

The activity of conventional DR5 targeting molecules as described above is dependent on Fc Receptor (FcR) mediated hyperclustering, and is influenced by the immune infiltration and activation status in the tumor (Li and Ravetch, PNAS 2012; Wilson, Cancer Cell 2011; WO 2011/098520). The Fc/FcR interactions can be impaired
5 by physiological human IgG levels. Thus, the activity of conventional DR5 targeting molecules is often limited to a few infiltrating cells (Moessner, Blood 2010). By using a bispecific antibody targeting both DR5 and FAP, the percentage of sensitive tumor cells can be significantly increased by hypercrosslinking via FAP and the risk of an intrinsic resistance to DR5 agonists is decreased. The novel DR5 binding moieties are only active
10 after crosslinking with FAP, which could result in an improved safety and toxicology profile compared to the DR5 binders Drozitumab and Tigatuzumab. The DR5 agonists that have been tested so far were safe in the clinic; however, these clinical programs have been impeded by a low efficacy of the DR5 targeting molecules.

It remains a problem in the art to find ways of effective therapies for targeting
15 cancer using DR5 agonist antibodies.

SUMMARY

Broadly, the present disclosure relates to bispecific antibodies combining a Death Receptor 5 (DR5) targeting antigen binding site with a second antigen binding site that
20 targets Fibroblast Activation Protein (FAP) and their use in combination with a further chemotherapeutic agent. The bispecific antibodies employed in accordance with the present disclosure enable the death receptors become cross linked and induce apoptosis of the targeted tumor cell. The advantage over conventional death receptor targeting antibodies is the specificity of induction of apoptosis only at the site where FAP is
25 expressed as well as the higher potency of these bispecific antibodies due to the induction of DR5 hyperclustering.

Accordingly, the present disclosure provides a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for
30 FAP for use as a combination therapy in a method of treating cancer, wherein the bispecific antibody is used in combination with a chemotherapeutic agent selected

(f) a light chain CDR3 of SEQ ID NO.:14.

In one embodiment, the bispecific antibody comprises at least one antigen binding site specific for DR5 comprising a variable heavy chain and a variable light chain

5 comprising an amino acid sequence of : SEQ ID NO.:7 and SEQ ID NO.:8.

In some embodiments, the present disclosure, the bispecific antibody comprises the antigen binding site specific for FAP comprises a variable heavy chain and a variable light chain comprising an amino acid sequence selected from the group of SEQ ID

10 NO.:15 and SEQ ID NO.:16.

In some embodiments, the present disclosure, the bispecific antibody comprises the antigen binding site specific for DR5 comprises: (a) a heavy chain CDR1 of SEQ ID NO.:1; (b) a heavy chain CDR2 of SEQ ID NO.:2; (c) a heavy chain CDR3 of SEQ ID NO.:3; (d) a light chain CDR1 of SEQ ID NO.:4; (e) a light chain CDR2 of SEQ ID

15 NO.:5; (f) a light chain CDR3 of SEQ ID NO.:6 and the antigen binding site specific for FAP comprises: (a) a heavy chain CDR1 of SEQ ID NO.:9; (b) a heavy chain CDR2 of SEQ ID NO.:10; (c) a heavy chain CDR3 of SEQ ID NO.:11; (d) a light chain CDR1 of SEQ ID NO.:12; (e) a light chain CDR2 of SEQ ID NO.:13; (f) a light chain CDR3 of SEQ ID NO.:14.

20

In one aspect, there is provided use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP and a chemotherapeutic agent in the manufacture of a medicament for

25 the treatment of cancer, wherein the bispecific antibody is to be used in combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, an MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody, and wherein the antigen binding site specific for DR5 comprises: (a) a heavy chain CDR1 of SEQ ID

30 NO.:1; (b) a heavy chain CDR2 of SEQ ID NO.:2; (c) a heavy chain CDR3 of SEQ ID NO.:3; (d) a light chain CDR1 of SEQ ID NO.:4; (e) a light chain CDR2 of SEQ ID NO.:5; (f) a light chain CDR3 of SEQ ID NO.:6 and the antigen binding site specific for FAP comprises: (a) a heavy chain CDR1 of SEQ ID NO.:9; (b) a heavy chain CDR2 of SEQ ID NO.:10; (c) a heavy chain CDR3 of SEQ ID NO.:11; (d) a light chain CDR1 of

SEQ ID NO.:12; (e) a light chain CDR2 of SEQ ID NO.:13; (f) a light chain CDR3 of SEQ ID NO.:14.

