

Methods of treating cancers expressing PDGFRalpha

Field of the invention

[0001] The invention relates to proteins and compositions for the treatment of cancers that express platelet derived growth factor receptor alpha (PDGFRalpha), and methods of use thereof.

Background of the invention

[0002] Soft tissue sarcoma (STS) originates in soft or connective tissue like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. STS is a heterogeneous disease for which there are relatively few effective regimens.

[0003] Accordingly there is a need for new and improved methods and reagents for the treatment of STS and related cancers.

[0004] Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person in the art.

Summary of the invention

[0005] The present invention relates to reagents and methods for treating cancers which express platelet derived growth factor receptor alpha (PDGFRalpha).

[0006] In a first aspect, the present invention provides an olaratumab antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof is conjugated to a radioisotope, for:

- treating or preventing or minimising the progression of a cancer characterised by or associated with the expression of PDGFRalpha.

[0007] It will be understood that an olaratumab antibody or antigen binding fragment thereof, wherein the antibody or antigen binding fragment thereof is conjugated to a radioisotope, may also be referred to as a radiolabelled olaratumab antibody or antigen binding fragment thereof.

[0008] In a second aspect, the present invention provides an olaratumab antibody or olaratumab antibody bioconjugate, suitable for radiolabelling with a therapeutic radioisotope.

[0009] Preferably the olaratumab bioconjugate comprises an olaratumab antibody conjugated to any chelating or linker group suitable for further conjugation to a radioisotope. Optionally the olaratumab bioconjugate is selected from: olaratumab-TMT (6,6"-bis[N,N",N"'-tetra(carboxymethyl)aminomethyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2"-terpyridine), olaratumab-DOTA (1,4,7,10-tetraazacyclododecane-NN',N"(N"'-tetraacetic acid), olaratumab-TCMC, olaratumab-DO3A, olaratumab-CB-DO2A, olaratumab-NOTA, olaratumab-Diamsar, olaratumab-DTPA, olaratumab-CHX-A"-DTPA, olaratumab-TETE, olaratumab-Te2A, olaratumab-HBED, olaratumab-DFO, olaratumab-DFOsq, olaratumab-DFO-NCS and olaratumab-HOPO or an olaratumab chelated to a chelator as disclosed in WO 2022/133537 or to any other chelator as described herein or known to the skilled person.

[0010] In any aspect, the olaratumab antibody or antigen binding fragment thereof preferably comprises an antigen binding domain that competitively inhibits the binding of an antibody comprising a VH comprising a sequence as set forth in SEQ ID NO: 4 and a VL comprising a sequence as set forth in SEQ ID NO: 12.

[0011] In any aspect or embodiment herein, the olaratumab antibody or antigen binding fragment thereof comprises an HCDR1, a HCDR2 and an HCDR3 of an antigen binding domain having a variable heavy chain as defined in in SEQ ID NO: 4 and a LCDR1, LCDR2 and LCDR3 of an antigen binding domain having a VL as defined in SEQ ID NO: 12.

[0012] As used herein, the complementarity determining region sequences (CDRs) of an antigen binding protein of the invention may be defined according to the IMGT, Chothia or Kabat numbering systems, or any other CDR numbering system known to the skilled person.

[0013] In any aspect or embodiment of the invention, the olaratumab antibody or antigen binding fragment thereof comprises an antigen binding domain comprising:

- (i) a VH comprising a complementarity determining region (CDR) 1 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at

least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set in SEQ ID NO: 2, and a CDR3 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 3;

(ii) a VH comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 4;

(iii) a VL comprising a CDR1 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 11;

(iv) a VL comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%,

at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 12;

(v) a VH comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence set forth in SEQ ID NO: 2 and a CDR3 comprising a sequence set forth in SEQ ID NO: 3;

(vi) a VH comprising a sequence set forth in SEQ ID NO: 4;

(vii) a VL comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence set forth in SEQ ID NO: 11;

(viii) a VL comprising a sequence set forth in SEQ ID NO: 12;

(ix) a VH comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence set forth between in SEQ ID NO: 2, and a CDR3 comprising a sequence set forth in SEQ ID NO: 3; and a VL comprising a CDR1 comprising a sequence set SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10, and a CDR3 comprising a sequence set forth in SEQ ID NO: 11; or

(x) a VH comprising a sequence set forth in SEQ ID NO: 4, and a VL comprising a sequence set forth in SEQ ID NO: 12.

[0014] The olaratumab antibody or antigen binding fragment thereof may further comprise:

(i) a VH comprising a framework region (FR) 1 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 5; a FR2 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 6; a FR3 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least

87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 7; a FR4 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 8; and

(ii) a VL comprising a framework region (FR) 1 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 13; a FR2 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 14; a FR3 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 15; a FR4 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 16.

[0015] In a further embodiment, the olaratumab antibody or antigen binding fragment thereof comprises:

(i) a VH comprising a framework region (FR) 1 comprising or consisting of a sequence as set forth in SEQ ID NO: 5; a FR2 comprising or consisting of a sequence as set forth in SEQ ID NO: 6; a FR3 comprising or consisting of a sequence as set forth in SEQ ID NO: 7; a FR4 comprising or consisting of a sequence as set forth in SEQ ID NO: 8, and

(ii) a VL comprising a framework region (FR) 1 comprising or consisting of a sequence as set forth in SEQ ID NO: 13; a FR2 comprising or consisting of a sequence as set forth in SEQ ID NO: 14; a FR3 comprising or consisting of a sequence as set forth in SEQ ID NO: 15; a FR4 comprising or consisting of a sequence as set forth in SEQ ID NO: 16.

[0016] In any embodiment, the olaratumab antibody or antigen binding fragment thereof comprises a VH comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 4; and/or a VL comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 12; wherein the sequence variation between the VH and VL and the sequence of SEQ ID NO: 4 and 12 is not in the CDRs and wherein the antigen binding protein retains the ability to bind to PDGFRalpha.

[0017] In any embodiment, the olaratumab antibody or antigen binding fragment thereof comprises a VH and/or a VL comprising no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, no more than 6, no more than 7, no more than 8, no more than 9, no more than 10, no more than 11, no more than 12, no more than 13, no more than 14, no more than 15, no more than 16, no more than 17, no more than 18, no more than 19 or no more than 20 amino acid residue substitutions, deletions or additions, compared to the amino acid sequences as set forth in SEQ ID NO: 4 or 12, respectively; wherein the amino acid substitutions, deletions or additions are not in the CDRs and the antigen binding protein retains the ability to bind to PDGFRalpha.

[0018] As used herein, the terms HCDR1, HCDR2 and HCDR3 will be understood to refer to the CDRs of the variable heavy chain; the terms LCDR1, LCDR2, and LCDR3, will be understood to refer to the CDRs of the variable light chain; and the terms HFR1, HFR2, HFR3, HFR4, LFR1, LFR2, LFR3 and LFR4 will be understood to refer to the framework regions of the heavy, and light chains respectively.

[0019] As described herein, the olaratumab antibody or antigen binding fragment thereof may be in the form of:

- (i) a single domain antibody (sdAb);
- (ii) a single chain Fv fragment (scFv);
- (iii) a dimeric scFv (di-scFv); or
- (iv) one of (ii) or (iii) linked to a constant region of an antibody, Fc or a heavy chain constant domain (CH) 2 and/or CH3.

[0020] Further, as described herein, the olaratumab or antigen binding fragment thereof may be in the form of:

- (i) a diabody;
- (ii) a triabody;
- (iii) a tetrabody;
- (iv) a Fab;
- (v) a F(ab')₂;
- (vi) a Fv;
- (vii) a bispecific antibody or other form of multispecific antibody; or
- (viii) one of (i) to (vii) linked to a constant region of an antibody, Fc or a heavy chain constant domain (CH) 2 and/or CH3.

[0021] Optionally, the variable heavy and variable light regions of the antigen binding domain are joined via a linker.

[0022] In any embodiment, the antigen binding domain may comprise:

FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4 – linker - FR1a - CDR1a – FR2a – CDR2a – FR3a – CDR3a – FR4a.

[0023] As defined herein, the linker may be a chemical, one or more amino acids, or a disulphide bond formed between two cysteine residues.

[0024] In any aspect or embodiment of the present invention, the olaratumab or antigen binding fragment thereof may comprise a human constant region, e.g., an IgG constant region, such as an IgG₁, IgG₂, IgG₃ or IgG₄ constant region or mixtures thereof. In the case of an antibody or protein comprising a V_H and a V_L, the V_H can be linked to a heavy chain constant region and the V_L can be linked to a light chain constant region.

[0025] In one example, the olaratumab or antigen binding fragment thereof comprises a constant region of an IgG₄ antibody or a stabilised constant region of an IgG₄ antibody. In one example, the olaratumab or antigen binding fragment thereof comprises an IgG₄ constant region with a proline at position 241 (according to the numbering system of Kabat (Kabat et al., Sequences of Proteins of Immunological Interest Washington DC United States Department of Health and Human Services, 1987 and/or 1991)).

[0026] In one example, the olaratumab or antigen binding fragment thereof comprises a heavy chain constant region, comprising a stabilised heavy chain constant region, comprising a mixture of sequences fully or partially with or without the C-terminal lysine residue.

[0027] In further embodiments of any aspect herein, the olaratumab or antigen binding fragment thereof comprises an Fc region wherein the Fc region is engineered to have enhanced capacity to induce antibody-dependent cell-mediated cytotoxicity (ADCC). Preferably, the enhanced capacity to induce ADCC is conferred by mutation, deletion or modification of amino acids in the Fc region which interact with an Fc receptor

[0028] In another embodiment, the olaratumab or antigen binding fragment thereof comprises an Fc region that is engineered to:

- have increased *in vitro* or *in vivo* half-life;
- have an increased capacity to induce antibody-dependent cell mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) or complement-dependent cytotoxicity; and/or
- have reduced effector function.

[0029] Preferably, the olaratumab antibody is in the form of an antibody (ie comprising a variable light and variable heavy chain, linked to a constant region of an antibody including a heavy chain CH2 and/or CH3).

[0030] In further embodiments, the olaratumab may comprise a heavy chain constant region as defined in SEQ ID NO: 17 and/or a light chain constant region as defined in SEQ ID NO: 18.

[0031] In certain embodiments, the olaratumab may comprise a heavy chain as set forth in SEQ ID NO: 19 and/or a light chain as set forth in SEQ ID NO: 20.

[0032] In still further embodiments, the olaratumab is in the form of an antibody and may comprise one or more amino acid substitutions in the constant regions, so as to reduce the *in vivo* half-life of the antibody. The present invention therefore provides for an olaratumab antibody having substitutions in the CH2 and/or CH3 domains of the constant region and comprising substitutions at one or more of residues His310, His435, His436 and Ile253 (Kabat numbering), thereby altering FcRn binding affinity and/or serum half-life of said antibody (eg relative to an olaratumab that comprises a native CH2 and CH3 domain).

[0033] In some examples, the amino acid at position 310 and/or 435 of the antibody may be alanine, glutamic acid, aspartic acid, leucine, isoleucine, arginine, proline, glutamine, methionine, serine, threonine, lysine, asparagine, phenylalanine, tyrosine, tryptophan, cysteine, valine or glycine.

[0034] Preferably, the residue at position 310 is selected from alanine, or glutamic acid or glutamine; or amino acid residue 435 from the heavy chain constant region is selected from arginine, glutamine or alanine. In other preferred embodiments, the antibody has an alanine residue at position 310 and glutamine residue at position 435.

[0035] In a further embodiment, the antibody also comprises an amino acid substitution at residue Lys322. Preferably the substitution is K322A.

[0036] In particularly preferred embodiments, the olaratumab antibody comprises substitutions K322A, H310A and H435Q.

[0037] In a preferred embodiment, the binding affinity for FcRn and/or the serum half-life of the modified antibody is decreased by at least about 2-fold, 3-fold, 4-fold, 5-fold, 10-

fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, or 100-fold. In a preferred embodiment of the present invention, the binding affinity for FcRn and/or the serum half-life of said modified antibody is reduced by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 98%, or 99%.

[0038] In any aspect or embodiment, the antibody may also comprise amino acid substitutions at residues equivalent to Ser228 and Leu235 of the constant heavy chain region, such as Ser228Pro and/or Leu235Glu.

[0039] In accordance with the first aspect and according to any embodiment thereof, the radiolabelled olaratumab is conjugated to any radioisotope suitable for treatment of tumour or cancer masses. Examples of suitable radioisotopes include: actinium-225 (^{225}Ac), astatine-211 (^{211}At), bismuth-212 and bismuth-213 (^{212}Bi , ^{213}Bi), copper-64 and copper-67 (^{64}Cu , ^{67}Cu), iodine -123, -124, -125 or -131 (^{123}I , ^{124}I , ^{125}I , ^{131}I) (^{123}I), lead-212 (^{212}Pb), lutetium-177 (^{177}Lu), radium-223 and radium-224 (^{223}Ra , ^{224}Ra), rhenium-186 and rhenium-188 (^{186}Re and ^{188}Re), samarium-153 (^{153}Sm), scandium-47 (^{47}Sc), strontium-90 (^{90}Sr), terbium-149 and terbium-161 (^{149}Tb and ^{161}Tb) and yttrium-90 (^{90}Y). In preferred embodiments, the radionuclide conjugated with the antibody or fragment thereof is actinium-225 or lutetium-177.

