

CLAIMS

1. A CD96-binding agonistic antibody being capable of stimulating activation and/or proliferation of T cells upon binding to CD96, and said agent specifically binds to at least one epitope in an extracellular domain D1 (SEQ ID NO: 269), domain D2 v1 or v2 (SEQ ID NO: 270 or SEQ ID NO: 273), or domain D3 (SEQ ID NO: 271).
2. The CD96-binding agent of claim 1, wherein the CD96-binding agent is capable of stimulating activation and/or proliferation of T cells in combination with a T cell co-stimulatory agent and/or T cell proliferation agent.
3. The CD96-binding agent of any preceding claim, wherein binding of the agent to CD96 induces dimerization or multimerization of CD96.
4. The CD96-binding agent of any preceding claim, wherein the CD96-binding agent is an anti-CD96 antibody or antigen-binding fragment thereof.
5. The CD96-binding agent of any preceding claim, wherein the T cells are CD4⁺ and/or CD8⁺ cells.
6. The CD96-binding agent of any preceding claim, wherein the agent binds to human CD96, preferably human CD96 variant 1 (SEQ ID NO: 267) and/or human CD96 variant 2 (SEQ ID NO: 268) and/or to rhesus CD96 (SEQ ID NO: 272).
7. The CD96-binding agent of any preceding claim, wherein the agent specifically binds an epitope shared by two domains selected from D1, D2, and D3, such as e.g. domains D1 and D2, domains D2 and D3 of human CD96.
8. The CD96-binding agent of any preceding claim, wherein the agent is capable of binding to human CD96 with a dissociation constant (K_D) of less than 50 nM, preferably less than 10 nM, most preferably less than 1 nM.

9. The CD96-binding agent of claim 8, wherein the agent is capable of binding to human CD96 with a dissociation constant (K_D) of 0.01 to 50 nM, preferably 0.1 to 10 nM, most preferably 0.1 to 1 nM.
10. The CD96-binding agent of any preceding claim, wherein the agent is capable of binding to human CD96 expressed on T-cells with a dissociation constant (K_D) of less than 50 nM, preferably less than 10 nM, most preferably less than 1 nM.
11. The CD96-binding agent of any of claims 4 to 10, wherein the antibody is a chimeric, humanized or fully human antibody.
12. The CD96-binding agent of any one of claims 4 to 11, wherein the antibody is an antigen-binding fragment, preferably wherein the antibody fragment is an $F(ab')_2$ or a Fab fragment.
13. The CD96-binding agent of any of claims 4 to 12, wherein the antibody is a monospecific antibody, a bispecific antibody or a multispecific antibody.
14. The CD96-binding agent of any of claims 4 to 13, wherein the antibody comprises a heavy chain having 3 CDR sequences set forth in SEQ ID NOs: 1-3, 13-15, 61-63, 73-75, 85-87, 109-111, 145-147, 157-159, 169-171, 181-183, 193-195, 205-207 or 217-219 (Kabat annotation) or SEQ ID NOs: 4-6, 16-18, 64-66, 76-78, 88-90, 112-114, 148-150, 160-162, 172-174, 184-186, 196-198, 208-210 or 220-222 (IMGT annotation) and a light chain having 3 CDR sequences set forth in SEQ ID NOs: 7-9, 19-21, 67-69, 79-81, 91-93, 115-117, 151-153, 163-165, 175-177, 187-189, 199-201, 211-213 or 223-225 (Kabat annotation) or SEQ ID NOs: 10-12, 22-24, 70-72, 82-84, 94-96, 118-120, 154-156, 166-168, 178-180, 190-192, 202-204, 214-216 or 226-228 (IMGT annotation).
15. The CD96-binding agent of claim 14, wherein the antibody comprises the following combinations of 3 heavy light chain CDR sequences with 3 light chain CDR sequences:
 - a. SEQ ID NOs: 1-3 in combination with SEQ ID NOs: 7-9 (Kabat annotation) or SEQ ID NOs: 4-6 in combination with SEQ ID NOs: 10-12 (IMGT annotation);

