to any one of claims 1, 2, or 51 to 53 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 230 (DWGVA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 234 (TMRSGGTDDNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 237 (GYLSGVHYA);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 239 (SGSSSNVGAGNYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (GATNRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI).

57. The specific binding molecule according to any one of claims 1, 2, or 51 to 53 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 231 (SWGVA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 233 (TMRSGGGTEYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 236 (GYLSGIHYA);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 240 (SGSSSNVGDGDYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 244 (SARNRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 247 (ASIDTSRSHI).

58. The specific binding molecule according to any one of claims 1, 2, or 51 to 57 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 379 to 391 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein

- i. The specific binding molecule has no detectable binding to SEQ ID NO: 1, and/or
- ii. The  $K_D$  for binding to SEQ ID NO: 4 is around 300 pM to around 10 nM.

59. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 293 (MAEPRQEFVMEHDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQPTEDGSEEPGSE TSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAAEEAGIGDTPSLEDEAAGHVTQARM VSKSKDGTGSDDKKAKGADGKTKIATPR).

60. The specific binding molecule according to any one of claims 1, 2, or 59 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 1 to 155 of SEQ ID NO: 1.

61. The specific binding molecule according to any one of claims 1, 2, or 59 to 60 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

- VHCDR1 comprises the sequence set forth in SEQ ID NO: 259 (SNGVG);
- VHCDR2 comprises the sequence set forth in SEQ ID NO: 157 (DISSVGKKYANPALKS);
- VHCDR3 comprises the sequence set forth in SEQ ID NO: 161 (CRDGGVTYGYDIDY);
- VLCDR1 comprises the sequence set forth in SEQ ID NO: 165 (SGSSGNVGYGDYVS);
- VLCDR2 comprises the sequence set forth in SEQ ID NO: 169 (GATNLAS); and
- VLCDR3 comprises the sequence set forth in SEQ ID NO: 173 (ASYDSSSGGV).

62. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 278 (DHAGTYGLGDRKD).

63. The specific binding molecule according to any one of claims 1, 2, or 62 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLYAYDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMYA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 13 to 25 of SEQ ID NO: 25.

64. The specific binding molecule according to any one of claims 1, 2, or 62 to 63 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 279 (NYRVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 280 (NIRSGGTTWYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 281 (DSSGDLYAYDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 282 (SGSSSNVGYGNMYA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 263 (ASYDSTSGGV).

65. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 283 (ADGKTKIATPRGA).

66. The specific binding molecule according to any one of claims 1, 2, or 62 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);



VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL);  
 or for each CDR sequence, an amino acid sequence with  
 (i) at least 85% identity thereto, and/or  
 (ii) one, two, or three amino acid substitutions relative thereto,  
 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
 an amino acid sequence comprising residues 145 to 157 of SEQ ID NO: 1.

67. The specific binding molecule according to any one of claims 1, 2, or 65 to 66 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 198 (SNAVI);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 200 (LIDVDGDAAYDPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 202 (DYGSWGYVSDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 292 (SGSYITGSSVG);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 284 (DNNDRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 285 (ASYDTSNIGL).

68. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises:

- i. an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 319 (TSKCGSLGNIHHK);
- ii. the amino acid sequence of SEQ ID NO: 320 (XXXXGSLGNIXXX, wherein X is any amino acid); or
- iii. the amino acid sequence of SEQ ID NO: 319, optionally wherein any one or more residue other than residue number 323 (G), 324 (S), 325 (L), 326 (G), 327 (N) and/or 328 (I) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1).

69. The specific binding molecule according to any one of claims 1, 2, or 68 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNVVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 319 to 331 of SEQ ID NO: 1.

70. The specific binding molecule according to any one of claims 1, 2, or 68 to 69 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 310 (NYPVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 311 (NIENDGSANYASALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 312 (EFGGSDGYTYFVDIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 313 (SGSSSNVGYGNVVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 141 (GATSRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 314 (ASYDGSSSGV).

71. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 321 (KPGGGQVEVKSEKLDKDRVQSKIGSLDNI).

72. The specific binding molecule according to any one of claims 1, 2, or 71 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGYDYLGTIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 331 to 360 of SEQ ID NO: 1.

73. The specific binding molecule according to any one of claims 1, 2, or 71 to 72 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 17 (SNAVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 20 (GCSSDGKCYNSALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 23 (GYYPVYGYDYLGTIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 25 (SGSSSNVGRNDVA);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 28 (GTTSRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 31 (ASGDSSAINDI).

74. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises:

- i. an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 330 (GSLDNITHVPGGG);
- ii. the amino acid sequence of SEQ ID NO: 331 (XXXDXITHXPXXX, wherein X is any amino acid); or
- iii. the amino acid sequence of SEQ ID NO: 330, optionally wherein any one or more residue other than residue number 358 (D), 360 (I), 361 (T), 362 (H) and/or 364 (P) is replaced by a conservative amino acid substitution (numbering according to SEQ ID NO: 1).

75. The specific binding molecule according to any one of claims 1, 2, or 74 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 355 to 367 of SEQ ID NO: 1.

76. The specific binding molecule according to any one of claims 1, 2, or 74 to 75 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 83 (SYSVY);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 84 (IMYASGRVDYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 89 (GIEN);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 91 (RTSQSVNNYLS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 95 (YATRLYT); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 97 (LQYDSTPLA).

77. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at

least 95% or at least 99% identity to SEQ ID NO: 332 (NITHVPGGGNKKIETHKLTFRNAAKAKTDHGAE).

78. The specific binding molecule according to any one of claims 1, 2, or 77 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 359 to 391 of SEQ ID NO: 1.

79. The specific binding molecule according to any one of claims 1, 2, or 77 to 78 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL).

80. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 333 (ITHVPGGGNKKIETHKLTFRNAAKAKTDHGA).

81. The specific binding molecule according to any one of claims 1, 2, or 80 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 334 (SVAVN);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 335 (GIISNGGTGYNPALKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 336 (GVEWEGSMDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 337 (SGSSSNVGAGSYVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 338 (GATKRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 339 (VSYQTDFTLV);  
or for each CDR sequence, an amino acid sequence with  
(i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 360 to 390 of SEQ ID NO: 1.

82. The specific binding molecule according to any one of claims 1, 2, or 80 to 81 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 334 (SVAVN);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 335 (GIISNGGTGYNPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 336 (GVEWEGSMDY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 337 (SGSSSNVGAGSYVG);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 338 (GATKRAS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 339 (VSYQTDFTLV).

83. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 351 (THKLTFRENAKAK).

84. The specific binding molecule according to any one of claims 1, 2, or 83 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);  
VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYYPALKS);  
VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);  
VLCDR1 comprises the sequence set forth in SEQ ID NO: 352 (SGSSSNVGIYDVS);  
VLCDR2 comprises the sequence set forth in SEQ ID NO: 353 (GTNNRPS); and  
VLCDR3 comprises the sequence set forth in SEQ ID NO: 354 (AAGDSSTIAV);

or for each CDR sequence, an amino acid sequence with  
(i) at least 85% identity thereto, and/or  
(ii) one, two, or three amino acid substitutions relative thereto,  
wherein the specific binding molecule binds to a polypeptide or protein molecule comprising  
an amino acid sequence comprising residues 373 to 385 of SEQ ID NO: 1.

85. The specific binding molecule according to any one of claims 1, 2, or 83 to 84 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 102 (RESIA);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 103 (GVGIDGTSYYPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 104 (NYIDFEY);  
 VLCDR1 comprises the sequence set forth in SEQ ID NO: 352 (SGSSSNVGIYDVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 353 (GTNNRPS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 354 (AAGDSSTIAV).

86. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 355 (VQIINKKLDLSNVQSKCGSKDNIKHVPGGGS) and/or SEQ ID NO: 356 (VEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN).

