

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
01 March 2018 (01.03.2018)

(10) International Publication Number
WO 2018/038684 A1

(51) International Patent Classification:
C07K 16/30 (2006.01) *A61P 35/00* (2006.01)
A61K 39/395 (2006.01) *G01N 33/53* (2006.01)

(71) Applicant: AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH [SG/SG]; 1 Fusionopolis Way, #20-10 Connexis North Tower, Singapore 138632 (SG).

(21) International Application Number:
PCT/SG2017/050424

(72) Inventors: LANE, David; c/o p53 Laboratory, 8A Biomedical Grove, #06-04/05 Neuros, Singapore 138646 (SG). KOH, Xin Yu; c/o p53 Laboratory, 8A Biomedical Grove, #06-04/05 Neuros, Singapore 138646 (SG). HWANG, Le-Ann; c/o p53 Laboratory, 8A Biomedical Grove, #06-04/05 Neuros, Singapore 138646 (SG).

(22) International Filing Date:
28 August 2017 (28.08.2017)

(74) Agent: SPRUSON & FERGUSON (ASIA) PTE LTD; P.O. Box 1531, Robinson Road Post Office, Singapore 903031 (SG).

(25) Filing Language: English

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,

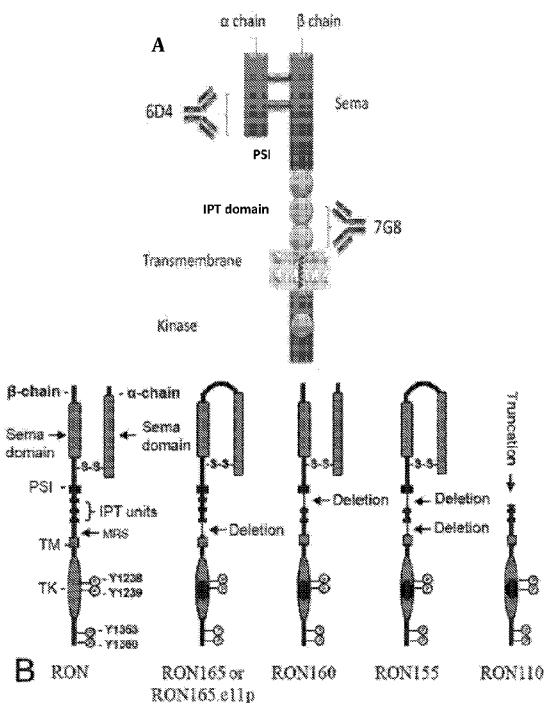
(26) Publication Language: English

(30) Priority Data:

10201607147P	26 August 2016 (26.08.2016)	SG
10201700393P	17 January 2017 (17.01.2017)	SG
10201700521V	20 January 2017 (20.01.2017)	SG
10201703234U	19 April 2017 (19.04.2017)	SG

(54) Title: MACROPHAGE STIMULATING PROTEIN RECEPTOR (OR RON - RECEPTEUR D' ORIGINE NANTAIS) ANTIBODIES AND USES THEREOF

FIGURE 4



(57) Abstract: Disclosed are monoclonal antibodies that bind specifically to macrophage stimulating protein receptor (or RON - Recepteur d' Origine Nantaïs). Also provided are the chimeric antigen receptors, bispecific antibodies, bivalent antibodies and biTE thereof, as well as pharmaceutical compositions and uses of said antibodies for the treatment of cancer and fibrosis and an *ex vivo* method of evaluating the status of a cancer patient using said antibodies. In particular, two monoclonal antibodies, 7G8 and 6D4, demonstrating good therapeutic efficacy in inhibiting tumour growth in human xenograft mice models and sensitivity in human xenograft mouse tumour imaging models are provided.



KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *of inventorship (Rule 4.17(iv))*

Published:

- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*

MACROPHAGE STIMULATING PROTEIN RECEPTOR (OR RON -
RECEPTEUR D' ORIGINE NANTAIS) ANTIBODIES AND USES
THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of Singapore patent application No. 5 10201607147P, filed 26 August 2016, Singapore patent application No. 10201700393P, filed on 17 January 2017, Singapore patent application No. 10201700521V, filed on 20 January 2017, and Singapore patent application No. 10201703234U, filed on 19 May 2017, the contents of it being hereby incorporated by reference in its entirety for all purposes.

10

FIELD OF THE INVENTION

[0002] The present invention relates to a preparation for medical purpose or specific therapeutic activity of a preparation. In particular, the present invention relates to antibodies and other agents that bind to RON (i.e. Macrophage stimulating protein receptor or RON-Recepteur d' Origine Nantais), as well as to methods of using the antibodies or other agents for 15 the treatment of diseases.

BACKGROUND OF THE INVENTION

[0003] Cancer treatments have advanced enormously in recent times, especially with the availability of immunotherapeutics, such as Herceptin®. However, there are a large number of 20 cancers for which no effective treatment is available. Furthermore, there are other cancers for which treatments are available but for which resistance develops during treatment. In the context of immunotherapeutics one approach to improve efficacy is to prepare an antibody drug conjugate. In other contexts combinations of chemotherapy have been employed to try and address tumour resistance. These approaches have provided limited success.

25 [0004] Thus, there is presently an unmet medical need for alternative cancer therapies.

SUMMARY OF THE INVENTION

[0005] In one aspect there is provided an antigen specific binding domain comprising the heavy chain CDRs of CDRH1, CDRH2, and CDRH3 and/or the light chain CDRs of CDRL1, CDRL2, 30 and CDRL3, wherein

- (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, SEQ ID NO: 100, SEQ ID NO: 116, and SEQ ID NO: 135 or a CDRH1 sequence differing 1 or 2 amino acids therefrom;
- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, SEQ ID NO: 101, SEQ ID NO: 117, and SEQ ID NO: 136; or a CDRH2 sequence differing 1 or 2 amino acids therefrom;

- (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, SEQ ID NO: 102, and SEQ ID NO: 137; or a CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, and SEQ ID NO: 144; or a CDRL1 sequence differing 1 or 2 amino acids therefrom;
- (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 109; or a CDRL2 sequence differing 1 or 2 amino acids therefrom; and
- (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 220, SEQ ID NO: 123, and SEQ ID NO: 145; or a CDRL2 sequence differing 1 or 2 amino acids therefrom.

[0006] In another aspect there is provided an antigen specific binding domain comprising CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein:

- (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, and SEQ ID NO: 100, SEQ ID NO: 116, SEQ ID NO: 135 and a CDRH1 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, and SEQ ID NO: 101, SEQ ID NO: 117, SEQ ID NO: 136 and a CDRH2 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, and SEQ ID NO: 102, SEQ ID NO: 137 and a CDRH3 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, SEQ ID NO: 144 and a CDRL1 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, SEQ ID NO: 109 and a CDRL2 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added.; and
- (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 110, SEQ ID NO: 123, SEQ ID NO: 145 and a CDRL3 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added.

[0007] In some examples, the antigen specific binding domain as described herein may have CDRH1 that is SEQ ID NO: 1, CRDH2 is SEQ ID NO: 2, and CDRH3 is SEQ ID NO: 3 or a RON specific binding domain wherein one or more modified sequences 1, 2, and 3 are employed and the modification(s) is independently selected from replacement, deletion or addition of 1 or 2 amino acids.

[0008] In some examples, the antigen specific binding domain as described herein may have the heavy chain CDRs are selected from the group consisting of

- (i) the CDRH1 is SEQ ID NO: 1, the CRDH2 is SEQ ID NO: 2, the CRDH3 is SEQ ID NO: 3;
- (ii) the CDRH1 is SEQ ID NO: 27, the CRDH2 is SEQ ID NO: 28, the CRDH3 is SEQ ID NO: 29;
- (iii) the CDRH1 is SEQ ID NO: 45, the CRDH2 is SEQ ID NO: 46, the CRDH3 is SEQ ID NO: 47;
- (iv) the CDRH1 is SEQ ID NO: 56, the CRDH2 is SEQ ID NO: 57, the CRDH3 is SEQ ID NO: 58;
- (v) the CDRH1 is SEQ ID NO: 73, the CRDH2 is SEQ ID NO: 74, the CRDH3 is SEQ ID NO: 75;
- (vi) the CDRH1 is SEQ ID NO: 89, the CRDH2 is SEQ ID NO: 90, the CRDH3 is SEQ ID NO: 91;
- (vii) the CDRH1 is SEQ ID NO: 100, the CRDH2 is SEQ ID NO: 101, the CRDH3 is SEQ ID NO: 102; and
- (viii) the CDRH1 is SEQ ID NO: 135, the CRDH2 is SEQ ID NO: 136, the CRDH3 is SEQ ID NO: 137.

[0009] In some examples, the antigen specific binding domain as described herein may have the light chain CDRs are selected from the group consisting of

- (i) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (ii) the CDRL1 is SEQ ID NO: 36, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 38;
- (iii) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (iv) the CDRL1 is SEQ ID NO: 65, the CDRL2 is SEQ ID NO: 66, the CDRL3 is SEQ ID NO: 67;
- (v) the CDRL1 is SEQ ID NO: 81, the CDRL2 is SEQ ID NO: 82, the CDRL3 is SEQ ID NO: 83;

(vi) the CDRL1 is SEQ ID NO: 108, the CDRL2 is SEQ ID NO: 109, the CDRL3 is SEQ ID NO: 110; and

(vii) the CDRL1 is SEQ ID NO: 144, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 145.

5 [0010] In some examples, the antigen specific binding domain as described herein, wherein the variable heavy domain has a sequence selected from the group consisting of:

(i) SEQ ID NO: 8;

(ii) SEQ ID NO: 34;

(iii) SEQ ID NO: 51;

10 (iv) SEQ ID NO: 63;

(v) SEQ ID NO: 79;

(vi) SEQ ID NO: 95;

(vii) SEQ ID NO: 106; and

(viii) SEQ ID NO: 142.

15 [0011] In some examples, the antigen specific binding domain as described herein, wherein the variable light domain has a sequence selected from the group consisting of

(i) SEQ ID NO: 25;

(ii) SEQ ID NO: 43;

(iii) SEQ ID NO: 54;

20 (iv) SEQ ID NO: 71;

(v) SEQ ID NO: 87;

(vi) SEQ ID NO: 98;

(vii) SEQ ID NO: 114; and

(viii) SEQ ID NO: 150.

25 [0012] In another aspect, there is provided a chimeric antigen receptor comprising a binding domain as described herein.

[0013] In another aspect, there is provided an isolated antibody or antibody comprising a binding domain as described herein.

30 [0014] In some examples, the isolated antibody or antibody as described herein may be selected from a group consisting of multispecific antibody, a full-length antibody, and an antibody binding fragment.

[0015] In some examples, the isolated antibody or antibody as described herein, where the multispecific antibody is bispecific antibody.

35 [0016] In some examples, the isolated antibody or antibody as described herein, wherein the bispecific antibody is a bispecific T cell engager (Bite®).

[0017] In some examples, the isolated antibody or antibody as described herein, wherein the bispecific antibody comprises one binding domain specifically binding to a first RON epitope, and a second binding domain specifically binding to a second RON epitope which is different from the first RON epitope.

5 [0018] In some examples, the isolated antibody or antibody as described herein, wherein a first RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20.

[0019] In some examples, the isolated antibody or antibody as described herein comprising a second RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 36, 37 and 38.

10 [0020] In some examples, the isolated antibody or antibody as described herein wherein the antibody molecule comprises an effector function.

[0021] In some examples, the isolated antibody or antibody as described herein wherein the antibody is conjugated to a payload. In some examples, the payload is selected from a wherein 15 the payload is selected from a group consisting of toxin, a polymer, biologically active proteins, nucleic acids and fragments thereof radionuclides chelated metals, nanoparticles and reporter groups.

20 [0022] In some examples, wherein the toxin in selected from a group consisting of an auristatin, MMAF (monomethyl auristatin F), pyrrolobenzodiazepine (PBD), doxorubicin, duocarmycin, a maytansinoid, calicheamicin, dolastatin, Maytansine, α -Amanitin, and a Tubulysin.

[0023] In yet another aspect, there is provided a pharmaceutical composition comprising an antibody as described herein and an excipient, diluent and/or carrier.

25 [0024] In some examples, the pharmaceutical composition as described herein comprises at least two antigen specific antibody as described herein. In some examples, one of the at least two antigen specific antibody comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20; optionally where a second antibody of the at least two antibodies comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 36, 37 and 38.

30 [0025] In yet another aspect, there is provided an antigen binding domain as described herein, or a chimeric antigen receptor as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein, for use in therapy or treatment.

[0026] In yet another aspect, there is provided a method of preventing or treating cancer or fibrosis in a patient comprising administering a therapeutic effective amount of an antigen 35 binding domain as described herein, or a chimeric antigen receptor as described herein, or an

antibody as described herein, or a pharmaceutical composition as described herein to the patient in need thereof.

[0027] In some examples, the patient is a patient population characterised in that patients making up the population have a RON positive tumour. In some examples, the patients making up the population have a RON positive and C-MET positive tumour.

[0028] In some examples, the method as described herein, comprises the step of identifying the patient to have a RON positive tumour before treatment.

[0029] In yet another aspect, there is provided the use of an antigen binding domain as described herein, or a chimeric antigen receptor as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of cancer or fibrosis.

[0030] In yet another aspect, there is provided an antibody which cross-blocks or binds the same epitope as an antibody comprising a variable heavy region (VH) of SEQ ID NO: 8, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 63, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 106, SEQ ID NO: 121, SEQ ID NO: 130, SEQ ID NO: 133 or 142.

[0031] In yet another aspect, there is provided antibody, which cross-blocks or binds the same epitope as an antibody comprising a variable heavy region/variable light region (VH/VL) pair selected from a group consisting of SEQ ID NO: 8 and 25, SEQ ID NO: 34 and 43, SEQ ID NO: 51 and 54, SEQ ID NO: 63 and 71, SEQ ID NO: 79 and 87, SEQ ID NO: 95 and 98, SEQ ID NO: 106 and 114, SEQ ID NO: 121 and 130 or SEQ ID NO: 142 and 150.

[0032] In yet another aspect, there is provided an ex vivo method of evaluating the status of a cancer; wherein the method comprises: a) scanning a patient or a specific site of the patient known to comprise a tumor of the cancer, wherein the patient had been administered with a labelled form of an antibody at a first time point, wherein the antibody is as defined herein, b) repeating a) at one or more further time points, and comparing the results from two or more time points to evaluate the status of the cancer.

BRIEF DESCRIPTION OF THE FIGURES

[0033] **Figure 1A** shows a bar graph illustrating the results of an ELISA-Based Binding Assay of exemplary anti-RON Antibodies (such as 6D4 and 7G8 clones) to Coated Recombinant Truncated RON Proteins as well as GST Protein. Proteins were coated at 0.1 μ g/ml. Antibody supernatants were tested and absorbance was observed at 650nm.

[0034] **Figure 1B** shows a bar graph illustrating the results of an ELISA-Based Binding Assay of exemplary anti-RON Antibodies to Coated Recombinant Truncated RON Proteins (GST-RON1 and GST-RON3) as well as GST Protein. Proteins were coated at 0.1 μ g/ml. Antibody supernatants were tested and absorbance was observed at 650nm. Thus, Figure 1 shows anti-

RON Antibodies as described herein binds to RON-GST with minimal background binding to GST protein.

[0035] **Figure 2** shows immunofluorescence staining of exemplary anti-RON Antibodies (6D4 and 7G8 antibodies) on PFA fixed HCT116 cells (human colorectal carcinoma). Cells were

5 stained with DAPI for nuclear visualization and anti-mouse conjugate to 488 was used as a secondary mouse antibody. Thus, Figure 2 shows anti-RON Antibodies as described herein binds to truncated RON proteins can stain human colorectal cells (such as HCT116 cells). In addition, staining is specific for RON as anti-RON Antibodies do not stain RON negative cell lines such as mouse embryonic fibroblast (named TKO).

10 [0036] **Figure 3** shows immunohistochemistry staining of xenograft mouse tumour tissues using exemplary anti-RON Antibodies (6D4 and 7G4 antibodies). Serums from mice were injected with recombinant RON protein was used as a positive control. Thus, Figure 3 shows anti-RON antibodies as described herein can be used in immunohistochemistry.

15 [0037] **Figure 4** shows schematic representations of RON protein domains. A shows the RON protein domains which 6D4 and 7G8 antibodies bind to; B shows various isoforms of RON protein. Figure 4 was extracted from Yao, Hang-Ping et al. "MSP-RON signalling in cancer: pathogenesis and therapeutic potential." *Nature reviews. Cancer* 13 7 (2013): 466-81.

20 [0038] **Figure 5** shows flow cytometry data for exemplary anti-RON Antibodies (6D4 and 7G8 antibodies) on triple-knockout (TKO) cells (left) and human breast cancer cells (T47D cells) (right). Figure 5 shows that exemplary anti-RON Antibodies as described herein does not bind to triple-knockout cells (i.e. negative control). In contrast, the anti-RON Antibodies as described herein binds to human breast cancer cells. Thus, Figure 5 shows the anti-RON Antibodies as described herein is specific to cancer cells.

25 [0039] **Figure 6** shows a curve illustrating the cell proliferation of mouse hybridoma cell line (HT29 cells) in complete media *in vitro* which were monitored over 7 days in the presence of control IgG, and anti-RON Antibodies as described herein (e.g. 6D4 and 7G8 antibodies), via IncuCyte Live Cell Analysis System (Essen BioScience). Figure 6 shows dose dependent (1.25 μ g/ml to 12.5 μ g/ml) suppression of cell proliferation by antibodies as described herein.

30 [0040] **Figure 7** shows a clear microscope image of the result of a scratch wound inhibition assay of mouse hybridoma (HT29 cell) in presence of control IgG, anti-RON Antibodies as described herein (6D4 or 7G8 antibodies) in scratch wound assay at 0 and 90 hours. Figure 7 shows 7G8 antibody provides significant inhibition of HT29 cell migration. Inhibition of migration of cancer cells is a desirable quality as RON overexpression leads to uncontrolled cell migration in tumours.

35 [0041] **Figure 8** shows a bar graph of the percentage inhibition of wound healing of mouse hybridoma (HT29 cells) in the presence of control IgG and anti-RON Antibodies as

described herein (6D4 or 7G8 antibodies) in scratch wound assay. Percentages were calculated based on remaining wound healing area estimated by Image J software. Figure 8 shows 7G8 antibody provides significant inhibition of HT29 cell migration.

[0042] **Figure 9** shows an immunoblot showing the relative protein levels of HT29 cells treated with exemplary RON-neutralising antibodies (7G8 or 6D4), or control IgG, in the presence and absence of 10 ng/ml of MSP. Cells were harvested at 48 hours post-treatment. Figure 9 shows treatment with anti-RON Antibodies (6D4 and 7G8) leads to decrease in the amount of RON detected, and lower levels of phosphorylated targets downstream of RON signalling. Thus, Figure 9 shows treatment with anti-RON Antibodies (6D4 and 7G8) can lead to degradation of RON and abrogation of its downstream signalling pathways (Ras/Raf pathway and PI3K/Akt pathway).

[0043] **Figure 10** shows percentage of specific cell lysis in human breast cancer cell lines (T47D cells) measured by europium-TDA (TDA, i.e. 2,2':6',2" -terpyridine-6,6" -dicarboxylic acid) in Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assay (Positive Control IgG W6/32 has ADCC functions). Percentage lysis was detected in europium-TDA release assay after co-incubation of antibodies with mouse splenocytes (effector cells) and T47D cells (target) at an effector:target ratio of 150:1 overnight at 37°C. Thus, Figure 10 shows the antibodies as described herein induce cell lysis in breast cancer cell lines in the presence of effector cells.

[0044] **Figure 11** shows exemplary immunofluorescence staining of anti-RON Antibodies (6D4 and 7G8) antibodies on live HCT116 cells. The two antibodies were incubated with human colon carcinoma cell lines (HCT116 cells) for 1 hour at 37°C or overnight at 4°C, with serum. Antibody binding was detected using a secondary anti-mouse-FITC antibody. Thus, Figure 11 shows both 6D4 and 7G8 are endocytosed into live cells, allowing for efficient targeting of live cancer cells expressing RON on the surface..

[0045] **Figure 12** shows IncuCyte image showing cell death 2 hours after addition of anti-mouse IgG-DM1 (2° ADC) with 7G8 antibody. Thus, Figure 12 shows 7G8 antibody can cause cell death in human colon carcinoma cell lines (HCT116 cells).

[0046] **Figure 13A** shows bar graphs of percentage cell growth of human colon carcinoma cell lines (HCT116 cell) and P53, P21 and MDM2 triple knockout mouse embryonic fibroblast (TKO cells), when incubated with the panel of anti-RON Antibodies with 2° ADC (antibody drug conjugate) for 72 hours under image monitoring by IncuCyte to measure cell growth. Thus, Figure 13A shows the antibodies as described herein, when coupled with antibody drug conjugate, retards cancer cell growth in RON positive cells and not in RON negative cell lines.

[0047] **Figure 13B** shows bar graphs of percentage cell viability of human colon carcinoma cell lines (HCT116 cells) when incubated with the panel of anti-RON Antibodies with 2°ADC (antibody drug conjugate) for 72 hours and cell viability investigated using Celltitre Glo

Luminescent cell viability assay. Thus, Figure 13B shows the antibodies (5A5, 5B9, 6D4 and 7G8) as described herein, when coupled with antibody drug conjugate, reduces cancer cell viability as seen from the decrease in luminescence readings of HCT116 cells treated with 5A5, 5B9, 6D4 and 7G8.

5 [0048] **Figure 13C** shows bar graphs of percentage cell viability of human colon carcinoma cell lines (HCT116 cell) with 2°ADC and treated with the panel of anti-RON Antibodies. Cell viabilities are plotted as percentage of unviable cells in Figure 13C. Thus, Figure 13C shows the antibodies as described herein (5A5, 5B9, 6D4 and 7G8), when coupled with antibody drug conjugate, reduces cancer cell viability.

10 [0049] **Figure 13D** shows the cytotoxic profiles of anti-RON Antibodies as described herein (6D4 and 7G8) in a dose dependent manner in the presence of 1 µg/ml of 2° ADC (antibody drug conjugate), on the RON positive human colorectal cancer cells (HCT116 cells). Thus, it can be seen that 6D4 and 7G8 display potent cytotoxicity against human colorectal cancer cells, although killing of HCT116 cells are limited by antibody: antibody drug conjugate ratio.

15 [0050] **Figure 14** shows 7G8 heavy chain 1 amino acid and nucleotide sequences, and 7G8 heavy chain 1 framework and CDR sequences.

[0051] **Figure 15** shows 7G8 kappa chain (light chain) amino acid and nucleotide sequences, and 7G8 kappa chain framework and CDR sequences.

20 [0052] **Figure 16** shows 6D4 heavy chain amino acid and nucleotide sequences, and 6D4 heavy chain framework and CDR sequences.

[0053] **Figure 17** shows 6D4 kappa chain (light chain) amino acid and nucleotide sequences, and 6D4 kappa framework and CDR sequences.

[0054] **Figure 18** shows 3E1 heavy chain amino acid and nucleotide sequences, and 3E1 heavy chain framework and CDR sequences.

25 [0055] **Figure 19** shows 3E1 kappa chain (light chain) amino acid and nucleotide sequences, and 3E1 kappa chain framework and CDR sequences.

[0056] **Figure 20** shows 3G4 heavy chain amino acid and nucleotide sequence, and 3G4 heavy chain framework and CDR sequences.

30 [0057] **Figure 21** shows 3G4 kappa chain (light chain) amino acid and nucleotide sequence, and 3G4 kappa chain framework and CDR sequences.

[0058] **Figure 22** shows 5B9 heavy chain amino acid and nucleotide sequence, and 5B9 heavy chain framework and CDR sequences.

[0059] **Figure 23** shows 5B9 kappa chain (light chain) amino acid and nucleotide sequence, and 5B9 kappa chain framework and CDR sequences.

[0060] **Figure 24** shows 6E6 heavy chain amino acid and nucleotide sequence, and 6E6 heavy chain framework and CDR sequences.

[0061] **Figure 25** shows 6E6 kappa chain (light chain) amino acid and nucleotide sequence, and 6E6 kappa chain framework and CDR sequences.

5 [0062] **Figure 26** shows 2F1 heavy chain amino acid and nucleotide sequence, and 2F1 kappa chain framework and CDR sequences.

[0063] **Figure 27** shows 2F1 kappa chain (light chain) amino acid and nucleotide sequence, and 2F1 kappa chain framework and CDR sequences.

10 [0064] **Figure 28** shows 1D2 heavy chain amino acid and nucleotide sequence, and 1D2 heavy chain framework and CDR sequences.

[0065] **Figure 29A** shows 2B3 heavy chain amino acid and nucleotide sequence, and 2B3 heavy chain framework and CDR sequences.

[0066] **Figure 29B** shows 2B3 light chain amino acid and nucleotide sequence, and 2B3 light chain framework and CDR sequences.

15 [0067] **Figure 30** shows 1B9 heavy chain amino acid and nucleotide sequence, and 1B9 heavy chain framework and CDR sequences.

[0068] **Figure 31** (A) shows a timeline depicting the dosing and imaging protocol, and photographic images showing bioluminescence from individual tumors measured in the mice treated with antibodies 6D4 and 7G8; (B) shows bar graphs of the tumour weight at day 35 from the mouse xenograft model; (C) shows photographic images showing bioluminescence from individual tumors measured in the mice treated with antibody 6D4. Thus, Figure 31 shows the antibodies as described herein inhibits tumor growth *in vivo*.

20 [0069] **Figure 32** shows a line graph showing an *in vivo* data on tumour volume in mice treated with antibody 6D4. Figure 32 shows mice treated with an exemplary antibody as described herein has reduced tumour volume.

25 [0070] **Figure 33** shows a timeline for experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents.

[0071] **Figure 34** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents.

30 [0072] **Figure 35** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 6 hours after administration.

[0073] **Figure 36** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 24 hours after administration.

35 [0074] **Figure 37** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 48 hours after administration.

[0075] **Figure 38** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 72 hours after administration.

[0076] **Figure 39** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 5 days after administration.

5 [0077] **Figure 40** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 7 days after administration.

[0078] **Figure 41** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 14 days after administration and measures the weight of the tumour at the end point.

10 [0079] **Figure 42** shows photographic images of the results of experiments employing 6D4 and 7G8 antibodies as *in vivo* imaging agents 21 days after administration and measures the tumour volume by measuring the photons reflected by expression of luciferase genes in the tumour cells.

15 [0080] **Figure 43** shows Western Blots results demonstrating that antibodies 3G4 and 6E6 recognise different cancer cells lines expressing RON. Cell lines tested are human colorectal carcinoma cell line (e.g. HCT116), human keratinocyte cell line (e.g. HaCat), mouse hybridoma (e.g. HT29), human lymphoblast Burkitt's lymphoma cell line (e.g. Raji), human gastric cancer cells (e.g. MKN45), human colon colorectal adenocarcinoma cell line (e.g. WiDr), human breast cancer cell line (e.g. T47D), non-small cell lung cancer (e.g. H1299), and rat brain cancer cell line (e.g. C6).

20 [0081] **Figure 44A** shows immunofluorescence staining images showing that the antibodies of the present disclosure (3G4, 6A5, 6E6, and 6D4) recognise RON transfected H1299 cells.

[0082] **Figure 44B** shows immunofluorescence staining images showing that the antibodies of the present disclosure (3E1, 5A5, 5D8, 5B9, 6B5, and 8A8) recognise RON transfected H1299 cells.

25 [0083] **Figure 45** shows Western Blots showing immunoprecipitation results for antibody 1D2 against mouse embryo fibroblast cell line (e.g. 3T3), human colorectal carcinoma cell line (e.g. HCT116) and mouse hybridoma (e.g. HT29) cell lines. Thus, Figure 45 shows that RON (MW 180kDa) can be immunoprecipitated by 1D2 in RON-positive HT29 and HCT116 cells but not in RON negative 3T3 cells.

30 [0084] **Figure 46** shows Western Blots showing immunoprecipitation results for antibodies 2F1, 2B3 and 1B9 against 3T3, HCT116 and HT29 cell lines. Thus, Figure 45 shows that RON (MW 180kDa) can be immunoprecipitated by 2F1, 2B3 and 1B9 in RON-positive HT29 and HCT116 cells but not in RON negative 3T3 cells.

35 [0085] **Figure 47A** shows a schematic showing Pepscan epitope mapping strategy.

[0086] **Figure 47B** shows schematic showing peptide phage display epitope mapping strategy.

[0087] **Figure 48A** shows the results of epitope mapping by Pepscan.

[0088] **Figure 48B** shows results of epitope mapping by phage display.

5 [0089] **Figure 49A** shows immunofluorescence images showing the endocytosis of anti-RON antibodies 5A5 and 6B5. Thus, Figure 49A shows that 5A5 and 6B5 are endocytosed into live cells, allowing for use as therapeutic drugs-delivering vehicles that target live cancer cells expressing RON on the surface.

10 [0090] **Figure 49B** shows immunofluorescence images showing the endocytosis of anti-RON antibody 6D4. Thus, Figure 49B shows the antibody 6D4 is endocytosed, thus allowing the antibody to be used as therapeutic drugs-delivering vehicles that target live cancer cells expressing RON on the surface.

[0091]

15 [0092] **Figure 50A** shows variable 5A5 heavy chain amino acid and nucleotide sequence, and 5A5 heavy chain framework and CDR sequences.

[0093] **Figure 50B** shows variable 5A5 kappa chain (light chain) amino acid and nucleotide sequence, and 5A5 kappa chain framework and CDR sequences.

20 [0094] **Figure 51** shows a line graph showing the study into the binding affinity of an example of the antibody as described herein (i.e. 2B3) as measured by Proteon. Figure 51 indicates that antibody 2B3 has a strong affinity for RON3.

[0095] **Table 1. Peptides Associated with Figure 58A**

No.	Antibody	Peptide Number	Epitope	SEQ ID NO:
1	5A5	48	HCPPKLTEFHPHSGP	10
		49	PHSGPLRGSTRLTL	11
2	2B3	48	HCPPKLTEFHPHSGP	10
3	3E1	67	AQVPGSWTFQYREDP	12
		68	YREDPVVLSISPNCG	13
		69	LHTRLARLSATEPEL	14
4	6E6	29	DPALPALVSCGSSLQ	15
		31	HDLEPQGTAVHLAAP	16
5	3G4	29	DPALPALVSCGSSLQ	15

DETAILED DESCRIPTION OF THE DISCLOSURE

[0096] Macrophage stimulating protein receptor (or RON- Recepteur d' Origine Nantais) is a c-MET-related tyrosine kinase receptor which transduces signals from the extracellular matrix into the cytoplasm when engaged by the ligand MSP. This signalling stimulates the intracellular domain of RON and provides active sites for engaging downstream signalling molecules, such as PIK3R1, PLCG1 or GAB1. Thus, RON is part of the signalling cascade. The human RON receptor tyrosine kinase has the UniProt number Q04912 and the murine protein has the UniProt number Q62190. The receptor is encoded in humans by gene *MST1R*.

[0097] Macrophage stimulating protein receptor (RON) is a c-MET-related tyrosine kinase receptor which the present inventors believe may be an important therapeutic target, in particular for the treatment of cancer. It may be that overexpression of RON is a factor which induces tumorigenesis and it appears to be a hallmark of many human cancers. Cancer patients with RON overexpression also seem to have a worse prognosis in comparison to patients without said overexpression.

[0098] Patients with RON positive tumours have a significantly worse 10-year disease-free survival rate than those patients with RON negative tumours (30.3% versus 58.6%, respectively; $P = 0.009$). Patients with both RON positive and MET positive tumours have the lowest 10-year disease-free survival (11.8%), and those with both RON negative and MET negative tumours have the highest 10-year disease-free survival (79.3%; $P = 0.008$). RON expression may also be used as a prognostic biomarker for disease progression and patient survival in some cancers.

[0099] In view of the statistics relating RON positivity with survival and progression of cancer patients, the inventors of the present disclosure set out to provide an antibody that recognizes and/or can bind to RON. In particular, various antibodies have been isolated and characterised to recognise cell surface expressed receptor tyrosine kinase RON.

[0100] Thus, in one aspect, there is provided a RON specific binding domain comprising the heavy chain CDRs of CDRH1, CDRH2, and CDRH3 and/or the light chain CDRs of CDRL1, CDRL2, and CDRL3, wherein

- (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, SEQ ID NO: 100, SEQ ID NO: 116, and SEQ ID NO: 135 or a CDRH1 sequence differing 1 or 2 amino acids therefrom;
- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, SEQ ID NO: 101, SEQ ID NO: 117, and SEQ ID NO: 136; or a CDRH2 sequence differing 1 or 2 amino acids therefrom;
- (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, SEQ ID NO: 102, and SEQ ID NO: 137; or a CDRH3 sequence differing 1 or 2 amino acids therefrom;

(d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, and SEQ ID NO: 144; or a CDRL1 sequence differing 1 or 2 amino acids therefrom;

(e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 109; or a CDRL2 sequence differing 1 or 2 amino acids therefrom; and

(f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 220, SEQ ID NO: 123, and SEQ ID NO: 145; or a CDRL2 sequence differing 1 or 2 amino acids therefrom.

10 [00101] Also disclosed is an antigen binding domain comprising (or consisting of) the heavy chain CDRs of CDRH1, CDRH2, and CDRH3 and/or the light chain CDRs of CDRL1, CDRL2, and CDRL3, wherein

(a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, SEQ ID NO: 100, SEQ ID NO: 116, and SEQ ID NO: 135;

(b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, SEQ ID NO: 101, SEQ ID NO: 117, and SEQ ID NO: 136;

(c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, SEQ ID NO: 102, and SEQ ID NO: 137;

(d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, and SEQ ID NO: 144;

(e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 109; and

(f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 220, SEQ ID NO: 123, and SEQ ID NO: 145.

[00102] Also provided is an isolated antibody, or fragment thereof, wherein the antibody, or fragment thereof, comprises (or consists of) the heavy chain CDRs of CDRH1, CDRH2, and CDRH3 and/or the light chain CDRs of CDRL1, CDRL2, and CDRL3, wherein

(a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 10, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, and SEQ ID NO: 116, S and SEQ ID NO: 100; or a CDRH1 sequence differing 1 or 2 amino acids therefrom;

- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 11, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, and SEQ ID NO: 101; or SEQ ID NO: 117 or a CDRH2 sequence differing 1 or 2 amino acids therefrom;
- 5 (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 12, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, and SEQ ID NO: 102; or a CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, and SEQ ID NO: 108; or a CDRL1 sequence differing 1 or 2 amino acids therefrom;
- 10 (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 109; or a CDRL2 sequence differing 1 or 2 amino acids therefrom; and
- (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, and SEQ ID NO: 123; or a CDRL2 sequence differing 1 or 2 amino acids therefrom.

[00103] In some examples, the antibody as described herein has the heavy chain CDRs that are selected from the group consisting of:

- (a) a CDRH1 having the sequence SEQ ID NO: 1, a CDRH2 having the sequence SEQ ID NO: 2, and a CDRH3 having the sequence SEQ ID NO: 3, and/or a CDRH1 having the sequence SEQ ID NO: 10, a CDRH2 having the sequence SEQ ID NO: 11, and a CDRH3 having the sequence SEQ ID NO: 12; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- 20 (b) a CDRH1 having the sequence SEQ ID NO: 27, a CDRH2 having the sequence SEQ ID NO: 28, and a CDRH3 having the sequence SEQ ID NO: 29; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (c) a CDRH1 having the sequence SEQ ID NO: 45, a CDRH2 having the sequence SEQ ID NO: 46, and a CDRH3 having the sequence SEQ ID NO: 47; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- 25 (d) a CDRH1 having the sequence SEQ ID NO: 56, a CDRH2 having the sequence SEQ ID NO: 57, and a CDRH3 having the sequence SEQ ID NO: 58; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (e) a CDRH1 having the sequence SEQ ID NO: 73, a CDRH2 having the sequence SEQ ID NO: 74, and a CDRH3 having the sequence SEQ ID NO: 75; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;

- (f) a CDRH1 having the sequence SEQ ID NO: 89, a CDRH2 having the sequence SEQ ID NO: 90, and a CDRH3 having the sequence SEQ ID NO: 101; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (g) a CDRH1 having the sequence SEQ ID NO: 116, a CDRH2 having the sequence SEQ ID NO: 117, and a CDRH3 having the sequence SEQ ID NO: 102; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- 5 (h) a CDRH1 having the sequence SEQ ID NO: 116, a CDRH2 having the sequence SEQ ID NO: 117, and a CDRH3 having the sequence SEQ ID NO: 102; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom;
- 10 (i) a CDRH1 having the sequence SEQ ID NO: 116, a CDRH2 having the sequence SEQ ID NO: 101, and a CDRH3 having the sequence SEQ ID NO: 102; or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom; and
- (a) a CDRH1 having the sequence SEQ ID NO: 100, a CDRH2 having the sequence SEQ ID NO: 101, and a CDRH3 having the sequence SEQ ID NO: 102 or a CDRH1, CDRH2, or CDRH3 sequence differing 1 or 2 amino acids therefrom; and
- 15 (j) a CDRH1, a CDRH2, and a CDRH3 as recited in Table 1, or CDRH1 or CDRH2 or CDRH3 differing 1 or 2 amino acids therefrom.

[00104] In some examples, the antibodies as described herein has light chain CDRs are selected from the group consisting of:

- 20 (b) a CDRL1 having the sequence SEQ ID NO: 18, a CDRL2 having the sequence SEQ ID NO: 19, and a CDRL3 having the sequence SEQ ID NO: 20; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;
- (c) a CDRL1 having the sequence SEQ ID NO: 36, a CDRL2 having the sequence SEQ ID NO: 37, and a CDRL3 having the sequence SEQ ID NO: 38; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;
- 25 (d) a CDRL1 having the sequence SEQ ID NO: 18, a CDRL2 having the sequence SEQ ID NO: 19, and a CDRL3 having the sequence SEQ ID NO: 20; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;
- (e) a CDRL1 having the sequence SEQ ID NO: 65, a CDRL2 having the sequence SEQ ID NO: 66, and a CDRL3 having the sequence SEQ ID NO: 67; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;
- 30 (f) a CDRL1 having the sequence SEQ ID NO: 81, a CDRL2 having the sequence SEQ ID NO: 82, and a CDRL3 having the sequence SEQ ID NO: 83; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;

(g) a CDRL1 having the sequence SEQ ID NO: 65, a CDRL2 having the sequence SEQ ID NO: 66, and a CDRL3 having the sequence SEQ ID NO: 67; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom;

(h) a CDRL1 having the sequence SEQ ID NO: 108, a CDRL2 having the sequence SEQ ID NO: 109, and a CDRL3 having the sequence SEQ ID NO: 123; or a CDRL1, CDRL2, or CDRL3 sequence differing 1 or 2 amino acids therefrom; and

(i) a CDRL1, a CDRL2, and a CDRL3 as recited in Table 1, or CDRL1 or CDRL2 or CDRL3 differing 1 or 2 amino acids therefrom.

[00105] In some examples, the antibodies as described herein has the heavy chain CDRs and

light chain CDRs are selected from the group consisting of:

(a) a CDRH1 having the sequence SEQ ID NO: 1, a CDRH2 having the sequence SEQ ID NO: 2, and a CDRH3 having the sequence SEQ ID NO: 3, and/or a CDRH1 having the sequence SEQ ID NO: 10, a CDRH2 having the sequence SEQ ID NO: 11, and a CDRH3 having the sequence SEQ ID NO: 12, and a CDRL1 having the sequence SEQ ID NO: 18, a CDRL2 having the sequence SEQ ID NO: 19, and a CDRL3 having the sequence SEQ ID NO: 20;

(b) a CDRH1 having the sequence SEQ ID NO: 27, a CDRH2 having the sequence SEQ ID NO: 28, and a CDRH3 having the sequence SEQ ID NO: 29, and a CDRL1 having the sequence SEQ ID NO: 36, a CDRL2 having the sequence SEQ ID NO: 37, and a CDRL3 having the sequence SEQ ID NO: 38;

(c) a CDRH1 having the sequence SEQ ID NO: 45, a CDRH2 having the sequence SEQ ID NO: 46, and a CDRH3 having the sequence SEQ ID NO: 47, and a CDRL1 having the sequence SEQ ID NO: 18, a CDRL2 having the sequence SEQ ID NO: 19, and a CDRL3 having the sequence SEQ ID NO: 20;

(d) a CDRH1 having the sequence SEQ ID NO: 56, a CDRH2 having the sequence SEQ ID NO: 57, and a CDRH3 having the sequence SEQ ID NO: 58, and a CDRL1 having the sequence SEQ ID NO: 65, a CDRL2 having the sequence SEQ ID NO: 66, and a CDRL3 having the sequence SEQ ID NO: 67;

(e) a CDRH1 having the sequence SEQ ID NO: 73, a CDRH2 having the sequence SEQ ID NO: 74, and a CDRH3 having the sequence SEQ ID NO: 75, and a CDRL1 having the sequence SEQ ID NO: 81, a CDRL2 having the sequence SEQ ID NO: 82, and a CDRL3 having the sequence SEQ ID NO: 83;

(f) a CDRH1 having the sequence SEQ ID NO: 89, a CDRH2 having the sequence SEQ ID NO: 90, and a CDRH3 having the sequence SEQ ID NO: 91, and a CDRL1 having the sequence SEQ ID NO: 65, a CDRL2 having the sequence SEQ ID NO: 66, and a CDRL3 having the sequence SEQ ID NO: 67;

(g) a CDRH1 having the sequence SEQ ID NO: 116, a CDRH2 having the sequence SEQ ID NO: 117, and a CDRH3 having the sequence SEQ ID NO: 102, and a CDRL1 having the sequence SEQ ID NO: 108, a CDRL2 having the sequence SEQ ID NO: 109, and a CDRL3 having the sequence SEQ ID NO: 123; and

5 (h) a CDRH1, a CDRH2, a CDRH3 having a sequence as recited in Table 1, and a CDRL1, a CDRL2, a CDRL3 as recited in Table 1.

[00106] In some examples, the antibodies as described herein comprises (or consists of) a heavy chain variable region encoded by a nucleotide sequence having at least 80%, or at least 85% or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity to one of the nucleotide sequence recited in Table 1 or selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 35, SEQ ID NO: 52 SEQ ID NO: 64, SEQ ID NO: 80, SEQ ID NO: 96, SEQ ID NO: 122, SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 107.

[00107] In some examples, the antibody as described herein comprises (or consists of) a light chain variable region encoded by a nucleotide sequence having at least 80%, or at least 85% or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity to one of the nucleotide sequence recited in Table 1 or selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 44, SEQ ID NO: 55, SEQ ID NO: 72, SEQ ID NO: 88, SEQ ID NO: 99, and SEQ ID NO: 128.

[00108] In some examples, the antibody as described herein comprises (or consists of) a heavy chain variable region encoded by a nucleotide sequence to one of selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 35, SEQ ID NO: 52, SEQ ID NO: 64, SEQ ID NO: 80, SEQ ID NO: 96, SEQ ID NO: 122, SEQ ID NO: 131, SEQ ID NO: 134, SEQ ID NO: 107.

[00109] In some examples, the antibody as described herein comprises (or consists of) a light chain variable region encoded by a nucleotide sequence to one of selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 44, SEQ ID NO: 55, SEQ ID NO: 72, SEQ ID NO: 88, SEQ ID NO: 99, and SEQ ID NO: 128.

[00110] In some examples, the antibody as described herein comprises (or consists of) a heavy chain variable region selected from the group consisting of:

(a) an amino acid sequence of SEQ ID NO: 8;

30 (b) an amino acid sequence SEQ ID NO: 34;

(c) an amino acid sequence SEQ ID NO: 51;

(d) an amino acid sequence SEQ ID NO: 63;

(e) an amino acid sequence SEQ ID NO: 79;

(f) an amino acid sequence SEQ ID NO: 95;

35 (g) an amino acid sequence SEQ ID NO: 121;

(h) an amino acid sequence SEQ ID NO: 130;

- (i) an amino acid sequence SEQ ID NO: 132;
- (j) an amino acid sequence SEQ ID NO: 106; and
- (k) an amino acid sequence having a sequence identity of at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or at least 99.95%, or 100% of (a) to (k).

5 [00111] In some examples, the antibody as described herein comprises (or consists of) a light chain variable region selected from the group consisting of:

- (a) an amino acid sequence of SEQ ID NO: 25;
- (b) an amino acid sequence SEQ ID NO: 43;
- 10 (c) an amino acid sequence SEQ ID NO: 54;
- (d) an amino acid sequence SEQ ID NO: 71;
- (e) an amino acid sequence SEQ ID NO: 87;
- (f) an amino acid sequence SEQ ID NO: 98;
- (g) an amino acid sequence SEQ ID NO: 127; and
- 15 (h) an amino acid sequence having a sequence identity of at least 85%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or at least 99.95%, or 100% of (a) to (h).

[00112] In some examples, the antibody as described herein may further comprises (or consists of) a framework sequence.

20 [00113] In some examples, the antibody as described herein may comprise the heavy chain framework sequence comprising (or consisting of) at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% sequence identity to framework selected from the group consisting of:

- (a) an FR1 having the sequence SEQ ID NO: 4, an FR2 having the sequence SEQ ID NO: 5, an FR3 having the sequence SEQ ID NO: 6, and an FR4 having the sequence SEQ ID NO: 7, an FR2 having the sequence SEQ ID NO: 14, and an FR3 having the sequence SEQ ID NO: 15;
- (b) an FR1 having the sequence SEQ ID NO: 30, an FR2 having the sequence SEQ ID NO: 31, an FR3 having the sequence SEQ ID NO: 32, and an FR4 having the sequence SEQ ID NO: 33;
- 25 (c) an FR1 having the sequence SEQ ID NO: 48, an FR2 having the sequence SEQ ID NO: 49, an FR3 having the sequence SEQ ID NO: 50, and an FR4 having the sequence SEQ ID NO: 7;
- (d) an FR1 having the sequence SEQ ID NO: 59, an FR2 having the sequence SEQ ID NO: 60, an FR3 having the sequence SEQ ID NO: 61, and an FR4 having the sequence SEQ ID NO: 62;

- (e) an FR1 having the sequence SEQ ID NO: 76, an FR2 having the sequence SEQ ID NO: 77, an FR3 having the sequence SEQ ID NO: 86, and an FR4 having the sequence SEQ ID NO: 7;
- (f) an FR1 having the sequence SEQ ID NO: 92, an FR2 having the sequence SEQ ID NO: 93, an FR3 having the sequence SEQ ID NO: 94, and an FR4 having the sequence SEQ ID NO: 62;
- 5 (g) an FR1 having the sequence SEQ ID NO: 118, an FR2 having the sequence SEQ ID NO: 119, an FR3 having the sequence SEQ ID NO: 120, and an FR4 having the sequence SEQ ID NO: 7;
- 10 (h) an FR1 having the sequence SEQ ID NO: 129, an FR2 having the sequence SEQ ID NO: 119, an FR3 having the sequence SEQ ID NO: 120, and an FR4 having the sequence SEQ ID NO: 7;
- (i) an FR1 having the sequence SEQ ID NO: 129, an FR2 having the sequence SEQ ID NO: 119, an FR3 having the sequence SEQ ID NO: 120, and an FR4 having the sequence SEQ ID NO: 132;
- 15 (j) an FR1 having the sequence SEQ ID NO: 103, an FR2 having the sequence SEQ ID NO: 104, an FR3 having the sequence SEQ ID NO: 105; and
- (k) an FR as recited in Table 1.

[00114] In some examples, the antibody as described herein may comprise (or consist of) the light chain framework sequence comprising at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100% sequence identity to framework selected from the group consisting of:

- (a) an FR1 having the sequence SEQ ID NO: 21, an FR2 having the sequence SEQ ID NO: 22, an FR3 having the sequence SEQ ID NO: 23, and an FR4 having the sequence SEQ ID NO: 24;
- 25 (b) an FR1 having the sequence SEQ ID NO: 39, an FR2 having the sequence SEQ ID NO: 40, an FR3 having the sequence SEQ ID NO: 41, and an FR4 having the sequence SEQ ID NO: 42;
- (c) an FR1 having the sequence SEQ ID NO: 53, an FR2 having the sequence SEQ ID NO: 22, an FR3 having the sequence SEQ ID NO: 23, and an FR4 having the sequence SEQ ID NO: 24;
- 30 (d) an FR1 having the sequence SEQ ID NO: 68, an FR2 having the sequence SEQ ID NO: 69, an FR3 having the sequence SEQ ID NO: 41, and an FR4 having the sequence SEQ ID NO: 70;

- (e) an FR1 having the sequence SEQ ID NO: 84, an FR2 having the sequence SEQ ID NO: 85, an FR3 having the sequence SEQ ID NO: 86, and an FR4 having the sequence SEQ ID NO:42;
- (f) an FR1 having the sequence SEQ ID NO: 97, an FR2 having the sequence SEQ ID NO: 69, an FR3 having the sequence SEQ ID NO: 41, and an FR4 having the sequence SEQ ID NO: 70; and
- 5 (g) an FR1 having the sequence SEQ ID NO: 124, an FR2 having the sequence SEQ ID NO: 125, and an FR3 having the sequence SEQ ID NO: 126, (and optionally an FR4 having the sequence SEQ ID NO: 42); and
- 10 (h) an FR as recited in Table 1.

