mAbs that could be used to detect low expression of GPC3 in tumor cells for cancer therapy and diagnostics.

Filmus and colleagues developed the widely-used 1G12 mAb specific for the C-terminus of GPC3 and established an ELISA method to detect serum GPC3 in HCC patients (Capurro *et al.*, *Gastroenterology* 125:89-97, 2003). Hippo *et al.* developed mAbs specific for the N-terminus of GPC3 (Hippo *et al.*, *Cancer Res*, 64:2418-2423, 2004). While both studies detected soluble GPC3 protein in HCC culture supernatant or in the circulating blood of cancer patients, it is not clear whether the N-terminal or C-terminal subunit actually represents the soluble GPC3 format (Capurro and Filmus, *Cancer Res* 65:372, 2005). Prior studies indicate that concentrations of serum GPC3 are generally not high in patients and that none of the readily available mAbs can be used to measure serum GPC3, most likely due to low affinity of the mAb for GPC3.

SUMMARY

Disclosed herein is a panel of monoclonal antibodies that bind with high affinity to cell surface and soluble GPC3 proteins. The antibodies provided herein include immunoglobulin molecules, such as IgG antibodies, as well as antibody fragments and humanized monoclonal antibodies and fragments. Further provided are compositions including the antibodies that bind, for example specifically bind, to GPC3, nucleic acid molecules encoding these antibodies, expression vectors comprising the nucleic acid molecules, and isolated host cells that express the nucleic acid molecules. Also provided are immunoconjugates comprising the antibodies disclosed herein and an effector molecule, such as a toxin.

Further provided is an isolated monoclonal antibody that binds glypican-3 (GPC3), wherein:

(i) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 12, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 8, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 16, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 20, and the light chain of the antibody comprises amino acid residues 27-38,

56-58 and 95-103 of SEQ ID NO: 22, amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 24 or amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 26

Further provided is an isolated monoclonal antibody that binds glypican-3 (GPC3), wherein:

(i) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 12 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 8 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 16 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 20 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 22, amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 24 or amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 26.

Further provided is an isolated monoclonal antibody that binds GPC3, wherein the antibody comprises:

(i) a variable heavy (VH) domain comprising the amino acid sequence of SEQ ID NO: 12, SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 37 or SEQ ID NO: 20; and

(ii) a variable light (VL) domain comprising the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 24 or SEQ ID NO: 26.

Further provided is a composition comprising a therapeutically effective amount of the antibody as described herein in a pharmaceutically acceptable carrier.

Further provided is an isolated immunoconjugate comprising the monoclonal antibody as described herein and an effector molecule.

Further provided is a chimeric antigen receptor (CAR), comprising the monoclonal antibody as described herein.

Further provided is a bispecific antibody, comprising the monoclonal antibody as described herein.

Further provided is a composition comprising a therapeutically effective amount of the isolated immunoconjugate as described herein, the CAR as described herein or the bispecific antibody as described herein, in a pharmaceutically acceptable carrier.

Further provided is a method of determining if a subject has cancer, or a method of confirming the diagnosis of cancer in a subject, comprising:

contacting a sample from the subject with the monoclonal antibody as described herein; and

detecting binding of the antibody to the sample,

wherein an increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having cancer, or confirms the diagnosis of cancer in the subject.

Further provided is an isolated nucleic acid molecule encoding the monoclonal antibody as described herein.

Further provided is an expression vector comprising the isolated nucleic acid molecule as described herein.

Further provided is an isolated host cell transformed with the nucleic acid molecule or expression vector as described herein.

The antibodies and compositions provided herein can be used for a variety of purposes, such as for confirming the diagnosis of a cancer that expresses GPC3, for example HCC, melanoma, squamous cell carcinoma of the lung or ovarian clear cell carcinoma. Thus, provided herein is a method of confirming the diagnosis of cancer in a subject by contacting a sample from the subject diagnosed with cancer with a monoclonal antibody that binds GPC3, and detecting binding of the antibody to the sample. An increase in binding of the antibody to the sample relative to binding of the antibody to a control sample confirms the cancer diagnosis. In some embodiments, the method further includes contacting a second antibody that specifically recognizes the GPC3-specific antibody with the sample, and detecting binding of the second antibody.

