

CLAIMS

1. An antibody or antigen binding fragment thereof that specifically binds to CD96, binding protein wherein the antibody or antigen binding fragment thereof comprises:
 - (a) (i) any one or a combination of CDRs selected from CDRH1 of SEQ ID NO: 115;
CDRH2 of SEQ ID NO: 145;
CDRH3 of SEQ ID NO: 147; from SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, and 94, and/or
CDRL1 of SEQ ID NO: 97;
CDRL2 of SEQ ID NO: 99; and
CDRL3 of SEQ ID NO: 101; from SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, and 93; or (ii) a CDR variant of (i) wherein the variant has 1, 2, or 3 amino acid modifications; or
- (b) 2. The antibody or antigen binding fragment thereof according to claim 1, wherein the antibody or antigen binding fragment thereof comprises:
 - a VH region comprising a sequence that is at least 80% identical to SEQ ID NO: 86; and the sequence of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, or 94; and/or
 - a VL region comprising a sequence that is at least 80% identical to SEQ ID NO: 85; the sequence of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, or 93.
23. The antibody or antigen binding fragment thereof according to claim 1, wherein the antibody or antigen binding fragment thereof comprises: CD96 binding protein according to claim 1, wherein the CDR of (a) (i) is:
 - a VH region that is 100% identical to SEQ ID NO: 86; and
 - a VL region that is 100% identical to SEQ ID NO: 85; (1) a CDRH1 selected from SEQ ID NOS: 105-125; a CDRH2 selected from SEQ ID NOS: 126-146; and/or a CDRH3 selected from SEQ ID NOS: 147-150; a CDRL1 selected from of SEQ ID NOS: 97-98; a CDRL2 selected from SEQ ID NOS: 99-100; and/or a CDRL3 selected from SEQ ID NOS: 101-104.

34. The antibody or antigen binding fragment thereof according to claim 1, wherein the antibody or antigen binding fragment thereof comprises a humanized sequence or a chimeric sequence. ~~CD96 binding protein according to any of the preceding claims wherein the binding protein comprises CDRH3 that is 100% identical to Seq ID NOS:~~
- 5 147, 148, 149, or 150.
4. ~~The CD96 binding protein according to any of the preceding claims wherein the binding protein comprises: a CDRH1 that is 100% identical to SEQ ID NOS: 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124 or 125; a CDRH2 that is 100% identical to SEQ ID NOS: 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, or 146; and/or a CDRH3 that is 100% identical to SEQ ID NOS: 147, 148, 149, or 150; a CDRL1 that is 100% identical to SEQ ID NO: 97 or 98; a CDRL2 that is 100% identical to SEQ ID NO: 99 or 100; and/or a CDRL3 that is 100% identical to SEQ ID NO: 101, 102, 103, or 104.~~
- 10 15 5. The antibody or antigen binding fragment thereof according to claim 1, which is an antibody.
- 20 6. The antibody or antigen binding fragment thereof according to claim 3, which is an antibody.
- 25 5. ~~The CD96 binding protein according to any one of the preceding claims wherein all 6 CDRs are present in the binding protein.~~
- 30 6. ~~A CD96 binding protein comprising the following 6 CDRs:~~
 CDRH1 of SEQ ID NO: 115;
 CDRH2 of SEQ ID NO: 145; and
 CDRH3 of SEQ ID NO: 147; and
 CDRL1 of SEQ ID NO: 97;
 CDRL2 of SEQ ID NO: 99; and
 CDRL3 of SEQ ID NO: 101.
- 35 7. The antibody or antigen binding fragment thereof according to claim 5, wherein the antibody further comprises a human wild-type IgG1 Fc domain.

8. The antibody or antigen binding fragment thereof according to claim 6, wherein the antibody further comprises a human wild-type IgG1 Fc domain.