[00115] In some examples, the antibody as described herein binds to a receptor tyrosine kinase RON (Recepteur d' Origine Nantais (RON), or Macrophage Stimulating Protein Receptor (MSP R, or MST1-R)).

15 [00116] In some examples, the antibody as described herein binds specifically to a human and/or a mouse RON.

[00117] In some examples, the antibody as described herein binds to a cell surface expressed RON.

20 [00118] In some examples, the antibody as described herein is capable of being (or is) endocytosed by a target cell. This may be particular advantageous when the antibody molecule is conjugated to a payload because the payload may be delivered into the cell (not just to the exterior of the cell). Thus the use of payloads that are activated by enzymes inside the cancer cell are envisaged.

[00119] In some examples, the antibody as described herein may be a monoclonal antibody.

25 [00120] In some examples, the antibody as described herein may be a chimeric antibody and/or multispecific antibody.

[00121] In some examples, the antibody as described herein may be a humanized antibody.

[00122] In some examples, the antibody as described herein may be a fragment, such as, but is not limited to, a Fab fragment, a Fab' fragment, a F(ab')2 fragment, a Fv fragment, a diabody, a 30 single chain antibody molecule, and the like.

[00123] In some examples, the antibody as described herein may be an IgG1 antibody, an IgG2 antibody, an IgG3 antibody, or an IgG4 antibody.

[00124] In some examples, the antibody as described herein may be transferred to a human IgG scaffold.

[00125] In some examples, the antibody as described herein may be conjugated to a chemical moiety selected from the group consisting of a therapeutic agent, an immunoadhesion molecule, and a detection label (such as an imaging label).

[00126] In some examples, the detection label may include, but is not limited to a radiolabel,

5 an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, a biotin, and the like.

[00127] In some examples, the therapeutic agent may be an anti-cancer treatment.

[00128] In some examples, there is provided a pharmaceutical composition comprising the antibody or fragment thereof as described herein.

10 [00129] In some example, wherein the pharmaceutical composition may further comprise a pharmaceutically acceptable carrier, excipient, and/or stabilizer.

[00130] In some example, there is provided a kit, comprising the RON specific binding domain, chimeric antigen receptor, antibody, or composition as described herein.

15 [00131] In some example, there is provided an isolated nucleic acid comprising any one selected from the group consisting of:

(g) a nucleotide sequence encoding the antibody or fragment thereof as described herein;

(h) a nucleotide sequence encoding:

20 a heavy chain region having at least 80%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100 % of one of heavy region recited in

Table 1, or one selected from the group consisting of SEQ ID NO: 9, SEQ ID NO: 35, SEQ ID NO: 52, SEQ ID NO: 64, SEQ ID NO: 80, SEQ ID NO: 96, SEQ ID NO: 122, SEQ ID NO: 131, SEQ ID NO: 134, and SEQ ID NO: 107; and/or

25 a light chain region having at least 80%, or at least 90%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99%, or 100 % of one light region recited in Table 1,

or one selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 44, SEQ ID NO: 55, SEQ ID NO: 72, SEQ ID NO: 88, SEQ ID NO: 99, and SEQ ID NO: 128.

(i) a nucleic acid complementary to any one of the sequences in (a) or (b); and

(j) a nucleic acid sequence capable of hybridizing to (a), (b), or (c) under stringent conditions.

30 [00132] In some examples, there is provided an expression vector comprising the nucleic acid as described herein.

[00133] In some examples, there is provided a host cell comprising the expression vector as described herein.

35 [00134] In some examples, there is provided method of producing a polypeptide comprising an immunoglobulin heavy chain variable region and/or an immunoglobulin light chain variable region, the method comprising: growing the host cell as described herein under conditions so

that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin heavy chain variable region.

[00135] In some examples, the method of producing the polypeptide as described herein further comprises the step of purifying the polypeptide comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region.

[00136] In some examples, the isolated antibody or fragment thereof as described herein, or pharmaceutical composition as described herein for use in medicine.

[00137] In some examples, the isolated antibody or fragment thereof as described herein to 140, or pharmaceutical composition as described herein, for use in treating cancer.

10 [00138] In some examples, there is provided a method of treating cancer in a subject in need thereof, comprising administering an isolated antibody, or fragment thereof, as described herein to the subject.

[00139] In some examples, the method of treating cancer as described herein further include administering a therapeutic agent selected from the group consisting of an anti-cancer agent 15 (such as a second anti-cancer antibody), and a chemotherapeutic agent.

[00140] In some examples, the therapeutic agent may be an anti-cancer agent such as, but is not limited to, a drug conjugate (such as mertansine or DM1(N2'-deacetyl-N2'-(3-mercaptopro-1-oxopropyl)-maytansine).

20 [00141] In some examples, the cancer may be a RON expressing cancer such as, but is not limited to colorectal cancer, non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, renal cancer, bladder cancer, gastrointestinal tumors, liver cancer, pancreatic cancer, gastric cancer, head and neck cancers, and the like.

[00142] In some examples, the isolated antibody or fragment thereof, may be administered in a pharmaceutically effective amount.

25 [00143] In some examples, there is provided a method of detecting a tumor cell in a subject, comprising detecting the expression of RON in a sample obtained from the subject using an antibody as described herein.

[00144] In some examples, the tumor cell may be a cancer cell.

30 [00145] In some examples, wherein the cancer is a RON expressing cancer, such as, but is not limited to colorectal cancer, non-small cell lung cancer, breast cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, renal cancer, bladder cancer, gastrointestinal tumors, liver cancer, pancreatic cancer, gastric cancer, head and neck cancers, and the like.

[00146] RON is expressed and may be over-expressed by many cancers, in particular many epithelial cancers.

[00147] The binding domains of the present disclosure can target the surface expressed RON. However, the data generated by the present inventions suggests that the antibody molecules comprising said binding domains are taken into the cell (expressing the RON) by a process involving active transport known as endocytosis. Once in the cells the antibody molecule may be localised in the cytoplasm or a cell nucleus. This is likely to be really beneficial in that the toxins or biological molecule conjugated to the antibody molecule may be internalized into the cancerous cell. Thus it may be possible to minimise the systemic toxicity and off target effects, for example by employing a toxin that is only activated inside the cell.

[00148] In particular wherein the binding domain is part of an antibody or binding fragment thereof. The disclosure also extends to pharmaceutical compositions comprising the binding domain (or an entity, such as an antibody or binding fragment, containing the binding domain), polynucleotides encoding the binding domain (or encoding an entity such as an antibody or binding fragment, containing the binding domain). In a further aspect there is provided a binding domain or an entity comprising the same or a pharmaceutical composition of any one of the same for use in treatment, in particular the treatment of cancer. In one example the binding domain according to the present disclosure is employed in a combination therapy with a further therapeutic agent. The entities, such as antibodies and binding fragments thereof may also be employed as research a tool, a reagent, a diagnostic or part-thereof and/or a prognostic agent or part thereof.

[00149] As mentioned above, RON is expressed and may be over-expressed by many cancers, in particular many epithelial cancers. As illustrated in the Figures generated from the Experimental section of the present disclosure, the binding domains of the present disclosure can target the surface expressed RON. Further, the data generated by the present inventions suggests that the antibody molecules comprising said binding domains are taken into the cell (expressing the RON) by a process involving active transport known as endocytosis. Once in the cells the antibody molecule may be localised in the cytoplasm or a cell nucleus. This is likely to be really beneficial in that the toxins or biological molecule conjugated to the antibody molecule may be internalized into the cancerous cell. Thus it may be possible to minimise the systemic toxicity and off target effects, for example by employing a toxin that is only activated inside the cell.

[00150] The binding domains (and antibody molecules) of the present disclosure are specific for human RON. However, they also recognise (i.e. are cross-reactive with) at least one non-human RON protein, for example murine RON. Thus the antibodies cross react with mouse and human protein. This is a very useful unexpected property as it allows easy preclinical analysis of potential toxicity to normal tissue and organs in a mouse therapeutic module allowing determination of the therapeutic index. Thus cross-reactivity is beneficial because it allows

preliminary toxicology and *in vivo* analysis to be performed to evaluate the safety of the molecule before it is administered to a human.

[00151] Thus, in another aspect, there is provided an antigen specific binding domain comprising (or consisting of) CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein:

- 5 (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, and SEQ ID NO: 100, SEQ ID NO: 116, SEQ ID NO: 135 and a CDRH1 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added;
- 10 (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, and SEQ ID NO: 101, SEQ ID NO: 117, SEQ ID NO: 136 and a CDRH2 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added;
- 15 (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, and SEQ ID NO: 102, SEQ ID NO: 137 and a CDRH3 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added;
- 20 (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, SEQ ID NO: 144 and a CDRL1 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added;
- (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, SEQ ID NO: 109 and a CDRL2 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added.; and
- 25 (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 110, SEQ ID NO: 123, SEQ ID NO: 145 and a CDRL3 differing from any one of the same in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added.

[00152] In some examples, the CDRH1 may be SEQ ID NO: 1, CDRH2 is SEQ ID NO: 2, and CDRH3 is SEQ ID NO: 3 or an antigen specific binding domain wherein one or more modified sequences 1, 2, and 3 are employed and the modification(s) is independently selected from replacement, deletion or addition of 1 or 2 amino acids.

[00153] In some examples, the antigen specific binding domain as described herein may have heavy chain CDRs including:

- 35 (a) the CDRH1 is SEQ ID NO: 1, the CDRH2 is SEQ ID NO: 2, the CDRH3 is SEQ ID NO: 3; or

- (b) the CDRH1 is SEQ ID NO: 27, the CDRH2 is SEQ ID NO: 28, the CDRH3 is SEQ ID NO: 29; or
- (c) the CDRH1 is SEQ ID NO: 45, the CDRH2 is SEQ ID NO: 46, the CDRH3 is SEQ ID NO: 47; or
- 5 (d) the CDRH1 is SEQ ID NO: 56, the CDRH2 is SEQ ID NO: 57, the CDRH3 is SEQ ID NO: 58; or
- (e) the CDRH1 is SEQ ID NO: 73, the CDRH2 is SEQ ID NO: 74, the CDRH3 is SEQ ID NO: 75; or
- 10 (f) the CDRH1 is SEQ ID NO: 89, the CDRH2 is SEQ ID NO: 90, the CDRH3 is SEQ ID NO: 91; or
- (g) the CDRH1 is SEQ ID NO: 100, the CDRH2 is SEQ ID NO: 101, the CDRH3 is SEQ ID NO: 102; or
- (h) the CDRH1 is SEQ ID NO: 135, the CDRH2 is SEQ ID NO: 136, the CDRH3 is SEQ ID NO: 137.

15 [00154] In some examples, the antigen specific binding domain may have the light chain CDRs including:

- (a) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (b) the CDRL1 is SEQ ID NO: 36, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 38;
- 20 (c) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (d) the CDRL1 is SEQ ID NO: 65, the CDRL2 is SEQ ID NO: 66, the CDRL3 is SEQ ID NO: 67;
- 25 (e) the CDRL1 is SEQ ID NO: 81, the CDRL2 is SEQ ID NO: 82, the CDRL3 is SEQ ID NO: 83;
- (f) the CDRL1 is SEQ ID NO: 108, the CDRL2 is SEQ ID NO: 109, the CDRL3 is SEQ ID NO: 110; and
- 30 (g) the CDRL1 is SEQ ID NO: 144, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 145.

[00155] In some examples, the antigen specific binding domain as described herein may have the variable heavy domain such as:

- (i) SEQ ID NO: 8;
- (ii) SEQ ID NO: 34;
- 35 (iii) SEQ ID NO: 51;
- (iv) SEQ ID NO: 63;

- (v) SEQ ID NO: 79;
- (vi) SEQ ID NO: 95;
- (vii) SEQ ID NO: 106; and
- (viii) SEQ ID NO: 142.

5 [00156] In some examples, the antigen specific binding domain as described herein may have the variable light domain such as:

- (i) SEQ ID NO: 25;
- (ii) SEQ ID NO: 43;
- (iii) SEQ ID NO: 54;
- 10 (iv) SEQ ID NO: 71;
- (v) SEQ ID NO: 87;
- (vi) SEQ ID NO: 98;
- (vii) SEQ ID NO: 114; and
- (viii) SEQ ID NO: 150.

15 [00157] In some examples, the antigen specific binding domain as described herein may have CDRH1 that is SEQ ID NO: 1 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00158] In some examples, the antigen specific binding domain as described herein may have CRDH2 that is SEQ ID NO: 2 or a sequence differing therefrom in that 1 or 2 amino acids are 20 independently replaced (with an alternative amino acid), deleted or added.

[00159] In some examples, the antigen specific binding domain as described herein may have CRDH3 that is SEQ ID NO: 3 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00160] In some examples, the antigen specific binding domain as described herein may have 25 CDRL1 that is SEQ ID NO: 18 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00161] In some examples, the antigen specific binding domain as described herein may have CDRL2 that is SEQ ID NO: 19 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

30 [00162] In some examples, the antigen specific binding domain as described herein may have CDRL3 that is SEQ ID NO: 20 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00163] In some examples, the antigen specific binding domain as described herein may have the variable heavy domain has a sequence: as shown in SEQ ID NO: 8, or a sequence derived 35 from SEQ ID NO: 8 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced

(with an alternative amino acid), deleted or added, in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 8 with at least 95% identity thereto.

[00164] In some examples, the antigen specific binding domain as described herein may include the variable light domain has a sequence: as shown in SEQ ID NO: 25; a sequence

5 derived from SEQ ID NO: 25 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 25 with at least 95% identity thereto;

[00165] In some examples, the antigen specific binding domain as described herein may have CDRH1 that is SEQ ID NO: 27 or a sequence differing therefrom in that 1 or 2 amino acids are

10 independently replaced (with an alternative amino acid), deleted or added.

[00166] In some examples, the antigen specific binding domain as described herein may have CDRH2 that is SEQ ID NO: 28 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00167] In some examples, the antigen specific binding domain as described herein may have CDRH3 that is SEQ ID NO: 29 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00168] In some examples, the antigen specific binding domain as described herein may have CDRL1 that is SEQ ID NO: 36 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

20 [00169] In some examples, the antigen specific binding domain as described herein may have CDRL2 that is SEQ ID NO: 37 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00170] In some examples, the antigen specific binding domain as described herein may have CDRL3 that is SEQ ID NO: 38 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

25 [00171] In some examples, the antigen specific binding domain as described herein may have the heavy chain variable domain having a sequence: as shown in SEQ ID NO: 34; or a sequence derived from SEQ ID NO: 34 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 34 with at least 95% identical thereto.

[00172] In some examples, the antigen specific binding domain as described herein, wherein the light chain variable domain has a sequence: as shown in SEQ ID NO: 43; a sequence derived from SEQ ID NO: 43 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure

35 there is provided a derivative of SEQ ID NO: 43 with at least 95% identical thereto.

[00173] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 45 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00174] In some examples, the antigen specific binding domain as described herein, wherein 5 CDRH2 is SEQ ID NO: 46 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00175] In some examples, the antigen specific binding domain as described herein, wherein CDRH3 is SEQ ID NO: 47 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

10 [00176] In some examples, the antigen specific binding domain as described herein, wherein CDRL1 is SEQ ID NO: 18 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00177] In some examples, the antigen specific binding domain as described herein, wherein 15 CDRL2 is SEQ ID NO: 19 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00178] In some examples, the antigen specific binding domain as described herein, wherein CDRL3 is SEQ ID NO: 20 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

20 [00179] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has a sequence: as shown in SEQ ID NO: 51; a sequence derived from SEQ ID NO: 51 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 51 with at least 95% identical thereto.

25 [00180] In some examples, antigen specific binding domain as described herein, wherein the light chain variable domain has a sequence: shown in SEQ ID NO: 54; or a sequence derived from SEQ ID NO: 54 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 54 with at least 95% identical thereto.

30 [00181] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 56 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00182] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 57 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00183] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 58 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00184] In some examples, the antigen specific binding domain as described herein, wherein 5 CDRL1 is SEQ ID NO: 65 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00185] In some examples, the antigen specific binding domain as described herein, wherein CDRL2 is SEQ ID NO: 66 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

10 [00186] In some examples, the antigen specific binding domain as described herein, wherein CDRL3 is a SEQ ID NO: 67 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

15 [00187] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: shown in SEQ ID NO: 63; or a sequence derived from SEQ ID NO: 63 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 63 with at least 95% identical thereto.

20 [00188] In some examples, the antigen specific binding domain as described herein, wherein the light chain variable domain has a sequence: show in SEQ ID NO: 71; a sequence derived from SEQ ID NO: 71 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 71 with at least 95% identical thereto.

25 [00189] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 73 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00190] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 74 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

30 [00191] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 75 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00192] In some examples, the antigen specific binding domain as described herein, wherein CDRL1 is SEQ ID NO: 81 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00193] In some examples, the antigen specific binding domain as described herein, wherein CDRL2 is SEQ ID NO: 82 or a sequence differing therefrom in that 1 or 2 amino acids are replaced (with an alternative amino acid), deleted or added.

[00194] In some examples, the antigen specific binding domain as described herein, wherein

5 CDRL3 is SEQ ID NO: 83 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00195] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: shown in SEQ ID NO: 79; a sequence derived from SEQ ID NO: 79 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced

10 (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 79 with at least 95% identical thereto.

[00196] In some examples, the antigen specific binding domain as described herein, wherein

the light chain variable domain has a sequence: as show in SEQ ID NO: 87; a sequence derived from SEQ ID NO: 87 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced

15 (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 87 with at least 95% identical thereto.

[00197] In some examples, the antigen specific binding domain as described herein, wherein

CDRH1 is SEQ ID NO: 89 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

20 [00198] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 90 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00199] In some examples, the antigen specific binding domain as described herein wherein

CDRH3 is SEQ ID NO: 91 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00200] In some examples, the antigen specific binding domain as described herein, wherein

CDRL1 is SEQ ID NO: 65 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00201] In some examples, the antigen specific binding domain as described herein, wherein

30 CDRL2 is SEQ ID NO: 66 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00202] In some examples, the antigen specific binding domain as described herein, wherein

CDRL3 is SEQ ID NO: 67 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00203] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: as shown in SEQ ID NO: 95; a sequence derived from SEQ ID NO: 95 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure 5 there is provided a derivative of SEQ ID NO: 95 with at least 95% identical thereto.

[00204] In some examples, the antigen specific binding domain as described herein, wherein the light chain variable domain has a sequence: show in SEQ ID NO: 98; a sequence derived from SEQ ID NO: 98 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there 10 is provided a derivative of SEQ ID NO: 98 with at least 95% identical thereto.

[00205] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 100 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00206] In some examples, the antigen specific binding domain as described herein, wherein 15 CDRH2 is SEQ ID NO: 101 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00207] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 102 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00208] In some examples, the antigen specific binding domain as described herein, wherein 20 CDRL1 is SEQ ID NO: 108 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00209] In some examples, the antigen specific binding domain as described herein, wherein CDRL2 is SEQ ID NO: 109 or a sequence differing therefrom in that 1 or 2 amino acids are 25 independently replaced (with an alternative amino acid), deleted or added.

[00210] In some examples, the antigen specific binding domain as described herein, wherein CDRL3 is SEQ ID NO: 110 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00211] In some examples, the antigen specific binding domain as described herein wherein 30 the heavy chain variable domain has sequence: shown in SEQ ID NO: 106; a sequence derived from SEQ ID NO: 106 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 106 with at least 95% identical thereto.

[00212] In some examples, the antigen specific binding domain as described herein, wherein 35 the light chain variable domain has a sequence: show in SEQ ID NO: 114; a sequence derived from SEQ ID NO: 114 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently

replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 114 with at least 95% identical thereto.

[00213] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 116 or a sequence differing therefrom in that 1 or 2 amino acids are

5 independently replaced (with an alternative amino acid), deleted or added.

[00214] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 117 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00215] In some examples, the antigen specific binding domain as described herein wherein 10 CDRH3 is SEQ ID NO: 102 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00216] In some examples, the antigen specific binding domain as described herein, wherein CDRL1 is SEQ ID NO: 108 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

15 [00217] In some examples, the antigen specific binding domain as described herein, wherein CDRL2 is SEQ ID NO: 109 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00218] In some examples, the antigen specific binding domain as described herein wherein 20 CDRL3 is SEQ ID NO: 123 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00219] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: as shown in SEQ ID NO: 121; a sequence derived from SEQ ID NO: 121 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the 25 disclosure there is provided a derivative of SEQ ID NO: 121 with at least 95% identical thereto.

[00220] In some examples, the antigen specific binding domain as described herein, wherein the light chain variable domain has sequence: as shown in SEQ ID NO: 127; a sequence derived from SEQ ID NO: 127 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the 30 disclosure there is provided a derivative of SEQ ID NO: 127 with at least 95% identical thereto.

[00221] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 116 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00222] In some examples, the antigen specific binding domain as described herein, wherein 35 CDRH2 is SEQ ID NO: 117 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00223] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 102 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

5 [00224] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: shown in SEQ ID NO: 130; or a sequence derived from SEQ ID NO: 130 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 130 with at least 95% identical thereto.

10 [00225] In some examples, the antigen specific binding domain as described herein, wherein CDRH1 is SEQ ID NO: 116 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

[00226] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 101 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

15 [00227] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 102 or a sequence differing therefrom in that 1 or 2 amino acids are independently replaced (with an alternative amino acid), deleted or added.

20 [00228] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence: shown in SEQ ID NO: 133; a sequence derived from SEQ ID NO: 133 wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids are independently replaced (with an alternative amino acid), deleted or added, or in an independent aspect of the disclosure there is provided a derivative of SEQ ID NO: 133 with at least 95% identical thereto.

[00229] In some examples, the antigen specific binding domain as described herein wherein CDRH1 is SEQ ID NO: 135.

25 [00230] In some examples, the antigen specific binding domain as described herein, wherein CDRH2 is SEQ ID NO: 136.

[00231] In some examples, the antigen specific binding domain as described herein wherein CDRH3 is SEQ ID NO: 137.

30 [00232] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence shown in SEQ ID NO: 142.

[00233] In some examples, the antigen specific binding domain as described herein, wherein CDRL1 is SEQ ID NO: 144.

[00234] In some examples, the antigen specific binding domain as described herein, wherein CDRL2 is SEQ ID NO: 37.

[00235] In some examples, the antigen specific binding domain as described herein, wherein CDRL3 is SEQ ID NO: 145.

[00236] In some examples, the antigen specific binding domain as described herein, wherein the heavy chain variable domain has sequence shown in SEQ ID NO: 150.

5

[00237] In yet another aspect, there is provided a chimeric antigen receptor comprising the binding domain as described herein.

[00238] In some examples, the chimeric antigen receptor as described herein, wherein the chimeric antigen receptor is expressed on a cell surface. In some examples, the chimeric antigen receptor as described herein, wherein the cell is includes a T cell (such as a cytotoxic T cell), an NK cell and a NKT cell. In some examples, the chimeric antigen receptor as described herein, which comprises an intracellular signalling domain. In some examples, the chimeric antigen receptor as described herein, wherein the intracellular signalling domain is from CD3-zeta, for example described in WO2013/040557 incorporated herein by reference.

15 [00239] In some examples, the chimeric antigen receptor as described herein which further comprises a co-stimulator domain. In some examples, the chimeric antigen receptor as described herein, wherein the co-stimulator domain is independently selected from a group consisting of CD28, 4-1BB or OX40, and combinations thereof, such as CD28 and 4-1BB or CD28 and OX40.

20

[00240] In yet another aspect there is provided an isolated antibody or antibody comprising a binding domain as described herein. In some examples, the isolated antibody or antibody as described herein, wherein the antibody may include, but is not limited to, a multispecific antibody (such as a bispecific antibody), a full-length antibody or an antibody binding fragment.

25 [00241] In some examples, the isolated antibody or antibody as described herein, wherein the multispecific antibody is bispecific antibody. In some examples, the isolated antibody or antibody as described herein, where the multispecific antibody is a bispecific T cell engager (BiTe®).

30 [00242] In some examples, the isolated antibody or antibody as described herein, wherein the multispecific antibody comprises two different RON binding domains. In some examples, the antibody as described herein, wherein the two different RON binding domains are specific for different epitopes.

[00243] In some examples, the isolated antibody or antibody as described herein is capable of binding (or binds) to an epitope within RON as described within Figure 48A, Figure 48B, and
35 Table 1. In some example, the antibody as described herein is capable of binding (or binds) to an

epitope within RON having sequences including, but is not limited to, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16.

[00244] In some examples, the isolated antibody or antibody as described herein, wherein a first RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 shown in SEQ ID NO: 18, 19 and 20 respectively (in particular employed in variable regions shown in SEQ ID NO: 8 and 25, or a variant of the VH and/or VL domain with at least 95% identity to said sequence).

[00245] In some examples, the isolated antibody or antibody as described herein comprising a second RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 shown in SEQ ID NO: 36, 37 and 38 respectively (in particular employed in variable regions shown in SEQ ID NO: 34 and 43 or a variant of the VH and/or VL with at least 95% identity thereto).

[00246] In some examples, the isolated antibody or antibody as described herein, wherein the antibody binding fragment may include, but is not limited to, a Fab, a modified Fab, a Fab', a modified Fab', a F(ab')2, an Fv, ds-FV, Fab-Fv, Fab-dsFv, a single domain antibody (e.g. VH or VL or VHH), a scFv, and a ds-scFv.

[00247] In some examples, the isolated antibody or antibody as described herein, wherein the antibody molecule comprises an effector function.

[00248] In some examples, the isolated antibody or antibody as described herein, wherein the effector function is provided by an antibody constant region (such as the Fc region). In some examples, the antibody molecule as described herein, wherein the effector function is provided by an antibody constant region or an active fragment thereof, for example a full-length IgG isotype, such as IgG1, IgG2, IgG3 or IgG4 (in particular IgG1 or IgG4).

[00249] In some examples, the isolated antibody or antibody as described herein, wherein the antibody is conjugated to a payload. In some examples, the antibody as described herein, wherein the payload includes, but is not limited to, a toxin, a polymer (for example synthetic or naturally occurring polymers), biologically active proteins (for example enzymes, other antibody or antibody fragments), nucleic acids and fragments thereof (for example DNA, RNA and fragments thereof) radionuclides (particularly radioiodide, radioisotopes) chelated metals, nanoparticles and reporter groups such as fluorescent or luminescent labels or compounds which may be detected by NMR or ESR spectroscopy.

[00250] In some examples, wherein the toxin is selected from an auristatin (for example MMAE (monomethyl auristatin E- CAS number: 474645-27-7), MMAF (monomethyl auristatin F- CAS number: 745017-94-1)), pyrrolobenzodiazepine (PBD), doxorubicin (CAS number: 23214-92-8), duocarmycin, a maytansinoid (for example N2'-deacetyl-N2'-(3-mercaptop-1-oxopropyl)-maytansine (DM1; CAS number: 139504-50-0), N2'-deacetyl-N2'-(4-mercaptop-1-

oxopentyl)-maytansine (DM3) and N2'-deacetyl-N2'(4-methyl-4-mercaptop-1-oxopentyl)-maytansine (DM4; CAS number: 796073-69-3)), calocheamicin (CAS number: 108212-75-5), dolastatin, maytansine (CAS number: 35846-53-8), α -amanitin (CAS number: 23109-05-9), and a tubulysin (CAS number: 205304-86-5). In some example, the toxin may include, but is not limited to, wherein the toxin is selected from a group consisting of an auristatin, MMAF (monomethyl auristatin F), pyrrolobenzodiazepine (PBD), doxorubicin, duocarmycin, a maytansinoid, calocheamicin, dolastatin, maytansine, α -amanitin, and a tubulysin.

[00251] In yet another aspect there is provided a pharmaceutical composition comprising an antibody as described herein and an excipient, diluent and/or carrier.

[00252] In some examples, the pharmaceutical composition as described herein, comprising at least two monoclonal antibody in admixture, for example two antigen specific antibody as described herein.

[00253] In some examples, the pharmaceutical composition comprises one of the at least two antigen specific antibody comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20; optionally wherein a second antibody of the at least two antibodies comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 as shown in SEQ ID NO: 36, 37 and 38. In some examples, the pharmaceutical composition comprises one of the at least two antigen specific antibody comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 as shown in SEQ ID NO: 36, 37 and 38; optionally wherein a second antibody of the at least two antibodies comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20.

[00254] In some examples, the pharmaceutical composition as described herein, wherein the least one antigen specific antibody comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20 respectively (in particular employed in variable regions shown in SEQ ID NO: 8 and 25, or a variant of the VH and/or VL with at least 95% identity thereto).

[00255] In some examples, the pharmaceutical composition as described herein, wherein the least one antigen comprising a second RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 36, 37 and 38 (in particular employed in variable regions shown in SEQ ID NO: 34 and 43, or a variant of the VH and/or VL with at least 95% identity thereto).

[00256] In some examples, the pharmaceutical composition as described herein, wherein the formulation is a parenteral.

[00257] In yet another aspect, there is provided a RON binding domain as described herein, or a chimeric antigen receptor as described herein, or a composition as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein, for use in treatment (or therapy).

5 [00258] In yet another aspect there is provided a RON binding domain as described herein, for use in treatment (or therapy).

[00259] In yet another aspect there is provided a chimeric antigen receptor as described herein or a pharmaceutical composition as described herein for use in treatment (or therapy).

10 [00260] In yet another aspect there is provided an antibody molecule as described herein, or a composition as described herein for use in treatment (or therapy).

15 [00261] In yet another aspect, there is provided the use of an antigen binding domain as described herein, or a chimeric antigen receptor as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of cancer or fibrosis (in particular in cancer). In some example, the cancer is a RON positive cancer.

20 [00262] In yet another aspect there is provided a use of an antigen binding domain as described herein, in the manufacture of a medicament for the treatment of cancer or fibrosis (in particular cancer).

25 [00263] In yet another aspect there is provided a use of a chimeric antigen receptor as described herein or a pharmaceutical composition as described herein for the manufacture of a medicament for the treatment of cancer or fibrosis (in particular cancer).

[00264] In yet another aspect there is provided a use of an antibody as described herein, or a composition as described herein for the manufacture of medicament for the treatment of tumor, cancer or fibrosis (in particular cancer, such as a solid cancer mass and/or metastatic cancer).

25 In some example, the cancer is a RON expressing cancer.

30 [00265] In yet another aspect, there is provided a method of preventing or treating cancer or fibrosis in a patient comprising administering a therapeutic effective amount of an antigen binding domain as described herein, or a chimeric antigen receptor as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein to the patient in need thereof.

[00266] In some examples, the patient is (or forms part of) a patient population characterised in that patients making up the population have a RON positive tumour. In some examples, the patients making up the population have a RON positive and C-MET positive tumour.

35 [00267] In some examples, the method as described herein, comprises the step of identifying the patient to have a RON positive tumour before treatment.

[00268] In yet another example, there is provided a method of treating a patient for cancer or fibrosis comprising administering a therapeutic amount of an RON binding domain as described herein, or a chimeric antigen receptor as described herein, or a composition as described herein, or an antibody as described herein, or a pharmaceutical composition as described herein.

5 [00269] In yet another example there is provided a method of treating a patient for cancer or fibrosis comprising administering a therapeutic amount of an RON binding domain as described herein.

[00270] In yet another example there is provided a method of treating a patient for cancer or fibrosis comprising administering a therapeutic amount of an chimeric antigen receptor as described herein or a composition as described herein.

10 [00271] In yet another example there is provided a method of treating a patient for cancer or fibrosis comprising administering a therapeutic amount of an antibody as described herein or a composition as described herein.

15 [00272] In yet another example, there is provided a method of treating a patient population with an RON binding domain as described herein, or a chimeric antigen receptor as described herein, or a composition as described herein, or an antibody as described herein, wherein the population is characterised in that patients making up the population have a RON positive tumour. In some examples, the patients making up the population have a RON positive and C-MET positive tumour.

20 [00273] In yet another example there is provided a method of treating a patient population with a chimeric antigen receptor as described herein, a composition comprising the same as described herein, antibody molecule as described herein or a composition comprising the same as described herein, wherein the population is characterised in that patients making up the population have a RON positive tumour.

25 [00274] In yet another example there is provided a method of treating a patient population as described herein, wherein the patients making up the population have a RON positive and MET positive tumour.

[00275] In yet another example there is provided a method of treating a patient population as described herein, which comprises the step of identifying the patient as in the population 30 before treatment according to the present disclosure is administered.

[00276] In yet another example, there is provided a use of a composition as described herein, or an antibody as described herein for use as diagnostic or prognostic agent. In yet another aspect there is provided a use of an antibody molecule as described herein, or a composition as described herein for use as diagnostic or prognostic agent, for example wherein the antibody 35 molecule is conjugated to a imaging agent, which is visualizable *in vivo*.

[00277] In some examples there is provided a method of downregulating RON expression in a patient by administering a therapeutically effective amount of a binding domain according to the present disclosure (in particular an antibody molecule as disclosed herein).

[00278] In yet another aspect there is provided an antibody which cross-blocks or binds the same epitope as an antibody comprising a VH of SEQ ID NO: 8, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 63, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 106, SEQ ID NO: 121, SEQ ID NO: 130 or SEQ ID NO: 132.

[00279] In yet another aspect there is provided an antibody, which cross-blocks or binds the same epitope as an antibody comprising a VH/VL pair selected from SEQ ID NO: 8 and 25, SEQ ID NO: 34 and 43, SEQ ID NO: 51 and 54, SEQ ID NO: 63 and 71, SEQ ID NO: 79 and 87, SEQ ID NO: 95 and 98, SEQ ID NO: 106 and 114 or SEQ ID NO: 121 and 130.

[00280] In some examples, the antibody as described herein cross-blocks or binds to the epitope as defined in Figure 48A, Figure 48B, or Table 1.

[00281] In yet another aspect, there is provided an ex vivo method of evaluating the status of a cancer; wherein the method comprises: a) scanning a patient or a specific site of the patient known to comprise a tumor of the cancer, wherein the patient had been administered with a labelled form of an antibody at a first time point, wherein the antibody is as defined herein, b) repeating a) at one or more further time points, and comparing the results from two or more time points to evaluate the status of the cancer.

[00282] In yet another example there is provided a method of monitor a cancer patient using an antibody molecule as defined herein, wherein the method comprises the steps of: using a labelled form of the antibody molecule to access the cancer, in particular a tumour, at a first time point, using a labelled form of the antibody molecule to access the cancer, in particular a tumour, at least a second time point, and comparing the results from the two or more time points to evaluate the status of the cancer. In some examples, in the method of monitoring a cancer patient as described herein, decreases in RON expression by the tumour between the first time point and a subsequent time point correlates with an improved prognosis.

[00283] In one example the epitope bound by an antibody of the present disclosure binds a conformational epitope.

[00284] In one example the epitope bound by an antibody of the present disclosure binds a linear epitope.

[00285] In one example there is provided an antibody which specifically binds at least 5 amino acids, such as 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids in peptide sequence

[00286] In some examples, the epitope bound by (recognised by) an antibody or antigen binding domain as described herein includes the peptides as described in Figure 48A, Figure 48B, and Table 1.

5 [00287] In one example there is provided a binding domain comprises SEQ ID NO: 8 or a sequence at least 95% identical thereto, and SEQ ID NO: 25 or a sequence at least 95% identical thereto.

[00288] In one example the binding domain of the present disclosure comprises SEQ ID NO: 34 or a sequence at least 95% identical thereto, and SEQ ID NO: 43 or a sequence at least 95%
10 identical thereto.

[00289] In one example the binding domain of the present disclosure comprises SEQ ID NO: 51 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95% identical thereto.

15 [00290] In one example the binding domain of the present disclosure comprises SEQ ID NO: 63 or a sequence at least 95% identical thereto, and SEQ ID NO: 71 or a sequence at least 95% identical thereto.

[00291] In one example the binding domain of the present disclosure comprises SEQ ID NO: 79 or a sequence at least 95% identical thereto, and SEQ ID NO: 97 or a sequence at least 95% identical thereto.

20 [00292] In one example the binding domain of the present disclosure comprises SEQ ID NO: 95 or a sequence at least 95% identical thereto, and SEQ ID NO: 98 or a sequence at least 95% identical thereto.

[00293] In one example the binding domain of the present disclosure comprises SEQ ID NO: 106 or a sequence at least 95% identical thereto, and SEQ ID NO: 114 or a sequence at least 95%
25 identical thereto.

[00294] In one example the binding domain of the present disclosure comprises SEQ ID NO: 121 or a sequence at least 95% identical thereto, and SEQ ID NO: 130 or a sequence at least 95% identical thereto.

30 [00295] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8 or a sequence at least 95% identical thereto, and SEQ ID NO: 43 or a sequence at least 95% identical thereto.

[00296] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95%
35 identical thereto.

[00297] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8 or a sequence at least 95% identical thereto, and SEQ ID NO: 71 or a sequence at least 95% identical thereto.

[00298] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8

5 or a sequence at least 95% identical thereto, and SEQ ID NO: 87 or a sequence at least 95% identical thereto.

[00299] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8

or a sequence at least 95% identical thereto, and SEQ ID NO: 98 or a sequence at least 95% identical thereto.

10 [00300] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8 or a sequence at least 95% identical thereto, and SEQ ID NO: 114 or a sequence at least 95% identical thereto.

[00301] In one example the binding domain of the present disclosure comprises SEQ ID NO: 8

or a sequence at least 95% identical thereto, and SEQ ID NO: 127 or a sequence at least 95% identical thereto.

[00302] In one example the binding domain of the present disclosure comprises SEQ ID NO: 34 or a sequence at least 95% identical thereto, and SEQ ID NO: 71 or a sequence at least 95% identical thereto.

20 [00303] In one example the binding domain of the present disclosure comprises SEQ ID NO: 34 or a sequence at least 95% identical thereto, and SEQ ID NO: 87 or a sequence at least 95% identical thereto.

[00304] In one example the binding domain of the present disclosure comprises SEQ ID NO:

34 or a sequence at least 95% identical thereto, and SEQ ID NO: 98 or a sequence at least 95% identical thereto.

25 [00305] In one example the binding domain of the present disclosure comprises SEQ ID NO: 34 or a sequence at least 95% identical thereto, and SEQ ID NO: 114 or a sequence at least 95% identical thereto.

[00306] In one example the binding domain of the present disclosure comprises SEQ ID NO:

30 34 or a sequence at least 95% identical thereto, and SEQ ID NO: 127 or a sequence at least 95% identical thereto.

[00307] In one example the binding domain of the present disclosure comprises SEQ ID NO:

35 51 or a sequence at least 95% identical thereto, and SEQ ID NO: 70 or a sequence at least 95% identical thereto.

[00308] In one example the binding domain of the present disclosure comprises SEQ ID NO: 51 or a sequence at least 95% identical thereto, and SEQ ID NO: 86 or a sequence at least 95% identical thereto.

[00309] In one example the binding domain of the present disclosure comprises SEQ ID NO:

5 51 or a sequence at least 95% identical thereto, and SEQ ID NO: 102 or a sequence at least 95% identical thereto.

[00310] In one example the binding domain of the present disclosure comprises SEQ ID NO:

51 or a sequence at least 95% identical thereto, and SEQ ID NO: 118 or a sequence at least 95% identical thereto.

10

[00311] In one example the binding domain of the present disclosure comprises SEQ ID NO: 62 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95% identical thereto.

[00312] In one example the binding domain of the present disclosure comprises SEQ ID NO:

15 62 or a sequence at least 95% identical thereto, and SEQ ID NO: 86 or a sequence at least 95% identical thereto.

[00313] In one example the binding domain of the present disclosure comprises SEQ ID NO:

62 or a sequence at least 95% identical thereto, and SEQ ID NO: 102 or a sequence at least 95% identical thereto.

20 [00314] In one example the binding domain of the present disclosure comprises SEQ ID NO: 62 or a sequence at least 95% identical thereto, and SEQ ID NO: 118 or a sequence at least 95% identical thereto.

[00315] In one example the binding domain of the present disclosure comprises SEQ ID NO:

25 78 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95% identical thereto.

[00316] In one example the binding domain of the present disclosure comprises SEQ ID NO:

78 or a sequence at least 95% identical thereto, and SEQ ID NO: 70 or a sequence at least 95% identical thereto.

30 [00317] In one example the binding domain of the present disclosure comprises SEQ ID NO: 78 or a sequence at least 95% identical thereto, and SEQ ID NO: 102 or a sequence at least 95% identical thereto.

[00318] In one example the binding domain of the present disclosure comprises SEQ ID NO:

78 or a sequence at least 95% identical thereto, and SEQ ID NO: 118 or a sequence at least 95% identical thereto.

35

[00319] In one example the binding domain of the present disclosure comprises SEQ ID NO: 96 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95% identical thereto.

5 [00320] In one example the binding domain of the present disclosure comprises SEQ ID NO: 96 or a sequence at least 95% identical thereto, and SEQ ID NO: 70 or a sequence at least 95% identical thereto.

[00321] In one example the binding domain of the present disclosure comprises SEQ ID NO: 96 or a sequence at least 95% identical thereto, and SEQ ID NO: 86 or a sequence at least 95%
10 identical thereto.

[00322] In one example the binding domain of the present disclosure comprises SEQ ID NO: 96 or a sequence at least 95% identical thereto, and SEQ ID NO: 118 or a sequence at least 95% identical thereto.

15 [00323] In one example the binding domain of the present disclosure comprises SEQ ID NO: 110 or a sequence at least 95% identical thereto, and SEQ ID NO: 54 or a sequence at least 95% identical thereto.

[00324] In one example the binding domain of the present disclosure comprises SEQ ID NO: 110 or a sequence at least 95% identical thereto, and SEQ ID NO: 70 or a sequence at least 95%
20 identical thereto.

[00325] In one example the binding domain of the present disclosure comprises SEQ ID NO: 110 or a sequence at least 95% identical thereto, and SEQ ID NO: 86 or a sequence at least 95% identical thereto.

[00326] In one example the binding domain of the present disclosure comprises SEQ ID NO: 110 or a sequence at least 95% identical thereto, and SEQ ID NO: 102 or a sequence at least 95% identical thereto.
25

[00327] In one example the binding domain according to the present disclosure, such as an antibody molecule, which is humanized.

30 [00328] In one example there is provided a polynucleotide (such as DNA) encoding a binding domain, chimeric receptor, or an antibody molecule according to the present disclosure, for example where heavy and light chains are encoded in the same polynucleotide (such as DNA) molecule or on different polynucleotide (such as DNA) molecules.

[00329] In one example there is provided a vector comprising a polynucleotide (such as DNA) according to the present disclosure.

[00330] A cell comprising a polynucleotide (such as DNA) according to the present disclosure or a vector as defined herein, for example a mammalian cell. In one example the cell is a host cell, simply designed for expression of the encoded protein, for example a CHO, HEK, PerC6, *E. coli* or similar cells. In one example the cell is a therapeutic mammalian cell, which is engineered to express a binding domain according to the present disclosure, for example T cell (such as a cytotoxic T cell), an NK cell or an NKT cell.

10

[00331] In one example there is provided a mammalian lymphocyte cell (in particular an NKT cell or a T cell), such as cytotoxic T cell with an engineered T cell receptor, wherein said receptor comprises 6 CDRs from an antibody as disclosed herein.

15

[00332] Thus in one example there is provided a method for the treatment of human cancer comprising administering a monoclonal antibody that binds to the RON protein; the antibody having the CDR sequences listed.

[00333] In one example there is provided a cell according to the present disclosure for use in treatment, in particular for the treatment of cancer.

20

[00334] In one example the binding domains of the present disclosure, such as an antibody molecule, downregulates RON expression on a tumour cells. This may for example render the cancer more susceptible or sensitive to a cancer treatment, such as sensitising the patient to chemotherapy.

25

[00335] Thus in one independent aspect there is provided a method of changing the prognosis of a cancer patient comprising converting the patient from a RON positive patient population to a RON negative patient population by administering an antibody molecule treatment according to the present disclosure.

[00336] Advantageously the off-target effects of the antibody molecule of the present disclosure seem to be minimal, as RON has limited expression in non-cancerous cells, while being highly overexpressed in cancer tissues.

30

[00337] In one example the antibody molecule is a RON inhibitor (antagonist). A RON inhibitor as employed herein refers to an entity, such as an antibody or binding fragment, which reduces or cancels or blocks a relevant biological activity of RON receptor tyrosine kinase (also known as MST1R), in particular inhibits the human protein. The inhibitor effects on cancer cells may include one or more the following, inhibition of cancer cell proliferation, inhibition of

cancer cell migration, reduced expression of RON (which may lead to an improved response to treatment and a better prognosis).

[00338] In one example the inhibitor reduces a relevant biological activity, for example by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100%, such as when measured in a relevant *in vitro* assay.

[00339] In one example the inhibitor according to the present disclosure is a direct inhibitor. Direct inhibition is where the inhibitor binds directly to or physically blocks a binding interaction to inhibit a biological activity.

[00340] Antibody molecule as employed herein refers to a complete antibody molecule having full length heavy and light chains, or a fragment thereof (which may be, but is not limited to Fab, modified Fab, Fab', modified Fab', F(ab')2, Fv, Fab-Fv, Fab-dsFv, single domain antibodies (e.g. VH or VL or VHH), scFv and a multispecific antibody format, for example comprising a binding domain according to the present disclosure (including as part of a full length antibody or antibody fragment), such as bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope-binding fragments of any of the above.

[00341] In the context of the antibodies specifically referred to herein it will be clear to the skilled person that the disclosure includes use of the variable domains, in particular as a pair from the said antibody in any antibody or fragment format, including a multispecific antibody. In one example 6 CDRs are employed from an antibody disclosed herein in combination with an alternative framework, such as a human framework.

[00342] Antibody as employed herein refers to a complete antibody having full length heavy and light chains or a multi-valent antibody comprising at least a complete antibody and which may comprise multiple specificities e.g. bispecific or may be monospecific (see for example WO92/22853 and WO05/113605). Bispecific and multispecific antibody variants are especially relevant as the role of the therapeutic molecules of the present disclosure in one example as the therapeutic objective is to inhibit two independent target proteins, namely RON receptor tyrosine kinase and for example second therapeutic target, such as a protein in the PD-1 pathway (in particular PD-1 or PD-L1).

[00343] In one example antibody molecule of the present disclosure is multivalent.

[00344] Multivalent as employed herein refers to an antibody molecule, which binds a given target (including the same target) more than once. Multivalent antibody molecules can cross-link targets and, for example induce complement pathways or the like.

[00345] In one example the antibody molecule of the present disclosure is monovalent. Monovalent as employed herein refers to an antibody molecule which is designed or engineered to bind a target only once.

[00346] In one example an antibody molecule according to the present disclosure is chimeric.

[00347] In one example an antibody molecule according to the present disclosure, in particular a binding domain therein is humanised.

[00348] In one example an antibody molecule according to the present disclosure is monoclonal.

5 [00349] "Multispecific molecule" as employed herein refers to a molecule with the ability to specifically bind at least two distinct antigens, for example different antigens. In one example the multispecific molecule is a bispecific, trispecific or tetraspecific molecule, in particular a bispecific or trispecific molecule. Multi-valent antibodies may comprise multiple specificities e.g bispecific or may be monospecific (see for example WO92/22853 and WO05/113605).

10 [00350] "Antibody fragment" as employed herein refers to an antibody binding fragment including but not limited to Fab, modified Fab, Fab', modified Fab', F(ab')2, Fv, single domain antibodies, scFv, Fv, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope-binding fragments of any of the above (see for example Holliger and Hudson, 2005, Nature Biotech. 23(9):1126-1136; Adair and Lawson, 2005, Drug Design Reviews - Online 2(3), 15 209-217).

20 [00351] "Epitope" as employed herein refers to a portion or portions of a macromolecule which is capable of being bound by a specific antibody, in the present disclosure, a portion of a polypeptide, in particular RON. Epitopes generally consist of chemically active surface groups and have specific three dimensional structural characteristics, as well as specific charge characteristics.

25 [00352] The term "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an amino acid sequence or other binding agents (such as the antigen binding domain as described herein) to interfere with the binding of other amino acid sequences or antigen binding domain as described herein to a given target (for example epitope as defined herein). The extent to which an amino acid sequence or the antigen binding domain as described herein is able to interfere with the binding of another to the target epitope, and therefore whether it can be said to cross-block according to the present disclosure, can be determined using competition binding assays known in the art.

