

ANTIBODIES WHICH BIND TO CANCER CELLS AND TARGET RADIONUCLIDES TO SAID CELLS

FIELD OF THE INVENTION

The present invention relates to antibodies which bind to antigens on target cells and which target radionuclides to said cells, and to methods of using the same.

BACKGROUND

Monoclonal antibodies have been developed to target drugs to cancer cells. By conjugating a toxic agent to an antibody which binds to a tumour-associated antigen, there is the potential to provide more specific tumour killing with less damage to surrounding tissues.

10 In pre-targeted radioimmunotherapy (PRIT), use is made of an antibody construct which has affinity for the tumour-associated antigen on the one hand and for a radiolabelled compound on the other. In a first step, the antibody is administered and localises to tumour. Subsequently, the radiolabelled compound is administered. Because the radiolabelled compound is small, it can be delivered quickly to the tumour and is fast-clearing, which reduces radiation exposure outside of the tumour (Goldenberg *et al* Theranostics 2012, 2(5), 523-540). A similar procedure can also be used for imaging. Pre-targeting can make use of a bispecific antibody or systems using avidin-biotin, although the latter has the disadvantage that avidin/streptavidin is immunogenic.

20 Methods of pre-targeted radioimmunotherapy or imaging commonly make use of a clearing or blocking agent, which is administered between the step of administering the antibody and the step of administering the radiolabelled compound. The purpose is to clear antibody from the blood and/or to block the binding site of the circulating antibody for the radiolabelled compound (see for instance Karacay et al, Bioconj. Chem., 13(5), 1054-1070 (2002)). The use of a clearing or blocking agent allows for sufficient levels of radioactivity to be administered for an efficient treatment while limiting adverse toxicity, but the timing and dosage must be chosen with care. Thus, the use of a clearing phase is a complicating aspect in pre-targeting methods.

SUMMARY

| The present ~~invention~~ disclosure provides sets of antibodies useful in pre-targeting methods, and methods of using the same.

In one aspect, the present ~~invention~~ disclosure provides a set of antibodies comprising:

i) a first antibody that binds to an antigen expressed on the surface of a target cell, and which further comprises a V_H domain of an antigen binding site for a radiolabelled compound, but which does not comprise a V_L domain of an antigen binding site for the radiolabelled compound; and

ii) a second antibody that binds to the antigen expressed on the surface of the target cell, and which further comprises a V_L domain of an antigen binding site for the radiolabelled compound, but which does not comprise a V_H domain of the antigen binding site for the radiolabelled compound,

wherein said V_H domain of the first antibody and said V_L domain of the second antibody are together capable of forming a functional antigen binding site for the radiolabelled compound.

Neither the first nor the second antibody comprise, on their own, a functional antigen binding site for a radiolabelled compound. The first antibody has only a V_H domain from the functional binding site for the radiolabelled compound, and not the V_L domain. The second antibody has only the V_L domain, and not the V_H domain.

A functional antigen binding site for the radiolabelled compound is formed when the V_H and V_L domains of the first and second antibodies are associated. This may occur, for example, when the first and second antibodies are bound to the same individual target cell or to adjacent cells.

The first and second antibodies described herein may be referred to herein as “single domain split antibodies”, “split antibodies” or “demibodies”. The V_H and V_L domain which together form an antigen binding site capable of binding to the radiolabelled compound are split between two antibodies, and not present as part of the same antibody.

The split domain format means that the radiolabelled compound cannot bind to either the first antibody on its own or to the second antibody on its own. In the blood, there is little or no stable association between the first and the second antibody, and so little or no stable binding of the radiolabelled compound.

An antigen expressed on the surface of a target cell may be referred to herein as a “target antigen” or “TA”. According to the present ~~invention~~ disclosure, the first and the second antibody described above have a binding site for the same target antigen. (For the avoidance of doubt, where it stated that the antibodies bind the same target antigen, this means that they have a binding site capable of binding to the same target antigen and includes the possibility

that the antibodies may bind to two individual antigen molecules that are the same as each other). For example, in one ~~embodiment~~example, both the first and the second antibody bind to CEA.

In some ~~embodiment~~examples, the first and second antibody may bind to (have a binding site for) the same epitope of the target antigen. In other ~~embodiment~~examples, the first antibody may bind to (have a binding site for) a different epitope of the target antigen from the second antibody.

10 In some ~~embodiment~~examples, the first and second antibody may comprise the same antigen binding site for the target antigen. That is, they may comprise an antigen binding site capable of binding to the target antigen, comprising a V_L and V_H sequence, where the V_L and V_H sequences forming this antigen binding site are the same in the first and in the second antibodies.

In some ~~embodiment~~examples, each of the first and the second antibodies are bivalent for the target antigen. In some ~~embodiment~~examples they are each bivalent and monospecific for an epitope. In other ~~embodiment~~examples, each of the first and second antibodies are biparatopic for the target antigen, i.e., the first and the second antibodies each have binding sites for two different epitopes of the target antigen.

20 In some ~~embodiment~~examples, it may be preferred that the first and/or second antibody comprise an Fc region. The presence of an Fc region has benefits in the context of radioimmunotherapy and radioimaging, e.g. prolonging the protein's circulating half-life and/or resulting in higher tumour uptake than may be observed with smaller fragments. The "split domain" format described herein may be particularly advantageous in this context, as it mitigates against the greater possibility of association with radiolabelled compound that would otherwise occur due to the prolonged presence of the circulating antibody.

In some ~~embodiment~~examples, the Fc domain is modified to reduce or eliminate effector function.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a pharmaceutical composition comprising the set of antibodies as described herein. In another ~~aspect~~example, the present ~~invention~~disclosure provides a kit comprising two separate pharmaceutical compositions, each comprising one of the antibodies described herein (i.e., the first and second antibody respectively).

30 In another aspect, the present disclosure refers to a set of nucleic acids expressing the set of antibodies as disclosed herein. In another aspect, the present disclosure refers to an expression vector or set of expression vectors comprising the set of nucleic acids as disclosed herein. In another aspect, the present disclosure refers to a host cell or set of host cells comprising the expression vector or set of expression vectors as disclosed herein. In a further ~~aspect~~example, the present ~~invention~~disclosure relates to a polynucleotide or set of polynucleotides encoding any of the antibodies or sets of antibodies described herein. In another ~~aspect~~example, the present ~~invention~~disclosure relates to a vector or set of vectors comprising said polynucleotide or polynucleotides, optionally an expression vector or set of expression vectors. In a further object the present ~~invention~~disclosure relates to a prokaryotic or eukaryotic host

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cell or a set of host cells comprising a vector or set of vectors of the present ~~invention~~disclosure. In addition there is provided a method of producing an antibody comprising culturing the host cell(s) so that the antibody is produced.