5 In one embodiment, the bispecific antibody comprises at least one antigen binding site specific for DR5 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO.:7 and a variable light chain comprising an amino acid sequence of SEQ ID NO.:8; and at least one antigen binding site specific for FAP comprising a heavy chain variable region comprising an amino acid sequence of SEQ ID NO.:15 and a light chain variable region comprising an amino acid sequence of SEQ ID NO.:16.

10

In some embodiments, the present disclosure, the bispecific antibody comprises the bispecific antibody comprises amino acid sequences of SEQ ID NO: 18, 19 and 20 or the bispecific antibody comprises amino acid sequences SEQ ID NO: 17, 19 and 20.

15 In the present disclosure, advantageously said bispecific antibody is human or humanized.

The present disclosure provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) as described herein and a chemotherapeutic agent in the manufacture of a medicament for the treatment of cancer, wherein the bispecific antibody is used in combination with a
5 chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody. The present disclosure also provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP), Paclitaxel and
10 Abraxane in the manufacture of a medicament for the treatment of cancer.

The present disclosure also provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) and a chemotherapeutic agent in the manufacture of a medicament for the treatment of
15 cancer, wherein the bispecific antibody is used in combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, the MDM2 inhibitor RG7388, the Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, the PARP inhibitor PJ34, Ifosfamide or an anti-VEGF antibody.

20 In a further aspect, the present disclosure provides a kit comprising:

- (i) a first container comprising a composition which comprises a bispecific antibody as described herein; and
- (ii) a second container comprising a composition comprising a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a
25 Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

The present disclosure also provides a kit comprising:

- (i) a first container comprising a composition which comprises a bispecific
30 antibody as described herein; and
- (ii) a second container comprising a composition comprising a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, the MDM2 inhibitor

Claims

1. Use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP and a
5 chemotherapeutic agent in the manufacture of a medicament for the treatment of cancer, wherein the bispecific antibody is to be used in combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, an MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody, and wherein the antigen binding site
10 specific for DR5 comprises:
 - (a) a heavy chain CDR1 of SEQ ID NO.:1;
 - (b) a heavy chain CDR2 of SEQ ID NO.:2;
 - (c) a heavy chain CDR3 of SEQ ID NO.:3;
 - (d) a light chain CDR1 of SEQ ID NO.:4;
 - 15 (e) a light chain CDR2 of SEQ ID NO.:5;
 - (f) a light chain CDR3 of SEQ ID NO.:6and the antigen binding site specific for FAP comprises:
 - (a) a heavy chain CDR1 of SEQ ID NO.:9;
 - (b) a heavy chain CDR2 of SEQ ID NO.:10;
 - 20 (c) a heavy chain CDR3 of SEQ ID NO.:11;
 - (d) a light chain CDR1 of SEQ ID NO.:12;
 - (e) a light chain CDR2 of SEQ ID NO.:13;
 - (f) a light chain CDR3 of SEQ ID NO.:14.
- 25 2. The use of claim 1, wherein the chemotherapeutic agent is selected from Irinotecan, Doxorubicin, Oxaliplatin, Ifosfamide or an anti-VEGF antibody.
3. The use of claim 1 or claim 2, wherein the chemotherapeutic agent is selected from an anti-VEGF antibody.

4. The use of any one of claims 1 to 3, wherein the bispecific antibody is to be used in combination with Irinotecan.

5. The use of claim 3 or 4, wherein the cancer is colorectal cancer.

5

6. The use of claim 1, wherein the bispecific antibody is to be used in combination with gemcitabine and abraxane.

7. The use of claim 6, wherein the cancer is pancreatic cancer.
8. The use of claim 1, wherein the bispecific antibody is to be used in combination with doxorubicin or Ifosfamide.
- 5
9. The use of claim 8, wherein the cancer is a sarcoma.
10. The use of claims 1-4, 6 and 8 wherein the cancer is colorectal cancer, sarcoma, head and neck cancer, squamous cell carcinoma, **breast cancer**, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer and mesothelioma.
- 10
11. The use of claims 9 or 10 wherein the sarcoma is chondrosarcoma, leiomyosarcoma, gastrointestinal stromal tumours, fibrosarcoma, osteosarcoma, liposarcoma or malignant fibrous histiocytoma.
- 15
12. The use of any one of claims 1 to 11, wherein the bispecific antibody and the chemotherapeutic agent are to be administered together, optionally as a combined formulation.

