

Claims

1. A multispecific antibody comprising a first antigen-binding region capable of binding human PSMA and a second antigen-binding region capable of binding a human V γ 9V δ 2 T cell receptor, wherein the first antigen-binding region comprises a CDR1 of SEQ ID NO: 14, a CDR2 of SEQ ID NO: 15, and a CDR3 of SEQ ID NO: 16, and wherein the first antigen-binding region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3.
2. The multispecific antibody according to claim 1, wherein the multispecific antibody is a bispecific antibody.
3. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region is a single-domain antibody.
4. The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region is a single-domain antibody.
5. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody competes for binding to human PSMA with an antibody having the sequence set forth in SEQ ID NO:2 or SEQ ID NO: 3, preferably wherein the multispecific antibody binds the same epitope on human PSMA as an antibody having the sequence set forth in SEQ ID NO:2 or SEQ ID NO: 3.
- ~~6. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region comprises the VH CDR1 sequence set forth in SEQ ID NO:14, the VH CDR2 sequence set forth in SEQ ID NO:15 and the VH CDR3 sequence set forth in SEQ ID NO:16.~~

~~7.6.~~ The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region is humanized, wherein preferably the first antigen-binding region comprises or consists of: the sequence set forth in SEQ ID NO:2, or a sequence having at ~~least 90%, such as~~ least 92%, ~~e.g.~~ at least 94%, ~~such as~~ at least 96%, ~~e.g. or~~ at least 98% sequence identity to the sequence set forth in SEQ ID NO:2 or SEQ ID NO: 3.

~~8.7.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is able to activate human V γ 9V δ 2 T cells.

~~9.8.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is capable of binding to human V δ 2.

~~10.9.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody competes for binding to human V δ 2 with an antibody having the sequence set forth in SEQ ID NO:5 or competes for binding to human V δ 2 with an antibody having the sequence set forth in SEQ ID NO:20.

~~11.10.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody binds the same epitope on human V δ 2 as an antibody having the sequence set forth in SEQ ID NO:5 or binds the same epitope on human V δ 2 as an antibody having the sequence set forth in SEQ ID NO:20.

~~12.11.~~ The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region comprises the VH CDR1 sequence set forth in SEQ ID NO:17, the VH CDR2 sequence set forth in SEQ ID NO:18 and the VH CDR3 sequence set forth in SEQ ID NO:19 or comprises the VH CDR1 sequence set forth in SEQ ID NO:21, the VH CDR2 sequence set forth in SEQ ID NO:22 and the VH CDR3 sequence set forth in SEQ ID NO:23.

~~13.12.~~ The multispecific antibody according to any one of the preceding claims, wherein the second antigen-binding region is humanized, wherein preferably the second antigen-binding region comprises or consists of the sequence set forth in SEQ ID NO:5, or a sequence having at least 90%, ~~such as at~~ least 92%, ~~e.g.~~ at least 94%, ~~such as~~ at least 96%, ~~e.g. or~~ at least 98% sequence identity to the sequence set forth in SEQ ID NO:5.

~~14.13.~~ The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region comprises the VH CDR1 sequence set forth in SEQ ID NO:14, the VH CDR2 sequence set forth in SEQ ID NO:15 and the VH CDR3 sequence set forth in SEQ ID NO:16 and wherein the second antigen-binding region comprises the VH CDR1 sequence set forth in SEQ ID NO:~~17~~~~15~~, the VH CDR2 sequence set forth in SEQ ID NO:18 and the VH CDR3 sequence set forth in SEQ ID NO:19.

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~~15.14.~~ The multispecific antibody according to any one of claims 1 to 8, wherein the multispecific antibody is capable of binding to human V γ 9.

~~16.15.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is capable of mediating killing of PSMA-expressing cells, such as LNCaP cells, by V γ 9V δ 2 T cells.

~~17.16.~~ The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody is capable of mediating killing of human PSMA-expressing cells from a prostate cancer patient.

~~18.17.~~ The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region and second antigen-binding region are covalently linked via a peptide linker.

19.18. The multispecific antibody according to claim 1718, wherein the peptide linker comprises or consists of the sequence set forth in SEQ ID NO:6.

5 20.19. The multispecific antibody according to any one of the preceding claims, wherein the first antigen-binding region capable of binding human PSMA is located N-terminally of the second antigen-binding region capable of binding a human V γ 9V δ 2 T cell receptor.

10 21.20. The multispecific antibody according to any one of the preceding claims, wherein the multispecific antibody further comprises a half-life extension domain.

22.21. The multispecific antibody according to claim 20, wherein the multispecific antibody has a terminal half-life that is longer than about 168 hours when
15 administered to a human subject.

23.22. The multispecific antibody according to any one of claims 1 to 1617, 2021 or 2122, wherein the multispecific antibody comprises an Fc region.

