

SUMMARY

[0006] In one example, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **GYSITSGYSWH** (SEQ ID NO: 9); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10) and a VHCDR3 having the amino acid sequence **GSNYGFDY** (SEQ ID NO: 11); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSNDQKNYLA** (SEQ ID NO: 12), a VLCDR2 having the amino acid sequence **WASIRES** (SEQ ID NO: 13), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14).

[0006a] In one aspect, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **GYSITSGYSWH** (SEQ ID NO: 9); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10) and a VHCDR3 having the amino acid sequence **GSNYGFDY** (SEQ ID NO: 11); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSNDQKNYLA** (SEQ ID NO: 12), a VLCDR2 having the amino acid sequence **WASIRES** (SEQ ID NO: 13), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14); wherein the antigen-binding protein, or antigen-binding fragment thereof, binds to annexin A2 (ANXA2).

[0007] In another t, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the nucleic acid sequence **GCTACTCCATCACCAGTGGTTATAGCTGGCAC** (SEQ ID NO: 15); a VHCDR2 having the nucleic acid sequence **ACATACACTACAGTGGTAGCACTAAGTACAACCCATCTCTCAAAAGTC** (SEQ ID NO: 16), and a VHCDR3 having the nucleic acid sequence **GGAGTAACTACGGATTTGACTACT** (SEQ ID NO: 17); and (ii) a light chain variable domain comprising a VLCDR1 having the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAACGATCAAAAGAACTACTTGGCCT** (SEQ ID NO: 18), a VLCDR2 having the nucleic acid sequence **GGGCATCTATTAGGGAATCTG** (SEQ ID NO: 19), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

[0007a] In another aspect, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having an amino acid sequence encoded by the nucleic acid sequence **GCTACTCCATCACCAGTGGTTATAGCTGGCAC** (SEQ ID NO: 15); a VHCDR2 having an amino acid sequence encoded by the nucleic acid sequence **ACATACACTACAGTGGTAGCACTAAGTACAACCCATCTCTCAAAAGTC** (SEQ ID NO: 16), and a VHCDR3 having an amino acid sequence encoded by the nucleic acid sequence **GGAGTAACTACGGATTTGACTACT** (SEQ ID NO: 17); and (ii) a light chain variable domain comprising a VLCDR1 having an amino acid sequence encoded by the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAACGATCAAAAGAACTACTTGGCCT** (SEQ ID NO: 18), a VLCDR2 having the nucleic acid sequence **GGGCATCTATTAGGGAATCTG** (SEQ ID NO: 19), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

[0008] In another example, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **VYSITSGYSWH** (SEQ ID NO: 21); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10), and a VHCDR3 having the amino acid sequence **GTDNAV DY** (SEQ ID NO: 22); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSSNQKNYLA** (SEQ ID NO: 23), a VLCDR2 having the amino acid sequence **WASSRES** (SEQ ID NO: 24), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14).

[0008a] In another aspect, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **VYSITSGYSWH** (SEQ ID NO: 21); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10), and a VHCDR3 having the amino acid sequence **GTDNAV DY** (SEQ ID NO: 22); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSSNQKNYLA** (SEQ ID NO: 23), a VLCDR2 having the amino acid sequence **WASSRES** (SEQ ID NO: 24), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14); wherein the antigen-binding protein, or antigen-binding fragment thereof, binds to ANXA2.

[0009] In another example, there is provided, an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the nucleic acid sequence **TCTACTCCATCACCAGTGGTTATAGCTGGCACT** (SEQ ID N: 25); a VHCDR2 having the nucleic acid sequence **ACATACACTACAGTGGTAGTACTAAGTACAACCCATCTCTCAAAAGTC** (SEQ ID NO: 26), and a VHCDR3 having the nucleic acid sequence **GGACCGACAATGCTGTGGACTACT** (SEQ ID NO: 27); and (ii) a light chain variable domain comprising a VLCDR1 having the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAGCAATCAAAAGAACTACTTGGCCT** (SEQ ID NO: 28), a VLCDR2 having the nucleic acid sequence **GGGCATCCAGTAGGGAATCTG** (SEQ ID NO: 29), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