[0040] In any embodiment, the radiolabelled olaratumab antibody or antigen binding fragment thereof is ^{89}Zr -, ^{225}Ac - or ^{177}Lu -olaratumab wherein the radioisotope is conjugated to the olaratumab antibody directly or indirectly.

[0041] In any aspect or embodiment, the radioisotope may be conjugated to the olaratumab directly e.g. by halogenation of amino acid residues. Preferably, the radioisotope of the radiolabelled olaratumab is linked indirectly to the olaratumab or antigen binding fragment thereof, for example via a chelator or other linking moiety. In one example, the olaratumab is conjugated to a chelating moiety, selected from the group consisting of: TMT (6,6"-bis[N,N",N""-tetra(carboxymethyl)aminomethyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2"-terpyridine), DOTA (1, 4,7,10-tetraazacyclododecane-NN',N"(N""-tetraacetic acid), TCMC, DO3A, CB-DO2A, NOTA, Diamsar, DTPA, CHX-A"-DTPA, TETE, Te2A, HBED, DFO, DFOsq, DFO-NCS and HOPO, a chelator as described in WO 2022/133537 (incorporated herein by reference) or other chelating agent as described herein or known to the skilled person.

[0042] In another example, the radiolabelled olaratumab or antigen binding fragment thereof or olaratumab antibody bioconjugate is conjugated to a bifunctional linker, for example, bromoacetyl, thiols, succinimide ester, TFP ester, a maleimide, or using any amine or thiol- modifying chemistry known in the art.

[0043] Preferably the radiolabelled olaratumab antibody or antigen binding fragment thereof is ^{177}Lu -olaratumab or a ^{177}Lu -labelled olaratumab, wherein the ^{177}Lu is conjugated to the olaratumab via a linker, such as ^{177}Lu -DOTA-olaratumab.

[0044] In a further aspect there is provided a method for obtaining a radiolabelled olaratumab of the first aspect of the invention, wherein the method comprises radiolabelling an olaratumab bioconjugate or antibody of the second aspect.

[0045] In a further aspect, there is provided a pharmaceutical composition comprising an olaratumab antibody, or antigen binding fragment thereof, an olaratumab bioconjugate or a radiolabelled olaratumab as herein described, optionally in combination with a pharmaceutically acceptable excipient.

[0046] Further still there is provided a nucleic acid or nucleic acid construct encoding an olaratumab antibody, or antigen binding fragment thereof, or an olaratumab bioconjugate as described herein.

[0047] There is also provided a host or host cell comprising a nucleic acid or nucleic acid construct of the invention.

[0048] In a fourth aspect, the present invention provides a method of treating, preventing or minimising progression of cancer in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof as described herein,

thereby treating, preventing or minimising progression of cancer in the subject.

[0049] In a further aspect, the present invention provides a method of minimising, reducing or preventing growth of a tumour in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof as described herein,

thereby minimising, reducing or preventing growth of a tumour in the subject.

[0050] In a further aspect, the present invention provides a method of minimising, reducing or preventing metastasis of cancer in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof as described herein,

thereby minimising, reducing or preventing metastasis of cancer in the subject.

[0051] In a further aspect, the present invention provides a method of increasing survival of a subject suffering from cancer, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof as described herein,

thereby increasing survival of the subject.

[0052] In another aspect, the present invention further provides use of a radiolabelled olaratumab or antigen binding fragment thereof as described herein in the manufacture of a medicament for:

- treating, preventing or minimising progression of cancer in a subject,
- minimising, reducing or preventing growth of a tumour in a subject,
- minimising, reducing or preventing metastasis in a subject, or
- increasing survival of a subject suffering from cancer.

[0053] In another aspect, the present invention further provides use of radiolabelled olaratumab or antigen binding fragment thereof as described herein for:

- treating, preventing or minimising progression of cancer in a subject,
- minimising, reducing or preventing growth of a tumor in a subject,
- minimising, reducing or preventing metastasis in a subject, or
- increasing survival of a subject.

[0054] In another aspect, the present invention further provides radiolabelled olaratumab or antigen binding fragment thereof as described herein for use in:

- treating, preventing or minimising progression of cancer in a subject,
- minimising, reducing or preventing growth of a tumor in a subject,
- minimising, reducing or preventing metastasis in a subject, or
- increasing survival of a subject.

[0055] In any aspect or embodiment of the invention, it will be understood that the amount of radiolabelled olaratumab or antigen binding fragment thereof administered to a subject, is a therapeutically effective amount of radiolabelled olaratumab or antigen binding fragment thereof.

[0056] In any aspect of the invention, any medicament or pharmaceutical composition described herein may be suitable for administration intraperitoneally, intratumorally, topically, orally, intravenously, to the respiratory tract, preferably by inhalation or intranasally, subcutaneously or intramuscularly. Typically, any medicament or pharmaceutical composition described herein is suitable for administration intravenously.

[0057] In any method or use described herein, the radiolabelled olaratumab or antigen binding fragment thereof may be administered as the sole treatment for a cancer or may be administered in combination with one or more additional treatments. The radiolabelled olaratumab or antigen binding fragment thereof may be administered subsequent to a previous treatment for cancer (optionally wherein the previous treatment comprises surgery, chemotherapy, immunotherapy, external beam radiation, autologous stem cell therapy, or combinations thereof). The radiolabelled olaratumab or antigen binding fragment thereof may be administered concomitantly with or sequentially with an additional treatment for cancer (optionally wherein the additional treatment comprises surgery, chemotherapy, immunotherapy, external beam radiation, autologous stem cell therapy, or combinations thereof).

[0058] It will be understood that preferably in accordance with the above mentioned aspects and embodiment, that the cancer is preferably one that expresses or overexpresses PDGFR- α .

[0059] The cancer may be selected from the list consisting of: soft tissue sarcoma (STS), chondrosarcoma, leiomyosarcoma, liposarcoma, osteosarcoma, and rhabdomyosarcoma. The methods of the invention may enable the treatment, prevention, minimisation of progression of a cancer characterised by the expression of PDGFRalpha in the tumour cells and/or the tumour stroma.

[0060] In any embodiment, the cancer may be pre-cancerous or non-metastatic. In any embodiment, the cancer may be malignant or metastatic.

[0061] In any embodiment, the methods further comprise identifying a subject in need of treatment as described herein. The method may comprise identifying that the subject has a cancer expressing or overexpressing PDGFR-alpha.

[0062] As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

[0063] Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

[0001] Figure 1: Schematic representation of DFOSq- and DOTA-bioconjugated Olaratumab.

[0002] Figure 2: Set-up of Biacore surface plasmon resonance assay

[0003] Figure 3: Total and surface PDGFRA expression in KRIB, HuO9 and A-204 sarcoma cell lines. A. Total PDGFRA expression was established with western blot. Surface expression of PDGFRA on unfixed cells was determined by FACS.

[0004] Figure 4: Western blot showing olaratumab-mediated inhibition of PDGFRA activation pathway.

[0005] Figure 5: A) Binding of ⁸⁹Zr-DFOSq-Olaratumab to A204 and HCC827 cells at 1 hr; B) Binding of ⁸⁹Zr-DFOSq-Olaratumab and ¹⁷⁷Lu-DOTA-Olaratumab to A204 cells at 1 and 4 hrs.

[0006] Figure 6: Example of the PET images across at 24, 48 and 120 hrs.

SUVmax, tumour:background ratio, tumour:liver ratio and tumour:bone ratio was measured for each image.

[0007] Figure 7: Biodistribution of ⁸⁹Zr-DFOsq-Olaratumab at 24, 48 and 120 hrs as measured by radioactivity counts in blood and dissected lungs, heart, liver, kidneys, muscle, spleen, bone and tumour of A204-bearing nude mice.

[0008] Figure 8: Mean tumour volume following treatment with radiolabelled olaratumab. Mean tumour volumes $\pm$ SEM measured in treatment group (¹⁷⁷Lu-Olaratumab, 10 MBq) and control group (cold-DOTA-Olaratumab) of A204-xenograft tumours bearing Balb/c Nude mice until the first mouse from each group reached tumour endpoint.

[0009] Figure 9: Individual tumour volumes are shown from the first day of treatment/vehicle (day 1) until the end of the experiment on day 90.

[0010] Figure 10: Survival measured in treatment group (¹⁷⁷Lu-Olaratumab, 10 MBq) and control group of A204-xenograft tumours bearing Balb/c Nude mice.

Sequence information

[0011] Table 1: Summary of amino acid sequences of PDGFRalpha-binding antibodies (olaratumab)

Region	SEQ ID NO:	Amino acid or nucleotide sequence
HCDR1 (protein)	1	SSSYY
HCDR2 (protein)	2	SFFYTGSTYYNPSLRS
HCDR3 (protein)	3	QSTYYYGSGNYYGWFD
VH (protein)	4	QLQLQESGPGLVKPSETLSLTCTVSGGSINSSSYYWGWLQSPG KGLEWIGSFFYTGSTYYNPSLRSRLTISVDTSKNQFSLMLSSVTAA DTAVYYCARQSTYYYGSGNYYGWFDWDQGTSLTVSS
HFR1 (protein)	5	QLQLQESGPGLVKPSETLSLTCTVSGGSIN
HFR2 (protein)	6	WGWLQSPGKGLEWIG
HFR3 (protein)	7	RLTISVDTSKNQFSLMLSSVTAAADTAVYYCAR
HFR4 (protein)	8	WDQGTSLTVSS
LCDR1 (protein)	9	RASQSVSSYLA
LCDR2 (protein)	10	DASNRAT
LCDR3 (protein)	11	QQRSNWPPA

Region	SEQ ID NO:	Amino acid or nucleotide sequence
VL (protein)	12	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPR LLIYDASNRATGIPARFSGSGSGTDFTLTSSLEPEDFAVYYCQQR SNWPPAFGQGTKVEIK
LFR1 (protein)	13	EIVLTQSPATLSLSPGERATLSC
LFR2 (protein)	14	WYQQKPGQAPRLLIY
LFR3 (protein)	15	GIPARFSGSGSGTDFTLTSSLEPEDFAVYYC
LFR1 (protein)	16	FGQGTKVEIK
Heavy chain constant region	17	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH EALHNHYTQKSLSLSPGK
Light chain constant region	18	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVT HQGLSSPVTKSFNRGEC
Olaratumab heavy chain	19	QLQLQESGPGLVKPSSETLSLTCTVSGGSINSSSYWGWLRSQPG KGLEWIGSFFYTGSTYYNPSLRSLTISVDTSKNQFSLMLSSVTAA DTAVYYCARQSTYYYGSGNYYGWDRWDQGTLLTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVH TFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH YTQKSLSLSPGK
Olaratumab light chain	20	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPR LLIYDASNRATGIPARFSGSGSGTDFTLTSSLEPEDFAVYYCQQR SNWPPAFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Detailed description of the embodiments

Platelet derived growth factor receptor alpha (PDGFRalpha)

[0012] Platelet derived growth factor receptor alpha (PDGFR α or PDGFRalpha) is a type III receptor tyrosine kinase. PDGFR α is critical for development and fulfills important functions into adulthood. For example, mice homozygous for a null mutation die during embryogenesis. At later stages of development, PDGFR α is expressed in many mesenchymal structures, whereas adjacent epithelial cells produce platelet derived growth factors (PDGFs).

[0013] The platelet-derived growth factor family of growth factors consists of five different disulphide-linked dimers, PDGF-AA, -BB, -AB, -CC, and -DD, that act via PDGFR α and PDGFR β . These growth factors are dimeric molecules composed of disulfide-linked polypeptide chains that bind to two receptor proteins simultaneously and induce receptor dimerization, autophosphorylation, and intracellular signaling. PDGFR α can form heterodimers with PDGFR β as well as homodimers. Because PDGFR β does not bind the PDGF-A chain with high affinity, PDGF-AA activates only $\alpha\alpha$ receptor dimers, whereas PDGF-AB and PDGF-CC activates $\alpha\alpha$ and $\alpha\beta$ receptor heterodimers.

[0014] PDGFR-alpha has also been detected on some tumour and stromal cells, including sarcomas, where signalling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumour microenvironment.

[0015] Olaratumab (LartruvoTM) is a fully human IgG1 monoclonal antibody which selectively binds human Platelet-derived growth factor (PDGF) receptor α (PDGFR α). The interaction between olaratumab and PDGFR- α prevents binding of the receptor by the PDGF-AA and -BB ligands as well as PDGF-AA, -BB, and -CC-induced receptor activation and downstream PDGFR- α pathway signalling. Olaratumab exhibits *in vitro* and *in vivo* anti-tumor activity against selected sarcoma cell lines and disrupted the PDGFR- α signaling pathway in *in vivo* tumor implant models.

[0016] In 2019, LartruvoTM failed to meet the primary overall survival endpoint in the confirmatory phase III trial in soft tissue sarcoma patients (ANNOUNCE trial; NCT02451943). However, the present inventors have surprisingly found that radiolabelled-olaratumab, or antigen binding fragments thereof, may be useful for the treatment of a range of cancers characterised by the expression of PDGFR α .

General definitions

[0017] Throughout this specification, unless specifically stated otherwise or the context requires otherwise, reference to a single step, composition of matter, group of steps or group of compositions of matter shall be taken to encompass one and a plurality (i.e. one or more) of those steps, compositions of matter, groups of steps or groups of compositions of matter. Thus, as used herein, the singular forms “a”, “an” and “the” include plural aspects, and vice versa, unless the context clearly dictates otherwise. For example, reference to “a” includes a single as well as two or more; reference to “an” includes a single as well as two or more; reference to “the” includes a single as well as two or more and so forth.