87. The specific binding molecule according to any one of claims 1, 2, or 86 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 357 (SYGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 358 (SISSGGTTFYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 359 (DVHIYYNDYGAAYGDRDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 360 (SGSSSNIGGGNYVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 361 (GTTSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 362 (ASYDTNSGSV);

or for each CDR sequence, an amino acid sequence with

- (i) at least 85% identity thereto, and/or
- (ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 275 to 305 and/or residues 337 to 368 of SEQ ID NO: 1.

88. The specific binding molecule according to any one of claims 1, 2, or 86 to 87 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 357 (SYGVG);  
 VHCDR2 comprises the sequence set forth in SEQ ID NO: 358 (SISSGGTTFYNPALKS);  
 VHCDR3 comprises the sequence set forth in SEQ ID NO: 359 (DVHIYYNDYGAAYGDRDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 360 (SGSSSNIGGGNYVS);  
 VLCDR2 comprises the sequence set forth in SEQ ID NO: 361 (GTTSRAS); and  
 VLCDR3 comprises the sequence set forth in SEQ ID NO: 362 (ASYDTNSGSV).

89. The specific binding molecule according to any one of claims 1, 2, or 59 to 88 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein the  $K_D$  for binding to SEQ ID NO: 1 is around 1 nM to around 20 nM.

90. The specific binding molecule according to any one of claims 1 or 2 wherein the epitope comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 90%, at least 95% or at least 99% identity to SEQ ID NO: 5 (IKHVPGGGSGVQIVYKPVDSLKVTSCGSLGNIHHKPGGGQVEVKSEKLDKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGA).

91. The specific binding molecule according to any one of claims 1, 2 or 90 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1 and the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 426 (S/T N/H S V G);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 427 (G I D T/S D G E E G Y/F N P A/V L N/K S);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 428 (S/T Y R A/T/S D G L/Y G Y V Q A I D Y);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 429 (S G S F/Y I G I/S S S/G V G);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (A S D G R P S); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 432 (G S S D R T Q Y T G V/L);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto.

92. The specific binding molecule according to any one of claims 1, 2, or 90 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG), SEQ ID NO: 187 (SHSVG), SEQ ID NO: 45 (TNSVG), SEQ ID NO: 102 (RESIA), or SEQ ID NO: 199 (DYGIG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS), SEQ ID NO: 205 (GINYDGRTEYNSALKS), SEQ ID NO: 103 (GVGIDGTSYSPALKS), SEQ ID NO: 53 (GIDTDGEEGFNPVLKS), or SEQ ID NO: 48 (GIDSDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY), SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY), SEQ ID NO: 210 (TYRSDGYAYGYVQAIDY), SEQ ID NO: 104 (NYIDFEY), or SEQ ID NO: 211 (DSKGGWGHVYQFDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG), SEQ ID NO: 68 (SGSYIGSSGVG), SEQ ID NO: 212 (SGSNIGSASVT), or SEQ ID NO: 213 (SGSSSNVGYGDYVS);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS), SEQ ID NO: 214 (RNRNRPS), or SEQ ID NO: 215 (DATNRAS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTG), SEQ ID NO: 79 (GSSDRTQYTGL), SEQ ID NO: 216 (ASHDNRISAV), or SEQ ID NO: 217 (GSYQSWGSGV);

or for each CDR sequence, an amino acid sequence with

(i) at least 85% identity thereto, and/or

(ii) one, two, or three amino acid substitutions relative thereto,

wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1.

93. The specific binding molecule according to any one of claims 1, 2, or 91 to 92 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 42 (SNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 46 (GIDTDGEEGYNPALNS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 54 (SYRADGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 63 (SGSFIGISSVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 74 (GSSDRTQYTG).