30 [00353] One particularly suitable quantitative assay uses a Biacore machine which can measure the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between amino acid sequence or antigen binding domain as described herein in terms of their binding to the target epitope.

35 [00354] The following generally describes a suitable Biacore assay for determining whether an amino acid sequence or antigen binding domain as described herein cross-blocks or is capable of cross- blocking. It will be appreciated that the assay can be used with any of the

amino acid sequence or antigen binding domain as described herein. The Biacore machine (for example the Biacore 3000) is operated in line with the manufacturer's recommendations. Thus in one cross-blocking assay, the target protein is coupled to a CM5 Biacore chip using standard amine coupling chemistry to generate a surface that is coated with the target. Typically 200-5 800 resonance units of the target would be coupled to the chip (an amount that gives easily measurable levels of binding but that is readily saturable by the concentrations of test reagent being used). Two test amino acid sequences (termed A* and B*) to be assessed for their ability to cross-block each other are mixed at a one to one molar ratio of binding sites in a suitable buffer to create the test mixture. When calculating the concentrations on a binding site basis the 10 molecular weight of an amino acid sequence is assumed to be the total molecular weight of the amino acid sequence divided by the number of target binding sites on that amino acid sequence. The concentration of each amino acid sequence in the test mix should be high enough to readily saturate the binding sites for that amino acid sequence on the target molecules captured on the Biacore chip. The amino acid sequences in the mixture are at the same molar concentration (on 15 a binding basis) and that concentration would typically be between 1.00 and 1.5 micromolar (on a binding site basis). Separate solutions containing A* alone and B* alone are also prepared. A* and B* in these solutions should be in the same buffer and at the same concentration as in the test mix. The test mixture is passed over the target-coated Biacore chip and the total amount of binding recorded. The chip is then treated in such a way as to remove the bound amino acid 20 sequences without damaging the chip-bound target. Typically this is done by treating the chip with 30 mM HCl for 60 seconds. The solution of A* alone is then passed over the target-coated surface and the amount of binding recorded. The chip is again treated to remove all of the bound amino acid sequences without damaging the chip-bound target. The solution of B* alone is then passed over the target-coated surface and the amount of binding recorded. The maximum 25 theoretical binding of the mixture of A* and B* is next calculated, and is the sum of the binding of each amino acid sequence when passed over the target surface alone. If the actual recorded binding of the mixture is less than this theoretical maximum then the two amino acid sequences are cross-blocking each other. Thus, in general, a cross-blocking amino acid sequence or antigen binding domain as described herein is one which will bind to the target in the above 30 Biacore cross-blocking assay such that during the assay and in the presence of a second amino acid sequence or antigen binding domain as described herein the recorded binding is between 80% and 0.1% (e.g. 80% to 4%) of the maximum theoretical binding, specifically between 75% and 0.1% (e.g. 75% to 4%) of the maximum theoretical binding, and more specifically between 70% and 0.1% (e.g. 70% to 4%) of maximum theoretical binding (as just defined above) of the 35 two amino acid sequences or antigen binding domain as described herein in combination. The Biacore assay described above is a primary assay used to determine if amino acid sequences or

antigen binding domain as described herein cross-block each other according to the present disclosure.

[00355] The following generally describes an ELISA assay for determining whether an amino acid sequence or antigen binding domain as described herein directed against a target cross-

5 blocks or is capable of cross-blocking as defined herein. It will be appreciated that the assay can be used with any of the amino acid sequences (or antigen binding domain as described herein) described herein. The general principal of the assay is to have an amino acid sequence or antigen binding domain that is directed against the target epitope coated onto the wells of an ELISA plate. An excess amount of a second, potentially cross-blocking, anti-target amino acid

10 sequence is added in solution (i.e. not bound to the ELISA plate). A limited amount of the target is then added to the wells. The coated amino acid sequence and the amino acid sequence in solution compete for binding of the limited number of target molecules. The plate is washed to remove excess target that has not been bound by the coated amino acid sequence and to also remove the second, solution phase amino acid sequence as well as any complexes formed

15 between the second, solution phase amino acid sequence and target. The amount of bound target is then measured using a reagent that is appropriate to detect the target. An amino acid sequence in solution that is able to cross-block the coated amino acid sequence will be able to cause a decrease in the number of target molecules that the coated amino acid sequence can bind relative to the number of target molecules that the coated amino acid sequence can bind in

20 the absence of the second, solution phase, amino acid sequence. In the instance where the first amino acid sequence, e.g. an Ab-X, is chosen to be the immobilized amino acid sequence, it is coated onto the wells of the ELISA plate, after which the plates are blocked with a suitable blocking solution to minimize non-specific binding of reagents that are subsequently added. An excess amount of the second amino acid sequence, i.e. Ab-Y, is then added to the ELISA plate

25 such that the moles of Ab-Y [target] binding sites per well are at least 10 fold higher than the moles of Ab-X [target] binding sites that were used, per well, during the coating of the ELISA plate, [target] is then added such that the moles of [target] added per well are at least 25-fold lower than the moles of Ab-X [target] binding sites that were used for coating each well. Following a suitable incubation period the ELISA plate is washed and a reagent for detecting the

30 target is added to measure the amount of target specifically bound by the coated anti-[target] amino acid sequence (in this case Ab-X). The background signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence (in this case Ab-X), second solution phase amino acid sequence (in this case Ab-Y), [target] buffer only (i.e. no target), and target detection reagents. The positive control signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence (in this case Ab- X), second solution phase amino acid sequence buffer only (i.e. no second solution phase amino acid sequence),

target and target detection reagents. The ELISA assay may be run in such a manner so as to have the positive control signal be at least 6 times the background signal. To avoid any artefacts (e.g. significantly different affinities between Ab-X and Ab-Y for [target]) resulting from the choice of which amino acid sequence to use as the coating amino acid sequence and which to use as the 5 second (competitor) amino acid sequence, the cross-blocking assay may be run in two formats: 1) format 1 is where Ab-X is the amino acid sequence that is coated onto the ELISA plate and Ab-Y is the competitor amino acid sequence that is in solution and 2) format 2 is where Ab-Y is the amino acid sequence that is coated onto the ELISA plate and Ab-X is the competitor amino acid sequence that is in solution. Ab-X and Ab-Y are defined as cross-blocking 10 if, either in format 1 or in format 2, the solution phase anti-target amino acid sequence is able to cause a reduction of between 60% and 100%, specifically between 70% and 100%, and more specifically between 80% and 100%, of the target detection signal (i.e. the amount of target bound by the coated amino acid sequence) as compared to the target detection signal obtained in the absence of the solution phase anti-target amino acid sequence (i.e. the positive control 15 wells).

[00356] The term “cross-block” is in contrast with “binding”, which when used herein, refers to the selective affinities between a pair of species that chemically bind together. In the present case, binding refers to the specific recognition of the antigen binding domain to the epitopes as described herein. Therefore, this is in contrast with “cross-block” which interfere with the 20 binding of the antigen binding domain as described herein to the RON epitope as described herein.

[00357] Other antibody fragments for use in the present invention include the Fab and Fab' fragments described in International patent applications WO2005/003169, WO2005/003170 and WO2005/003171.

25 [00358] A “binding fragment” as employed herein refers to an antibody fragment capable of binding a target peptide or antigen with sufficient specificity to characterise the fragment as specific for the peptide or antigen.

[00359] Specific as employed herein refers to an antibody molecule that only recognises the antigen to which it is specific or an antibody molecule that has significantly higher binding 30 affinity for the antigen to which it is specific compared to the binding affinity for antigens to which it is non-specific, for example 5, 6, 7, 8, 9, 10 or more times higher binding affinity.

[00360] The term “Fab fragment” as used herein refers to an antibody fragment comprising a light chain fragment comprising a V_L (variable light) domain and a constant domain of a light chain (C_L), and a V_H (variable heavy) domain and a first constant domain (CH_1) of a heavy chain.

35 [00361] The Fv refers to two variable domains, for example co-operative variable domains, such as a cognate pair or affinity matured variable domains, such as a V_H and V_L pair.

[00362] Co-operative variable domains as employed herein are variable domains that complement each other and/or both contribute to antigen binding to render the Fv (V_H/V_L pair) specific for the antigen in question.

[00363] Binding domain as employed herein refers to two co-operative variable regions, such

5 as a VH and VL each comprising 3 CDRs, wherein the binding domain is specific to a particular (target) antigen.

[00364] In one example the antibody molecules of the present disclosure have high affinity, for example affinity of 500nM or higher affinity, such as 400, 300, 200, 150, 125, 115, 114, 113, 112, 111, 110, 109, 108, 107, 106, 105, 104, 103, 102, 101, 100, 99, 98, 97, 96, 95, 94, 93, 92, 91, 10 90, 89, 88, 87, 86, 85, 84, 83, 82, 81, 80, 79, 78, 77, 76, 75, 74, 73, 72, 71, 70, 69, 68, 67, 66, 65, 64, 63, 62, 61, 60, 59, 58, 57, 56, 55, 54, 53, 52, 51, 50, 49, 48, 47, 46, 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1nM or higher affinity.

[00365] Higher binding affinity as employed herein refers to a lower numerical affinity value,

15 for example 1nM affinity is higher affinity (also referred to as increased affinity) than 10nM affinity.

[00366] Binding affinity (affinity) may be measured by a number of standard assays, for example surface plasmon resonance, such as BIAcore.

[00367] The affinity of the original antibody may be increased by employing an affinity

20 maturation protocols including mutating the CDRs (Yang *et al* J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks *et al.*, Bio/Technology, 10, 779-783, 1992), use of mutator strains of E. coli (Low *et al.*, J. Mol. Biol., 250, 359-368, 1996), DNA shuffling (Patten *et al.*, Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson *et al.*, J. Mol. Biol., 256, 77-88, 1996) and sexual PCR (Crameri *et al* Nature, 391, 288-291, 1998). Vaughan *et al.* (*supra*) discusses 25 these methods of affinity maturation. Increased affinity as employed herein in this context refers to an improvement over the starting molecule.

[00368] In one example the antibody molecule of the present disclosure comprises an amino acid sequence at least 95% identical to a sequence disclosed herein. This example also extends to sequences 96, 97, 98 or 99% to a given sequence disclosed herein.

30 [00369] The methods for creating and manufacturing these antibodies and antibody fragments are well known in the art. Antibodies for use in the present disclosure may be obtained using any suitable method known in the art. The polypeptide/protein including: fusion proteins, for example polypeptide-Fc fusions proteins; or cells, recombinantly or naturally, expressing the polypeptide (as activated T cells), can be used to, for example 35 immunise a host and produce antibodies which specifically recognise the target

polypeptide/protein. The polypeptide may be the full length polypeptide or a biologically active fragment or derivative thereof.

[00370] Polypeptides may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems or they may be recovered from natural biological sources. In the present application, the term "polypeptides" includes peptides, polypeptides and proteins. These are used interchangeably unless otherwise specified. The antigen polypeptide may in some instances be part of a larger protein such as a fusion protein for example fused to an affinity tag.

[00371] Antibodies generated against the antigen polypeptide may be obtained, where immunisation of an animal is necessary, by administering the polypeptides to an animal, preferably a non-human animal, using well-known and routine protocols, see for example *Handbook of Experimental Immunology*, D. M. Weir (ed.), Vol 4, Blackwell Scientific Publishers, Oxford, England, 1986). Many warm-blooded animals, such as rabbits, mice, rats, sheep, cows, camels or pigs may be immunized. However, mice, rabbits, pigs and rats are generally most suitable.

[00372] Monoclonal antibodies may be prepared by any method known in the art such as the hybridoma technique (Kohler & Milstein, 1975, *Nature*, 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, *Immunology Today*, 4:72) and the EBV-hybridoma technique (Cole *et al* *Monoclonal Antibodies and Cancer Therapy*, pp77-96, Alan R Liss, Inc., 1985).

[00373] Antibodies for use in the disclosure may also be generated using single lymphocyte antibody methods by cloning and expressing immunoglobulin variable region cDNAs generated from single lymphocytes selected for the production of specific antibodies by, for example, the methods described by Babcock, J. *et al* 1996, *Proc. Natl. Acad. Sci. USA* 93(15):7843-7848; WO92/02551; WO2004/051268 and WO2004/106377.

[00374] Humanised antibodies (which include CDR-grafted antibodies) are antibody molecules having one or more complementarity determining regions (CDRs) from a non-human species and a framework region from a human immunoglobulin molecule (see, e.g. US5,585,089; WO91/09967). It will be appreciated that it may only be necessary to transfer the specificity determining residues of the CDRs rather than the entire CDR (see for example, Kashmiri et al., 2005, *Methods*, 36, 25-34). Humanised antibodies may optionally further comprise one or more framework residues derived from the non-human species from which the CDRs were derived.

[00375] As used herein, the term 'humanised antibody molecule' refers to an antibody molecule wherein the heavy and/or light chain contains one or more CDRs (including, if desired, one or more modified CDRs) from a donor antibody (e.g. a murine monoclonal antibody) grafted into a heavy and/or light chain variable region framework of an acceptor antibody (e.g. a human

antibody). For a review, see Vaughan *et al*, *Nature Biotechnology*, 16, 535-539, 1998. In one example rather than the entire CDR being transferred, only one or more of the specificity determining residues from any one of the CDRs described herein above are transferred to the human antibody framework (see for example, Kashmiri *et al.*, 2005, *Methods*, 36, 25-34). In one example only the specificity determining residues from one or more of the CDRs described herein above are transferred to the human antibody framework. In another example only the specificity determining residues from each of the CDRs described herein above are transferred to the human antibody framework.

[00376] When the CDRs or specificity determining residues are grafted, any appropriate

10 acceptor variable region framework sequence may be used having regard to the class/type of the donor antibody from which the CDRs are derived, including mouse, primate and human framework regions. Suitably, the humanised antibody according to the present invention has a variable domain comprising human acceptor framework regions as well as one or more of the CDRs provided herein.

15 [00377] CDRs as referred to herein are defined by the VBASE2 software: Retter I, Althaus HH, Münch R, Müller W: VBASE2, an integrative V gene database. *Nucleic Acids Res.* 2005 Jan 1;33 (Database issue):D671-4.

20 [00378] In an alternative independent there is provided the CDRs defined in each of the a variable domains disclosed herein wherein the CDRs are defined by Kabat/Clothia numbering as a defined below.

25 [00379] CDRs of the heavy chain variable domain are located at residues 31-35 (CDR-H1), residues 50-65 (CDR-H2) and residues 95-102 (CDR-H3) according to the Kabat numbering system. However, according to Chothia (Chothia, C. and Lesk, A.M. *J. Mol. Biol.*, 196, 901-917 (1987)), the loop equivalent to CDR-H1 extends from residue 26 to residue 32. Thus unless indicated otherwise 'CDR-H1' as employed herein is intended to refer to residues 26 to 35, as described by a combination of the Kabat numbering system and Chothia's topological loop definition.

30 [00380] The CDRs of the light chain variable domain are located at residues 24-34 (CDR-L1), residues 50-56 (CDR-L2) and residues 89-97 (CDR-L3) according to the Kabat numbering system.

35 [00381] The Kabat residue designations do not always correspond directly with the linear numbering of the amino acid residues. The actual linear amino acid sequence may contain fewer or additional amino acids than in the strict Kabat numbering corresponding to a shortening of, or insertion into, a structural component, whether framework or complementarity determining region (CDR), of the basic variable domain structure. The correct

Kabat numbering of residues may be determined for a given antibody by alignment of residues of homology in the sequence of the antibody with a “standard” Kabat numbered sequence.

[00382] The term “antibody effector function(s)” or “effector function” as used herein refers to a function contributed by the constant region of an antibody (e.g. the Fc effector domain(s) of an immunoglobulin). Such function can be effected by, for example, binding of an Fc effector domain(s) to an Fc receptor on an immune cell with pathogenic or lytic activity or by binding of an Fc effector domain(s) to components of the complement system. Examples of effector functions include, but is not limited to, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC).

[00383] In one example an antibody molecule according to the present disclosure may induce (or increase) antibody-dependent cell-mediated cytotoxicity (ADCC) of target (cancer) cells. ADCC is an immune mechanism leading to the lysis of antibody-coated target cells by immune effector cells. The target cells are cells to which antibodies or fragments thereof comprising an Fc region specifically bind, generally via the protein part that is N-terminal to the Fc region. An exemplary method of determining ADCC can be found in the Experimental section of the present disclosure.

[00384] In one example an antibody molecule according to the present disclosure may be conjugated to at least one payload. It will be appreciated that the payload may comprise a single molecule or two or more such molecules so linked as to form a single moiety that can be attached to the antibodies of the present invention. Where it is desired to obtain an antibody fragment linked to a molecule, this may be prepared by standard chemical or recombinant DNA procedures in which the antibody fragment is linked either directly or via a coupling agent to the effector molecule. Techniques for conjugating such effector molecules to antibodies are well known in the art (see, Hellstrom *et al* Controlled Drug Delivery, 2nd Ed., Robinson *et al* eds., 1987, pp. 623-53; Thorpe *et al*, 1982, Immunol. Rev., 62:119-58 and Dubowchik *et al* 1999, Pharmacology and Therapeutics, 83, 67-123). Particular chemical procedures include, for example, those described in WO 93/06231, WO 92/22583, WO 89/00195, WO89/01476 and WO03031581. Alternatively, where the molecule is a protein or polypeptide the linkage may be achieved using recombinant DNA procedures, for example as described in WO 86/01533 and EP0392745.

[00385] The term payloads as used herein includes, for example, biologically active proteins, for example enzymes, other antibody or antibody fragments, synthetic or naturally occurring polymers, nucleic acids and fragments thereof e.g. DNA, RNA and fragments thereof, radionuclides, particularly radioiodide, radioisotopes, chelated metals, nanoparticles and

reporter groups such as fluorescent compounds or compounds which may be detected by NMR or ESR spectroscopy.

[00386] Other payloads may include chelated radionuclides such as 111In and 90Y, Lu177, Bismuth213, Californium252, Iridium192 and Tungsten188/Rhenium188; or drugs such as but not limited to, alkylphosphocholines, topoisomerase I inhibitors, taxoids and suramin.

[00387] Other payloads include proteins, peptides and enzymes. Enzymes of interest include, but are not limited to, proteolytic enzymes, hydrolases, lyases, isomerases, transferases. Proteins, polypeptides and peptides of interest include, but are not limited to, immunoglobulins, toxins such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin, a protein such as insulin, tumour necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor or tissue plasminogen activator, a thrombotic agent or an anti-angiogenic agent, e.g. angiotatin or endostatin, or, a biological response modifier such as a lymphokine, interleukin-1 (IL-1), interleukin-2 (IL-2), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), nerve growth factor (NGF) or other growth factor and immunoglobulins.

[00388] Other payloads may include detectable substances useful for example in diagnosis. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive nuclides, positron emitting metals (for use in positron emission tomography), and nonradioactive paramagnetic metal ions. See generally U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics. Suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; suitable prosthetic groups include streptavidin, avidin and biotin; suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; suitable luminescent materials include luminol; suitable bioluminescent materials include luciferase, luciferin, and aequorin; and suitable radioactive nuclides include 125I, 131I, 111In and 99Tc.

[00389] In another example the payload may increase the half-life of the antibody *in vivo*, and/or reduce immunogenicity of the antibody and/or enhance the delivery of an antibody across an epithelial barrier to the immune system. Examples of suitable effector molecules of this type include polymers, albumin, albumin binding proteins or albumin binding compounds such as those described in WO05/117984.

[00390] Where the effector molecule is a polymer it may, in general, be a synthetic or a naturally occurring polymer, for example an optionally substituted straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer or a branched or unbranched polysaccharide, e.g. a homo- or hetero- polysaccharide.

[00391] Specific optional substituents which may be present on the above-mentioned synthetic polymers include one or more hydroxy, methyl or methoxy groups.

[00392] Specific examples of synthetic polymers include optionally substituted straight or branched chain poly(ethyleneglycol), poly(propyleneglycol) poly(vinylalcohol) or derivatives

5 thereof, especially optionally substituted poly(ethyleneglycol) such as methoxypoly(ethyleneglycol) or derivatives thereof.

[00393] Specific naturally occurring polymers include lactose, amylose, dextran, glycogen or derivatives thereof.

10 [00394] “Derivatives” as used herein is intended to include reactive derivatives, for example thiol-selective reactive groups such as maleimides and the like. The reactive group may be linked directly or through a linker segment to the polymer. It will be appreciated that the residue of such a group will in some instances form part of the product as the linking group between the antibody fragment and the polymer.

15 [00395] The size of the polymer may be varied as desired, but will generally be in an average molecular weight range from 500Da to 50000Da, for example from 5000 to 40000Da such as from 20000 to 40000Da. The polymer size may in particular be selected on the basis of the intended use of the product for example ability to localize to certain tissues such as tumors or extend circulating half-life (for review see Chapman, 2002, Advanced Drug Delivery Reviews, 20 54, 531-545).

25 [00396] Thus, for example, where the product is intended to leave the circulation and penetrate tissue, for example for use in the treatment of a tumour, it may be advantageous to use a small molecular weight polymer, for example with a molecular weight of around 5000Da. For applications where the product remains in the circulation, it may be advantageous to use a higher molecular weight polymer, for example having a molecular weight in the range from 20000Da to 40000Da.

[00397] Suitable polymers include a polyalkylene polymer, such as a poly(ethyleneglycol) or, especially, a methoxypoly(ethyleneglycol) or a derivative thereof, and especially with a molecular weight in the range from about 15000Da to about 40000Da.

30 [00398] In one example antibodies for use in the present invention are attached to poly(ethyleneglycol) (PEG) moieties. In one particular example the antibody is an antibody fragment and the PEG molecules may be attached through any available amino acid side-chain or terminal amino acid functional group located in the antibody fragment, for example any free amino, imino, thiol, hydroxyl or carboxyl group. Such amino acids may occur naturally in the 35 antibody fragment or may be engineered into the fragment using recombinant DNA methods (see for example US 5,219,996; US 5,667,425; WO98/25971, WO2008/038024). In one

example the antibody molecule of the present invention is a modified Fab fragment wherein the modification is the addition to the C-terminal end of its heavy chain one or more amino acids to allow the attachment of an effector molecule. Suitably, the additional amino acids form a modified hinge region containing one or more cysteine residues to which the effector molecule 5 may be attached. Multiple sites can be used to attach two or more PEG molecules.

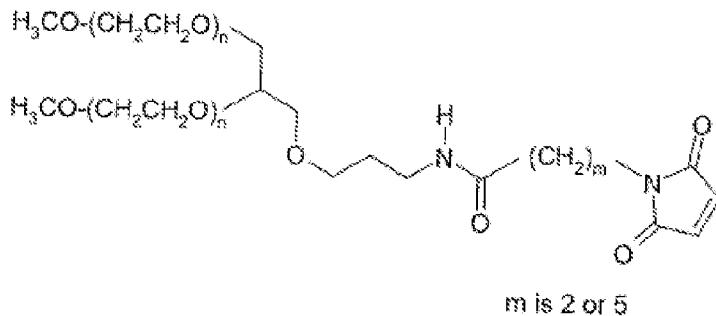
[00399] Suitably PEG molecules are covalently linked through a thiol group of at least one cysteine residue located in the antibody fragment. Each polymer molecule attached to the modified antibody fragment may be covalently linked to the sulphur atom of a cysteine residue 10 located in the fragment. The covalent linkage will generally be a disulphide bond or, in particular, a sulphur-carbon bond. Where a thiol group is used as the point of attachment appropriately activated effector molecules, for example thiol selective derivatives such as maleimides and cysteine derivatives may be used. An activated polymer may be used as the starting material in the preparation of polymer-modified antibody fragments as described 15 above. The activated polymer may be any polymer containing a thiol reactive group such as an α -halocarboxylic acid or ester, e.g. iodoacetamide, an imide, e.g. maleimide, a vinyl sulphone or a disulphide. Such starting materials may be obtained commercially (for example from Nektar, formerly Shearwater Polymers Inc., Huntsville, AL, USA) or may be prepared from commercially 20 available starting materials using conventional chemical procedures. Particular PEG molecules include 20K methoxy-PEG-amine (obtainable from Nektar, formerly Shearwater; Rapp Polymere; and SunBio) and M-PEG-SPA (obtainable from Nektar, formerly Shearwater).

[00400] In one example, the antibody is a modified Fab fragment or diFab which is PEGylated, i.e. has PEG (poly(ethyleneglycol)) covalently attached thereto, e.g. according to the method disclosed in EP 0948544 or EP1090037 [see also "Poly(ethyleneglycol) Chemistry, Biotechnical 25 and Biomedical Applications", 1992, J. Milton Harris (ed), Plenum Press, New York, "Poly(ethyleneglycol) Chemistry and Biological Applications", 1997, J. Milton Harris and S. Zalipsky (eds), American Chemical Society, Washington DC and "Bioconjugation Protein Coupling Techniques for the Biomedical Sciences", 1998, M. Aslam and A. Dent, Grove Publishers, New York; Chapman, A. 2002, Advanced Drug Delivery Reviews 2002, 54:531-545]. 30 In one example PEG is attached to a cysteine in the hinge region. In one example, a PEG modified Fab fragment has a maleimide group covalently linked to a single thiol group in a modified hinge region. A lysine residue may be covalently linked to the maleimide group and to each of the amine groups on the lysine residue may be attached a methoxypoly(ethyleneglycol) polymer having a molecular weight of approximately 20,000Da. The total molecular weight of 35 the PEG attached to the Fab fragment may therefore be approximately 40,000Da.

[00401] Particular PEG molecules include 2-[3-(N-maleimido)propionamido]ethyl amide of N,N'-bis(methoxypoly(ethylene glycol) MW 20,000) modified lysine, also known as PEG2MAL40K (obtainable from Nektar, formerly Shearwater).

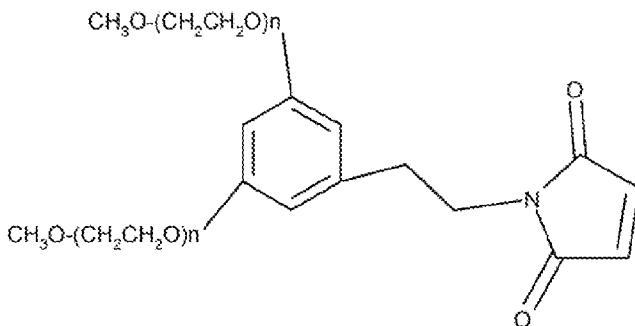
[00402] Alternative sources of PEG linkers include NOF who supply GL2-400MA2 (wherein m

5 in the structure below is 5) and GL2-400MA (where m is 2) and n is approximately 450:



[00403] That is to say each PEG is about 20,000Da.

[00404] Further alternative PEG effector molecules of the following type:



are available from Dr Reddy, NOF and Jenkem.

[00405] In one example there is provided an antibody which is PEGylated (for example with a PEG described herein), attached through a cysteine amino acid residue at or about amino acid 20 226 in the chain, for example amino acid 226 of the heavy chain (by sequential numbering).

[00406] T Cell Receptor and Chimeric Antigen Receptors

[00407] A comparison and review of T cell receptor and chimeric antigen receptor technology is provided in Dotti *et al* 2009 (Human Gene Therapy 20: 1229-1239 (November 2009).

25 [00408] In one example a chimeric antigen receptor according to the present disclosure comprises the technology disclosed in WO2013/040557, incorporated herein by reference. In brief, as used herein, the term "chimeric antigen receptor" refers to molecules that combine antibody-based specificity for an antigen with cell receptor-activating intracellular domains

with specific cellular immune activity. For example, the chimeric antigen receptor may combine the antigen binding domain as described herein with a cell receptor-activating intracellular domain (e.g. T cell receptor-activating intracellular domain) with specific anti-tumor cellular immune activity. The chimeric antigen receptor would then allow a T cell to achieve MHC-
5 independent primary activation through a single chain Fv (scFv) antigen-specific extracellular region fused to intracellular domains that provide T cell activation and co-stimulatory signals.

[00409] **Pharmaceutical Compositions**

[00410] In one aspect a pharmaceutical formulation or composition according to the
10 invention comprises an antibody molecule according to the present disclosure and a pharmaceutically acceptable excipient, diluent and/or carrier.

[00411] Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the patient.

15 [00412] Pharmaceutically acceptable carriers in therapeutic compositions may additionally contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such compositions.

20 [00413] The pharmaceutical compositions of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, transcutaneous (for example, see WO98/20734), subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, intravaginal or rectal routes. Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Typically, the therapeutic compositions may be prepared as
25 injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared.

30 [00414] Suitable forms for administration include forms suitable for parenteral administration, e.g. by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative, stabilising and/or dispersing agents. Alternatively, the antibody molecule may be in dry form (such as lyophilised), for reconstitution before use with an appropriate sterile liquid, such as glycose, saline, water for injection or a combination of two or more of the same.

35 [00415] Thus in one example the formulation is provided for parenteral administration, in particular for intravenous or subcutaneous injection.

[00416] Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals. However, in one or more examples the compositions are adapted for administration to human subjects.

[00417] Suitably in formulations according to the present disclosure, the pH of the final formulation is not similar to the value of the isoelectric point of the antibody or fragment, for example if the pH of the formulation is 7 then a pI of from 8-9 or above may be appropriate. Whilst not wishing to be bound by theory it is thought that this may ultimately provide a final formulation with improved stability, for example the antibody or fragment remains in solution.

[00418] In one example the pH of a liquid formulation according to the present disclosure is 10 in range pH 5.5 to 8, such as pH 6, 6.5, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8 or 7.9.

[00419] In one example the formulation is provide is isotonic or is isotonic after constitution.

[00420] In one example the composition or formulation of the present disclosure comprises 1-200mg/mL of an antibody molecule according to the present disclosure, for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 15 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 20 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198 or 199 mg/ml.

[00421] **Evaluation**

[00422] As illustrated in the Experimental Section, the antibodies of the present disclosure can be used to track the growth of tumor *in vivo*. Thus, it is envisaged that the antibody as defined herein may be used to evaluate the status of a cancer in a patient.

[00423] The term "status" as used herein, refers to the situation or state of the tumor or cancerous mass at a given time point. Thus, as used herein, the status of a cancer patient may be 30 defined by the size of the tumour, the location (or number of locations) of the tumor, and the stage of tumour observed. Thus, depending on the type of cancer, the status of the patient may be the same as the stage of tumour observed. In some examples, the status may be "nodal status", "local", "distant", or "recurrence".

35 [00424] **Treatment**

[00425] Thus one example there is provided an antibody molecule or a composition according to the present disclosure for use in therapy, in particular the treatment of cancer or fibrosis.

[00426] The term "fibrosis" as used herein refers to the formation of excess fibrous connective tissue in an organ or tissue, for example, in reparative or reactive process. This is as opposed to formation of fibrous tissue as a normal constituent of an organ or tissue. Thus, in the present disclosure, the term "fibrosis" is used to distinguish abnormal from normal healing processes. In some examples, the term "fibrosis" is limited to fibrosis relating to cancer, for example solid cancer mass or metastatic cancer).

[00427] In one example the treatment of the present disclosure is administered for epithelial cancer, for example is selected from liver cancer (such as hepatocellular carcinoma), biliary duct cancer, breast cancer (such as non ER+ breast cancer), prostate cancer, colorectal cancer, ovarian cancer, endometrial cancer, cervical cancer, lung cancer, gastric cancer, oesophageal cancer, pancreatic, bone cancer, bladder cancer, head and neck cancer, thyroid cancer, skin cancer, renal cancer, and oesophagus cancer and combinations thereof, for example gastric cancer.

[00428] In one example the cancer is selected from selected from the group comprising hepatocellular carcinoma, biliary duct cancer, breast cancer, prostate cancer, colorectal cancer, ovarian cancer, lung cancer, gastric cancer, pancreatic and oesophagus cancer.

[00429] In one example the biliary duct cancer is in a location selected from intrahepatic bile ducts, left hepatic duct, right hepatic duct, common hepatic duct, cystic duct, common bile duct, Ampulla of Vater and combinations thereof.

[00430] In one example the biliary duct cancer is in an intrahepatic bile duct. In one example the biliary duct cancer is in a left hepatic duct. In one example the biliary duct cancer is in a right hepatic duct. In one example the biliary duct cancer is in a common hepatic duct. In one example the biliary duct cancer is in a cystic duct. In one example the biliary duct cancer is in a common bile duct. In one example the biliary duct cancer is in an Ampulla of Vater.

[00431] In one example the epithelial cancer is a carcinoma.

[00432] In one example the cancer is tumour, for example a solid tumour, a liquid tumour or a combination of the same.

[00433] In one example the treatment according to the disclosure is adjuvant therapy, for example after surgery.

[00434] In one example the therapy according to the disclosure is neoadjuvant treatment, for example to shrink a tumour before surgery.

[00435] In one example the tumour is a solid tumour. In one example the cancer is a primary cancer, secondary cancer, metastasis or combination thereof. In one example the treatment according to the present disclosure is suitable for the treatment of secondary tumours. In one example the cancer is metastatic cancer. In one example the treatment according to the present disclosure is suitable for the treatment of primary cancer and metastases. In one example the treatment according to the present disclosure is suitable for the treatment of secondary cancer and metastases. In one example the treatment according to the present disclosure is suitable for the treatment of primary cancer, secondary cancer and metastases.

5 [00436] In one example the treatment according to the present disclosure is suitable for the treatment of cancerous cells in a lymph node, for a cancer of the present disclosure.

10 [00437] In one example the liver cancer is primary liver cancer. In one example the liver cancer is secondary liver cancer. In one example the liver cancer is stage 1, 2, 3A, 3B, 3C, 4A or 4B.

15 [00438] In one example the gastric cancer is stage 0, I, II, III or IV.

[00439] In one example the cancer is a RON positive. In one example the cancer is Met positive. In one example the cancer is RON positive and Met positive.

[00440] In one example the cancer is refractory or resistant to one or more available cancer treatments.

20 [00441] In one example the therapy of the present disclosure is first line therapy. In one example the therapy according to the present disclosure is second line or subsequent line therapy.

[00442] In one example the antibody molecule according to the present disclosure is employed in a combination therapy.

25 [00443] In one example the combination therapy comprises a checkpoint inhibitor, such as a CTLA4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor, in particular an antibody or binding fragment thereof.

[00444] In one example the combination therapy of the present disclosure comprises or further comprises a chemotherapeutic agent.

30 [00445] In one example the combination therapy comprises a HER inhibitor, for example herceptin or the pan-HER inhibitor varlitinib [(R)-N4-[3-Chloro-4-(thiazol-2-ylmethoxy)-phenyl]-N6-(4-methyl-4,5-dihydro-oxazol-2-yl)-quinazoline-4,6-diamine (Varlitinib Example 52 disclosed in WO2005/016346)] for example administered once or twice daily at a dose in the range 10 mg to 500mg, such as 200mg, 300mg or 400mg.

[00446] Chemotherapeutic agent and chemotherapy or cytotoxic agent are employed interchangeably herein unless the context indicates otherwise.

[00447] Chemotherapy as employed herein is intended to refer to specific antineoplastic chemical agents or drugs that are “selectively” destructive to malignant cells and tissues, for example alkylating agents, antimetabolites including thymidylate synthase inhibitors, anthracyclines, anti-microtubule agents including plant alkaloids, taxanes, topoisomerase inhibitors, parp inhibitors and other antitumour agents. Selectively in this context is used loosely because of course many of these agents have serious side effects.

[00448] The preferred dose may be chosen by the practitioner, based on the nature of the cancer being treated.

[00449] Examples of alkylating agents, which may be employed in the method of the present disclosure include an alkylating agent, nitrogen mustards, nitrosoureas, tetrazines, aziridines, platins and derivatives, and non-classical alkylating agents.

[00450] Examples of platinum containing chemotherapeutic agents (also referred to as platins), include cisplatin, carboplatin, oxaliplatin, satraplatin, picoplatin, nedaplatin, triplatin and lipoplatin (a liposomal version of cisplatin), in particular cisplatin, carboplatin and oxaliplatin.

[00451] The dose for cisplatin ranges from about 20 to about 270 mg/m² depending on the exact cancer. Often the dose is in the range about 70 to about 100mg/m².

[00452] Nitrogen mustards include mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide and busulfan.

[00453] Nitrosoureas include *N*-Nitroso-*N*-methylurea (MNU), carmustine (BCNU), lomustine (CCNU) and semustine (MeCCNU), fotemustine and streptozotocin. Tetrazines include dacarbazine, mitozolomide and temozolomide.

[00454] Aziridines include thiotepa, mytomycin and diaziquone (AZQ).

[00455] Examples of antimetabolites, which may be employed in the method of the present disclosure, include anti-folates (for example methotrexate and pemetrexed), purine analogues (for example thiopurines, such as azathioprine, mercaptopurine, thiopurine, fludarabine (including the phosphate form), pentostatin and cladribine), pyrimidine analogues (for example fluoropyrimidines, such as 5-fluorouracil (5-FU) and prodrugs thereof such as capecitabine [Xeloda®]), floxuridine, gemcitabine, cytarabine, decitabine, raltitrexed (tomudex) hydrochloride, cladribine and 6-azauracil.

[00456] Examples of anthracyclines, which may be employed in the method of the present disclosure, include daunorubicin (Daunomycin), daunorubicin (liposomal), doxorubicin

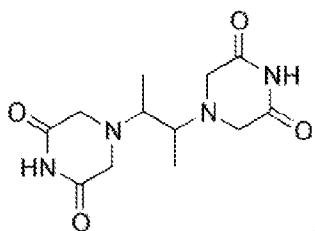
(Adriamycin), doxorubicin (liposomal), epirubicin, idarubicin, valrubicin currently are used only to treat bladder cancer and mitoxantrone an anthracycline analog, in particular doxorubicin.

[00457] Examples of anti-microtubule agents, which may be employed in the method of the present disclosure, include include vinca alkaloids and taxanes.

5 [00458] Vinca alkaloids include completely natural chemicals for example vincristine and vinblastine and also semi-synthetic vinca alkaloids, for example vinorelbine, vindesine, and vinflunine.

[00459] Taxanes include paclitaxel, docetaxel, abraxane, carbazitaxel and derivatives of thereof. Derivatives of taxanes as employed herein includes reformulations of taxanes like 10 taxol, for example in a micelluar formulaitons, derivatives also include chemical derivatives wherein synthetic chemistry is employed to modify a starting material which is a taxane.

[00460] Topoisomerase inhibitors, which may be employed in a method of the present disclosure include type I topoisomerase inhibitors, type II topoisomerase inhibitors and type II topoisomerase poisons. Type I inhibitors include topotecan, irinotecan, indotecan and 15 indimitecan. Type II inhibitors include genistein and ICRF 193 which has the following structure:



[00461] Type II poisons include amsacrine, etoposide, etoposide phosphate, teniposide and doxorubicin and fluoroquinolones.

20 [00462] In one example the chemotherapeutic is a PARP inhibitor.

[00463] In one example a combination of chemotherapeutic agents employed is, for example a platin and 5-FU or a prodrug thereof, for example cisplatin or oxaplatin and capecitabine or gemcitabine, such as FOLFOX.

[00464] In one example the chemotherapy comprises a combination of chemotherapy agents, 25 in particular cytotoxic chemotherapeutic agents.

[00465] In one example the chemotherapy combination comprises a platin, such as cisplatin and fluorouracil or capecitabine.

[00466] In one example the chemotherapy combination is capecitabine and oxaliplatin (XELOX).

30 [00467] In one example the chemotherapy is a combination of folinic acid and 5-FU, optionally in combination with oxaliplatin (FOLFOX).

[00468] In one example the chemotherapy is a combination of folinic acid, 5-FU and irinotecan (FOLFIRI), optionally in combination with oxaliplatin (FOLFIRINOX). The regimen, for example includes: irinotecan (180 mg/m² IV over 90 minutes) concurrently with folinic acid (400 mg/m² [or 2 x 250 mg/m²] IV over 120 minutes); followed by fluorouracil (400–500 mg/m² IV bolus) then fluorouracil (2400–3000 mg/m² intravenous infusion over 46 hours). This cycle is typically repeated every two weeks. The dosages shown above may vary from cycle to cycle.

[00469] In one example the chemotherapy combination employs a microtubule inhibitor, for example vincristine sulphate, epothilone A, N-[2-[(4-Hydroxyphenyl)amino]-3-pyridinyl]-4-methoxybenzenesulfonamide (ABT-751), a taxol derived chemotherapeutic agent, for example paclitaxel, abraxane, or docetaxel or a combination thereof.

[00470] In one example the chemotherapy combination employs an mTor inhibitor. Examples of mTor inhibitors include: everolimus (RAD001), WYE-354, KU-0063794, papamycin (Sirolimus), Temsirolimus, Deforolimus(MK-8669), AZD8055 and BEZ235(NVP-BEZ235).

[00471] In one example the chemotherapy combination employs a MEK inhibitor. Examples of MEK inhibitors include: AS703026, CI-1040 (PD184352), AZD6244 (Selumetinib), PD318088, PD0325901, AZD8330, PD98059, U0126-EtOH, BIX 02189 or BIX 02188.

[00472] In one example the chemotherapy combination employs an AKT inhibitor. Examples of AKT inhibitors include: MK-2206 and AT7867.

[00473] In one example the combination employs an aurora kinase inhibitor. Examples of aurora kinase inhibitors include: Aurora A Inhibitor I, VX-680, AZD1152-HQPA (Barasertib), SNS-314 Mesylate, PHA-680632, ZM-447439, CCT129202 and Hesperadin.

[00474] In one example the chemotherapy combination employs a p38 inhibitor, for example as disclosed in WO2010/038086, such as *N*-[4-({4-[3-(3-*tert*-Butyl-1-*p*-tolyl-1*H*-pyrazol-5-yl)ureido]naphthalen-1-yloxy}methyl)pyridin-2-yl]-2-methoxyacetamide.

[00475] In one example the combination employs a Bcl-2 inhibitor. Examples of Bcl-2 inhibitors include: obatoclax mesylate, ABT-737, ABT-263(navitoclax) and TW-37.

[00476] In one example the chemotherapy combination comprises an antimetabolite such as capecitabine (xeloda), fludarabine phosphate, fludarabine (fludara), decitabine, raltitrexed (tomudex), gemcitabine hydrochloride and/or cladribine.

[00477] In one example the chemotherapy combination comprises ganciclovir, which may assist in controlling immune responses and/or tumour vasculation.

[00478] “Administering a combination therapy” as employed herein does not require the therapies employed in the combination to be administered at the same time. Combination therapy as employed herein refers to two or more modes of therapy being employing over the

same treatment period, i.e. the opposite of sequential therapy. Two or more modes of therapy as employed herein refers to at least two therapies which have different modes of action and/or different activities and/or different routes of administration.

[00479] Terms such as "treating" or "treatment" or "to treat" as employed herein refers to therapeutic measures that: cure, slow down, ameliorate symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; or prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented and those in whom reoccurrence of the disorder needs to be prevented (e.g. those in remission). In certain aspects, a subject is successfully "treated" for a disease or condition, for example cancer if the patient shows, e.g. total, partial, or transient remission of the disease or condition.

[00480] A therapeutically effective amount as employed herein refers to an amount suitable to elicit the requisite therapeutic effect. In the combination therapy of the present disclosure the RON inhibitor may be employed at a dose which is the same or lower than the monotherapy dose with said inhibitor. In one example the dose of the PD-1 pathway inhibitor employed is the same or lower than the monotherapy dose with said inhibitor. In one example the dose on the RON inhibitor is the same as the dose employed in monotherapy and the dose of the PD-1 pathway inhibitor is the same as the dose employed in monotherapy. In one example the dose on the RON inhibitor is lower than the dose employed in monotherapy and the dose of the PD-1 pathway inhibitor is the same as the dose employed in monotherapy. In one example the dose on the RON inhibitor is the same as the dose employed in monotherapy and the dose of the PD-1 pathway inhibitor is lower than the dose employed in monotherapy. In one example the dose on the RON inhibitor is lower than the dose employed in monotherapy and the dose of the PD-1 pathway inhibitor is lower than the dose employed in monotherapy. In one example the dose on the RON inhibitor is lower than the dose employed in monotherapy and the dose of the PD-1 pathway inhibitor is lower than the dose employed in monotherapy. A suitable dose can be established by those skilled in the art.

[00481] Cancer Types In more Detail

[00482] In one example the gastric cancer is selected from the group comprising adenocarcinoma of the stomach, squamous cell carcinomas, lymphoma of the stomach, gastric stromal tumour, and neuroendocrine tumours.

[00483] In one example the liver cancer is, for example selected from the group hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma, and hepatoblastoma, in particular hepatocellular carcinoma. In one example the primary liver cancer is stage 1, 2, 3 or 4. In one example the liver cancer is secondary or metastasized liver cancer.

[00484] Lung cancers are classified according to histological type and are categorized by the size and appearance of the malignant cells seen by a histopathologist under a microscope. For therapeutic purpose, two broad classes are distinguished: non-small cell lung carcinoma and small cell lung carcinoma.

5 [00485] In one example the epithelial cancer is lung cancer, for example small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC).

[00486] **Non-small-cell lung carcinoma**-The three main subtypes of NSCLC are adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma.

10 [00487] Nearly 40% of lung cancers are adenocarcinoma, which usually originates in peripheral lung tissue. A subtype of adenocarcinoma, the bronchioloalveolar carcinoma, is more common in female never-smokers, and may have a better long term survival.

[00488] Squamous-cell carcinoma accounts for about 30% of lung cancers. They typically occur close to large airways. A hollow cavity and associated cell death are commonly found at 15 the center of the tumor. About 9% of lung cancers are large-cell carcinoma. These are so named because the cancer cells are large, with excess cytoplasm, large nuclei and conspicuous nucleoli.

[00489] **Small-cell lung carcinoma**-In small-cell lung carcinoma (SCLC), the cells contain 20 dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association. Most cases arise in the larger airways (primary and secondary bronchi). These cancers grow quickly and spread early in the course of the disease. Sixty to seventy percent have metastatic disease at presentation.

[00490] In one example the cancer is non-small lung carcinoma.

[00491] In one example the cancer is liver cancer, for example a liver metastasis from a 25 primary cancer, for example colon cancer, which has spread to the liver. In one example the liver cancer is HCC hepatocellular carcinoma.

[00492] In one example there is provided treatment of renal cancer, for example renal cell carcinoma and/or urothelial cell carcinoma. Other examples of renal cancer include squamous cell carcinoma, juxtaglomerular cell tumor (reninoma), angiomyolipoma, renal oncocytoma, 30 Bellini duct carcinoma, clear-cell sarcoma of the kidney, mesoblastic nephroma, Wilms' tumor, mixed epithelial stromal tumor, clear cell adenocarcinoma, transitional cell carcinoma, inverted papilloma, renal lymphoma, teratoma, carcinosarcoma, and carcinoid tumor of the renal pelvis.

[00493] In one example the cancer is bladder cancer, for example is any of several types of malignancy arising from the epithelial lining (i.e., the urothelium) of the urinary bladder. About 35 90% of bladder cancers are transitional cell carcinoma. The other 10% are squamous cell

carcinoma, adenocarcinoma, sarcoma, small cell carcinoma, and secondary deposits from cancers elsewhere in the body. The staging of is given below.

[00494] **T (Primary tumour)**

- 5 [00495] TX Primary tumour cannot be assessed
- [00496] T0 No evidence of primary tumour
- [00497] Ta Non-invasive papillary carcinoma
- [00498] Tis Carcinoma in situ ('flat tumour')
- [00499] T1 Tumour invades subepithelial connective tissue
- 10 [00500] T2a Tumour invades superficial muscle (inner half)
- [00501] T2b Tumour invades deep muscle (outer half)
- [00502] T3 Tumour invades perivesical tissue:
- [00503] T3a Microscopically
- [00504] T3b Macroscopically (extravesical mass)
- 15 [00505] T4a Tumour invades prostate, uterus or vagina
- [00506] T4b Tumour invades pelvic wall or abdominal wall
- [00507] **N (Lymph nodes)**
- [00508] NX Regional lymph nodes cannot be assessed
- [00509] N0 No regional lymph node metastasis
- 20 [00510] N1 Metastasis in a single lymph node 2 cm or less in greatest dimension
- [00511] N2 Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- [00512] N3 Metastasis in a lymph node more than 5 cm in greatest dimension
- [00513] **M (Distant metastasis)**
- 25 [00514] MX Distant metastasis cannot be assessed
- [00515] M0 No distant metastasis
- [00516] M1 Distant metastasis.

[00517] **Bladder cancer**

- 30 [00518] The current disclosure extends to any stage of bladder cancer.