[0018] Those skilled in the art will appreciate that the present invention is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

[0019] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described.

[0020] All of the patents and publications referred to herein are incorporated by reference in their entirety.

[0021] The present invention is not to be limited in scope by the specific examples described herein, which are intended for the purpose of exemplification only. Functionally-equivalent products, compositions and methods are clearly within the scope of the present invention.

[0022] Any example or embodiment of the present invention herein shall be taken to apply mutatis mutandis to any other example or embodiment of the invention unless specifically stated otherwise.

[0023] Unless specifically defined otherwise, all technical and scientific terms used herein shall be taken to have the same meaning as commonly understood by one of ordinary skill in the art (for example, in diagnostic technology, radioimaging, cell culture, molecular genetics, immunology, immunohistochemistry, protein chemistry, and biochemistry).

[0024] The term “and/or”, e.g., “X and/or Y” shall be understood to mean either “X and Y” or “X or Y” and shall be taken to provide explicit support for both meanings or for either meaning.

Selected Definitions

[0025] The term “isolated protein” or “isolated polypeptide” is a protein or polypeptide that by virtue of its origin or source of derivation is not associated with naturally-associated components that accompany it in its native state; is substantially free of other proteins from the same source. A protein may be rendered substantially free of naturally associated components or substantially purified by isolation, using protein purification techniques known in the art. By “substantially purified” is meant the protein is substantially free of contaminating agents, e.g., at least about 70% or 75% or 80% or 85% or 90% or 95% or 96% or 97% or 98% or 99% free of contaminating agents.

[0026] The term “recombinant” shall be understood to mean the product of artificial genetic recombination. Accordingly, in the context of a recombinant protein comprising an antibody antigen binding domain, this term does not encompass an antibody naturally-occurring within a subject’s body that is the product of natural recombination that occurs during B cell maturation. However, if such an antibody is isolated, it is to be considered an isolated protein comprising an antibody antigen binding domain. Similarly, if nucleic acid encoding the protein is isolated and expressed using recombinant means, the resulting protein is a recombinant protein comprising an antibody antigen binding domain. A recombinant protein also encompasses a protein expressed by artificial recombinant means when it is within a cell, tissue or subject, e.g., in which it is expressed.

[0027] The term “protein” shall be taken to include a single polypeptide chain, i.e., a series of contiguous amino acids linked by peptide bonds or a series of polypeptide chains covalently or non-covalently linked to one another (i.e., a polypeptide complex). For example, the series of polypeptide chains can be covalently linked using a suitable

chemical or a disulphide bond. Examples of non-covalent bonds include hydrogen bonds, ionic bonds, Van der Waals forces, and hydrophobic interactions.

[0028] The term “polypeptide” or “polypeptide chain” will be understood from the foregoing paragraph to mean a series of contiguous amino acids linked by peptide bonds.

[0029] As used herein, the term “antigen binding protein” is used interchangeably with “antigen binding domain” and shall be taken to mean a region of an antibody that is capable of specifically binding to an antigen, i.e., a VH or a VL or an Fv comprising both a VH and a VL. The antigen binding domain need not be in the context of an entire antibody, e.g., it can be in isolation (e.g., a domain antibody) or in another form, e.g., as described herein, such as a scFv.

[0030] For the purposes for the present disclosure, the term “antibody” includes a protein capable of specifically binding to one or a few closely related antigens by virtue of an antigen binding domain contained within a Fv. This term includes four chain antibodies (e.g., two light chains and two heavy chains), recombinant or modified antibodies (e.g., chimeric antibodies, humanized antibodies, human antibodies, CDR-grafted antibodies, primatized antibodies, de-immunized antibodies, synhumanized antibodies, half-antibodies, bispecific antibodies). An antibody generally comprises constant domains, which can be arranged into a constant region or constant fragment or fragment crystallizable (Fc). Exemplary forms of antibodies comprise a four-chain structure as their basic unit. Full-length antibodies comprise two heavy chains (~50 to 70 kDa) covalently linked and two light chains (~23 kDa each). A light chain generally comprises a variable region (if present) and a constant domain and in mammals is either a κ light chain or a λ light chain. A heavy chain generally comprises a variable region and one or two constant domain(s) linked by a hinge region to additional constant domain(s). Heavy chains of mammals are of one of the following types α , δ , ϵ , γ , or μ . Each light chain is also covalently linked to one of the heavy chains. For example, the two heavy chains and the heavy and light chains are held together by inter-chain disulfide bonds and by non-covalent interactions. The number of inter-chain disulfide bonds can vary among different types of antibodies. Each chain has an N-terminal variable region (VH or VL wherein each are ~110 amino acids in length) and one or more constant domains at the C- terminus. The constant domain of the light chain (CL which is ~110 amino acids in length) is aligned with and disulfide bonded to the first constant domain of the heavy chain (CH1 which is 330 to 440 amino acids in length). The light chain variable region is aligned with the

variable region of the heavy chain. The antibody heavy chain can comprise 2 or more additional CH domains (such as, CH2, CH3 and the like) and can comprise a hinge region between the CH1 and CH2 constant domains. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. In one example, the antibody is a murine (mouse or rat) antibody or a primate (such as, human) antibody. In one example the antibody heavy chain is missing a C-terminal lysine residue. In one example, the antibody is humanized, synhumanized, chimeric, CDR-grafted or deimmunized.

[0031] The terms "full-length antibody", "intact antibody" or "whole antibody" are used interchangeably to refer to an antibody in its substantially intact form, as opposed to an antigen binding fragment of an antibody. Specifically, whole antibodies include those with heavy and light chains including an Fc region. The constant domains may be wild-type sequence constant domains (e.g., human wild-type sequence constant domains) or amino acid sequence variants thereof.

[0032] As used herein, "variable region" refers to the portions of the light and/or heavy chains of an antibody as defined herein that is capable of specifically binding to an antigen and, includes amino acid sequences of complementarity determining regions (CDRs); i.e., CDR1, CDR2, and CDR3, and framework regions (FRs). For example, the variable region comprises three or four FRs (e.g., FR1, FR2, FR3 and optionally FR4) together with three CDRs. VH refers to the variable region of the heavy chain. VL refers to the variable region of the light chain.

[0033] As used herein, the term "subject" shall be taken to mean any animal including humans, for example a mammal. Exemplary subjects include but are not limited to humans and non-human primates. For example, the subject is a human.

[0034] "Antibodies" or "immunoglobulins" or "Igs" are gamma globulin proteins that are found in blood, or other bodily fluids of vertebrates that function in the immune system to bind antigen, hence identifying and neutralizing foreign objects.

[0035] Antibodies are generally a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. Each L chain is linked to a H chain by one covalent disulfide bond. The two H chains are linked to each other by one

or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges.

[0036] H and L chains define specific Ig domains. More particularly, each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α and γ chains and four CH domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V L) followed by a constant domain (CL) at its other end. The VL is aligned with the VH and the CL is aligned with the first constant domain of the heavy chain (CH1).

[0037] Antibodies can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in CH sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

[0038] The constant domain includes the Fc portion which comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies such as ADCC are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

[0039] The pairing of a VH and VL together forms a "variable region" or "variable domain" including the amino -terminal domains of the heavy or light chain of the antibody. The variable domain of the heavy chain may be referred to as "VH." The variable domain of the light chain may be referred to as "VL." The V domain contains an antigen binding protein which affects antigen binding and defines specificity of a particular antibody for its particular antigen. V regions span about 110 amino acid residues and consist of relatively invariant stretches called framework regions (FRs) (generally about 4) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" (generally about 3) that are each 9-12 amino acids long. The FRs largely adopt a β -sheet configuration and the hypervariable regions form loops connecting, and in some cases forming part of, the β -sheet structure.

[0040] "Hypervariable region", "HVR", or "HV" refers to the regions of an antibody variable domain which are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six hypervariable regions; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). A number of hypervariable region delineations are in use and are encompassed herein.

[0041] As used herein, the term "complementarity determining regions" (syn. CDRs; i.e., CDR1, CDR2, and CDR3) refers to the amino acid residues of an antibody variable region the presence of which are major contributors to specific antigen binding. Each variable region domain (VH or VL) typically has three CDRs identified as CDR1, CDR2 and CDR3. The CDRs of VH are also referred to herein as CDR H1, CDR H2 and CDR H3, respectively, wherein CDR H1 corresponds to CDR 1 of VH, CDR H2 corresponds to CDR 2 of VH and CDR H3 corresponds to CDR 3 of VH. Likewise, the CDRs of VL are referred to herein as CDR L1, CDR L2 and CDR L3, respectively, wherein CDR L1 corresponds to CDR 1 of VL, CDR L2 corresponds to CDR 2 of VL and CDR L3 corresponds to CDR 3 of VL. In one example, the amino acid positions assigned to CDRs and FRs are defined according to Kabat Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., 1987 and 1991 (also referred to herein as "the Kabat numbering system"). In another example, the amino acid positions assigned to CDRs and FRs are defined according to the Enhanced Chothia Numbering Scheme (<http://www.bioinfo.org.uk/mdex.html>). The present invention is not limited to FRs and CDRs as defined by the Kabat numbering system, but includes all numbering systems, including the canonical numbering system or of Chothia and Lesk J. Mol. Biol. 196: 901-917, 1987; Chothia et al., Nature 342: 877-883, 1989; and/or Al-Lazikani et al., J. Mol. Biol. 273: 927-948, 1997; the numbering system of Honnegher and Plückthun J. Mol. Biol. 309: 657-670, 2001; or the IMGT system discussed in Giudicelli et al., Nucleic Acids Res. 25: 206-211 1997. In one example, the CDRs are defined according to the Kabat numbering system. Optionally, heavy chain CDR2 according to the Kabat numbering system does not comprise the five C-terminal amino acids listed herein or any one or more of those amino acids are substituted with another naturally-occurring amino acid. In this regard, Padlan et al., FASEB J., 9: 133-139, 1995 established that the five C-terminal amino acids of heavy chain CDR2 are not generally involved in antigen binding.

[0042] "Framework" or "FR" residues are those variable domain residues other than the hypervariable region or CDR residues herein defined. The FRs of VH are also referred to

herein as FR H1, FR H2, FR H3 and FR H4, respectively, wherein FR H1 corresponds to FR 1 of VH, FR H2 corresponds to FR 2 of VH, FR H3 corresponds to FR 3 of VH and FR H4 corresponds to FR 4 of VH. Likewise, the FRs of VL are referred to herein as FR L1, FR L2, FR L3 and FR L4, respectively, wherein FR L1 corresponds to FR 1 of VL, FR L2 corresponds to FR 2 of VL, FR L3 corresponds to FR 3 of VL and FR L4 corresponds to FR 4 of VL.

[0043] “A peptide for forming an antigen binding protein” generally refers to a peptide that may form a conformation that confers the specificity of an antibody for antigen. Examples include whole antibody or whole antibody related structures, whole antibody fragments including a variable domain, variable domains and fragments thereof, including light and heavy chains, or fragments of light and heavy chains that include some but not all of hypervariable regions or constant regions.

[0044] An “intact” or “whole” antibody is one which comprises an antigen-binding protein as well as a CL and at least heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof.

[0045] “Whole antibody related structures” include multimerized forms of whole antibody.

[0046] “Whole antibody fragments including a variable domain” include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies, single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0047] The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (VH), and the first constant domain of one heavy chain (CH1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding protein.

[0048] A Fab' fragment differs from Fab fragments by having additional few residues at the carboxy terminus of the CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group.

[0049] A F(ab')₂ fragment roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen.

[0050] An "Fv" is an antibody fragment which contains a complete antigen-recognition and - binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association.

[0051] In a single-chain Fv (scFv) species, one heavy- and one light-chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a "dimeric" structure analogous to that in a two-chain Fv species. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody.

[0052] "Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the VH and VL antibody domains connected to form a single polypeptide chain. Preferably, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding.

[0053] A "single variable domain" is half of an Fv (comprising only three CDRs specific for an antigen) that has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0054] "Diabodies" refers to antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH-VL). The small antibody fragments are prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the VH and VL domains such that interchain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites.

[0055] Diabodies may be bivalent or bispecific. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the VH and VL domains of the two antibodies are present on different polypeptide chains. Triabodies and tetrabodies are also generally known in the art.

[0056] An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its pre-existing environment. Contaminant components are materials that would interfere with therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes.

[0057] A "human antibody" refers to an antibody which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage -display libraries. Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled.

[0058] "Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0059] "Monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed

against a single antigenic site or determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. Monoclonal antibodies may be prepared by the hybridoma methodology, or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells. The "monoclonal antibodies" may also be isolated from phage antibody libraries.

[0060] The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

[0061] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Generally, "binding affinity" refers to intrinsic binding affinity which reflects a 1: 1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present invention.

[0062] As used herein, the term "binds" in reference to the interaction of an antigen binding protein or an antigen binding domain thereof with an antigen means that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the antigen. For example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody binds to epitope "A", the presence of a molecule containing epitope "A" (or free, unlabelled "A"),

in a reaction containing labeled "A" and the protein, will reduce the amount of labelled "A" bound to the antibody.

[0063] As used herein, the term "specifically binds" or "binds specifically" shall be taken to mean that an antigen binding protein of the invention reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular antigen or cell expressing same than it does with alternative antigens or cells.