20 24.23. The multispecific antibody according claim 2223, wherein the Fc region is a heterodimer comprising two Fc polypeptides, wherein the first antigen-binding region is fused to the first Fc polypeptide and the second antigen-binding region is fused to the second Fc polypeptide and wherein the first and second Fc polypeptides comprise asymmetric amino acid mutations that favor the formation of heterodimers over the
25 formation of homodimers.

25.24. The multispecific antibody according claim 2324, wherein the CH3 regions of the Fc polypeptides comprise said asymmetric amino acid mutations, preferably wherein the first Fc polypeptide comprises a T366W substitution and the second Fc

polypeptide comprises T366S, L368A and Y407V substitutions, or vice versa, wherein the amino acid positions correspond to human IgG1 according to the EU numbering system.

5 ~~26.25.~~ The multispecific antibody according any one of claims ~~2223~~ to ~~2425~~, wherein the cysteine residues at position 220 in the first and second Fc polypeptides have been deleted or substituted, wherein the amino acid position corresponds to human IgG1 according to the EU numbering system.

10 ~~27.26.~~ The multispecific antibody according any one of claims ~~2223~~ to ~~2526~~, wherein the first and second Fc polypeptides further comprise a mutation at position 234 and/or 235, preferably wherein the first and second Fc polypeptide comprise an L234F and an L235E substitution, wherein the amino acid positions correspond to human IgG1 according to the EU numbering system.

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~~28.27.~~ The multispecific antibody according to any one of the claims ~~2223~~ to ~~2627~~, wherein the first antigen-binding region comprises the sequence set forth in SEQ ID NO:2, the second antigen-binding region comprises the sequence set forth in SEQ ID NO:5 and wherein

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- the first Fc polypeptide comprises the sequence set forth in SEQ ID NO:12 and the second Fc polypeptide comprises the sequence set forth in SEQ ID NO:13, or
 - the first Fc polypeptide comprises the sequence set forth in SEQ ID NO:12 and the second Fc polypeptide comprises the sequence set forth in SEQ ID NO:13.

25 ~~29.28.~~ A pharmaceutical composition comprising a multispecific antibody according to any one of the preceding claims and a pharmaceutically-acceptable excipient.

~~30.29.~~ The pharmaceutical composition according to claim ~~2829~~, wherein the multispecific antibody is an antibody according to any one of claims ~~2223~~ to ~~2728~~,

and wherein the pharmaceutical composition comprises a buffer, sucrose, polysorbate 80 and methionine, wherein the pH of the composition is between 5.4 and 7.4, such as between 5.4 and 6.1.

5 ~~31.30.~~ The multispecific antibody according to any one of claims 1 to ~~2728~~ for use as a medicament.

~~32.31. The Use of the~~ multispecific antibody according to any one of claims 1 to ~~2728~~ ~~for use~~ in the manufacture of a medicament for the treatment of cancer.

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~~33.32. The Use of the~~ multispecific antibody according to any one of claims 1 to ~~2728~~ ~~for use~~ in the manufacture of a medicament for the treatment of prostate cancer.

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~~34.33. The Use of the~~ multispecific antibody according to any one of claims 1 to ~~2728~~ ~~for use~~ in the manufacture of a medicament for the treatment of cancers in which PSMA is expressed on the tumor neo-vasculature or tumor-associated endothelial cells of primary or metastatic tumors including from colorectal cancer, lung cancer, breast cancer, endometrial and ovarian cancer, gastric cancer, renal cell cancer, urothelial cancer, hepatocellular cancer, oral squamous cancer, thyroid tumors and glioblastomas.

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~~35.34. The Use of the~~ multispecific antibody according to any one of claims 1 to ~~2728~~ ~~for use~~ in the manufacture of a medicament for the treatment of adenoid cystic carcinoma of the head and neck.

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~~36. A method of treating a disease comprising administration of a multispecific antibody according to any one of claims 1 to 28 to a human subject in need thereof.~~

~~37. The method according to claim 36, wherein the disease is cancer.~~

~~38.35.~~ A nucleic acid construct encoding the multispecific antibody according to any one of claims 1 to ~~2728~~.

5 ~~39.36.~~ An expression vector comprising a nucleic acid construct according to claim ~~3538~~.

~~40.37.~~ A host cell, such as a mammalian host cell, preferably a CHO cell comprising a nucleic acid construct according to claim ~~3538~~ or an expression vector according to
10 claim ~~3639~~.

~~41.38.~~ A method for production of a multispecific antibody as defined in any one of claims 1-~~2728~~, preferably a multispecific antibody as defined in any one of claims ~~2223-2728~~, by (co-)expression of one or more nucleic acid constructs encoding the
15 multispecific antibody in a suitable host cell, such as a mammalian cells, preferably a CHO cell, followed by purification of the produced recombinant antibody.