[00519] **Ovarian cancer**

- [00520] There are more than 30 different types of ovarian cancer which are classified according to the type of cell from which they start. Cancerous ovarian tumors can start from 35 three common cell types:

- [00521] Surface Epithelium - cells covering the lining of the ovaries
- [00522] Germ Cells - cells that are destined to form eggs
- [00523] Stromal Cells - Cells that release hormones and connect the different structures of the ovaries

5 [00524] The present disclosure relates to treatment of ovarian cancer from any source, for example as described herein, in particular epithelium cells. Epithelial ovarian carcinomas (EOCs) account for 85 to 90 percent of all cancers of the ovaries.

[00525] Common Epithelial Tumors - Epithelial ovarian tumors develop from the cells that cover the outer surface of the ovary. Most epithelial ovarian tumors are benign (noncancerous).

10 There are several types of benign epithelial tumors, including serous adenomas, mucinous adenomas, and Brenner tumors. Cancerous epithelial tumors are carcinomas - meaning they begin in the tissue that lines the ovaries. These are the most common and most dangerous of all types of ovarian cancers. Unfortunately, almost 70 percent of women with the common epithelial ovarian cancer are not diagnosed until the disease is advanced in stage.

15 [00526] There are some ovarian epithelial tumors whose appearance under the microscope does not clearly identify them as cancerous. These are called borderline tumors or tumors of low malignant potential (LMP tumors). The method of the present disclosure includes treatment of the latter.

20 [00527] Germ Cell Tumors - Ovarian germ cell tumors develop from the cells that produce the ova or eggs. Most germ cell tumors are benign (non-cancerous), although some are cancerous and may be life threatening. The most common germ cell malignancies are maturing teratomas, dysgerminomas, and endodermal sinus tumors. Germ cell malignancies occur most often in teenagers and women in their twenties. Today, 90 percent of patients with ovarian germ cell malignancies can be cured and their fertility preserved.

25 [00528] Stromal Tumors - Ovarian stromal tumors are a rare class of tumors that develop from connective tissue cells that hold the ovary together and those that produce the female hormones, estrogen and progesterone. The most common types are granulosa-theca tumors and Sertoli-Leydig cell tumors. These tumors are quite rare and are usually considered low-grade cancers, with approximately 70 percent presenting as Stage I disease (cancer is limited to one or 30 both ovaries).

35 [00529] Primary Peritoneal Carcinoma-The removal of one's ovaries eliminates the risk for ovarian cancer, but not the risk for a less common cancer called Primary Peritoneal Carcinoma. Primary Peritoneal Carcinoma is closely rated to epithelial ovarian cancer (most common type). It develops in cells from the peritoneum (abdominal lining) and looks the same under a microscope. It is similar in symptoms, spread and treatment.

[00530] Stages of Ovarian Cancer

[00531] Once diagnosed with ovarian cancer, the stage of a tumor can be determined during surgery, when the doctor can tell if the cancer has spread outside the ovaries. There are four stages of ovarian cancer - Stage I (early disease) to Stage IV (advanced disease). The treatment

5 plan and prognosis (the probable course and outcome of your disease) will be determined by the stage of cancer you have.

[00532] Following is a description of the various stages of ovarian cancer:

[00533] Stage I - Growth of the cancer is limited to the ovary or ovaries.

[00534] Stage IA - Growth is limited to one ovary and the tumor is confined to the inside of 10 the ovary. There is no cancer on the outer surface of the ovary. There are no ascites present containing malignant cells. The capsule is intact.

[00535] Stage IB - Growth is limited to both ovaries without any tumor on their outer surfaces. There are no ascites present containing malignant cells. The capsule is intact.

[00536] Stage IC - The tumor is classified as either Stage IA or IB and one or more of the 15 following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

[00537] Stage II - Growth of the cancer involves one or both ovaries with pelvic extension.

[00538] Stage IIA - The cancer has extended to and/or involves the uterus or the fallopian 20 tubes, or both.

[00539] Stage IIB - The cancer has extended to other pelvic organs.

[00540] Stage IIC - The tumor is classified as either Stage IIA or IIB and one or more of the 25 following are present: (1) tumor is present on the outer surface of one or both ovaries; (2) the capsule has ruptured; and (3) there are ascites containing malignant cells or with positive peritoneal washings.

[00541] Stage III - Growth of the cancer involves one or both ovaries, and one or both of the following are present: (1) the cancer has spread beyond the pelvis to the lining of the abdomen; and (2) the cancer has spread to lymph nodes. The tumor is limited to the true pelvis but with histologically proven malignant extension to the small bowel or omentum.

30 [00542] Stage IIIA - During the staging operation, the practitioner can see cancer involving one or both of the ovaries, but no cancer is grossly visible in the abdomen and it has not spread to lymph nodes. However, when biopsies are checked under a microscope, very small deposits of cancer are found in the abdominal peritoneal surfaces.

[00543] Stage IIIB - The tumor is in one or both ovaries, and deposits of cancer are present in the abdomen that are large enough for the surgeon to see but not exceeding 2 cm in diameter. The cancer has not spread to the lymph nodes.

[00544] Stage IIIC - The tumor is in one or both ovaries, and one or both of the following is

5 present: (1) the cancer has spread to lymph nodes; and/or (2) the deposits of cancer exceed 2 cm in diameter and are found in the abdomen.

[00545] Stage IV - This is the most advanced stage of ovarian cancer. Growth of the cancer involves one or both ovaries and distant metastases (spread of the cancer to organs located outside of the peritoneal cavity) have occurred. Finding ovarian cancer cells in pleural fluid 10 (from the cavity which surrounds the lungs) is also evidence of stage IV disease.

[00546] In one example the ovarian cancer is: type I, for example IA, IB or IC; type II, for example IIA, IIB or IIC; type III, for example IIIA, IIIB or IIIC; or type IV.

[00547] In one example the breast cancer is one selected from the group comprising ductal carcinoma in situ, lobular carcinoma in situ, invasive breast cancer, invasive lobular breast cancer, Paget's disease, angiosarcoma of the breast, medullary breast cancer, mucinous breast cancer, tubular breast cancer, adenoid cystic carcinoma of the breast, metaplastic breast cancer, lymphoma of the breast, basal type breast cancer, phyllodes or cystosarcoma phyllodes and papillary breast cancer.

20

[00548] In one example the prostate cancer is selected from the group comprising ductal adenocarcinoma, transitional cell (urothelial) cancer, squamous cell cancer, carcinoid, small cell cancer, sarcomas and sarcomatoid cancers.

25 [00549] **Table 2. Summary of RON antibody sequences**

7G8 (Heavy chain 1)		
	SEQ ID NO:	Sequence
CDRH1	1	GFTFNTYT
CDRH2	2	ISNGGGST
CDRH3	3	ARGYRYAAMDY
FR1	4	EVQLEQSGGLVQPGGSLKLSAACAS
FR2	5	MSWVRQTPEKRLEWVAY
FR3	6	YYPDTVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYCYC
FR4	7	WGQGTSVTVSS

Heavy chain variable (amino acid)	8	EVQLEQSGGLVQPGGSLKLSCAAS GFTNTY MSWVRQTPEKLEWV AYISNGGGSTYY PDTVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYYCA RGYRYAAMDY WGQGTSVTVSS
Heavy chain variable (nucleotide sequence)	9	GAGGTGCAGCTGGAGCAGTCTGGGGGAGGTTAGTGCAGCCTGGAGGGT CCCTGAAACTCTCCTGTGCAGCCTGGATTCACTTCATAACCTATAACC ATGTCTGGGTTCGCCAGACTCCAGAGAAGAGGCTGGAGTGGGTCGCAT ACATTAGTAATGGTGGTAGTACCTACTATCCAGACACTGTAAAGGG CCGATTCACCATCTCCAGAGACAATGCCAAGAACACCCGTACCTGCAA ATGAGCAGTCTGAAGTCTGAGGACACGCCATGTATTACTGTGCAAGAG GCTATAGGTACGCTGCTATGGACTACTGGGTCAAGGAACCTCAGTCAC CGTCTCCTCA

7G8 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	18	QSINNN
CDRL2	19	FAS
CDRL3	20	QQSNWPLT
FR1	21	DIVMTQTTATLSVTPGDGVSLSCRAS
FR2	22	LHWYQQKSHESPRLLIK
FR3	23	QSISGIPSRFGSGSGTDFTLSINSVETEDFGMYFC
FR4	24	FGAGTKLELK
Light chain variable (amino acid)	25	DIVMTQTTATLSVTPGDGVSLSCRAS QSINNN LHWYQQKSHESPRLLIKF ASQSISGIPSRFGSGSGTDFTLSINSVETEDFGMYFCQQSNWPLT FGAG TKLELK
Light chain variable (nucleotide sequence)	26	GATATTGTGATGACCCAGACTACAGCCACCCGTCTGTGACTCCAGGAG ATGGCGTCAGTCTTCCTGCAGGGCCAGCCAAAGTATTAACAACAAACCT ACACTGGTATCAACAAAAATCACATGAGTCTCAAGACTTCTCATCAAG TTGCTTCCAGTCCATCTCTGGATCCCTCCAGGTTCACTGGCAGTGG ATCAGGGACAGATTTCACTCTCACTATCAACAGTGTGGAGACTGAAGAT TTTGAATGTATTCGTCAACAGAGTAACAGCTGGCCTCTCACGTTCG GTGCTGGACCAAGCTGGAGCTGAAAC

6D4 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	27	GFTFSNYA
CDRH2	28	ISSGGST
CDRH3	29	AREGPLYYGPSYGGYYFDY
FR1	30	EVQLLETGGGLVKPGGSLKLSAAS
FR2	31	MSWVRQTPEKRLEWGAS
FR3	32	YYPD SVKGRFTISRDNARNI LYLQMSSLRSEDTALYYC
FR4	33	WGQGTTLT VSS
Heavy chain variable (amino acid)	34	EVQLLETGGGLVKPGGSLKLSAAS GFTFSNYAMSWVRQTPEKRLEWGA SISSGGSTYYPD SVKGRFTISRDNARNI LYLQMSSLRSEDTALYYCAREGP LYYGPSYGGYYFDYWGQGTTLT VSS
Heavy chain variable (nucleotide sequence)	35	GAAGTGCAGCTGTTGGAGACTGGGGGAGGCTTAGTGAAGCCTGGAGGGT CCCTGAAACTCTCCTGTGCAGCCTCTGGATTCACTTCACTAATGCC ATGTCTGGGTTGCCAGACTCCAGAGAAGAGGCTGGAGTGGGGCGCAT CCATTAGTAGTGGTGGTAGCACCTACTATCCAGACAGTGTGAAGGGCCG ATTCACCATCTCCAGAGATAATGCCAGGAACATCCTGTACCTGCAAATG AGCAGTCTGAGGTCTGAGGACACGGCCCTGTATTACTGTGCAAGAGAGG GTCCCCCTTACTACGGTCCTAGCTACGGAGGGTACTACTTGACTACTG GGGCCAAGGCACCACTCTCACAGTCTCCTCA

6D4 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	36	QRLVYSNGNTY
CDRL2	37	KVS
CDRL3	38	SQSTHVPWT
FR1	39	DIVMTQSPLSLPVSLGDQASISCRSS
FR2	40	LHWYLQKPGQSPKLLIY
FR3	41	NRFSGVPDRFSGSGSGTDFTLKRISRVEAEDLGVYFC
FR4	42	FGGGTKLEIK
Light chain variable	43	DIVMTQSPLSLPVSLGDQASISCRSS QRLVYSNGNTY LHWYLQKPGQSPK LLIY KVS NRFSGVPDRFSGSGSGTDFTLKRISRVEAEDLGVYFC SQSTHVP

(amino acid)		WTFGGGTKLEIK
Light chain variable (nucleotide sequence)	44	GACATTGTGATGACACAGTCTCCACTCTCCCTGCCTGTCAGTCTTGGAG ATCAAGCCTCCATCTCTTGCAGATCTAGTCAGAGGCTTGTATACAGTAA TGGAAACACCTATTACATTGGTACCTGCAGAAGCCAGGCCAGTCTCCA AAGCTCCTGATCTACAAAGTTCCAACCGATTTCTGGGTCCCAGACA GGTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAG AGTGGAGGCTGAGGATCTGGAGTTATTCTGCTCTCAAAGTACACAT GTTCCGTGGACGTTCGGTGGAGGCACCAAGCTGGAATCAAAC

3E1 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	45	GFSFSDYW
CDRH2	46	IRLKSSNYAT
CDRH3	47	TRGDY
FR1	48	DVMLVESGGGLVQPGGSMKLSVVAS
FR2	49	MNWVRQSPEKGLEWVAE
FR3	50	HYAESVKGRFTISRDDSESSVYLQMNNLRPEDTGFYYC
FR4	7	WGQGTSVTVSS
Heavy chain variable (amino acid)	51	DVMLVESGGGLVQPGGSMKLSVVAS GFSFSDYWMNWVRQSPEKGLEWVAEIRLKSSNYATHYAESVKGRFTISRDDSESSVYLQMNNLRPEDTGFYYC CTRGDYWGQGTSVTVSS
Heavy chain variable (nucleotide sequence)	52	GACGTGATGCTGGTGGAGTCTGGAGGAGGCTTGGTGCAACCTGGAGGAT CCATGAAACTCTCCTGTGTTGCCTCTGGATTCACTTCACTGACTACTG GATGAACTGGTCCGCCAGTCTCCAGAGAAGGGCTTGAATGGTTGCT GAGATTAGATTGAAATCTAGTAATTATGCAACACATTATGCGGAGTCTG TGAAAGGGAGGTTACCATCTCAAGAGATGATTCCGAAAGTAGTGTCTA CCTGCAAATGAACAACTTAAGACCTGAAGACACTGGCTTTATTACTGT ACCAGGGGGACTATTGGGTCAAGGAACCTCAGTCACCGTCTCTCA

3E1 (Kappa / light chain)		
	SEQ ID NO:	Sequence

CDRL1	18	QSINNN
CDRL2	19	FAS
CDRL3	20	QQSNSWPLT
FR1	53	DIVMTQSPATLSVTPGDGVSLSCRAS
FR2	22	LHWYQQKSHESPRLLIK
FR3	23	QSISGIPSRFGSGSGTDFTLSINSVETEDFGMYFC
FR4	24	FGAGTKLELK
Light chain variable (amino acid)	54	DIVMTQSPATLSVTPGDGVSLSCRAS QSINNNLHWYQQKSHESPRLLIKF ASQSISGIPSRFGSGSGTDFTLSINSVETEDFGMYFCQQSNSWPLTFGAG TKLELK
Light chain variable (nucleotide sequence)	55	GATATTGTGATGACCCAGTCTCCAGCCACCCCTGTCTGTGACTCCAGGAG ATGGCGTCAGTCTTCCTGCAGGGCCAGCCAAAGTATTAACAACAAACCT ACACTGGTATCAACAAAAATCACATGAGTCTCCAAGACTTCTCATCAAG TTTGCTTCCCAGTCCATCTCTGGGATCCCTCCAGGTTAGTGGCAGTGG ATCAGGGACAGATTTCACTCTCAGTATCAACAGTGTGGAGACTGAAGAT TTTGAATGTATTTCTGTCAACAGAGTAACAGACTGGCCTCTCACGTTCG GTGCTGGGACCAAGCTGGAGCTGAAAC

3G4 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	56	GYIFTSYW
CDRH2	57	IYPGNSDT
CDRH3	58	TRDGYYFAY
FR1	59	EVQLEESGTVLARPGASVVKMSCKAS
FR2	60	MHWIKQRPGQGLEWIGA
FR3	61	STNQKFKDKAKLTAVTSTSTAYLELSSLTNEDSAVFYC
FR4	62	WGQGTLTVSA
Heavy chain variable (amino acid)	63	EVQLEESGTVLARPGASVVKMSCKAS GYIFTSYWMHWIKQRPGQGLEWI GAIYPGNSDTSTNQKFKDKAKLTAVTSTSTAYLELSSLTNEDSAVFYCTR DGYYPFAYWGQGTLTVSA
Heavy chain variable (nucleotide sequence)	64	GAAGTGCAGCTGGAGGAGTCAGGGACTGTGCTGGCAAGGCCTGGGCTT CA GTGAAGATGTCCTGCAAGGCTTCTGGCTACATTTTACCAAGCTACTG GATGCACTGGATAAAACAGAGGCCTGGACAGGGTCTGGATGGATTGGC GCTATTTATCCTGGAAATAGTGTACTAGTACTAATCAGAAGTTCAAGG ACAAGGCCAAACTGACTGCAGTCACATCCACCAAGCACTGCCTATTTGGA ACTCAGCAGCCTGACAAATGAGGACTCAGCGGTCTTTACTGTACAAGA GATGGTTACTACCCGTTGCTTACTGGGGCCAAGGGACTCTGGTCACTG TCTCTGCA

3G4 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	65	QSLVYINGDTY
CDRL2	66	RVS
CDRL3	67	SQTKHVPYT
FR1	68	DIVLTQSPLSLPVSLGDQASISCRSS
FR2	69	FHWYLQKPGQSPKLLIY
FR3	41	NRFSGVPDRFSGSG SGTDFTLKISRVEAEDLGVYC
FR4	70	FGGGTKLEMK
Light chain variable (amino acid)	71	DIVLTQSPLSLPVSLGDQASISCRSS QSLVYINGDTYFHWYLQKPGQSPKL LIYRVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFC SQTKHVPY TFGGGTKLEMK
Light chain variable (nucleotide sequence)	72	GACATTGTGCTGACCCAATCTCCACTCTCCCTGCCTGTCAGTCTTGGAGA TCAAGCCTCCATCTCTTGAGATCTAGTCAGAGCCTTGTATATATTAAAT GGAGACACCTATTTCATTGGTACTTGCAGAAGCCAGGCCAGTCTCCAA AGCTCCTGATCTACAGAGTTCCAACCGATTTCTGGGTCCCAGACAG GTTCACTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGA GTGGAGGCTGAGGATCTGGGAGTTATTTCTGCTCTCAAACAAACATG TTCCGTACACGTTGGAGGGGGACCAAGCTGGAAATGAAACAG
5B9 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	73	GYEFSKYW
CDRH2	74	IFPGDGDI
CDRH3	75	ARWYYGSNYAMDY
FR1	76	EVQLQQPGAEVVRPGSSVKISCKAS
FR2	77	MNWVKQRPGQGLEWIGQ
FR3	78	NYNGKFKGKATLTADKSSSTAYMQLSSLTSEESAVYFC
FR4	7	WGQGTSVTVSS
Heavy chain variable (amino acid)	79	EVQLQQPGAEVVRPGSSVKISCKAS GYEFSKYW MNWVKQRPGQGLEWI GQIFPGDGDI NYNGKFKGKATLTADKSSSTAYMQLSSLTSEESAVYFC AR WYYGSNYAMDY WGQGTSVTVSS

Heavy chain variable (nucleotide sequence)	80	GAGGTCCAGCTGCAGCAGCCTGGGCTGAGCTGGTGAGGCCTGGTCCT CAGTGAAGATTCCTGCAAGGCTCTGGCTATGAATTAGTAAGTACTG GATGAACTGGGTGAAGCAGAGCCTGGACAGGGTCTTGAGTGGATTGGA CAGATTTCAGGAGACGGTGATATTAAATTACAATGGAAAATTCAAGG GTAAAGCCACACTGACTGCAGACAAATCCTCCAGCACAGCCTACATGCA GCTCAGCAGCCTAACATCTGAGGAATCTGGGTCTATTCCTGTGCAAGA TGGTACTACGGTAGTAACATGCTATGGACTACTGGGTCAAGGAACCT CAGTCACCGTCTCCTCA
--	----	--

5B9 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	81	QSLLYSSNQKNY
CDRL2	82	WAS
CDRL3	83	QQYYAYRT
FR1	84	DIVMTQTPSSLAVSVGEKITMSCKSS
FR2	85	LAWYQQKPGQSPKLLIY
FR3	86	TRESGVPDFRTGSGSGTDFTLTISSVKAEDLAVYYC
FR4	42	FGGGTKLEIK
Light chain variable (amino acid)	87	DIVMTQTPSSLAVSVGEKITMSCKSS QSLLYSSNQKNY LAWYQQKPGQSPKLLIY WASTRESGVPDFRTGSGSGTDFTLTISSVKAEDLAVYYC QQYYAYRT FGGGTKLEIK
Light chain variable (nucleotide sequence)	88	GACATTGTGATGACCCAGACTCCATCCTCCCTAGCTGTGTCAGTTGGAG AGAAGATTACTATGAGCTGCAAGTCCAGTCAGAGCCTTTATATAGTAG CAATCAAAGAACTACTTGGCCTGGTACCAGCAGAAACCAGGGCAGTCT CCTAAACTGCTGATTACTGGGCATCCACTAGGGAATCTGGGTCCCTG ATCGCTTCACAGGCAGTGGATCTGGACAGATTCACTCTCACCATCAG CAGTGTGAAGGCTGAAGACCTGGCAGTTATTACTGTCAGCAATATTAT GCCTATCGGACGTTCGTGGAGGCACCAAGCTGGAAATCAAAC

6E6 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	89	GYIFTSYW

CDRH2	90	IYPGNNDT
CDRH3	91	TRDGFYPFAY
FR1	92	EVKLQQSGTVLARPGTSVKMSCKAS
FR2	93	MHWIKERPGQGLEWIGA
FR3	94	STNQKFKGKAKLTAVTSTSTAYLELSSLTNEDSAVYYC
FR4	62	WGQGTLVTVSA
Heavy chain variable (amino acid)	95	EVKLQQSGTVLARPGTSVKMSCKAS GYIFTSYWMHWIKERPGQGLEWI GAIYPGNNDTSTNQKFKGKAKLTAVTSTSTAYLELSSLTNEDSAVYYCTR DGFYPFAYWGQGTLVTVSA
Heavy chain variable (nucleotide sequence)	96	GAGGTTAACGCTGCAGCAGTCTGGACTGTGCTGGCAAGGCCTGGACTT CAGTGAAGATGTCTTGCAGGCTTCTGGCTACATTTTACCAAGCTACTG GATGCATTGGATAAAAAGAGAGGCCCTGGACAGGGTCTGGAATGGATTGGC GCTATTTATCCTGAAATAATGATACTAGTACTAATCAGAAGTTCAAGG GCAAGGCCAAACTGACTGCAGTCACATCCACCAGCACTGCCTATTGGA ACTCAGCAGCCTGACAAATGAGGACTCAGCGGTCTATTACTGTACAAGA GATGGTTTTACCCGTTGCTTACTGGGCCAAGGGACTCTGGTCAGT TCTCTGCA

6E6 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	65	QSLVYINGDTY
CDRL2	66	RVS
CDRL3	67	SQTKHVPYT
FR1	97	DIVLTQTPLSLPVSLGDQASISCRSS
FR2	69	FHWYLQKPGQSPKLLIY
FR3	41	NRFSGVPDRFGSGSGTDFTLKISRVEAEDLGVYFC
FR4	70	FGGGTKLEMK
Light chain variable (amino acid)	98	DIVLTQTPLSLPVSLGDQASISCRSS QSLVYINGDTYFHWYLQKPGQSPKL LIYRVSNRFGVPDRFGSGSGTDFTLKISRVEAEDLGVYFC SQTKHVPY TFGGGTKLEMK
Light chain	99	GATATTGTGCTGACCCAGACTCCACTCTCCCTGCCTGTCAGTCTTGGAGA

variable (nucleotide sequence)		TCAAGCCTCCATCTCTGCAGATCTAGTCAGAGCCTGTATATATTAAT GGAGACACCTATTTCATTGGTACCTGCAGAAGCCAGGCCAGTCTCCAA AGCTCCTGATCTACAGAGTTCCAACCGATTTCTGGGGTCCCAGACAG GTTCAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGA GTGGAGGCTGAGGATCTGGGAGTTTATTTCTGCTCTCAAACAAACATG TTCCGTACACGTTCGGAGGGGGACCAAGCTGGAAATGAAACG
--------------------------------------	--	---

2B3 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	100	GYIFTSYY
CDRH2	101	INPITGGT
CDRH3	102	ARMGRDAMDY
FR1	103	QVQLKQSGSELVKPGASV р KLSCKAS
FR2	104	MYWVKQRPGQGLEWIGG
FR3	105	DFNEKFKDКATLTLAASSSTAYIQLSSLT S E D S A V Y F C
FR4	7	WGQGTSVTVSS
Heavy chain variable (amino acid)	106	QVQLKQSGSELVKPGASV р KLSCKASGYIFTSYYMYWVKQRPGQGLEWIGG INPITGGTDFNEKFKDКATLTLAASSSTAYIQLSSLTSEDSAVYFCARMGR DAMDYWGQGTSVTVSS
Heavy chain variable (nucleotide sequence)	107	CAGGTGCAGCTGAAGCAGTCAGGGTCTGAACCTGGTГAAACCTGGGCTT CAGTGAAGTTGTCCTGCAAGGCTTCTGGCTACATCTCACCAGCTACTA TATGTAСTGGGTGAAGCAGAGGCCCTGGACAAGGCCTTGAGTGGATTGGG GGGATTAATCCTATCACTGGTGGTACTGACTTCAATGAGAAGTTCAAGG ACAAGGCCACACTGACTCTGGCCGATCCTCCAGCACAGCCTACATACAA CTCAGCAGCCTGACATCTGAGGACTCTGGGTCTATTCTGTGCAAGAA TGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCACCGT CTCCTC

2B3 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	108	KSVSTSGYSY
CDRL2	109	LVS

CDRL3	110	QHIRELYT
FR1	111	DIVLTQSPASLAVALGQRATISYRAS
FR2	112	MHWNQQKPGQPPRLLIY
FR3	113	NLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYC
FR4	42	FGGGTKEIK
Light chain variable (amino acid)	114	DIVLTQSPASLAVALGQRATISYRAS KSVSTSGYSYM HWNQQKPGQPPRL LIYLVS NLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYC QHIRELYT F GGGTKEIK
Light chain variable (nucleotide sequence)	115	GACATTGTGCTGACACAGTCTCCTGCTTCCTTAGCTGTATCTCTGGGGCA GAGGGCCACCATCTCATACAGGGCCAGCAAAAGTGTCACTACATCTGGC TATAGTTATATGCACTGGAACCAACAGAAACCAGGACAGCCACCCAGAC TCCTCATCTATCTTGTATCCAACCTAGAATCTGGGGTCCCTGCCAGGTTCT AGTGGCAGTGGTCTGGGACAGACTTCACCCCTAACATCCATCCTGTGG AGGAGGAGGATGCTGCAACCTATTACTGTCAGCACATTAGGGAGCTTTA CACGTTCGGAGGGGGGACCAAGCTGGAAATAAAACG

2F1 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	116	GYTFTSYY
CDRH2	117	INPTTGGT
CDRH3	102	ARMGRDAMDY
FR1	118	QVQLKESGAELVKPGTSVKLSCKAS
FR2	119	MYWLKQRPGQGLEWIGG
FR3	120	DFNENFKNKATLTLATSSSTAYIQLSSLTSEDSAVYFC
FR4	7	WGQGTSVTVSS
Heavy chain variable (amino acid)	121	QVQLKESGAELVKPGTSVKLSCKAS GYTFTSYY MYWLKQRPGQGLEWIG GINPTTGGT DFNENFKNKATLTLATSSSTAYIQLSSLTSEDSAVYFC ARM GRDAMDY WGQGTSVTVSS
Heavy chain variable	122	CAGGTGCAGCTGAAGGAGTCAGGGCTGAACCTGGTGAACCTGGGACTT CAGTGAAGTTGTCCTGCAAGGCTTCTGGCTACACCTCACCAAGCTACTA

(nucleotide sequence)		TATGTACTGGTTGAAGCAGAGGCCTGGACAAGGCCTTGAGTGGATTGGG GGGATTAATCCTACCACTGGTGGTACTGACTTCAATGAGAACTTCAAGA ACAAGGCCACACTGACTTTGCCACATCCTCCAGCACAGCCTACATACAA CTCAGCAGCCTGACATCTGAGGACTCTGCGGTCTATTCTGTGCAAGAA TGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCACCGT CTCCTCA
-----------------------	--	--

2F1 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	108	KSVSTSGYSY
CDRL2	109	LVS
CDRL3	123	QHIRELTR
FR1	124	DIVLTQSPASLA VSLGQRATISYRAS
FR2	125	MHWNQQKPGQPPRLLIY
FR3	126	NLESGVPARFSGSGSGTDFTLNIHPVEEDAATYYC
Light chain variable (amino acid)	127	DIVLTQSPASLA VSLGQRATISYRAS KSVSTSGYSY MHWNQQKPGQPPRL LIYLVSNLESGVPARFSGSGSGTDFTLNIHPVEEDAATYYC QHIRELTRS EGGPSWK
Light chain variable (nucleotide sequence)	128	GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT GTA TCT CTG GGG CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC AAA AGT GTC AGT ACA TCT GGC TAT AGT TAT ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC AGA CTC CTC ATC TAT CTT GTA TCC AAC CTA GAA TCT GGG GTC CCT GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC ATC CAT CCT GTG GAG GAG GAG GAT GCT GCA ACC TAT TAC TGT CAG CAC ATT AGG GAG CTT ACA CGT TCG GAG GGG GGA CCA AGC TGG AAA

1B9 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	116	GYTFTSYY
CDRH2	117	INPTTGGT

CDRH3	102	ARMGRDAMDY
FR1	129	EVQLQQSGAELVKPGTSVKLSCKAS
FR2	119	MYWLKQRPGQGLEWIGG
FR3	120	DFNENFKNKATLTLATSSSTAYIQLSSLTSEDSAVYFC
FR4	7	WGQGTSVTVSS
Heavy chain variable (amino acid)	130	EVQLQQSGAELVKPGTSVKLSCKAS GYIFTSYMYWLKQRPGQGLEWIG GINPTTGGTDFNENFKNKATLTLATSSSTAYIQLSSLTSEDSAVYFCARM GRDAMDYWGQGTSVTVSS
Heavy chain variable (nucleotide sequence)	131	GAGGTTCAGCTGCAGCAGTCTGGGCTGAACCTGGTGAACACCTGGACTT CACTGAAGTTGTCCTGCAAGGCTCTGGCTACACCTCACCAAGCTACTA TATGTACTGGTTGAAGCAGAGGCCTGGACAAGGCCTTGAGTGGATTGGG GGGATTAATCCTACCACTGGTGGTACTGACTTCAATGAGAACTTCAAGA ACAAGGCCACACTGACTTTGCCACATCCTCCAGCACAGCCTACATACAA CTCAGCAGCCTGACATCTGAGGACTCTGGGTCTATTCTGTGCAAGAA TGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCACCGT CTCCTCA

1D2 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	100	GYIFTSYY
CDRH2	101	INPITGGT
CDRH3	102	ARMGRDAMDY
FR1	129	EVQLQQSGSELVKPGASVKLSCKAS
FR2	119	MYWVKQRPGQGLEWIGG
FR3	120	DFNEKFKNKATLTLATSSSTAYIHLSSLTSEDSAVYFC
FR4	132	WGQGTSVTVS
Heavy chain variable (amino acid)	133	EVQLQQSGSELVKPGASVKLSCKAS GYIFTSYYMYWWKQRPGQGLEWIG GINPITGGTDFNEKFKNKATLTLATSSSTAYIHLSSLTSEDSAVYFCARM GRDAMDYWGQGTSVTVS
Heavy chain variable (nucleotide	134	GAGGTTCAGCTGCAGCAGTCTGGTCTGAACCTGGTGAACACCTGGGCTT CACTGAAGTTGTCCTGCAAGGCTCTGGCTACATCTCACCAAGCTACTA TATGTACTGGGTGAAGCAGAGGCCTGGACAAGGCCTTGAGTGGATTGGG

sequence)		GGGATTAATCCTATCACTGGTGGTACTGACTTCATGAGAAGTTCAAGA ACAAGGCCACACTGACTCTGCCACATCCTCCAGCACAGCCTACATACAT CTCAGCAGCCTGACATCTGAGGACTCTGCCGTCTATTCTGTGCAAGAA TGGGACGGGATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGT CTCC
-----------	--	--

5A5 (Heavy chain)		
	SEQ ID NO:	Sequence
CDRH1	135	DYSITSDYA
CDRH2	136	ILYSGST
CDRH3	137	ASLGRGGS
FR1	138	LEVKLEQSGPGLVKPSQLSLTCTVT
FR2	139	WNWIRQFPGNKLEWMGY
FR3	140	TYNPSLKSRSITRDTSKNQFFLHLD SVT TEDAATYYC
FR4	141	WGQGTTLAVSS
Heavy chain variable (amino acid)	142	LEVKLEQSGPGLVKPSQLSLTCTVTDYSITSDYAWN WIRQFPGNKLEW MGYILYSGSTTYNPSLKSRSITRDTSKNQFFLHLD SVT TEDAATYYC ASL GRGGSWGQGTTLAVSS
Heavy chain variable (nucleotide sequence)	143	CTTGAGGTTAACGCTGGAGCAGTCAGGACCTGGCCTGGTGA AACCTTCTC AGTCTCTGTCCTCACCTGCACTGACTACTCAATC ACCAGTGAT TATGCCTGGA ACTGGATCCGGCA ATTCCAGGAA ACAAACTGGAGTGG A TGGGTTACATACTCTACAGTGGTCCACTACGTACA ATCCGTCTCAA AA AGTCGAGTCTCTATCA CTCGAGACACATCCA AAGAACCA AGTTCTTCTG CACTTG GATTCTGTGACTACTGAGGAC GCTGCCACATATT ACTGTGCAA GCCTCGGGCGTGGGGGTCTGGGCCAGGG CACC ACTCTCGCAGTCTCC TCA

5A5 (Kappa / light chain)		
	SEQ ID NO:	Sequence
CDRL1	144	QSIVHSNGNTY
CDRL2	37	KVS
CDRL3	145	FQGSHAPWT

FR1	146	DILMTQTPLSLPVSLGDQASISCRSS
FR2	147	LEWYLQKPGQSPKLLIY
FR3	148	NRFSGVPDRFTGSGSGTDFTLKISRVEAEDLGIYYC
FR4	149	FGGGTKLEIR
Light chain variable (amino acid)	150	DILMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKL LIYKVSNRFGVPDRFTGSGSGTDFTLKISRVEAEDLGIYYCFQGSHAPWT FGGGTKLEIR
Light chain variable (nucleotide sequence)	17	GATATTGGATGACCCAAACTCCTCTCCCTGCCTGTCAGTCAGTCTTGGAGA TCAAGCCTCCATCTCTTGAGATCTAGTCAGAGCATTGTACATAGTAAT GGAAACACCTATTGGAATGGTACCTGCAGAAACCAGGCCAGTCTCCAA AGCTCCTTATCTACAAAGTTCCAACCGATTCTGGGGTCCCAGACAG GTTCACTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGA GTGGAGGCTGAGGATCTGGGAATTATTACTGCTTCAAGGTTCACATG CTCCGTGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAGAC

[00550] The invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein.

Thus, for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred examples and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[00551] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[00552] Other examples are within the following claims and non-limiting examples. In addition, where features or aspects of the invention are described in terms of Markush groups,

those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

EXPERIMENTAL SECTION

5

[00553] EXAMPLE 1: Recombinant RON antigen design, expression and purification

[00554] The translated sequence for RON was analysed for antigenicity with Jameson-Wolf algorithm in Lasergene Protean v8.1 program (DNASTAR Inc., Madison, WI) to predict the antigenic index of RON. This algorithm integrates several parameters to calculate the antigenicity of the sequence based on the characteristics of its primary amino acid chain: hydrophilicity (Hopp-Woods), surface probability (Emini), flexibility of the protein backbone (Karplus-Schulz), and secondary structure prediction (Chou-Fasman and Garnier) (Jameson & Wolf, 1988).

[00555] The entry vector containing full length human RON cDNA in pCMV6 vector (RC212786) was obtained from Origene. Three truncated regions of RON were selected based on the most antigenic sequences in the extracellular regions and subcloned into pGEX-4T1 vector (GE Healthcare) using EcoRI and XhoI restriction sites. The recombinant plasmids were transformed into BL21 E.coli competent cells (Invitrogen) and plated on LB plate incubated at 37 °C overnight. Single colonies were picked for prokaryotic expression. Transformed cells were grown in a 1L culture until an OD 600 of 0.6-0.8 was reached. Protein expression was induced by addition of IPTG (isopropyl-β-D-thio-galactoside) to a final concentration of 300 µM. Cultures were then further allowed to grow for overnight at 18 °C. Cells were recovered by centrifugation at 6000 rpm for 15 mins and resuspended in 20 ml of lysis buffer (20 mM Tris-HCl, pH 8.0, 1 M NaCl, 10% glycerol, 0.1% Triton-X 100 and 1 mM DTT). Cells were incubated in lysis buffer for 30 mins at 4°C, with constant swirling before sonication. Resuspended cells were lysed by sonication on ice using a sonicator (Sonics, Vibracell, USA) for 3 minutes. Sonication was performed for four cycles at 38% amplitude with 1 sec ON and 0.1 sec OFF. The resulting suspension was centrifuged at 18,000 rpm for 40 mins and the supernatant (pre-purified supernatant) obtained was used for protein purification. The supernatant of the bacterial lysate was loaded on a glutathione column, washed with 20 mM Tris-HCl, pH 8.0, 1 M NaCl, 10% glycerol, 0.1% Triton-X 100, and 1 mM DTT. The GST-tagged RON protein was eluted using a buffer of 20 mM Tris-HCl, pH 9.6, 100 mM NaCl, 1 mM DTT, and 10 mM glutathione. The eluted protein fractions were collected for analysis by SDS-PAGE.

35

[00556] EXAMPLE 2: Immunization of truncated RON into mice

[00557] Five 8 weeks old Balb/c female mice were obtained from Biological Resource Center (Singapore) and inoculated with recombinant human protein RON immunogens. The first immunisation was performed intraperitoneally with Sigma Adjuvant System (Sigma) as adjuvant, followed by five intraperitoneal and subcutaneous injections at 3 weeks interval. One week after the fourth immunization, blood was drawn from each mouse via cheek bleed using a lancet (MEDIpoint International Inc.). Approximately 10µl of blood was centrifuged for 10 min at 1600 rpm and serum was aspirated and stored at 4°C. Subsequently the antibody response was measured by enzyme-linked immunosorbent assay (ELISA) with the RON protein used for immunisation immobilized on the ELISA plate. The mouse with the highest serum antibody titer was selected as the spleen donor for fusion with myeloma cell line SP2/0.

[00558] Fusion of mice spleen with myeloma cells to obtain hybridoma cells

[00559] The mice received a final boost by intravenous injection of the RON fusion protein without adjuvant. Mouse myeloma SP2/0 cell line was used as the fusion partner. Thus, one week before fusion, cells were cultured in RPMI (Gibco) and 10% FBS until they attained >70% confluence in the logarithmic phase. The spleen cells of the immunised mouse were removed under sterile conditions. Generation, selection and cloning of hybridoma cells were performed using the ClonaCell-HY Hybridoma Cloning kit (STEMCELL Technologies) following the manufacturer's protocol.

20 [00560] EXAMPLE 3: Screening of hybridoma cells for RON antibodies

[00561] ELISA

[00562] Hybridoma clones secreting mAbs targeting human RON were selected by ELISA assay with the use of 96- well Maxisorp plates (Nunc) coated separately with recombinant RON and GST. Supernatant collected from individual hybridoma wells were tested on ELISA plates. 10% fetal bovine serum (FBS) was used for blocking and antibody dilution. 1XPBS with 0.05% Tween 20 (PBST) was used for washes. After washing, IgGs were detected using 1: 5000 goat anti-mouse IgG conjugated to HRP (Biorad) in PBST with 10% FBS. After washing, plates were developed with 1 X TMB ELISA substrate solution (Sigma). Absorbance was measured at 650 nm with EnVision Plate Reader (Perkin Elmer).

30

[00563] EXAMPLE 4: Immunofluorescence staining

[00564] The 4% paraformaldehyde fixed HCT116 and TKO cells were subjected to permeabilization with 0.4% Triton X-100 for 20 minutes. After rinsing with PBS, cells were blocked with 5% BSA in PBSTritonX (PBSTX) for 20 min, followed by overnight incubation in hybridoma supernatant at 4°C. IgGs were detected using 1:1000 goat Alexaflor 488 Donkey anti-

mouse IgG conjugated (Life technologies) in PBSTX with 1%BSA. Subsequently, cells were counterstained with DAPI, and viewed with Incell Analyzer (GE Healthcare).

[00565] EXAMPLE 5: Immunohistochemical staining of paraffin-embedded sections

[00566] Tumour tissues from the HT29 xenograft mouse model were processed into paraffin blocks by the Advanced Molecular Pathology Laboratory (AMPL), Institute of Molecular and Cell Biology. Wax sections at 5 µm were then collected onto slides (Leica Biosystems) and dried on a 50°C hot plate for 1 h.

[00567] Sections were deparaffinized in xylene (ChemTech Trading) and rehydrated through descending percentages of ethanol (ChemTech Trading) to water. Tissue sections were heated with Target Retrieval Solution, pH9 (Dako) in the 2100 Antigen Retriever (Aptum Biologics) to expose the antigens, then rinsed thrice in PBS. Endogenous peroxidase was blocked with 2% (v/v) hydrogen peroxide (Merck) in PBS for 30 min, rinsed with water then PBS. Sections were blocked with 10% (v/v) goat serum (Dako) in PBS for 1 h then incubated with primary antibodies 6D4 or 7G8 at 4°C overnight.

[00568] Sections were washed in running tap water then rinsed in PBS before being incubated with EnVision peroxidase labeled polymer conjugated to goat anti-mouse or anti-rabbit immunoglobulins (Dako; neat concentrations) or 1:100 diluted peroxidase labeled goat anti-mouse or anti-mouse IgG (Fcγ fragment specific) (Jackson ImmunoResearch). Antigen-antibody interaction was then visualized using 3,3'-diaminobenzidine as a substrate, and the sections were lightly counterstained with hematoxylin before dehydrating and mounting in Cytoseal 60 synthetic resin (Richard-Allan Scientific™, Fisher Scientific). Slides were imaged under bright field using the AxioImager (Zeiss) light microscope and analyzed with AxioVision Rel 4.8 software (Carl Zeiss AG).

[00569] EXAMPLE: 6 Ascites fluid production

[00570] BALB/c mice were given a single 0.25 mL intraperitoneal (IP) injection of Incomplete Freund's Adjuvant (Sigma Chemical Co.). Fourteen days later, mice were injected with a single IP injection of 4×10^5 in a volume of 0.5 mL of the hybridoma cells described above, after which they were examined daily for development of ascites fluid recognized by abdominal distention.

[00571] Seven to ten days after the injection of hybridoma cells, mice were anesthetized and the collection of ascites fluid was performed on all mice in all groups. Ascites fluid was collected aseptically from anesthetized mice by abdominal paracentesis with an 18-22 gauge needle by gravity flow into sterile centrifuge tubes. Digital pressure was gently applied to the abdomen

and the position of the mouse was altered as needed to facilitate removal of the ascites fluid. Ascites was pooled for each separate cage of mice.

[00572] **EXAMPLE 7: Epitope mapping of obtained antibodies**

5 [00573] **Pepscan**

[00574] Overlapping (5 amino acids) 25-mer peptides, covering the extracellular human RON sequence, were ordered from Mimotopes, generating 93 biotinylated peptides in total. The peptides were resuspended in 100% DMSO to prepare a 30 mg/ml stock solution, which were then diluted to 10 μ g/ml before adding into Streptavidin High Binding Capacity Coated 96-Well 10 Plates (Pierce) for 1 hr at room temperature. ELISA was performed as per manufacturer's protocol. Briefly, 1 μ g/ml purified antibody was added into the plate and incubated for 30 minutes at room temperature. After washing with PBST, IgGs were detected using 1: 5000 goat 15 anti-mouse IgG conjugated to HRP (Biorad) in PBST with 10% FBS. Subsequently, plates were stained with 1 X TMB ELISA substrate solution (Sigma) and absorbance was measured at 650 nm with EnVision Plate Reader (Perkin Elmer).

[00575] **Peptide phage display**

[00576] An M13 phage library (Ph.D.-12, New England Biolabs) encoding random 12-mer peptides at the NH₂ terminus of pIII coat protein (2.7×10^9 sequences) was used. 50 nm purified antibody was coated on 96 well Maxisorp plates (Nunc). The wells were incubated with 20 blocking buffer (1XPBS, 0.5% Tween20, 2% BSA) for 1 h at room temperature, washed with washing buffer (1XPBS, 1% Tween20, 2% BSA), and incubated in washing buffer at room temperature with 4×10^{10} phages. Bound phages were eluted with 0.2 M glycine (pH 2.2) and neutralized with 1 M Tris (pH 9.1). The eluted phages were amplified as instructed by the manufacturer. The selection process was repeated for three cycles. Phage plaques from the final 25 round were picked as described by the manufacturer and sequenced.

[00577] **EXAMPLE 8: Cell proliferation assay of using antibodies**

[00578] RON expressing HCT116 cells were seeded in 96-well plates (Nunc) at 1000 cells each well. After an 8 h serum starvation period, specific concentrations of filter sterilized 30 purified mAbs were added to the wells and the cells were incubated for an additional 3 days. IncuCyte system

[00579] RON expressing HCT116 cells were transferred to a 96 well plate and imaged using the IncuCyte HD system (Essen BioScience). Frames were captured at 2 hrs intervals from 4 separate 950 \times 760- μ m² regions per well using a 20 \times objective. Seeded cells were serum 35 starved for 8 hrs and filter-sterilized purified mAb were added into each treatment wells. IgGs Anti-Mouse IgG Fc-DM1 2 $^{\circ}$ ADC (Moradec) were added to cells 30 minutes after anti-RON mAbs

were added at 10 μ g/ml. Cultures were maintained at 37°C in a water jacketed CO₂ incubation chamber (Thermo Scientific) throughout and run in triplicates for 72 hrs. Cell confluence data was calculated by the IncuCyte software. Values from all three regions of each well were pooled and averaged across all three replicates.

5

[00580] **EXAMPLE 9: Receptor mediated endocytosis**

[00581] Cells at 5 X 10⁴ cells per well in a 96 well plate were treated with 10 μ g/ml mAb overnight at 4°C or for 37°C for 1 hour followed by goat anti-mouse IgG coupled with FITC. Fixation was subsequently performed using 4% PFA for 20 minutes. Nuclear DNA was stained 10 with 4'6-diamino-2-phenylindole (DAPI). Immunofluorescence was observed under an Olympus Confocal Microscope FV1000.

[00582] **EXAMPLE 10: Western blot assays**

[00583] Lysis was performed using RIPA buffer (Thermo Scientific) supplemented with 15 protease inhibitor cocktail (Roche). QuickStart Bradford protein assay (BioRad) was used to determine protein concentration with BSA as standard. Equal amounts of total protein were mixed with NuPAGE lithium dodecyl sulphate (LDS) and sample reducing buffer (Thermo Scientific), heated for 5 min at 95°C and loaded into NuPAGE 10% or 12% Bis-Tris gels (Life Technologies) for electrophoresis. Separated proteins were transferred onto nitrocellulose 20 membranes using iBlot 2 gel transfer device (Thermo Scientific). Blocking was performed with 5% milk or bovine serum albumin (BSA) in tris-buffered saline supplemented with 0.1% tween (TBST). AKT (4298S), ERK1/2 (4348S), p-AKT (9271S), and p-ERK (8544S) antibodies were from Cell Signaling Technology. RON antibody was made in-house and Actin-HRP (A3854) was from Sigma-Aldrich. Anti-rabbit (P0217) and anti-mouse (P0161) secondary antibodies were 25 from Dako. The enhanced chemiluminescence (ECL) reagent used was SuperSignal West Dura Extended Duration Substrate (Thermo Scientific, #34076). Imaging and acquisition was performed with Licor Odyssey Fc and Image Studio (version 3.1).

[00584] **EXAMPLE 11: Cell viability assay**

[00585] Cell viability assays were performed to quantitate ATP generated by metabolically 30 active cells. Assays were performed using a CellTiter-Glo luminescent cell viability assay (Promega) as per the manufacturer's instruction. Briefly, 5 x 10³ cells/ml was cultured in sterile 96-well plates in the presence of increasing concentrations of mAbs (0 to 20 μ M) in complete 35 McCoy 5A medium. The plates were then incubated for 72 h, and then 100 μ l of CellTiter-Glo reagent was added to lyse the cells. After a 10-min incubation at room temperature, the luminescence was recorded in a luminometer with an integration time of 1 s per well on an

Envision reader (PerkinElmer). The luminescence signals for the antibody-treated cells were normalized by the luminescence signal obtained from dimethyl sulfoxide (DMSO)-treated cells.