[0064] As used herein, the term "does not detectably bind" shall be understood to mean that an antigen binding protein, e.g., an antibody, binds to a candidate antigen at a level less than 10%, or 8% or 6% or 5% above background. The background can be the level of binding signal detected in the absence of the protein and/or in the presence of a negative control protein (e.g., an isotype control antibody) and/or the level of binding detected in the presence of a negative control antigen. The level of binding is detected using biosensor analysis (e.g. Biacore) in which the antigen binding protein is immobilized and contacted with an antigen.

[0065] As used herein, the term "does not significantly bind" shall be understood to mean that the level of binding of an antigen binding protein of the invention to a polypeptide is not statistically significantly higher than background, e.g., the level of binding signal detected in the absence of the antigen binding protein and/or in the presence of a negative control protein (e.g., an isotype control antibody) and/or the level of binding detected in the presence of a negative control polypeptide. The level of binding is detected using biosensor analysis (e.g. Biacore) in which the antigen binding protein is immobilized and contacted with an antigen.

[0066] An "affinity matured" antibody is one with one or more alterations in one or more HVRs thereof which result in an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by procedures known in the art.

[0067] "ADCC" refers to a process called antibody-dependent cellular cytotoxicity, which is an immune response mediated primarily by natural killer (NK) cells in humans. In ADCC, FcγRIII on the surface of an NK cell recognizes the Fc region of antibody that is

bound to antigen displayed on the surface of a target cell. This activates the NK cell, which releases perforins and granzymes, leading to lysis and apoptosis of the target cells.

[0068] "CDC" refers to a complex process called complement-dependent cytotoxicity that can lead to cell killing through the action of a cascade of proteins that can act through either of two major pathways.

[0069] "ADCP" refers to a process called antibody dependent cell-mediated phagocytosis. In this Fc receptor-mediated process, target cells to which antibodies are bound are engulfed by phagocytic cells, such as macrophage, monocytes, neutrophils, and dendritic cells. Multiple Fc receptors are involved in this process.

[0070] A "blocking" antibody or an "antagonist" antibody is one which inhibits or reduces biological activity of the antigen it binds. Preferred blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen.

[0071] An "agonist antibody", as used herein, is an antibody which mimics at least one of the functional activities of a polypeptide of interest.

[0072] As meant herein, an "Fc region" is a dimer consisting of two polypeptide chains joined by one or more disulfide bonds, each chain comprising part or all of a hinge domain plus a CH2 and a CH3 domain. Each of the polypeptide chains is referred to as an "Fc polypeptide chain." To distinguish the two Fc polypeptide chains, one is referred to herein as an "A chain" and the other is referred to as a "B chain." More specifically, the Fc regions contemplated for use with the present invention are IgG Fc regions, which can be mammalian or human IgG1, IgG2, IgG3, or IgG4 Fc regions. Among human IgG1 Fc regions, at least two allelic types are known.

[0073] An "Fc-containing protein," as meant herein, is a protein comprising an Fc region as described herein and a binding region that binds to a target molecule. The term "Fc containing protein" encompasses an antibody or an Fc fusion protein that contains an Fc region.

[0074] The words "treat" or "treatment" refer to therapeutic treatment wherein the object is to slow down (lessen) an undesired physiological change or disorder. For the purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening)

state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. Treatment can also mean prolonging survival as compared to expected survival if not receiving treatment. Treatment may not necessarily result in the complete clearance of a disease or disorder but may reduce or minimise complications and side effects of infection and the progression of a disease or disorder.

[0075] The phrase “pharmaceutically acceptable” indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

Antibodies

[0076] The present invention relates to the use of radiolabelled olaratumab or antigen binding fragments thereof that specifically bind to PDGFR α , for the treatment of cancers. As used herein, olaratumab may also be referred to as IMC-3G3 and is an antibody that specifically binds to the human PDGFR α .

[0077] As used herein, the term “specifically binds” or “binds specifically” shall be taken to mean that an agent for use according to the invention, reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a PDGFR α or cell expressing same than it does with alternative antigens or cells. For example, an antigen binding protein that binds to PDGFR α with materially greater affinity (e.g., 1.5 fold or 2 fold or 5 fold or 10 fold or 20 fold or 40 fold or 60 fold or 80 fold to 100 fold or 150 fold or 200 fold) than it does to other antigens.

[0078] Methods for assessing binding to a protein (eg PDGFR α) are known in the art, e.g., as described in Scopes (In: Protein purification: principles and practice, Third Edition, Springer Verlag, 1994). Such a method generally involves immobilizing the agent (eg antibody) and contacting it with labeled target (in the case of an antibody, the antigen). Following washing to remove non-specific bound protein, the amount of label and, as a consequence, bound antigen is detected. Of course, the antigen binding site can be labeled and the antigen immobilized. Panning-type assays can also be used. Alternatively, or additionally, surface plasmon resonance assays can be used.

Constant regions

[0079] Any antibody and/or antigen binding fragment thereof as described herein for use in the present invention may comprise a constant region of an antibody. This includes antigen binding fragments of an antibody fused to an Fc.

[0080] Sequences of constant regions useful for producing the antibodies or antigen binding fragment thereof as described herein may be obtained from a number of different sources. In some examples, the constant region or portion thereof of the protein is derived from a human antibody. The constant region or portion thereof may be derived from any antibody class, including IgM, IgG, IgD, IgA and IgE, and any antibody isotype, including IgG1, IgG2, IgG3 and IgG4. In one example, the constant region is human isotype IgG4 or a stabilized IgG4 constant region.

[0081] In various embodiments of the invention, the Fc region of the antibody may comprise one or more substitutions for altering effector function (including increasing or decreasing effector functions), and circulation half-life. Various examples of such substitutions and modifications are described in Saunders (2019) Front. Immunol. article 1296, incorporated herein by reference in its entirety.

[0082] In one example, the Fc region of the constant region has a reduced ability to induce effector function, e.g., compared to a native or wild-type human IgG1 or IgG3 Fc region. In one example, the effector function is antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cell-mediated phagocytosis (ADCP) and/or complement-dependent cytotoxicity (CDC). Methods for assessing the level of effector function of an Fc region containing protein are known in the art and/or described herein.

[0083] In one example, the Fc region is an IgG4 Fc region (i.e., from an IgG4 constant region), e.g., a human IgG4 Fc region. Sequences of suitable IgG4 Fc regions will be apparent to the skilled person and/or available in publically available databases (e.g., available from National Center for Biotechnology Information).

[0084] In one example, the constant region is a stabilized IgG4 constant region. The term "stabilized IgG4 constant region" will be understood to mean an IgG4 constant region that has been modified to reduce Fab arm exchange or the propensity to undergo Fab arm exchange or formation of a half-antibody or a propensity to form a half antibody. "Fab

arm exchange" refers to a type of protein modification for human IgG4, in which an IgG4 heavy chain and attached light chain (half-molecule) is swapped for a heavy-light chain pair from another IgG4 molecule. Thus, IgG4 molecules may acquire two distinct Fab arms recognizing two distinct antigens (resulting in bispecific molecules). Fab arm exchange occurs naturally in vivo and can be induced in vitro by purified blood cells or reducing agents such as reduced glutathione. A "half antibody" forms when an IgG4 antibody dissociates to form two molecules each containing a single heavy chain and a single light chain.

[0085] In one example, a stabilized IgG4 constant region comprises a proline at position 241 of the hinge region according to the system of Kabat (Kabat et al., Sequences of Proteins of Immunological Interest Washington DC United States Department of Health and Human Services, 1987 and/or 1991). This position corresponds to position 228 of the hinge region according to the EU numbering system (Kabat et al., Sequences of Proteins of Immunological Interest Washington DC United States Department of Health and Human Services, 2001 and Edelman et al., Proc. Natl. Acad. USA, 63, 78-85, 1969). In human IgG4, this residue is generally a serine. Following substitution of the serine for proline, the IgG4 hinge region comprises a sequence CPPC. In this regard, the skilled person will be aware that the "hinge region" is a proline-rich portion of an antibody heavy chain constant region that links the Fc and Fab regions that confers mobility on the two Fab arms of an antibody. The hinge region includes cysteine residues which are involved in inter-heavy chain disulfide bonds. It is generally defined as stretching from Glu226 to Pro243 of human IgG1 according to the numbering system of Kabat. Hinge regions of other IgG isotypes may be aligned with the IgG1 sequence by placing the first and last cysteine residues forming inter-heavy chain disulphide (S-S) bonds in the same positions (see for example WO2010/080538).

[0086] Additional examples of stabilized IgG4 antibodies are antibodies in which arginine at position 409 in a heavy chain constant region of human IgG4 (according to the EU numbering system) is substituted with lysine, threonine, methionine, or leucine (e.g., as described in WO2006/033386). The Fc region of the constant region may additionally or alternatively comprise a residue selected from the group consisting of: alanine, valine, glycine, isoleucine and leucine at the position corresponding to 405 (according to the EU numbering system). Optionally, the hinge region comprises a proline at position 241 (i.e., a CPPC sequence) (as described above).

[0087] In another example, the Fc region is a region modified to have reduced effector function, i.e., a “non-immunostimulatory Fc region”. For example, the Fc region is an IgG1 Fc region comprising a substitution at one or more positions selected from the group consisting of 268, 309, 330 and 331. In another example, the Fc region is an IgG1 Fc region comprising one or more of the following changes E233P, L234V, L235A and deletion of G236 and/or one or more of the following changes A327G, A330S and P331S (Armour et al., *Eur J Immunol.* 29:2613-2624, 1999; Shields et al., *J Biol Chem.* 276(9):6591-604, 2001). Additional examples of non-immunostimulatory Fc regions are described, for example, in Dall'Acqua et al., *J Immunol.* 177: 1129-1138 2006; and/or Hezareh *J Virol* ;75: 12161-12168, 2001).

[0088] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (as described in U.S. Patent No. 6,737,056, incorporated herein by reference). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called “DANA” Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581). For example, an antibody variant may comprise an Fc region with one or more amino acid substitutions which diminish FcγR binding, e.g., substitutions at positions 234 and 235 of the Fc region (EU numbering of residues). For example, the substitutions are L234A and L235A (LALA) (See, e.g., WO 2012/130831). The substitutions may additionally include substitution of the proline residue at position 329, such as a P329G mutation to disable binding to FcR. Further, alterations may be made in the Fc region that result in altered (i.e., diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164: 4178-4184 (2000).

[0089] In some aspects, the Fc region includes mutations to the complement (C1q) and/or to Fc gamma receptor (FcγR) binding sites. In some aspects, such mutations can render the antibody incapable of antibody directed cytotoxicity (ADCC) and complement directed cytotoxicity (CDC). One example of a CDC-deficient antibody is one that comprises a substitution at one or more of Glu318, Lys320, Pro 329, Pro331 and Lys322 (for example, K322A), wherein the numbering of the residues in the Fc region is according to the EU index as described in Kabat et al.

[0090] In another example, the Fc region is a chimeric Fc region, e.g., comprising at least one CH2 domain from an IgG4 antibody and at least one CH3 domain from an IgG1

antibody, wherein the Fc region comprises a substitution at one or more amino acid positions selected from the group consisting of 240, 262, 264, 266, 297, 299, 307, 309, 323, 399, 409 and 427 (EU numbering) (e.g., as described in WO2010/085682). Exemplary substitutions include 240F, 262L, 264T, 266F, 297Q, 299A, 299K, 307P, 309K, 309M, 309P, 323F, 399S, and 427F.

Additional Modifications

[0091] The present invention also contemplates additional modifications to an antibody or antigen binding protein comprising an Fc region or constant region.

[0092] The neonatal Fc-receptor (FcRn) is important for the metabolic fate of antibodies of the IgG class *in vivo*. The FcRn functions to salvage IgG from the lysosomal degradation pathway, resulting in reduced clearance and increased half-life. FcRn binds with high affinity to the CH2-CH3 portion of the Fc-region of an antibody of the class IgG. The interaction between an antibody of the class IgG and the FcRn is pH dependent and occurs in a 1 :2 stoichiometry, i.e. one IgG antibody molecule can interact with two FcRn molecules via its two heavy chain Fc-region polypeptides (see e.g. Huber, A.H., et al, J. Mol. Biol. 230 (1993) 1077-1083).

[0093] In certain embodiments of the invention, an antibody may comprise one or more amino acid substitutions that increase the half-life of the protein. For example, the antibody comprises a Fc region comprising one or more amino acid substitutions that increase the affinity of the Fc region for the neonatal Fc region (FcRn). For example, the Fc region has increased affinity for FcRn at lower pH, e.g., about pH 6.0, to facilitate Fc/FcRn binding in an endosome. In one example, the Fc region has increased affinity for FcRn at about pH 6 compared to its affinity at about pH 7.4, which facilitates the re-release of Fc into blood following cellular recycling. These amino acid substitutions are useful for extending the half-life of a protein, by reducing clearance from the blood.

[0094] Exemplary amino acid substitutions include T250Q and/or M428L or T252A, T254S and T266F or M252Y, S254T and T256E or H433K and N434F according to the EU numbering system. Additional or alternative amino acid substitutions are described, for example, in US20070135620 or US7083784.

[0095] In further embodiments, the antibody comprises one or more amino acid substitutions that decrease the half-life of the protein. For example, the antibody

comprises a Fc region comprising one or more amino acid substitutions that decrease or reduce the affinity of the Fc region for the neonatal Fc region (FcRn).