In some ~~embodiment~~examples, antibodies as described herein find use in a method of pre-targeted radioimmunotherapy (PRIT) or in a method of pre-targeted radioimaging.

In another aspect, the present disclosure refers to use of the set of antibodies as disclosed herein in the manufacture of a medicament for use in a method of pretargeting radioimmunotherapy of a tumour or cancer, comprising i) that the set of antibodies as disclosed herein is to be administered, wherein the first and second antibodies are to be administered simultaneously or sequentially, in either order, wherein the antibodies bind to the target antigen and localise to the surface of a cell expressing the target antigen; and wherein association of the first and second antibody forms a functional binding site for the radiolabelled compound; and ii) subsequently that a radiolabelled compound is to be administered, wherein the radiolabelled compound binds to functional binding site for the radiolabelled compound. In one ~~aspect~~example, the present ~~invention~~disclosure provides a method of pre-targeted radioimmunotherapy which comprises:

i) administering to a subject a first antibody and a second antibody as described above; and

ii) subsequently administering to said subject a radiolabelled compound.

In another aspect, the present disclosure refers to use of a set of antibodies as disclosed herein in the manufacture of an imaging agent for use in a method of targeting a radioisotope to a tissue or organ for radioimaging comprising: i) that the first and second antibodies are to be administered simultaneously or sequentially, in either order, wherein the antibodies bind to a target antigen and localise to the surface of a cell expressing the target antigen, wherein association of the first and second antibody forms a functional binding site for the radiolabelled compound; and ii) subsequently that a radiolabelled compound is to be administered, wherein the radiolabelled compound binds to the functional binding site for the radiolabelled compound. In another ~~aspect~~example, the present ~~invention~~disclosure provides a first and a second antibody described above for use in a method of treatment comprising administering the first antibody and the second antibody to a subject, and subsequently administering to said subject a radiolabelled compound. In another ~~aspect~~example, the ~~invention~~disclosure provides a first antibody as described above for use in a method of treatment comprising administering the first antibody and the second antibody to a subject, and subsequently administering to said subject a radiolabelled compound. In another ~~aspect~~example the ~~invention~~disclosure provides the second antibody as described above for use in a method of treatment comprising administering the first antibody and the second antibody to a subject, and subsequently administering to said subject a radiolabelled compound.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a method of radioimaging which comprises:

i) administering to a subject a first and a second antibody as described herein, wherein the antibodies bind to the target antigen and localise to the surface of a cell expressing the target antigen;

ii) subsequently administering a radiolabelled compound; and optionally

iii) imaging the tissue or organ where the radionuclide has localised.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a first and a second antibody as described herein for use in a method of diagnosis carried out on the human or animal body, wherein the method comprises

i) administering to subject a first and a second antibody as described herein, wherein the antibodies bind to the target antigen and localise to the surface of a cell expressing the target antigen;

- ii) subsequently administering a radiolabelled compound; and optionally
- iii) imaging the tissue or organ where the radionuclide has localised.

The imaging step may be followed by a step of forming a diagnosis and optionally a step of delivering that diagnosis to the subject. In some ~~embodiment~~examples the method may further comprise determining an appropriate treatment and optionally administering that treatment to the subject.

In each of the above methods/uses, binding of the first and the second antibody to the same or adjacent target cells results in association of the V_H and V_L domains of an antigen binding site for a radiolabelled compound and the formation of a functional antigen binding site for the radiolabelled compound. Thus, after administration of the radiolabelled compound, the radiolabelled compound binds to the functional antigen binding site formed by association of the V_H and V_L.

In any of the methods and uses described herein, the first and second antibodies can be administered simultaneously or sequentially, in either order.

Frequently in the art, methods of PRIT or radioimaging involve a clearing step. The clearing step comprises administering an agent between the administration of the antibody and the administration of the radiolabelled compound, wherein the agent increases the rate of removal of the antibody from blood and/or blocks binding of radiolabelled compound to the antibody.

In an ~~embodiment~~example of the methods and uses described herein, the method does not comprise a clearing step. That is, it does not comprise a step of administering a clearing agent or a blocking agent between the administration of the first and second antibodies and the administration of radiolabelled compound (i.e., after the administration of the antibodies but before administration of the radiolabelled compound). In another ~~embodiment~~example, no agent is administered between the administration of the first and second antibodies and the administration of radiolabelled compound, other than optionally a radiosensitizer, immunotherapeutic and/or a chemotherapeutic agent. In another ~~embodiment~~example, no agent is administered between the administration of the first and second antibodies and the administration of radiolabelled compound.

In some ~~embodiment~~examples, the antibodies described herein may be administered as part of a combination therapy. For example, they may be administered in combination with one or more radiosensitizers, immunotherapeutics and/or chemotherapeutic agents: the

radiosensitizer, immunotherapeutic or chemotherapeutic agent and the antibodies may be administered simultaneously or sequentially, in either order.

The methods of radioimaging and radioimmunotherapy described herein may optionally be combined as discussed further herein.

In a further ~~aspect~~example, the present ~~invention~~disclosure provides a kit comprising:

- i) a first and a second antibody as described herein;
- ii) a radiolabelled compound which binds to the antigen binding site formed by association of the first and the second antibody.

10 Optionally the kit may exclude (i.e., does not comprise) a clearing agent or a blocking agent as described herein.

Optionally the kit may further comprise a radiosensitizer, immunotherapeutic or chemotherapeutic agent.

In some ~~embodiment~~examples, the first and the second antibody may be present in the same pharmaceutical composition. In other ~~embodiment~~examples, the first and second antibody may be present in separate pharmaceutical compositions. In some ~~embodiment~~examples, the radiolabelled compound is present in a pharmaceutical composition separate from the antibodies.

BRIEF DESCRIPTION OF THE FIGURES

20 Figure 1 shows the schematic structure of a target antigen (TA)-DOTAM bispecific antibody (TA-DOTAM BsAb) belonging to the comparative examples, and exemplary TA-split-DOTAM-VH/VL antibodies according to the invention.