- b. SEQ ID NOs: 13-15 in combination with SEQ ID NOs: 19-21 (Kabat annotation) or SEQ ID NOs: 16-18 in combination with SEQ ID NOs: 22-24 (IMGT annotation);
- c. SEQ ID NOs: 61-63 in combination with SEQ ID NOs: 67-69 (Kabat annotation) or SEQ ID NOs: 64-66 in combination with SEQ ID NOs: 70-72 (IMGT annotation);
- d. SEQ ID NOs: 73-75 in combination with SEQ ID NOs: 79-81 (Kabat annotation) or SEQ ID NOs: 76-78 in combination with SEQ ID NOs: 82-84 (IMGT annotation);
- e. SEQ ID NOs: 85-87 in combination with SEQ ID NOs: 91-93 (Kabat annotation) or SEQ ID NOs: 88-90 in combination with SEQ ID NOs: 94-96 (IMGT annotation);
- f. SEQ ID NOs: 109-111 in combination with SEQ ID NOs: 115-117 (Kabat annotation) or SEQ ID NOs: 112-114 in combination with SEQ ID NOs: 118-120 (IMGT annotation);
- g. SEQ ID NOs: 145-147 in combination with SEQ ID NOs: 151-153 (Kabat annotation) or SEQ ID NOs: 148-150 in combination with SEQ ID NOs: 154-156 (IMGT annotation);
- h. SEQ ID NOs: 157-159 in combination with SEQ ID NOs: 163-165 (Kabat annotation) or SEQ ID NOs: 160-162 in combination with SEQ ID NOs: 166-168 (IMGT annotation);
- i. SEQ ID NOs: 196-171 in combination with SEQ ID NOs: 175-177 (Kabat annotation) or SEQ ID NOs: 172-174 in combination with SEQ ID NOs: 178-180 (IMGT annotation);
- j. SEQ ID NOs: 181-183 in combination with SEQ ID NOs: 187-189 (Kabat annotation) or SEQ ID NOs: 184-186 in combination with SEQ ID NOs: 190-192 (IMGT annotation);
- k. SEQ ID NOs: 193-195 in combination with SEQ ID NOs: 199-201 (Kabat annotation) or SEQ ID NOs: 196-198 in combination with SEQ ID NOs: 202-204 (IMGT annotation);

- l. SEQ ID NOs: 205-207 in combination with SEQ ID NOs: 211-213 (Kabat annotation) or SEQ ID NOs: 208-210 in combination with SEQ ID NOs: 214-216 (IMGT annotation); or
 - m. SEQ ID NOs: 217-219 in combination with SEQ ID NOs: 223-225 (Kabat annotation) or SEQ ID NOs: 220-222 in combination with SEQ ID NOs: 226-228 (IMGT annotation).
16. The CD96-binding agent of claim 14 or 15, wherein the antibody comprises a heavy chain variable domain and a light chain variable domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 229-244, 247-248, or 253-266.
 17. The CD96-binding agent of any of claims 4 to 16, wherein the antibody has an increased effector function such as e.g. an increased agonistic effect, upon Fc mutation.
 18. An isolated nucleic acid encoding the amino acid sequence of the anti-CD96 agonistic antibody of anyone of claims 1 to 17.
 19. An isolated cell that produces the CD96-binding agent of anyone of claims 1 to 17.
 20. A pharmaceutical composition comprising the CD96-binding agent of any of claims 1 to 17 and a pharmaceutical acceptable excipient or carrier.
 21. A CD96-binding agent of any of claims 1 to 17 or a pharmaceutical composition of claim 20 for use for the treatment of a disease in a patient.
 22. The CD96-binding agent or pharmaceutical composition for use of claim 21, wherein the disease is a cancer or an infectious disease.
 23. The CD96-binding agent or pharmaceutical composition for use of claim 21 or 22, wherein the treatment is a monotherapy.
 24. The CD96-binding agent or pharmaceutical composition for use of claim 21 or 22, wherein the treatment is a combination therapy.

25. The CD96-binding agent or pharmaceutical composition for use of claim 24, wherein the agent is for use in combination with a co-stimulating agent or an immune checkpoint inhibitor; in particular a T cell co-stimulating agent or an immune checkpoint inhibitor.
26. A CD96-binding agent according to anyone of claims 1 to 17 or 21 to 25, or a pharmaceutical composition according to anyone of claims 20 to 25 for use in the treatment of a disease in a patient, via stimulation of the activation and/or proliferation of T cells upon binding to CD96.
27. The CD96-binding agent for use according to claim 26 wherein the CD96-binding agent is capable of proliferating T cells in combination with a T cell co-stimulatory agent and/or T cell proliferation agent.
28. The CD96-binding agent for use according to claim 26 or 27 wherein the CD96-binding agent is a CD96 agonist.
29. The CD96-binding agent for use according to anyone of claims 26 to 28 wherein binding of the agent to CD96 induces dimerization or multimerization of CD96.
30. The CD96-binding agent for use according to anyone of claims 26 to 29 wherein the T cells are CD4⁺ and/or CD8⁺ cells.
31. A CD96-binding agent of any of claims 1 to 17 or a pharmaceutical composition of claim 20 for use as an adjuvant in a prophylactic or therapeutic vaccine.