94. The specific binding molecule according to any one of claims 1, 2, or 91 to 92 wherein the specific binding molecule comprises the CDRs VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2 and VLCDR3, wherein each of said CDRs comprises an amino acid sequence as follows:

VHCDR1 comprises the sequence set forth in SEQ ID NO: 45 (TNSVG);

VHCDR2 comprises the sequence set forth in SEQ ID NO: 53 (GIDTDGEEGFNPVLKS);

VHCDR3 comprises the sequence set forth in SEQ ID NO: 55 (SYRTDGLAYGYVQAIDY);

VLCDR1 comprises the sequence set forth in SEQ ID NO: 68 (SGSYIGSSGVG);

VLCDR2 comprises the sequence set forth in SEQ ID NO: 70 (ASDGRPS); and

VLCDR3 comprises the sequence set forth in SEQ ID NO: 79 (GSSDRTQYTGL).

95. The specific binding molecule according to any one of claims 1, 2, or 91 to 94 wherein the specific binding molecule binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 297 to 390 of SEQ ID NO: 1 with a  $K_D$  of less than around 25 nM, optionally wherein:

- i. The  $K_D$  for binding to SEQ ID NO: 1 is around 500 pM to around 1 nM; or
- ii. The  $K_D$  for binding to SEQ ID NO: 1 is around 1 nM to around 15 nM.



96. The specific binding molecule according to any one of claims 1 to 22, 51 to 58 and 68 to 95 wherein the specific binding molecule competes with the binding of:

- a) a first region within residues 296 to 391 of SEQ ID NO: 1 to a second region within residues 296 to 391 of SEQ ID NO: 1; and/or
- b) a first region within residues 296 to 390 of SEQ ID NO: 1 to a second region within residues 296 to 390 of SEQ ID NO: 1; and/or
- c) a first region within residues 308 to 378 of SEQ ID NO: 1 to a second region within residues 308 to 378 of SEQ ID NO: 1.

97. The specific binding molecule according to claim 96 wherein the first and second region are within different polypeptide molecules, and wherein the specific binding molecule competes with the binding of:

- a) a first polypeptide comprising residues 333 to 353 of SEQ ID NO: 1 to a second polypeptide comprising residues 333 to 353 of SEQ ID NO: 1;
- b) a first polypeptide comprising residues 322 to 333 of SEQ ID NO: 1 to a second polypeptide comprising residues 322 to 333 of SEQ ID NO: 1;
- c) a first polypeptide comprising residues 356 to 364 of SEQ ID NO: 1 to a second polypeptide comprising residues 356 to 364 of SEQ ID NO: 1;
- d) a first polypeptide comprising residues 306 to 314 of SEQ ID NO: 1 to a second polypeptide comprising residues 306 to 314 of SEQ ID NO: 1; or
- e) a first polypeptide comprising residues 369 to 378 of SEQ ID NO: 1 to a second polypeptide comprising residues 369 to 378 of SEQ ID NO: 1.

98. The specific binding molecule according to claim 96 wherein the first and second region are within the same polypeptide molecule, and wherein the specific binding molecule competes with the binding of:

- a) residues 337 to 355 of SEQ ID NO: 1 to residues 337 to 355 of SEQ ID NO: 1;
- b) residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1;
- c) residues 327 to 331 of SEQ ID NO: 1 to residues 356 to 363 of SEQ ID NO: 1;
- d) residues 313 to 322 of SEQ ID NO: 1 to residues 368 to 378 of SEQ ID NO: 1; or
- e) residues 306 to 311 of SEQ ID NO: 1 to residues 373 to 378 of SEQ ID NO: 1.

99. The specific binding molecule of any preceding claim, wherein the specific binding molecule is an antibody or a fragment thereof.

100. The specific binding molecule of claim 99, wherein the antibody or fragment thereof is humanised.

101. The specific binding molecule of any one of claims 99 or 100, wherein said specific binding molecule is an antibody, the antibody is a monoclonal antibody, or when said specific binding

molecule is a fragment of an antibody, said fragment is a Fab or F(ab')<sub>2</sub> antibody fragment, or an scFv molecule.

102. The specific binding molecule of any preceding claim, wherein the specific binding molecule binds to SEQ ID NO: 1 or a fragment thereof with a K<sub>D</sub> of less than 10 nM.