- ~~7. The CD96 binding protein according to claim 6 wherein the binding protein comprises:
 5 a VH region that is 75% identical to SEQ ID NO: 86; and/or
 a VL region that is 75% identical to SEQ ID NO: 85.~~

- ~~8. The CD96 binding protein according to any one of the preceding claims wherein the binding protein comprises :
 10 a VH region that is 100% identical to SEQ ID NO: 86; and/or
 a VL region that is 100% identical to SEQ ID NO: 85.~~

- ~~9. The CD96 binding protein according to any one of the preceding claims wherein the binding protein comprises a synthetic polypeptide, a humanised sequence, or a chimeric sequence.~~

- ~~10. The CD96 binding protein according to any one of the preceding claims, wherein said protein binds to CD96 with a binding affinity (KD) which is equal to or better than that of CD155 or which can prevent or displace CD155 from binding to CD96.~~

- ~~11. The CD96 binding protein according to any of the preceding claims, which binds to CD96 with a binding affinity (KD) of at least about 30nM.~~

- ~~12. The CD96 binding protein according to any one of the preceding claims, which is an antibody and which comprises an antibody Fc region which can bind to the Fc gamma receptor and/or can promote IFN gamma release.~~

- ~~13. The CD96 binding protein according to claim 12, wherein said Fc region is the wild type IgG1Fc or a functional variant thereof.~~

- ~~14. A CD96 binding protein which is an antibody and wherein the binding protein comprises: a heavy chain that is 100% identical to the amino acid sequence of SEQ ID NO: 165; and/or a light chain that is 100% identical to the amino acid sequence of SEQ ID NO: 166.~~

- 5 15. ~~A CD96 binding protein which is an antibody and wherein the binding protein comprises: a heavy chain that is 100% identical to the amino acid sequence of SEQ ID NO: 170; and/or a light chain that is 100% identical to the amino acid sequence of SEQ ID NO: 169.~~
- 10 16. ~~A CD96 binding protein which is an antibody and wherein the binding protein comprises: a heavy chain that is 100% identical to the amino acid sequence of SEQ ID NO: 174; and/or a light chain that is 100% identical to the amino acid sequence of SEQ ID NO: 173.~~
- 15 17. ~~A nucleic acid molecule comprising a nucleic acid sequence which encodes encoding the CD96 binding protein as defined in any one of the preceding claims antibody or antigen binding fragment thereof according to claim 1.~~
- 20 18. ~~The nucleic acid sequence according to claim 17, wherein the sequence comprises SEQ ID NOS 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 167, 172, or 176 encoding the heavy chain; and/or SEQ ID NOS: 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 51, 55, 59, 63, 67, 71, 75, 79, 83, 87, 91, 95, 168, 171, or 175 encoding the light chain.~~ 10. The nucleic acid molecule according to claim 9, wherein the nucleic acid sequence comprises SEQ ID NO: 87 encoding a VH region and SEQ ID NO: 88 encoding a VL region.
- 25 19. ~~An expression vector comprising the nucleic acid sequence as defined in claim 17 or 18 molecule according to claim 10.~~
- 30 20. ~~An expression vector according to claim 19, selected from the following: (i) a vector encoding the nucleic acid sequence of the heavy chain of SEQ ID NO 167 and the light chain of SEQ ID NO 168, (ii) a vector encoding the nucleic acid sequence of the heavy chain of SEQ ID NO 172 and the light chain of SEQ ID NO 171, and (iii) a vector encoding the nucleic acid sequence of the heavy chain of SEQ ID NO 176 and the light chain of SEQ ID NO 175.~~
- 35 21. ~~A recombinant host cell comprising the nucleic acid sequence(s) as defined in claim 17 or 18, or the expression vector(s) as defined in claims 19 or 20 according to claim 11.~~

5

~~22. A method for the production of an C96 binding protein, which method comprises culturing the host cell as defined in claim 21 under conditions suitable for expression of said nucleic acid sequence(s) or vector(s), whereby a polypeptide comprising the CD96 binding protein is produced.~~

10

~~23. The CD96 binding protein produced by the method of claim 22.~~

~~24~~13. A cell line engineered to express the CD96 binding protein of any one of claims ~~1 to 16~~1 to 16, antibody or antigen binding fragment thereof according to claim 1.