[0096] The present invention therefore provides for an antibody having substitutions in the CH2 and/or CH3 domains of the constant region and comprising substitutions at one or more of residues His310, His435, His436 and Ile253 (Kabat numbering), thereby altering FcRn binding affinity and/or serum half-life of said antibody relative to a naturally occurring antibody.

[0097] In some examples, the amino acid at position 310 and/or 435 of the antibody may be alanine, glutamic acid, aspartic acid, leucine, isoleucine, arginine, proline, glutamine, methionine, serine, threonine, lysine, asparagine, phenylalanine, tyrosine, tryptophan, cysteine, valine or glycine.

[0098] Preferably, the residue at position 310 is selected from alanine, or glutamic acid or glutamine; or amino acid residue 435 from the heavy chain constant region is selected from arginine, glutamine or alanine. In other preferred embodiments, the antibody has an alanine residue at position 310 and glutamine residue at position 435.

[0099] In a preferred embodiment of the present invention, the binding affinity for FcRn and/or the serum half-life of the modified antibody is decreased by at least about 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, or 100-fold. In a preferred embodiment of the present invention, the binding affinity for FcRn and/or the serum half-life of said modified antibody is reduced by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 98%, or 99%.

[0100] The antibody may also comprise amino acid substitutions at residues equivalent to Ser228 and Leu235 of the constant heavy chain region, such as Ser228Pro and/or Leu235Glu.

Protein Production

[0101] The production of an antigen binding protein of the invention generally requires an expression vector containing a polynucleotide that encodes the antigen binding protein of the invention. A polynucleotide encoding an antigen binding protein of the invention may be obtained and sub cloned into a vector for the production of an antigen binding

protein by recombinant DNA technology using techniques well-known in the art, including techniques described herein. Many different expression systems are contemplated including the use of mammalian cells including human cells for production and secretion of antigen binding proteins. Examples of cells include 293F, CHO and the NSO cell line.

[0102] Expression vectors containing protein coding sequences and appropriate transcriptional and translational control signals can be constructed using methods known in the art. These include in vitro recombinant DNA techniques, synthetic techniques and in vivo genetic recombination. In certain embodiments there is provided a replicable vector having a nucleic acid encoding an antigen binding protein operably linked to a promoter.

[0103] Cells transfected with an expression vector may be cultured by conventional techniques to produce an antigen binding protein. Thus, in certain embodiments, there is provided host cells or cell transfectants containing a polynucleotide encoding an antigen binding protein of the invention operably linked to a promoter. The promoter may be heterologous. A variety of host-expression vector systems may be utilized and in certain systems the transcription machinery of the vector system is particularly matched to the host cell. For example, mammalian cells such as Chinese hamster ovary cells (CHO) may be transfected with a vector including the major intermediate early gene promoter element from human cytomegalovirus. Additionally or alternatively, a host cell may be used that modulates the expression of inserted sequences, or modifies and processes the gene product as required, including various forms of post translational modification. Examples of mammalian host cells having particular post translation modification processes include CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, W138, BT483, Hs578T, HTB2, BT20 and T47D, NSO, CRL7030 and HsS78Bst cells.

[0104] Depending upon the use intended for the protein molecule, a number of bacterial expression vectors may be advantageously selected. In one example, vectors that cause the expression of high levels of fusion protein products that are readily purified, such as the E. coli expression vector pUR278 may be used where a large quantity of an antigen binding protein is to be produced. The expression product may be produced in the form of a fusion protein with lacZ. Other bacterial vectors include pIN vectors and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione-S-transferase (GST). These fusion proteins are generally soluble and can easily be purified from lysed cells by adsorption and binding to glutathione-agarose affinity

matrix followed by elution in the presence of free glutathione. A thrombin and/or factor Xa protease cleavage site may be provided in the expressed polypeptide so that the cloned target gene product can be released from the GST moiety.

[0105] *Autographa californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes in an insect system including *Spodoptera frugiperda* cells. The particular promoter used may depend on where the protein coding is inserted into the sequence. For example, the sequence may be cloned individually into the polyhedrin gene and placed under control of the polyhedrin promoter.

[0106] Virus based expression systems may be utilized with mammalian cells such as an adenovirus whereby the coding sequence of interest may be ligated to the adenoviral late promoter and tripartite leader sequence. In vitro or in vivo recombination may then be used to insert this chimeric gene into the adenoviral genome. Insertions into region E1 or E3 will result in a viable recombinant virus that is capable of expressing the antigen binding protein in infected host cells. Specific initiation signals including the ATG initiation codon and adjacent sequences may be required for efficient translation of inserted antigen binding protein coding sequences. Initiation and translational control signals and codons can be obtained from a variety of origins, both natural and synthetic. Transcription enhancer elements and transcription terminators may be used to enhance the efficiency of expression of a viral based system.

[0107] Where long-term, high-yield production of recombinant proteins is required, stable expression is preferred. Generally a selectable marker gene is used whereby following transfection, cells are grown for 1-2 days in an enriched media and then transferred to a medium containing a selective medium in which cells containing the corresponding selectable marker, for example, antibiotic resistance can be screened. The result is that cells that have stably integrated the plasmid into their chromosomes grow and form foci that in turn can be cloned and expanded into cell lines. The herpes simplex virus thymidine kinase, hypoxanthineguanine phosphoribosyltransferase and adenine phosphoribosyltransferase genes are examples of genes that can be employed in tk-, hgpRT- or aprT- cells, respectively, thereby providing appropriate selection systems. The following genes: dhfr, which confers resistance to methotrexate; gpt, which confers resistance to mycophenolic acid; neo, which confers resistance to the aminoglycoside G-418; and hygR, which confers resistance to hygromycin are examples of genes that can be used in anti-metabolite selection systems.

[0108] An antigen binding protein of the invention may be purified by a recombinant expression system by known methods including ion exchange chromatography, affinity chromatography (especially affinity for the specific antigens Protein A or Protein G) and gel filtration column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Purification may be facilitated or assisted by providing the antigen binding protein in the form of a fusion protein.

[0109] Large quantities of the antigen binding proteins of the invention may be produced by a scalable process starting with a pilot expression system in a research laboratory that is scaled up to an analytical scale bioreactor (typically from 5L to about 50L bioreactors) or production scale bioreactors (for example, but not limited to 75L, 100L, 150L, 300L, or 500L). Desirable scalable processes include those wherein there are low to undetectable levels of aggregation as measured by HPSEC or rCGE, typically no more than 5% aggregation by weight of protein down to no more than 0.5% by weight aggregation of protein. Additionally or alternatively, undetectable levels of fragmentation measured in terms of the total peak area representing the intact antigen binding protein may be desired in a scalable process so that at least 80% and as much as 99.5% or higher of the total peak area represents intact antigen binding protein. In other embodiments, the scalable process of the invention produces antigen binding proteins at production efficiency of about from 10 mg/L to about 300 mg/L or higher.

[0110] Various techniques have been developed for the production of antibody fragments including proteolytic digestion of intact antibodies and recombinant expression in host cells. With regard to the latter, as described below, Fab, Fv and scFv antibody fragments can all be expressed in and secreted from *E. coli*, antibody fragments can be isolated from the antibody phage libraries and Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments. In another approach, F(ab')₂ fragments are isolated directly from recombinant host cell culture.

[0111] In another embodiment there is provided a vector including a nucleic acid described above. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription

termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

[0112] The antigen binding site may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the antigen binding site-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader, or acid phosphatase leader or the *C. albicans* glucoamylase leader. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

[0113] Polynucleotide sequences encoding polypeptide components of the antigen binding protein of the invention can be obtained using standard recombinant techniques as described above. Polynucleotides can be synthesized using nucleotide synthesizer or PCR techniques. Once obtained, sequences encoding the polypeptides are inserted into a recombinant vector capable of replicating and expressing heterologous polynucleotides in prokaryotic hosts. Many vectors that are available and known in the art can be used for the purpose of the present invention. Selection of an appropriate vector will depend mainly on the size of the nucleic acids to be inserted into the vector and the particular host cell to be transformed with the vector. Each vector contains various components, depending on its function (amplification or expression of heterologous polynucleotide, or both) and its compatibility with the particular host cell in which it resides.

[0114] In general, plasmid vectors containing replicon and control sequences which are derived from species compatible with the host cell are used in connection with these hosts. Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells, as well as marking sequences which are capable of providing phenotypic selection in transformed cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322, which contains genes encoding ampicillin (Amp) and tetracycline (Tet) resistance and thus provides easy means for identifying

transformed cells, is suitable for most Gram-negative bacteria, the 2 μ m plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells. pBR322, its derivatives, or other microbial plasmids or bacteriophage may also contain, or be modified to contain, promoters which can be used by the microbial organism for expression of endogenous proteins.

[0115] In addition, phage vectors containing replicon and control sequences that are compatible with the host microorganism can be used as transforming vectors in connection with these hosts. For example, bacteriophage such as λ GEM.TM.-11 may be utilized in making a recombinant vector which can be used to transform susceptible host cells such as *E. coli* LE392.

[0116] The expression vector of the invention may comprise two or more promoter-cistron (a cistron being segment of DNA that contains all the information for production of single polypeptide) pairs. A promoter is an untranslated regulatory sequence located upstream (5') to a cistron that modulates its expression. Prokaryotic promoters typically fall into two classes, inducible and constitutive. Inducible promoter is a promoter that initiates increased levels of transcription of the cistron under its control in response to changes in the culture condition, e.g. the presence or absence of a nutrient or a change in temperature.

[0117] A large number of promoters recognized by a variety of potential host cells are well known. The selected promoter can be operably linked to cistron DNA encoding the light or heavy chain by removing the promoter from the source DNA via restriction enzyme digestion and inserting the isolated promoter sequence into the vector of the invention. Both the native promoter sequence and many heterologous promoters may be used to direct amplification and/or expression of the target genes. In some embodiments, heterologous promoters are utilized, as they generally permit greater transcription and higher yields of expressed target gene as compared to the native target polypeptide promoter.

[0118] Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the PhoA promoter, the β -galactamase and lactose promoter systems, alkaline phosphatase, a tryptophan (trp) promoter system and hybrid promoters such as the tac or the trc promoter. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably

linked to the DNA encoding an antigen binding protein of the invention. However, other promoters that are functional in bacteria (such as other known bacterial or phage promoters) are suitable as well. Their nucleotide sequences have been published, thereby enabling a skilled person operably to ligate them to cistrons encoding the target light and heavy chains using linkers or adaptors to supply any required restriction sites.

[0119] In one aspect of the invention, each cistron within the recombinant vector comprises a secretion signal sequence component that directs translocation of the expressed polypeptides across a membrane. In general, the signal sequence may be a component of the vector, or it may be a part of the target polypeptide DNA that is inserted into the vector. The signal sequence selected for the purpose of this invention should be one that is recognized and processed (i.e. cleaved by a signal peptidase) by the host cell. For prokaryotic host cells that do not recognize and process the signal sequences native to the heterologous polypeptides, the signal sequence is substituted by a prokaryotic signal sequence selected, for example, from the group consisting of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP. In one embodiment of the invention, the signal sequences used in both cistrons of the expression system are STII signal sequences or variants thereof.

[0120] In another aspect, the production of the immunoglobulins according to the invention can occur in the cytoplasm of the host cell, and therefore does not require the presence of secretion signal sequences within each cistron. In that regard, immunoglobulin light and heavy chains are expressed, folded and assembled to form functional immunoglobulins within the cytoplasm. Certain host strains (e.g., the E. coli trxB strains) provide cytoplasm conditions that are favourable for disulfide bond formation, thereby permitting proper folding and assembly of expressed protein subunits.

[0121] The present invention provides an expression system in which the quantitative ratio of expressed polypeptide components can be modulated in order to maximize the yield of secreted and properly assembled antigen binding proteins of the invention. Such modulation is accomplished at least in part by simultaneously modulating translational strengths for the polypeptide components.

[0122] In terms of expression in eukaryotic host cells, the vector components generally include, but are not limited to, one or more of the following: a signal sequence, an origin

of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence.

[0123] A vector for use in a eukaryotic host cell may also contain a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide of interest. The heterologous signal sequence selected preferably is one that is recognized and processed {i.e., cleaved by a signal peptidase) by the host cell. In mammalian cell expression, mammalian signal sequences as well as viral secretory leaders, for example, the herpes simplex gD signal, are available.

[0124] The DNA for such precursor region is ligated in reading frame to DNA encoding the antibody.

[0125] Generally, an origin of replication component is not needed for mammalian expression vectors. For example, the SV40 origin may typically be used only because it contains the early promoter.

[0126] Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli.

[0127] One example of a selection scheme utilizes a drug to arrest growth of a host cell. Those cells that are successfully transformed with a heterologous gene produce a protein conferring drug resistance and thus survive the selection regimen. Examples of such dominant selection use the drugs neomycin, mycophenolic acid and hygromycin.

[0128] An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the antigen binding protein-encoding nucleic acid, such as DHFR or thymidine kinase, metallothionein-I and -II, preferably primate metallothionein genes, adenosine deaminase, ornithine decarboxylase, etc. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity (e.g., ATCC CRL-9096), prepared and propagated. For example, cells transformed with the DHFR selection gene are first identified by culturing all of the transformants in a culture medium that contains methotrexate (Mtx), a competitive antagonist of DHFR. Alternatively, host cells

(particularly wild-type hosts that contain endogenous DHFR) transformed or co-transformed with DNA sequences encoding an antibody, wild-type DHFR protein, and another selectable marker such as aminoglycoside 3'-phosphotransferase (APH) can be selected by cell growth in medium containing a selection agent for the selectable marker such as an aminoglycosidic antibiotic, e.g., kanamycin, neomycin, or G418.