[00586] **EXAMPLE 12: Complement dependent cytotoxicity (CDC)**

5 [00587] Target cells were labeled with DELFIA BATDA reagent (PerkinElmer) according to the manufacturer's instructions. After labeling, the cells were coated with antibodies for 60 min at 37°C. The cells were washed and then co-cultured with rabbit complement (10%) for 60mins at 37°C. Cell supernatants were then reacted with DELFIA Europium solution, and the fluorescence was measured using the EnVision Plate Reader (Perkin Elmer). Specific lysis was 10 calculated by a formula: (experimental lysis count minus spontaneous lysis count) divided by (maximum lysis count [by lysis buffer] minus spontaneous lysis count) times 100%.

[00588] **EXAMPLE 13: Antibody-dependent cell-mediated cytotoxicity (ADCC)**

15 [00589] Target cells were labeled with DELFIA BATDA reagent (PerkinElmer) according to the manufacturer's instructions. After labeling, the cells were coated with antibodies for 60 min at 37°C. The cells were washed and then co-cultured with effector cells in a 150:1 ratio (effector to target) for overnight at 37°C. Cell supernatants were then reacted with DELFIA Europium solution, and the fluorescence was measured using the EnVision Plate Reader (Perkin Elmer). Specific lysis was calculated by a formula: (experimental lysis count minus spontaneous lysis 20 count) divided by (maximum lysis count [by lysis buffer] minus spontaneous lysis count) times 100%.

[00590] **EXAMPLE 14: *In vivo* experimental results and animal model**

25 [00591] Antibodies inhibit tumour growth in HT29 human xenograft mouse model [00592] Monoclonal antibodies have a huge role to play in targeting cancer immunotherapy. RON is identified as an ideal candidate to target for cancer therapy as it is over-expressed in cancer cells and minimally expressed in normal cells. Targeting RON has a good safety profile as RON is not expressed in fibroblasts, endothelial cells, and blood leukocytes. Anti-RON mouse mAbs 7G8 and 6D4 were tested for their abilities to inhibit tumour growth in-vivo in human 30 xenograft mice models. For HT-29 cancer cell xenograft experiments, female *nu/nu* nude mice (ages 8 weeks; Biological Resource Centre) were inoculated subcutaneously with 5×10^6 HT-29-luc2 cells (Perkin Elmer) per mouse. Mice were randomized into different groups (5 mice per group). The study was performed by treating mice with antibodies at 10 mg/kg every 3-4 days for a total of 8 intravenous injections. Control group was injected intravenously with PBS. 35 Bioluminescence from individual tumours was measured at Day 21 using Caliper IVIS image

system (Perkin Elmer). Animals were euthanized when tumour volumes exceeded 2,000 mm³ or if tumours became necrotic or ulcerated through the skin.

[00593] Therapeutic effect of multiple doses (15mg/kg) of mAbs 6D4 or 7G8 on human cell line HT29-luc derived tumours was investigated. Dosing was performed according to Figure

5 31A. At Day 21, nude mice treated with mAb 7G8 showed an inhibition of 76.45% tumour size compared to control and mice treated with mAb 6D4 showed an inhibition of 50.19% tumour size compared to PBS control. Antibodies 7G8 and 6D4 both showed therapeutic abilities to inhibit HT29 tumour xenograft growth in nude mice (Figure 31A).

10 [00594] **EXAMPLE 15: Human xenograft mouse imaging**

[00595] Monoclonal antibodies have a huge role to play in targeting cancer immunotherapy. RON is identified as an ideal candidate to target for cancer therapy as it is over-expressed in cancer cells and minimally expressed in normal cells. Targeting RON has a good safety profile as RON is not expressed in fibroblasts, endothelial cells, and blood leukocytes.

15 [00596] Anti-RON mouse mAbs 7G8 and 6D4 were tested for their abilities to inhibit tumour growth *in vivo* in human xenograft mice models. For HT-29 cancer cell xenograft experiments, female nu/nu nude mice (ages 8 weeks; Biological Resource Centre) were inoculated subcutaneously with 5×10^6 HT-29-luc2 cells (Perkin Elmer) per mouse.

20 [00597] Mice were randomized into different groups (5 mice per group). The study was performed by treating mice with antibodies at 10 mg/kg every 3-4 days for a total of 8 intravenous injections. Control group was injected intravenously with PBS.

[00598] Bioluminescence from individual tumours was measured at Day 21 using Caliper IVIS image system (Perkin Elmer). Animals were euthanized when tumour volumes exceeded 2,000 mm³ or if tumours became necrotic or ulcerated through the skin.

25 [00599] Therapeutic effect of multiple doses (15mg/kg) of mAbs 6D4 or 7G8 on human cell line HT29-luc derived tumours was investigated. Dosing was performed according to Figures 31-42. At Day 21, nude mice treated with mAb 7G8 showed an inhibition of 76.45% tumour size compared to control and mice treated with mAb 6D4 showed an inhibition of 50.19% tumour size compared to PBS control. Antibodies 7G8 and 6D4 both showed therapeutic abilities to inhibit HT29 tumour xenograft growth in nude mice (Figures 31-42).

30 [00600] HT-29 tumour bearing nude mice were used for the imaging experiment. Investigation was performed to determine whether mAbs 6D4 and 7G8 could be used as *in vivo* molecules to detect RON expressing tumours in cancer. A fluorescent dye, (XenoLight CF750, Perkin Elmer), was conjugated via its reactive groups with 6D4 and 7G8. Detection of the 35 fluorescent signal of CF750 was performed non-invasively using Caliper IVIS image system (Perkin Elmer), with excitation set at wavelength 710nm and emission at 780nm.

Claims

1. A antigen binding domain comprising the heavy chain CDRs of CDRH1, CDRH2, and CDRH3 and/or the light chain CDRs of CDRL1, CDRL2, and CDRL3, wherein

- (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, SEQ ID NO: 100, SEQ ID NO: 116, and SEQ ID NO: 135 or a CDRH1 sequence differing 1 or 2 amino acids therefrom;
- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, SEQ ID NO: 101, SEQ ID NO: 117, and SEQ ID NO: 136; or a CDRH2 sequence differing 1 or 2 amino acids therefrom;
- (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, SEQ ID NO: 102, and SEQ ID NO: 137; or a CDRH3 sequence differing 1 or 2 amino acids therefrom;
- (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, and SEQ ID NO: 144; or a CDRL1 sequence differing 1 or 2 amino acids therefrom;
- (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, and SEQ ID NO: 109; or a CDRL2 sequence differing 1 or 2 amino acids therefrom; and
- (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 220, SEQ ID NO: 123, and SEQ ID NO: 145; or a CDRL2 sequence differing 1 or 2 amino acids therefrom.

2. A antigen specific binding domain comprising CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein:

- (a) CDRH1 is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 27, SEQ ID NO: 45, SEQ ID NO: 56, SEQ ID NO: 73, SEQ ID NO: 89, and SEQ ID NO: 100, SEQ ID NO: 116, SEQ ID NO: 135 and a CDRH1 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (b) CDRH2 is selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 28, SEQ ID NO: 46, SEQ ID NO: 57, SEQ ID NO: 74, SEQ ID NO: 90, and SEQ ID NO: 101, SEQ ID NO: 117, SEQ ID NO: 136 and a CDRH2 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;

- (c) CDRH3 is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 29, SEQ ID NO: 47, SEQ ID NO: 58, SEQ ID NO: 75, SEQ ID NO: 91, and SEQ ID NO: 102, SEQ ID NO: 137 and a CDRH3 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (d) CDRL1 is selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 36, SEQ ID NO: 65, SEQ ID NO: 81, SEQ ID NO: 108, SEQ ID NO: 144 and a CDRL1 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added;
- (e) CDRL2 is selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 37, SEQ ID NO: 66, SEQ ID NO: 82, SEQ ID NO: 109 and a CDRL2 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added.; and
- (f) CDRL3 is selected from the group consisting of SEQ ID NO: 20, SEQ ID NO: 38, SEQ ID NO: 67, SEQ ID NO: 83, SEQ ID NO: 110, SEQ ID NO: 123, SEQ ID NO: 145 and a CDRL3 differing from any one of the same in that 1 or 2 amino acids are replaced, deleted or added.

3. The antigen specific binding domain according to claim 1 or 2, wherein CDRH1 is SEQ ID NO: 1, CRDH2 is SEQ ID NO: 2, and CDRH3 is SEQ ID NO: 3 or an antigen specific binding domain wherein one or more modified sequences 1, 2, and 3 are employed and the modification(s) is independently selected from replacement, deletion or addition of 1 or 2 amino acids.

4. The antigen specific binding domain according to any one of claims 1 to 3, wherein the heavy chain CDRs are selected from the group consisting of

- (a) the CDRH1 is SEQ ID NO: 1, the CRDH2 is SEQ ID NO: 2, the CRDH3 is SEQ ID NO: 3;
- (b) the CDRH1 is SEQ ID NO: 27, the CRDH2 is SEQ ID NO: 28, the CRDH3 is SEQ ID NO: 29;
- (c) the CDRH1 is SEQ ID NO: 45, the CRDH2 is SEQ ID NO: 46, the CRDH3 is SEQ ID NO: 47;
- (d) the CDRH1 is SEQ ID NO: 56, the CRDH2 is SEQ ID NO: 57, the CRDH3 is SEQ ID NO: 58;
- (e) the CDRH1 is SEQ ID NO: 73, the CRDH2 is SEQ ID NO: 74, the CRDH3 is SEQ ID NO: 75;
- (f) the CDRH1 is SEQ ID NO: 89, the CRDH2 is SEQ ID NO: 90, the CRDH3 is SEQ ID NO: 91;
- (g) the CDRH1 is SEQ ID NO: 100, the CRDH2 is SEQ ID NO: 101, the CRDH3 is SEQ ID NO: 102; and

(h) the CDRH1 is SEQ ID NO: 135, the CRDH2 is SEQ ID NO: 136, the CRDH3 is SEQ ID NO: 137.

5. The antigen specific binding domain according to any one of claims 1 to 4, wherein the light chain CDRs are selected from the group consisting of

- (a) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (b) the CDRL1 is SEQ ID NO: 36, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 38;
- (c) the CDRL1 is SEQ ID NO: 18, the CDRL2 is SEQ ID NO: 19, the CDRL3 is SEQ ID NO: 20;
- (d) the CDRL1 is SEQ ID NO: 65, the CDRL2 is SEQ ID NO: 66, the CDRL3 is SEQ ID NO: 67;
- (e) the CDRL1 is SEQ ID NO: 81, the CDRL2 is SEQ ID NO: 82, the CDRL3 is SEQ ID NO: 83;
- (f) the CDRL1 is SEQ ID NO: 108, the CDRL2 is SEQ ID NO: 109, the CDRL3 is SEQ ID NO: 110; and
- (g) the CDRL1 is SEQ ID NO: 144, the CDRL2 is SEQ ID NO: 37, the CDRL3 is SEQ ID NO: 145.

6. The antigen specific binding domain according to any one of claims 1 to 5, wherein the variable heavy domain has a sequence selected from the group consisting of:

- (i) SEQ ID NO: 8;
- (ii) SEQ ID NO: 34;
- (iii) SEQ ID NO: 51;
- (iv) SEQ ID NO: 63;
- (v) SEQ ID NO: 79;
- (vi) SEQ ID NO: 95;
- (vii) SEQ ID NO: 106; and
- (viii) SEQ ID NO: 142.

7. The antigen specific binding domain according to any one of claims 1 to 6, wherein the variable light domain has a sequence selected from the group consisting of

- (i) SEQ ID NO: 25;
- (ii) SEQ ID NO: 43;
- (iii) SEQ ID NO: 54;

- (iv) SEQ ID NO: 71;
- (v) SEQ ID NO: 87;
- (vi) SEQ ID NO: 98;
- (vii) SEQ ID NO: 114; and
- (viii) SEQ ID NO: 150.

8 A chimeric antigen receptor comprising an antigen binding domain according to any one of claims 1 to 7.

9. An isolated antibody comprising an antigen binding domain according to any one of claims 1 to 7.

10. The antibody according to claim 9, wherein the antibody molecule is selected from a multispecific antibody, a full-length antibody or an antibody binding fragment.

11. The antibody according to claim 10, where the multispecific antibody is bispecific antibody.

12. The antibody according to claim 10 or 11, wherein the bispecific antibody is a bispecific T cell engager.

13. The antibody according to claim 12, wherein the bispecific antibody comprises one binding domain specifically binding to a first RON (Macrophage stimulating protein receptor or RON- Recepteur d' Origine Nantais) epitope, and a second binding domain specifically binding to a second RON epitope which is different from the first RON epitope.

14. The antibody according to claim 13, wherein a first RON binding domain comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20.

15. The antibody according to any one of claims 9 to 14 comprising a second RON binding domain comprising CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 36, 37 and 38.

16. The antibody according to any one of claims 9 to 15 wherein the antibody comprises an effector function.

17. The antibody according to any one of claims 9 to 16, wherein the antibody is conjugated to a payload.

18. The antibody according to claim 17, wherein the payload is selected from a group consisting of toxin, a polymer, biologically active proteins, nucleic acids and fragments thereof radionuclides chelated metals, nanoparticles and reporter groups.

19. The antibody according to claim 18, wherein the toxin is selected from a group consisting of an auristatin, MMAF (monomethyl auristatin F), pyrrolobenzodiazepine (PBD), doxorubicin, duocarmycin, a maytansinoid, calicheamicin, dolastatin, maytansine, α -amanitin, and a tubulysin.

20. A pharmaceutical composition comprising an antibody according to any one of claims 9 to 19 and an excipient, diluent and/or carrier.

21. The pharmaceutical composition according to claim 20, comprising at least two antigen specific antibody of any one of claims 9 to 19.

22. The pharmaceutical composition according to claim 21, wherein one of the at least two antigen specific antibody comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 1, 2, 3 respectively and CDRL1, L2 and L3 show in SEQ ID NO: 18, 19 and 20; optionally wherein a second antibody of the at least two antibodies comprises CDRH1, H2 and H3 as shown in SEQ ID NO: 27, 28, 29 respectively and CDRL1, L2 and L3 as shown in SEQ ID NO: 36, 37 and 38.

23. A antigen binding domain according to any one of claims 1 to 7, or a chimeric antigen receptor according to claim 8, or an antibody according to any one of claims 9 to 19, or a pharmaceutical composition according to any one of claims 20 to 22, for use in therapy.

24. A method of preventing or treating cancer or fibrosis in a patient comprising administering a therapeutically effective amount of an antigen binding domain according to any one of claims 1 to 7, or a chimeric antigen receptor according to claim 8, or an antibody according to any one of claims 9 to 19, or a pharmaceutical composition according to any one of claims 20 to 22 to the patient in need thereof.

25. The method of claim 24, wherein the patient is a patient population characterised in that patients making up the population have a RON positive tumour.

26. The method of claim 24 or 25, wherein the patient has a RON positive and C-MET positive tumour.

27. The method of any one of claims 24 to 26, comprises the step of identifying the patient to have a RON positive tumour before treatment.

28. Use of an antigen binding domain according to any one of claims 1 to 7, or a chimeric antigen receptor according to claim 8, or an antibody according to any one of claims 9 to 19, or a pharmaceutical composition according to any one of claims 20 to 22 in the manufacture of a medicament for the treatment of cancer or fibrosis.

29. An antibody which cross-blocks or binds the same epitope as an antibody comprising a variable heavy region (VH) of SEQ ID NO: 8, SEQ ID NO: 34, SEQ ID NO: 51, SEQ ID NO: 63, SEQ ID NO: 79, SEQ ID NO: 95, SEQ ID NO: 106, SEQ ID NO: 121, SEQ ID NO: 130, SEQ ID NO: 133 or 142.

30. An antibody, which cross-blocks or binds the same epitope as an antibody comprising a variable heavy region/variable light region (VH/VL) pair selected from SEQ ID NO: 8 and 25, SEQ ID NO: 34 and 43, SEQ ID NO: 51 and 54, SEQ ID NO: 63 and 71, SEQ ID NO: 79 and 87, SEQ ID NO: 95 and 98, SEQ ID NO: 106 and 114, SEQ ID NO: 121 and 130 or SEQ ID NO: 142 and 150.

31. An *ex vivo* method of evaluating the status of a cancer; wherein the method comprises:
a) scanning a patient or a specific site of the patient known to comprise a tumor of the cancer, wherein the patient had been administered with a labelled form of an antibody at a first time point, wherein the antibody is as defined in any one of claims 9 to 19,
b) repeating a) at one or more further time points, and
comparing the results from two or more time points to evaluate the status of the cancer.

FIGURE 1A

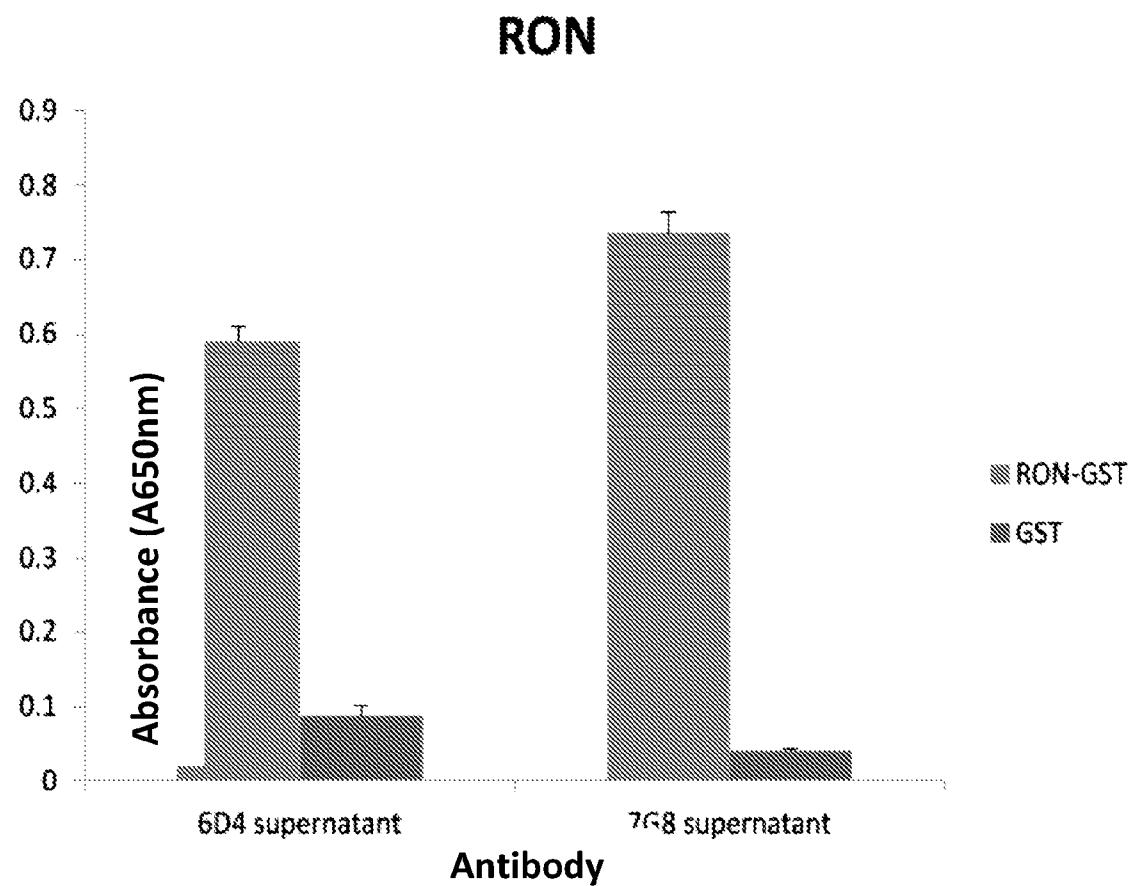


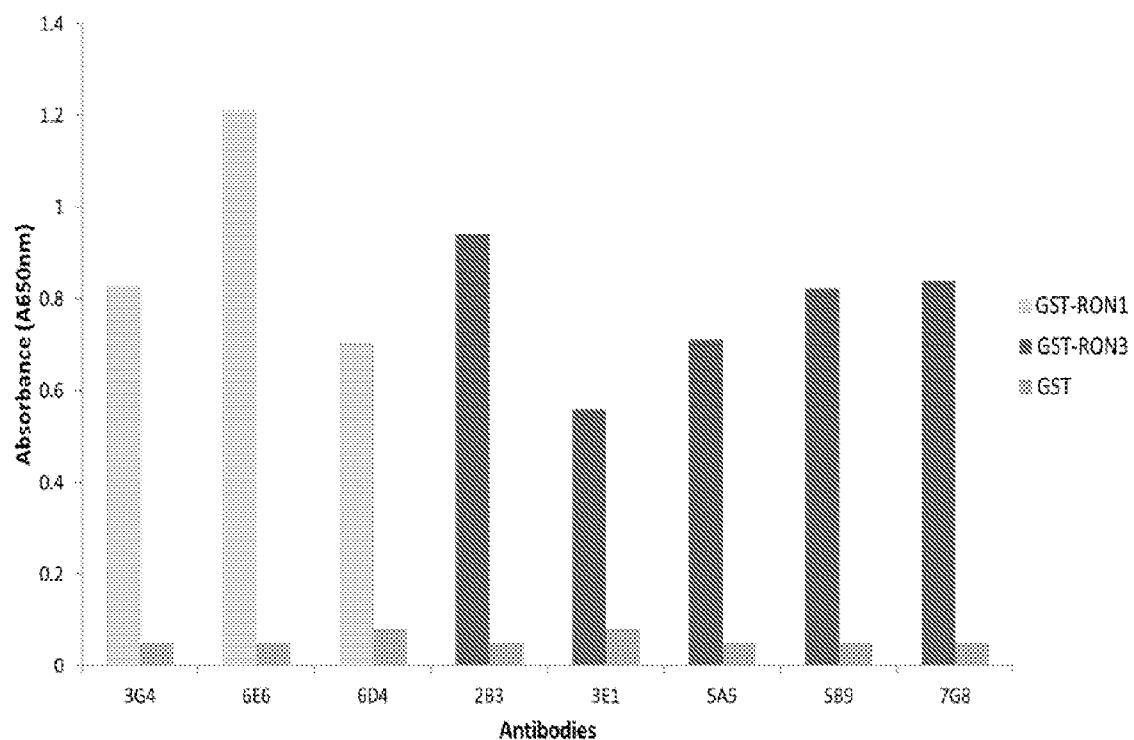
FIGURE 1B

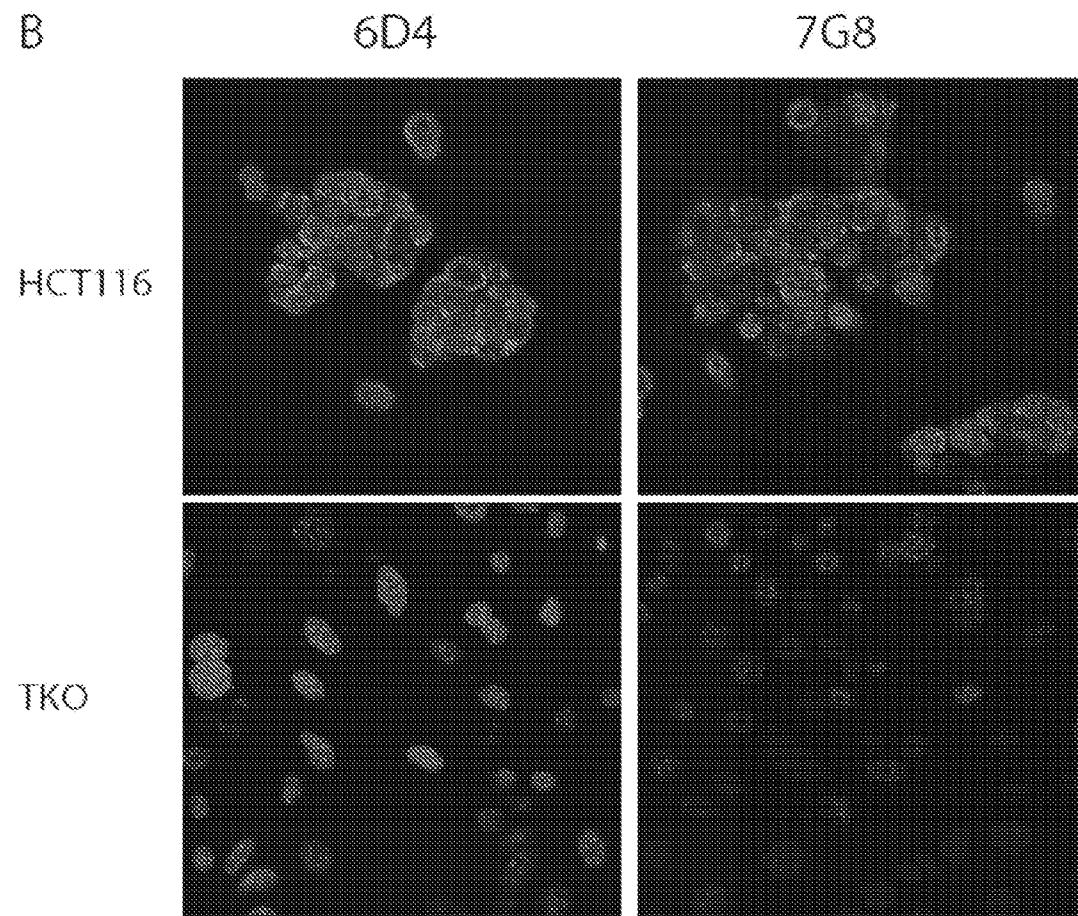
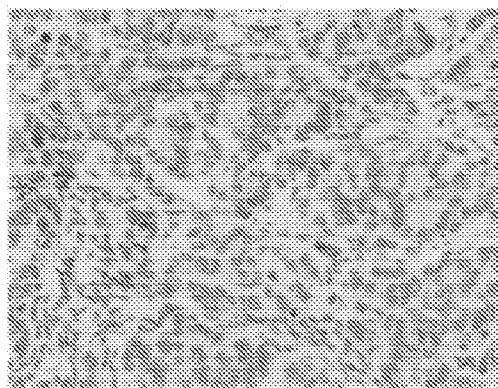
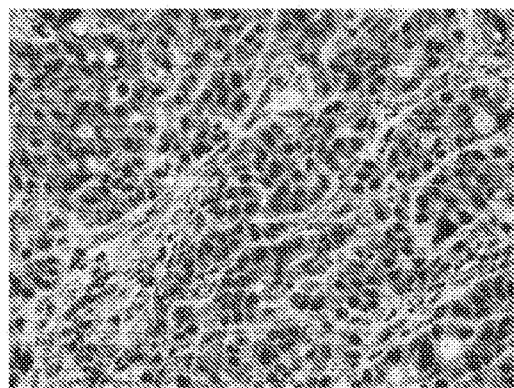
FIGURE 2