103. A composition comprising a specific binding molecule according to any preceding claim, wherein at least 90% of the specific binding molecules in the composition that bind an epitope within SEQ ID NO: 1 bind with a K<sub>D</sub> of less than 25 nM.

104. A nucleic acid molecule comprising a nucleic acid sequence encoding a specific binding molecule according to any one of claims 1 to 102.

105. A nucleic acid molecule according to claim 104 wherein the nucleic acid sequence is selected from the group consisting of SEQ ID Nos: 43, 219, 249, 251, 253, 380 to 411 and 431, or a nucleic acid sequence with at least 70% identity to any one of SEQ ID Nos: 43, 219, 249, 251, 253, 380 to 411 and 431.

106. A construct comprising a nucleic acid molecule according to claim 104 or claim 105.

107. A vector comprising a nucleic acid molecule of claim 104 or claim 105 or a construct of claim 106.

108. A host cell comprising a nucleic acid molecule of claim 104 or claim 105, a construct of the claim 106 or a vector of claim 107.

109. A method of preparing a specific binding molecule according to any one of claims 1 to 102 comprising:

- i) introducing into a host cell a nucleic acid molecule of claim 104 or claim 105, a construct of the claim 106 or a vector of claim 107;
- ii) expressing the nucleic acid molecule such that the specific binding molecule is produced; and
- iii) collecting the specific binding molecule, preferably by purification.

110. A specific binding molecule obtainable by a method according to the claim 109.

111. A pharmaceutical composition comprising a specific binding molecule according any one of claims 1 to 102 or a composition according to claim 103 and one or more pharmaceutically acceptable diluents, carriers or excipients.

112. A specific binding molecule according to any one of claims 1 to 102, a composition according to claim 103 or a pharmaceutical composition according to claim 111 for use in therapy.
113. A specific binding molecule according to any one of claims 1 to 102, a composition according to claim 103 or a pharmaceutical composition according to claim 111 for use in treatment of a tauopathy.
114. A method of treating a tauopathy, comprising administering to a subject in need thereof a specific binding molecule according to any one of claims 1 to 102, a composition according to claim 103 or a pharmaceutical composition according to claim 111.
115. The specific binding molecule, composition or pharmaceutical composition for use according to claim 113 or the method of treating a tauopathy according to claim 114, wherein the tauopathy is selected from the group consisting of Alzheimer's disease, Primary age-related tauopathy (PART), Neurofibrillary tangle-predominant senile dementia, Chronic traumatic encephalopathy (CTE), Progressive supranuclear palsy (PSP), Corticobasal degeneration (CBD), Frontotemporal dementia (FTD), Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), Pick disease, disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC), pallido-ponto-nigral degeneration (PPND), Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD), Dementia with Argrophilic grains (AgD), Down's Syndrome (DS), dementia with Lewy bodies (DLB), Postencephalitic parkinsonism (PEP), Dementia pugilistica (DP), traumatic brain injury (TBI), stroke, ischemia, Lytico-bodig disease (Parkinson-dementia complex of Guam), Ganglioglioma, Gangliocytoma, Meningioangiomas, Postencephalitic parkinsonism, Subacute sclerosing panencephalitis (SSPE), Lead encephalopathy, tuberous sclerosis, Pantothenate kinase-associated neurodegeneration, lipofuscinosis and mild cognitive impairment (MCI).
116. An *in vitro* method of inhibiting aggregation of a tau protein or a fragment thereof comprising contacting the tau protein or a fragment thereof with a specific binding molecule according any one of claims 1 to 102.
117. An *in vitro* method for detecting a tau protein or a fragment thereof in a sample comprising contacting the sample with a specific binding molecule of any one of claims 1 to 102.
118. A diagnostic method comprising contacting a sample with a specific binding molecule of any one of claims 1 to 102.
119. The *in vitro* method for detecting a tau protein or a fragment thereof according to claim 117 or the diagnostic method according to claim 118, comprising contacting the sample with a first specific binding molecule that binds to an epitope within residues 296 to 391 of SEQ ID NO: 1 and

contacting the sample with a second specific binding molecule that binds to an epitope within SEQ ID NO: 1.