[0009a] In another aspect, there is provided an antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having an amino acid sequence encoded by the nucleic acid sequence **TCTACTCCATCACCAGTGGTTATAGCTGGCACT** (SEQ ID NO: 25); a VHCDR2 having an amino acid sequence encoded by the nucleic acid sequence **ACATACACTACAGTGGTAGTACTAAGTACAACCCATCTCTCAAAAGTC** (SEQ ID NO: 26), and a VHCDR3 having an amino acid sequence encoded by the nucleic acid sequence **GGACCGACAATGCTGTGGACTACT** (SEQ ID NO: 27); and (ii) a light chain variable domain comprising a VLCDR1 having an amino acid sequence encoded by the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAGCAATCAAAAGAACTACTTGGCCT**

(SEQ ID NO: 28), a VLCDR2 having the nucleic acid sequence **GGGCATCCAGTAGGGAATCTG** (SEQ ID NO: 29), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

[0010] In another aspect, there is provided a composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the antigen-binding protein, or an antigen-binding fragment thereof, as described herein.

[0011] In another aspect, there is provided use of an antigen-binding protein, or an antigen-binding fragment thereof, as described herein, in the manufacture of a medicament for treating or preventing cancer.

[0012] In another aspect, there is provided a method for detecting cancer in a subject, the method comprising: contacting a sample obtained from the subject with an antigen-binding protein, or an antigen-binding fragment thereof as described herein *in vitro*; detecting the binding of the antigen-binding protein, or an antigen-binding fragment thereof in the sample; correlating the binding with a level of binding in a control sample to determine the level of binding in the sample, wherein an increase in the level of binding in the sample relative to the control sample is indicative of cancer.

[0013] In another aspect, there is provided a method for identifying a subject susceptible to cancer the method comprising: contacting a sample obtained from the subject with an antigen-binding protein, or an antigen-binding fragment thereof as described herein *in vitro*; detecting the binding of the antigen-binding protein, or an antigen-binding fragment thereof in the sample; correlating the binding with a level of binding in a control sample to

Claims

1. An antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **GYSITSGYSWH** (SEQ ID NO: 9); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10) and a VHCDR3 having the amino acid sequence **GSNYGFDY** (SEQ ID NO: 11); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSNDQKNYLA** (SEQ ID NO: 12), a VLCDR2 having the amino acid sequence **WASIRES** (SEQ ID NO: 13), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14); wherein the antigen-binding protein, or antigen-binding fragment thereof, binds to annexin A2 (ANXA2).
2. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1.
3. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 1, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2.
4. An antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having an amino acid sequence encoded by the nucleic acid sequence **GCTACTCCATCACCAGTGGTTATAGCTGGCAC** (SEQ ID NO: 15); a VHCDR2 having an amino acid sequence encoded by the nucleic acid sequence **ACATACACTACAGTGGTAGCACTAAGTACAACCCATCTCTCAAAAGTC** (SEQ ID NO: 16), and a VHCDR3 having an amino acid sequence encoded by the nucleic acid sequence **GGAGTAACTACGGATTGACTACT** (SEQ ID NO: 17); and (ii) a light chain variable domain comprising a VLCDR1 having an amino acid sequence encoded by the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAACGATCAAAAGAACTACTTGGCCT** (SEQ ID NO: 18), a VLCDR2 having the nucleic acid sequence

GGGCATCTATTAGGGAATCTG (SEQ ID NO: 19), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

- 5 5. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 4, wherein the heavy chain variable region comprises the nucleic acid sequence set forth in SEQ ID NO:3.
- 10 6. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 4, wherein the light chain variable region comprises the nucleic acid sequence set forth in SEQ ID NO:4.
- 15 7. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in any one of claims 1 to 6, wherein the antigen binding protein is selected from the group consisting of monoclonal, recombinant, polyclonal, chimeric, humanised, bispecific and heteroconjugate antibodies; a chimeric antigen receptor (CAR), a single variable domain, a domain antibody, antigen binding fragments, immunologically effective fragments, single chain Fv, a single chain antibody, a univalent antibody lacking a hinge region, a minibody, diabodies, and Tandabs™.
- 20 8. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 7, wherein the binding protein is a monoclonal antibody.
- 25 9. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 8, wherein the monoclonal antibody is 2448.
- 30 10. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 8 or 9, wherein the monoclonal antibody is humanised.
- 30 11. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 8 or 9, wherein the monoclonal antibody is chimeric.

12. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in any one of claims 8 to 11, wherein the monoclonal antibody is defucosylated.
- 5 13. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 12, wherein the degree of fucosylation is less than 10%, preferably less than 5%, and more preferably is less than 1.5% relative to the wild-type antibody.
- 10 14. An antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having the amino acid sequence **VYSITSGYSWH** (SEQ ID NO: 21); a VHCDR2 having the amino acid sequence **YIHYSGSTKYNPSLKS** (SEQ ID NO: 10), and a VHCDR3 having the amino acid sequence **GTDNAV DY** (SEQ ID NO: 22); and (ii) a light chain variable domain comprising a VLCDR1 having the amino acid sequence **KSSQSLLYSSNQKNYLA** (SEQ ID NO: 23), a VLCDR2 having the amino acid sequence **WASSRES** (SEQ ID NO: 24), and a VLCDR3 having the amino acid sequence **QQYYIYPLT** (SEQ ID NO: 14); wherein the antigen-binding protein, or antigen-binding fragment thereof, binds to ANXA2.
- 15 15. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 14, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:5.
- 20 16. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 14, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:6.
- 25 17. An antigen-binding protein, or an antigen-binding fragment thereof, comprising (i) a heavy chain variable domain comprising a VHCDR1 having an amino acid sequence encoded by the nucleic acid sequence **TCTACTCCATCACCAGTGGTTATAGCTGGCACT** (SEQ ID NO: 25); a VHCDR2 having an amino acid sequence encoded by the nucleic acid sequence **ACATACACTACAGTGGTAGTACTAAGTACAACCCATCTCTCAAAAGTC**
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(SEQ ID NO: 26), and a VHCDR3 having an amino acid sequence encoded by the nucleic acid sequence **GGACCGACAATGCTGTGGACTACT** (SEQ ID NO: 27); and (ii) a light chain variable domain comprising a VLCDR1 having an amino acid sequence encoded by the nucleic acid sequence **AGTCCAGTCAGAGCCTTTTATATAGTAGCAATCAAAAGAACTACTTGG CCT** (SEQ ID NO: 28), a VLCDR2 having the nucleic acid sequence **GGGCATCCAGTAGGGAATCTG** (SEQ ID NO: 29), and a VLCDR3 having the nucleic acid sequence **AGCAATATTATATCTATCCTCTCACGT** (SEQ ID NO: 20).

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18. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 17, wherein the heavy chain variable region comprises the nucleic acid sequence set forth in SEQ ID NO:7.

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19. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 17, wherein the light chain variable region comprises the nucleic acid sequence set forth in SEQ ID NO:8.

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20. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in any one of claims 14 to 19, wherein the antigen binding protein is selected from the group consisting of monoclonal, recombinant, polyclonal, chimeric, humanised, bispecific and heteroconjugate antibodies; a chimeric antigen receptor (CAR), a single variable domain, a domain antibody, antigen binding fragments, immunologically effective fragments, single chain Fv, a single chain antibody, a univalent antibody lacking a hinge region, a minibody, diabodies, and Tandabs™.

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21. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 20, wherein the binding protein is a monoclonal antibody.

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22. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 21, wherein the monoclonal antibody is C51.

23. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 21 or 22, wherein the monoclonal antibody is humanised.
- 5 24. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 21 or 22, wherein the monoclonal antibody is chimeric.
25. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 24, wherein the antigen-binding protein, or antigen-binding fragment thereof binds to a glycan on ANXA2.
- 10 26. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 25, wherein the antigen-binding protein, or an antigen-binding fragment thereof binds to an N-linked glycan on ANXA2.
- 15 27. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 26, wherein the N-linked glycan is located at amino acid residue 62 of ANXA2.
28. An antigen-binding protein, or antigen-binding fragment thereof, as claimed in any one of claims 1 to 27, comprising a radioisotope or a cytotoxin conjugated thereto.
- 20 29. The antigen-binding protein, or antigen-binding fragment thereof, as claimed in claim 28, wherein the antibody is conjugated with a cytotoxin selected from the group consisting of monomethyl auristatin E (MMAE-1), mertansine (DM-1) and saporin.
- 25 30. The antigen-binding protein, or antigen-binding fragment thereof as claimed in any one of the preceding claims, wherein the antigen-binding protein, or an antigen-binding fragment is internalized into a cell upon binding to ANXA2.
- 30 31. An antigen-binding protein, or antigen-binding fragment thereof, as claimed in any one of claims 1 to 30, wherein the antigen-binding protein, or an antigen-binding fragment thereof has a cytotoxic activity selected from one or more of the group