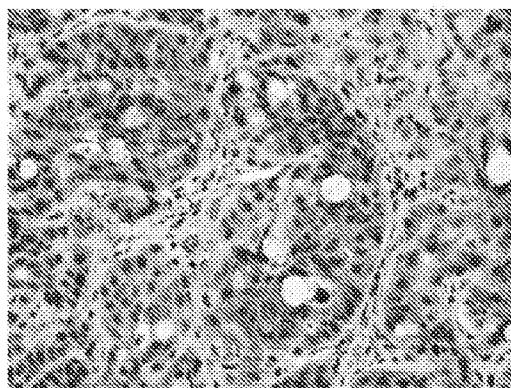
FIGURE 3



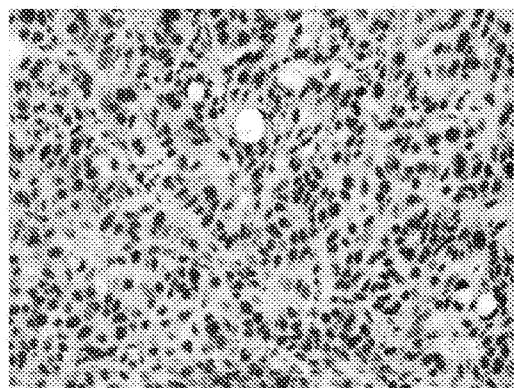
Control goat serum



Mouse serum 1:500



6D4



7G8

FIGURE 4

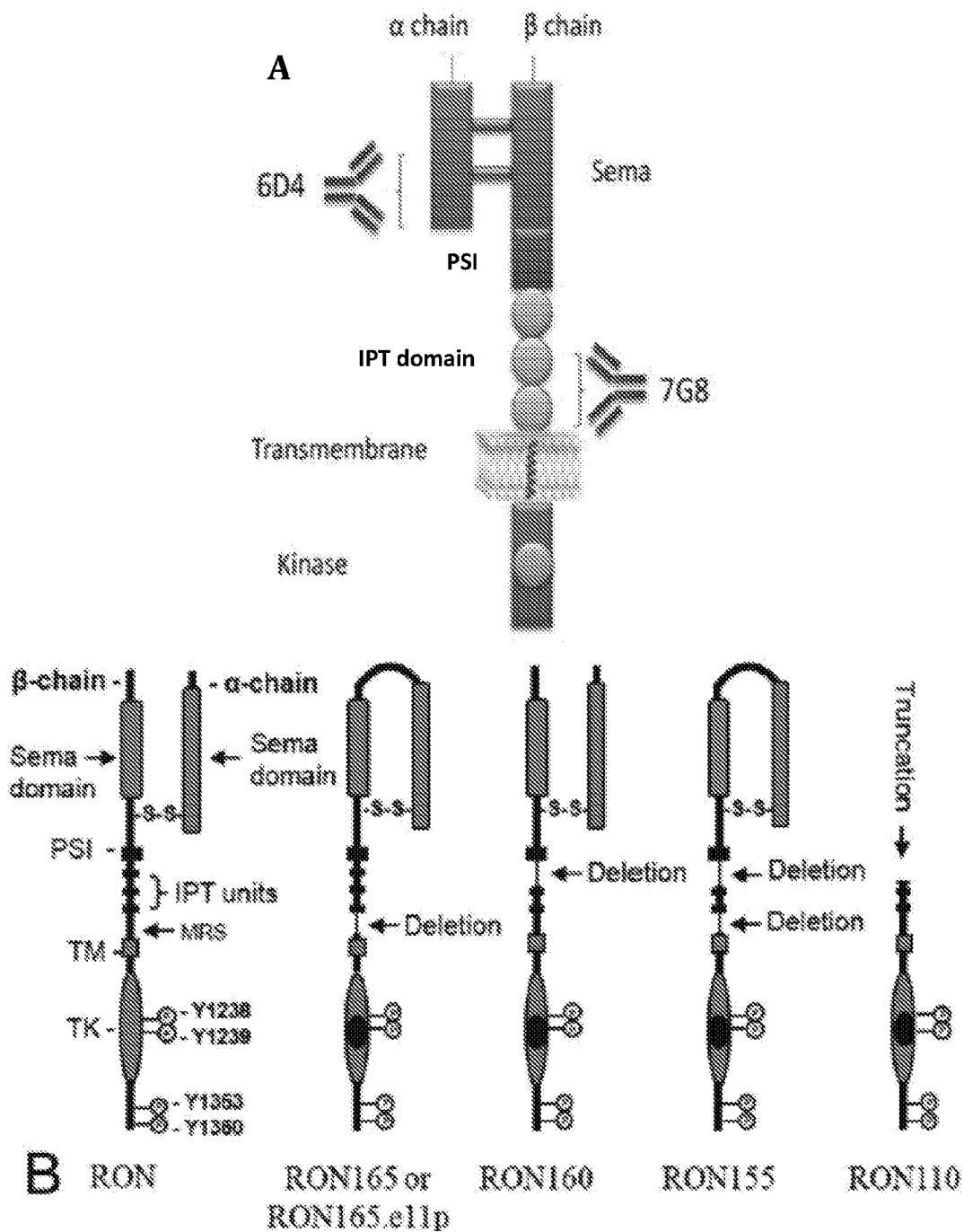


FIGURE 5

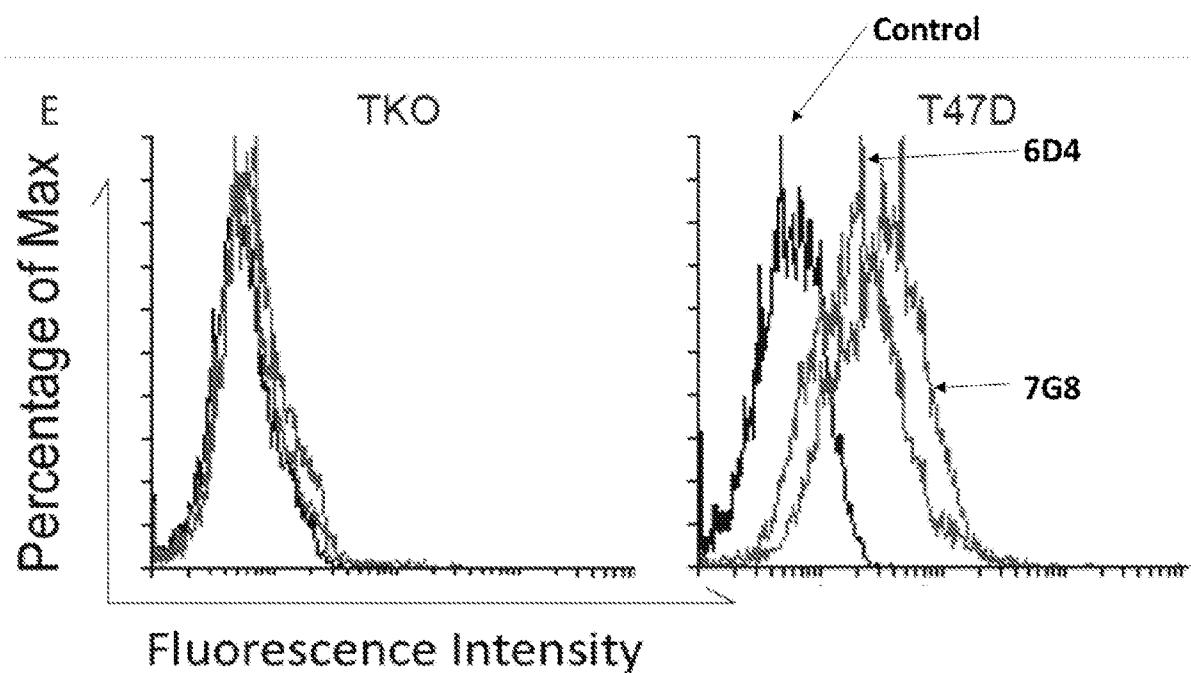


FIGURE 6A

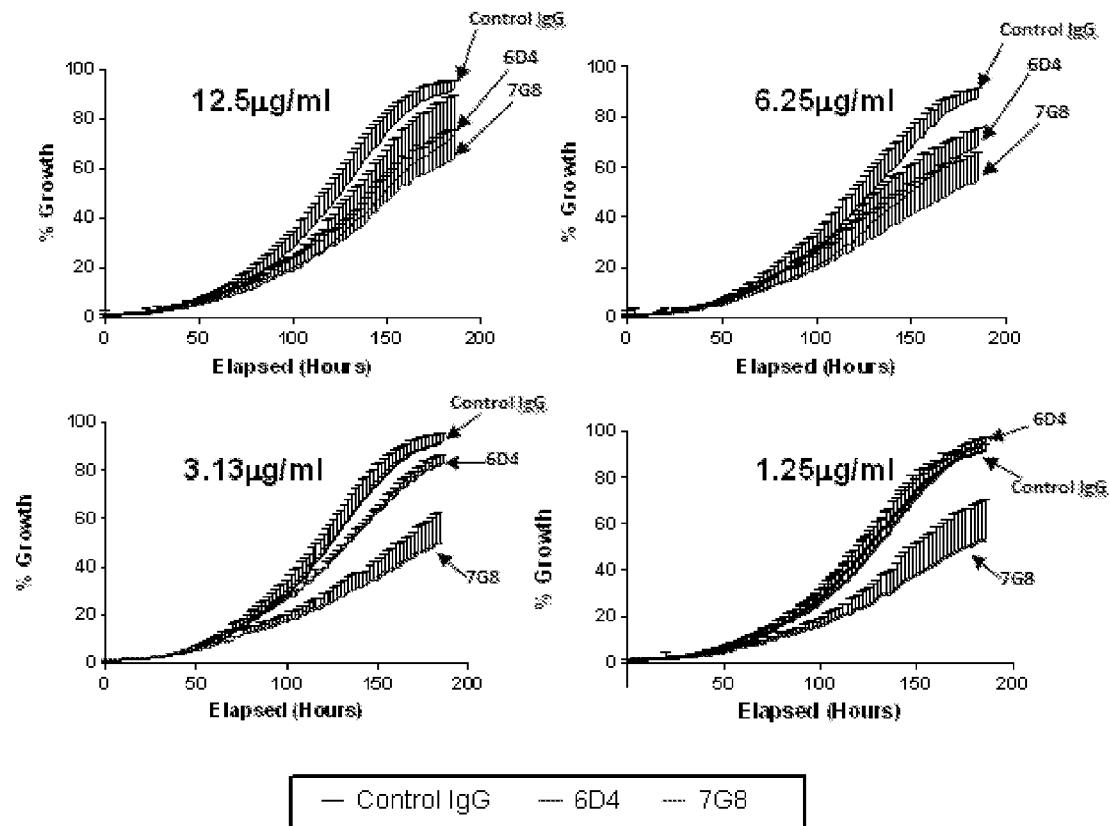


FIGURE 7

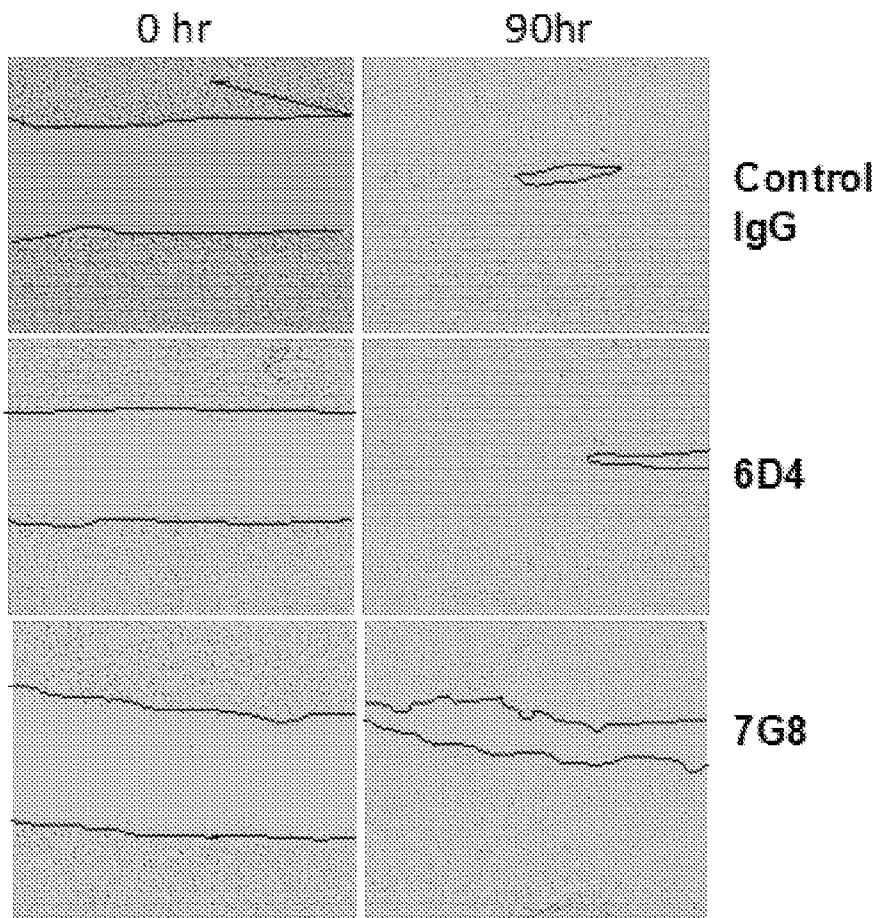


FIGURE 8

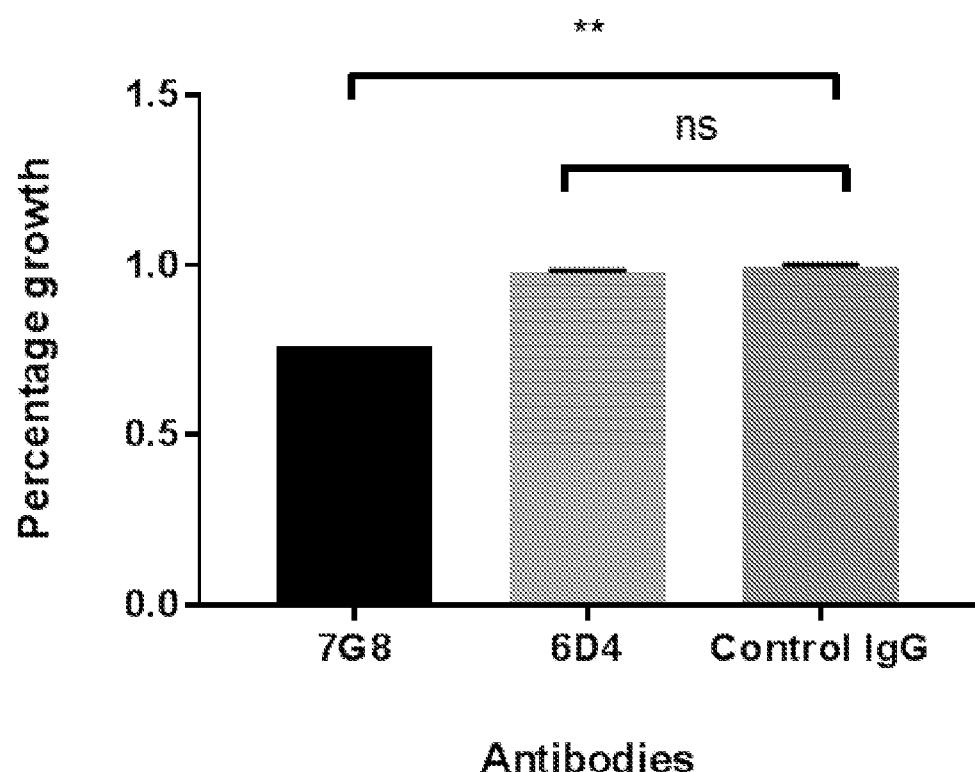


FIGURE 9

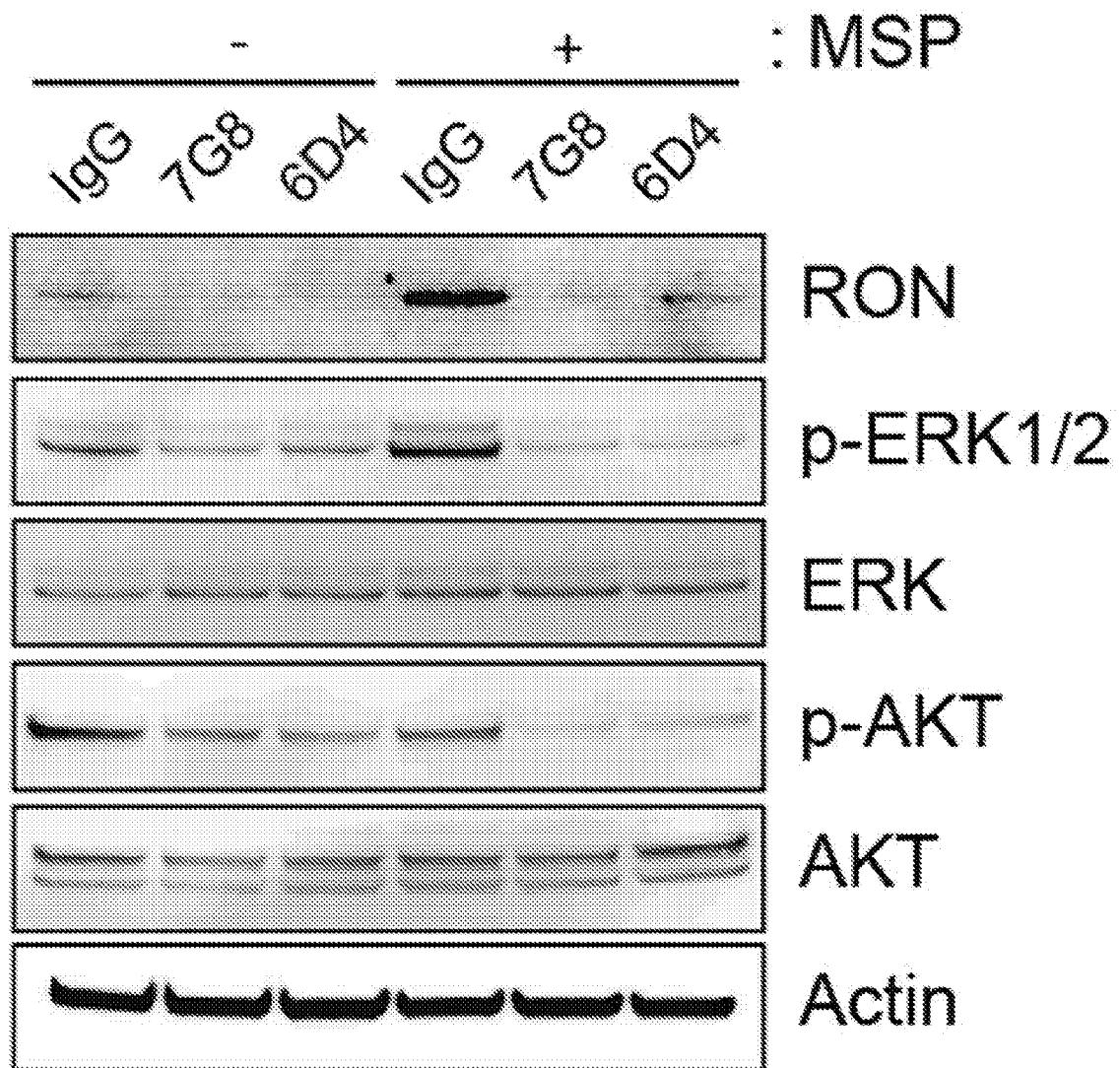


FIGURE 10

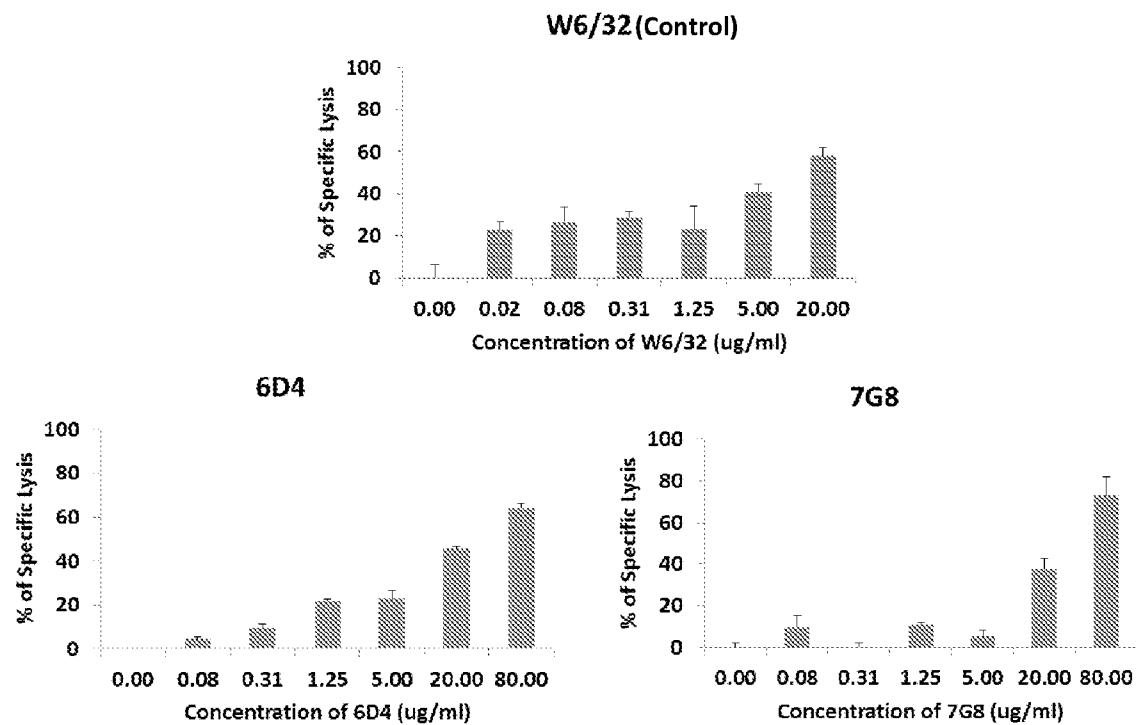


FIGURE 11

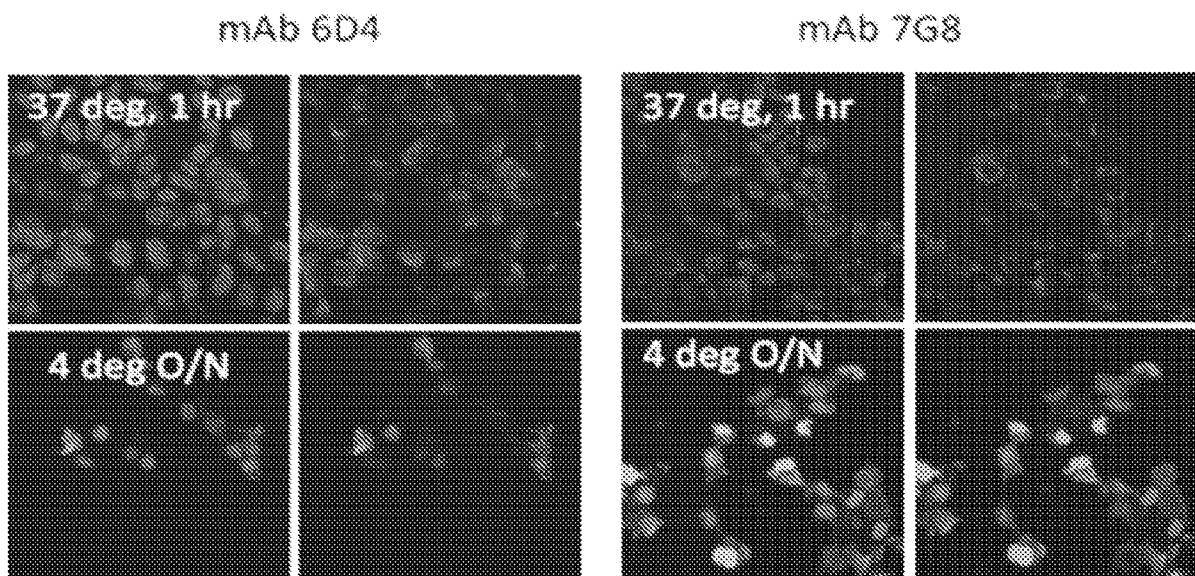


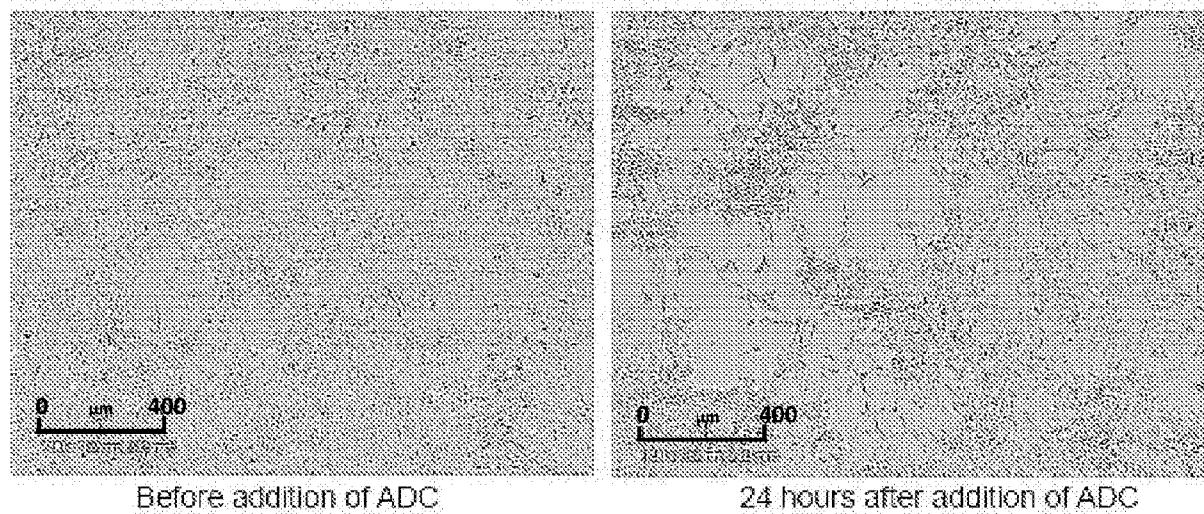
FIGURE 12

FIGURE 13A

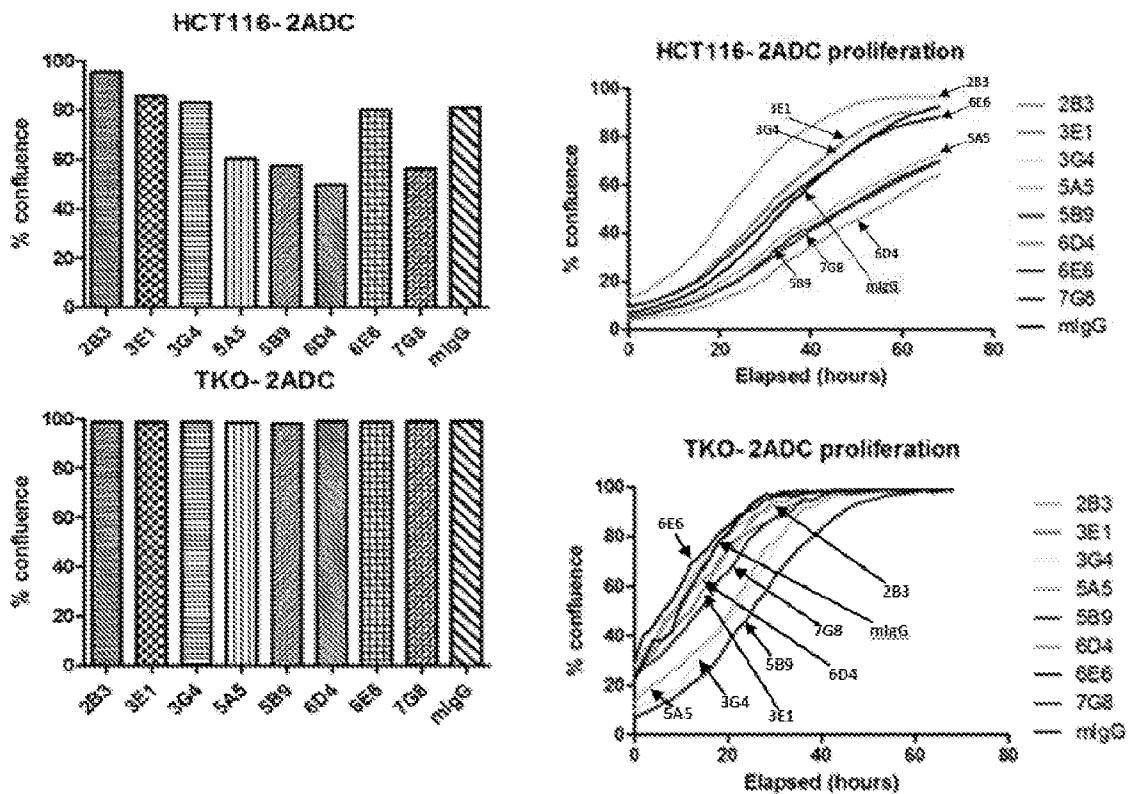


FIGURE 13B

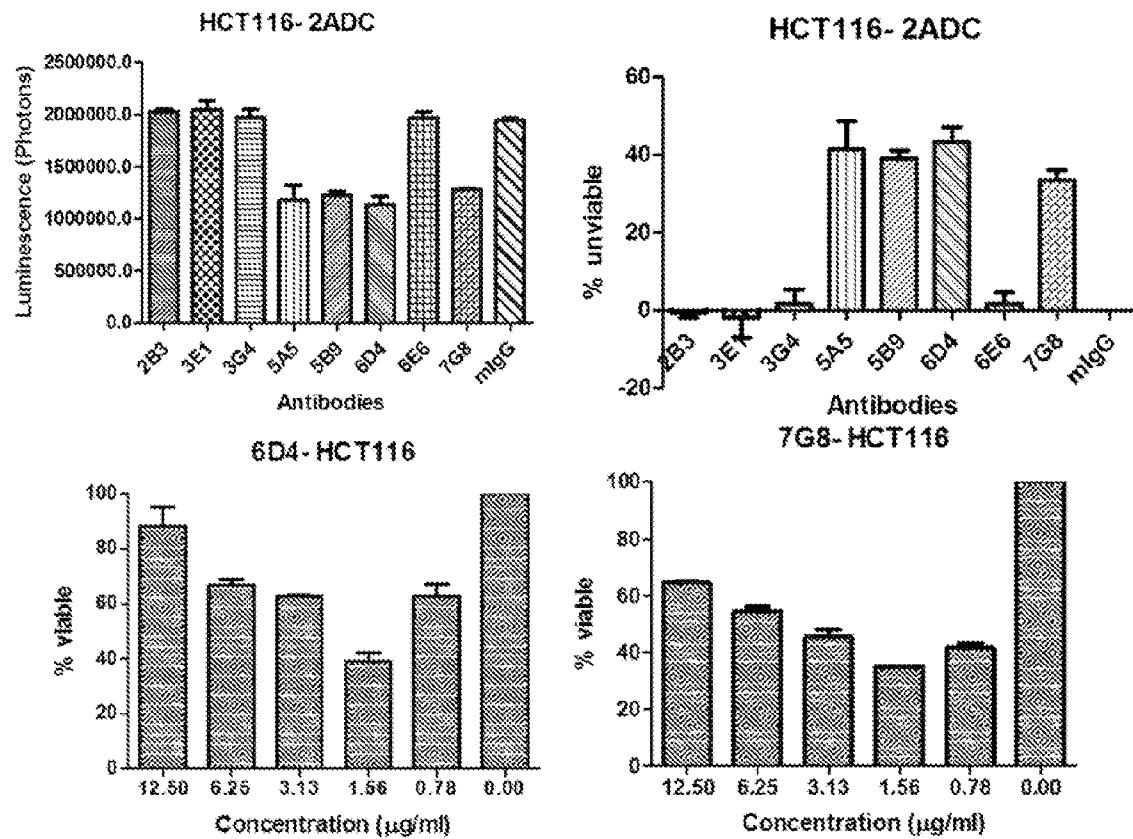


FIGURE 14**7G8 Heavy chain**

7G8H1 FR1 - IMGT
 1 5 10 15
 E V Q L E Q S G G G L V Q P
 gag gtg cag ctg gag cag tct ggg gga ... ggt tta gtg cag cct

7G8H1 20 25 30
 G G S L K L S C A A S G F T F
 gga ggg tcc ctg aaa ctc tcc tgt gca gcc tct gga ttc act ttc

7G8H1 CDR1 - IMGT 35 40 45
 N T Y T M S W V R Q T
 aat acc tat acc atg tct tgg gtt cgc cag act

7G8H1 FR2 - IMGT 50 55 60 CDR2
 P E K R L E W V A Y I S N G
 cca gag aag agg ctg gag tgg gtc gca tac att agt aat ggt ...

7G8H1 - IMGT 65 70 75
 G G S T Y Y P D T V K G R
 ... ggt ggt agt acc tac tat cca gac act gta aag ... ggc cga

7G8H1 FR3 - IMGT 80 85 90
 F T I S R D N A K N T L Y L Q
 ttc acc atc tcc aga gac aat gcc aag aac acc ctg tac ctg caa

7G8H1 95 100 104
 M S S L K S E D T A M Y Y C A
 atg agc agt ctg aag tct gag gac acg gcc atg tat tac tgt gca

7G8H1 CDR3 - IMGT
 R G Y R Y A A M D Y W G Q G T
 aga ggc tat agg tac gct gct atg gac tac tgg ggt caa gga acc

7G8H1 S V T V S S
 tca gtc acc gtc tcc tca

FIGURE 14 (CONTINUED)**Amino Acid Sequence in FASTA format (7G8H1)**

```
> 7G8H1
EVQLEQSGGGLVQPGGSLKLSCAASGFTFNTYTMWSVRQTPEKRLEWVAYISNGGGSTYYPDTVKGRF
TISRDNAKNTLYLQMSSLKSEDTAMYYCARGYRYAAMDYWGQGTSVTVSS
```

Nucleotide Sequence in FASTA format (7G8H1)

```
> 7G8H1
GAGGTGCAGCTGGAGCAGTCGGGGGAGGTTAGTGCAGCCTGGAGGGTCCCTGAAACTCTCCTGTGC
AGCCTCTGGATTCACTTCAATACTACCTATACCATGTCTGGGTTGCCAGACTCCAGAGAAGAGGCTGG
AGTGGGTCGCATACATTAGTAATGGTGGTGGTAGTACCTACTATCCAGACACTGTAAAGGGCCGATTC
ACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGGACAC
GGCCATGTATTACTGTGCAAGAGGCTATAGGTACGCTGCTATGGACTACTGGGTCAAGGAACCTCAG
TCACCGTCTCCTCA
```

Figure 15
7G8 Kappa chain (light chain)

7G8K

----- FR1 - IMGT -----
 1 5 10 15
 D I V M T Q T T A T L S V T P
 gat att gtg atg acc cag act aca gcc acc ctg tct gtg act cca

----->
 20 25 30
 G D G V S L S C R A S Q S I
 gga gat ggc gtc agt ctt tcc tgc agg gcc agc caa agt att ...

----- CDR1 - IMGT -----<
 35 40 45
 N N N L H W Y Q Q K
 aac aac aac cta cac tgg tat caa caa aaa

FR2 - IMGT -----> CDR2
 50 55 60
 S H E S P R L L I K F A
 tca cat gag tct cca aga ctt ctc atc aag ttt gct

- IMGT -----<
 65 70 75
 S Q S I S G I P S R
 tcc cag tcc atc tct ggg atc ccc ... tcc agg

----- FR3 - IMGT -----
 80 85 90
 F S G S G S G T D F T L S
 ttc agt ggc agt gga tca ggg aca gat ttc act ctc agt

----->
 95 100 104
 I N S V E T E D F G M Y F C Q Q S N S W P L T F G A G T K L E L K
 atc aac agt gtg gag act gaa gat ttt gga atg tat ttc tgt caa

----- CDR3 - IMGT -----
 105 110 115
 Q S N S W P L T F G A G T K L
 cag agt aac agc tgg cct ctc acg ttc ggt gct ggg acc aag ctg

7G8K

E L K
 gag ctg aaa c

Amino Acid Sequence in FASTA format (7G8K)

> 7G8K
 DIVMTQTTATLSVTPGDGVSLSRASQSINNNLHWYQQKSHESPRLLIKFASQSIISGIPSREFSGSGSG
 TDFTLSINSVETEDFGMYFCQQSNSWPPLTFGAGTKLELK

FIGURE 15 (CONTINUED)**Nucleotide Sequence in FASTA format (7G8K)**

> 7G8K
GATATTGTGATGACCCAGACTACAGCCACCCCTGTCTGTGACTCCAGGAGATGGCGTCAGTCTTCCTG
CAGGGCCAGCAAAGTATTAACAACAACCTACACTGGTATCAACAAAAATCACATGAGTCTCCAAGAC
TTCTCATCAAGTTGCTTCCCAGTCCATCTGGGATCCCCTCCAGGTTCAGTGGCAGTGGATCAGGG
ACAGATTCACTCTCAGTATCAACAGTGTGGAGACTGAAGATTTGGAATGTATTCTGTCAACAGAG
TAACAGCTGGCCTCTCACGTTGGTGCTGGGACCAAGCTGGAGCTGAAAC

FIGURE 16**6D4 Heavy chain**

<----- FR1 - IMGT ----->
 1 5 10 15
 E V Q L L E T G G G T V K P
 6D4H gaa gtg cag ctg ttg gag act ggg gga ... ggc tta gtg aag cct

-----> 20 25 30
 G G S L K L S C A A S G F T F
 6D4H gga ggg tcc ctg aaa ctc tcc tgt gca gcc tct gga ttc act ttc

— CDR1 - IMGT -----<-----
 35 40 45
 S N Y A M S W V R Q T
 6D4H agt aac tat gcc atg tct tgg gtt cgc cag act

FR2 - IMGT -----> CDR2
 50 55 60
 P E K R L E W G A S I S S G G T Y P D S V K G
 6D4H cca gag aag agg ctg gag tgg ggc gca tcc att agt agt ggt ...

- IMGT -----<----- 65 70 75
 G S T Y Y P D S V K G R
 6D4H ggt agc acc tac tat cca gac agt gtg aag ... ggc cga

----- FR3 - IMGT ----->
 80 85 90
 F T I S R D N A R R N I L Y L Q M S S L R S E D T A L Y Y C A R E G P L Y Y G P S Y G G Y Y F D Y W G Q G T T L V S S
 6D4H ttc acc atc tcc aga gat aat gcc agg aac atc ctg tac ctg caa

-----> 95 100 104
 M S S L R S E D T A L Y Y C A
 6D4H atg agc agt ctg agg tct gag gac acg gcc ctg tat tac tgt gca

CDR3 - IMGT -----<
 R E G P L Y Y G P S Y G G Y Y
 6D4H aga gag ggt ccc ctt tac tac ggt cct agc tac gga ggg tac tac

-----<
 F D Y W G Q G T T L T V S S
 6D4H ttt gac tac tgg ggc caa ggc acc act ctc aca gtc tcc tca

Amino Acid Sequence in FASTA format (6D4H)

>6D4H
 EVQLLETGGGLVKPGGSLKLSCAASGFTFSNYAMSWVRQTPEKRLEWGASISSGGSTYYPDSVKKG
 RFTISRDNARNILYLOMSSLRSEDTALYYCAREGPLYYGPSYGGYYFDYWGQGTTLTSS

FIGURE 16 (CONTINUED)**Nucleotide Sequence in FASTA format (6D4H)**

>6D4H
GAAGTGCAGCTGTTGGAGACTGGGGGAGGCTTAGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGTGC
AGCCTCTGGATTCACTTCAGTAACATGCCATGTCTGGGTTGCCAGACTCCAGAGAAAGAGGCTGG
AGTGGGGCGCATCCATTAGTAGTGGTAGCACCTACTATCCAGACAGTGTGAAGGGCCGATTCA
ATCTCCAGAGATAATGCCAGAACATCCTGTACCTGCAAATGAGCAGTCTGAGGTCTGAGGACACGGC
CCTGTATTACTGTGCAAGAGAGGGTCCCTTACTACGGTCTAGCTACGGAGGGTACTACTTGACT
ACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCA

FIGURE 17**6D4 Kappa (Light chain)**

<----- FR1 - IMGT ----->
 1 5 10 15
 6D4K D I V M T Q S P L S L P V S L
 gac att gtg atg aca cag tct cca ctc tcc ctg cct gtc agt ctt

----->
 20 25 30
 6D4K G D Q A S I S C R S S Q R L V
 gga gat caa gcc tcc atc tct tgc aga tct agt cag agg ctt gta

CDR1 - IMGT -----<
 35 40 45
 6D4K Y S N G N T Y L H W Y L Q K
 tac agt ... aat gga aac acc tat tta cat tgg tac ctg cag aag

FR2 - IMGT -----> CDR2
 50 55 60
 6D4K P G Q S P K L L I Y K V
 cca ggc cag tct cca aag ctc ctg atc tac aaa gtt

- IMGT -----<
 65 70 75
 6D4K S N R F S G V P D R
 tcc aac cga ttt tct ggg gtc cca ... gac agg

----- FR3 - IMGT ----->
 80 85 90
 6D4K F S G S G S G T D F T L K
 ttc agt ggc agt gga tca ggg aca gat ttc aca ctc aag

----->
 95 100 104
 6D4K I S R V E A E D L G V Y F C S
 atc agc aga gtg gag gct gag gat ctg gga gtt tat ttc tgc tct

CDR3 - IMGT -----
 104
 6D4K Q S T H V P W T F G G G T K L
 caa agt aca cat gtt ccg tgg acg ttc ggt gga ggc acc aag ctg

6D4K E I K
 gaa atc aaa c

Amino Acid Sequence in FASTA format (6D4K)

> 6D4K

FIGURE 17 (CONTINUED)

DIVMTQSPLSLPVSLGDQASISCRSSQRLVY SNGNTYLHWYLQKPGQSPKLLIYKVSNRSGVPDRES
GSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKEIK

Nucleotide Sequence in FASTA format (6D4K)

> 6D4K
GACATTGTGATGACACAGTCTCCACTCTCCCTGCCCTGTCAGTCTGGAGATCAAGCCTCCATCTCTTG
CAGATCTAGTCAGAGGCTTGTATACAGTAATGGAAACACCTATTTACATTGGTACCTGCAGAACGCCAG
GCCAGTCTCAAAGCTCCTGATCTACAAAGTTCCAACCGATTTCTGGGTCCCAGACAGGTTCACT
GGCAGTGGATCAGGGACAGATTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTA
TTTCTGCTCTCAAAGTACACATGTTCCGTGGACGTTGGAGGCACCAAGCTGGAAATCAAAC

FIGURE 18**3E1 Heavy chain**

<----- FR1 - IMGT
 1 5 10 15
 D V M L V E S G G G L V Q P G G S M K L S C V A S G E S F R 1 - I M G T
 3E1H gac gtg atg ctg gtg gag tct gga gga ... ggc ttg gtg caa cct

 -----> 20 25 30
 G G S M K L S C V A S G F S F
 3E1H gga gga tcc atg aaa ctc tcc tgt gtt gcc tct gga ttc agt ttc

 CDR1 - IMGT 35 40 45
 S D Y W M N W V R Q S
 3E1H agt gac tac tgg atg aac tgg gtc cgc cag tct

 FR2 - IMGT 50 55 60 CDR2
 P E K G L E W V A E I R L K S
 3E1H cca gag aag ggg ctt gaa tgg gtt gct gag att aga ttg aaa tct

 - IMGT 65 70 75
 S N Y A T H Y A E S V K G R
 3E1H agt aat tat gca aca cat tat gcg gag tct gtg aaa ... ggg agg

 ----- FR3 - IMGT 80 85 90
 F T I S R D D S E S S V Y L Q
 3E1H ttt acc atc tca aga gat gat tcc gaa agt agt gtc tac ctg caa

 -----> 95 100 104
 M N N L R P E D T G F Y Y C T
 3E1H atg aac aac tta aga cct gaa gac act ggc ttt tat tac tgt acc

 CDR3 - IMGT

 R G D Y W G Q G T S V T V S S
 3E1H agg ggg gac tat tgg ggt caa gga acc tca gtc acc gtc tct tca

Amino Acid Sequence in FASTA format (3E1H)

> 3E1H
 DVMLVESGGGLVQPGGSMKLSCVASGEFSFSDYWMNWRQSPEKGLEWVAEIRLKSSNYATHYAES
 VKGRFTISRDDSESSVYLQMNRLRPEDTGFYYCTRGDYWGQGTSVTVSS

Nucleotide Sequence in FASTA format (3E1H)

> 3E1H
 GACGTGATGCTGGTGGAGTCTGGAGGAGGCTTGGTGCAACCTGGAGGATCCATGAAACTCTCCTG
 TGTTGCCTCTGGATTCAAGTTCACTGACTACTGGATGAACCTGGTCCGCCAGTCTCCAGAGAAGG
 GGCTTGAATGGGTTGCTGAGATTAGATTGAAATCTAGTAATTATGCAACACATTATGCGGAGTCT

FIGURE 18 (CONTINUED)

GTGAAAGGGAGGTTACCATCTCAAGAGATGATTCCGAAAGTAGTGTCTACCTGCAAATGAACAACTT
AAGACCTGAAGACACTGGCTTTATTACTGTACCAGGGGGACTATTGGGTCAAGGAACCTCAGTCA
CCGTCTCTTCA

FIGURE 19**3E1Kappa chain (light chain)**

<----- FR1 - IMGT ----->
 1 5 10 15
 D I V M T Q S P A T L S V T P A
 3E1K gat att gtg atg acc cag tct cca gcc acc ctg tct gtg act cca

 ----->
 20 25 30
 G D G V S L S C R A S Q S I
 3E1K gga gat ggc gtc agt ctt tcc tgc agg gcc agc caa agt att ...

— CDR1 - IMGT ————— <-----
 35 40 45
 N N N L H W Y Q Q K
 3E1K aac aac aac cta cac tgg tat caa caa aaa

FR2 - IMGT -----> CDR2
 50 55 60
 S H E S P R L L I K F A
 3E1K tca cat gag tct cca aga ctt ctc atc aag ttt gct

- IMGT ————— <-----
 65 70 75
 S Q S I S G I P S R
 3E1K tcc cag tcc atc tct ggg atc ccc ... tcc agg

----- FR3 - IMGT ----->
 80 85 90
 F S G S G S G T D F T L S
 3E1K ttc agt ggc agt gga tca ggg aca gat ttc act ctc agt

----->
 95 100 104
 I N S V E T E D F G M Y F C Q
 3E1K atc aac agt gtg gag act gaa gat ttt gga atg tat ttc tgt caa

— CDR3 - IMGT —————
 Q S N S W P L T F G A G T K L
 3E1K cag agt aac agc tgg cct ctc acg ttc ggt gct ggg acc aag ctg

E L K
 3E1K gag ctg aaa c

Amino Acid Sequence in FASTA format (3E1K)

> 3E1K
 DIVMTQSPATLSVTPGDGVSLSCRASQSINNNLHWYQQKSHESPRLLIKFASQSISGIPSREFGS
 GSGTDFTLSINSVETEDFGMYFCQQNSWPLTFGAGTKLELK

Nucleotide Sequence in FASTA format (3E1K)

> 3E1K

FIGURE 19 (CONTINUED)

GATATTGTGATGACCCAGTCTCCAGCCACCCTGTCTGTGACTCCAGGAGATGGCGTCAGTCTTC
CTGCAGGGCCAGCCAAAGTATTAACAACAACCTACACTGGTATCAACAAAAATCACATGAGTCTC
CAAGACTTCTCATCAAGTTGCTTCCCAGTCCATCTCTGGGATCCCTCCAGGTTAGTGGCAGT
GGATCAGGGACAGATTCACTCTCAGTATCAACAGTGTGGAGACTGAAGAGATTTGGAATGTATTT
CTGTCAACAGAGTAACAGCTGGCCTCTCACGTTGGTGTGGACCAAGCTGGAGCTGAAAC

FIGURE 20**3G4 Heavy chain**

3G4H <----- F R 1 - I M G T -
 1 5 10
 E V Q L E E S G T V L
 GAA GTG CAG CTG GAG GAG TCA GGG ACT ... GTG CTG

3G4H ----->
 15 20 25
 A R P G A S V K M S C K A S
 GCA AGG CCT GGG GCT TCA GTG AAG ATG TCC TGC AAG GCT TCT

3G4H CDR1 - IMGT
 30 35
 G Y I F T S Y W
 GGC TAC ATT TTT ACC AGC TAC TGG
 <----- F R 2 - I M G T
 40 45 50
 M H W I K Q R P G Q G L E W
 ATG CAC TGG ATA AAA CAG AGG CCT GGA CAG GGT CTG GAA TGG

3G4H -----> CDR2 - IMGT
 55 60
 I G A I Y P G N S D T
 ATT GGC GCT ATT TAT CCT GGA AAT AGT GAT ACT
 <-----
 65 70 75
 S T N Q K F K D K A K L
 AGT ACT AAT CAG AAG TTC AAG ... GAC AAG GCC AAA CTG

3G4H ----- F R 3 - I M G T -----
 80 85 90
 T A V T S T S T A Y L E
 ACT GCA GTC ACA TCC ACC AGC ACT GCC TAT TTG GAA
 ----->

3G4H 95 100
 L S S L T N E D S A V F Y C
 CTC AGC AGC CTG ACA AAT GAG GAC TCA GCG GTC TTT TAC TGT

3G4H CDR3 - IMGT <-----
 105 109 113 115
 T R D G Y Y P F A Y W G
 ACA AGA GAT GGT TAC TAC CCG TTT GCT TAC TGG GGC

3G4H FR4 - IMGT ----->
 120 125
 Q G T L V T V S A
 CAA GGG ACT CTG GTC ACT GTC TCT GCA

Amino Acid Sequence in FASTA format (3G4H)

```
> 3G4H
EVQLEESGTVLARPGASVKMSCKASGYIFTSYWMHWIKQRPGQGLEWIGAIYPGNSDTSTNQKFKDKA
KLTAVTSTSTAYLELSSLTNEDSAVFYCTRDGYYPFAYWGQGTLTVSA
```

Nucleotide Sequence in FASTA format (3G4H)

```
> 3G4H
GAAGTCAGCTGGAGGAGTCAGGGACTGTGCTGGCAAGGCCTGGGCTTCAGTGAAGATGTCCTGCAA
GGCTTCTGGCTACATTTTACCAAGCTACTGGATGCAGCTGGATAAAACAGAGGCCTGGACAGGGTCTGG
AATGGATTGGCGCTATTATCTGGAAATAGTGATACTAGTACTAATCAGAAGTTCAAGGACAAGGCC
AAACTGACTGCAGTCACATCCACCAGCACTGCCTATTGGAACTCAGCAGCCTGACAAATGAGGACTC
AGCGGTCTTTACTGTACAAGAGATGGTTACTACCGTTGCTTACTGGGCCAAGGGACTCTGGTCA
CTGTCTCTGCA
```

FIGURE 21**3G4 Kappa chain (light chain)**

<----- FR1 - IMGT ----->
 1 5 10 15
 3G4K D I V L T Q S P L S L P V S L
 gac att gtg ctg acc caa tct cca ctc tcc ctg cct gtc agt ctt

 ----->
 20 25 30
 3G4K G D Q A S I S C R S S Q S L V
 gga gat caa gcc tcc atc tct tgc aga tct agt cag agc ctt gta

 ----- CDR1 - IMGT -----<
 35 40 45
 3G4K Y I N G D T Y F H W Y L Q K
 tat att ... aat gga gac acc tat ttt cat tgg tac ttg cag aag

 FR2 - IMGT -----> CDR2
 50 55 60
 3G4K P G Q S P K L L I Y R V
 cca ggc cag tct cca aag ctc ctg atc tac aga gtt

 - IMGT -----<
 65 70 75
 3G4K S N R F S G V P D R
 tcc aac cga ttt tct ggg gtc cca ... gac agg

 ----- FR3 - IMGT ----->
 80 85 90
 3G4K F S G S G S G T D F T L K
 ttc agt ggc agt gga tca ggg aca gat ttc aca ctc aag

 ----->
 95 100 104 ----->
 3G4K I S R V E A E D L G V Y F C S
 atc agc aga gtg gag gct gag gat ctg gga gtt tat ttc tgc tct

 ----- CDR3 - IMGT ----->
 3G4K Q T K H V P Y T F G G G T K L
 caa act aaa cat gtt ccg tac acg ttc gga ggg ggg acc aag ctg

 3G4K E M K
 gaa atg aaa cg

Amino Acid Sequence in FASTA format (3G4K)

> 3G4K

FIGURE 21 (CONTINUED)

DIVLTQSPLSLPVSLGDQASISCRSSQLVYINGDTYFHWYLQKPGQSPKLLIYRVSNRSGVPDRES
GSGSGTDFTLKISRVEAEDLGVYFCSQTKHVPYTGGGTLEMKR

Nucleotide Sequence in FASTA format (3G4K)

> 3G4K
GACATTGTGCTGACCCAATCTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAAGCCTCC
ATCTCTTGAGATCTAGTCAGAGCCTGTATATATTAAATGGAGACACCTATTTCTATTGGT
ACTTGCAGAACGCCAGGCCAGTCTCAAAGCTCCTGATCTACAGAGTTCCAACCGATT
CTGGGGTCCCAGACAGGTTAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATC
AGCAGAGTGGAGGGCTGAGGATCTGGAGTTATTCTGCTCTCAAACATGTTCCG
TACACGTTCGGAGGGGGGACCAAGCTGGAAATGAAACG

FIGURE 22**5B9 Heavy chain**

5B9H FR1 - IMGT
 1 E V Q L Q Q P G A 10 E L V R P
 gag gtc cag ctg cag cag cct ggg gct ... gag ctg gtg agg cct
 20 G S S V K I S C K A S G Y E F
 ggg tcc tca gtg aag att tcc tgc aag gct tct ggc tat gaa ttc
 35 S K Y W M N W V K Q R
 5B9H agt aag tac tgg atg aac tgg gtg aag cag agg
 50 P G Q G L E W I G Q I F P G
 5B9H cct gga cag ggt ctt gag tgg att gga cag att ttt cca gga ...
 65 D G D I N Y N G K F K G K
 5B9H ... gac ggt gat att aat tac aat gga aaa ttc aag ... ggt aaa
 80 A T L T A D K S S S T A Y M Q
 5B9H gcc aca ctg act gca gac aaa tcc tcc agc aca gcc tac atg cag
 95 L S S L T S E E S A V Y F C A
 5B9H ctc agc agc cta aca tct gag gaa tct gcg gtc tat ttc tgt gca
 100 CDR3 - IMGT
 104 R W Y Y G S N Y A M D Y W G Q
 5B9H aga tgg tac tac ggt agt aac tat gct atg gac tac tgg ggt caa
 5B9H G T S V T V S S
 gga acc tca gtc acc gtc tcc tca

Amino Acid Sequence in FASTA format (5B9H)

> 5B9H

FIGURE 22 (CONTINUED)

EVQLQQPGAEELVRPGSSVKISCKASGYEFSKYWMNWVKQRPGQGLEWIGQIFPGDGDINYNGKFKGKA
TLTADKSSSTAYMQLSSLTSEESAVYFCARWYYGSNYAMDYWGQGTSVTVSS

Nucleotide Sequence in FASTA format (5B9H)

> 5B9H
GAGGTCCAGCTGCAGCAGCCTGGGGCTGAGCTGGTGAGGCCTGGGTCTCAGTGAAGATTCTGCAA
GGCTTCTGGCTATGAATTCAAGTACTGGATGAACCTGGTGAAAGCAGAGGCCTGGACAGGGCTTG
AGTGGATTGGACAGATTTCAGGAGACGGTGATATTACAATGGAAAATTCAAGGGTAAAGCC
ACACTGACTGCAGACAAATCTCCAGCACAGCCTACATGCAGCTCAGCAGCCTAACATCTGAGGAATC
TGCAGCTATTCTGTGCAAGATGGTACTACGGTAGTAACATGCTATGGACTACTGGGTCAAGGAA
CCTCAGTCACCGTCTCCTCA

FIGURE 23**5B9 Kappa chain (light chain)**

<----- FR1 - IMGT
 1 5 10 15
 D I V M T Q T P S S L A V S V
 5B9K gac att gtg atg acc cag act cca tcc tcc cta gct gtg tca gtt

-----> 20 25 30
 G E K I T M S C K S S Q S L L
 5B9K gga gag aag att act atg agc tgc aag tcc agt cag agc ctt tta

CDR1 - IMGT 35 40 45
 Y S S N Q K N Y L A W Y Q Q K
 5B9K tat agt agc aat caa aag aac tac ttg gcc tgg tac cag cag aaa

FR2 - IMGT 50 55 60 CDR2
 P G Q S P K L L I Y W A
 5B9K cca ggg cag tct cct aaa ctg ctg att tac tgg gca

- IMGT 65 70 75
 S T R E S G V P D R
 5B9K tcc act agg gaa tct ggg gtc cct ... gat cgc

----- FR3 - IMGT 80 85 90
 F T G S G S G T D F T L T
 5B9K ttc aca ggc agt gga tct ggg aca gat ttc act ctc acc

-----> 95 100 104
 I S S V K A E D L A V Y Y C Q
 5B9K atc agc agt gtg aag gct gaa gac ctg gca gtt tat tac tgt cag

CDR3 - IMGT
 Q Y Y A Y R T F G G G T K L E
 5B9K caa tat tat gcc tat cgg acg ttc ggt gga ggc acc aag ctg gaa

I K
 5B9K atc aaa c

Amino Acid Sequence in FASTA format (5B9K)

> 5B9K

FIGURE 23 (CONTINUED)

DIVMTQTPSSLAVSVGEKITMSCKSSQSLYSSNQKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVKAEDLAVYYCQQYYAYRTFGGGTKLEIK

Nucleotide Sequence in FASTA format (5B9K)

>5B9K

GACATTGTGATGACCCAGACTCCATCCTCCCTAGCTGTGTCAGTTGGAGAGAAGATTACTATGAGCTGCAAGTCCAGTCAGAGCCTTTATATAGTAGCAATCAAAAGAACTACTTGGCCTGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTGCTGATTACTGGGCATCCACTAGGGAATCTGGGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTCACTCTCACCATCAGCAGTGTGAAGGCTGAAGACCTGGCAGTTATTACTGTCAAGCAATATTATGCCTATCGGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAAC

FIGURE 24**6E6 Heavy chain**

<----- FR1 - IMGT ----->
 1 5 10 15
 E V K L Q Q S G T V L A R P
 6E6H gag gtt aag ctg cag cag tct ggg act ... gtg ctg gca agg cct

----->
 20 25 30
 G T S V K M S C K A S G Y I F
 6E6H ggg act tca gtc aag atg tct tgc aag gct tct ggc tac att ttt

CDR1 - IMGT -----<----- 45
 35 40
 T S Y W M H W I K E R
 6E6H acc agc tac tgg atg cat tgg ata aaa gag agg

FR2 - IMGT -----> CDR2
 50 55 60
 P G Q G L E W I G A I Y P G
 6E6H cct gga cag ggt ctg gaa tgg att ggc gct att tat cct gga ...

- IMGT -----<----- 75
 65 70
 N N D T S T N Q K F K G K
 6E6H ... aat aat gat act agt act aat cag aag ttc aag ... ggc aag

----- FR3 - IMGT ----->
 80 85 90
 A K L T A V T S T S T A Y L E
 6E6H gcc aaa ctg act gca gtc aca tcc acc agc act gcc tat ttg gaa

----->
 95 100 104
 L S S L T N E D S A V Y Y C T
 6E6H ctc agc agc ctg aca aat gag gac tca gcg gtc tat tac tgt aca

CDR3 - IMGT -----
 R D G F Y P F A Y W G Q G T L
 6E6H aga gat ggt ttt tac ccg ttt gct tac tgg ggc caa ggg act ctg

6E6H V T V S A
 gtc act gtc tct gca

Amino Acid Sequence in FASTA format (6E6H)

FIGURE 24 (CONTINUED)

>6E6H
EVKLQQSGTQLARPQTSVKMSCKASGYIFTSYWMHWIKERPGQGLEWIGAIYPGNNDTSTNQKFKGKA
KLTAVTSTSTAYLELSSLTNEDSAVYYCTRDGFYPFAYWGQGTLVTVSA

Nucleotide Sequence in FASTA format (6E6H)

>6E6H
GAGGTAAAGCTGCAGCAGTCAGTCTGGACTGTGCTGGCAAGGCCTGGACTTCAGTGAAGATGTCTGCAA
GGCTTCTGGCTACATTTACCAGCTACTGGATGCATTGGATAAAAGAGAGGCCTGGACAGGGTCTGG
AATGGATTGGCGCTATTATCCTGGAAATAATGATACTAGTACTAATCAGAAGTTCAAGGGCAAGGCC
AAACTGACTGCAGTCACATCCACCAGCACTGCCTATTGGAACTCAGCAGCCTGACAAATGAGGACTC
AGCGGTCTATTACTGTACAAGAGATGGTTTACCGTTGCTTACTGGGCCAAGGGACTCTGGTCA
CTGTCTTGCA

FIGURE 25**6E6 Kappa chain (light chain)**

6E6K FR1 - IMGT
 1 D I V L T Q T P L S L P V S L
 gat att gtg ctg acc cag act cca ctc tcc ctg cct gtc agt ctt

6E6K 20 25 30
 G D Q A S I S C R S S Q S L V
 gga gat caa gcc tcc atc tct tgc aga tct agt cag agc ctt gta

6E6K CDR1 - IMGT 35 40 45
 Y I N G D T Y F H W Y L Q K
 tat att ... aat gga gac acc tat ttt cat tgg tac ctc cag aag

6E6K FR2 - IMGT 50 55 60 CDR2
 P G Q S P K L L I Y R V
 cca ggc cag tct cca aag ctc ctc atc tac aga gtt

6E6K - IMGT 65 70 75
 S N R F S G V P D R
 tcc aac cga ttt tct ggg gtc cca ... gac agg

6E6K FR3 - IMGT 80 85 90
 F S G S G S G T D F T L K
 ttc agt ggc agt gga tca ggg aca gat ttc aca ctc aag

FIGURE 25 (CONTINUED)

----->

				95				100			104				
6E6K	I	S	R	V	E	A	E	D	L	G	V	Y	F	C	S
	atc	agc	aga	gtg	gag	gct	gag	gat	ctg	gga	gtt	tat	ttc	tgc	tct

CDR3 - IMGT

6E6K	Q	T	K	H	V	P	Y	T	F	G	G	G	T	K	L
	caa	act	aaa	cat	gtt	ccg	tac	acg	ttc	gga	ggg	ggg	acc	aag	ctg
6E6K	E	M	K												
	gaa	atg	aaa	cg											

Amino Acid Sequence in FASTA format (6E6K)

> 6E6K

DIVLTQTPLSLPVSLGDQASISCRSSQSLVYINGDTYFHWYLQKPGQSPKLLIYRVSNRFSGVPDRFS
GSGSGTDFTLKISRVEAEDLGVYFCSQTKHVPYTFGGGTLEMKR

Nucleotide Sequence in FASTA format (6E6K)

>6E6K

GATATTGTGCTGACCCAGACTCCACTCTCCCTGCCTGTCAGTCAGTCTTGGAGATCAAGCCTCCATCTC
TTGCAGATCTAGTCAGAGCCTTGTATATATTAAATGGAGACACCTATTTCATGGTACCTGCAGA
AGCCAGGCCAGTCTCAAAGCTCCTGATCTACAGAGTTCCAACCGATTTCTGGGTCCAGAC
AGGTTCAGTGGCAGTGGATCAGGGACAGATTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGA
TCTGGGAGTTATTCTGCTCTCAAACATAACATGTTCCGTACACGTTGGAGGGGGACCAAGC
TGGAAATGAAACG

FIGURE 26**2F1 Heavy chain**

<----- FR1 - IMGT ----->
 1 5 10 15
 Q V Q L K E S G A E L V K P
 2F1H cag gtg cag ctg aag gag tca ggg gct ... gaa ctg gtg aaa cct

 ----->
 20 25 30
 G T S V K L S C K A S G Y T F
 2F1H ggg act tca gtg aag ttg tcc tgc aag gct tct ggc tac acc ttc

 CDR1 - IMGT -----<
 35 40 45
 T S Y Y M Y W L K Q R
 2F1H acc agc tac tat atg tac tgg ttg aag cag agg

 FR2 - IMGT -----> CDR2
 50 55 60
 P G Q G L E W I G G I N P T
 2F1H cct gga caa ggc ctt gag tgg att ggg ggg att aat cct acc ...

 - IMGT -----<
 65 70 75
 T G G T D F N E N F K N K
 2F1H ... act ggt ggt act gac ttc aat gag aac ttc aag ... aac aag

 ----- FR3 - IMGT ----->
 80 85 90
 A T L T L A T S S T A Y I Q
 2F1H gcc aca ctg act ttg gcc aca tcc tcc agc aca gcc tac ata caa

 ----->
 95 100 104
 L S S L T S E D S A V Y F C A
 2F1H ctc agc agc ctg aca tct gag gac tct gcg gtc tat ttc tgt gca

 CDR3 - IMGT -----<
 R M G R D A M D Y W G Q G T S
 2F1H aga atg gga cg gat gct atg gac tac tgg ggt caa gga acc tca

 2F1H V T V S S
 gtc acc gtc tcc tca

Amino Acid Sequence in FASTA format (2F1H)

> 2F1H

FIGURE 26 (CONTINUED)

QVQLKESGAELVKPGTSVKLSCKASGYFTSYYMYWLKQRPGQGLEWIGGINPTTGGTDFNENFKNKA
TLTLATSSSTAYIQLSSLTSEDSAVYFCARMGRDAMDYWGQGTSVTVSS

Nucleotide Sequence in FASTA format (2F1H)

> 2F1H
CAGGTGCAGCTGAAGGAGTCAGGGCTGAACCTGGTGAACACTGGGACTTCAGTGAAGTTGTCCTGCAA
GGCTTCTGGCTACACCTCACAGCTACTATATGTACTGGTTGAAGCAGAGGCCTGGACAAGGCCTTG
AGTGGATTGGGGGATTAATCCTACCACTGGTGGTACTGACTTCATGAGAACCTCAAGAACACAAGGCC
ACACTGACTTTGGCCACATCCTCCAGCACAGCCTACATACAACTCAGCAGCCTGACATCTGAGGACTC
TGCAGGTCTATTCTGTGCAAGAATGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCA
CCGTCTCCTCA

FIGURE 27**2F1 Kappa (light chain)**

<----- FR1 - IMGT ----->
 1 5 10 15
 D I V L T Q S P A S L A V S L G Q R A T I S Y R A S K S V S T S G Y S Y M H W N Q Q K P G Q P P R L L I Y L V S N L E S G V P A R F S G
 2F1K gac att gtg ctg aca cag tct cct gct tcc tta gct gta tct ctg

 ----->
 20 25 30
 G Q R A T I S Y R A S K S V S
 2F1K ggg cag agg gcc acc atc tca tac agg gcc agc aaa agt gtc agt

 CDR1 - IMGT -----<
 35 40 45
 T S G Y S Y M H W N Q Q K
 2F1K aca tct ggc tat agt tat atg cac tgg aac caa cag aaa

 FR2 - IMGT -----> CDR2
 50 55 60
 P G Q P P R L L I Y L V
 2F1K cca gga cag cca ccc aga ctc ctc atc tat ctt gta

 - IMGT -----<
 65 70 75
 S N L E S G V P A R
 2F1K tcc aac cta gaa tct ggg gtc cct ... gcc agg

 ----- FR3 - IMGT ----->
 80 85 90
 F S G S G S G T D F T L N
 2F1K ttc agt ggc agt ggg tct ggg aca gac ttc acc ctc aac

 ----->
 95 100 104
 I H P V E E D A A T Y Y C Q
 2F1K atc cat cct gtg gag gag gat gct gca acc tat tac tgt cag

 CDR3 - IMGT -----
 H I R E L T R S E G G P S W K
 2F1K cac att agg gag ctt aca cgt tcg gag ggg gga cca agc tgg aaa

Amino Acid Sequence in FASTA format (2F1K)

```
> 2F1K
DIVLTQSPASLAVSLGQRATISYRASKSVSTSGYSYMHWNQQKPGQPPRLLIYLVSNLESGVPARFSG
SGSGTDFTLNIHPVEEDAATYYCQHIRELTRSEGGPSWK
```

Nucleotide Sequence in FASTA format (2F1K)

FIGURE 27 (CONTINUED)

> 2F1K
GACATTGTGCTGACACAGTCTCCTGCTTCCTTAGCTGTATCTCTGGGGCAGAGGGCCACCATCTCATA
CAGGGCCAGCAAAAGTGTCAAGTACATCTGGCTATAGTTATATGCACTGGAACCAACAGAAACCAGGAC
AGCCACCCAGACTCCTCATCTATCTTGATCCAACCTAGAATCTGGGGTCCCTGCCAGGTCAGTGGC
AGTGGGTCTGGGACAGACTTCACCCTAACATCCATCCTGTGGAGGAGGAGGATGCTGCAACCTATT
CTGTCAGCACATTAGGGAGCTTACACGTTGGAGGGGGACCAAGCTGGAAA

FIGURE 28**1D2 Heavy Chain**

1D2H FR1 - IMGT
 1 5 10 15
 E V Q L Q Q S G S E L V K P
 gag gtt cag ctg cag cag tct ggg tct ... gaa ctg gtg aaa cct

1D2H 20 25 30
 G A S V K L S C K A S G Y I F 30
 ggg gct tca gtg aag ttg tcc tgc aag gct tct ggc tac atc ttc

1D2H CDR1 - IMGT 35 40 45
 T S Y Y M Y W V K Q R
 acc agc tac tat atg tac tgg gtg aag cag agg

1D2H FR2 - IMGT 50 55 60 CDR2
 P G Q G L E W I G G I N P I
 cct gga caa ggc ctt gag tgg att ggg ggg att aat cct atc ...