120. The *in vitro* method for detecting a tau protein or a fragment thereof according to claim 117 or 119, or the diagnostic method according to claim 118 or 119, comprising contacting the sample with at least one pair of first and second specific binding molecules, wherein the pair of first and second specific binding molecules are selected from the group consisting of:

- a) A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 367 to 379 of SEQ ID NO: 1;
- b) A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 379 to 391 of SEQ ID NO: 1; and
- c) A first specific binding molecule that binds to an epitope within residues 337 to 355 of SEQ ID NO: 1 and a second specific binding molecule that binds to an epitope within residues 13 to 25 of SEQ ID NO: 1.

121. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119 to 120, or the diagnostic method according to any one of claims 118 to 120, comprising:

- a) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule according to any one of claims 3 to 7 and a specific binding molecule according to any one of claims 8 to 18;
  - b) contacting the sample with a second pair of specific binding molecules comprising a specific binding molecule according to any one of claims 3 to 7 and a specific binding molecule according to any one of claims 50 to 58; and
  - c) contacting the sample with a third pair of specific binding molecules comprising a specific binding molecule according to any one of claims 3 to 7 and a specific binding molecule according to any one of claims 62 to 64;
- wherein each pair of specific binding molecules is contacted to the sample in parallel.

122. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119 to 121, or the diagnostic method according to any one of claims 118 to 121, comprising:

- a) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule according to claim 6 and a specific binding molecule according to claim 11;
  - b) contacting the sample with a second pair of specific binding molecules comprising a specific binding molecule according to claim 6 and a specific binding molecule according to claim 54;
- and

- c) contacting the sample with a third pair of specific binding molecules comprising a specific binding molecule according to claim 6 and a specific binding molecule according to claim 64; wherein each pair of specific binding molecules is contacted to the sample in parallel.

123. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119 to 122, or the diagnostic method according to any one of claims 118 to 122 wherein the sample is a plasma sample.

124. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119 to 123, or the diagnostic method according to any one of claims 118 to 123, further comprising a step of denaturing the tau protein or fragment thereof prior to contacting the sample with the specific binding molecule.

125. The diagnostic method according to any one of claims 118 to 124, comprising contacting a plasma sample with a pair of specific binding molecules comprising a first specific binding molecule according to any one of claims 3 to 7 and a second specific binding molecule according to any one of claims 8 to 18, wherein the tauopathy is Alzheimer's disease.

126. The diagnostic method according to any one of claims 118 to 125, comprising contacting a plasma sample with a pair of specific binding molecules comprising a first specific binding molecule according to claim 6 and a second specific binding molecule according to claim 11, wherein the tauopathy is Alzheimer's disease.

127. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119, or the diagnostic method according to any one of claims 118 to 119, comprising:

- (a) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule according to any one of claims 3 to 7 and a specific binding molecule according to any one of claims 62 to 64; and/or
- (b) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule according to any one of claims 8 to 18 and a specific binding molecule according to any one of claims 62 to 64.

128. The *in vitro* method for detecting a tau protein or a fragment thereof according to any one of claims 117 or 119, or the diagnostic method according to any one of claims 118 to 119, comprising:

- (a) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule according to any one of claims 45 to 50 and a specific binding molecule according to any one of claims 62 to 64; and/or
- (b) contacting the sample with a first pair of specific binding molecules comprising a specific binding molecule that binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 159 to 163 of SEQ ID NO: 1 and a specific binding molecule

according to any one of claims 62 to 64, optionally wherein the specific binding molecule that binds to a polypeptide or protein molecule comprising an amino acid sequence comprising residues 159 to 163 of SEQ ID NO: 1 is HT7.

129. A diagnostic device for use in a method according to any one of claims 117 to 128.
130. A kit comprising a specific binding molecule according to any one of claims 1 to 102 and reagents for detecting a tau protein or a fragment thereof in a sample.