consisting of complement dependent cytotoxic (CDC) activity, antibody dependent cellular cytotoxic (ADCC) activity and oncolytic activity.

- 5 32. A composition comprising a physiologically acceptable carrier and a therapeutically effective amount of the antigen-binding protein, or an antigen-binding fragment thereof, as claimed in any one of claims 1 to 31.
- 10 33. The composition as claimed in claim 32, wherein the composition comprises a further active pharmaceutical ingredient selected from the group consisting of bevacizumab, carboplatin, paclitaxel or gefitinib.
- 15 34. Use of an antigen-binding protein, or an antigen-binding fragment thereof, as claimed in any one of claims 1 to 31, in the manufacture of a medicament for treating or preventing cancer.
35. The use of claim 34, wherein the cancer is selected from the group consisting of breast cancer, ovarian cancer and teratoma.
- 20 36. The use of claims 34 or 35, wherein the medicament is to be administered with a further active pharmaceutical ingredient.
37. The use of claims 34 or 35, wherein the medicament is to be administered with chemotherapy.
- 25 38. The use of claims 36 or 37, wherein the further pharmaceutical agent or chemotherapy is to be administered separately, simultaneously or sequentially.
- 30 39. A method for detecting cancer in a subject, the method comprising: contacting a sample obtained from the subject with an antigen-binding protein, or an antigen-binding fragment thereof as claimed in any one of claims 1 to 31 *in vitro*; detecting the binding of the antigen-binding protein, or an antigen-binding fragment thereof in the sample; correlating the binding with a level of binding in a control sample to

determine the level of binding in the sample, wherein an increase in the level of binding in the sample relative to the control sample is indicative of cancer.

- 5 40. A method for identifying a subject susceptible to cancer the method comprising:
 contacting a sample obtained from the subject with an antigen-binding protein, or an
 antigen-binding fragment thereof as claimed in any one of claims 1 to 13 *in vitro*;
 detecting the binding of the antigen-binding protein, or an antigen-binding fragment
 thereof in the sample; correlating the binding with a level of binding in a control
10 sample to determine the level of binding in the sample, wherein an increase in the
 level of binding in the sample relative to the control sample indicates that the subject
 is susceptible to cancer.
- 15 41. The method according to claims 39 or 40, wherein the control sample is from the
 same subject.
42. The method according to claims 39 or 40, wherein the control sample is from a
 different subject.
- 20 43. The method according to any one of claims 39 to 42, wherein the antigen-binding
 protein, or antigen-binding fragment thereof, binds ANXA2.
44. The method according to any one of claims 39 to 43, wherein the antigen-binding
 protein, or antigen-binding fragment thereof, comprises a detectable label.
- 25 45. The method according to claim 44, wherein the detectable label is selected from the
 group consisting of a fluorescent label, a chemiluminescent label, an enzymatic label
 and a radionuclide label.
- 30 46. The method according to claim 45, wherein the detectable label is selected from the
 group consisting of biotin, alkaline phosphatase, horseradish peroxidase, FITC, PE
 and Cy Dyes.

47. The method according to claims any one of claims 44 to 46, wherein the detectable label is detected in an assay selected from flow cytometry, tissue section, immunofluorescence, immunocytochemistry or immunohistochemistry.
- 5 48. The method as claimed in any one of claims 39 to 47, wherein the cancer is selected from the group consisting of breast cancer, liver cancer, kidney cancer, colorectal cancer, ovarian cancer and teratoma.
- 10 49. A kit when used in the method of any one of claims 39 to 48, comprising an antigen-binding protein, or antigen-binding fragment thereof as claimed in any one of claims 1 to 31, together with instructions for use.