(Yong and Brechbiel, Dalton Trans. 2001 June 21; 40(23)6068-6076). Failure of the chelator to stably bind a radionuclide creates the risk of reducing delivery of radiation to the tumour while increasing toxicity.

SUMMARY

The present disclosure provides antibodies that bind to a metal chelate comprising DOTAM and lead (Pb). DOTAM is able to chelate Pb in a stable manner, to form a Pb[DOTAM] complex.

In one aspect, the present disclosure refers to an antibody comprising an antigen binding site specific for DOTAM-lead (Pb) chelate, wherein said antigen binding site comprises at least: a) a heavy chain CDR1; b) heavy chain CDR2 comprising the amino acid sequence FIGSRGDTYYASWAKG (SEQ ID NO:2), or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 2, wherein these substitutions do not include Phe50, Asp56 and Tyr58, and optionally also do not include Gly52 and/or Arg 54; c) heavy chain CDR3 comprising the amino acid sequence ERDPYGGGAYPPHL (SEQ ID NO:3), or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 3, wherein these substitutions do not include Glu95, Arg96, Asp97, Pro98, Ala100C, Tyr100D, and Tyr99 and optionally also do not include Pro100E; d) light chain CDR1 comprising the amino acid sequence QSSHSVYSDNDLA (SEQ ID NO:4) or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 4, wherein these substitutions do not include Tyr28 and Asp32; e) a light chain CDR2; and f) light chain CDR3 comprising the amino acid sequence LGGYDDESDTYG (SEQ ID NO:6) or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 6, wherein these substitutions do not include Gly91, Tyr92, Asp93, Thr95c and Tyr96, wherein numbering is according to Kabat.

In one example, the present disclosure refers to an antibody as disclosed herein, wherein the antigen binding site comprises a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 7 and SEQ ID NO 9, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 7 or SEQ ID NO: 9.

In another example, the present disclosure refers to an antibody as disclosed herein, wherein the antigen binding site comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 10, or a variant thereof

CLAIMS

1. An antibody comprising an antigen binding site specific for DOTAM-lead (Pb) chelate, wherein said antigen binding site comprises at least:

a) a heavy chain CDR1;

b) heavy chain CDR2 comprising the amino acid sequence FIGSRGDTYYASWAKG (SEQ ID NO:2), or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 2, wherein these substitutions do not include Phe50, Asp56 and Tyr58, and optionally also do not include Gly52 and/or Arg 54;

c) heavy chain CDR3 comprising the amino acid sequence ERDPYGGGAYPPHL (SEQ ID NO:3), or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 3, wherein these substitutions do not include Glu95, Arg96, Asp97, Pro98, Ala100C, Tyr100D, and Tyr99 and optionaly also do not include Pro100E;

d) light chain CDR1 comprising the amino acid sequence QSSHSVYSDNDLA (SEQ ID NO:4) or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 4, wherein these substitutions do not include Tyr28 and Asp32;

e) a light chain CDR2; and

f) light chain CDR3 comprising the amino acid sequence LGGYDDESDTYG (SEQ ID NO:6) or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 6, wherein these substitutions do not include Gly91, Tyr92, Asp93, Thr95c and Tyr96,

wherein numbering is according to Kabat.

2. The antibody of claim 1, wherein:

i) the heavy chain CDR1 comprises the amino acid sequence GFSLSTYSMS (SEQ ID NO:1) or a variant thereof having up to 1, 2, or 3 substitutions in SEQ ID NO: 1, optionally conservative substitutions; and/or

ii) the light chain CDR2 comprises the amino acid sequence QASKLAS (SEQ ID NO: 5) or a variant thereof having at least 1, 2 or 3 substitutions in SEQ ID NO: 5, optionally conservative substitutions.

3. The antibody of claim 1, wherein:

heavy chain CDR2 comprises the amino acid sequence FIGSRGDTYYASWAKG (SEQ ID NO:2);

heavy chain CDR3 comprises the amino acid sequence ERDPYGGGAYPPHL (SEQ ID NO:3);

light chain CDR1 comprises the amino acid sequence QSSHSVYSDNDLA (SEQ ID NO:4); and

light chain CDR3 comprises the amino acid sequence LGGYDDESDTYG (SEQ ID NO:6).