Figure 2 is a schematic diagram showing the assembly of the split-VH/VL DOTAM binder on tumour cells. The TA-split-DOTAM-VH/VL antibodies will not significantly bind ²¹²Pb-DOTAM unless bound to tumour antigen (TA) on targeted cells, where the two domains of the DOTAM binder are assembled.

Figure 3 shows a schematic overview of an example of the Three-Step TA-PRIT concept, involving use of a clearing agent.

Figure 4 shows a schematic overview of an example of the Two-Step TA-PRIT concept, in which a clearing agent is not used.

30 Figure 5 shows binding of split antibodies to MKN45 cells to demonstrate CEA binding competence. Detection of antibodies is done using human IgG specific secondary antibodies

WHAT IS CLAIMED IS:

1. A set of antibodies comprising:

i) a first antibody that binds to an antigen expressed on the surface of a target cell, and which further comprises a VH domain of an antigen binding site for a radiolabelled compound, but which does not comprise a VL domain of an antigen binding site for the radiolabelled compound; and

ii) a second antibody that binds to said antigen expressed on the surface of the target cell, and which further comprises a VL domain of an antigen binding site for the radiolabelled compound, but which does not comprise a VH domain of the antigen binding site for the radiolabelled compound,

wherein said VH domain of the first antibody and said VL domain of the second antibody are together capable of forming a functional antigen binding site for the radiolabelled compound.

2. The set of antibodies of claim 1, wherein the first and second antibody each comprise

i) an antibody fragment comprising an antigen binding site specific for said antigen expressed on the surface of a target cell and ii) either a VL domain or a VH domain of the antigen binding site for the radiolabelled compound, optionally;

~~3. The set of antibodies of claim 2, wherein the antibody fragment is selected from at least one Fv, scFv, or Fab or cross-Fab fragment.~~

~~4. The set of antibodies of claim 3, wherein the first antibody comprises or consists of:~~

~~a) a Fab fragment binding said antigen, and~~

~~b) a polypeptide comprising or consisting of~~

~~i) an antibody heavy chain variable domain (VH) of an antigen binding site for a radiolabelled compound, or~~

~~ii) an antibody heavy chain variable domain (VH) of an antigen binding site for a radiolabelled compound and an antibody heavy chain constant domain, wherein the C terminus of VH domain is fused to the N terminus of the constant domain;~~

~~wherein the polypeptide is fused by the N terminus of the VH domain to the C terminus of the CL or CH1 domain of the Fab fragment;~~

and wherein the second antibody comprises or consists of:

- ~~—— c) a Fab fragment binding said antigen, and~~
 - ~~d) a polypeptide comprising or consisting of
 - ~~iii) an antibody light chain variable domain (VL) of an antigen binding site for a radiolabelled compound; or~~
 - ~~iv) an antibody light chain variable domain (VL) of an antigen binding site for a radiolabelled compound and an antibody light chain constant domain, wherein the C-terminus of the VL domain is fused to the N-terminus of the constant domain;~~~~
- ~~wherein the polypeptide is fused by the N-terminus of the VL domain to the C-terminus of the CL or CH1 domain of the Fab fragment;~~
- ~~and wherein antibody heavy chain variable domain (VH) of the polypeptide of (b) and antibody light chain variable domain (VL) of polypeptide of (d) are together capable of forming a functional antigen binding site for the radiolabelled compound.~~

~~5. — The set of antibodies according to claim 4, wherein the polypeptide of (b) is fused by the N-terminus of the VH domain to the C-terminus of the CL or CH1 domain of the Fab fragment of (a) via a peptide linker; and wherein the polypeptide of (d) is fused by the N-terminus of the VL domain to the C-terminus of the CL or CH1 domain of the Fab fragment of (c) via a peptide linker.~~

- ~~6. — The set of antibodies according to claim 3, wherein the first antibody comprises~~
- ~~a) a tandem Fab comprising two Fab fragments, wherein the first and the second Fab fragment each bind the same epitope of said antigen and wherein the first and the second Fab fragment are connected via a peptide tether, wherein the first Fab is connected via its C-terminus to the N-terminus of the second Fab; and~~
 - ~~b) a polypeptide comprising or consisting of
 - ~~—— i) an antibody heavy chain variable domain (VH); or~~
 - ~~ii) an antibody heavy chain variable domain (VH) and an antibody constant domain (CH1), wherein the C-terminus of VH domain is fused to the N-terminus of the CH1 domain;~~~~
- ~~wherein said polypeptide is fused by the N-terminus of the VH domain to the C-terminus of the CL or CH1 domain of the second Fab fragment;~~
- ~~and the second antibody comprises~~

e) a tandem Fab comprising two Fab fragments, wherein the first and the second Fab fragment each bind the same epitope of said antigen and wherein the first and the second Fab fragment are connected via a peptide tether, wherein the first Fab is connected via its C terminus to the N terminus of the second Fab; and

d) a polypeptide comprising or consisting of

i) an antibody light chain variable domain (VL); or

ii) an antibody light chain variable domain (VL) and an antibody light chain constant domain (CL), wherein the C terminus of VL domain is fused to the N terminus of the constant domain;

wherein said polypeptide is fused by the N terminus of the VL domain to the C terminus of the CL or CH1 domain of the second Fab fragment;

and wherein antibody heavy chain variable domain (VH) of the polypeptide of (b) and antibody light chain variable domain (VL) of polypeptide of (d) are together capable of forming a functional antigen binding site for the radiolabelled compound.

7. — The set of antibodies according to claim 6, wherein the polypeptide of (b) is fused by the N terminus of the VH domain to the C terminus of the CL or CH1 domain of the second Fab fragment of (a) via a peptide linker; and wherein the polypeptide of (d) is fused by the N terminus of the VL domain to the C terminus of the CL or CH1 domain of the second Fab fragment of (c) via a peptide linker.