[0129] Expression and cloning vectors usually contain a promoter operably linked to the antigen binding protein encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known.

[0130] Eukaryotic genes generally have an AT-rich region located approximately 25 to 30 bases upstream from the site where transcription is initiated. Another sequence found 70 to 80 bases upstream from the start of transcription of many genes is a CNCAAT region where N may be any nucleotide. At the 3' end of most eukaryotic genes is an AATAAA sequence that may be the signal for addition of the poly A tail to the 3' end of the coding sequence. All of these sequences are suitably inserted into eukaryotic expression vectors.

[0131] Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3- phosphoglycerate kinase or other glycolytic enzymes including enolase, glyceraldehyde-3- phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3 -phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

[0132] Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3- phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization.

[0133] Antigen binding protein transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an

immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

[0134] Transcription of a DNA encoding the antigen binding protein by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancer sequences include those known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

[0135] Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding an antigen binding protein.

[0136] In another embodiment there is provided a cell including a vector or nucleic acid described above. The nucleic acid molecule or vector may be present in the genetically modified host cell or host either as an independent molecule outside the genome, preferably as a molecule which is capable of replication, or it may be stably integrated into the genome of the host cell or host.

[0137] The host cell of the present invention may be any prokaryotic or eukaryotic cell.

[0138] Examples of prokaryotic cells are those generally used for cloning like *E. coli* or *Bacillus subtilis*. Furthermore, eukaryotic cells comprise, for example, fungal or animal cells.

[0139] Examples for suitable fungal cells are yeast cells, preferably those of the genus *Saccharomyces* and most preferably those of the species *Saccharomyces cerevisiae*.

[0140] Examples of animal cells are, for instance, insect cells, vertebrate cells, preferably mammalian cells, such as e.g. HEK293, NSO, CHO, MDCK, U2-OS, Hela, NIH3T3, MOLT-4, Jurkat, PC-12, PC-3, IMR, NT2N, Sk-n-sh, CaSki, C33A. These host

cells, e.g. CHO-cells, may provide post- translational modifications to the antibody molecules of the invention, including leader peptide removal, folding and assembly of H (heavy) and L (light) chains, glycosylation of the molecule at correct sides and secretion of the functional molecule.

[0141] Further suitable cell lines known in the art are obtainable from cell line depositories, like the American Type Culture Collection (ATCC).

[0142] In another embodiment there is provided an animal including a cell described above. In certain embodiments, animals and tissues thereof containing a transgene are useful in producing the antigen binding proteins of the invention. The introduction of the nucleic acid molecules as transgenes into non-human hosts and their subsequent expression may be employed for the production of the antigen binding proteins, for example, the expression of such a transgene in the milk of the transgenic animal provide for means of obtaining the antigen binding proteins in quantitative amounts. Useful transgenes in this respect comprise the nucleic acid molecules of the invention, for example, coding sequences for the antigen binding proteins described herein, operatively linked to promoter and/or enhancer structures from a mammary gland specific gene, like casein or beta-lactoglobulin. The animal may be non-human mammals, most preferably mice, rats, sheep, calves, dogs, monkeys or apes.

Radiolabelled antibodies

[0143] The skilled person will be familiar with standard methods for conjugating a detectable moiety such as a radionuclide (radiolabel) to an antibody or antigen binding fragment thereof.

[0144] As used herein, the term radionuclide may be used interchangeably with the term radioisotope and radiolabel.

[0145] In any embodiment of the invention, radiolabel may be conjugated to the olaratumab or antigen binding fragment thereof, directly via binding to single or multiple amino acid residues in the protein (e.g. halogenation of tyrosine residues) or indirectly (via a chelating agent or prosthetic group or linker) linked to the radioisotope (ie the radiolabel).

[0146] Examples of suitable chelating agents or linkers may be selected from the group consisting of: TMT (6,6"-bis[N,N",N""-tetra(carboxymethyl)aminomethyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2"-terpyridine), DOTA (1, 4,7,10-tetraazacyclododecane-NN',N"(N""-tetraacetic acid, also known as tetraxetan), TCMC (the tetra-primary amide of DOTA), DO3A (1,4,7,10-Tetraazacyclododecane-1,4,7-tris(acetic acid)-10-(2-thioethyl)acetamide), CB-DO2A (4,10-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecan), NOTA (1,4,7-triazacyclononane-triacetic acid) Diamsar (3,6,10,13,16,19-hexaazabicyclo[6.6.6]eicosane-1,8-diamine), DTPA (Pentetic acid or diethylenetriaminepentaacetic acid), CHX-A"-DTPA ([[(R)-2-Amino-3-(4-isothiocyanatophenyl)propyl]-trans-(S,S)-cyclohexane-1,2-diamine-pentaacetic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8), 11-tetraacetic acid, Te2A (4,11 - bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane), HBED, DFO (Desferrioxamine), DFOsq (DFO-squaramide) and HOPO (3,4,3-(LI-1,2-HOPO) or other chelating agent as described herein. Other known chelating moieties include 3p-C-NETA ({4-[2-(bis-carboxy-methylamino)-5-(4-nitrophenyl)pentyl]-7-carboxymethyl-[1,4,7]triazanonan-1-yl} acetic acid), 5p-C-NETA (2-({1-[4,7-bis(carboxymethyl)-1,4,7-triazanonan-1-yl]-7-(4-nitrophenyl)heptan-2-yl}(carboxymethyl) amino)acetic acid), NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid) and NODA (1,4,7-triazacyclononane-1,4-diacetic acid).

[0147] Further suitable chelating agents (eg comprising DOTA and DFO) are disclosed in WO 2022/133537, incorporated herein by reference.

[0148] In certain embodiments, the olaratumab may be covalently coupled to the radioactive isotope ¹²⁴I. This isotope is a positron emitter that can be attached to antibodies e.g. as described by Larsson et al. (J. Nucl. Med. 33 (1992), 2020-2023) or US 5,185,142, the content of which is herein incorporated by reference.

[0149] In any embodiment, radiolabelling of a protein or antibody is accomplished by covalent iodination, particularly with the Iodogen Reagent (1,3,4,6-tetrachloro-3a,6a-diphenyl glycoluril). Iodogen labeling is a solid phase oxidative method that is similar to the Chloramine-T method, but is generally considered to be milder, since the reaction takes place on the surface of the oxidant, minimizing exposure of the substrate (Salaczki, P.R.P., et al., Anal.Biochem. 117:136 (1981)).

[0150] Chelators with radiometals and other halogenated radioisotopes may be bound to antibodies via one or more amino acid residues or reactive moieties in the protein/antibody, including but not limited to one or more lysine residues, tyrosine residues or thiol moieties.

[0151] In another example, the antibody may be conjugated to a bifunctional linker, for example, bromoacetyl, thiols, succinimide ester, TFP ester, a maleimide, or using any amine or thiol- modifying chemistry known in the art.

[0152] The skilled person will be familiar with standard methods for conjugating chelating agents to antibodies and derivatives or fragments thereof. In addition, the skilled person will be familiar with approaches for selecting a relevant chelating agent for pairing with a radiometal, for example as described in Chem. Soc. Rev., 2014,43, 260, incorporated herein by reference.

[0153] In any aspect or embodiment, the radiolabelled olaratumab may comprise any radioisotope suitable for treatment of tumour or cancer masses. The radioisotope may be for use in alpha (α) or beta (β) or gamma (γ) therapy.

[0154] Examples of suitable radioisotopes include: actinium-225 (^{225}Ac), astatine-211 (^{211}At), bismuth-212 and bismuth-213 (^{212}Bi , ^{213}Bi), copper-64 and copper-67 (^{64}Cu , ^{67}Cu), iodine -123, -124, -125 or -131 (^{123}I , ^{124}I , ^{125}I , ^{131}I) (^{123}I), lead-212 (^{212}Pb), lutetium-177 (^{177}Lu), radium-223 and radium-224 (^{223}Ra , ^{224}Ra), rhenium-186 and rhenium-188 (^{186}Re and ^{188}Re), samarium-153 (^{153}Sm), scandium-47 (^{47}Sc), strontium-90 (^{90}Sr), terbium-149 and terbium-161 (^{149}Tb and ^{161}Tb) and yttrium-90 (^{90}Y). In preferred embodiments, the radionuclide conjugated with the antibody or fragment thereof is actinium-225 or lutetium-177.

[0155] In any embodiment, the radiolabelled olaratumab antibody or antigen binding fragment thereof is ^{89}Zr -, ^{225}Ac - or ^{177}Lu -olaratumab wherein the radioisotope is conjugated to the olaratumab antibody directly or indirectly.

Administration of radiolabelled olaratumab and methods of treatment

[0156] Methods for preparing an antigen binding protein into a suitable form for administration to a subject (e.g. a pharmaceutical composition) are known in the art and include, for example, methods as described in Remington's Pharmaceutical Sciences

(18th ed., Mack Publishing Co., Easton, Pa., 1990) and U.S. Pharmacopeia: National Formulary (Mack Publishing Company, Easton, Pa., 1984).

[0157] The radiolabelled olaratumab antibody is usually administered as a pharmaceutical composition with a pharmaceutically acceptable carrier, e.g. physiological saline solution, or other aqueous carrier, optionally comprising a protein stabilizer such as human serum albumin (HSA). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of an antigen binding protein according to the present invention, in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. Exemplary carriers include water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Non-aqueous vehicles such as mixed oils and ethyl oleate may also be used. Liposomes may also be used as carriers. The vehicles may contain minor amounts of additives that enhance isotonicity and chemical stability, e.g., buffers and preservatives.

[0158] Administering refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art including those described herein. Pharmaceutical compositions may be formulated from active agents of the invention as described herein for any appropriate route of administration.

[0159] The radiolabelled olaratumab is preferably administered intravenously, preferably by infusion or intravenous injections. The administration of the antibody by infusion is preferably performed over a period of up to about 30 minutes, more preferably in about 15 minutes. Of course, the radiolabelled olaratumab can also be administered by subcutaneous, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal, and intracranial injection or infusion techniques.

[0160] The phrase 'therapeutically effective amount' or 'effective amount' generally refers to an amount of a radiolabelled olaratumab or antigen binding fragment thereof that (i) treats the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii)

delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what is an appropriate "effective amount".

[0161] For instance, for the treatment of tumours, a therapeutically effective amount of the radiolabelled antibodies or compositions described herein may inhibit tumour growth by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, by at least about 80%, or by at least about 90% or more, relative to untreated subjects. Alternatively, the treatments described herein may cause complete regression of the tumour mass. In other embodiments of the invention, tumour regression can be observed and continue for a period of at least about 10 days, at least about 20 days, at least about 30 days, at least about 40 days, at least about 50 days or at least about 60 days, at least about 70 days, at least about 80 days, at least about 90 days, at least about 100 days or longer.

[0162] A therapeutically effective amount of a drug may also include a "preventative" or "prophylactically effective amount," which is any amount of the radiolabelled olaratumab or antigen binding fragment thereof administered to a subject at risk of developing a cancer (eg a subject having a pre-malignant condition) or of suffering a recurrence of cancer, that inhibits the development or recurrence of the cancer. In certain embodiments, the prophylactically effective amount prevents the development or recurrence of the cancer entirely. "Inhibiting" or "preventing" the development or recurrence of a cancer means either lessening the likelihood of the cancer's development or recurrence, or preventing the development or recurrence of the cancer entirely.

[0163] The terms "treatment" or "treating" of a subject includes the application or administration of a compound of the invention to a subject with the purpose of delaying, slowing, stabilizing, curing, healing, alleviating, relieving, altering, remedying, less worsening, ameliorating, improving, or affecting the disease or condition, the symptom of the disease or condition, or the risk of (or susceptibility to) the disease or condition. The term "treating" refers to any indication of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; lessening of the rate of worsening; lessening severity of the disease; stabilization, diminishing of symptoms or making the injury, pathology or condition more tolerable to the subject; slowing in the rate of degeneration or decline;

making the final point of degeneration less debilitating; or improving a subject's physical or mental well-being.

[0164] As used herein, minimising or preventing the progression of cancer means treating the subject so as to prevent or delay the recurrence or metastasis of a tumour, or to prevent growth of an existing tumour. Minimising or preventing the progression of cancer includes preventing or delaying the recurrence of cancer, or preventing growth of an existing tumour, following treatment of cancer. The recurrence that is being prevented includes a recurrence for example, in the tumour bed, following surgical excision. Alternatively, recurrence includes metastasis of the cancer in another part of the body. The terms “preventing recurrence” and “preventing relapse” as used herein, are interchangeable.

[0165] The present invention also includes methods of preventing the development of cancer in an individual. For example, the individual for whom prevention of cancer is required may be considered to be at risk of developing cancer, but does not yet have detectable cancer. An individual at risk of the development of cancer may be an individual with a family history of cancer, and/or an individual for whom genetic testing or other testing indicates a high risk or high likelihood of the development of cancer. The individual may have cancer stem cells but does not yet have any detectable tumours. It will be understood that methods of preventing the development of cancer include methods of delaying the onset of cancer in a subject.