4. The antibody according to claim 1, wherein the antigen binding site comprises:

a) heavy chain CDR1 comprising the amino acid sequence GFSLSTYSMS (SEQ ID NO:1)

b) heavy chain CDR2 comprising the amino acid sequence FIGSRGDTYYASWAKG (SEQ ID NO:2)

c) heavy chain CDR3 comprising the amino acid sequence ERDPYGGGAYPPHL (SEQ ID NO:3)

d) light chain CDR1 comprising the amino acid sequence QSSHSVYSDNDLA (SEQ ID NO:4)

e) light chain CDR2 comprising the amino acid sequence QASKLAS (SEQ ID NO: 5)

f) light chain CDR3 comprising the amino acid sequence LGGYDDESDTYG (SEQ ID NO:6).

5. The antibody according to claim 1, which is human, chimeric or humanized.

6. An antibody according to claim 1, wherein the antigen binding site comprises a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 7 and SEQ ID NO 9, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 7 or SEQ ID NO: 9.

7. An antibody according to claim 1, wherein the antigen binding site comprises a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 8 and SEQ ID NO: 10, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 8 or 10.

8. An antibody according to claim 1, wherein the antigen binding site comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID No. 7 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO. 8.

9. An antibody according to claim 1, wherein the antigen binding site comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID No. 9 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO. 10.

10. An antibody according to claim 1, wherein the antigen binding site binds to the Pb-DOTAM chelate with a Kd value of 100pM, 50pM, 20pM, 10pM, 5pM, 1pM or less.

11. An antibody according to claim 1, wherein the antigen binding site binds to the Pb-DOTAM chelate and to a Bi-DOTAM chelate, and wherein the ratio of Kd values for the Bi-DOTAM chelate/Pb-DOTAM chelate is in the range of 0.1-10 or 1-10.

12. An antibody according to claim 1, which is a whole antibody, or which is an antibody fragment selected from the group consisting of an Fv, Fab, Fab', Fab'-SH, $F(ab')_2$, diabody, linear antibody, or single-chain antibody molecule.

13. An antibody according to claim 1, wherein the antibody is coupled to a moiety which binds specifically to a target antigen.

14. The antibody according to claim 13, wherein the target antigen is a tumour specific antigen.

15. The antibody according to claim 13, which is a multispecific or bispecific antibody.

16. The antibody according to claim 15, wherein the target antigen is a tumour specific antigen.

17. The multispecific or bispecific antibody of claim 16, wherein the tumour specific antigen is selected from the group consisting of carcinoembryonic antigen (CEA), HER2 and CD20.

18. The multispecific or bispecific antibody of claim 17, wherein the tumour specific antigen is CEA.

19. The multispecific or bispecific antibody of claim 15, wherein the multispecific or bispecific antibody comprises at least one antigen binding

site specific for the Pb-DOTAM chelate and at least one antigen binding site specific for CEA, and wherein the antigen binding site specific for CEA comprises a heavy chain comprising:

a) heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 11

b) heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 12

c) heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 13;

and the antigen binding site specific for CEA comprises a light chain comprising:

d) light chain CDR1 comprises the amino acid sequence SEQ ID NO: 14;

e) light chain CDR2 comprises the amino acid sequence SEQ ID NO:15;

f) light chain CDR3 comprises the amino acid sequence SEQ ID NO: 16.

20. The multispecific or bispecific antibody of claim 19, wherein the multispecific or bispecific antibody comprises at least one antigen binding site specific for the Pb-DOTAM chelate and at least one antigen binding site specific for CEA, and wherein the antigen binding site specific for CEA comprise

i) a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 17, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 17; and

ii) a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 18, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 18.

21. The multispecific or bispecific antibody of claim 20, wherein the antigen binding site specific for CEA comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 17 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 18.

22. The multispecific or bispecific antibody according to claim 15, wherein the multispecific or bispecific antibody comprises at least one antigen binding site specific for a Pb-DOTAM chelate and at least one antigen binding site specific for ERBB2, and wherein the antigen binding site specific for ERBB2 comprises (a)CDR-H1 comprising the amino acid sequence of SEQ ID NO:28; (b) CDR-H2 comprising the amino acid sequence of

SEQ ID NO:29; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:30; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:31; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:32; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:33.