8. — The set of antibodies according to claim 3, wherein the first antibody comprises

a) a tandem Fab comprising a first fragment and a second fragment, wherein the first fragment is connected by its C terminus via a peptide tether to the N terminus of the second fragment, wherein the first fragment binds a first epitope of said antigen and the second fragment binds a second epitope of said antigen, and wherein one of the fragments selected from the first and second fragments is a Fab and the other is a cross Fab;

b) a polypeptide comprising or consisting of

— i) an antibody heavy chain variable domain (VH); or

ii) an antibody heavy chain variable domain (VH) and an antibody heavy chain constant domain (CH1), wherein the C terminus of VH domain is fused to the N terminus of the CH1 domain;

wherein said polypeptide is fused by the N terminus of the VH domain to the C terminus of one of the chains of the second fragment; and

wherein the second antibody comprises

e) a tandem Fab comprising a first fragment and a second fragment, wherein the first fragment is connected by its C terminus to the N terminus of the second fragment, wherein the first fragment binds the a first epitope of said antigen and the second fragment binds a second epitope of said antigen, and wherein one of the fragments selected from the first and second fragments is a Fab and the other is a cross-Fab; and

d) a polypeptide comprising or consisting of

i) an antibody light chain variable domain (VL); or

ii) an antibody light chain variable domain (VL) and an antibody light chain constant domain (CL), wherein the C terminus of VL domain is fused to the N terminus of the light chain constant domain

wherein said polypeptide is fused by the N terminus of the VL domain to the C terminus of one of the chains of the second fragment;

and wherein antibody heavy chain variable domain (VH) of the polypeptide of (b) and antibody light chain variable domain (VL) of polypeptide of (d) are together capable of forming a functional antigen binding site for the radiolabelled compound.

9. — The set of antibodies according to claim 8, wherein the polypeptide of (b) is fused by the N terminus of the VL domain to the C terminus of one of the chains of the second fragment of (a) via a peptide linker; and wherein the polypeptide of (d) is fused by the N terminus of the VL domain to the C terminus of one of the chains of the second fragment of (c) via a peptide linker.

3+10. The set of antibodies according to ~~any one of claims 1 or claim 2-3~~, wherein the first and second antibody each further comprise an Fc domain.

11. — The set of antibodies of claim 10, wherein the first and second antibody each comprise i) an antibody fragment comprising an antigen binding site specific for said antigen expressed on the surface of a target cell, ii) an Fc region and iii) either a VL domain or a VH domain of the antigen binding site for the radiolabelled compound fused to the Fc region.

~~412.~~ The set of antibodies of claim ~~310 or 11~~, wherein the Fc domain is modified to reduce or eliminate effector function.

~~513.~~ The set of antibodies according to ~~any one of claims 310 or to claim 412~~, wherein the first antibody comprises or consists of:

- i) a complete light chain fragment;
- ii) a complete heavy chain;
- iii) an additional Fc chain lacking Fd; -and
- iv) a polypeptide comprising or consisting of the VH domain of the antigen binding site for the radiolabeled compound;

wherein the light chain of (i) and the heavy chain of (ii) together provide an antigen binding site for said antigen; and wherein the polypeptide comprising or consisting of the VH domain of the antigen binding site for the radiolabeled compound is fused, optionally via a linker, by its N-terminus to the C-terminus of either (ii) or (iii); and

wherein the second antibody comprises or consists of

- v) a complete light chain fragment;
- vi) a complete heavy chain;
- vii) an additional Fc chain lacking Fd; and
- viii) a polypeptide comprising or consisting of the VL domain of the antigen binding site for the radiolabeled compound;

wherein the light chain of (v) and the heavy chain of (vi) together provide an antigen binding site for said antigen; and wherein the polypeptide comprising or consisting of the VL domain of the antigen binding site for the radiolabeled compound is fused by its N-terminus,

optionally via a linker, to the C-terminus of either (vi) or (vii);

wherein the antibody heavy chain variable domain (VH) of the polypeptide of (iv) and the antibody light chain variable domain (VL) of the polypeptide of (viii) are together capable of forming a functional antigen binding site for the radiolabelled compound.

~~14. The set of antibodies according to claim 13, wherein the polypeptide of (iv) is fused by its N terminus to the C terminus of either (ii) or (iii) via a linker; and the polypeptide of (viii) is fused by its N terminus to the C terminus of either (vi) or (vii) via a linker.~~

~~645~~. The set of antibodies according to ~~any one of claims 3 or claim 410-12~~, wherein each of the first and second antibody comprise a) an Fc domain b) at least one antibody fragment, such as an scFv, Fv, Fab or cross-Fab fragment, comprising an antigen binding site for the target antigen and c) a polypeptide comprising either a VL domain or a VH domain of the antigen binding site for the radiolabelled compound, wherein the C-terminus of the antibody fragment of (b) is fused to the N-terminus of one chain of the Fc domain, and the C-terminus of the polypeptide of (c) is fused to the N-terminus of the other chain of the Fc domain.

~~746~~. The set of antibodies of claim ~~645~~, wherein the first antibody comprises:

- i) a complete light chain;
- ii) a complete heavy chain;
- iii) an additional Fc chain; and
- iv) a polypeptide comprising or consisting of the VH domain of the antigen binding site for the radiolabeled compound;

wherein the light chain of (i) and the heavy chain of (ii) together provide an antigen binding site for the target antigen; and wherein the polypeptide comprising or consisting of the VH domain of the antigen binding site for the radiolabeled compound is fused by its C-terminus via a linker to the N-terminus of (iii); and

the second antibody comprises:

- v) a complete light chain;
 - vi) a complete heavy chain;
 - vii) an additional Fc chain; and
 - viii) a polypeptide comprising or consisting of the VL domain of the antigen binding site for the radiolabeled compound;
- wherein the light chain of (v) and the heavy chain of (vi) together provide an antigen binding site for the target antigen; and wherein the polypeptide comprising or consisting of the VL domain of the antigen binding site for the radiolabeled compound is fused by its C-terminus via a linker to the N-terminus of (vii).

~~847~~. The set of antibodies according to claim ~~746~~, wherein:

- i) the first antibody comprises a first heavy chain of SEQ ID NO:112, a second heavy chain of SEQ ID NO: 114 and a light chain of SEQ ID NO: 115; and
- ii) the second antibody comprises a first heavy chain of SEQ ID NO:112, a second heavy chain of SEQ ID NO: 113 and a light chain of SEQ ID NO: 115.

~~18.~~ 18. The set of antibodies of ~~any of claims 3 or claim 410 to 12,~~ wherein the first antibody comprises

a) a first full length antibody and consisting of two antibody heavy chains and two antibody light chains, wherein at least one arm of the full length antibody binds said antigen; and

b) a polypeptide consisting of

i) an antibody heavy chain variable domain (VH); or

ii) an antibody heavy chain variable domain (VH) and an antibody constant domain (CH1),

wherein said polypeptide is fused by the N-terminus of the VH domain to the C-terminus of one of the two heavy chains of said first full-length antibody, optionally via a linker, and

wherein the second antibody comprises:

c) a second full length antibody and consisting of two antibody heavy chains and two antibody light chains, wherein at least one arm of the antibody binds to said antigen; and

d) a polypeptide consisting of

i) an antibody light chain variable domain (VL); or

ii) an antibody light chain variable domain (VL) and an antibody light chain constant domain (CL),

wherein said polypeptide is fused by the N-terminus of the VL domain to the C-terminus of one of the two heavy chains of said second full-length antibody, optionally via a linker,

wherein the polypeptide of (b) and the polypeptide of (d) are together capable of forming a functional antigen-binding site for the radiolabelled compound.