[0166] In some embodiments of the present disclosure, the cancer to be treated or prevented, or for which minimisation of progression is desired, is a soft tissue sarcoma, chondrosarcoma, leiomyosarcoma, liposarcoma, osteosarcoma, or rhabdomyosarcoma. In an embodiment of the present disclosure the cancer is a primary tumor. In an embodiment the cancer is a metastatic cancer. In yet other embodiments the cancer has metastasized.

[0167] The terms “soft tissue sarcoma” or “STS” as used herein, is a type of cancer that begins in the tissues that connect, support and surround other body structures. This includes fat, muscle, fibrous tissues, blood vessels, nerves, tendons, linings of joints, or deep skin tissues, and/or the lining of joints. They can be found in any part of the body. More than 50 subtypes of soft tissue sarcoma exist. Types of STS include, but are not limited to: angiosarcoma, dermatofibrosarcoma protuberans, epithelioid sarcoma,

gastrointestinal stromal tumor (GIST), Kaposi's sarcoma, liposarcoma, malignant peripheral nerve sheath tumors, myxofibrosarcoma, rhabdomyosarcoma, solitary fibrous tumor, synovial sarcoma, or undifferentiated pleomorphic sarcoma.

[0168] In any aspect or embodiment herein, the radiolabelled olaratumab may be administered in combination with (ie sequentially, simultaneously or following) administration of another treatment for the cancer. In any embodiment, the treatment may be any treatment for cancer, optionally selected from: surgery, immunotherapy, external beam radiation, chemotherapy or radio-immunotherapy.

[0169] Chemotherapeutic agents are chemical agents or drugs that are selectively destructive to cancer cells and tissues. Chemotherapeutics may include but are not limited to compounds such as, taxane compounds, compounds that act via taxane mechanisms, platinum compounds, anthracycline compounds, antimetabolites, epipodophyllotoxin compounds, camptothecin compounds, or any combination thereof.

[0170] In any aspect of the invention, the radiolabelled olaratumab and the additional treatment for cancer may be administered at the same time. Alternatively, they may be administered sequentially. For instance, the additional therapeutic (eg chemotherapeutic) may be administered prior to the radiolabelled olaratumab or the radiolabelled olaratumab may be administered prior to the additional therapeutic (eg chemotherapeutic). Alternatively, treatment with the additional therapeutic (eg chemotherapeutic) and/or the radiolabelled olaratumab may be staggered.

[0171] Suitable dosages of radiolabelled olaratumab or antigen binding fragment thereof for use according to the present invention will vary depending on the condition to be treated and/or the subject being treated. It is within the ability of a skilled physician to determine a suitable dosage, e.g., by commencing with a sub-optimal dosage and incrementally modifying the dosage to determine an optimal or useful dosage. Alternatively, to determine an appropriate dosage for treatment/prophylaxis, data from the cell culture assays or animal studies are used, wherein a suitable dose is within a range of circulating concentrations that include the ED₅₀ of the active compound with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. A therapeutically/prophylactically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that

includes the IC₅₀ (i.e., the concentration or amount of the compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma maybe measured, for example, by high performance liquid chromatography.

[0172] The skilled person will appreciate that dosage of the agent for use in accordance with the methods of the invention will depend on various factors including the age, sex, height and weight of the subject to whom the agent is administered, and depending on the agent.

[0173] Preferably the olaratumab is administered to a subject or infused at a dose from about 1 mg to about 50 mg, preferably in a dose from about 5 mg to about 20 mg, and more preferably in a dose of about 10 mg. The specific activity of the radiolabeled antibody is preferably about 15 to about 20 MBq/mg, more preferably about 18 to about 19 MBq/mg.

[0174] In certain embodiments, the radiolabelled olaratumab is administered at a mass dose of about 5 to 20 mg of olaratumab by slow infusion.

[0175] In some embodiments an effective amount of antibody or antigen binding fragment thereof is administered to the patient identified as having a cancer at a loading dose of about 15 mg/kg, or about 20 mg/kg, or about 25 mg/kg on each of day 1 and day 8 of a first 21 -day cycle or on each of day 1 and day 8 of a first 28-day cycle, followed by administering a standard dose of the antibody or antigen binding fragment thereof to the patient, at about 15 mg/kg, about 20 mg/kg, or about 25 mg/kg on each of day 1 and day 8 of a subsequent 21 -day cycle or on each of day 1 and day 8 of a subsequent 28-day cycle.

[0176] In some embodiments, the radiolabelled olaratumab or antigen binding fragment thereof disclosed herein, is continued for a minimum duration of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 1 year, at least about 18 months, at least about 24 months, at least about 3 years, at least about 5 years, or at least about 10 years. In some embodiments, treatment with a radiolabelled olaratumab or antigen binding fragment thereof disclosed herein, is

continued for a maximum duration of up to about 18 months, 16 months, 14 months, 12 months, 10 months, 8 months, or 6 months. The treatment duration may be from any of these minimum durations to any of these maximum durations, for example from 1 to 18 months.

[0177] As used herein, the terms “subject” “individual” and “patient” will be understood to be interchangeable. Although the invention finds application in humans, the invention is also useful for therapeutic veterinary purposes. The invention is useful for domestic or farm animals such as cattle, sheep, horses and poultry; for companion animals such as cats and dogs; and for zoo animals.

Kits

[0178] In another embodiment there is provided a kit or article of manufacture including a radiolabelled olaratumab or antigen binding fragment, as described above, preferably provided for use in a method or use outlined herein.

[0179] Optionally the kit further comprises a label or package insert with instructions for use.

[0180] The kit or “article of manufacture” may comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a therapeutic composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The label or package insert indicates that the therapeutic composition is used for treating the condition of choice. In one embodiment, the label or package insert includes instructions for use.

[0181] The kit may comprise (a) a therapeutic composition; and (b) a second container with a second active principle or ingredient contained therein. The kit in this embodiment of the invention may further comprise a package insert indicating that the and other active principle can be used to treat a disorder or prevent a complication stemming from cancer. Alternatively, or additionally, the kit may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWI), phosphate-buffered saline, Ringer's solution and dextrose solution. It

may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0182] In certain embodiments the therapeutic composition may be provided in the form of a device, disposable or reusable, including a receptacle for holding the therapeutic composition. In one embodiment, the device is a syringe. The device may hold 1-2 mL of the therapeutic composition. The therapeutic composition may be provided in the device in a state that is ready for use or in a state requiring mixing or addition of further components.

[0183] It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

[0184] The examples that follow are intended to illustrate but in no way limit the present invention.

Examples

Example 1: Synthesis and characterisation of bioconjugates

[0185] An olaratumab immunoglobulin antibody (eg comprising a VH as set forth in SEQ ID NO: 4 and a VL as set forth in SEQ ID 12) was used to generate olaratumab-bioconjugates in the form of DOTA-Olaratumab and DFOSq-Olaratumab.

[0186] DOTA-Oloratumab and DFOSq-Olaratumab bioconjugation was performed using standard methods. 30 mg of each conjugate was synthesized, and analytical characterisation of the conjugates was undertaken.

[0187] Table 2: Conjugation reaction of Olaratumab with DOTA-NHS ester

Reagents	Antibody: 0.2 mg	
	DOTA-NHS ester: MW 501.5 g/mol @35 mg/mL; 25-30 eq per mAb	
	Buffer: 100 mM sodium borate, pH 9	
Reaction conditions	Time	2 hrs
	Temperature	22°C

[0188] DOTA-NHS conjugate demonstrated high monomeric purity (>98%) and values of 4.4 and 4.3 for DOTA-Olaratumab 1 and DOTA-Olaratumab 2 (generated using two different cell culture methods respectively); value of degree of antibody labelling (DOL) (data not shown).

[0189] Table 3: Conditions of the conjugation reaction of Olaratumab with DFO-sq

Reagents	Antibody: 0.2 mg	
	DFO-sq: MW 684.8 g/mol @5 mg/mL; 16-18 eq per mAb	
	Buffer: 100 mM sodium borate, pH 9	
	Organic co-solvent: 10% DMSO	
Reaction conditions	Time	3 hrs
	Temperature	22°C

[0190] Size exclusion chromatography (SEC) screening of DFOsq-olaratumab conjugate with DFPsq indicated high monomeric purity (>98%) after conjugation (data not shown).

[0191] DFOsq-conjugated olaratumab was further assessed for the characteristics listed below in table 3.

[0192] Table 4: analytical characterisation of DOTA and DFOsq bioconjugates produced in stable and transient transfection cell lines

	Assay	DOTA	DFOsq
Batch Number		TEPH-2187-MI002-2	TEPH-2187-MI002-3
Purity	SEC	>99.5% monomeric	>99.1% monomeric
	Endotoxin	0.12 EU/mg	0.03 EU/mg
Identity and DOL	LC-MS	DAR 3.8	DAR 2-3
Concentration	UV	2.5 mg/mL	3.44 mg/mL
Formulation and storage		50 mM Sodium acetate, 150 mM sodium chloride, pH 5.5 -80°C	PBS, pH 7.1 -80°C

Biacore antibody and conjugate screening for binding to PDGFR α

[0193] Comparative binding of the produced conjugates and Olaratumab to PDGFR α (Sino Biological, #10556-H08H, Lot#LC15MY0708) was tested using Biacore MCK, surface plasmon resonance-based technology (Figure 2). Instrument used was Biacore

T200. Running buffer: HBS-P+ buffer containing 1 mg/ml BSA. Chip: Protein A capture Sensor chip. Analysis temperature: 25 °C. Flow rate: 30 µl/min. Ligand: purified antibody ~80 RU at 10 µl/min. Analyte: human PDGFRα. Dilution range: 8 point 3-fold dilution from 270 nM to 0.123 nM. Analyte injection time: 240 s. Analyte dissociation time: 1200 s. Regeneration: glycine pH 1.5. Analysis: 1:1 binding with double reference subtraction.

[0194] The results indicated that all tested antibodies bind with similar affinity to PDGFRα (Table 5).

[0195] Table 5: Characterisation of naked olaratumab, DOTA- and DFOSq-conjugated olaratumab binding to PDGFRα

Ligand	K _a (1/Ms)	K _d (1/s)	K _D (M)	R _{MAX}	Chi ² (RU ²)
Olaratumab	3.39E+05	2.07E-03	6.11E-09	37.6	0.259
DOTA-Olaratumab	3.88E+05	2.09E-03	5.38E-09	32.3	0.305
DFOSq-Olaratumab	3.75E+05	2.10E-03	5.61E-09	35.8	0.328
Olaratumab	3.31E+05	1.93E-03	5.83E-09	43.8	0.362
DOTA-Olaratumab	3.82E+05	2.07E-03	5.41E-09	35.9	0.181
DFOSq-Olaratumab	3.62E+05	2.01E-03	5.56E-09	32.1	0.203

Example 2: Validation of PDGFRα expression in selected cell lines

[0196] Selection of the cell lines for the subsequent tests in xenograft tumour models was based on data published by Lowery et al, 2017, where efficacy of olaratumab has been demonstrated in HuO9 (osteosarcoma) and A-204 (embryonal rhabdomyosarcoma) cell lines.

[0197] Figure 3 shows total and surface PDGFRA expression was ascertained with in KRIB, HuO9 and A-204 sarcoma cell lines. All three cell lines expressed PDGFRA, which was most abundant in the HuO9; however, HuO9 cells were found to have smaller proportion of the total amount of PDGFRA localised to the plasma membrane.

[0198] PDGF-AA stimulation of all three cell lines triggered phosphorylation of AKT on serine 473. This was abolished by prior incubation with olaratumab (Figure 4).

Example 3: Development of *in vivo* xenograft model

[0199] KRIB and A204 cell line growth properties were tested in a xenograft model in Balb/c Nude mice. Both cell lines showed reproducible growth and good “take-rates”. The

A204 cell clone was selected for subsequent biodistribution studies in view of greater radiosensitivity of that cell line to ionising radiation.

[0200] Radiolabelling of DFOSq-Olaratumab yielded 94% radiochemical purity as assessed with Quality Control methods. Surface binding and internalisation of the radiolabelled antibodies to the chosen reference cell line was assessed in binding and Immunoreactive Fraction (IRF) assay.

[0201] Ratio of activity to cells was based on initial pilot which showed similar saturated binding with 1.25 and 2.5 kBq/5 million cells at 1 hour, and no binding to negative control cells (specific activity at 1 MBq/ 4 µg). Saturated binding (IRF) was established to be at around 40% in the A204 cells at 1 h and ~3% binding in the negative control line (HCC827) (Figure 5, A). 30-50% of the total binding was found to be internalised after 1 h (Figure 5, B).

Example 4: Imaging and biodistribution studies

[0202] Balb/c nude mice (N=4) were injected with 5.03 MBq at antibody mass dose of 20 µg and PET images were taken at 1, 2, 4 and 6 days after injection (Figure 6). For the blocking 344 µg (a nominal 17-fold excess) of unlabelled antibody conjugate was co-injected. Blocking mice were imaged at 1-day post-injection and re-imaged at the later timepoint(s) or harvested by biodistribution. Mice were euthanised and tissues harvested for biodistribution at 1, 2 and 4 days post injection (n=4 per time point) (Figure 7).

[0203] Imaging and biodistribution analyses demonstrated that radiolabelled Olaratumab is targeted to tumour with high tumour/background ratio over the tested period. High tumour uptake of ~55% of ID/g was observed at 120 hrs post-injection and demonstrated tumour/background ratio ~20.