15

~~25~~14. A pharmaceutical composition comprising the CD96 binding protein as defined in any one of claims 1 to 16 and a pharmaceutically acceptable excipient antibody or antigen binding fragment thereof according to claim 1, and a pharmaceutically acceptable carrier.

20

15. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof according to claim 3, and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof according to claim 7, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof according to claim 8, and a pharmaceutically acceptable carrier.

25

~~26. A pharmaceutical composition according to claim 25 comprising the CD96 binding protein as defined in any of claims 6 ,8 or 14-16 and a pharmaceutically acceptable excipient.~~

30

~~27. A method for the treatment of a disease in a subject in need thereof comprising administering to said subject a therapeutically effective amount of the CD96 binding protein as defined in any one of claims 1 to 16, or the pharmaceutical composition as defined in any of claims 25-26.~~

35

~~28. A method for the treatment of a disease in a subject in need thereof comprising administering to said subject a therapeutically effective amount the CD96 binding protein as defined in any of claims 6 ,8 or 14-16.~~

29. ~~The method of claim 27 or 28 further comprising determining whether the subject expresses CD96.~~
18. The antibody or antigen binding fragment thereof according to claim 2, which is an antibody.
19. The antibody or antigen binding fragment thereof according to claim 18, wherein the antibody further comprises a human wild-type IgG1 Fc domain.
20. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof according to claim 19, and a pharmaceutically acceptable carrier.
30. ~~A CD96 binding protein as defined in any one of claims 1 to 16, or a pharmaceutical composition as defined in any of claims 25-26 for use in therapy.~~
31. ~~A CD96 binding protein as defined in any one of claims 1 to 16 or a pharmaceutical composition as defined in any of claims 25-26 for use in the treatment of a disease in a subject.~~
32. ~~A CD96 binding protein for use according to claim 31 wherein said patient is a human subject.~~
33. ~~A CD96 binding protein according to claim 31-32, for use in treating a solid tumour.~~
34. ~~A CD96 binding protein for use according to claim 31-32, wherein said protein is an antibody according to claim 14-16 and said solid tumour is selected from ovarian, lung (e.g. NSCLC), gastric, bladder, colorectal, liver (e.g. HCC), renal (e.g. RCC), and head and neck squamous cell carcinoma (HNSCC).~~
35. ~~Use of a CD96 binding protein as defined in any one of claims 1 to 16, or a pharmaceutical composition as defined in any of claims 25-26, in the manufacture of a medicament for use in the treatment of a disease.~~
36. ~~A pharmaceutical composition according to claims any of claims 25-26, which further comprises a PD-1 antagonist and/or an anti-TIGIT antibody.~~

37. A pharmaceutical composition according to claim 36, wherein said PD-1 antagonist is an antibody comprising a heavy chain sequence of SEQ ID NO:160 and a light chain sequence of SEQ ID NO:162.
- 5 38. The method of claim 27 or 28 further comprising administering a PD-1 antagonist and/or an anti-TIGIT antibody.
39. The method of claim 38 wherein said disease is cancer and wherein the CD96 binding protein and the PD-1 antagonist and/or anti-TIGIT antibody are administered to a patient such as a human patient in a route which is simultaneously or sequentially in any order.
- 10 40. The method of claim 39 wherein said cancer is a solid tumour and wherein said PD1 antagonist is an antibody comprising a heavy chain sequence of SEQ ID NO:160 and a light chain sequence of SEQ ID NO:162.
- 15 41. The method of claim 40 wherein said solid tumour is selected from ovarian, lung (e.g. NSCLC), gastric, bladder, colorectal, liver (e.g. HCC), renal (e.g. RCC), and head and neck squamous cell carcinoma (HNSCC).