~~19. — The set of antibodies according to claim 18, wherein the polypeptide (b) is fused by the N terminus of the VH domain to the C terminus of one of the two heavy chains of said first full length antibody via a peptide linker; and the polypeptide of (d) is fused by the N-terminus of the VL domain to the C terminus of one of the two heavy chains of said second full length antibody via a peptide linker.~~

~~1020.~~ The set of antibodies of claim ~~918 or 19~~, wherein each of the first and second antibodies is bivalent for said antigen, optionally wherein ~~it~~.

~~21.~~—The set of antibodies of claim 20, wherein both arms of the full-length antibody bind to the same epitope of said antigen.

~~22.~~—The set of antibodies of claim 18 or 19, or wherein each of the first and second antibodies is biparatopic for said antigen.

~~23.~~—The set of antibodies of claim 22, wherein the two arms of the first antibody each bind to an epitope on said antigen and bind to different epitopes from each other; and wherein the two arms of the second antibody each bind to an epitope on said antigen and bind to different epitopes from each other.

~~24.~~—The set of antibodies of any one of the preceding claims, wherein the radiolabelled compound comprises radiolabelled DOTA or a salt or functional variant thereof.

~~25.~~—The set of antibodies of any one of the preceding claims, wherein the radiolabelled compound is DOTA or a salt or functional variant thereof radiolabelled with a Lu or Y radioisotope.

~~26.~~—The set of antibodies according to claim 24 or 25, wherein the VH domain of the antigen binding site for the radiolabelled compound comprises (a) CDR H1 comprising the amino acid sequence of 35; (b) CDR H2 comprising the amino acid sequence of 36; (c) CDR H3 comprising the amino acid sequence of 37.

~~27.~~—The set of antibodies according to any one of claims 24 to 26, wherein the VH domain of the antigen binding site for the radiolabelled compound comprises the amino acid sequence of SEQ ID NO: 41, 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: 41.

~~28.~~—The set of antibodies of claim 27, wherein one or more alanine residues are added to the C terminus of the VH domain of the antigen binding site for the radiolabelled compound,

~~or wherein one or more residues from the N terminus of the CH1 domain are added to the C terminus of the VH domain of the antigen binding site for the radiolabelled compound.~~

~~29. The set of antibodies of claim 28, wherein residues AST are added to the C terminus of the VH domain of the antigen binding site for the radiolabelled compound.~~

~~30. The set of antibodies of any one of claims 24 to 29, wherein the VL domain of the antigen binding site for the radiolabelled compound comprises (d) CDR-L1 comprising the amino acid sequence of 38; (e) CDR-L2 comprising the amino acid sequence of 39; and (f) CDR-L3 comprising the amino acid sequence of 40.~~

~~31. The set of antibodies of any one of claims 24 to 30, wherein the VL domain of the antigen binding site for the radiolabelled compound comprises an amino acid sequence of SEQ ID NO: 42 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: 42.~~

1132. The set of antibodies of any one of the preceding claims ~~claims 1 to 23~~, wherein the radiolabelled compound comprises Pb-DOTAM.

1233. The set of antibodies according to claim 1132, wherein the functional binding site for Pb-DOTAM binds with a Kd value of the binding affinity of 100pM, 50pM, 20pM, 10pM, 5pM, 1pM or less, e.g. 0.9pM or less, 0.8pM or less, 0.7pM or less, 0.6pM or less or 0.5pM or less.

1334. The set of antibodies according to claim 1132 or claim 1233, wherein the functional binding site for Pb-DOTAM binds to Pb-DOTAM and to Bi-DOTAM.

1435. The set of antibodies of any one of claims 1132 to 1334, wherein the VH domain of the antigen binding site for the radiolabelled compound comprises:

- a) 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/or Tyr58, and optionally also do not include Gly52 and/or Arg54;

b) 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, and optionally also do not include Ala100C, Tyr100D, and/or Pro100E and/or optionally also do not include Tyr99;

and a heavy chain CDR1 which is optionally:

c) a heavy chain CDR1 comprising 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;

and wherein the VL domain of the antigen binding site for the radiolabelled compound comprises:

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) 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; and a light chain CDR2 which is optionally

f) light chain CDR 2 comprising 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 not including Gln50.

1536. The set of antibodies of claim 1435, wherein

the VH domain of the antigen binding site for the radiolabelled compound comprises

(a) CDR-H1 comprising the amino acid sequence of GFSLSTYSMS (SEQ ID NO:1); (b) CDR-H2 comprising the amino acid sequence of FIGSRGDTYYASWAKG (SEQ ID NO:2) and (c) CDR-H3 comprising the amino acid sequence of ERDPYGGGAYPPHL (SEQ ID NO:3); and

the VL domain of the antigen binding site for the radiolabelled compound comprises

(d) CDR-L1 comprising the amino acid sequence of QSSHSVYSDNDLA (SEQ ID NO:4); (e) CDR-L2 comprising the amino acid sequence of QASKLAS (SEQ ID NO:5); and (f) CDR-L3 comprising the amino acid sequence of LGGYDDESDTYG (SEQ ID NO:6).-

1637. The set of antibodies of any one of claims 1132 to 1536, wherein

the VH domain of the antigen binding site for the radiolabelled compound comprises 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; and

the VL domain of the antigen binding site for the radiolabelled compound comprises an amino acid sequence of SEQ ID NO: 8, 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.

~~1738.~~ The set of antibodies of claim ~~1637~~, wherein one or more alanine residues are added to the C-terminus of the VH domain of the antigen binding site for the radiolabelled compound, or wherein one or more residues from the N-terminus of the CH1 domain are added to the C-terminus of the VH domain of the antigen binding site for the radiolabelled compound:-

~~39.~~—The set of antibodies of claim ~~38~~, optionally wherein residues AST are added to the C-terminus of the VH domain of the antigen binding site for the radiolabelled compound.