13. The use of any one of claims 1 to 11, wherein the bispecific antibody and the chemotherapeutic agent are to be administered by alternation.

14. The use of claim 13, wherein the chemotherapeutic agent is to be administered
5 before the bispecific antibody.

15. The use of claim 13, wherein the chemotherapeutic agent is to be administered
after the bispecific antibody.

10 16. The use of any one of claims 1 to 15, wherein the combination is to be
administered at intervals from about one week to three weeks.

17. The use of any one of claims 1 to 16, wherein the antigen binding site specific for DR5 comprises a variable heavy chain and a variable light chain comprising an amino acid sequence selected from the group of: SEQ ID NO.:7 and SEQ ID NO.:8.

5 18. The use of any one of claims 1 to 17, wherein the antigen binding site specific for FAP comprises a variable heavy chain and a variable light chain comprising an amino acid sequence selected from the group of SEQ ID NO.:15 and SEQ ID NO.:16.

19. The use of any one of claims 1 to 18, wherein the antigen binding site specific for DR5 comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO.:7 and a variable light chain comprising an amino acid sequence of SEQ ID NO.:8; and the antigen binding site specific for FAP comprises a heavy chain variable region
5 comprising an amino acid sequence of SEQ ID NO.:15 and a light chain variable region comprising an amino acid sequence of SEQ ID NO.:16.
20. The use of any one of claims 1 to 19, wherein the bispecific antibody comprises amino acid sequences SEQ ID NO: 18, 19 and 20 or the bispecific antibody comprises
10 amino acid sequences SEQ ID NO: 17, 19 and 20.
21. The use of any one of claims 1 to 21, wherein the antibody is human.
22. The use of any one of claims 1 to 21, wherein the antibody is humanized.
15
23. The use of any of claims 1 to 22, wherein the bispecific antibody comprises an Fc domain, at least one Fab fragment comprising the antigen binding site specific for

DR5, and at least one Fab fragment comprising the antigen binding site specific for FAP.

24. The use of any of claims 1 to 23, wherein the bispecific antibody comprises an Fc domain, two Fab fragments comprising each an antigen binding site specific for DR5, and
5 two Fab fragments comprising each an antigen binding site specific for FAP.

25. The use of any one of claims 1 to 24, wherein the bispecific antibody is bivalent both for DR5 and FAP.

10 26. The use of any of claims 1 to 25, wherein either the variable regions or the constant regions of the heavy and light chain of the Fab fragment(s) comprising an antigen binding site specific for FAP are exchanged.

27. The use of any one of claims 1 to 26, wherein the bispecific antibody comprises
15 an Fc domain, at least one Fab fragment comprising the antigen binding site specific for DR5, and at least one Fab fragment comprising the antigen binding site specific for FAP wherein either the variable regions or the constant regions of the heavy and light chain of at least one Fab fragment are exchanged.

28. The use of any of claims 23 to 27, wherein at least one of the Fab fragments are connected to the Fc domain via a peptide linker.

29. The use of any one of claims 23 to 28, wherein the Fc domain comprises one or
5 more amino acid substitution that reduces binding to an Fc receptor and/or effector function.

30. The use of claim 29, wherein said one or more amino acid substitution is at one or more position selected from the group of L234, L235, and P329.

10

31. The use of claim 30, wherein each subunit of the Fc domain comprises three amino acid substitutions that reduce binding to an activating or inhibitory Fc receptor and/or effector function wherein said amino acid substitutions are L234A, L235A and P329G.

15

32. A pharmaceutical composition comprising a bispecific antibody as defined in any one of claims 1 to 31 and a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor or an anti-VEGF
20 antibody.

33. A kit comprising:

a first container comprising a composition which comprises a bispecific antibody as defined in any one of claims 1 to 31;

5 a second container comprising a composition comprising a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

34. The use of any one of claims 1 to 31, wherein the medicament is for treatment of
10 colorectal cancer, sarcoma, head and neck cancers, squamous cell carcinomas, **breast cancer**, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer and mesothelioma.

35. The use of claim 34, wherein the sarcoma is chondrosarcoma, leiomyosarcoma,
15 gastrointestinal stromal tumours, fibrosarcoma, osteosarcoma, liposarcoma or malignant fibrous histiocytoma.