23. The multispecific or bispecific antibody according to claim 22, wherein the multispecific or bispecific antibody comprises at least one antigen binding site specific for the Pb-DOTAM chelate and at least one antigen binding site specific for ERBB2, and wherein the antigen binding site specific for ERBB2 comprises
i) a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 34; and
ii) a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 35, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 35.

24. The multispecific or bispecific antibody according to claim 23, wherein the antigen binding site specific for ERBB2 comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 34 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 35.

25. The multispecific or bispecific antibody according to claim 15, wherein the multispecific or bispecific antibody comprises at least one antigen binding site specific for a Pb-DOTAM chelate and at least one antigen binding site specific for CD20, and wherein the antigen binding site specific for CD20 comprises (a)CDR-H1 comprising the amino acid sequence of SEQ ID NO:39; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:40; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:41; (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:42; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:43; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:44.

26. The multispecific or bispecific antibody according to claim 25, wherein the multispecific or bispecific antibody comprises at least one antigen binding site specific for the Pb-DOTAM chelate and at least one antigen binding site specific for CD20, and wherein the antigen binding site specific for CD20 comprises

i) a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 45, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 45; and

ii) a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 46, or a variant thereof comprising an amino acid sequence having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to SEQ ID NO: 46.

27. The multispecific or bispecific antibody according to claim 26, wherein the antigen binding site specific for CD20 comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 45 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 46.

28. The multispecific or bispecific antibody of claim 15, which comprises an Fc region.

29. The multispecific or bispecific antibody of claim 28, wherein the Fc region is engineered to reduce effector function.

30. The multispecific or bispecific antibody of claim 29, wherein the Fc region comprises substitution of one or more of Fc region residues 234, 235, 238, 265, 269, 270, 297, 327 and/or 329.

31. The multispecific or bispecific antibody of claim 28, comprising:

i) a full length antibody comprising an antigen binding site for a first antigen; and

ii) at least a second heavy chain variable domain and second light chain variable domain which together form an antigen binding site for a second antigen,

wherein either the first or the second antigen is the Pb-DOTAM chelate, and the other is the target antigen.

32. The multispecific or bispecific antibody of claim 31, comprising a full length antibody comprising an antigen binding site for the first antigen, wherein the N- or C-terminus of one of the heavy chains is linked via a polypeptide linker to a first polypeptide and wherein the first polypeptide associates with a second polypeptide to form a Fab or a cross-Fab comprising a binding site for the second antigen.

33. The multispecific or bispecific antibody of claim 32, which comprises:
i) a first polypeptide consisting of a VH domain and a CH1 domain, which is associated with a second polypeptide consisting of a VL and CL domain; or
ii) a first polypeptide consisting of a VL domain and a CH1 domain, which is associated with a second polypeptide consisting of a VH and CL domain; or
iii) a first polypeptide consisting of a VH domain and a CL domain, which is associated with a second polypeptide consisting of a VL and CH1 domain; such that the first and second polypeptide together form an antigen binding site for the second antigen.

34. The multispecific or bispecific antibody of claim 33, which comprises a full length antibody comprising an antigen binding site for the first antigen, wherein the C-terminus of one of the heavy chains is linked via a polypeptide linker to a first polypeptide consisting of a VL domain and a CH1 domain, which is associated with a second polypeptide consisting of a VH and CL domain.

35. The multispecific or bispecific antibody according to claim 31, wherein the first antigen is the target antigen and the second antigen is the Pb-DOTAM chelate.

36. The multispecific or bispecific antibody according to claim 35, wherein the first antigen is CEA.

37. An isolated polynucleotide or an isolated set of polynucleotides encoding an antibody according to claim 1.

38. An expression vector or set of expression vectors comprising the polynucleotide or the set of polynucleotides according to claim 37.

39. A prokaryotic or eukaryotic host cell comprising an isolated polynucleotide or an isolated set of polynucleotides according to claim 37, optionally comprising the vector or set of vectors of claim 38.

40. A method of producing an antibody according to claims 1, comprising expressing the antibody from the host cell of claim 39.