1D2H - IMGT 65 70 75
 T G G T D F N E K F K N K
 ... act ggt ggt act gac ttc aat gag aag ttc aag ... aac aag

1D2H FR3 - IMGT 80 85 90
 A T L T L A T S S T A Y I H N
 gcc aca ctg act ctg gcc aca tcc tcc agc aca gcc tac ata cat

1D2H 95 100 104
 L S S L T S E D S A V Y F C A
 ctc agc agc ctg aca tct gag gac tct gcg gtc tat ttc tgt gca

1D2H CDR3 - IMGT
 R M G R D A M D Y W G Q G T S
 aga atg gga cgg gat gct atg gac tac tgg ggt caa gga acc tca

1D2H V T V S
 gtc acc gtc tcc

Amino Acid Sequence in FASTA format (1D2H)

> 1D2H
 EVQLQQSGSELVKPGASVKLSCKASGYIFTSYMYWVKQRPGQGLEWIGGINPITGGTDFNEKFKN
 KATLTLATSSSTAYIHLSSLTSEDSAVYFCARMGRDAMDYWGQGTSVTVS

FIGURE 28 (CONTINUED)**Nucleotide Sequence in FASTA format (1D2H)**

```
> 1D2H
GAGGTTCAGCTGCAGCAGTCAGTCTGGGTCTGAACCTGGGTGAAACCTGGGGCTTCAGTGAAGTTGTCCTGCAA
GGCTTCTGGCTACATCTCACCCAGCTACTATATGTACTGGGTGAAGCAGAGGCCTGGACAAGGCCTTG
AGTGGATTGGGGGGATTAATCCTATCCTACTGGTGGTACTGACTTCAATGAGAAGTTCAAGAACAGGCC
ACACTGACTCTGGCCACATCTCCAGCACAGCCTACATACATCTCAGCAGCCTGACATCTGAGGACTC
TGCAGGTCTATTCTGTGCAAGAATGGGACGGGATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCA
CCGTCTCC
```

FIGURE 29A**2B3 Heavy Chain**

<----- FR1 - IMGT ----->
 1 5 10 15
 2B3H Q V Q L K Q S G S E L V K P
 cag gtg cag ctg aag cag tca ggg tct ... gaa ctg gtg aaa cct

----->
 20 25 30
 2B3H G A S V K L S C K A S G Y I F
 ggg gct tca gtg aag ttg tcc tgc aag gct tct ggc tac atc ttc

CDR1 - IMGT -----<-----
 35 40 45
 2B3H T S Y Y M Y W V K Q R
 acc agc tac tat atg tac tgg gtg aag cag agg

FR2 - IMGT -----> CDR2
 50 55 60
 2B3H P G Q G L E W I G G I N P R I
 cct gga caa ggc ctt gag tgg att ggg ggg att aat cct atc ...

- IMGT -----<-----
 65 70 75
 2B3H T G G T D F N E K F K D K
 ... act ggt ggt act gac ttc aat gag aag ttc aag ... gac aag

-----> FR3 - IMGT ----->
 80 85 90
 2B3H A T L T L A A S S S T A Y I Q
 gcc aca ctg act ctg gcc gca tcc tcc agc aca gcc tac ata caa

----->
 95 100 104
 2B3H L S S L T S E D S A V Y F C A
 ctc agc agc ctg aca tct gag gac tct gcg gtc tat ttc tgt gca

CDR3 - IMGT ----->
 2B3H R M G R D A M D Y W G Q T S
 aga atg gga cgg gat gct atg gac tac tgg ggt caa gga acc tca

2B3H V T V S
 gtc acc gtc tcc tc

Amino Acid Sequence in FASTA format (2B3H)

> 2B3H
 QVQLKQSGSELVKPGASVKLSCKASGYIFTSYYMYWVKQRPGQGLEWIGGINPITGGTDFNEKFKDKA
 TLTLAASSSTAYIQLSSLTSEDSAVYFCARMGRDAMDYWGQGTSVTVSS

Nucleotide Sequence in FASTA format (2B3H)

> 2B3H

FIGURE 29A (CONTINUED)

CAGGTGCAGCTGAAGCAGTCAGGGTCTGAACCTGGTGAACACCTGGGGCTTCAGTGAAGTTGTCCTGCAA
GGCTTCTGGCTACATCTCACCGCTACTATATGTACTGGGTGAAGCAGAGGCCTGGACAAGGCCTTG
AGTGGATTGGGGGATTAATCCTATCACTGGTGGTACTGACTTCAATGAGAAGTTCAAGGACAAGGCC
ACACTGACTCTGGCCGCATCCTCCAGCACAGCCTACATACAACTCAGCAGCCTGACATCTGAGGACTC
TGCAGTCTATTTCTGTGCAAGAATGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCA
CCGTCTCCTC

Figure 29B

2B3 Kappa Chain

1 F R 1 - I M G T -
 5 D I V L T Q S P A S L A
 10 GAC ATT GTG CTG ACA CAG TCT CCT GCT TCC TTA GCT
 15 V S L G Q R A T I S Y R A S
 20 GCA TCT CTG GGG CAG AGG GCC ACC ATC TCA TAC AGG GCC AGC
 25 CDR1 - IMGT <-----
 30 K S V S T S G Y S Y
 35 AAA AGT GTC AGT ACA TCT GGC TAT AGT TAT
 40 M H W N Q Q K P G Q P P R L
 45 ATG CAC TGG AAC CAA CAG AAA CCA GGA CAG CCA CCC AGA CTC
 50 CDR2 - IMGT <-----
 55 L I Y L V S
 60 CTC ATC TAT CTT GTA TCC
 65 N L E S G V P A R F S G
 70 AAC CTA GAA TCT GGG GTC CCT ... GCC AGG TTC AGT GGC
 75 F R 3 - I M G T -
 80 S G S G T D F T L N
 85 AGT GGG TCT GGG ACA GAC TTC ACC CTC AAC
 90 CDR3 - IMGT <-----
 95 I H P V E E E D A A T Y Y C
 100 ATC CAT CCT GTG GAG GAG GAG GAT GCT GCA ACC TAT TAC TGT
 105 Q H I R E L Y T F G G G G
 114 CAG CAC ATT AGG GAG CTT TAC ACG TTC GGA GGG GGG ACC
 120 FR4 - IMGT ----->
 125 T K L E I K
 AAG CTG GAA ATA AAA

FIGURE 29B (CONTINUED)**Amino Acid Sequence in FASTA format (2B3)**

```
> 2B3
DIVLTQSPASLAVSLGQRATISYRASKSVSTSGYSYMHWNQQKPGQPPRLLIYLVSNLESGVPARFSGSGSGTDF
TLNIHPVEEDAATYYCQHIRELYTFGGTKLEIK
```

Nucleotide Sequence in FASTA format (2B3)

```
> 2B3
GACATTGTGCTGACACAGTCTCTGCTTCCTTAGCTGTATCTCTGGGGCAGAGGGCCACCATCTCATACAGGGCC
AGCAAAAGTGTCACTACATCTGGCTATAGTTATATGCACTGGAACCAACAGAAAACCAGGACAGCCACCCAGACTC
CTCATCTATCTTGTATCCAACCTAGAATCTGGGGTCCCTGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTC
ACCCTCAACATCCATCCTGTGGAGGAGGATGCTGCAACCTATTACTGTCAAGCACATTAGGGAGCTTACACG
TTCGGAGGGGGGACCAAGCTGGAAATAAAC
```

FIGURE 30

1B9 Heavy chain

1B9H FR1 - IMGT
 1 5 10 15
 E V Q L Q Q S G A E L V K P
 gag gtt cag ctg cag cag tct ggg gct ... gaa ctg gtg aaa cct

1B9H 20 25 30
 G T S V K L S C K A S G Y T F
 ggg act tca gtg aag ttg tcc tgc aag gct tct ggc tac acc ttc

1B9H CDR1 - IMGT 35 40 45
 acc agc tac tat atg tac tgg ttg aag cag agg

1B9H FR2 - IMGT 50 55 60 CDR2
 P G Q G L E W I G G I N P T
 cct gga caa ggc ctt gag tgg att ggg ggg att aat cct acc ...

1B9H - IMGT 65 70 75
 T G G T D F N E N F K N K
 ... act ggt ggt act gac ttc aat gag aac ttc aag ... aac aag

1B9H FR3 - IMGT 80 85 90
 A T L T L A T S S S T A Y I Q
 gcc aca ctg act ttg gcc aca tcc tcc agc aca gcc tac ata caa

1B9H 95 100 104
 L S S L T S E D S A V Y F C A
 ctc agc agc ctg aca tct gag gac tct gcg gtc tat ttc tgt gca

1B9H CDR3 - IMGT
 R M G R D A M D Y W G Q G T S
 aga atg gga cgg gat gct atg gac tac tgg ggt caa gga acc tca

1B9H V T V S S
 gtc acc gtc tcc tca

Amino Acid Sequence in FASTA format (1B9H)

> 1B9H

FIGURE 30 (CONTINUED)

EVQLQQSGAELVKPGTSVKLSCKASGYFTSYYMYWLQRPQGLEWIGGINPTTGGTDFNENFKNKA
TLTLATSSSTAYIQLSSLTSEDSAVYFCARMGRDAMDYWGQGTSVTVSS

Nucleotide Sequence in FASTA format (1B9H)

> 1B9H
GAGGTTCAGCTGCAGCAGTCAGTCTGGGCTGAACCTGGTAAACCTGGGACTTCAGTGAAGTTGCCTGCAA
GGCTTCTGGCTACACCTCACCAAGCTACTATATGTACTGGTTGAAGCAGAGGCCTGGACAAGGCCTTG
AGTGGATTGGGGGATTAATCCTACCACTGGTGGTACTGACTTCATGAGAACCTCAAGAACACAAGGCC
ACACTGACTTTGGCCACATCCTCCAGCACAGCCTACATACAACTCAGCAGCCTGACATCTGAGGACTC
TGCAGGCTATTTCTGTGCAAGAATGGGACGGGATGCTATGGACTACTGGGTCAAGGAACCTCAGTCA
CCGTCTCCTCA

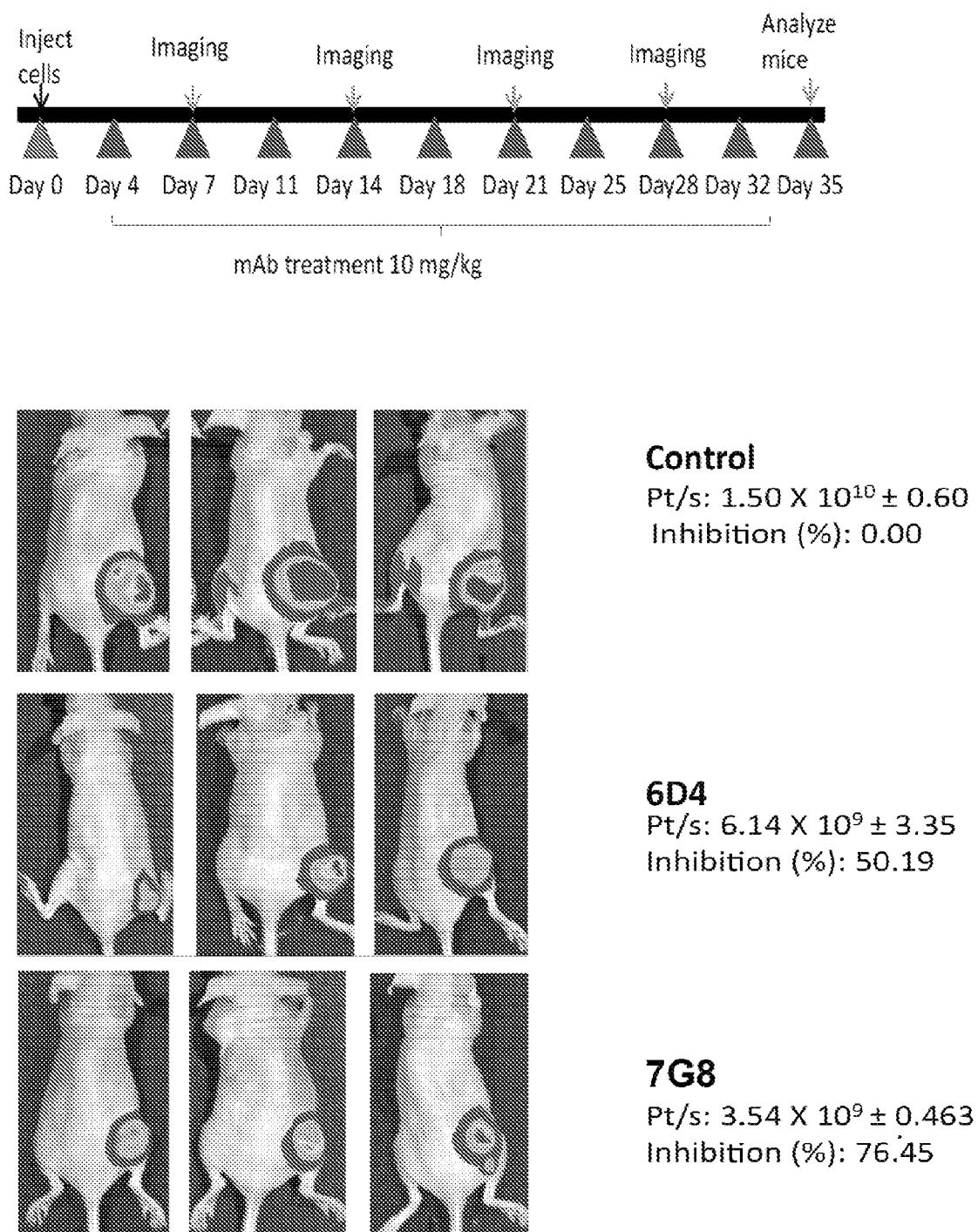
FIGURE 31A

FIGURE 31B

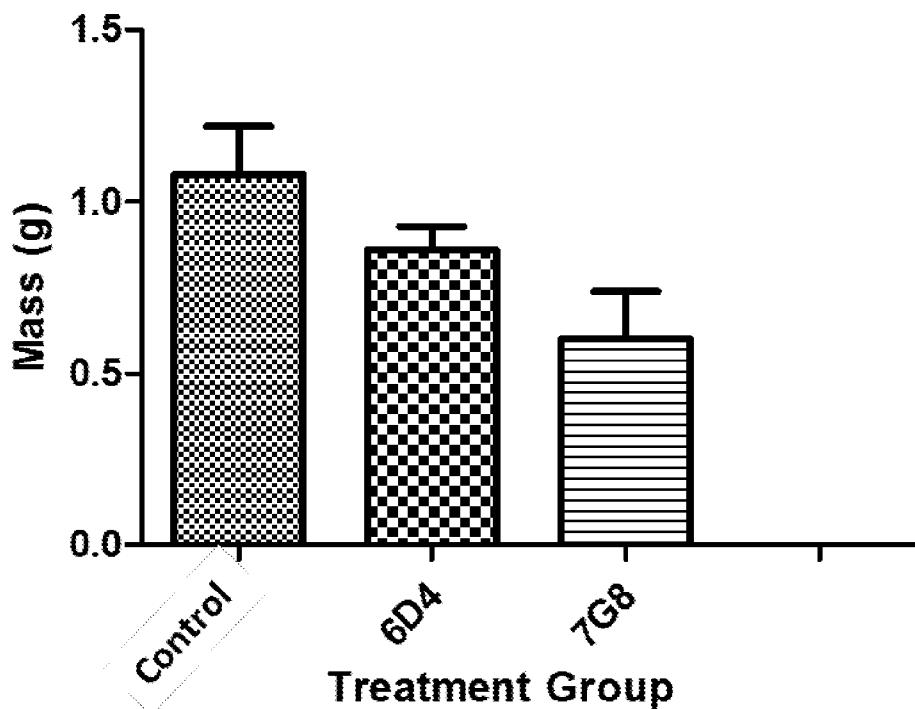
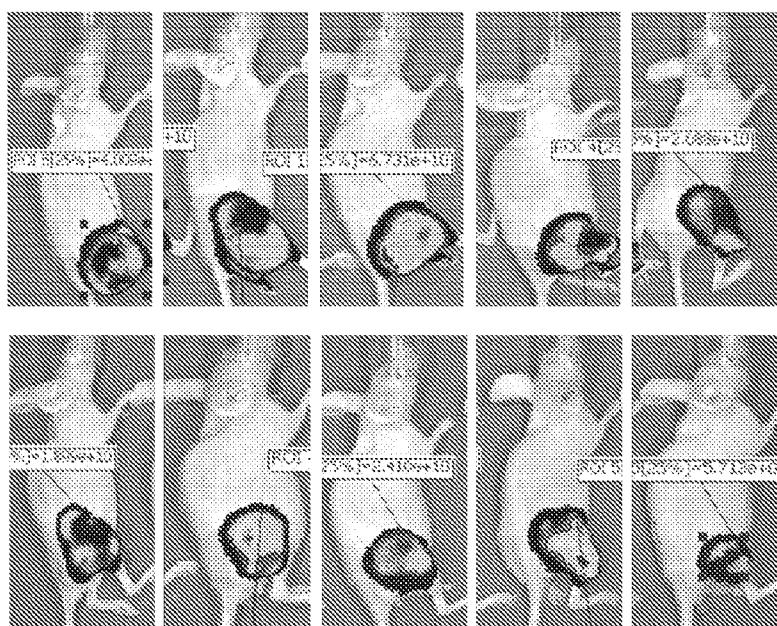


FIGURE 31C



Pt/s: $4.380E+10 \pm 1.53E+10$
Inhibition (%): 0.00

Pt/s: $2.4043E+10 \pm 1.26E+10$
Inhibition (%): 45.0

FIGURE 32

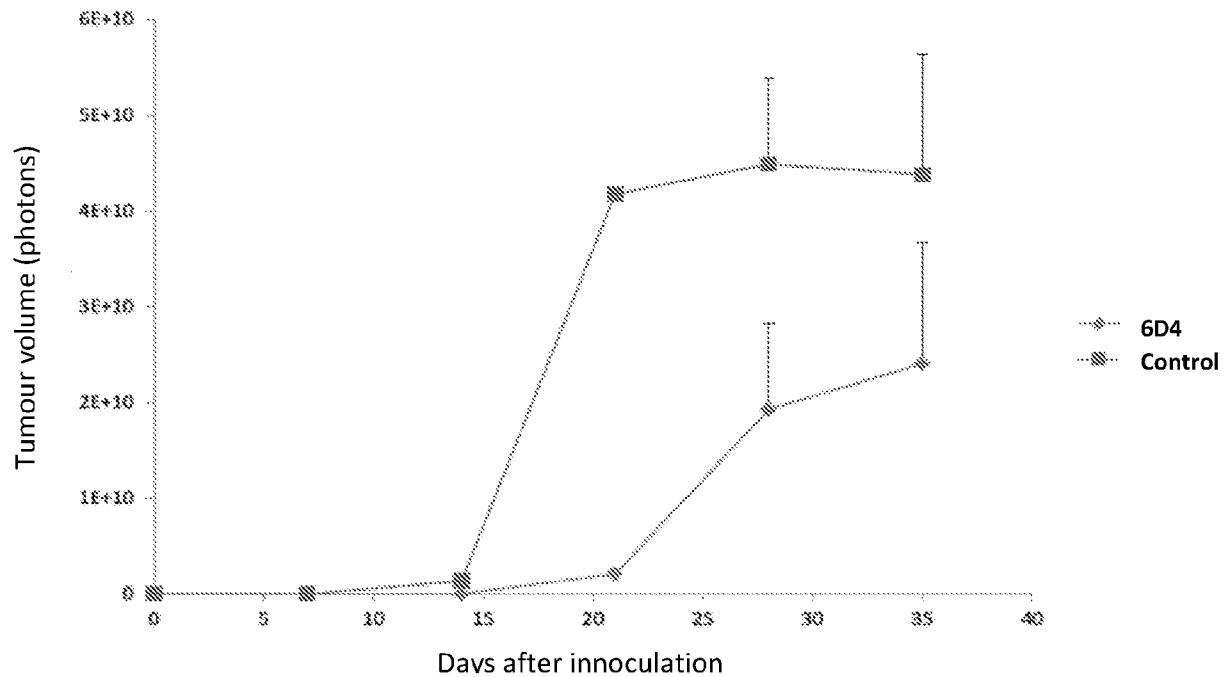


FIGURE 33

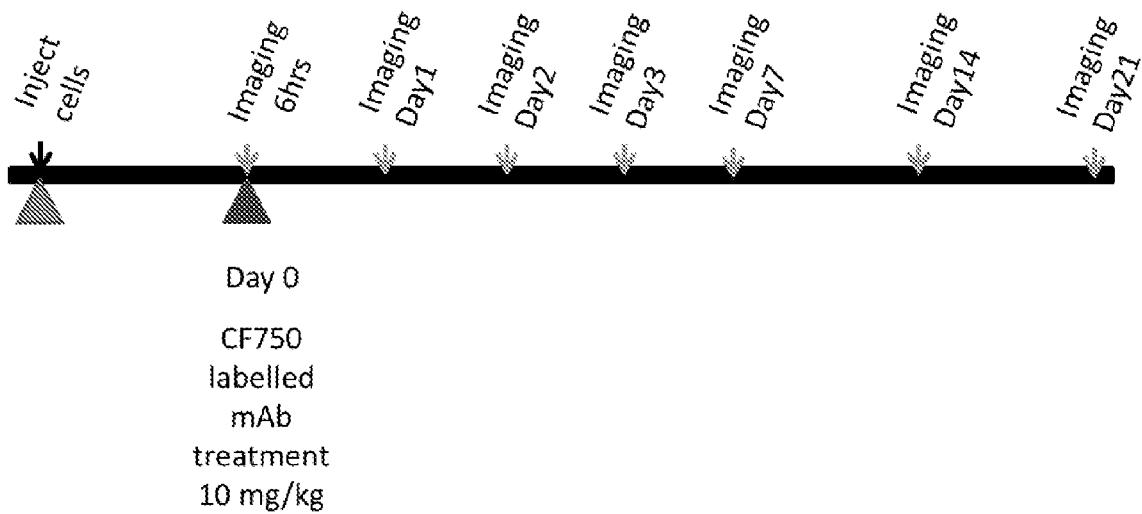


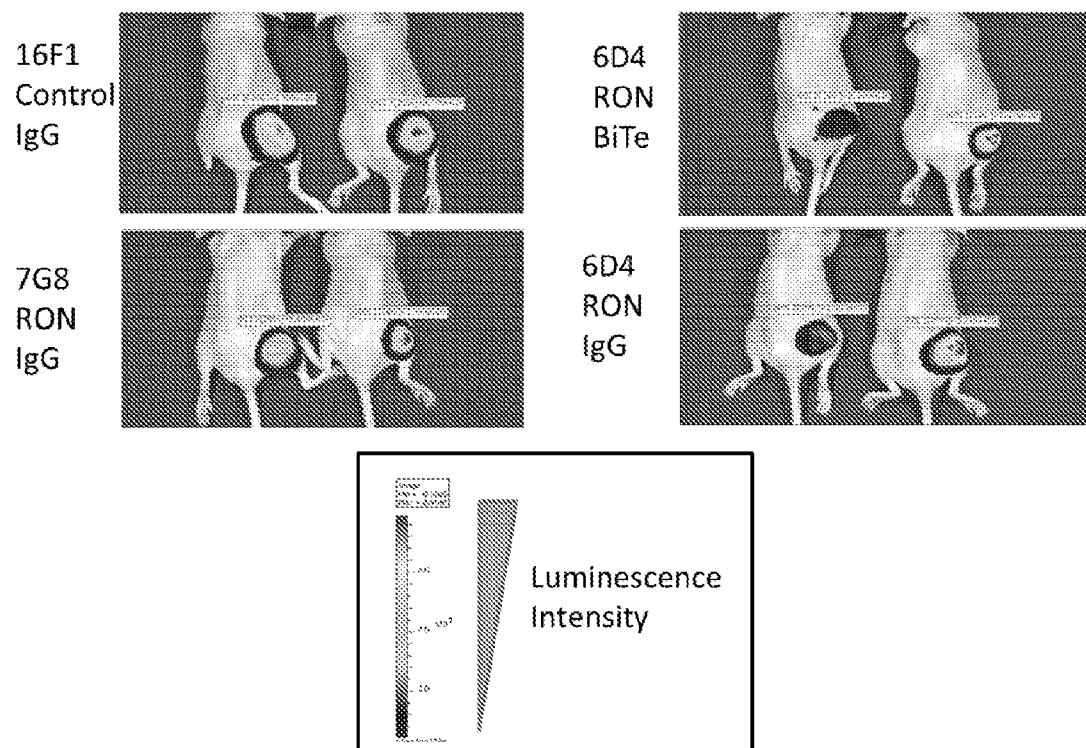
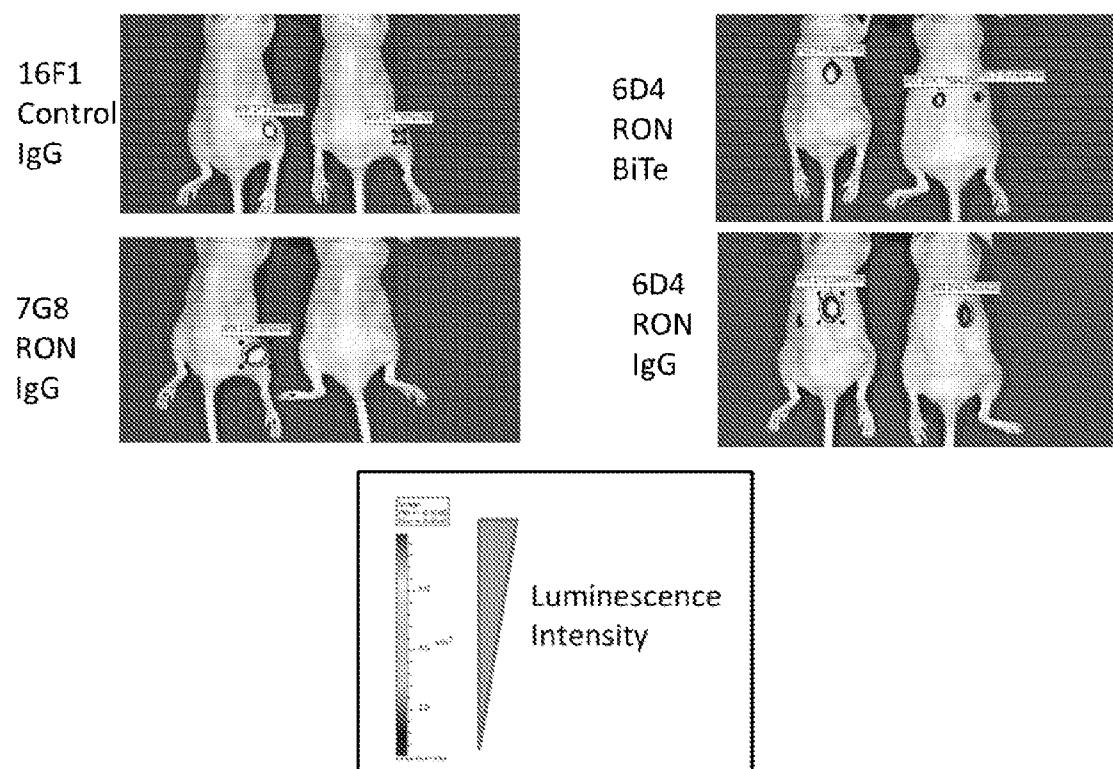
FIGURE 34**FIGURE 35**

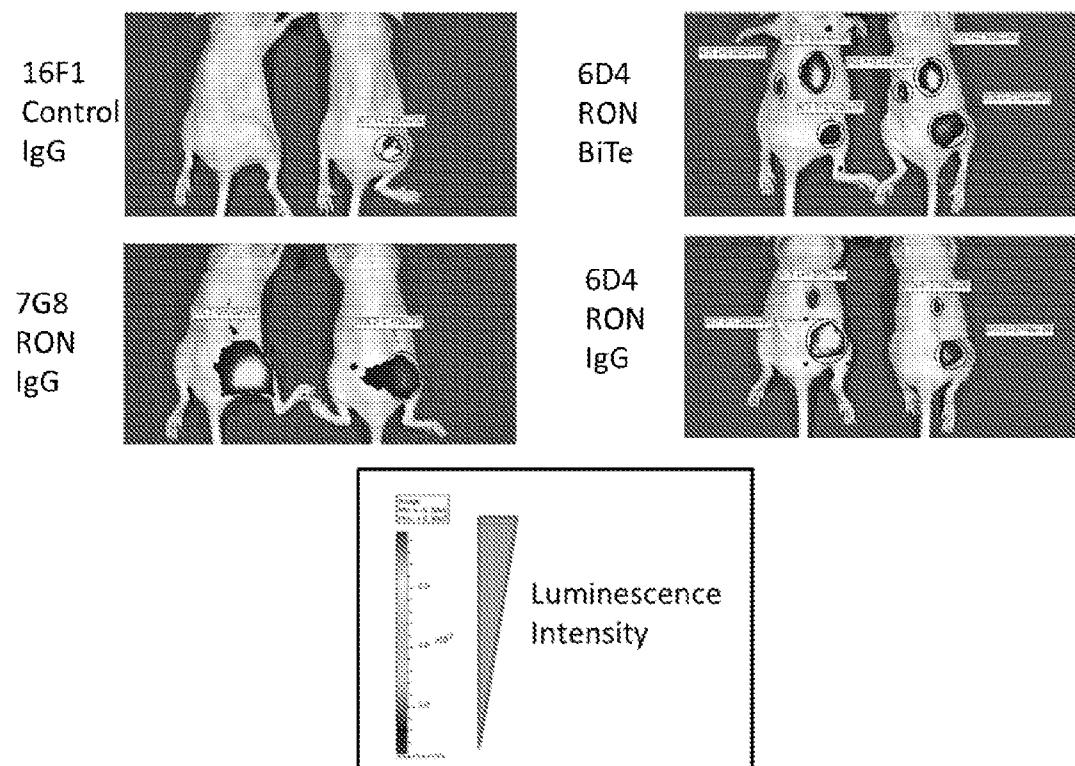
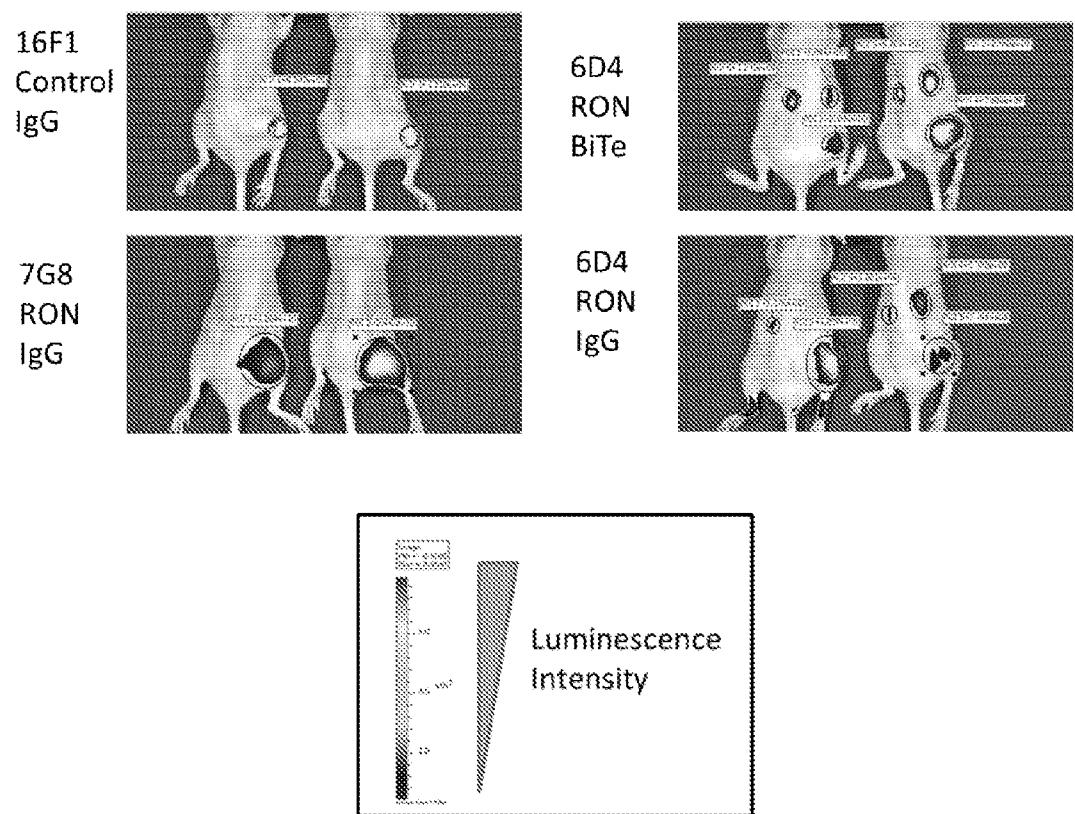
FIGURE 36**FIGURE 37**

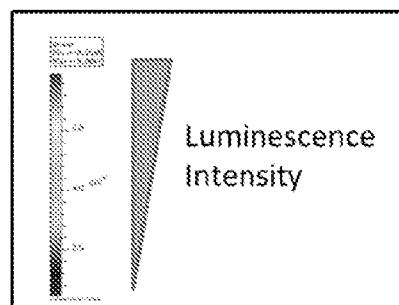
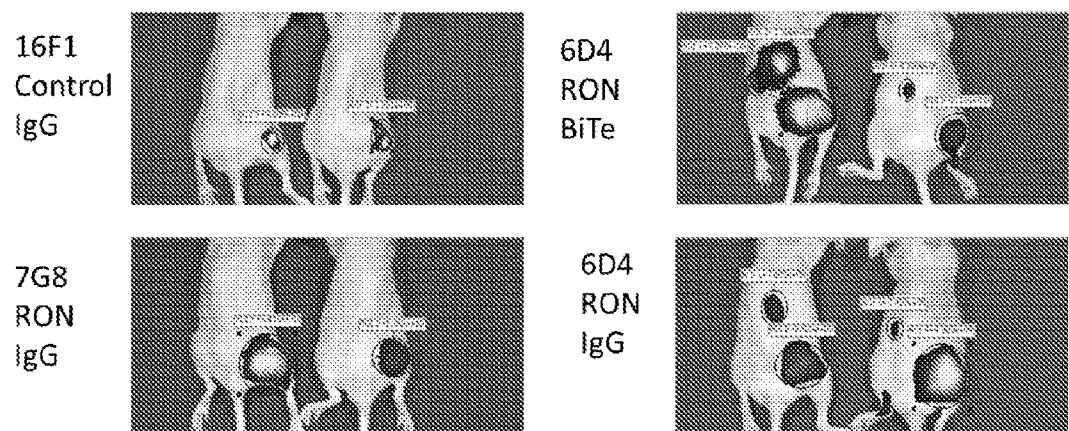
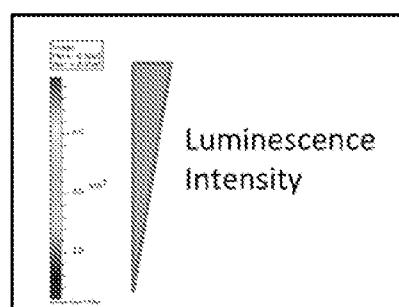
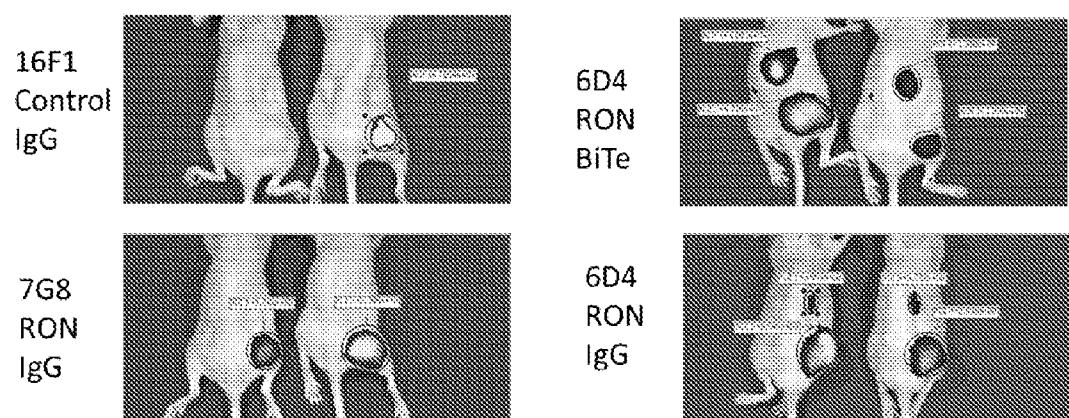
FIGURE 38**FIGURE 39**

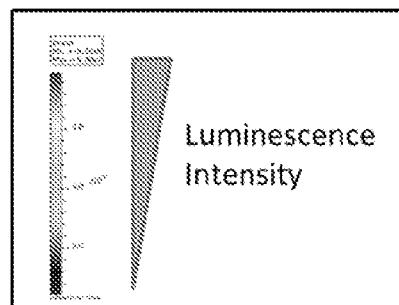
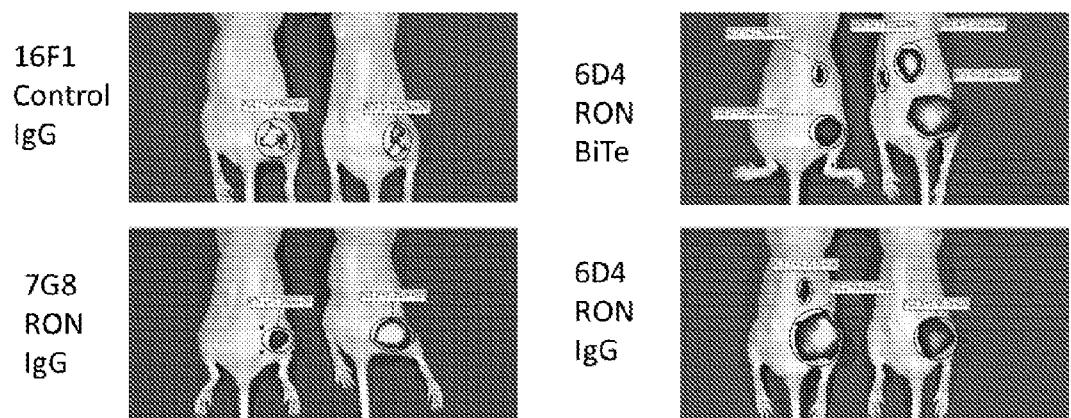
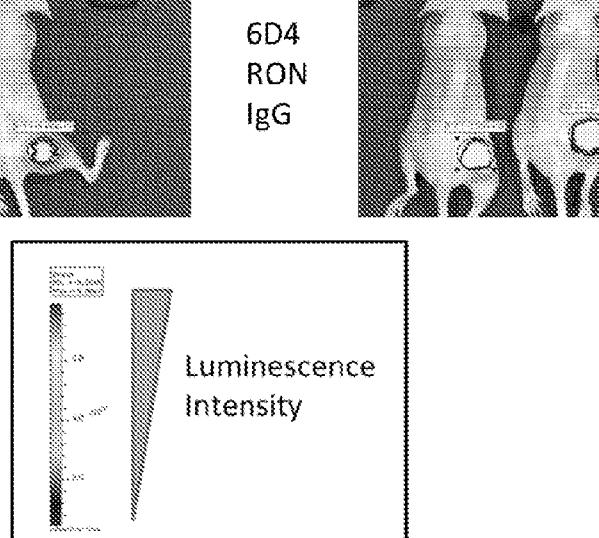
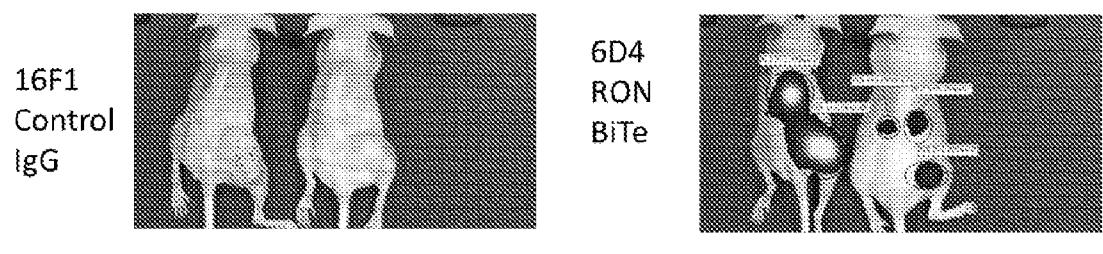
FIGURE 40**FIGURE 41**

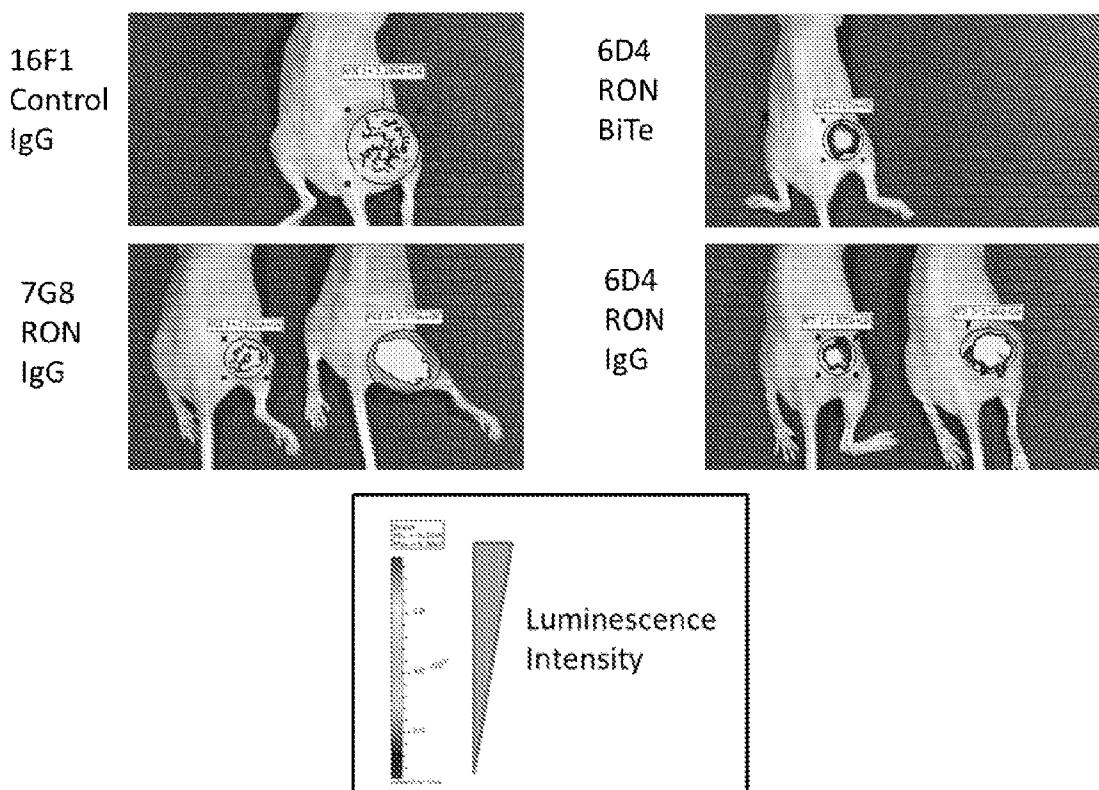
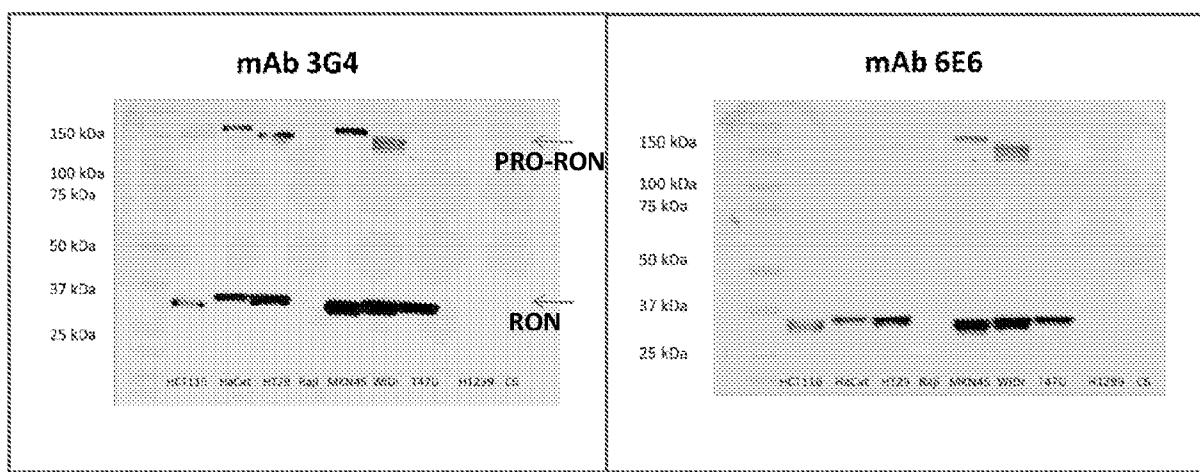
FIGURE 42**FIGURE 43**