Similarly, provided herein is a method of detecting a cancer that expresses GP3 in a subject. The method includes contacting a sample from the subject with a monoclonal antibody described herein, and detecting binding of the antibody to the sample. An increase in binding of

CLAIMS

1. An isolated monoclonal antibody that binds glypican-3 (GPC3), wherein:

(i) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 12, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 8, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 16, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 20, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 22, amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 24 or amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 26.

2. An isolated monoclonal antibody that binds glypican-3 (GPC3), wherein:

(i) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 12 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 8 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 16 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 20 and the light chain of the antibody comprises amino acid residues

24-40, 56-62 and 95-103 of SEQ ID NO: 22, amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 24 or amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 26.

3. The isolated monoclonal antibody of claim 1 or claim 2, wherein:

(i) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 12; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 14;

(ii) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 8; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 10;

(iii) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 16; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 18; or

(iv) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 20; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 22, 24 or 26.

4. The isolated monoclonal antibody of any one of claims 1-3, wherein:

(i) the heavy chain of the antibody comprises SEQ ID NO: 12 and the light chain of the antibody comprises SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises SEQ ID NO: 8 and the light chain of the antibody comprises SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises SEQ ID NO: 16 or SEQ ID NO: 37 and the light chain of the antibody comprises SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises SEQ ID NO: 20 and the light chain of the antibody comprises SEQ ID NO: 22, 24 or 26.

5. An isolated monoclonal antibody that binds GPC3, wherein the antibody comprises:

(i) a variable heavy (VH) domain comprising the amino acid sequence of SEQ ID NO: 12, SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 37 or SEQ ID NO: 20; and

(ii) a variable light (VL) domain comprising the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 24 or SEQ ID NO: 26.

6. The isolated monoclonal antibody of any one of claims 1-5, wherein the antibody is a Fab fragment, a Fab' fragment, a $F(ab)'_2$ fragment, a single chain variable fragment (scFv), or a disulfide stabilized variable fragment (dsFv).

7. The isolated monoclonal antibody of any one of claims 1-5, wherein the antibody is an IgG.

8. The isolated monoclonal antibody of any of claims 1-7, wherein the antibody is labeled.

9. The isolated monoclonal antibody of claim 8, wherein the label is a fluorescence, enzymatic, or radioactive label.

10. The isolated monoclonal antibody of any one of claims 1-9, wherein the monoclonal antibody is a humanized monoclonal antibody.

11. A composition comprising a therapeutically effective amount of the antibody of any one of claims 1-10 in a pharmaceutically acceptable carrier.

12. An isolated immunoconjugate comprising the monoclonal antibody of any of claims 1-10 and an effector molecule.

13. The isolated immunoconjugate of claim 12, wherein the effector molecule is a toxin.

14. The isolated immunoconjugate of claim 13, wherein the toxin is *Pseudomonas* exotoxin or a variant thereof.

15. The isolated immunoconjugate of claim 14, wherein the toxin is PE38 comprising the amino acid sequence of SEQ ID NO: 1.

16. The isolated immunoconjugate of any one of claims 12-15, comprising the amino acid sequence of residues 2-597 of SEQ ID NO: 35, residues 2-597 of SEQ ID NO: 28, residues 2-597 of SEQ ID NO: 31, or residues 2-597 of SEQ ID NO: 33.

17. The isolated immunoconjugate of claim 12, wherein the effector molecule is a drug.

18. The isolated immunoconjugate of claim 12, wherein the effector molecule is a detectable label.

19. A chimeric antigen receptor (CAR), comprising the monoclonal antibody of any one of claims 1-10.

20. A bispecific antibody, comprising the monoclonal antibody of any one of claims 1-10.

21. A composition comprising a therapeutically effective amount of the isolated immunoconjugate of any one of claims 12-18, the CAR of claim 19 or the bispecific antibody of claim 20, in a pharmaceutically acceptable carrier.

22. Use of a therapeutically effective amount of the composition of claim 11 or claim 21 in the manufacture of a medicament for treating cancer in a subject with a cancer that expresses GPC3.