~~40.~~—The set of antibodies of any one of claims ~~32 to 39~~, wherein the VL domain of the antigen binding site for the radiolabelled compound comprises

~~d) light chain CDR1 comprising the amino acid sequence QSSHVSVDNDLA (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) light chain CDR3 comprising the amino acid sequence LGGYDDESPTYG (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,~~

~~and a light chain CDR2 which is optionally~~

~~f) light chain CDR 2 comprising 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 not including Gln50.~~

~~41.~~—The set of antibodies of claim ~~40~~, wherein the VL domain of the antigen binding site for the radiolabelled compound comprises ~~(d) CDR L1 comprising the amino acid sequence of QSSHVSVDNDLA (SEQ ID NO:4); (e) CDR L2 comprising the amino acid sequence of~~

~~QASKLAS (SEQ ID NO:5); and (f) CDR L3 comprising the amino acid sequence of LGGYDDESDTYG (SEQ ID NO:6).~~

~~42. The set of antibodies of any one of claims 32 to 41, wherein the VL domain of the antigen binding site for the radiolabelled compound comprises an amino acid sequence of SEQ ID NO: 8, 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.~~

1843. The set of antibodies of any one of the preceding claims, wherein the first and second antibody bind to the same epitope of the antigen expressed on the surface of a target cell.

1944. The set of antibodies of any one of claims 1 to 1742, wherein the first antibody binds to a different epitope of the antigen from the second antibody.

2045. The set of antibodies of any one of the preceding claims, wherein the antigen expressed on the surface of a target cell is a tumour-associated antigen.

2146. The set of antibodies of any one of the preceding claims, wherein the antigen expressed on the surface of a target cell is selected from the group consisting of carcinoembryonic antigen (CEA), CD20, HER2, EGP-1 (epithelial glycoprotein-1, also known as trophoblast-2), colon-specific antigen-p (CSAp), a pancreatic mucin MUC1, GPRC5D and FAP.

~~47. The set of antibodies of any one of the preceding claims, wherein the antigen expressed on the surface of a target cell is selected from the group consisting of CEA, GPRC5D and FAP.~~

~~48. The set of antibodies according to claim 47, wherein:~~

~~i) the first antibody comprises a first heavy chain of SEQ ID NO: 104, a second heavy chain of SEQ ID NO: 106, wherein the C terminal alanine of SEQ ID NO: 106 is optional and may be absent or replaced by an alternative C terminal extension, and a light chain of SEQ ID NO: 107; and~~

~~ii) the second antibody comprises a first heavy chain of SEQ ID NO: 104, a second heavy chain of SEQ ID NO: 105 and a light chain of SEQ ID NO: 107.~~

~~49. The set of antibodies according to claim 47, wherein~~

~~i) the first antibody comprises a first heavy chain of SEQ ID NO: 108, a second heavy chain of SEQ ID NO: 110, wherein the C terminal alanine of SEQ ID NO: 110 is optional and may be absent or replaced by an alternative C terminal extension, and a light chain of SEQ ID NO: 111; and~~

~~ii) the second antibody comprises a first heavy chain of SEQ ID NO: 108, a second heavy chain of SEQ ID NO: 109 and a light chain of SEQ ID NO: 111.~~

~~2250. The set of antibodies of any one of the preceding claims-claims 1 to 47, wherein the antigen expressed on the surface of a target cell is CEA.~~

~~2351. The set of antibodies according to claim 2250, wherein the first and/or second antibody comprises an antigen-binding site which binds to CEA, comprising:~~

~~a) a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:19; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:21; and~~

~~a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:24; or~~

~~52. The set of antibodies according to any one of claims 50-51, wherein the first antibody comprises an antigen-binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 25, 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:25.~~

~~53. The set of antibodies according to any one of claims 50-52, wherein the first antibody comprises an antigen-binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 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:26. b)~~

~~54. The set of antibodies according to claim 50, wherein the first antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:43; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:44; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:45; and~~

~~a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:46; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:47; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:48; or;~~

~~55. The set of antibodies according to claim 50 or 54, wherein the first antibody comprises an antigen binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 49, 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:49.~~

~~56. The set of antibodies according to any one of claims 50, 54 or 55, wherein the first antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 50, 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:50.~~

~~c) 57. The set of antibodies according to claim 50, wherein the first antibody comprises an antigen binding site which binds to CEA, comprising~~

~~a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:11; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:12; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:13; and~~

~~a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:14; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:15; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:16; or;~~

~~58. The set of antibodies according to claim 50 or 57, wherein the first antibody comprises an antigen binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting 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.~~

~~59. The set of antibodies according to claim 50, 57 or 58, wherein the first antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting 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.~~

~~_____ d)~~

~~60. The set of antibodies according to claim 50, wherein the first antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:59; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:60; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:61; and a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:62; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:63; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:64; or~~

~~61. The set of antibodies according to claim 50 or claim 60, wherein the first antibody comprises an antigen binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 65, 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:65.~~

~~62. The set of antibodies according to claim 50, 60 or 61, wherein the first antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 66, 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:66.~~

~~_____ e)~~

~~63. The set of antibodies according to claim 50, wherein the first antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:156; (b) CDR-~~

H2 comprising the amino acid sequence of SEQ ID NO:157 or 158; (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:159; and

a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:160, 161 or 162; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:163, 164 or 165; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:166.

24. The set of antibodies according to claim 22, wherein the first and/or second antibody comprises an antigen-binding site for CEA comprising

a) a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 25, 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:25; and

a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 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:26; or

b)

a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 49, 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:49; and

a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 50, 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:50; or

c) a VH sequence comprising an amino acid sequence selected from the group consisting 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

a VL sequence comprising an amino acid sequence selected from the group consisting 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; or

d)

~~64. The set of antibodies according to claim 50 or 63, wherein the first antibody comprises an antigen-binding site which binds to CEA, comprising a heavy chain variable~~

region (VH) comprising an amino acid sequence selected from SEQ ID NO: 169, 170, 171, 172, 173 or 174, or a sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity thereto; and

a light chain variable region (VL) comprising an amino acid sequence selected from SEQ ID NO: 175, 176, 177, 178, 179 or 180, or a sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity thereto; or -

e) a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 65, 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:65; and

a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 66, 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:66.