FIGURE 44A

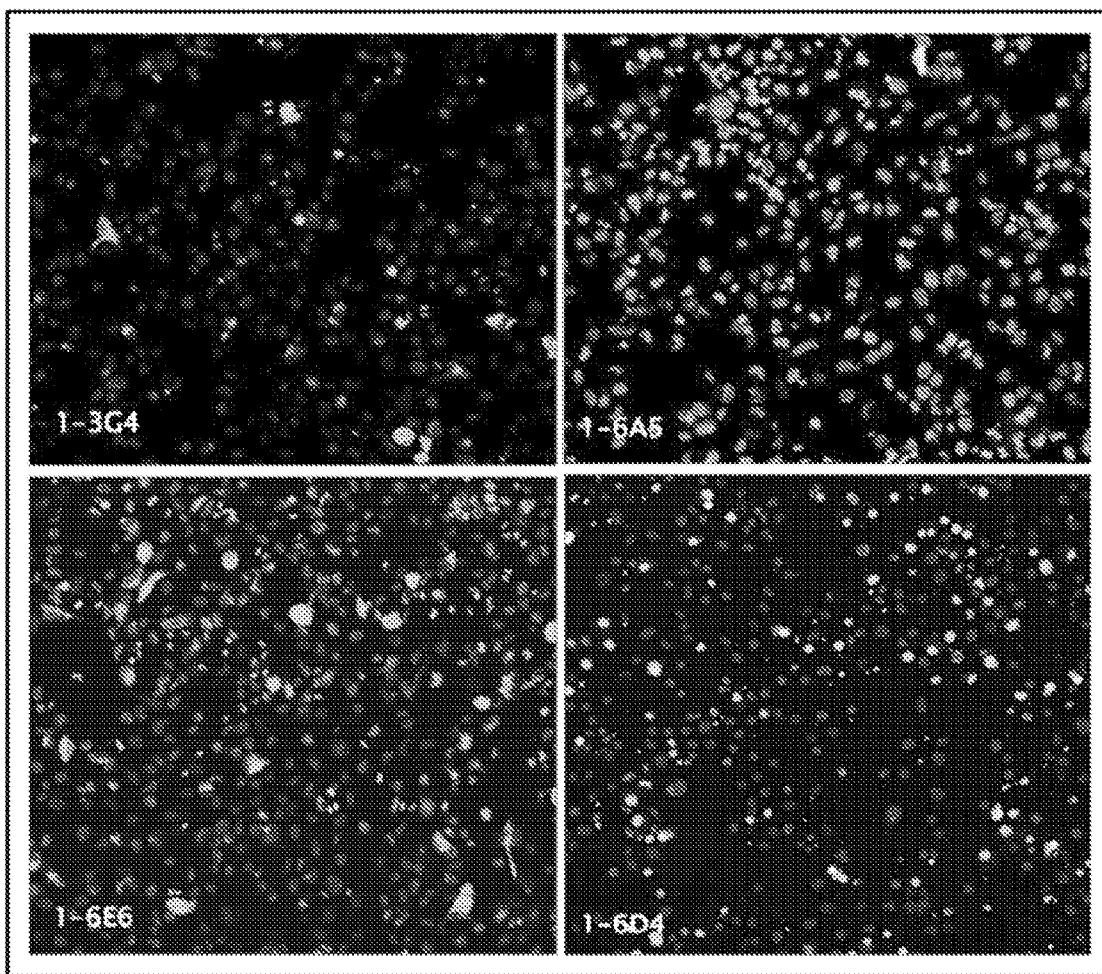


FIGURE 44B

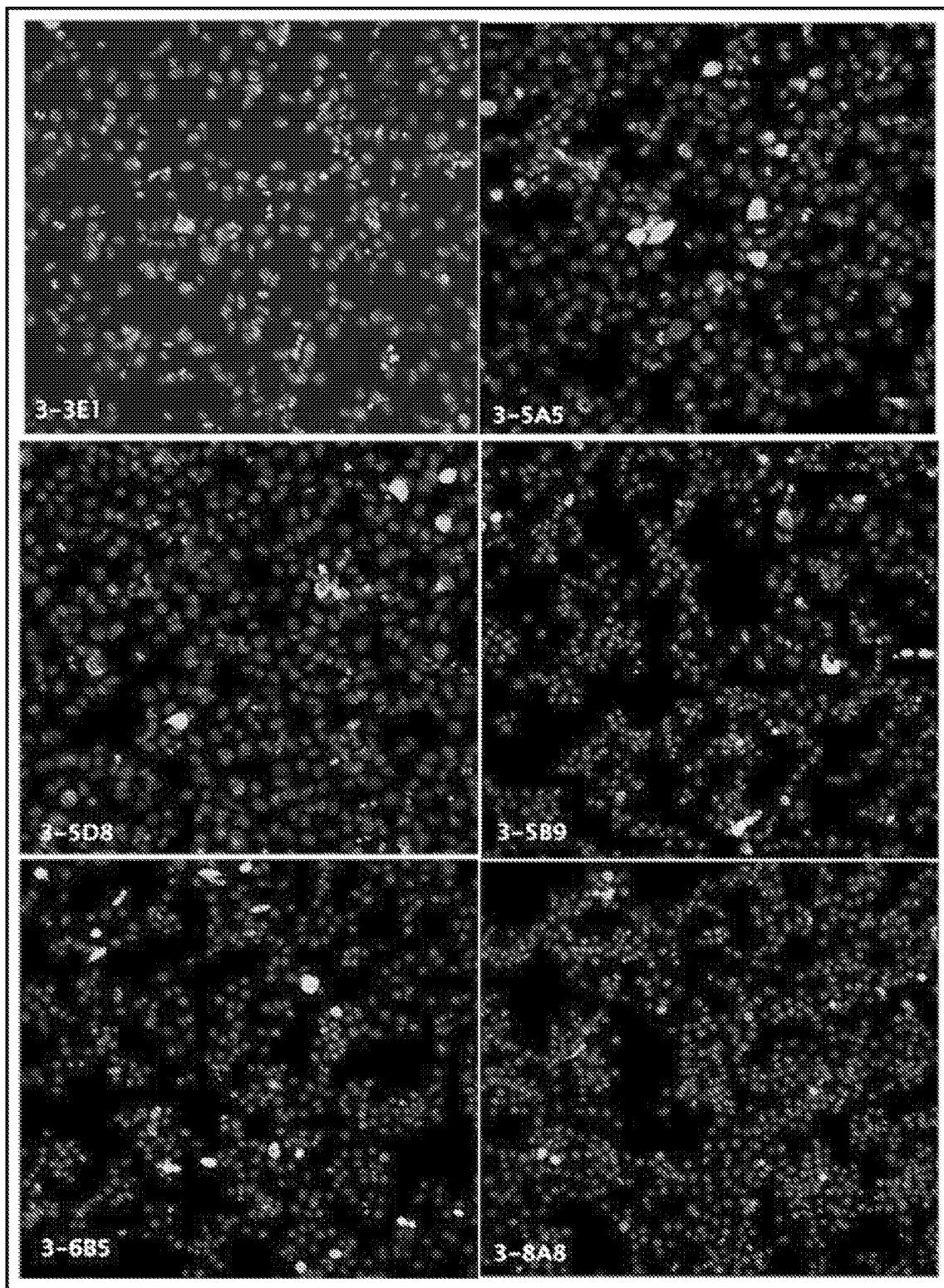
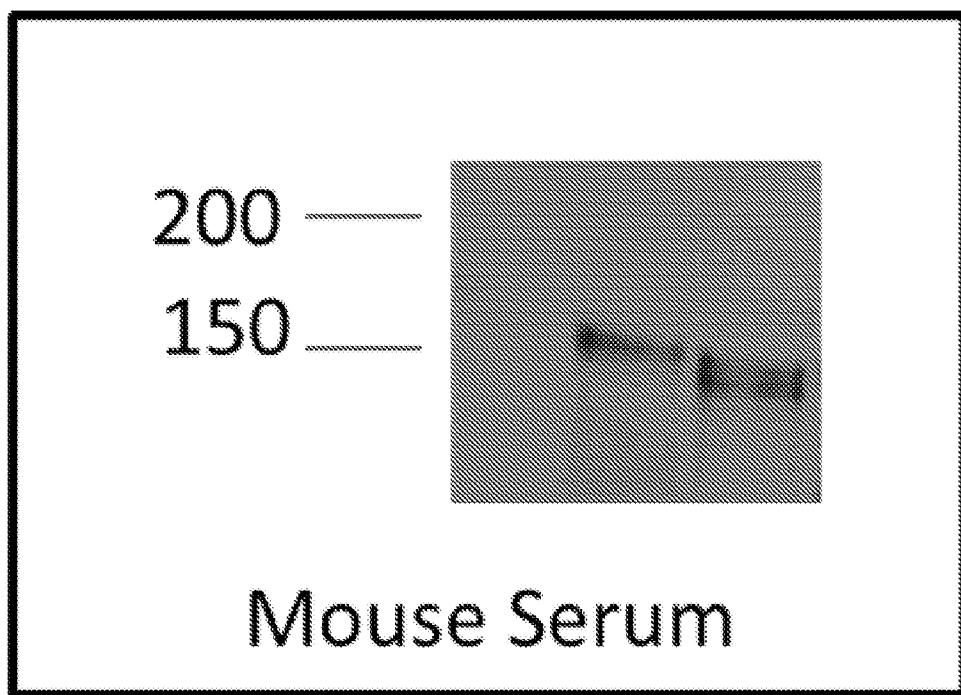
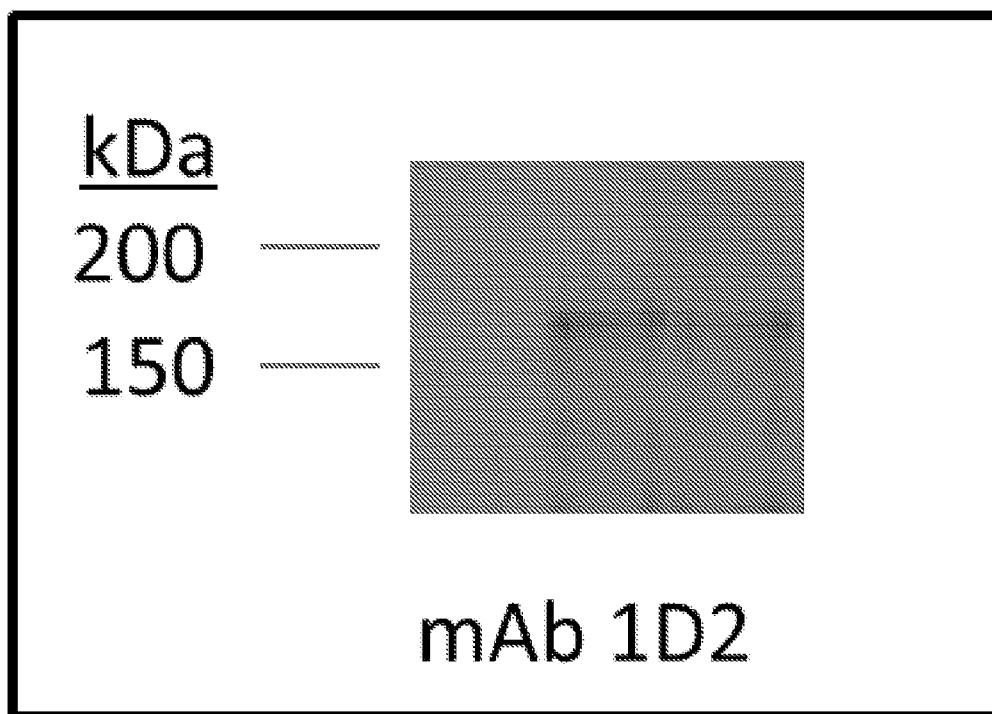


FIGURE 45

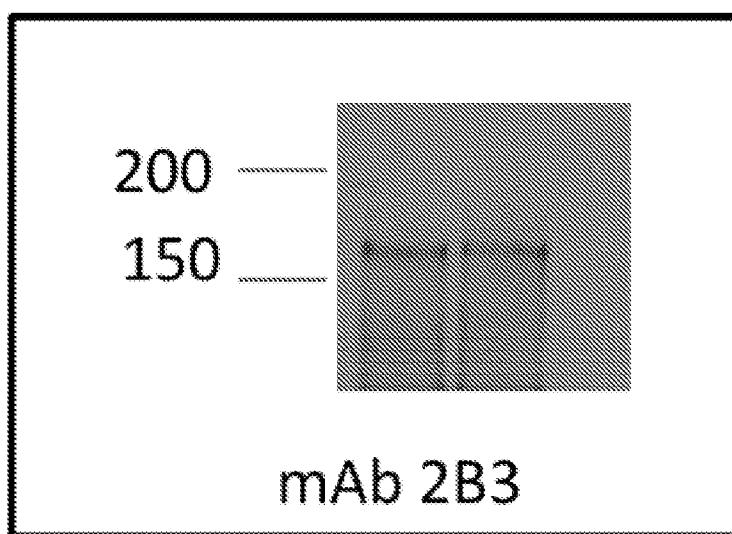
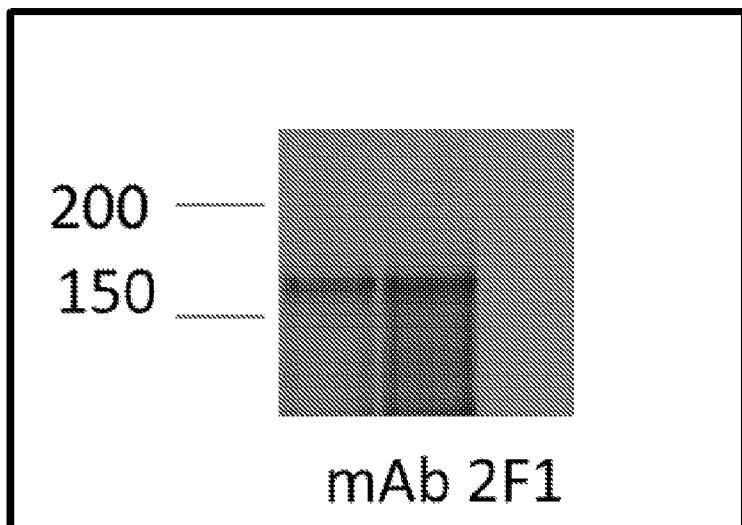


1st Lane: 3T3

2nd Lane: HCT116

3rd Lane: HT29

FIGURE 46



1st lane: HCT116
2nd Lane: HT29
3rd Lane: 3T3

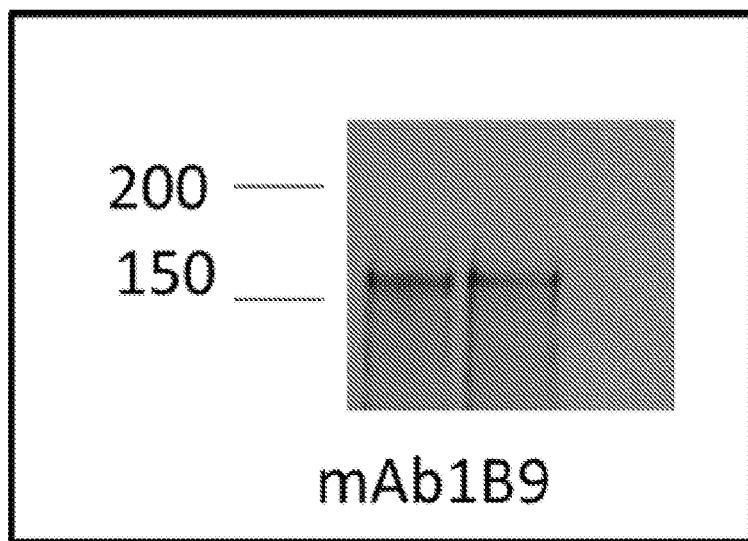


FIGURE 47A

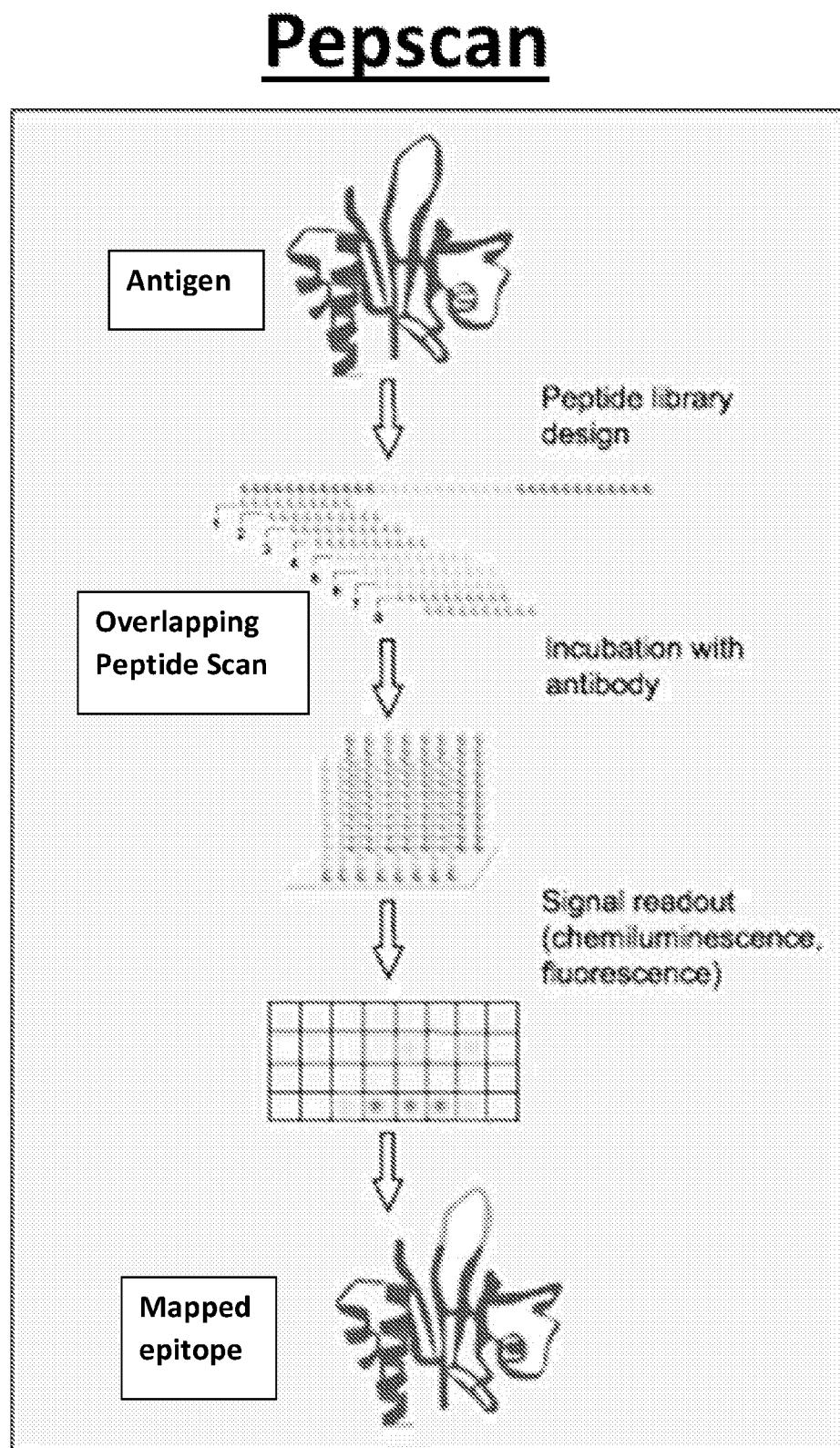


FIGURE 47B

Peptide phage display

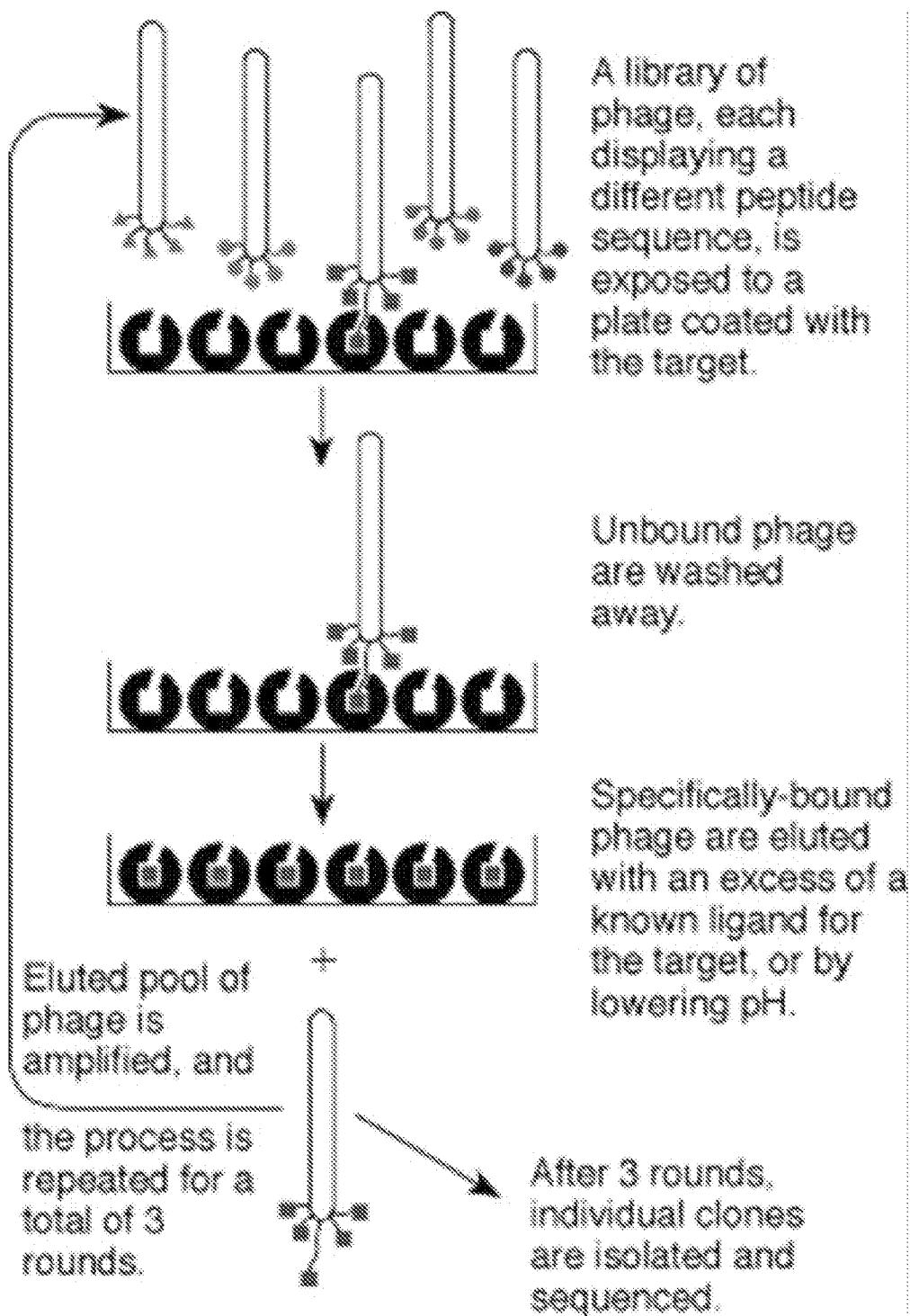


FIGURE 48A

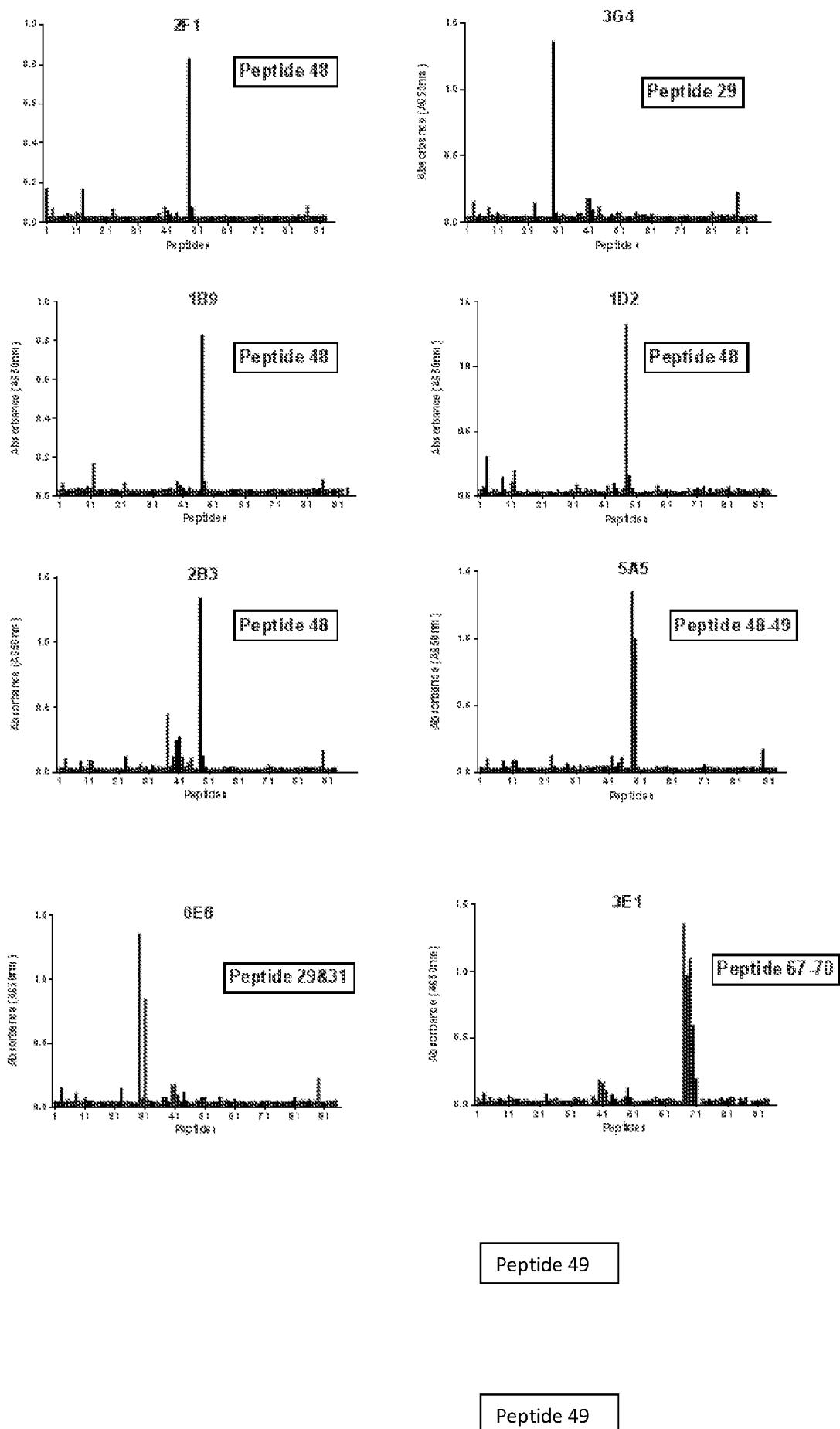


FIGURE 48B

2B3	Sequence	Score	2B3	Sequence	Score
1	ISSPYHNSHHHHNS	0.655	1	-----SSPTHNHHHNS-----	13
2	IVHNHPQHPHIIR	0.725	2	-----GLDQ-----GHHHNS-----	12
3	NIKRPDHPHNPNR	0.643	3	-----GLDH-----THHHHNS-----	12
4	GLDPSRHPHGSW	0.589	4	-----VHHH-----PQHSHI-----13-----	12
5	GLIYHNSHHSYHAP	0.595	5	-----NIKS-----PQHSHP-----13-----	12
6	GLNNHTHHHHSNC	0.639	6	-----GHCFSKLT-----PQHSHP-----13-----	12
7			7	-----GLD-----VHHH-----13-----	12
8			8		
9			9		
10			10		
11			11		
12			12		
13			13		
14			14		
15			15		
16			16		
17			17		
18			18		
19			19		
20			20		
21			21		
22			22		
23			23		
24			24		
25			25		
26			26		
27			27		
28			28		
29			29		
30			30		
31			31		
32			32		
33			33		
34			34		
35			35		
36			36		
37			37		
38			38		
39			39		
40			40		
41			41		
42			42		
43			43		
44			44		
45			45		
46			46		
47			47		
48			48		
49			49		
50			50		
51			51		
52			52		
53			53		
54			54		
55			55		
56			56		
57			57		
58			58		
59			59		
60			60		
61			61		
62			62		
63			63		
64			64		
65			65		
66			66		
67			67		
68			68		
69			69		
70			70		
71			71		
72			72		
73			73		
74			74		
75			75		
76			76		
77			77		
78			78		
79			79		
80			80		
81			81		
82			82		
83			83		
84			84		
85			85		
86			86		
87			87		
88			88		
89			89		
90			90		
91			91		
92			92		
93			93		
94			94		
95			95		
96			96		
97			97		
98			98		
99			99		
100			100		

12mer library- Multiple sequence alignment

Clone 1 -TTNSWHPHNRML--
 Clone 2 -RPLEHPHSREM--
 Clone 3 --GKNHPHPGPLFR-
 Clone 4 -ASIWSHPSPLY--
 Clone 5 -AGPSYHPHHYHY--
 Clone 6 ---SPHPHAPSFLRL
 Clone 7 NIKRPDHHPNRP---
 Clone 8 GLNHHTHHSNC---
 Clone 9 GRPAPRHPHHSW---
 Clone 10 GLEASRHPHGSW---

Consensus KLTEFHPHSGPLRGS565 PPKLTEFHPHSGPLRGST 585

2B3 epitope

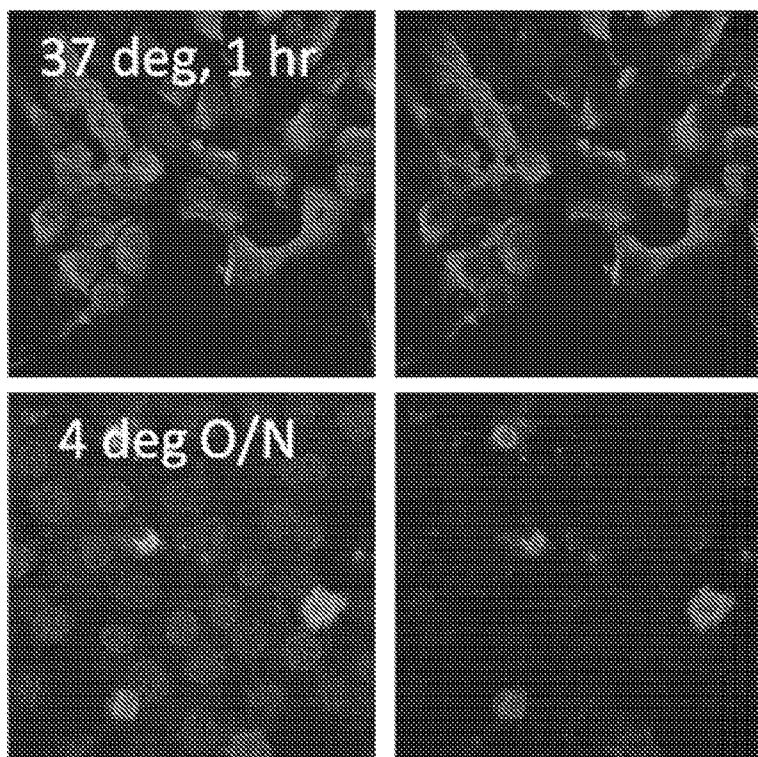
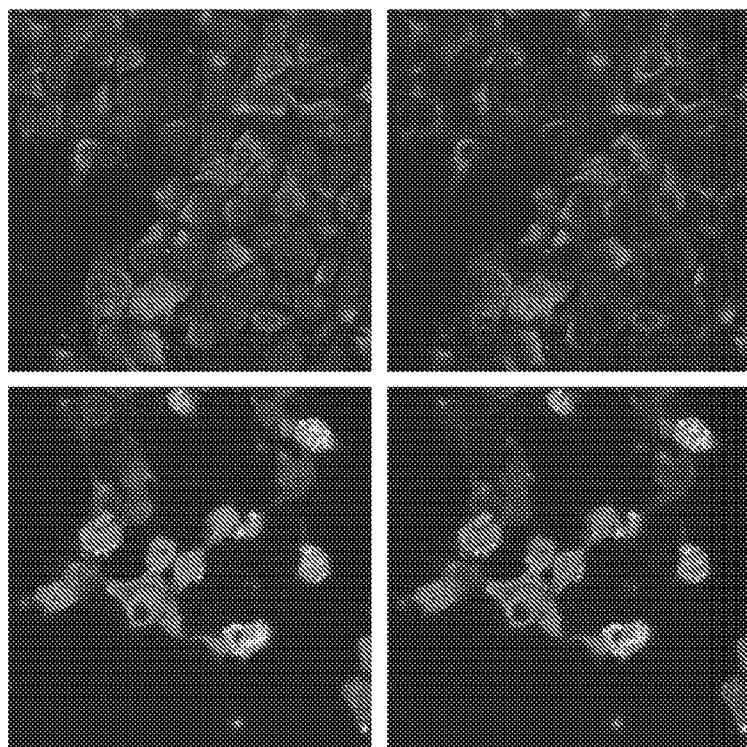
FIGURE 49A**mAb 5A5****mAb 6B5**

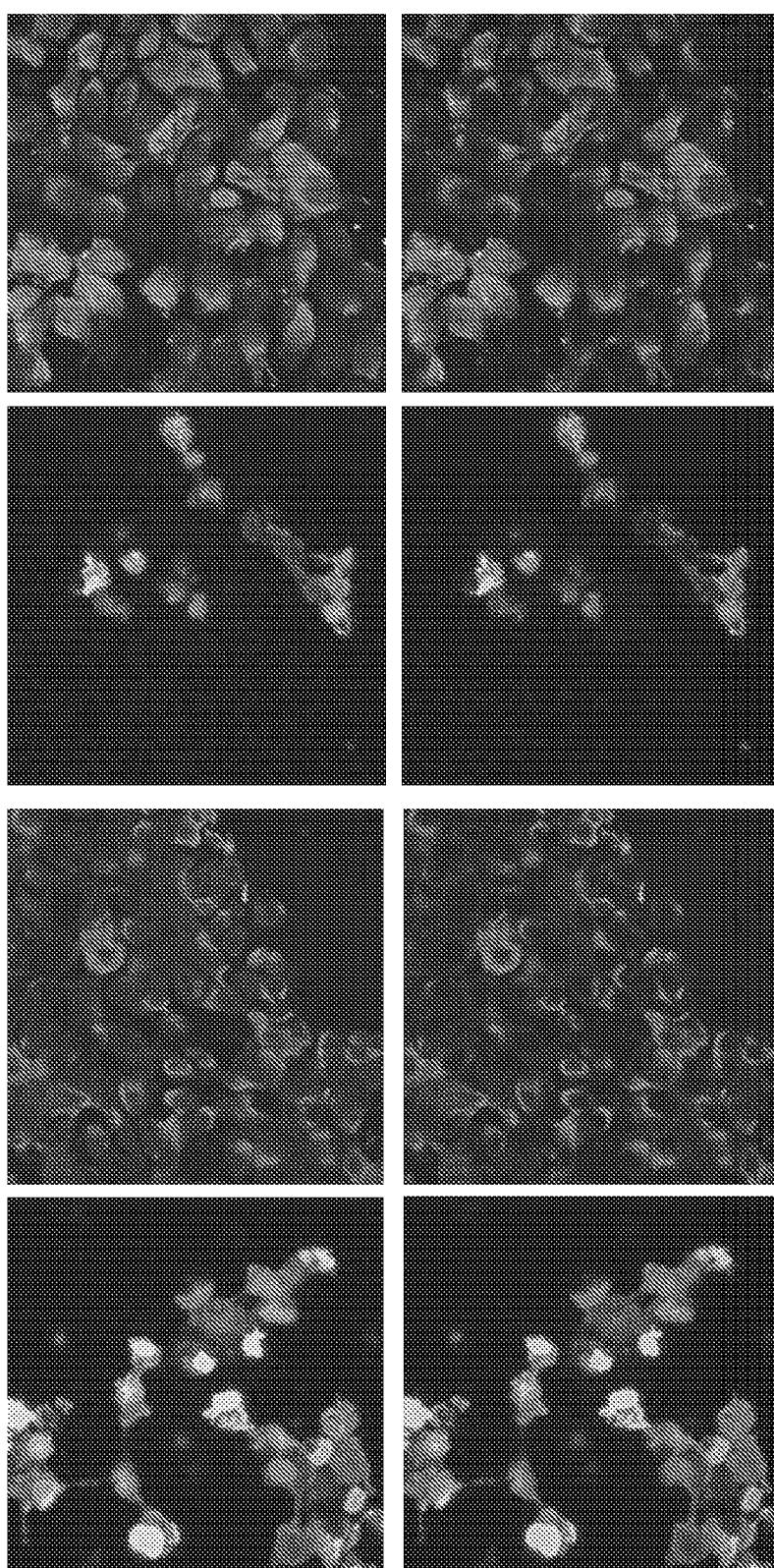
FIGURE 49B**mAb 6D4**

FIGURE 50A**5A5 Heavy Chain**

5A5H CDR1 - IMGT: 1-10, 15-25, 30-35, 40
 5A5H CDR2 - IMGT: 2-50, 55-65, 70-75, 80-90, 95-100, 105-120, 125
 5A5H CDR3 - IMGT: 105-114, 125
 5A5H FR4 - 120

5A5H 5A5H 5A5H 5A5H 5A5H 5A5H 5A5H 5A5H	<----- 1 5 10 -----> 15 20 25 -----> 30 35 40 -----> 45 50 55 60 65 -----> 70 75 80 85 90 95 100 105 108 114 120 125 -----> 125	F R 1 - I M G T L E V K L E Q S G P G L V K CTT GAG GTT AAG CTG GAG CAG TCA GGA CCT GGC CTG GTG AAA -----> P S Q S L S L T C T V T CCT TCT CAG TCT CTG TCC CTC ACC TGC ACT GTC ACT -----> CDR1 - IMGT -----< D Y S I T S D Y A GAC TAC TCA ATC ACC AGT GAT TAT GCC TGG AAC -----> F R 2 - I M G T W I R Q F P G N K L E W TGG ATC CGG CAA TTT CCA GGA AAC AAA CTG GAG TGG -----> CDR2 - IMGT -----< M G Y I L Y S G S T ATG GGT TAC ATA CTC TAC AGT GGT TCC ACT ACG -----> Y N P S L K S R V S I TAC AAT CCG TCT CTC AAA ... AGT CGA GTC TCT ATC -----> F R 3 - I M G T T R D T S K N Q F F L H L D ACT CGA GAC ACA TCC AAG AAC CAG TTC TTG CAC TTG GAT -----> S V T T E D A A T Y Y C TCT GTG ACT ACT GAG GAC GCT GCC ACA TAT TAC TGT CDR3 - IMGT <----- FR4 - A S L G R G G S W G Q G T T 105 108 114 120 GCA AGC CTC GGG CGT GGG GGG TCC TGG GGC CAG GGC ACC ACT IMGT -----> 125 L A V S S CTC GCA GTC TCC TCA
--	---	--

FIGURE 50A (CONTINUED)**Amino Acid Sequence in FASTA format (5A5H)**

```
> 5A5H
LEVKLEQSGPGLVKPSQSLTCTVTDYSITS DYAWNWI RQFPGNKLEWMGYI LYSGSTTYNPSLKS
VSITRDTSKNQFFLHLD SVTTE DAATYYCASLGRGGSWQGTTLAVSS
```

Nucleotide Sequence in FASTA format (5A5H)

```
> 5A5H
CTTGAGGTTAACGCTGGAGCAGTCAGGACCTGGCCTGGTGAACACCTCTCAGTCAGTCACCTG
CACTGTCACTGACTACTCAATCACCAAGT GATTATGCCTGGAACCTGGATCCGGCAATTCCAGGAAACA
AACTGGAGTGGA TGGATGGGTTACATACTCTACAGTGGTCCACTACGTACAATCCGCTCTCAAAAGTCGA
GTCTCTATCACTCGAGACACATCCAAGAACCAAGCAGTTCTCCTGCAC TTGGATTCTGTGACTACTGAGGA
CGCTGCCACATATTACTGTGCAAGCCTCGGGCGTGGGGGTCTGGGCCAGGGCACCAC TCTCGCAG
TCTCCTCA
```

FIGURE 50B

5A5K

1	5	10	I M G T
D I L M T Q T P L S L P			
GAT ATT TTG ATG ACC CAA ACT CCT CTC TCC CTG CCT			

5A5K

15	20	25	V S L G D Q A S I S C R S S
GTC AGT CTT GGA GAT CAA GCC TCC ATC TCT TGC AGA TCT AGT			

5A5K

CDR1 - IMGT									
30	35	Q S I V H S N G N T Y							
CAG AGC ATT GTA CAT AGT AAT GGA AAC ACC TAT ...									
40	45	F R 2 - I M G T	50						
L E W Y L Q K P G Q S P K L									
TTG GAA TGG TAC CTG CAG AAA CCA GGC CAG TCT CCA AAG CTC									

5A5K

CDR2 - IMGT									
55	60	L I Y K V S							
CTT ATC TAC AAA GTT TCC									
65	70	D R F T G	75						
N R F S G V P									
AAC CGA TTT TCT GGG GTC CCA ... GAC AGG TTC ACT GGC									
80	85	I M G T	90						
S G									
S G T D F T L K									
AGT GGA TCA GGG ACA GAT TTC ACA CTC AAG									

5A5K

CDR3 - IMGT									
95	100	I S R V E A E D L G I Y Y C							
ATC AGC AGA GTG GAG GCT GAG GAT CTG GGA ATT TAT TAC TGC									
105	109 114	D R F G G	120						
F Q G S H A P W T F G G									
TTT CAA GGT TCA CAT GCT CCG TGG ACG TTC GGT GGA									
- IMGT - - - ->									
125	G T K L E I R	FR4							
GGC ACC AAG CTG GAA ATC AGA C									

FIGURE 50B (CONTINUED)**Amino Acid Sequence in FASTA format (5A5K)**

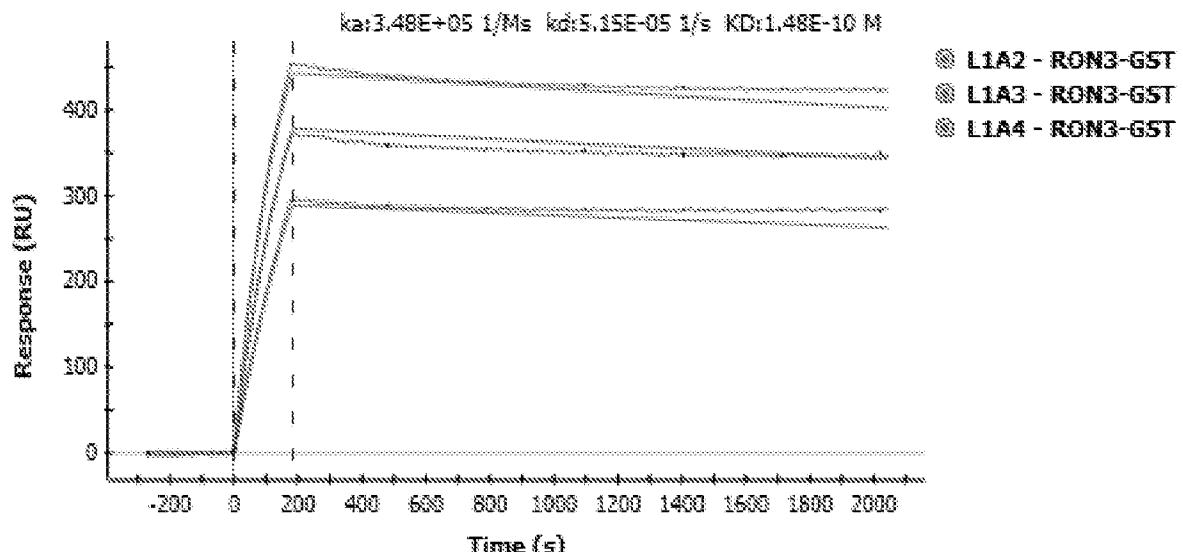
```
> 5A5K
DILMTQTPLSLPVSLGDQASISCRSSQSIVHSNGNTYLEWYLQKPGQSPKLLIYKVSNRSGVPDRFT
GSGSGTDFTLKISRVEAEDLGIYYCFQGSHAPWTFGGGTKLEIR
```

Nucleotide Sequence in FASTA format (5A5K)

```
> 5A5K
GATATTTGATGACCCAAACTCCTCTCCCTGCCTGTCAGTCTGGAGATCAAGCCTCCATCTCTTG
CAGATCTAGTCAGAGCATTGTACATAGTAATGGAAACACCTATTGGAATGGTACCTGCAGAAACAG
GCCAGTCTCCAAAGCTCCTTATCTACAAAGTTCCAACCGATTTCTGGGGTCCCAGACAGGTTCACT
GGCAGTGGATCAGGGACAGATTACACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGAAATTAA
TTACTGCTTCAAGGTTCACATGCTCCGTGGACGTTGGAGGCACCAAGCTGGAAATCAGAC
```

FIGURE 51

2B3 binding affinity as measured by Proteon



	Ka (1/Ms)	Kd (1/s)	KD (M)	Rmax (RU)	Chi2 (RU)
2B3	3.48E5	5.15E-5	1.48E-10	619.55	60.87

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2017/050424

A. CLASSIFICATION OF SUBJECT MATTER

C07K 16/30 (2006.01) A61K 39/395 (2006.01) A61P 35/00 (2006.01) G01N 33/53 (2006.01)

According to International Patent Classification (IPC)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K; A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC/WPI/BIOSIS/MEDLINE/EMBASE/REGISTRY: recepteur d'origine nantais or receptor origin nantaise or RON or macrophage stimulating protein receptor or MSPR or MST1R or CD136 or c-Met related tyrosine kinase or protein tyrosine kinase or PTK8 and antibodies or immunoglobulins and cancer or fibrosis and related terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/095002 A1 (TEXAS TECH UNIVERSITY SYSTEM) 25 June 2015 pg 18, ln 15 to pg 19, ln 2; pg 19, ln 28 to pg 20, ln 6, Fig. 1A	1-31
X	WO 2010/093055 A1 (DAICHI SANKYO COMPANY, LIMITED) 19 August 2010 para [0013], [0044], [0081]-[0087], Examples 4 & 6, claims 52-57	1-31
X	WO 2012/006341 A2 (AVEO PHARMACEUTICALS, INC.) 12 January 2012 para [0107]-[0111], [0281]-[0294], Examples 2, 14 & 17	1-31
X	WO 2011/090762 A1 (EMERGENCY PRODUCT DEVELOPMENT SEATTLE, LLC) 28 July 2011 pg 15, ln 32 to pg 16, ln 10, pg 40, ln 19-29, pg 70, ln 15 to pg 76, ln 21, Example 4, Fig. 8	1-31
X	WO 2009/070294 A2 (IMCLONE SYSTEMS INCORPORATED) 4 June 2009 para [0063], [0066], [0117], [0124]-[0127], [0163]-[0164], Example 3	1-31

Further documents are listed in the continuation of Box C.

See patent family annex.

*Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 02/11/2017 (day/month/year)	Date of mailing of the international search report 07/11/2017 (day/month/year)
Name and mailing address of the ISA/SG IPOS INTELLECTUAL PROPERTY OFFICE OF SINGAPORE 51 Bras Basah Road #01-01 Manulife Centre Singapore 189554 Email: pct@ipos.gov.sg	Authorized officer <u>Ang Xiu Min (Dr)</u> IPOS Customer Service Tel. No.: (+65) 6339 8616

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2017/050424**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/006490 A2 (ABBOTT LABORATORIES) 12 January 2012 pg 58, ln 27 to pg 60, ln 4, Section IV on pg 100, pg 141, ln 2-15, pg 145, ln 4-8, Example 2.5, claim 30	1-31
A	WANG MH. ET AL., Potential therapeutics specific to c-MET/RON receptor tyrosine kinases for molecular targeting in cancer therapy. <i>Acta Pharmacol Sin.</i> , 9 August 2010, Vol. 31, No. 9, pages 1181-1188 [Retrieved on 2017-11-02] <DOI: 10.1038/APS.2010.106> whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050424

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015/095002 A1	25/06/2015	CA 2932480 A1 CN 105916882 A EP 3083695 A1 US 2016311918 A1	25/06/2015 31/08/2016 26/10/2016 27/10/2016
WO 2010/093055 A1	19/08/2010	AU 2010214301 A1 CA 2752136 A1 CN 102438702 A CO 6420322 A2 EP 2396084 A1 ES 2583281 T3 HK 1164193 A1 JP 2012517223 A KR 20110117677 A MX 2011008456 A NZ 594452 A RU 2011137405 A SG 173196 A1 SG 2014009195 A TW 201036635 A US 2012034215 A1 ZA 201105725 B	01/09/2011 19/08/2010 02/05/2012 16/04/2012 21/12/2011 20/09/2016 28/07/2017 02/08/2012 27/10/2011 26/09/2011 25/01/2013 20/03/2013 29/08/2011 28/04/2014 16/10/2010 09/02/2012 25/04/2012
WO 2012/006341 A2	06/07/2010	AR 082194 A1 AU 2011276285 A1 CA 2804399 A1 EP 2591005 A2 JP 2013533746 A US 2012027773 A1 US 2014066603 A1	21/11/2012 24/01/2013 12/01/2012 15/05/2013 29/08/2013 02/02/2012 06/03/2014
WO 2011/090762 A1	28/07/2011	AU 2010343049 A1 AU 2010343056 A1 AU 2010343057 A1 BR 112012016135 A2 CA 2784814 A1 CA 2785661 A1 CN 102958942 A CN 103124743 A CN 105693861 A CY 1118008 T1 DK 2519543 T3	19/07/2012 02/08/2012 19/07/2012 07/03/2017 28/07/2011 28/07/2011 06/03/2013 29/05/2013 22/06/2016 17/05/2017 26/09/2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050424

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EA 201290570 A1 EA 201290568 A1 EA 201492253 A1 EP 2519541 A1 EP 2519543 A1 EP 2519544 A1 EP 3112382 A1 ES 2592385 T3 HK 1170741 A1 HRP 20160819 T1 HUE 029257 T2 JP 2013515509 A JP 2013515508 A JP 2015180226 A JP 2015221829 A KR 20120125611 A LT 2519543 T MX 2012007533 A NZ 600820 A PL 2519543 T3 PT 2519543 T3 RS 55229 B1 SG 181952 A1 SI 2519543 T1 SMT 201600335 B US 2013089554 A1 US 2013095097 A1 US 2015274844 A1	28/02/2013 28/02/2013 30/06/2015 07/11/2012 07/11/2012 07/11/2012 04/01/2017 29/11/2016 17/03/2017 12/08/2016 28/02/2017 09/05/2013 09/05/2013 15/10/2015 10/12/2015 16/11/2012 10/10/2016 30/07/2012 24/12/2014 30/12/2016 07/10/2016 28/02/2017 30/07/2012 31/08/2016 10/11/2016 11/04/2013 18/04/2013 01/10/2015
WO 2009/070294 A2	04/06/2009	AR 069393 A1 AU 2008330089 A1 BRPI 0820218 A2 CA 2706583 A1 CN 101868478 A EA 201070636 A1 EP 2222703 A2 IL 204743 A JP 2011504176 A KR 20100074293 A MX 2010005651 A	20/01/2010 04/06/2009 23/06/2015 04/06/2009 20/10/2010 29/10/2010 01/09/2010 31/10/2013 03/02/2011 01/07/2010 11/06/2010

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2017/050424

Note: This Annex lists known patent family members relating to the patent documents cited in this International Search Report. This Authority is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		NZ 584271 A PA 8804901 A1 PE 17132009 A1 TW 200936161 A UA 99633 C2 US 2009136510 A1 US 2011135631 A1 UY 31478 A1	25/05/2012 23/06/2009 13/11/2009 01/09/2009 10/09/2012 28/05/2009 09/06/2011 17/07/2009
WO 2012/006490 A2	12/01/2012	AR 082131 A1 AU 2011274515 A1 BR 11201300630 A2 CA 2804686 A1 CL 2013000074 A1 CN 103167879 A CO 6670524 A2 CR 20130074 A ECSP 13012425 A EP 2590671 A2 EP 2921177 A2 JP 2013535187 A KR 20130105601 A MX 2013000366 A PE 14132013 A1 RU 2013105338 A SG 188182 A1 TW 201206470 A US 2012014957 A1 US 2016046730 A1 UY 33492 A	14/11/2012 28/02/2013 24/05/2016 12/01/2012 06/12/2013 19/06/2013 15/05/2013 12/06/2013 28/03/2013 15/05/2013 23/09/2013 12/09/2013 25/09/2013 29/04/2013 19/01/2014 20/08/2014 30/04/2013 16/02/2012 19/01/2012 18/02/2016 31/01/2012