23. Use of a therapeutically effective amount of the composition of claim 11 or claim 21 in the manufacture of a medicament for inhibiting tumor growth or metastasis in a subject with a cancer that expresses GPC3.

24. A method of determining if a subject has cancer, or a method of confirming the diagnosis of cancer in a subject, comprising:

contacting a sample from the subject with the monoclonal antibody of any of claims 1-10; and

detecting binding of the antibody to the sample,

wherein an increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having cancer, or confirms the diagnosis of cancer in the subject.

25. The method of claim 24, wherein the monoclonal antibody is directly labeled.

26. The method of claim 24, further comprising:

contacting a second antibody that specifically binds the monoclonal antibody with the sample, and

detecting the binding of the second antibody,

wherein an increase in binding of the second antibody to the sample as compared to binding of the second antibody to a control sample detects cancer in the subject or confirms the diagnosis of cancer in the subject.

27. The method of any one of claims 24-26, wherein the cancer is hepatocellular carcinoma (HCC), melanoma, squamous cell carcinoma of the lung or ovarian clear cell carcinoma.

28. An isolated nucleic acid molecule encoding the monoclonal antibody of any of claims 1-5.

29. The isolated nucleic acid molecule of claim 28, wherein:

(i) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 11 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 13;

(ii) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 7 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 9;

(iii) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 15 or SEQ ID NO: 36 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 17; or

(iv) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 19 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 21, SEQ ID NO: 23 or SEQ ID NO: 25.

30. An expression vector comprising the isolated nucleic acid molecule of claim 28 or claim 29.

31. An isolated host cell transformed with the nucleic acid molecule or expression vector of any one of claims 28-30.

CLAIMS

1. An isolated monoclonal antibody that binds glypican-3 (GPC3), wherein:

(i) the heavy chain of the antibody comprises SEQ ID NO: 38, SEQ ID NO: 39 and SEQ ID NO: 40, and the light chain of the antibody comprises SEQ ID NO: 44, amino acid residues 56-58 of SEQ ID NO: 14, and SEQ ID NO: 45; or

(ii) the heavy chain of the antibody comprises SEQ ID NO: 41, SEQ ID NO: 42 and SEQ ID NO: 43, and the light chain of the antibody comprises SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 45.

2. The isolated monoclonal antibody of claim 1, wherein:

(i) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 12, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 8, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 16, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 26-33, 51-60 and 99-106 of SEQ ID NO: 20, and the light chain of the antibody comprises amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 22, amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 24 or amino acid residues 27-38, 56-58 and 95-103 of SEQ ID NO: 26.

3. The isolated monoclonal antibody of claim 1, wherein:

(i) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 12 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 8 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 16 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises amino acid residues 31-35, 50-68 and 101-106 of SEQ ID NO: 20 and the light chain of the antibody comprises amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 22, amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 24 or amino acid residues 24-40, 56-62 and 95-103 of SEQ ID NO: 26.

4. The isolated monoclonal antibody of any one of claims 1-3, wherein:

(i) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 12; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 14;

(ii) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 8; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 10;

(iii) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 16; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 18; or

(iv) the amino acid sequence of the heavy chain is at least 90% or at least 95% identical to SEQ ID NO: 20; and the amino acid sequence of the light chain is at least 90% or at least 95% identical to SEQ ID NO: 22, 24 or 26.

5. The isolated monoclonal antibody of any one of claims 1-4, wherein:

(i) the heavy chain of the antibody comprises SEQ ID NO: 12 and the light chain of the antibody comprises SEQ ID NO: 14;

(ii) the heavy chain of the antibody comprises SEQ ID NO: 8 and the light chain of the antibody comprises SEQ ID NO: 10;

(iii) the heavy chain of the antibody comprises SEQ ID NO: 16 or SEQ ID NO: 37 and the light chain of the antibody comprises SEQ ID NO: 18; or

(iv) the heavy chain of the antibody comprises SEQ ID NO: 20 and the light chain of the antibody comprises SEQ ID NO: 22, 24 or 26.