~~2565.~~ The set of antibodies according to claim ~~2250, 63 or 64,~~ wherein the first and/or second antibody comprises an antigen-binding site which binds to CEA, comprising:

(a) a VH domain comprising an amino acid sequence of SEQ ID NO:169 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or

(b) a VH domain comprising an amino acid sequence of SEQ ID NO:173 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or

(c) a VH domain comprising an amino acid sequence of SEQ ID NO:170 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or

(d) a VH domain comprising an amino acid sequence of SEQ ID NO:174 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or

(e) a VH domain comprising an amino acid sequence of SEQ ID NO:173 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or

(f) a VH domain comprising an amino acid sequence of SEQ ID NO:171 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or

(g) a VH domain comprising an amino acid sequence of SEQ ID NO:169 and a VL domain comprising an amino acid sequence of SEQ ID NO:178.

~~66.—The set of antibodies according to any one of claims 50 to 65, wherein the second antibody comprises an antigen-binding site which binds to CEA, comprising~~

a heavy chain variable region comprising (a) CDR H1 comprising the amino acid sequence of SEQ ID NO:19; (b) CDR H2 comprising the amino acid sequence of SEQ ID NO:20; and (c) CDR H3 comprising the amino acid sequence of SEQ ID NO:21; and

a light chain variable region comprising (d) CDR L1 comprising the amino acid sequence of SEQ ID NO:22; (e) CDR L2 comprising the amino acid sequence of SEQ ID NO:23; and (f) CDR L3 comprising the amino acid sequence of SEQ ID NO:24.

67.—The set of antibodies according to any one of claims 50-66, wherein the second antibody comprises an antigen-binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 25, 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:25.

68.—The set of antibodies according to any one of claims 50-67, wherein the second antibody comprises an antigen-binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 26, 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:26.

69.—The set of antibodies according to any one of claim 50 to 65, wherein the second antibody comprises an antigen-binding site which binds to CEA, comprising a heavy chain variable region comprising (a)CDR H1 comprising the amino acid sequence of SEQ ID NO:43; (b) CDR H2 comprising the amino acid sequence of SEQ ID NO:44; and (c) CDR H3 comprising the amino acid sequence of SEQ ID NO:45; and a light chain variable region comprising (d) CDR L1 comprising the amino acid sequence of SEQ ID NO:46; (e) CDR L2 comprising the amino acid sequence of SEQ ID NO:47; and (f) CDR L3 comprising the amino acid sequence of SEQ ID NO:48.

70.—The set of antibodies according to any one of claims 50 to 65 or 69, wherein the second antibody comprises an antigen-binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 49, 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:49.

71.—The set of antibodies according to any one of claims 50 to 65, 69 or 70, wherein the second antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 50, 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:50.

72.—The set of antibodies according to any one of claims 50 to 65, wherein the second antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR H1 comprising the amino acid sequence of SEQ ID NO:11; (b) CDR H2 comprising the amino acid sequence of SEQ ID NO:12; and (c) CDR H3 comprising the amino acid sequence of SEQ ID NO:13; and a light chain variable region comprising (d) CDR L1 comprising the amino acid sequence of SEQ ID NO:14; (e) CDR L2 comprising the amino acid sequence of SEQ ID NO:15; and (f) CDR L3 comprising the amino acid sequence of SEQ ID NO:16.

73.—The set of antibodies according to any one of claims 50 to 65 or 72, wherein the second antibody comprises an antigen binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting 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.

74.—The set of antibodies according to any one of claims 50 to 65, 72 or 73, wherein the second antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting 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.

75.—The set of antibodies according to any one of claim 50 to 65, wherein the second antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR H1 comprising the amino acid sequence of SEQ ID NO:59; (b) CDR H2 comprising the amino acid sequence of SEQ ID NO:60; and (c) CDR H3 comprising the amino acid sequence of SEQ ID NO:61; and

a light chain variable region comprising (d) CDR L1 comprising the amino acid sequence of SEQ ID NO:62; (e) CDR L2 comprising the amino acid sequence of SEQ ID NO:63; and (f) CDR L3 comprising the amino acid sequence of SEQ ID NO:64.

76. — The set of antibodies according to any one of claims 50 to 65 or 75, wherein the second antibody comprises an antigen binding site for CEA comprising a VH sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 65, 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:65.

77. — The set of antibodies according to claim 50 to 65, 75 or 76, wherein the second antibody comprises an antigen binding site for CEA comprising a VL sequence comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 66, 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:66.

78. — The set of antibodies according to claim 50 to 65, wherein the second antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region comprising (a) CDR H1 comprising the amino acid sequence of SEQ ID NO:156; (b) CDR H2 comprising the amino acid sequence of SEQ ID NO:157 or 158; (c) CDR H3 comprising the amino acid sequence of SEQ ID NO:159; and a light chain variable region comprising (d) CDR L1 comprising the amino acid sequence of SEQ ID NO:160, 161 or 162; (e) CDR L2 comprising the amino acid sequence of SEQ ID NO:163, 164 or 165; and (f) CDR L3 comprising the amino acid sequence of SEQ ID NO:166.

79. — The set of antibodies according to claim 50 to 65 or 78, wherein the second antibody comprises an antigen binding site which binds to CEA, comprising a heavy chain variable region (VH) comprising an amino acid sequence selected from SEQ ID NO: 169, 170, 171, 172, 173 or 174, or a sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity thereto; and a light chain variable region (VL) comprising an amino acid sequence selected from SEQ ID NO: 175, 176, 177, 178, 179 or 180, or a sequence with 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity thereto.

80. ~~The set of antibodies according to claim 50 to 65, 78 or 79, wherein the second antibody comprises an antigen-binding site which binds to CEA, comprising:~~

- ~~(a) a VH domain comprising an amino acid sequence of SEQ ID NO:169 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or~~
- ~~(b) a VH domain comprising an amino acid sequence of SEQ ID NO:173 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or~~
- ~~(c) a VH domain comprising an amino acid sequence of SEQ ID NO:170 and a VL domain comprising an amino acid sequence of SEQ ID NO:179, or~~
- ~~(d) a VH domain comprising an amino acid sequence of SEQ ID NO:174 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or~~
- ~~(e) a VH domain comprising an amino acid sequence of SEQ ID NO:173 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or~~
- ~~(f) a VH domain comprising an amino acid sequence of SEQ ID NO:171 and a VL domain comprising an amino acid sequence of SEQ ID NO:178, or~~
- ~~(g) a VH domain comprising an amino acid sequence of SEQ ID NO:169 and a VL domain comprising an amino acid sequence of SEQ ID NO:178.~~