Example 5: Efficacy studies in xenograft tumour model

[0204] 20 x Balb/c Nude mice were implanted subcutaneously on the right flank with A204 cells. Of these, 16 mice were subsequently treated with 10 MBq of ¹⁷⁷Lu-DOTA-Olaratumab, at antibody mass dose of 40 µg. 4 Mice received vehicle (non-radiolabelled-DOTA-Olaratumab).

[0205] Tumour volumes (Figure 8 and 9) and mice survival (Figure 10) were monitored over several weeks.

[0206] The A204 xenograft model showed exponential growth in the vehicle control group (cold-DOTA-Olaratumab) with a doubling time of approximately 7 days. Treatment with 10 MBq of ^{177}Lu -DOTA-Olaratumab induced initial stasis and gradual tumour regression and suppression (Figure 8 and 9), with 3 mice still alive at the end of the study on Day 90 (Figure 10), 2 mice reaching tumour endpoint (Day 50 and 68) and 2 euthanised due to weight loss.

[0207] The differences in tumour volume (change from Day 1) between the groups were statistically significant at day 20 ($P = 0.0003$ unpaired T-test) after which the differences continued to increase (but could not be statistically tested due to mice reaching endpoint).

CLAIMS

1. An olaratumab antibody or olaratumab antibody bioconjugate, suitable for radiolabelling with a therapeutic radioisotope.
2. The olaratumab bioconjugate of claim 1, wherein the bioconjugate comprises an olaratumab antibody conjugated to a chelating or linker group selected from: TMT (6,6"-bis[N,N",N""-tetra(carboxymethyl)aminomethyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2"-terpyridine), DOTA (1,4,7,10-tetraazacyclododecane-NN',N"(N""-tetraacetic acid), TCMC, DO3A, CB-DO2A, NOTA, Diamsar, DTPA, CHX-A"-DTPA, TETE, Te2A, HBED, DFO, DFOsq, DFO-NCS and HOPO.
3. An olaratumab antibody or antigen binding fragment thereof, conjugated to a radioisotope suitable for therapeutic use, for:
 - treating or preventing or minimising the progression of a cancer characterised by or associated with the expression of PDGFRalpha.
4. The olaratumab antibody or antigen binding fragment thereof, or the antibody bioconjugate of any one of claims 1 to 3, comprising an antigen binding domain that competitively inhibits the binding of an antibody comprising a VH comprising a sequence as set forth in SEQ ID NO: 4 and a VL comprising a sequence as set forth in SEQ ID NO: 12.
5. The olaratumab antibody or antigen binding fragment thereof, or the antibody bioconjugate of any one of claims 1 to 4, wherein the antibody or fragment thereof comprises an HCDR1, a HCDR2 and an HCDR3 of an antigen binding domain having a variable heavy chain as defined in in SEQ ID NO: 4 and a LCDR1, LCDR2 and LCDR3 of an antigen binding domain having a VL as defined in SEQ ID NO: 12.
6. The olaratumab antibody or antigen binding fragment thereof of any one of claims 1 to 5, wherein the antibody or antigen binding fragment comprises an antigen binding domain comprising:
 - (i) a VH comprising a complementarity determining region (CDR) 1 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%,

at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set in SEQ ID NO: 2, and a CDR3 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 3;

(ii) a VH comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 4;

(iii) a VL comprising a CDR1 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 11;

(iv) a VL comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 12;

- (v) a VH comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence set forth in SEQ ID NO: 2 and a CDR3 comprising a sequence set forth in SEQ ID NO: 3;
- (vi) a VH comprising a sequence set forth in SEQ ID NO: 4;
- (vii) a VL comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence set forth in SEQ ID NO: 11;
- (viii) a VL comprising a sequence set forth in SEQ ID NO: 12;
- (ix) a VH comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 1, a CDR2 comprising a sequence set forth between in SEQ ID NO: 2, and a CDR3 comprising a sequence set forth in SEQ ID NO: 3; and a VL comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10, and a CDR3 comprising a sequence set forth in SEQ ID NO: 11; or
- (x) a VH comprising a sequence set forth in SEQ ID NO: 4, and a VL comprising a sequence set forth in SEQ ID NO: 12.

7. The olaratumab antibody or antigen binding fragment thereof of claim 6, further comprising:

- (i) a VH comprising a framework region (FR) 1 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 5; a FR2 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 6; a FR3 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical

to a sequence as set forth in SEQ ID NO: 7; a FR4 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 8; and

(ii) a VL comprising a framework region (FR) 1 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 13; a FR2 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 14; a FR3 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 15; a FR4 comprising or consisting of a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% at least 99% identical to a sequence as set forth in SEQ ID NO: 16.

8. The olaratumab antibody or antigen binding fragment thereof of claim 6, further comprising:

(i) a VH comprising a framework region (FR) 1 comprising or consisting of a sequence as set forth in SEQ ID NO: 5; a FR2 comprising or consisting of a sequence as set forth in SEQ ID NO: 6; a FR3 comprising or consisting of a sequence as set forth in SEQ ID NO: 7; a FR4 comprising or consisting of a sequence as set forth in SEQ ID NO: 8, and

(ii) a VL comprising a framework region (FR) 1 comprising or consisting of a sequence as set forth in SEQ ID NO: 13; a FR2 comprising or consisting of a sequence

as set forth in SEQ ID NO: 14; a FR3 comprising or consisting of a sequence as set forth in SEQ ID NO: 15; a FR4 comprising or consisting of a sequence as set forth in SEQ ID NO: 16.

9. The olaratumab antibody or antigen binding fragment thereof of any one of claims 1 to 8, wherein the antibody or antigen binding fragment thereof comprises a VH comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 4; and/or a VL comprising a sequence at least about 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to a sequence set forth in SEQ ID NO: 12; wherein the sequence variation between the VH and VL and the sequence of SEQ ID NO: 4 and 12 is not in the CDRs and wherein the antigen binding protein retains the ability to bind to PDGFRalpha.

10. The olaratumab antibody or antigen binding fragment thereof of any one of claims 1 to 9, wherein the antibody or antigen binding fragment thereof comprises a VH and/or a VL comprising no more than 1, no more than 2, no more than 3, no more than 4, no more than 5, no more than 6, no more than 7, no more than 8, no more than 9, no more than 10, no more than 11, no more than 12, no more than 13, no more than 14, no more than 15, no more than 16, no more than 17, no more than 18, no more than 19 or no more than 20 amino acid residue substitutions, deletions or additions, compared to the amino acid sequences as set forth in SEQ ID NO: 4 or 12, respectively; wherein the amino acid substitutions, deletions or additions are not in the CDRs and the antigen binding protein retains the ability to bind to PDGFRalpha.

11. The olaratumab antibody or antigen binding fragment thereof of any one of claims 1 to 10, wherein the antibody or antigen binding fragment is in the form of:

- (i) a single domain antibody (sdAb);
- (ii) a single chain Fv fragment (scFv);
- (iii) a dimeric scFv (di-scFv); or

(iv) one of (ii) or (iii) linked to a constant region of an antibody, Fc or a heavy chain constant domain (CH) 2 and/or CH3.

12. The olaratumab or antigen binding fragment thereof of any one of claims 1 to 10, wherein the antibody or antigen binding fragment thereof is in the form of:

(i) a diabody;

(ii) a triabody;

(iii) a tetrabody;

(iv) a Fab;

(v) a F(ab')₂;

(vi) a Fv;

(vii) a bispecific antibody or other form of multispecific antibody; or

(viii) one of (i) to (vii) linked to a constant region of an antibody, Fc or a heavy chain constant domain (CH) 2 and/or CH3.

13. The olaratumab antibody or antigen binding fragment thereof of any one of claims 1 to 12, wherein the antibody or antigen binding fragment thereof is in the form of an immunoglobulin, such as an IgG₁, IgG₂, IgG₃ or IgG₄.

14. The olaratumab antibody of claim 13, wherein the olaratumab antibody comprises a heavy chain constant region as defined in SEQ ID NO: 17 and/or a light chain constant region as defined in SEQ ID NO: 18.

15. The olaratumab antibody of claim 13 or 14, wherein the olaratumab antibody comprises a heavy chain as set forth in SEQ ID NO: 19 and/or a light chain as set forth in SEQ ID NO: 20.

16. The olaratumab antibody of any one of claims 13 to 15, wherein the olaratumab antibody comprises one or more amino acid substitutions in the constant regions, so as to reduce the *in vivo* half-life of the antibody.

17. The olaratumab antibody of any one of claims 13 to 16, wherein the antibody comprises substitutions at one or more of residues His310, His435, His436 and Ile253 of the constant region of the antibody.
18. The olaratumab antibody of any one of claims 13 to 17 wherein the antibody comprises an amino acid substitution at position 310 selected from alanine, glutamic acid or glutamine.
19. The olaratumab antibody of any one of claims 13 to 18, wherein the antibody comprises an amino acid substitution at position 435 selected from arginine, glutamine or alanine.
20. The olaratumab antibody of any one of claims 13 to 19, wherein the antibody comprises an alanine residue at position 310 and glutamine residue at position 435.
21. The olaratumab antibody of any one of claims 13 to 20, wherein the antibody comprises an amino acid substitution at residue Lys322, preferably wherein the substitution is K322A.
22. The olaratumab antibody of any one of claims 16 to 21, wherein the binding affinity for FcRn and/or the serum half-life of the antibody is decreased by at least about 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, or 100-fold; or wherein the binding affinity for FcRn and/or the serum half-life of said modified antibody is reduced by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 98%, or 99%, compared to an immunoglobulin that does not comprise the same substitutions.
23. The olaratumab antibody or antigen binding fragment of any one of claims 3 to 22, wherein the antibody or antigen binding fragment is conjugated to a radioisotope suitable for treatment of tumour or cancer masses.
24. The olaratumab antibody or antigen binding fragment of claim 23, wherein the radioisotope is selected from: actinium-225 (^{225}Ac), astatine-211 (^{211}At), bismuth-212 and bismuth-213 (^{212}Bi , ^{213}Bi), copper-64 and copper-67 (^{64}Cu , ^{67}Cu), iodine -123, -124, -125 or -131 (^{123}I , ^{124}I , ^{125}I , ^{131}I) (^{123}I), lead-212 (^{212}Pb), lutetium-177 (^{177}Lu), radium-223 and radium-224 (^{223}Ra , ^{224}Ra), rhenium-186 and rhenium-188 (^{186}Re and ^{188}Re), samarium-

^{153}Sm), scandium-47 (^{47}Sc), strontium-90 (^{90}Sr), terbium-149 and terbium-161 (^{149}Tb and ^{161}Tb) and yttrium-90 (^{90}Y).

25. The olaratumab antibody or antigen binding fragment of claim 24, wherein the radioisotope is actinium-225 or lutetium-177 and wherein the radioisotope is conjugated to the olaratumab antibody directly or indirectly.

26. The olaratumab antibody of any one of claims 23 to 25, wherein the radioisotope is conjugated to the olaratumab directly e.g. by halogenation of amino acid residues.

27. The olaratumab of any one of claims 23 to 25, wherein the radioisotope is linked indirectly to the olaratumab or antigen binding fragment thereof, for example via a chelator or other linking moiety.

28. The olaratumab of claim 27, wherein the olaratumab is conjugated to a chelating moiety selected from the group consisting of: TMT (6,6"-bis[N,N",N'''-tetra(carboxymethyl)aminomethyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2"-terpyridine), DOTA (1, 4,7,10-tetraazacyclododecane-NN',N''(N'''-tetraacetic acid), TCMC, DO3A, CB-DO2A, NOTA, Diamsar, DTPA, CHX-A"-DTPA, TETE, Te2A, HBED, DFO, DFOsq, DFO-NCS and HOPO or other chelating agent known to the skilled person.

29. The radiolabelled olaratumab antibody or antigen binding fragment thereof of any one of claims 24 to 28, wherein the antibody is ^{177}Lu -olaratumab or a ^{177}Lu -labelled olaratumab, preferably wherein the ^{177}Lu is conjugated to the olaratumab via a linker.

30. A method of treating, preventing or minimising progression of cancer in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof of any one of claims 3 to 29,

thereby treating, preventing or minimising progression of cancer in the subject.

31. A method of minimising, reducing or preventing growth of a tumour in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof of any one of claims 3 to 29,

thereby minimising, reducing or preventing growth of a tumour in the subject.

32. A method of minimising, reducing or preventing metastasis of cancer in a subject, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof of any one of claims 3 to 29,

thereby minimising, reducing or preventing metastasis of cancer in the subject.

33. A method of increasing survival of a subject suffering from cancer, the method comprising:

- administering to a subject in need thereof, a radiolabelled olaratumab antibody or antigen binding fragment thereof of any one of claims 3 to 29,

thereby increasing survival of the subject.

34. Use of a radiolabelled olaratumab or antigen binding fragment thereof of any one of claims 3 to 29, in the manufacture of a medicament for:

- treating, preventing or minimising progression of cancer in a subject,
- minimising, reducing or preventing growth of a tumour in a subject,
- minimising, reducing or preventing metastasis in a subject, or
- increasing survival of a subject suffering from cancer.

35. The method of any one of claims 30 to 33 or the use of claim 34, wherein the cancer is selected from the list consisting of: soft tissue sarcoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, liposarcoma and rhabdomyosarcoma.

36. The method of any one of claims 30 to 33, or 35, wherein the cancer is characterised by the expression of PDGFRalpha in the tumour cells and/or the tumour stroma.

37. The method or use of claim 35 or 36 wherein the tumour or cancer is non-metastatic.

38. The method or use of claim 35 or 36, wherein the cancer is malignant or metastatic.