6. An isolated monoclonal antibody that binds GPC3, wherein the antibody comprises:

(i) a variable heavy (VH) domain comprising the amino acid sequence of SEQ ID NO: 12, SEQ ID NO: 8, SEQ ID NO: 16, SEQ ID NO: 37 or SEQ ID NO: 20; or

(ii) a variable light (VL) domain comprising the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 10, SEQ ID NO: 18, SEQ ID NO: 22, SEQ ID NO: 24 or SEQ ID NO: 26; or

(iii) both (i) and (ii).

7. The isolated monoclonal antibody of any one of claims 1-6, wherein the antibody is a VH single-domain antibody, a Fab fragment, a Fab' fragment, a $F(ab)'_2$ fragment, a single chain variable fragment (scFv), or a disulfide stabilized variable fragment (dsFv).

8. The isolated monoclonal antibody of any one of claims 1-6, wherein the antibody is an IgG.

9. The isolated monoclonal antibody of any of claims 1-8, wherein the antibody is labeled.

10. The isolated monoclonal antibody of claim 9, wherein the label is a fluorescence, enzymatic, or radioactive label.

11. The isolated monoclonal antibody of any one of claims 1-10, wherein the monoclonal antibody is a humanized monoclonal antibody.

12. A composition comprising a therapeutically effective amount of the antibody of any one of claims 1-11 in a pharmaceutically acceptable carrier.

13. An isolated immunoconjugate comprising the monoclonal antibody of any of claims 1-11 and an effector molecule.

14. The isolated immunoconjugate of claim 13, wherein the effector molecule is a toxin.

15. The isolated immunoconjugate of claim 14, wherein the toxin is *Pseudomonas* exotoxin or a variant thereof.

16. The isolated immunoconjugate of claim 15, wherein the toxin is PE38 comprising the amino acid sequence of SEQ ID NO: 1.

17. The isolated immunoconjugate of any one of claims 13-16, comprising the amino acid sequence of residues 2-597 of SEQ ID NO: 35, residues 2-597 of SEQ ID NO: 28, residues 2-597 of SEQ ID NO: 31, or residues 2-597 of SEQ ID NO: 33.

18. The isolated immunoconjugate of claim 13, wherein the effector molecule is a detectable label.

19. A composition comprising a therapeutically effective amount of the isolated immunoconjugate of any one of claims 13-18 in a pharmaceutically acceptable carrier.

20. Use of a therapeutically effective amount of the composition of claim 12 or claim 19 in the manufacture of a medicament for treating cancer in a subject with a cancer that expresses GPC3.

21. Use of a therapeutically effective amount of the composition of claim 12 or claim 19 in the manufacture of a medicamentfor inhibiting tumor growth or metastasis in a subject with a cancer that expresses GPC3 .

22. A method of determining if a subject has cancer, or a method of confirming the diagnosis of cancer in a subject, comprising:

contacting a sample from the subject with the monoclonal antibody of any of claims 1-11; and

detecting binding of the antibody to the sample,

wherein an increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having cancer, or confirms the diagnosis of cancer in the subject.

23. The method of claim 22, wherein the monoclonal antibody is directly labeled.

24. The method of claim 22, further comprising:

contacting a second antibody that specifically binds the monoclonal antibody with the sample, and

detecting the binding of the second antibody,

wherein an increase in binding of the second antibody to the sample as compared to binding of the second antibody to a control sample detects cancer in the subject or confirms the diagnosis of cancer in the subject.

25. The method of any one of claims 22-24, wherein the cancer is hepatocellular carcinoma (HCC), melanoma, squamous cell carcinoma of the lung or ovarian clear cell carcinoma.

26. An isolated nucleic acid molecule encoding the monoclonal antibody of any of claims 1-6.

27. The isolated nucleic acid molecule of claim 26, wherein:

(i) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 11 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 13;

(ii) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 7 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 9;

(iii) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 15 or SEQ ID NO: 36 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 17; or

(iv) the nucleotide sequence encoding the heavy chain of the monoclonal antibody comprises SEQ ID NO: 19 and the nucleotide sequence encoding the light chain of the monoclonal antibody comprises SEQ ID NO: 21, SEQ ID NO: 23 or SEQ ID NO: 25.

28. An expression vector comprising the isolated nucleic acid molecule of claim 26 or claim 27.

29. An isolated host cell transformed with the nucleic acid molecule or expression vector of any one of claims 26-28.