2681. The set of antibodies according to claim 2250, wherein:

the first antibody is an antibody comprises an antigen-binding site which binds to CEA, comprising

a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:11; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:12; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:13; and

a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:14; (e) CDR-L2 comprising the amino acid sequence of SEQ ID NO:15; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:16;

according to any one of claims 57 to 59 and the second antibody comprises an antigen-binding site which binds to CEA, comprising

a heavy chain variable region comprising (a) CDR-H1 comprising the amino acid sequence of SEQ ID NO:19; (b) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20; and (c) CDR-H3 comprising the amino acid sequence of SEQ ID NO:21; and

a light chain variable region comprising (d) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22; (e) CDR-L2 comprising the amino acid sequence of SEQ ID

NO:23; and (f) CDR-L3 comprising the amino acid sequence of SEQ ID NO:24 ~~is an antibody according to any one of claims 66 to 68.~~

~~2782.~~ The set of antibodies according claim 1, wherein the first antibody is selected from the group consisting of:

a) ~~a~~the first antibody comprises a first heavy chain of SEQ ID NO: 28, a second heavy chain of SEQ ID NO: 32 and a light chain of SEQ ID NO: 34, optionally:-

~~83. — The set of antibodies according to claim 82, wherein one or more alanine residues is added to the C-terminus of SEQ ID NO: 32, or wherein the sequence AST is added to the C-terminus of SEQ ID NO: 32;~~

b) ~~84. The set of antibodies according to claim 1, wherein the a first antibody comprises~~ a first heavy chain of SEQ ID NO: 51, and second heavy chain of SEQ ID NO: 52 and a light chain of SEQ ID NO: 54, optionally:-

~~85. — The set of antibodies according to claim 84, wherein one or more alanine residues is added to the C-terminus of SEQ ID NO:52 or wherein the sequence AST is added to the C-terminus of SEQ ID NO: 32;~~

c) ~~86. The set of antibodies according to claim 1, wherein the a first antibody comprises~~ a first heavy chain of SEQ ID NO: 86, a second heavy chain of SEQ ID NO: 87 wherein the C-terminal AST residues are optional and may be absent or replaced by a different C-terminal extension, and a light chain of SEQ ID NO: 89; and:-

~~87. — The set of antibodies according to claim 1, wherein d) a~~the first antibody comprises a first heavy chain of SEQ ID NO: 93, a second heavy chain of SEQ ID NO: 94 wherein the C-terminal AST residues are optional and may be absent or replaced by a different C-terminal extension, and a light chain of SEQ ID NO: 96;

and/or the second antibody is selected from the group consisting of:-

~~88. The set of antibodies according to claim 1, or 82-87 wherein e) a~~ second antibody comprising a first heavy chain of SEQ ID NO: 30, a second heavy chain of SEQ ID NO: 33 and a light chain of SEQ ID NO: 34; ~~;~~

~~89. — The set of antibodies according to claim 1, or 82-87, wherein f) the~~ a second antibody comprising a first heavy chain of SEQ ID NO: 55, and second heavy chain of SEQ ID NO: 56 and a light chain of SEQ ID NO: 58; ~~;~~

~~90. — The set of antibodies according to claim 1 or 82-87, wherein the g) a~~ second antibody comprising a first heavy chain of SEQ ID NO: 83, and second heavy chain of SEQ ID NO: 84 and a light chain of SEQ ID NO: 89; ~~and;~~

~~91. — The set of antibodies according to claim 1 or 82-87, wherein the h) a~~ second antibody comprising a first heavy chain of SEQ ID NO: 90, and second heavy chain of SEQ ID NO: 91 and a light chain of SEQ ID NO: 96.

~~2892.~~ A set of nucleic acids expressing the set of antibodies of any one of the preceding claims.

~~2993.~~ An expression vector or set of expression vectors comprising the set of nucleic acids according to claim ~~2892~~.

~~3094.~~ A host cell or set of host cells comprising the expression vector or set of expression vectors of claim ~~2993~~.

~~3195.~~ Use of the set of antibodies according to any one of claims 1 to 27 in the manufacture of a medicament for use in a method of pretargeting radioimmunotherapy of a tumour or cancer~~A method of pretargeting radioimmunotherapy, comprising~~

i) ~~administering to a subject that~~ the set of antibodies according to any one of claims 1 to ~~2794~~ is to be administered, wherein the first and second antibodies are to be administered simultaneously or sequentially, in either order, wherein the antibodies bind to the target antigen and localise to the surface of a cell expressing the target antigen; and wherein association of the first and second antibody forms a functional binding site for the radiolabelled compound;

and

ii) subsequently ~~administering that~~ a radiolabelled compound is to be administered, wherein the radiolabelled compound binds to functional binding site for the radiolabelled compound.

~~96. The method of claim 95, wherein the method does not comprise a step of administering a clearing or blocking agent.~~

~~3297. The use method of claim 3195 or 96, wherein the subject is human.~~

~~3398. The use method of any one of claims 3195 or claim to 3297, wherein the target antigen is a cancer- or tumour-associated antigen and the method is a method of radioimmunotherapy of a tumour or cancer.~~

~~99. The set of antibodies according to any one of claims 1 to 91, for use in a method of pretargeting radioimmunotherapy according to any one of claims 95 to 98.~~

~~34100. Use of a set of antibodies according to any one of claims 1 to 27 in the manufacture of an imaging agent for use in a~~ method of targeting a radioisotope to a tissue or organ for radioimaging comprising:

i) ~~administering to a subject a set of antibodies according to any one of claims 1 to 27~~ ~~91, wherein that~~ the first and second antibodies are to be administered simultaneously or sequentially, in either order, wherein the antibodies bind to a target antigen and localise to the surface of a cell expressing the target antigen, wherein association of the first and second antibody forms a functional binding site for the radiolabelled compound;

and

ii) subsequently ~~administering that~~ a radiolabelled compound is to be administered, wherein the radiolabelled compound binds to the functional binding site for the radiolabelled compound.

~~101. The method of claim 100, wherein the method does not comprise a step of administering a clearing or blocking agent.~~

35102. The ~~method-use~~ of claim ~~34100 or 101~~, wherein the ~~method-use~~ further comprises a step of imaging.

36103. The ~~method-use~~ of claim ~~34~~ or claim ~~35102~~, wherein the target antigen is a cancer or tumour-associated antigen and the method is a method of imaging tumours or cancer.

37. The use of any one of claims 31 to 36, wherein the use does not comprise that a clearing or blocking agent is to be administered.